Operational Aspects of Continuous Pharmaceutical Production

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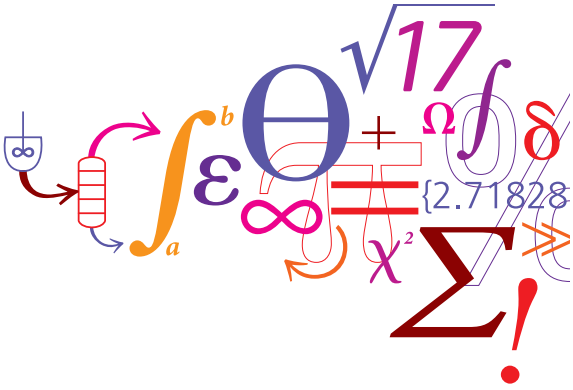

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Operational Aspects of Continuous Pharmaceutical Production

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Preface

This work was performed at the Department of Chemical and Biochemical Engineering at the Technical University of Denmark (DTU). It was done as a part of collaboration between DTU Chemical Engineering and H. Lundbeck A/S. The theoretical part was performed in the Center for Process Enginerring and Technology (PROCESS) whereas experimental work was done in the Center for Combustion and Harmful Emission Control (CHEC). It is important to note that short external stays were done in the R&D department of H. Lundbeck A/S (Valby, Denmark).

The main focus of the dissertation was to accelerate slow chemical reactions and establish continuous pharmaceutical manufacturing of specific API intermediates. It is important to emphasize that all of the applications that were investigated are suited for lab scale production. The thesis represents the follow-up activities to the PhD project titled “Moving from batch towards continuous organic-chemical pharmaceutical production”, a project that was carried out by Albert Emili Cervera Padrell (2011).

The PhD project was supervised by Prof. Krist V. Gernaey as the principal supervisor (DTU Chemical Engineering, PROCESS), then Kim-Dam Johansen as first cosupervisor (CHEC, DTU Chemical Engineering) and Tommy Skovby as second cosupervisor (H. Lundbeck, A/S).

Acknowledgments

Work associated with this PhD dissertation involved plenty of cooperation both inside and outside the borders of DTU. Therefore, plenty of people deserve to be mentioned in the acknowledgments due to their great influence on my work and on my motivation to work. Nevertheless, it always happens that some important persons get excluded accidentally. Hence, I would apologize immediately if some of the names are not mentoined here.

First of all, I would like to thank to my main supervisor for all the assistance during my work at DTU, as well as for the high level of understaning and the smooth cooperation in the last 3 years. Hence, Krist V. Gernaey is greatly acknowledged for all the support which I have received from him. Big thanks should also be given to my cosupervisors who provided me with constructive and useful advices during our biannual meetings - Kim-Dam Johansen from CHEC (DTU Chemical Engineering) and Tommy Skovby (H. Lundbeck A/S).

Albert Emili Cervera Padrell is greatly acknowledged, as well, because he provided me with an excellent introduction to the project and also with many practical advices about specific issues in the experimental work. It saved plenty of time and additionally influenced my lab performance positively. Moreover, the practical work in the lab was greatly supported by three technicians in CHEC – Mette Larsen, Emine Yüksel Coskun and Anders Tiedje, who are also acknowledged for the good cooperation during my PhD studies. People from CERE and DPC additionally deserved big thanks because of their help and becaue they allowanced me to use some of their equipment. Hence, thank so Irakli Javakhishvili, Anders Egede Daugaard and Zacarias Tecle here.

Furthermore, some people from H. Lundbeck A/S deserve big thanks for their support during the performance of my experimental work. More precisely, people from the manufacturing site of the company provided me with the necessary chemicals, as well as with very constructive advices about practical work in the lab. Hence, I would like to thank Steen Søgaard, Michael Jønch Pedersen and Jesper Pram Rahbek for all the support which I received from them, as well as Asmus Ringlebjerg Mortensen who was my personal driver to Lumsås. In addition, Andreas Ritzén and Trine Puggaard Petersen from the R&D section of the company (Medicinal Chemistry I) are acknowledged for their assistance in performing the microwave assisted experiments and NMR analyses.

Besides the practical cooperations, there were plenty of people who supported me on my way to submitting the PhD thesis. Hence, I would like to thank to my family who showed an high level of understanding and support in the last three years. Furthermore, I would also like to thank the people in CAPEC-PROCESS who organized plenty of social and sport activities that had a terrific impact on relieving the stress and consequently increased my motivation to work better. Furthermore, I would like to thank to some of my additional friends who showed a big support in the crucial moments of my life in Denmark. Hence, big thanks should be given to Thomas, Johnnie, Jovan, Darko, Živa, Ognjen, Anna-Lena, Olivera, Watson, Hema, Rita, Andrijana, Krešimir, Søren...

Kgs. Lyngby,
14 February 2014

Abstract

Introduction of the Process Analytical Technology (PAT) Initiative, the Quality by Design (QbD) approach and the Continuous Improvement (CI) methodology/philosophy is considered as a huge milestone in the modern pharmaceutical industry. The above concepts, when applied to a pharmaceutical production process, should enable better designs of products and processes. Furthermore, easier process monitoring, control and automation are just some of the advantages that can be achieved as a consequence.

Traditional production methods of Active Pharmaceutical Ingredients (APIs) are based on batch and semi-batch processes which include plenty of supportive actions defined as non-value added activities (NVAs) or simply waste. It is therefore desirable to implement a switch from batch based production to continuous manufacturing modes in order to minimize NVAs, as well as to enable easier satisfaction of the demands defined by the PAT Initiative. This approach could be considered as establishing a Lean Production System (LPS) which is usually supported with tools associated with Process Intensifaction (PI) and Process Optimization (PO).

Development of continuous processes is often connected with many obstacles due to the very long reaction sequences, inhomogenous reaction mixtures, the presence of slurries.... It is therefore important to adapt the reaction conditions as much as possible to the desired production in continuous mode. Small-scale manufacturing could be supported with modern PI tools, such as microwave assisted organic synthesis (MAOS), ultrasounds, meso-scale flow chemistry and microprocess technology. Furthermore, development of chemical catalysts and enzymes enabled further acceleration of some chemical reactions that were known as very slow or impossible to be performed.

The main goal of this work is to develop a PI strategy that would include different chemical and physical approaches with the main purpose to accelerate slow chemical reactions and adapt them to continuous manufacturing modes. Detailed insight into the PAT, QbD, CI and Lean Production System (LPS) is additionally provided in the introduction. The practical implementation of the PI strategy is covered with three different examples.

The first example process is the dehydration of 9-Allyl-2-Chlorothioxanthen-9-Ol (“N714-Allylcarbinol”) to the mixture of cis and trans 9H-thioxanthene,2-chloro-9-(2-propenylidene)-(9CI) (“N746-Butadienes”). Both components are intermediate products in the synthesis of Zuclopenthixol – a product of H. Lundbeck A/S. Successful transfer from batch towards meso-flow chemistry is performed together with demonstration of the potential for in-/at- and off-line process monitoring.

The second example process is the anti-Markovnikov hydroamination between the “N746-Butadienes” and 1-(2-hydroxyethyl)piperazine (HEP) resulting into a mixture of cis/trans 4-[3-(2-Chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol (Clopenthixol). This chemical reaction is well-known as very slow and difficult to be accelerated by applying chemical catalysts.

Some authors claim that hydroamination of unsaturated hydrocarbons is known as one of the “ten challenges for homogeneous catalysis”. Nevertheless, implementation of the PI strategy by using microwave irradiation resulted in significant improvements.

The third example process includes the small-scale production of (2-Bromophenyl)(phenyl)sulfane. This important API intermediate is receiving significant attention in the pharmaceutical industry due to the fact that there are plenty of APIs which includes C-S bonds in their chemical structure. The production of such compounds is based on Carbon-Sulfur cross coupling reactions, involving expensive chemical catalysts, chemical ligands, bases and unfriendly solvents. Implementation of the PI strategy with a significantly modified chemical pathway resulted in several benefits from an economic, environmental and manufacturing point of view.

Considering the results achieved in the case studies, it can be concluded that successful implementation of the PI strategy has been achieved while satisfying the PAT demands and implementing Lean Production System. Significant accelerations of often considered difficult chemical reactions have been achieved, and therefore it can be concluded that a successful transfer from batch towards continuous manufacturing has been achieved.

Resumé

Introduktionen af koncepter/filosofier som Proces Analytisk Teknologi (PAT), kvalitet ved design (QbD) og kontinuert optimering (CI) har i stor stil forbedret den farmaceutiske industri. Brugen af disse koncepter i farmaceutisk produktion, vil potentielt hjælpe med at sikre bedre produktionsmetoder, samt sikre produkt kvalitet. Derudover, kan man ved introduktion af disse koncepter drage nytte af forbedret process kontrol og automatisering.

Traditionel produktion af aktive farmaceutiske ingredienser (APIs) er baseret på batch og semi-batch processer, der involverer mange økonomisk dyre manuelle aktiviteter og producerer relativt store mængder affald per kg produkt. Det er derfor fordelagtigt at udskifte batch med kontinuerte produktionsmetoder, for at minimere de dyre manuelle aktiviteter. Ydermere, er det nemmere at opfylde kravene for PAT implementering gennem kontinuert produktion. Denne fremgangsmåde kan svare til at etablere et Lean Produktions System (LPS), som normalt er understøttet af redskaber som Proces Intensivering (PI) og Proces Optimering (PO).

Udviklingen af kontinuerte processer kommer med mange udfordringer, f.eks. konsekvenser af lange reaktionstider, ikke homogene reaktionsblandinger, væske-fast stof-blandinger, osv. Det er derfor vigtigt at tilpasse reaktionsforholdene så godt som muligt til den kontinuerte produktionsmetode. Lille skala produktion kan drage nytte af moderne PI-værktøjer, som mikrobølge assisteret organisk syntese (MAOS), ultralyd, meso-skala flow kemi og mikroprocesteknologi. Derudover kan udviklingen af både kemiske og biologiske (f.eks. enzymer) katalysatorer hjælpe med at accelerere reaktionshastigheder. I visse tilfælde vil sådanne katalysatorer også gøre det muligt at udføre reaktioner der ellers ikke ville være mulige.

Formålet med dette arbejde er at udvikle en PI strategi, der inkluderer forskellige kemiske of fysiske fremgangsmåder, der kan hjælpe med at accelerere langsomme kemiske reaktioner og tilpasse disse reaktioner til kontinuert produktion. Et detaljeret indblik i PAT, QbD, CI og LPS koncepterne er givet i introduktionen. Den praktiske implementering af den foreslåede PI strategi er illustreret gennem 3 proces eksempler.

Det første proces eksempel er baseret på dehydrering af 9-Allyl-2-chlorothioxanthen-9-ol (”N714-Allylcarbionol”) til en blanding af *cis* og *trans* 9H-thioxanthene,2-chloro-9-(2-propenylidene)-(9Cl) (”N746-butadienes”). Disse to komponenter er mellemprodukter i syntesen af Zuclopenthixol – et produkt af H. Lundbeck A/S. Dette proces eksempel resulterede i en succesfuld overgang fra batch produktion til meso-skala flow produktion. Potentialet for in-/at- og off-line procesovervågning blev også illustreret her.

Det andet proces eksempel er anti-Markovnikov hydroamineringen mellem”N746-butadienes” og 1-(2-hydroxyethyl)piperazine (HEP), der giver en blanding af *cis*/*trans* 4-[3-(2-chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol (Clophenthixol). Dette er en kemisk reaktion som er kendt for at være meget langsom og svær at accelerere ved brugen af kemiske katalysatorer. Nogle forskere postulerer at hydroamineringen af umættede carbonhydrider er en af de ”10 udfordringer

for homogen katalyse". Ikke desto mindre resulterede implementeringen af PI strategien og brugen af mikrobølgestråling i betydelige forbedringer.

Det tredje proces eksempel er baseret på produktion af (2-Bromophenyl)(phenyl)sulfane i lille skala. Dette vigtige API mellemprodukt har stor interesse fra den farmaceutiske industri, grundet mange APIs indeholder sådanne C-S bindinger i deres kemiske struktur. Produktionen af stoffer med sådanne forbindelser er baseret på karbon-svovl krydskoblingsreaktioner, der involverer meget værdifulde kemiske katalysatorer, kemiske ligander, baser og problematiske solventer. Implementeringen af PI strategien med en signifikant forbedret reaktionsvej, resulterede i flere økonomiske, miljø- og produktionsmæssige fordele.

Resultaterne opnået i disse casestudies indikerer succesfuld implementering af den foreslåede PI strategi. Ligeledes er PAT kravene og implementering af LPS opnået. Betydelig accelerering af svære og relativt langsomme kemiske reaktioner er opnået, hvilket leder til konklusionen at der gennem dette arbejde er opnået en succesfuld overgang fra batch til kontinuert produktion.

List of general abbreviations

Abbreviation	Description
5S	Seiri, Seiton, Seiso, Seiketsu and Shitsuke (sifting, sorting, sweeping, standardization and sustainability)
API	Acrive Pharmaceutical Ingredient
BLC	Baseline correction
cGMPs	Current Good Manufacturing Practices
CI	Continuous Improvement
CLR	Categories of Legitimate Reservation
CLSR	Classical Least Square Regression
CMA	Critical material attribute
CPP	Critical process parameter
CQA	Critical quality attribute
CSTR	Continous stirred tank reractor
DAD	Diode array detector
DF	Dilution factor
DFSS	Design for Six Sigma method
DMAIC	Define-Measure-Analyze-Improve-Control
DPMO	Defects per million opportunities
EFCE	European Federation of Chemical Engineering
EMCS	Extendend multiplicative scatter correction
EMMS	Energy minimization multiscale models
f	factors (latent variable)
FFP	Fit for purpose
FT-NIR	Fourier transform near infrared spectroscopy
GSK	GlaxoSmithKline
HP	Hewlett-Packard
HPLC	High performance liquid chromatography

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICI	Imperial Chemcial Industries
ICOV	Identify-Characterize-Optimize-Verify
ILS	Inverse least squares
ISO	Organization for Standardization
JIT	Just in time
LC	Liquid chromatography
LC-MS	Liquid chromatography –mass spectrometry
LERC	Lean Enterprise Research Centre
L-L	Liquid-liquid
LPS	Lean production system
LSR	Least squares regression
LSS	Lean Six Sigma
LV	Latent variable
MAOS	Microwave assisted organic synthesis
MC	Mean centereing
MIR	Middle infrared
MS	Mass spectrometry
MSC	Multiplicative scatter correction
NIR	Near fnfrared
NIST MEP	US National Institute of Stadrard and Technology Manufacturing Extension Partenership's LEAN Network
NMR	Nuclear magnetic resonance spectroscopy
non-CPP	non-Critical process parameters
NVA	Non-Value added activities
p	Points
PAC	Process analytical chemistry
PAT	Process analytical technology
PCR	Principal component regression
PDCA	Plan-Do-Check-Act
PDSA	Plan-Do-Study-Act

PI	Process intensification
PLS	Partial least squares
PO	Process optimization
PSE	Process system engineering
QbD	Quality by Design
R&D	Research & development
R^2	Correlation coefficients
RMSEC	Root mean squared error of calibration
RMSECV	Root mean squared error of cross validation
RMSEP	Root mean square error of prediction
SEC	Size exclusion chromatography
SG1	Savitzky-Golay first derivative
SG2	Savitzky-Golay second derivative
SMED	Single minute exchange of dies
SNV	Standard normal variate
SPC	Statistical process control
STY	Space time yield
TAS	Total chemical analysis system
ToC	Theory of constraints
TPM	Total productive maintenance
TPP	Target product profile
TPQP	Target product quality profile
TPS	Toyota Production System
UPP	Unclassified process parameter
US FDA	Food and Drug Administration
UV	Ultraviolet
VIS	Visible
VPE	Virtual process engineering

List of chemical compound formulas and chemical abbreviations

Abbreviation	Description
$(([C_6H_5)_3P]_3Rh(CO)H)$	Tris(triphenylphosphine)rhodium(I) carbonyl hydride
$(SIPr)Pd(Py)Cl_2$	Catalyst prepared by using 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride, palladium(II) chloride, potassium carbonate and pyridine
[(IPr)Ni(allyl)Cl	1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride
$[2,6\text{-}(Ph_2PO)_2C_6H_3]NiCl$	Complex obtained my from resorcinol sodium-hydride, chlorodiphenylphosphine and nickelchloride
$[Cu(phen)(PPh_3)_2]NO_3$	(1,10-phenanthroline)bis(triphenylphosphine)copper(I) nitrate
"N714-Allylcarbinol"	9-Allyl-2-Chlorothioxanthen-9-Ol
"N746-Butadienes"	9H-Thioxanthene,2-chloro-9-(2-propenylidene)-(9CI)
ACA	Acetic acid anhydride
Al_2O_3	Aluminium oxide
$BaTiO_3$	Barium-titanate
BEN	Benzene
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BiPhePhos	6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]bis(dibenzo[*d,f*][1,3,2]dioxaphosphepin)
C=C	Carbon-Carbon double bond
C-C	Carbon-Carbon
CeO_2	Cerium(IV) oxide
Clopenthixol	*cis/trans* 4-[3-(2-Chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol
C-N	Carbon-Nitrogen
C-S	Carbon-Sulfur
Cs_2CO_3	Cesium carbonate
CTX	2-Chlorothioxanthene-9-one
$Cu(OAc)_2$	Copper(II) acetate
$Cu(OTf)_2$	Copper(II) trifluoromethanesulfonate
Cu_2O	Copper(I) oxide
Cu_2S	Copper(I) sulfide

CuBr	Copper(I) bromide
CuCl	Copper(I) chloride
CuI	Copper(I) iodide
CuI	Copper(I) iodide
CuO	Copper(II) oxide
$CuSO_4$	Copper(II) sulfate
DCM	Dichloromethane
DMAP	p-(Dimethylamino)pyridine
DME	Dimethyl ether
DMSO	Dimethyl sulfoxide
DPPF	1,1′-Bis(diphenylphosphino)ferrocene
Dy_2O_3	Dysprosium Oxide
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Eu_2O_3	Europim(III) oxide
Fe_2O_3	Iron(III) oxide
Ga_2O_3	Galium(III) oxide
H_3O^+	Hydronium ions
H-BEA	Type of zeolite
H-BRA	Type of zeolite
HEP	1-(2-Hydroxyethyl)piperazine
HPMA	Hexamethylphophoramide
In_2O_3	Indium(III) oxide
K_2CO_3	Potassium carbonate
$KN(SiMe_3)_2$	Potassium bis(trimethylsilyl)amide
KOH	Potassium hydroxide
KOtBu	Potassium *tert* butoxide
La_2O_3	Lanthanum oxide
$LiN(SiMe_3)_2$	Lithium bis(trimethylsilyl)amide
$LiNbO_4$	Lithium-niobiate
Me_2EtN	Dimethylethylamine

Me_3N	Trimethylamine
NaH	Sodium hydride
n-Bu_4NOH	Tetrabutylammonium hydroxide
n-BuLi	*normal* Butyllithium
NH_4HCO_2	Ammonium formate
NH_4OH	Ammonium hydroxide
NiO-ZrO_2	Nickle(II) oxide – Zirconium dioxide
PAL	Phenylalanine ammonia lyase
$PbTiZrO_3$	Lead-zirconate titanat
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
PEGs	Polyethylene glycol
poly-THF	Polymerized tetrahydrofuran
Pr_6O_{11}	Praseodymium oxide
sec-BuLi	*secondary* Buthyllithium
Sm_2O_3	Samarium Oxide
$SOCl_2$	Thionyl chloride
TBAB	Tetrabutylammonium bromide
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TiO_2	Titanium dioxide
TMEDA	Tetramethylethylenediamine
TOL	Toluene
TsOH	Toluensulfonic acid
WO_3	Tungsted trioxide
Yb_2O_3	Ytterbium oxide
Zuclopenthixol	*cis* 4-[3-(2-Chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol

List of nomenclature

Nomenclature	Description	Unit
σ	Dielectric conductivity	$\frac{1}{s}$
ε'	Dielectric constant	-
ε''	Dielectric loss	-
ν_A	Stochiometric coefficient in the reaction rate	-
τ_r	Average residence time in a tubular reactor	s
Bo	Bond number	-
c_p	Specific heat capacity	$\frac{J}{kg\,K}$
C_x	Molar concentrations of component x	M
C_{xo}	Initial molar concentration of componenet x	M
d	Hydraulic diameter	m
D	Diffusion coefficient	$\frac{m^2}{s}$
Da	Damköhler number	-
E_A	Energy of activation	$\frac{kJ}{mol}$
f	Frequency	Hz
Fx and F(r)	Volumetric flow rates at different points in tubular reactors	$\frac{m^3}{s}$
g	Gravitational acceleration	$\frac{m}{s^2}$
G_s	Transfer function	
k	Rate constant	s^{-1}
K	Process gain	-
k^*	Reaction rate constant for the pseudo-first order kinetics	$\frac{1}{s}$
k_o	Arrhenius pre-exponential factor	
K_T	Heat transfer coefficient	$\frac{J}{m^2 K\,s}$
L	Traveled Length	m
L_D	Length over which diffusion must occur	m

Mw	Molecular weight	$\frac{g}{mol}$
Nu	Nusselt number	-
Pe	Peclet number	-
Q	Heating energy rate per area	$\frac{J}{m^2 s}$
r	Radius of a molecule	m
R	Universal Gas constant	$\frac{kJ}{mol\ K}$
Re	Reynolds number	-
R_r	Radius of a reactor	m
r_x	Reaction rates of chemical reaction x	$\frac{mol}{dm^3 s}$
S	Sross sectional area	m^2
T	Absolute temperature	K
t	Residence time	s
tanδ	Loss tangent (dissipation factor)	-
u	Velocity	$\frac{m}{s}$
w	Average speed of the fluid	$\frac{m}{s}$
α	Heat transfer coefficient	$\frac{W}{m^2 K}$
γ	Surface tension at interface	$\frac{N}{m}$
ε	Permetivity	-
η	Dynamic viscosity	$\frac{N\,s}{m^2}$
κ, λ	Thermal conductivity	$\frac{W}{m\ K}$
ρ	Density	$\frac{kg}{m^3}$
τ	Average relaxation time	s

Contents

1. Introduction

1. Introduction

1.1 Background and motivation

Organic synthesis is essential for the production of an important class of pharmaceuticals. Implementation of organic chemistry on an industrial scale is a great challenge and it is mainly based on batch and semi-batch processes. Besides the flexibility and versatility of these processes, one is usually also facing a considerable number of disadvantages. For instance, long reaction sequences, occurrence of non-uniform conditions inside the vessels, limited potential to apply real time process monitoring, and difficulties in automating the production, are just some of the obstacles connected with operating a production process in batch vessels. On the other hand, the requirements to store intermediates, as well as the complicated cleaning procedures, to name a few examples, are non-value added activities (NVAs) whose number should be minimized in order to achieve the most profitable production of active pharmaceutical ingredients (APIs).

The most suitable way to avoid problems associated with batch processeing is to establish continuous manufacturing of pharmaceuticals. These processes are potentially considerably more eco-friendly and economical, including a better usage of raw materials, smaller waste production, less energy consumption, higher throughput, improved yields, better temperature profiles inside chemical reactors, and so on. Furthermore, due to the high degree of automation and process controllability that can be achieved, the Process Analytical Technology (PAT) Initiative may be implemented in a very efficient way in continuous reactors. In addition, plenty of the NVAs could be excluded and therefore a Lean Production System (LPS) approach could be applied successfully.

One of the problems when switching an organic synthesis based process from batch to continuous operation is that not all of the chemical reactions are suited to be operated in continuous modes. Slow reactions cause operational problems and therefore have to be accelerated. One approach to obtain such acceleration is to implement suitable chemical catalysts or biocatalysts, as well as to find a new synthetic route to the desired product. This last approach changes the chemistry of the reaction, but – if successful – can lead to the final product in a more efficient and economic way. The second approach for accelerating such reactions consists of applying physical effects, such as microwave irradiation, ultrasounds, high-pressurized meso-flow chemistry and microreactors. All these options could be used independently from each other, or in suitable combinations. They are the most commonly used tools for process intensification (PI) in modern organic synthesis, and consequently they show a great potential for small-scale manufacturing in the pharmaceutical industry and for production of fine chemicals.

The main aim of this thesis is to develop process intensification (PI) strategy which would explain the implementation of the different PI tools in the manufacturing of APIs and API intermediates. The main focus is on the Zuclopenthixol production – a product of H. Lundbeck A/S, as well as on (2-Bromophenyl)(phenyl)sulfane. Acceleration of chemical reactions will be described with three case study examples together with the development of continuous manufacturing modes for two particular examples.

1.2 Structure of the thesis

The PhD thesis is divided in 10 chapters including three case studies. It is important to note that this work represents a continuation of the project started by the previous PhD student - Albert Emili Cervera Padrell. The biggest overlap between these two projects is in the chapter 5.

Chapter 1 gives a general introduction to the thesis together with a motivation for this work and a short background about continuous pharmaceutical manufacturing.

Chapter 2 explains several important concepts in the pharmaceutical industry. Hence, pharmaceutical quality is defined as the first point followed by the introduction of concepts such as Quality-by-Design (QbD), Knowledge Space, current Good Manufacturing Practice (cGMP) and the PAT guidance. In addition, this chapter covers a major driver in the pharmaceutical industry – continuous improvement (CI) together with its constitutive elements: Lean Production System (LPS), Six Sigma, Theory of Constraints (ToC), Plan-Do-Study-Act (PDSA) cycle, and so on.

Chapter 3 includes a detailed explanation of the PI strategy applied in this PhD thesis. Applications of microwave assisted organic synthesis (MAOS), mesoscale flow chemistry, ultrasounds and Microprocess technology are described in detail from a theoretical point of view. Practical examples are additionally included, and the PI strategy is developed.

Chapter 4 describes the case studies used in the thesis. Hence, description of the chemical reactions is provided together with a brief explanation of the respective implementations of the PI and LPS approaches in developing continuous manufacturing processes.

Chapter 5 is focused on dehydration of “N714-Allylcarbinol” in the mixture of geometrical isomers – cis/trans “N746-Butadienes”. The main goal here is to implement PI strategy described in chapter 3, and additionally to implement requirements defined in the PAT guidance. Mesoscale flow chemistry is therefore applied together with in-line process monitoring. Analysis of side reactions (polymerization) is additionally performed.

Chapter 6 describes experimental work which main purpose is to perform stereo-selective synthesis of cis-“N746-Butadiene” starting from “N714-Allylcarbinol”. To this purpose, screening of different Lewis acids and bases is done.

Chapter 7 describes the hydroamination reaction between a mixture of “N746-Butadienes” and 1-(2-hydroxyethyl)piperazine (HEP). This type of chemical reactions is labeled as one of the ten challenges in modern homogeneous catalysis. Application of the PI strategy is performed together with screening of some chemical catalysts. The main focus is on the application of MAOS.

Chapter 8 is focused on the small-scale production of compounds containing Carbon-Sulfur bonds. More precisely, the application of the PI strategy in the manufacturing of (2-Bromophenyl)(phenyl)sulfane is described. The main focus is on changing the synthetic route from C-S cross coupling reactions towards the application of chlorinating agents and Grignard reagents. In addition, an economic evaluation of a few manufacturing routes is done.

Chapter 9 represents conclusions of the work and gives future perspectives. Finally, chapter 10 lists the literature material that is consulted and formed the basis for writing this thesis.

2. Achievements of high pharmaceutical quality throughout the implementation of Quality by Design (QbD) approach, Process Analytical Technology (PAT) Initiative and Continuous Improvement (CI) Philosophy/Methodology

Abstract

High pharmaceutical quality is strictly demanded in the modern pharmaceutical industry. Several changes have been implemented over the decades in order to achieve such a desired goal. Plenty of them have followed continuous improvement philosophy which has evolved from the Plan-Do-Study-Act cycle towards Lean Production System and Six Sigma. As results, Quality by Design, then current Good Manufacturing practice together with the PAT Initiative have appeared in the last 30 years. Plenty of benefits have been achieved which are mostly correlated to the pharmaceutical quality on one hand, as well as to environmental friendly and economical processes on the other one. In addition, very sophisticated management systems have been developed which are occasionally extended outside of the pharmaceutical industry scopes. A perfect example is the LEAN Enterprise which connects suppliers, industry and customers in a perfect flow. The main focus in this chapter is to become familiar with the mentioned concepts, as well as with additional tools and techniques used for achieving continuous improvement in the pharmaceutical industry.

2. Achievements of high pharmaceutical quality throughout the implementation of Quality-by-Design (QbD) Approach, Process Analytical Technology (PAT) Initiative and Continuous Improvement (CI) Philosophy/Methodology

2.1 Introduction

The main goal in the modern process industry is to develop and operate with economical processes that could constantly deliver high quality products. Several methodologies have been used throughout the years in order to eliminate or reduce the impact of any obstacles that could obstruct process industry in achieving that main goal. The pharmaceutical industry has followed this trend, and thereby the level of understanding of processes and products has been evolving with the main purpose to obtain a high level of quality and consequently a high level of customer's satisfaction.

Introduction of concepts such as Quality by Design (QbD), then Process Analytical Technology (PAT) and Knowledge space was considered as a milestone in the modern pharmaceutical industry. Furthermore, Continuous improvement (CI) was accepted and followed as a general philosophy/methodology in order to achieve high quality of processes and products. The mentioned concepts are strictly dependent on each other and also follow the rules of CI, such as depicted in Figure 2.1.

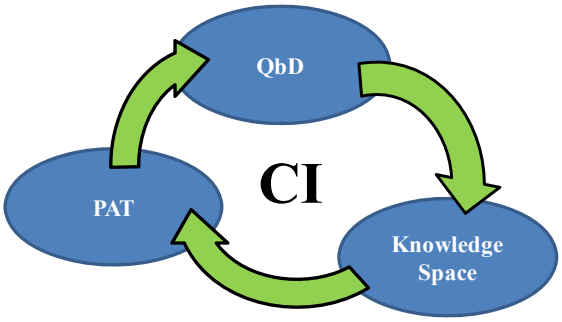


Figure 2.1 Relationships between the concepts: Quality by Design (QbD), Process Analytical Technology (PAT), knowledge space and continuous improvement (CI)

The main objective of this chapter is to become familiar with pharmaceutical quality and how it could be obtained. Hence, the concept of quality is defined as the first point. Furthermore, CI philosophy/methodology is described with the main focus on Lean Production System (LPS) and Six Sigma concepts. In addition, QbD, then PAT and Knowledge Space are explained in more details.

2.2 Concept of quality in the pharmaceutical industry

The pharmaceutical industry is well known as being innovative in developing new drugs and therapies. As a result of such development efforts, the pharmaceutical industry provides the public with high quality medicines. However, a general and unique definition of the pharmaceutical quality is still missing. More particularly, the definition has been evolving due to the constant increase in demands of customers and regulators, as well as a consequence of customer's growing understanding about the actual meaning of the concept of quality.

There are different opinions on how to interpret this concept. One interesting approach is provided by Woodcock[1] who states that the pharmaceutical quality is a "product that is free of contamination and reproducibly delivers the therapeutic benefits promised in the label to the consumer". A customer's safety is put as the main focus in this way, as well as product performance for the intended use. However, the Woodcock definition has plenty of space for further improvements due to its very narrow focus.

A slightly extended approach is provided by the Management Science for Health[2]. This organization defines five different categories of criteria necessary for a high quality of pharmaceutical products: identity, strength or potency, purity, bioavailability and uniformity of dosage forms. Hence, the scope of the Woodcock definition is covered throughout the first four categories, whereas uniformity of dosage forms includes several additional features. They are: consistency, colour, shape, and size of tablets, capsules, creams and liquids. Nevertheless, further extensions of this definition are needed mostly referring to economic analysis, as well as to the behaviour of raw materials, intermediates and final products during manufacturing processes.

A very applicable and extensive approach is done by Kessler[3] who tried to give a general definition of a product quality by defining five categories of product functionality. Hence, the first category is defined as the fundamental functionality and it involves physical and chemical properties of a product, such as contents of ingredients and particle size distributions. The second category includes product behaviour during production processes. It is named technical functionality and mostly refers to flow and mixing properties, then purification and downstream operations. Fitness for the intended use is the third important category and it is known as technological functionality. The main purpose here is to emphasize strength, hardness, efficacy and durability of a product. Furthermore, appearance and design of a product could play an important role and thereby these features are placed under the sensory functionality. Lastly, economic aspects are considered which display product features versus price. This cost-benefit ratio is defined as the value-oriented functionality. Therefore, a very broad definition is achieved in this way covering most of the aspects important for obtaining high quality of a final product. However, this definition is very general and therefore an increased focus on the patient's safety[4] is desired in order to achieve more detailed definition of the pharmaceutical quality. Furthermore, extensions to the overall life cycle of the final product should be considered.

Furthermore, the regulatory bodies, such as the International Organization for Standardization (ISO)[5] and the US Food and Drug Administration (US FDA)[6], have tried to provide the public with

a universal single definition of the product quality. According to the ISO 9000 standard, the quality is defined as "the totality of features and characteristics of a product or services that bears on its ability to satisfy stated or implied needs"[7]. Furthermore, the US FDA came with a broader interpretation claiming that the pharmaceutical quality is "a function of drug substance, excipients, manufacturing and packaging whose main goal is to achieve higher understanding about influences of formulation and manufacturing process variables on product quality"[8]. However, both definitions exclude economic aspects, as well as additional support services which are important for a broad definition of the concept of pharmaceutical quality[9].

Despite the fact that definitions of Kessler and the US FDA are very comprehensive, a slight extension of the mentioned interpretations would lead to the most general definition of the pharmaceutical quality. Hence, the idea on how this definition could be interpreted is the following:

The concept of pharmaceutical quality could be defined throughout five categories of criteria. As the first point, the product should be fit for the intended use meaning that patients are not put at any risk. Hence, the product should fulfil the specifications defined by its designers and marketing authorities, such as: identity, strength, purity, potency and bioavailability. Secondly, undesired defects during the manufacturing and packaging processes caused by physical-chemical properties of raw materials, intermediates and the product itself, should be avoided. Uniformity of dosage forms is achieved in this way leading to a high level of customer's satisfaction whose judgemental evaluations are very important (especially with children). Furthermore, a significant role is given to the value obtained for a certain price paid, through criteria involving the ratio between usefulness of a product and its cost. Lastly, support services after purchasing the product could be very important and thereby have to be considered as a part of the product quality.

2.3 Continuous improvement (CI)

Scientific methods and their integration with improvement methodologies was a major issue in the past. The first steps were taken almost four centuries ago when G. Galilei (1564-1642) integrated mathematics with designed experiments[10], as well as when Francis Bacon (1561-1626) completed the relationship between deductive and inductive logics[11]. These approaches are defined as groundwork for modern scientific methods whose integration with improvement methodologies started in the middle of the 19th century. For this purpose, philosophic approaches were used in the beginning, such as pragmatism[12] and its combination with empiricism[13].

Considering modern process industry, scientific methods developed by Galilei and Bacon are still in use together with modern philosophic methodologies for achieving continuous improvement. The central idea here is that a desired level of perfection requires many continuous changes, representing CI as a never ending process cycle. Establishing this kind of a culture in the process industry is actually very difficult and it usually involves investments of efforts, time and money. Furthermore, plenty of doubts might be present if changes of well-running processes should be applied.

There are a couple of philosophies/methodologies for implementing and achieving CI in the modern process industry. One of the first attempts was back in the 1950s with the Deming wheel, of which a modified version was incorporated in the KAIZEN philosophy later on. KAIZEN is well known because it influenced on the economical re-birth of Japan in the middle of the last century. Later in the 20th century, LEAN, Six Sigma and Theory of Constraints (ToC) appeared and showed excellent results. Furthermore, several combinations of the mentioned methodologies showed impressive results in the beginning of the 21st century.

The main purpose of this section is to become familiar with the PDSA cycle, KAIZEN and LEAN philosophies. Furthermore, example applications of the mentioned philosophic approaches will be mentioned with the main focus on the pharmaceutical industry. Lastly, Six Sigma, ToC and combinations of all the mentioned methodologies will be described.

2.3.1 PDSA and PDCA cycle

2.3.1.1 PDSA cycle

The Deming wheel is the first philosophic approach which was implemented as a methodology for CI in the modern process industry. The base was founded by Walter A. Shewhart in the 1930s and therefore the initial name of this approach was the Shewhart cycle[14]. However, the approach was further sophisticated by W. Edwards Deming in the 1950s and the new name was registered as the Deming wheel[15]. It was actively used till the end of the 20th century when further improvements were made and the newest version was developed as Plan-Do-Study-Act or PDSA cycle.

The main purpose of this philosophic approach is to develop, test and implement changes which would lead to the improvement by initiating immediate actions based on careful study[16]. The simplicity of this philosophic approach makes it very versatile and applicable to a wide range of projects, even outside the scope of the process industry[17].

The general concept of the PDSA cycle involves a model which is based on a scientific method that has to be improved, then three key questions and a process for testing the introduced changes. Conceptual design is depicted in Figure 2.2.

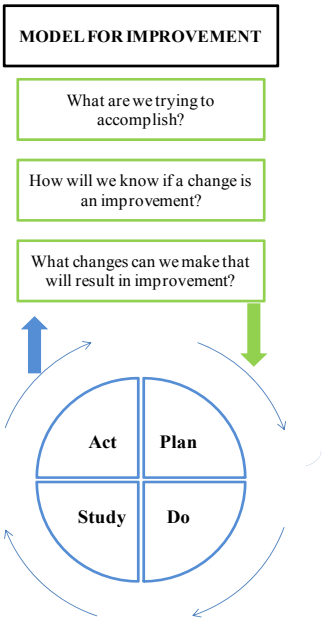


Figure 2.2 Plan-Do-Study-Act (PDSA) cycle with the key questions[16]

Successful implementation of the PDSA cycle starts with a clear and focused definition of the goals which should be achieved. In this way, an answer to the first key question is given, as well as the first step of the PDSA implementation procedure is initiated – "Plan". Furthermore, measuring outcomes of the introduced small changes could lead to an answer of the second key question whose main purpose is to investigate which changes are useful. Statistical Process Control (SPC) charts are shown to be a great tool for this. Moreover, a good literature review and previous improvement programs could lead to an answer about which changes could be made in order to improve the model[16]. Hence, finding answers on all the key questions is considered as a part of the first step in the PDSA cycle. Therefore, the "Plan" step is mostly based on documenting current procedures, collecting data and indentifying problems. Furthermore, implementation of the defined plan is needed and it is performed throughout the step "Do". It is also necessary to analyze and study data collected in the previous steps. Hence, the step "Study" is implemented whose additional goal is to check if the goals established in the first step have been achieved. The last phase is called "Act" and it involves actions based on the results of the first three steps as well as making new plans for further improvement of the process[9].

Applications of the PDSA cycles are very common in improvements of healthcare systems[18], for instance. Furthermore, risk management systems in the chemical industries could also benefit substantially by implementing this scientific method[19]. Nevertheless, the PDSA cycle is a constructive element of more sophisticated methodologies for CI, and therefore the area of PDSA cycle applications is very broad.

2.3.1.2 PDCA cycle

Despite the PDSA cycle, evolution of the Deming wheel in Japan led to another approach, Plan-Do-Check-Act or PDCA cycle. Basically, the main purpose of both methods are similar, however the PDCA cycle contains small changes in some of the steps compared to the PDSA cycle. Hence, prevention of errors by establishing some standards, then formulating methods in order to achieve pre-defined goals are just some of the examples which were introduced in the step "Plan"[20]. As could be noticed here, quality started to be designed by paying increased attention to planning activities.

Applications of the PDCA cycle are mostly related to the Japanese companies and their affiliations worldwide. However, further improvements of the CI methodology include combinations of the PDCA cycle with different tools and techniques and consequently limited applications of the basic PDCA cycle as such. Nevertheless, some examples are found in the pharmaceutical sector, such as continuous improvement of information sharing methodologies[21], as well as in the quality improvement planning processes[22].

2.3.2 KAIZEN and LEAN

2.3.2.1 KAIZEN

Further improvement of the CI involves combination of the PDCA cycle with additional tools. Introduction of an additional toolkit (Table 2.1) lead to the development of a new approach. Hence, the scope of the PDCA cycle was significantly extended and thereby a new concept have been introduced - KAIZEN.

Table 2.1 Additional Tools in the early KAIZEN development[23]

Tool	Brief Description
Check Sheets	A table form with the main purpose to record data by making a check mark on a page
Pareto Diagrams	Useful tool for identification and focusing on the most critical areas with the philosophy: "relatively few factors generally account for a large percentage of the total problems"
Cause-and-effect Diagrams	A tool for structural search of the possible causes of the problem (Fishbone Diagram, Godzilla-bone Graph, Ishikawa Diagram)
Histograms	A graph which displays distribution of data constructed from the data obtained in a frequency table (Frequency Distribution Diagram)
Control Charts	Useful tool for monitoring processes in order to notice if the process outputs are random, then to help in detecting controllable causes of variations, as well as to indicate a moment of problem occurrence and cause of the problems
Scatter Diagrams	A graph that shows the degree and direction of correlation between two variables
Graphs	Different types of graph for showing the obtained data

The word Kaizen is of Japanese origin and could be translated as gradual and orderly continuous improvement or simply "change for the better"[24]. It is a very comprehensive approach which is defined as an umbrella concept applicable to a large number of Japanese business practices. In addition, it is focused on the way how people should approach to work and also explains how managers and workers could work together in order to improve the overall productivity[25]. Furthermore, it is a constitutive element of LEAN[26] and it is often said that "KAIZEN paves the way for the LEAN journey"[27].

The KAIZEN concept involves many tools and their classification is performed differently. Nevertheless, the most original structure is presented here according to the first person who introduced KAIZEN. Hence, the Masaaki Imai definition is depicted in Figure 2.3 and it involves tools such as: customer orientation, total quality control, robotics, quality control circles, suggestion systems, automation, discipline in workplaces, total productive maintenance, kanban, quality

improvement, zero defects, small-group activities, cooperative labor-management relations, productivity improvement and new product development. The most commonly used tools are described later in Table 2.3 whereas detailed explanation of the additional toolkit is done by Imai[25].

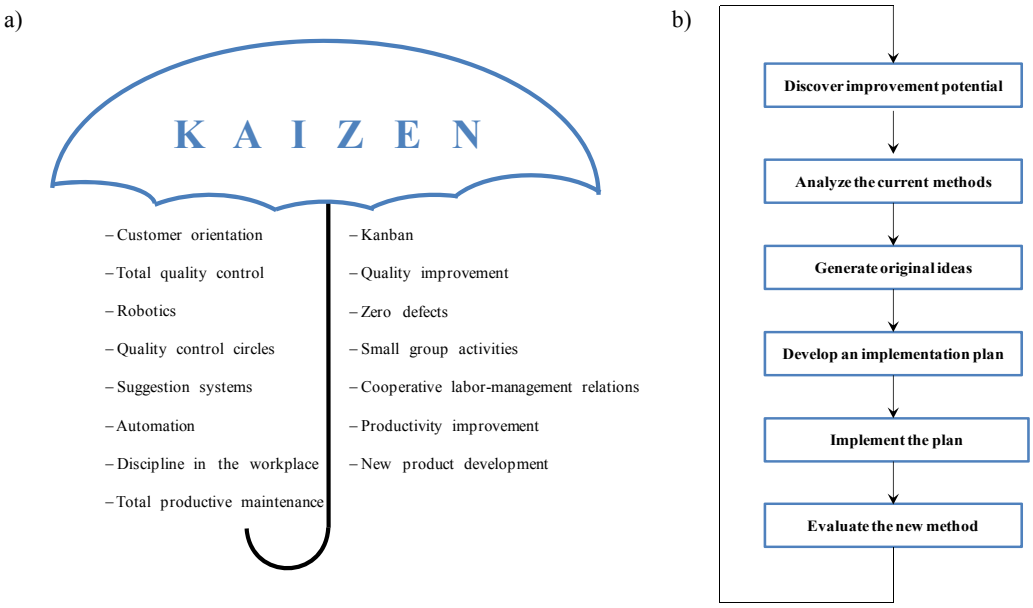


Figure 2.3 KAIZEN concept for the continuous improvement. (a) Definition of the KAIZEN concept involving its constitutive elements[25]; (b) Implementation of the KAIZEN concept in Toyota throughout a six-step workflow[28]

Implementation procedure of the KAIZEN concept is depicted in Figure 2.3 b). It requires a step-by-step procedure in a closed loop pattern. Therefore, it is important to discover potential improvements in the early beginning of the implementation procedure. Furthermore, analyses of the current methods are needed and later generation of the original ideas. The fourth step is to develop a suitable plan which is followed by its implementation. After these actions, evaluation of the new method should be done and then returns to the first step again should be performed in order to repeat the overal procedure[28]. Note that this cyclic pattern is in accordance with the CI defined with the PDCA cycle.

2.3.2.2 Lean

Lean philosophy, Lean thinking, or just simply LEAN, is a generic process management philosophy which was originally developed on the basis of the Toyota Production System (TPS)[29]. It could be defined as "a systematic approach to identifying and eliminating waste (non-value added activities) through continuous improvement, following the product at the pull of the customer in pursuit of perfection"[30, 31]. The definition was provided by the US National Institute of Standards and Technology Manufacturing Extension Partnership's LEAN Network (NIST MEP)[31] who additionally adapted lean philosophy for fulfilling environmental issues called cLEAN[30, 31].

According to the LEAN Enterprise Research Centre (LERC)[32], 35% of the production related operations can be defined as necessary non-value added activities (NVA) and consequently cannot be excluded from the process scheme. Despite this, around 60% of the production activities give no value at all, and thereby they are considered as a waste in the Lean philosophy. There are seven types of waste which should be minimized: overproduction, waiting, transportation, inventory, overprocessing, motion and defects[33]. Some authors add an additional category called skills[34]. All types of the NVA are described in Table 2.2.

Table 2.2 Non-value added activities (waste) according to the LEAN Philosophy[34]

Non-value added activity	Brief Description
Overproduction	Production should be based just on the customer needs
Waiting	Waiting for information, material, tools, diagrams, instruction, etc.
Transportation	Material should be shipped directly from vendors to locations
Excess Inventory	Inventory beyond that needed to meet customer demands
Overprocessing	Consequence of the excess of inventory (just a product demanded by customers should be processed because everything else leads to unnecessary usage of valuable labour and material)
Motion	Unnecessary movement because of the poor "workflow" (movement of people, equipment and materials during process activities)
Defects	Production errors lead to wastes of resources, materials, overhead, and so on (everything related to poor quality, scrap, rework...)
Skills	Wasting mental, physical and creative skills and abilities due to poor workflow, project management, organization culture, personal agendas, constant re-training, lack of training, lack of skills, lack of experience...

2.3.2.2.1 Implementation of LEAN

Implementation procedure of the LEAN philosophy involves five steps: specify value, identify value stream, flow, pull and pursue perfection. The implementation procedure is depicted in Figure 2.4 and represents a closed circle. It can be noticed that CI approach is respected as well as a significant influence of the PDCA cycle in the LEAN philosophy.

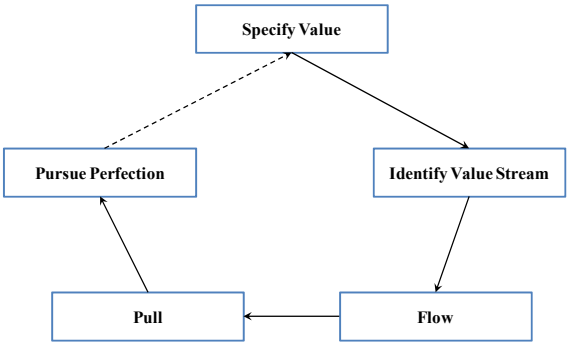


Figure 2.4 Implementation of the LEAN Philosophy in five steps

Specifying value is defined as a critical point in LEAN philosophy, and it is mainly based on the relationship between customers and producers. A very high level of understanding of the customer's needs is mandatory in order to make a good product proposal. For instance, if a customer is a major pharmaceutical manufacturer of drug products, the value proposition might be a robust process and product developments at fast track speed[33].

The second step in the LEAN implementation procedure is to identify value stream which means that set of all specific actions which are necessary to bring a specific product to the market should be defined. This is usually done throughout three management tasks:

- problem-solving task (running from concept to production launch through detailed design and engineering);
- information management task (running from order-taking to delivery via detailed scheduling);
- physical transformation task (proceeding from raw materials to products that are satisfying customer's demands).

It is important to emphasize that this step is labeled as a generator of the highest amount of waste and therefore this step usually receives considerable attention[35].

After identifying value streams, it is necessary to establish a link between these activities and events with the customer's needs. Hence, it is important to make them "flow" continuosly[33]. It is possible to establish this connection by using three actions together. Therefore, after defining the first three steps in the LEAN implementation procedure, it is necessary not to lose focus from the actual objects at the first point. Hence, specific design, specific order and the product itself should be

respected from the beginning till the completion. Furthermore, ignorance of traditional boundaries and removing of all obstacles is necessary. Lastly, rethinking of specific work practices is demanded in order to avoid backflows, scrap, interruptions of all sorts, is also demanded[35].

The fourth step in the LEAN implementation philosophy is to develop ability to design, schedule and make what customer wants and exactly when it is demanded. In this case, sale forecast could be thrown away and customer's satisfaction could reach the highest level. This step is called "pull" and the main objective here is to allow customers to "pull" the product from a producer (instead of "pushing" products which might be unwanted on the market)[35].

The last step in the LEAN implementation procedure is to achieve perfection. However, achieving perfection is not always possible and thereby reducing time, efforts, costs, mistakes, and so on, is a never-ending process. Therefore, the last step is connected to the first step in Figure 2.4 emphasizing demands for the continuous improvement.

2.3.2.2.2 Lean Production System (LPS)

Implementation of the Lean philosophy into the process environment is called LEAN manufacturing or Lean production. It follows the steps of the Lean implementation procedure by using special principles, techniques and tools. The main purpose is to achieve three main goals: to improve quality, reduce costs and reduce lead time[36].

Traditional LEAN manufacturing approach is called Toyota Production System (TPS)[36] and it is graphically presented in Figure 2.5. The house structure has a roof with the goals to be achieved, and then a strong basis where are placed the following: Hejunka (Leveled Production), Visual Management, Stable and Standardized Processes. Connection between roof and basis is established with two pillars called Just-in-Time (JIT) production and Jidoka.

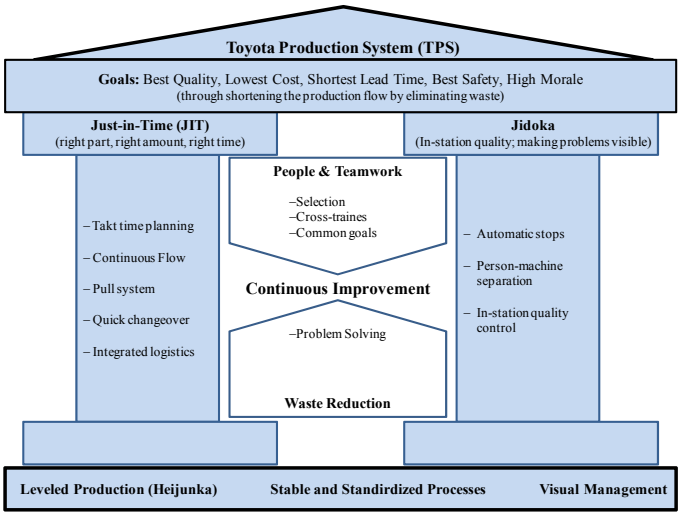


Figure 2.5 Structural definition of the Toyota Production system (TPS)[36]

Main purpose of the JIT is to deliver just what is needed, when it is needed and just needed amounts. Furthermore, the second pillar called Jidoka is broadly defined and includes everything about physical improvement of the manufacturing process/value streams[37]. All tools and techniques used as building blocks of the TPS house are depicted in Table 2.3.

However, traditional TPS has been changing over the time due to easier adaptability of the LEAN philosophy to different companies. Herrmann and coworkers[26] came out with a new and more applicable name for the LEAN Manufacturing. They proposed the term Lean Production System (LPS) and it will be used here in the remaining text. In this way, a more comprehensive and adaptable approach is founded. Nevertheless, coming up with a very general and comprehensive structure of LPS was a major problem. A very good approach was proposed by William M. Feld[38] who introduced five primary elements which are necessary for successful implementation of the LEAN philosophy. They are: "Organization", "Metrics", "Logistics", "Manufacturing Flow" and "Process Control", such as depicted in Figure 2.6.

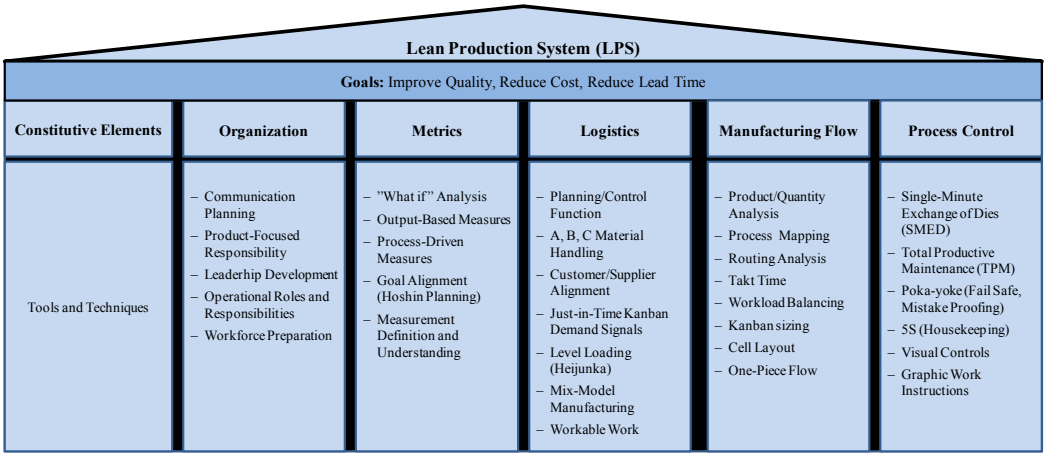


Figure 2.6 Lean Production System (LPS) with its constitutive elements, techniques and tools (building blocks)[38]

The main focus in this thesis is on the last two elements: "Manufacturing Flow" and "Process Control". The "Manufacturing Flow" is focused on addressing physical changes and designing standards whereas the main purpose of the "Process Control" elements is to improve processes throughout monitoring, controlling and pursuing ways of the improvement[38]. Tools and techniques used for the LPS and TPS are described briefly in Table 2.3.

Table 2.3 Tools and Techniques used in the Lean Production System[38]

Tools/Techniques	Brief description
Communication Planning	The main purpose is to give answers to the following questions: why and what we are changing, as well as where we are now and what in it is for me
Product-Focused Responsibility	Development of the "functional organization" by connecting functions on one side to suitable operators on the other
Leadership Development	Selection procedure for future leaders
Operational Roles and Responsibilities	Giving roles and responsibilities to employees
Workforce Preparation	Building skill matrix in order to evaluate skills of employees
"What if" Analysis	Building relationships between items in order to produce several different ratios as indicators for the performance trends (useful for top levels in order to establish overall goals and objectives of the business)
Output-Based Measures	"Localized optimization" involving analysis and evaluation of all particular steps in the process throughout measuring product quality and product delivery
Process-Driven Measures	Achieving infinite continuous improvement through analysis of process cycle time and cumulative performance of each operation in a process
Goal Alignment (Hoshin planning)	Pulling the overall company in the same direction in order to perform corrective actions easier, as well as easier adjustments of the course
Measurement Definition and Understanding	Importance of a high level of understanding about what to do from the operator's side through a good definition of performance targets
Planning/Control Function	The main purpose is to define specific work rules which should be utilized during operations via forward planning (future workload requirements), capacity planning (review and agree upon the upcoming workload, manpower, and overtime requirements), capacity control (providing team with capability to maintain workload visibility and monitor progress to plan) and priority controls-Dispatch List (produce only at the moment when product is demanded and if there is enough capacity and resources)
A, B, C Material Handling	Easier control of material flows and additionally easier managing of inventory in case if new operating rules for material handling are introduced (reclassification of different parts according to their demand behaviour characteristics – weight, time cycle...)
Customer/Supplier Alignment	Identification and establishment of strong direct lines of communication between customers and suppliers
Just-in-Time Kanban Demand Signals	Focusing on managing Kanban by using six rules: Kanban demand signal is the authorization to start to work, no job releases without customer demands, controls of work in processes and manufacturing lead-times and avoiding defects
Level Loading (Heijunka)	A level production schedule over a defined production time in order to align customer demands with the takt time (achieving rate that is conductive for both – customers and suppliers)

Mix-Model Manufacturing	Designing workstations producing a variety of products and volumes over a given time
Workable Work	Term referring to elements contained within the manufacturing process which are necessary for work (materials, tools, work instruction, demands and skilled workers)
Product/Quantity Analysis	Gathering and understanding product demanded data with consequent product groupings (product groups are later sorted according to volumes)
Process Mapping	Identification of operations that are required in order to produce a desired product by using two types of diagrams: block process mapping and Spaghetti diagrams
Routing Analysis	Assessment of workflow patterns and volume/process variations by creating process matrices, work content matrix and volume matrices
Takt Time	Rate of consumption by the marketplace defined as ratio of scheduled production time and designed daily production rate
Workflow Balancing	Design a balanced workflow by comparing man time and takt time (automation, workload balance), then machine time and takt time (corrective actions if the fixed cycle time is greater than the takt time) and lastly setup time and takt time (improving setups in order to create a flexible work environment)
Kanban Sizing	Identification of limiting factors on inventory levels (raw material, work in process, finished goods) and control elements on lead-times
Cell layout	Graphical representation of the operator and material flows in order to describe designed operator's sequences and operations, as well as to get info about material movement
One-Piece Flow	Products are passed one piece at a time from operation to operation in order to achieve a product manufacturing lead-time as long as the sum of all takts on the way, as well as to achieve instantaneous feedback in case of defects
Single-Minute Exchange of Dies (SMED)	The main purpose of this cornerstone technique is to minimize losses, then to increase flexibility of the equipment and to "build today what is needed today" via three steps: segregation of activities; recategorization and reduction or elimination of steps which are done (making the setup process standardized, consistent, repeatable, and easy to learn)
Total Productive Maintenance (TPM)	Achieving high reliability of equipment through: preventive maintenance (preventing breakdowns to happen), corrective maintenance (improving repaired equipment) and maintenance prevention (daily operator "autonomous prevention")
Poka-Yoke (Fail Safe, Mistake Proofing)	Achieving a defect free environment through capturing feedback on defect as close as possible to the route cause in order to avoid defective product and processes (usage of physical, mechanical and electrical tools for "catching errors")
5S (Housekeeping)	Seiri, Seiton, Seiso, Seiketsu and Shitsuke are the 5S necessary to provide a good working place through sifting, sorting, sweeping, standardization and sustainability
Visual Controls	Achieving line-of-site management by using different displays as visual control devices
Graphic Work Instructions	Performing work in the standardized format by following instructions given in graphical form (easily recognizable format)

2.3.2.2.3 Lean Production System in the process industry

Applications of the Lean philosophy and later LPS in the production environment could lead to plenty of benefits. Less process waste, reduced lead-time, less re-work, financial savings, increased process understanding, reduced inventory, and so on[33], are just some of good examples. Companies such as Bosch[26, 39], Autoliv[26, 40], Mercedes-Benz[26, 41], HP[42, 43], and Wal-Mart[43, 44] have implemented LPS successfuly. For instance, implementation of LPS in HP resulted with improved inventory turnovers for almost 7% in a 10-year-period (2000-2009)[43].

Applications of LPS in the pharmaceutical industry usually involve special requirements. For instance, the JIT approach tends to avoid large batch productions and prefers productions of items in "batches" of one. In other words, the producer and system should be flexible, as well as Single Minute Exchange of Dies (Table 2.3) becomes the norm[45]. The pharmaceutical sector was lacking overall improvements in the previous decades as a result of unsuccessful LPS implementation. Reasons for this might be a narrowed focus which was just on the manufacturing process. Furthermore, lack of leadership commitment, then excessive cost reductions, improper project selection and suboptimal execution could be additional reasons for the overall weak improvement that was achieved in the pharmaceutical industry[43].

Nevertheless, there are recent examples of the great results. For instance, Novo Nordisk A/S and their cLEAN® program resulted in a significant decrease of the CO_2 emission by almost 55%, whereas sales got doubled in the same period (2004-2011)[46]. Furthermore, Bristol-Myers Squibb[47] achieved plenty of benefits in the drug discovery processes whereas good results were obtained in the R&D part of the TAP Pharmaceutical Products Inc. (Takeda Pharmaceuticals now)[48, 49]. In addition, Clinical Supply Management in Pfizer[50] achieved benefits by applying Lean philosophy and LPS[51]

Succesful implementation of the LPS initiated the following improvement methodology called Lean enterprise. It is an extension of the LPS and could be defined as "a group of individuals, functions, and legally separated but operationally synchronized companies"[52]. In other words, it is important to achieve holistic management of the value added activities throughout the whole system including companies, employees, managers, suppliers and customers.

Despite its benefits, there is a certain number of potential difficulties in implementing LPS. Hence, changes in production culture are not always very welcome. Then, lacks of availability of time, scepticism on the validity of the Lean philosophy, and so on, are just some of the reasons for not implementing Lean philosophy into the production processes[33]. Consequently, different approaches could be used, such as Business Process Reengineering whose main purpose is to perform radical restructuring and redefinition of business processes[53].

2.3.3 Six Sigma concept

Six Sigma is a concept originally developed by Motorola Inc.[54] as a project-driven management approach with the main purpose to improve organization's products, services and processes by continually reducing defects in the organization[55]. Hence, a general strategy is that integration of processes with statistics, engineering and project management could lead to many advantages, such as improving understanding of customer requirements, business systems, productivity and financial performances[56].

There is not a universal and single definition of this concept, but a good attempt might be the following: "Six Sigma is an organized and systematic method for strategic process improvement and new product and service development that relies on statistical and scientific methods to make dramatic reductions in customer defined defect rates"[57]. Therefore, it is not that difficult to notice that the concept of Six Sigma has two perspectives: statistical and business. More precisely, the concept originates from statisticians who claim that Six Sigma is a method relying on a statistical, probabilistic and quantitative point of view[58]. Hence, it is important to have less than 3.4 Defects per Million Opportunities (DPMO) or a success rate of 99.9997%[59]. Despite this statistical viewpoint, Six Sigma can be considered as a "business strategy used to improve business profitability, effectiveness and efficiency of all operations to meet or exceed customer's needs and expectations"[60].

Implementation of the Six Sigma concept is often called Design for Six Sigma Method (DFSS)[61]. It involves different philosophic methodologies as step-by-step implementation procedures[62]. The PDCA cycle was used in the early beginnings which afterwards evolved in the Define-Measure-Analyze-Improve-Control (DMAIC) cycle, as a more suitable methodology for the Six-Sigma purposes[63]. A detailed review of the Six Sigma tools and techniques was published by Adams and coworkers[64] who collected and classified tools and techniques according to the steps in the DMAIC implementation procedure. Furthermore, Identify-Characterize-Optimize-Verify or ICOV[61] became also very useful, and was in fact the main focus of Yang and El-Haik[61] who also classified the tools according to the steps in that implementation procedure[62].

Nevertheless, Six Sigma is a very wide concept involving several business strategies and principles. A detailed classification of these was done by Kwark and coworkers[55] who emphasized eight different groups: project management, data-based decision making, knowledge discovery, process control mapping, data collection tools and techniques, variability reduction, belt system, change management tools and appropriate implementation methodology.

Applications of the Six Sigma concept caused plenty of benefits across the industry. For instance, Motorola Inc.[54] decreased "in-process defect levels" down to 150 times[55]. This statistical concept is also prominently present in the pharmaceutical industry[65] and has led to many benefits, such as in Johnson&Johnson[66] who achieved $500 million savings by introducing DFSS[55].

2.3.4 Lean Sigma

Lean Sigma or Lean Six Sigma (LSS) is a methodological approach which combines Lean Philosophy with the Six Sigma concept. Incorporation of the tools and techniques under the umbrella of the Six Sigma concept during the conversion of a company into Lean Production System could be defined as the main principle of the Lean Sigma philosophy. It uses the precision of Six Sigma and combines it with speed and agility of the Lean philosophy. As a consequence, customer focused products and services with higher quality levels and lower prices can be obtained[67]. This is a way to achieve operational excellence in any business.

Several pharmaceutical companies have achieved many benefits by adopting LSS. For instance, AstraZeneca[68] and its Medicinal Chemistry Department achieved higher speed, quality and cost delivery[69]. Furthermore, GlaxoSmithKline (GSK)[70] announced savings of almost £300 million in 2004 as a result of successful introduction of the Lean Sigma methodological approach[49]. West Pharmaceutical Services[71] achieved performances and efficiency breakthroughs more quickly by using LSS than just Six Sigma concept[72].

2.3.5 Theory of Constraints (ToC)

Theory of Constraints (ToC) is a philosophic approach developed by Dr. Eliyahu Goldratt. His main motivation was to make a synchronous manufacturing because all parts of the entire organization are supposed to work together and achieve the organization's goals[73].

Tools for the implementation of ToC are classified in five distinct logic trees: Current Reality Tree, "Evaporating Cloud", Future Reality Tree, Prerequisite Tree and Transition Tree[74]. They are depicted in Figure 2.7. Despite tools, there are additional rules of logics called the Categories of Legitimate Reservation whose main purpose is to govern the construction of the trees.

The first step in the ToC implementation procedure is the Current Reality Tree. Its main focus is to find undesirable effects present in the organization and to identify a few root causes. It is noteworthy to mention that a single core problem could cause all undesirable effects and it is therefore defined as a constraint. The second step is the "Evaporating Cloud" and it resolves conflicts which are hidden and usually perpetuate chronic problems. It gives a first part of the answer to the question "what to change to?". Furthermore, the Future Reality Tree is the next step and it has two functions. Firstly, it is supposed to verify the actions which we would like to perform, and secondly to identify potential undesired consequences of the mentioned actions. Plenty of energy, resources and time could be saved in this way. This step could be a very important strategic tool. The fourth step is the Prerequisite Tree and its main purpose is to implement the actions defined in the Future Reality Tree with the main goal to find the best ways of overcoming obstacles and additionally completing major milestones in the ToC implementation procedure. The Transition Tree is the last step which provides users with the step-by-step procedure in implementing the defined set of actions. It gives information about the steps to be taken and the rationalization to each of the steps[74].

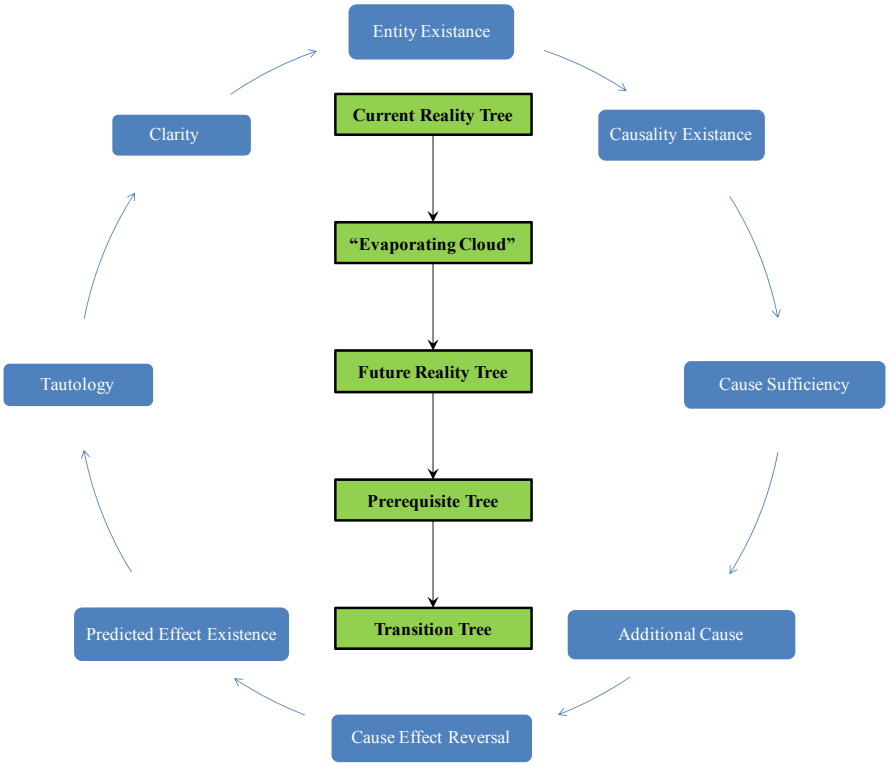


Figure 2.7 Overview of tools for implementation of the Theory of Constraints (ToC)[74]

The Categories of Legitimate Reservation (CLR) are defined as a logical guide throughout the ToC implementation procedure. Each tree should pass all of the following tests: Clarity, Entity Existence, Causality Existence, Cause (In)sufficiency, Additional Cause, Cause-Effect Reversal, Predicted Effect Existence and Tautology[74]. Clarity is defined as the elimination of all potential misunderstandings due to inaccurate or incomplete communication of an idea. The second test is called Entity Existence and its main purpose is to transfer the complete idea into the statement form. Hence, it is important to fulfil three criteria: completeness, good structure and validity. Causality Existence is the third step whose main aim is to challenge the validity of the connections between entities in the statement. Furthermore, Cause (In)sufficiency is focused on stated causes in case that they are not sufficient, by themselves, to produce the stated effects. The fifth test is Additional Cause and its main purpose is to emphasize if similar effects could be caused by several independent causes. The sixth step is based on suitable distinction: why an effect exists versus how we know that it exists. Furthermore, Predicted Effect Existence is based on finding additional unstated effects, even if a proposed cause-effect analysis is valid. Lastly, Tautology or Circular Logic is used if the effect is offered as a rationale for existence of the cause. It is usually not

observable before it has been verbalized by the tree builder and the causality of one of the connections is questioned. Tautology becomes obvious when a reason for the causation is challenged[75].

Theory of Constraints could be an important add-on to the Lean philosophy, Six Sigma or Lean Sigma concepts. For instance, the ToC thinking was used in GSK[70] in order to find and relieve bottlenecks for making progress in the flow of the drug knowledge development processes[49]. Furthermore, Eli Lilly and Co.[76] achieved great results in reducing cycle times as a consequence of the ToC implementation procedure[77].

2.4 Quality by Design (QbD)

Obtaining a high product quality is the main objective of every process industry. However, it is crucial to involve reasonably low costs in order to achieve that goal. Therefore, minimizing all the production costs is a necessity in the modern pharmaceutical industry, as well.

Around 60% of the total quality costs are correlated to the internal and external failures according to Kerzner[7]. Discovering poor product quality before it reaches customers (internal failure costs), as well as avoidance of problems on the customer site (external failure costs), have significant influence on the total quality costs[9]. Nevertheless, complete elimination of failures would lead to the ideal situation of having perfect processes which would manufacture perfect products. As shown in Figure 2.8, one of the approaches is to involve more resources into preventions, together with better evaluations of products and processes in order to determine how well the customer's requirements are met (appraisal costs)[7]. However, achieving this level of perfection is impossible and therefore the most optimum solutions should be defined.

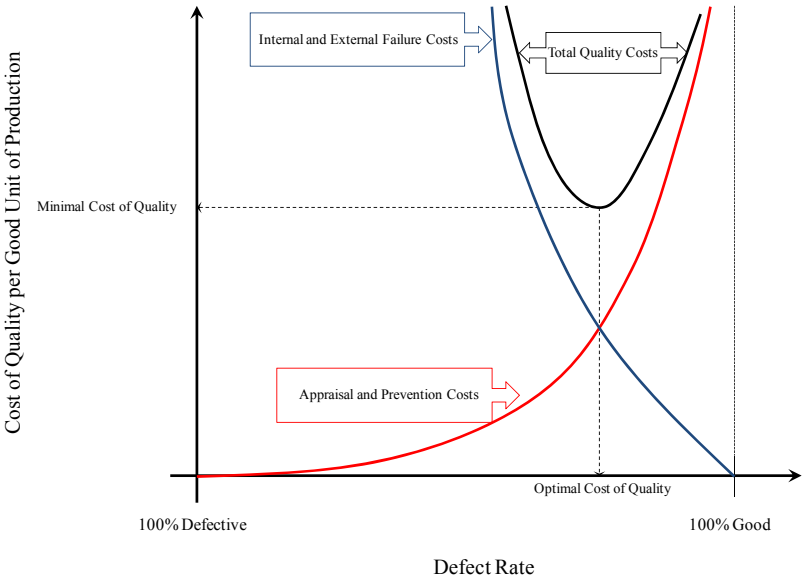


Figure 2.8 Illustrative diagram showing the relationship between the cost of quality per good unit of production and defect rates, with the main purpose to emphasize the influence of internal, external, prevention and appraisal costs on achieving optimal levels of the quality cost of a product[7]

High internal and consequently external failure costs had a big influence on the introduction of a new paradigm in the process industry. In the late 1970's, quality started to be considered as something that should be expected and corrected, not tested after production[9]. This decision resulted in increased prevention costs, but significantly decreased total costs of quality by almost 50%[7].

In order to achieve high benefits in the pharmaceutical industry, the US FDA announced the Quality by Design concept. The concept is defined as "building in quality from the development phase throughout a product life cycle"[78]. However, the general meaning stayed somehow very unclear in the early beginnings and thereby additional interpretations were provided. One of the first extensive explanations came out in the FDA's report on Critical Path Opportunities for Generic Drugs stating that "under the QbD paradigm, quality is built into the final product by understanding and controlling formulation and manufacturing variables: testing is used to confirm the quality of the product"[79]. However, the most comprehensive definition could be interpreted as shown in Figure 2.9. It involves continuous improvement via adjustment to products and processes throughout the product lifecycle[80].

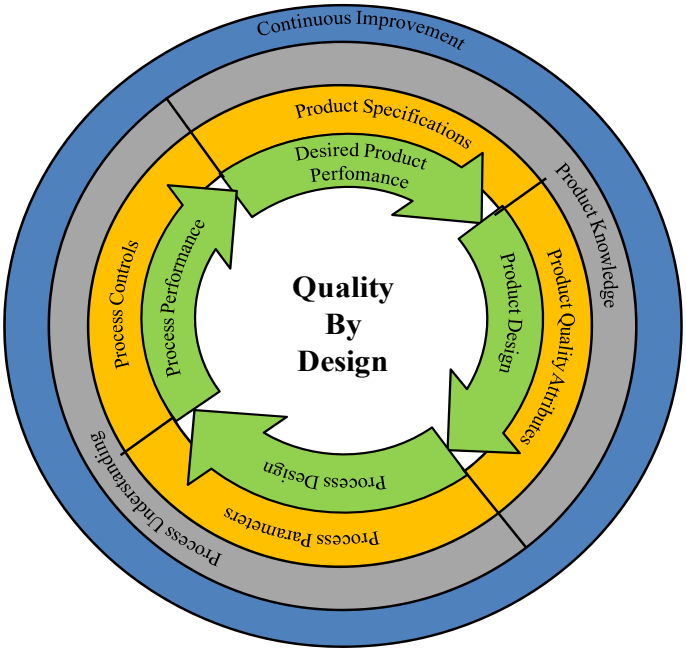


Figure 2.9 Definition of Quality by Design concept (QbD)[80]

The best approach to understand such a complex concept is to focus on its implementation procedure. According to the US FDA, the implementation of the QbD concept means "designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process"[78]. More detailed explanations are provided at the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[81] where the QbD concept was interpreted as a systematic approach to pharmaceutical development which starts with defining objectives and furthermore continues with emphasizing product/process understanding and process control, based on science and quality risk management (ICH Q8 guideline)[82]. It is therefore highlighted that the QbD concept requires a very detailed understanding of the influence of formulation processes and process variables on the quality of a final product. In addition, the ICH Q9 – Quality Risk Management[83] – and ICH Q10 – Pharmaceutical Quality Systems[84] – guidelines are trials to explain how QbD actually acts in order to obtain a high quality of pharmaceutical products.

Furthermore, in 2007 Nasr[85] has announced a procedure for the QbD implementation with six different stages. The procedure is depicted in Figure 2.10 within the pyramid structure.

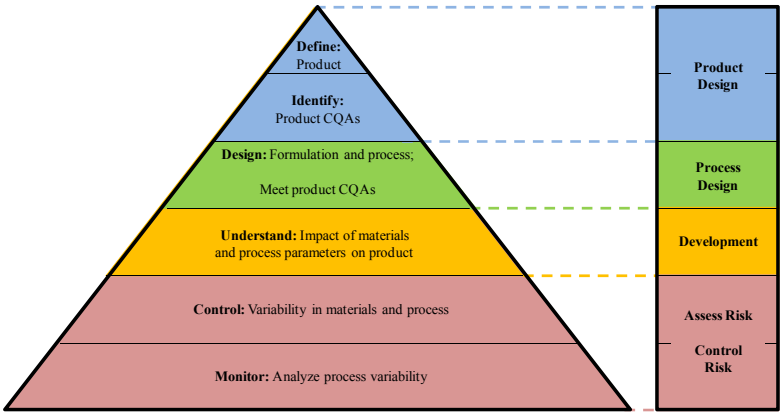


Figure 2.10 Implementation procedure of the Quality-by-Design concept involving six different stages[86]

The initial action is to define a product which would meet the patient requirements. This action is placed at the top of the pyramid and begins with defining the Target Product Profile (TPP)[8] which is usually considered as a tool for setting a strategic foundation for drug development – "planning with the end in mind"[87]. According to the US FDA, the official definition of the TPP term is "a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development"[88]. It could have a major influence on optimization of a medical drug, then on making decisions within the organization, as well as designing of clinical research strategies and constructive communication with regulatory authorities[87]. The second action in the product definition stage is to define the Target Product Quality Profile (TPQP). This term is considered as an extension to the TPP term focusing mainly on the product quality. More precisely, it is a quantitative surrogate for aspects of clinical safety and efficacy that could be used to design and optimize formulation and manufacturing processes[89].

The second stage in the QbD implementation procedure is to identify Critical Quality Attributes (CQAs) of the product. This means identification of physical, chemical and (micro)biological properties or characteristics which have to be controlled in a direct or indirect manner with the main aim to ensure desired product quality[90]. Besides CQAs, Lionberger[8] defined Critical Material Attributes (CMAs) as an additional term focusing on properties of raw materials and their influence on the product quality. Examples are particle size and hardness of raw materials which could have influence on manufacturing process parameters and consequently on the product quality.

After the first two stages, the product design level is completed and the next levels should be implemented – process design and development. It is important to emphasize a strong connection between all of the mentioned levels. For instance, product design and properties of the used materials have a considerable influence on the selection of a process. Furthermore, process design is the initial action in the process development level[87].

Therefore, a process design and formulation stage should mostly focus on meeting CQAs of the final product. Furthermore, a good initial connection between process design and development should be established due to the fact that plenty of factors are involved in a successful process development procedure. A strategic approach involves identification of Critical Process Parameters (CPPs). They are defined as "input operating parameters and process state variables of a process or unit operation" leading to the conclusion that the state of the process depends on CPPs and CMAs of input materials[8]. Therefore, precise identification of CPPs and CMAs is the main goal of the third stage in the process development level, as depicted in Figure 2.10 in the middle of the pyramid. There are three categories of process parameters, namely:

- Unclassified Process Parameters (UPPs) which are indeterminate or unknown and without established sensitivity in the potential operating space;
- non-Critical Process Parameters (non-CPPs) which are without interactions with other parameters and do not cause failure in TPQPs;
- Critical Process Parameters which have interactions with other parameters and cause failure in TPQPs[8].

However, despite the definition of the CPPs, additional factors should be considered. For instance, availability of facilities, equipment and material transfer have a major influence on successful process development, as well[91].

After the appropriate selection of CPPs, control strategies should be applied. Hence, successful control of CMAs, CQAs, as well as different variability in manufacturing processes are the main goals in these stages, Furthermore, continuous monitoring and updating of the process variability is important due to ensuring continuous quality of the final product. To this purpose, Process Analytical Technology, then Design of Experiments and Knowledge space are techniques that are preferably used.

It is important to emphasize that the QbD implementation procedure is very dependent on the predictive modeling. Estimations of physical properties for formulations belong to molecular modelling with the main focus on physical property prediction, such as solubility, polymorphism, reactivity, selectivity, and so on. Furthermore, unit operations form the basis for process modelling, and the model is supposed to predict process results and scale-up performance based on equilibrium and kinetic knowledge. Lastly, system modelling focuses on chemical route selection, process cost analysis, quality risk assessment and scheduling plant and equipment activities[92]. A great example about QbD implementation procedure is proposed by Lawrence[87] who selected and correlated different unit operations, CPPs and potential CQAs for tableting processes.

2.5 Process Analytical Technology (PAT)

The main aim of Process Analytical Technology is to achieve a high level of process understanding by predicting product quality attributes accurately and reliably, then by identifying and explaining all critical sources of variability, as well as by managing variability within processes[93]. PAT is a constitutive element of the Current Good Manufacturing Practices (cGMPs) which is announced as the "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st century – A risk Based Approach Initiative"[80] and defined as a set of principles and procedures which cover methods, equipment, facilities, and controls required for producing human and veterinary products, medical devices and processed food to the required quality. Most countries have their own cGMPs, but at a generic level it should involve the following requirements:

- equipment and facilities to be properly designed, maintained, and cleaned;
- standard operating procedures to be written, approved and followed;
- an independent quality unit to be established (like quality control and/or quality assurance);
- both personnel and management should be well trained[94].

With the main focus on PAT, it is important to note that Process Analytical Chemistry (PAC) might be considered as the origin of the PAT. Real time process monitoring and quality control of the obtained products were some of the main reasons for introducing the PAC concept in the past[95, 96]. Its main approach involved incorporation of process analyzers in the process streams and equipment in order to monitor process conditions and consequently follow quality control of chemical products[97]. The main need for this approach was based on very time consuming off-line analyses which involved manual sampling, sample transportation and time consuming protocols in central analytical laboratories[98].

The PAT Initiative is an extended and more sophisticated paradigm compared to PAC because it includes several science and engineering sub-disciplines[95, 98, 99]. It is actually defined as "system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality". Performance of these actions is possible by applying PAT tools: process analyzers, process chemometrics (multivariate tools for design, data acquisition and analysis), process control and automation, as well as CI and knowledge management tools[93].

At the end, it is important to emphasize that a proper use of the PAT guidance could result in plenty of benefits, such as: deeper understanding of production processes, integration of quality into process steps, reduction of quality overhead costs, higher production quality, lower production costs, self-adjusting production processes, etc[100]. As a result, the Initiative has found many of applications in other types of industries, such as food, chemical, life science and biotechnology industries[96].

2.5.1 Process Analyzers

Process states are analyzed indirectly through physical-chemical properties obtained via analytical measurements[101]. Measured properties could be univariate quantities (scalars), such as pH, temperatures, process flow rate, and so on. Furthermore, more sophisticated analytical measurements could be performed by using multivariate quantities (vector and matrix), by applying spectroscopic and chromatographic methods[98].

The main focus here is on the spectroscopic sensors due to their versatility in dealing with inorganic and organic constituents, as well as on broad applications in the modern pharmaceutical industry[95]. They have multiplexing capability because more than ten different and spatially separated measurement positions could be monitored with just one device[102]. However, spectroscopic techniques are different and selection of the appropriate technique is crucial for successful analysis of the process states. Kessler[3] compared different spectroscopic techniques considering eight categories: selectivity, sensitivity, sampling, applicability, process analytical tool, signal type, sampling and relative costs. The results which are summarized in Table 2.4 imply on the conclusion that the most optimum choice is to use UV/VIS/-NIR or NIR spectroscopy due to their relatively low cost and good performances.

Table 2.4 Selection of the best possible optical spectroscopy[3]

Parameter	**UV/VIS/-NIR**	**NIR**	**MIR**	**Fluorescence**	**Raman**
Selectivity	+	+ +	+ + +	+ +	+ + +
Sensitivity	+ + +	+ (+)	+ + +	+ + + (+)	+ (+ +)
Sampling	+ + +	+ + +	+	+ +	+ + +
Applicability	+ + +	+ +	+	+	+
Process analytical tool	+ + +	+ + +	+	+	+ + +
Signal	absorption	absorption	absorption	emission	scattering
Sampling	solid, liquid, gas	solid, liquid	solid, liquid, gas	solid, liquid, (gas)	solid, liquid, (gas)
Relative cost	1	3-5	6-10	4-6	8-12

The second group of process sensors is based on chromatographic methods and physical-chemical separation principles[103]. Furthermore, soft sensors have appeared whose basic principle is that material properties are not directly measured but can be deduced indirectly by analyzing secondary variables, which actually could be related to properties of interest by using mathematical models[104].

The selection procedure for suitable process analyzers additionally involves a process control perspective. Hence, a very high importance is given to the selection of the appropriate measurement strategy at the first point and afterwards of the suitable sampling technique. The main reason for this approach is in increased needs for real-time process monitoring and consequently better control and automation of processes[105].

There are four different measurement strategies in process analytics. The most commonly used approach involves sample withdrawal activities. Hence, a sample is withdrawn manually from a process line and transferred in a container for transportation to an analyzer. The second strategy is based on the extractive principle meaning that a sample from a process line is automatically taken to the analyzer on either continuous basis or in frequent intervals. Furthermore, *in situ* probing is useful and based on establishing contact with a sample by inserting probes in process lines or vessels. Lastly, non-invasive testing is based on non-contact measurements through windows into the process lines or other modes[100].

Furthermore, there are four types of measurement techniques. The most desired option is the in-line technique which involves the sample interface in the process line and thereby eliminates needs for a separate sampling system. Furthermore, automated sampling and transport through a sample line to an automated analyzer is the second desired option called on-line. The remaining two techniques are at-line and off-line which involve manual sampling and taking samples to analyzers that are placed in the manufacturing area or in the central analytical laboratory, respectively. They are undesired options from a process control point of view[98, 106].

The desired approach in the pharmaceutical industry is to use NIR spectroscopy with non-invasive testing as the measuring strategy and in-line sampling as the measurement technique[107]. However, many different factors could have influence on the selection of the appropriate process analyzers, sampling strategies and sampling techniques. For instance, homogeneous or heterogeneous media, then required preteatments of samples, and so on are just some examples[95, 100].

Further improvement of the optical instrumentation would lead to changes on the market. In the last two decades a major progress has been made in developing UV-VIS[95, 108], then Raman spectroscopy[95, 108, 109] and lastly NIR and MIR[95, 110, 111]. A list of the most well-known producers of the spectroscopic instrumentation and tools is shown in Table 2.5.

Furthermore, innovations in solid-state detectors[109, 112], fiber optics[109, 111, 113] and instrumentation for in- and on-line sampling[95, 108-111] have influenced technological development significantly. In addition, spectroscopic methods for micro-spectroscopic measurements based on acquiring hyperspectral data[109, 114-116] throughout chemical mapping[109, 114, 115] or imagining[109, 114, 115] could be a major milestone for Microreactor technology. However, usage of hyperspectral data still looks far away due to the significant numerical challenges that are involved for their analysis and modeling (they consist of multi-way data which have variations in more than two dimensions[115, 117, 118]).

Table 2.5 Overview of manufacturers of process analytical instrumentation[98]

Company	Instrumentation	Software	Ref.
Bruker Optics	MIR, NIR, Raman spectrometers, OEM IR cube	OPUS Suite	119
Foss	XDS series of NIR spectrometers	-	120
Kaiser Optical System Inc.	Raman RXN systems with non contact optics and varied immersion, PhAt, Airhead, Pilot Probes	HoloGRAMS, HoloPro, HoloReact, SDK	121
Malvern Instruments	Insitec particle size analyzers	NIR-CI, Isys software for NIR image analysis	122
Mettler Toledo	Automated lab reactors and reaction calorimeters: EAsyMAX™, MultiMax™, RC1™ In sity analytics: ReactIR™, FBRM®, PVM®	iC/iControl software suite (including iSafety, iC PAT)	123
Thermo Fisher Scientific	On-line and in-line process analytical instrumentation (elemental, gases, NIR, UV, MS...)	Atlas CDS, EP Series, GRAMS, GRAMS/3D, OMNIC, Spectral DB, Spectral ID	124

2.5.2 Process Chemometrics

Chemometrics originates from the 1970's when the Institute of Chemistry at the Umea University announced this concept as "the art of extracting chemically relevant information from data provided in chemical instruments"[125]. Hence, the extraction of this chemical information (or process signatures in other words) and their association with the process states has a crucial importance in the modern pharmaceutical industry. For instance, the FDA PAT guidance states that "based on the level of process understanding, these signatures may also be useful for process monitoring, control, and end point determination when these patterns or signatures relate to product and process quality"[93]. In order to associate the extracted chemical information and process states, it is necessary to use mathematical and statistical methods[126].

The main purpose of using Process Chemometrics in this project is to develop calibration models and establish continuous process monitoring afterwards. The procedure applied for that purpose is depicted in Figure 2.11 and involves five basic steps shown as blue boxes, then supporting actions colored in green, as well as some additional explanations in black.

In the early beginning it is crucial to treat the extracted raw chemical data appropriately. Hence, the data have to be investigated in order to find ranges of wavelengths/wavenumbers suitable for the compounds which are supposed to be analyzed. After this step, the preprocessing of raw data is

usually done in order to minimize potential errors and retain mostly relevant information in the pretreated spectra. This is the most challenging step in the calibration procedure and involves appropriate and careful selection of the mathematical pretreatment methods[127]. For instance, baseline corrections[128], mean centering[129], autoscaling[130], smoothing[131], first and second order derivation[132], multiplicative scatter correction (MSC)[133] and standard normal variate (SNV)[134] are some of the methods which could be used separately or in different combinations in order to pretreat spectral data. Furthermore, several additional methods could be applied, such as: *A priori* variable scaling, normalization, extended MSC (EMSC), Fourier compression, wavelets, etc.[95].

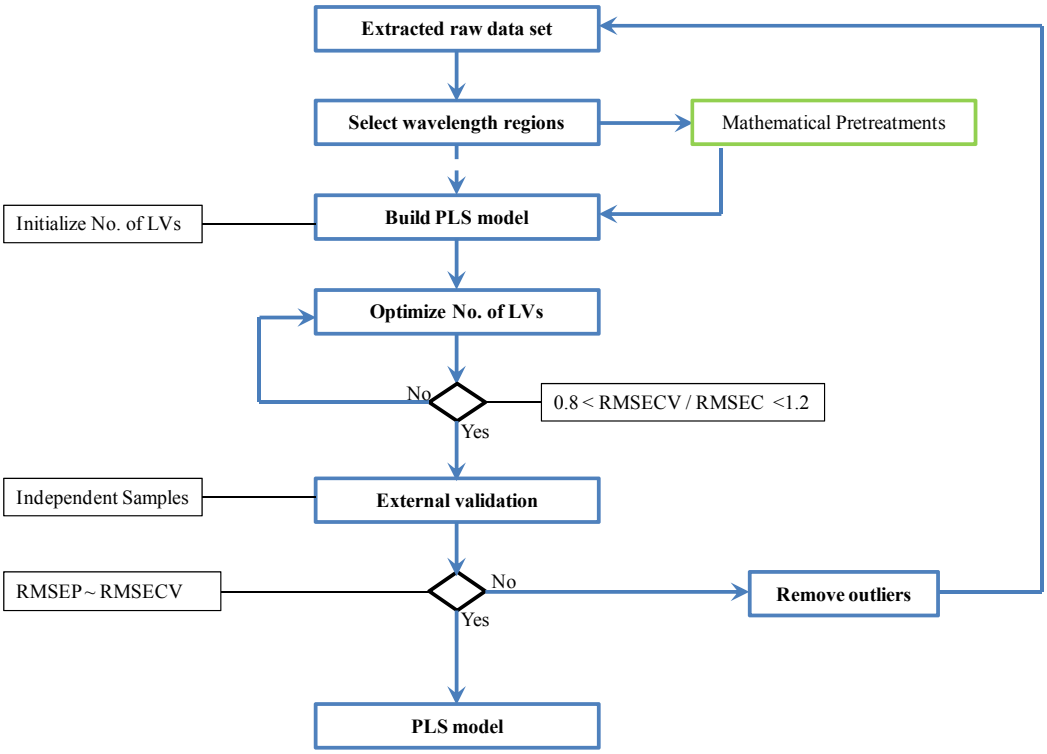


Figure 2.11 Multivariate calibration procedure involving five basic steps depicted in blue boxes, then additional helping steps colored in green and further explanations in black boxes. PLS – Partial Least Squares Regression, RMSEC – Root Mean Squared Error of Calibration, LV – Latent Variable, RMSECV – Root Mean Squared Error of Cross Validation, RMSEP – Root Mean Squared Error of Prediction

The third step involves development of the Partial Least Squares (PLS) model[135] whose number of latent variables is optimized through the cross-validation procedure. The cross-validation is usually based on the leave-one-out variable technique meaning that calibration is made with one variable excluded from the calibration data set. The excluded variable is afterwards used for the validation procedures. Therefore, if the Root Mean Squared Error of Cross-Validation (RMSECV) is

minimized, the optimum number of latent variables is achieved theoretically. However, over- or under-fitting should be avoided and therefore Root Mean Squared Error of Calibration (RMSEC) should be calculated and compared to RMSECV. The most suitable criterion is to achieve a small difference between RMSECV and RMSEC which should be bellow 20% according to Shenk and coworkers[136]. If the obtained value is higher than 20%, then a new number of latent variables should be applied and therefore a new values for RMSECV and RMSEC would be obtained (often higher with decreasing a number of LVs). From the practical point of view, the best choice for a number of LVs is the first value which causes a significant drop of RMSECV. When the overfitting criteron is satisfied, then RMSEP should be calculated. If the value is in the range with RMSECV then a relevant calibration model is achieved. If not, checking the presence of practical errors should be performed. In case of having obvious outliers, they should be removed from the calibration data set and the overal procedure should be repeated.

It is important to note that the calibration procedure should be repeated for several different mathematical pretreatments (or combinations of them). The best calibration model would involve the lowest value for RMSEP. Practical application of such algorithm is descrebed in chapter 5.

Scope of process chemometrics is very broad and additionally involves many important fields[137-144]. Therefore, several different software applications have been developed such as shown in Table 2.6.

Table 2.6 Overview of frequently used chemometrics software[98]

Company	Software	Ref.
Applied Chemometrics, Inc.	Chemometrics, Toolbox	[145]
	Factor Analysis, Toolbox	
CAMO Software	Unscrambler Software Suite (includes On-Line Predictor, OLUP, Optimizer, Classifier, GenX family)	[146]
	Quali-Sense	
Eigenvector Research, Inc	PLS Toolbox	[147]
	MIA Toolbox	
	Solo	
Thermo Fisher Scientific	GRAMS Suite (includes Grams/AI, Spectral DB, Spectral ID, GRAMS/3D)	[124]
	GRAMS IQ, IQ Predict, PLSplus/IQ chmometrics packages	
InfoMetrix	Pirouette 4.5	[148]
Umetrics	UbAtep	[149]
	SIMCA Software Suite (P/P+, Q/Q+, QP/QP+, QM/QM+, SBOL,4000)	
	MODDE 9 (including M-Link)	

Despite the fact that the PLS method is quite powerful, additional quantification methods could be applied. For instance, Principal Component Regression (PCR), then Least Squares Regression (LSR) models, Classical Least Square Regression (CLSR) models and Inverse Least Squares (ILS) models[128] are some of the examples.

Application of chemometric methods has historically been linked to NIR spectroscopy[131], but several applications have been developed in the last decade by using other techniques such as: UV-VIS spectrophotometry[150], Raman spectroscopy[95], fluorimetry[151], voltammetry[152] and additionally chromatographic techniques[153].

2.5.3 Process control and automation

Modern pharmaceutical industry has increased demands regarding environmental and safety issues. It is therefore necessary to establish safe and efficient operations which could be achieved by applying process control techniques[154, 155]. Furthermore, the PAT framework[93] states that "process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain a desired state" implying the need for techniques which would regulate the operation of manufacturing systems, as well as do the computation of the manufacturing support systems[156]. Development of computer based process control and automation systems is crucial in fulfilling the PAT requirements. Hence, some of the most frequently used software packages in industry specifically for this purpose are summarized in Table 2.7.

Table 2.7 Examples of process automation software[98]

Company	Software	Ref.
The ABB Group	Industrial^{IT} Technology (includes Extended Automation System 800xA and Extended Process Analytical Technology platform – xPAT)	157
	Analyze^{IT} Suite	
GE Intelligent Platforms	Proficy Process Systems and Software (includes Historian, HMI/SCADA (iFIX and CIMPLICITY), Batch Analysis, Real-Time Information Portal, RX modules)	158
	Partnerhip with Symbion (includes RX Script Assistants, Tcl command set)	
National Instruments	LabVIEW (includes toolkits such as DSC, Real-Time, PID, Data Connectivity, OPC client...)	159
	PAC hardware (includes PXI/CompactPCI, CompactRIO, Compact FieldPoint, Industrial PC, Wireless Sensor Networks, HMI...)	
	ANSI C LabWindows/CVI	
	MathScripts RT	
SIEMENS	SIMATIC series (including WINCC, sensors, HMI, controllers...)	160
	Data acquisition hardware	
	SIPAT (includes Base Station, High Level, analyzer instrument interface, offline Model builder, open interfaces...)	

2.6. Design space

Design space is a concept which is strictly correlated to PAT. It is a subsection of the knowledge space and it is usually developed during the process design activities. It is defined as "the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality"[161]. It is however difficult to select appropriate parameters and parameter settings for the design because parameters might be the factors (independent variables) which predominantly influence process and product qualities[3].

A very significant assistance of Design of Experiments is important in order to evaluate influence of different parameters on the product quality, as well as to determinate limits for parameter controls within normal operating ranges. As a consequence, a subsection of the design space is therefore formed and named control space. It defines a space where the manufacturer prefers to operate[162]. An illustration about connections between design space with knowledge and control spaces is depicted in Figure 2.12.

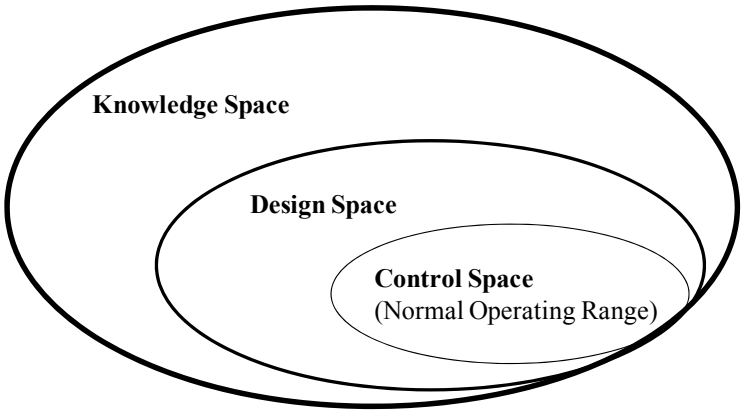


Figure 2.12 Schematic representation of the Design space[3] as a subset of the Knowledge space

Mhatre and Rathore[163] described a few examples how design space is implementation during the process development. For instance, it is crucial to check influence of temperature, pH and feed timing in the cell culture process design. Usage of the Design of Experiments tools therefore reduces number of parameters from the knowledge space into the range which determinates design space. Furthermore, application of the same tools evaluates normal operating ranges for such parameters and therefore implies to desired space for manufactures to operate in. These normal operating ranges are occasionally called "operational windows".

2.7 Conclusions

Applications of tools and techniques based on the continuous improvement methodology/philosophy have resulted with plenty of economic and environmental benefits in the process industry. Starting from very simple approaches, such as trial and error, tools and techniques for CI got a form of very developed and complex systems, such as Lean Production System, Six Sigma, Theory of Constraints, as well as suitable combinations of them. Their importance and development has been increasing over the decades due to increased requirements defined with the customers' needs. It means that establishment of high quality of processes and products will need to be improved in the future, so that CI is a never-ending journey.

Focusing on the pharmacetical industry, continuous improvement philosophy/methodology indicated development of three major drivers in the modern pharmaceutical sector. At the first point, the QbD approach was developed with the main aim to achieve high savings by noticing failures in early stage of processes and product developments. The second driver is the PAT Initiative which applications resulted with increased performances in manufacturing pharmaceuticals. In addition, both of these approaches influenced on further development of the process intensification concept. Lastly, design space together with statistical tools and techniques

significantly increases focus in the process and product developments. As a consequence, clearer path to desired levels of perfection could be achieved.

Further improvement of the pharmaceutical industry is associated with successful implementation of the Lean Enterprise concept. Connections between customers on one side and suppliers of raw materials on the other one should be more dependent and "in-flow". Plenty of chemical and car industries are making a development based on this relation. Hence, manufacturing products when they are needed and in desired amounts, as well as having flexible processes which can easily adapt to new demands at the market are actually goals to which pharmaceutical industry should aim.

3. Development of the Process intensification (PI) strategy for adapting slow chemical recations to continuous manufacturing modes in the modern pharmaceutical industry

Abstract

Process intensification (PI) is taking significant attention in the modern chemical-process industry with the main focus on increasing productivity, improving economic status of the companies, as well as on protecting the environment. The pharmaceutical industry is going in the same direction and therefore plenty of processes are in the stage of changes. However, not all of the processes could be intensified fast and easily and therefore supplementive actions are needed. Examples are slow chemical reactions, then reaction mixtures including solids, slurries, and so on. The main focus here is to describe applications of microwave radiation, microreactors, ultrasounds and mesoscale tubular reactors. In addition, applications of chemical catalysts/biocatalysts, as well as development of new synthetic routes to desired products are mentioned as potentially helpful actions in order to establish continuous manufacturing modes.

3. Development of the Process intensification (PI) strategy for adapting slow chemical reactions to continuous manufacturing modes in the modern pharmaceutical industry

3.1 Introduction

The pharmaceutical industry has been traditionally based on batch and semi-batch processes for organic synthesis based production of so-called 'small molecules'. Batch and semi-batch processes are known as very versatile and flexible manufacturing tools, however there are plenty of disadvantages associated with the use of such processes. Many of these disadvantages are major limitations for successful implementation of the PAT Initiative and therefore a switch towards continous manufacturing modes has been performing in the last decade. It is however important to note that not all the chemical reactions are suited for continuous production modes, and therefore majority of them – the so-called slow chemical reactions – have to be accelerated.

A main focus point of the pharmaceutical industry is therefore to try to establish continuous manufacturing modes suitable for on- and in-line process monitoring and therefore to achieve better process control and automation. A way to obtain such goals is to apply Process intensification (PI) concept which includes many different tools known in the chemical process industry. However, the modern pharmaceutical industry has been focused on four new ones. They are:

- microwave assisted organic synthesis (MAOS);
- Microprocess technology;
- meso-flow chemistry;
- ultrasounds.

The main objective of this chapter is to describe PI concept and develop PI strategy. Furthermore, each of the four above-mentioned PI tools will be described in detail and several examples explaining lab-scale implementations will be given. Additionally, two important chemical approaches will be added as promising tools for the acceleration of slow chemical reactions:

- chemical catalysis and biocatalysis;
- changes or modifications of synthetic routes.

3.2 Process intensification (PI) in the pharmaceutical industry

The concept of PI was introduced in the 1970s by Imperial Chemical Industries (ICI) with the main aim to decrease capital costs of production systems[164]. However, the definition of this concept has evolved over the years along with the development of the chemical process industry. Hence, there are different interpretations of the PI concept and some of them are summarized in Table 3.1. Nevertheless, a comprehensive and unique definition is still missing.

Table 3.1 Definitions of Process Intensification (PI) Concept

No.	Definition	Year[Ref.]
1.	"PI is a strategy to devise exceedingly compact plant which reduces both the main plant item and the installation costs"	1983[165]
2.	"PI is a strategy of reducing the size of chemical plants needed to achieve a given production objective."	1986[166]
3.	"PI is a development of innovative apparatuses and techniques that offer drastic improvements in chemical manufacturing and processing, substantially decreasing equipment volume, energy consumption, or waste formation, and ultimately leading to cheaper, safer, sustainable technologies"	2000[167]
4.	" PI provides radically innovative principles ('paradigm shift') in process and equipment design which can benefit (often with more than a factor two) process and chain efficiency, capital and operating expenses, quality, wastes, process safety and more"	2008[168]
5.	"PI can be achieved by adding/enhancing phenomena in a process through the integration of operations, functions, phenomena or alternatively through the targeted enhancement of phenomena in an operation"	2010[169]
6.	PI significantly enhances transport rates which gives every molecule the same processing experience	2013[170]

The most comprehensive definition of the PI concept was announced in 2008 by the The European Roadmap for Process Intensification[168]. It is depicted as entry 4 in Table 3.1 and covers a really broad field which might influence difficulties in complete understanding and implementation of the PI concept. The main reason for that is the overlap of PI with several other process-engineering related areas, such as process optimization (PO), process system engineering (PSE), and so on.

Hessel[171] made a clear distinction between PO and PI claiming that first concept is defined as a "usage of traditional apparatus with modified (improved) processing or a modified (improved) apparatus with similar processing capabilities or both" whereas PI "involves entirely new processing and apparatus". According to this definition, PI is only involved if changes in processing plants are included, such as miniaturization of the production equipment, for example.

Furthermore, overlap with PSE is very common. More precisely, it is very challenging to make a clear distinction between PSE and PI. Grossmann and Westerberg[172] tried to define PSE as a

concept based on "improving decision-making for the creation and operation of the chemical supply chain (discovery, design, manufacturing and distribution of chemical products)". Nevertheless, Moulijn and coworkers[173] went a step further and described a symbiosis of PI and PSE claiming that those two disciplines share the same object of interest: the processing plant, but that there are certain differences. Their approach to differentiate between those two concepts is depicted in Table 3.2.

Table 3.2 Comparison of PI and PSE skill areas[173]

No.	PI Skill Area	PSE Skill Area
1.	Effective usage of resources	Efficient usage of resources
2.	Equipment and materials oriented	Information and software oriented
3.	Experimental techniques enable	Computer technology enables
4.	New processing methods	New simulation methods and decision making tools
5.	Development of processing devices, catalysts, integrated unit devices	Functional, integrated design of product and processes
6.	Creation of spatial structures	Control over time events
7.	Compact and robust structures	Optimization of performance
8.	Resolution at micro- and nano-scales	Multi-scale integration
9.	Bottom-up, phenomena driven, model based	Top-down, system's view, model based

Hence, better definition of the PI concept would lead to better understanding and consequently would initiate easier implementation of the concept in the pharmaceutical industry. A good point is therefore to define PI goals, such as done by Moulijn and Stankiewicz[174]. They are focused on the following:

- cheaper processes;
- smaller equipment/plants;
- safer processes;
- less energy consumption;
- shorter time to market;
- less waste/by-products;
- better company image.

Adaptation of such goals in the pharmaceutical industry was done under the umbrella of the European Federation of Chemical Engineering (EFCE) in the European Roadmap for Process Intensification[168]. There are three different levels to be distinguished in this document with the main

purpose to categorize the relative importance of the drivers for implementing PI. The levels are definend as follows:

- high: selectivity, cost, competitiveness, sustainability;
- medium: safety, reliability;
- low: energy savings[168].

The PAT Initiative has boosted the PI drivers in the pharmaceutical industry. It was quickly realized that PAT applications cannot reach their full benefits in traditionally based batch and semi-batch processes. A solution to such problems is therefore to switch manufacturing from batch towards continuous manufacturing modes. Continuous production is often cited as both eco-friendly and economic[171], as well as allowing improved energy efficiency and reduced consumption of resources[175]. Hence, the PI drivers could be achieved easier if continuous manufacturing would be applied in the pharmaceutical sector.

However, not all chemical reactions are suited to fit in a continuous manufacturing framework. First of all, plenty of reactions should be accelerated in order to reach sufficiently low holdup times in a continuous reaction. In this work, the basic tools are divided in two groups: physical and chemical approaches. Illustrative interpretation of the physical and chemical approaches is depicted in Figure 3.1.

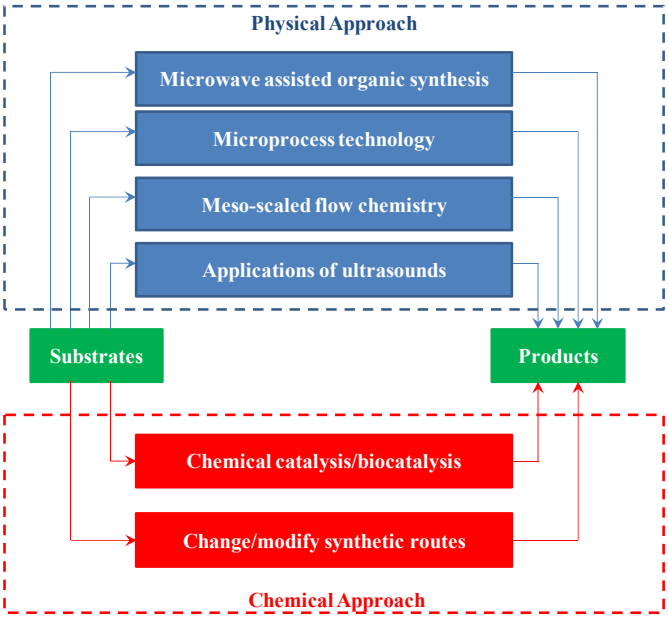


Figure 3.1 Different approaches to adapt slow chemical reactions in organic synthesis for processing in continuous manufacturing modes

Considering physical approaches, microwave assisted organic synthesis (MAOS) has received considerable attention in recent years mostly because of the very efficient application in organic synthesis[176, 177]. However, this manufacturing mode involves very high capital investments and additionally difficulties to implement PAT requirements. Hence, the current trend is to focus on the development of flow chemistry devices. Applications of microreactors and mesoscale flow reactors have thus become the main focus of the pharmaceutical industry[178]. Furthermore, applications of ultrasounds have started to be of increased interest as well[179].

Despite these physical approaches, there are still plenty of chemical reactions which cannot be performed without the presence of chemical catalysts[180] or biocatalysts[181]. Hence, the investigation of suitable catalysts is a never-ending activity. For instance, cross-coupling reactions are increasingly important for the pharmaceutical industry and therefore different homogeneous and heterogeneous chemical catalysts have been developed for this type of reactions[182]. However, it is important to realize that the main priority in the pharmaceutical industry is not just to operate a process efficiently, but to deliver products of high quality[183]. This is mostly linked to the very toxic transition metals[184] which are nowadays replaced with biocatalysts or with new synthetic routes to the desired products. For instance, C-S and C-N cross-coupling reactions have been modified successfully from transition metal catalyzed reactions to Grignard chemistry[185, 186]. Significant acceleration of such reactions has been achieved in this way, as well as significantly simplified downstream processing and plenty of other economic benefits.

Combining physical and chemical approaches together, or applying two or more physical approaches in the same time could be very beneficial. Application of MAOS and mesoscale flow chemistry, to name an example, is an interesting choice from the process engineering perspective[187]. On the other hand, a combination of ultrasounds and mesoscale flow chemistry is very interesting for processing slurries and reaction mixtures consisting of two immiscible liquids, for instance[179, 188]. In addition, combinations of microwave radiation and ultrasounds are also known and labeled as a good choice for industry in general[189].

Apart from MAOS[190], ultrasounds[191], micro-[192, 193] and meso-scale equipment[194], there are additional operational tools which could be successfully applied in the pharmaceutical industry. For instance:

- reversed flow for reaction-regeneration;
- unsteady operations;
- cyclic processes;
- extreme conditions;
- low-frequency vibrations for improving gas-liquid contacts in bubble columns;
- high temperature and high pressure technologies;
- supercritical media[164, 191, 193].

The latter techniques are mostly focused on lab and pilot plant scales, and their applications are versatile in the chemical process industry.

3.3 Microwave Assisted Organic Synthesis (MAOS)

Microwave ovens form a very suitable choice for heating applications, and therefore they have had an overwhelming success in home usage. They have also found plenty of applications in several process related areas, such as food processing, heating and vulcanization of rubber, as well as analytical chemistry[195]. As a consequence of the numerous advantages achieved in mentioned fields, there are also an enormous number of investigations about implementation of microwave radiation in the pharmaceutical industry[196].

3.3.1 Theoretical background

The microwave spectrum is just a small part of the overall electromagnetic spectrum and as depicted in Figure 3.2, it covers frequencies from 0.3 to 300 GHz[197]. The frequency of 2.45 GHz (corresponding to a wavelength of 12.25 cm) is chosen for scientific applications. Overlaps with applications of microwaves in military and related applications are avoided in this way. Furthermore, domestic microwave ovens work at 2.45 GHz, and thereby industrial manufacturers adopted that frequency for scientific use as well[197].

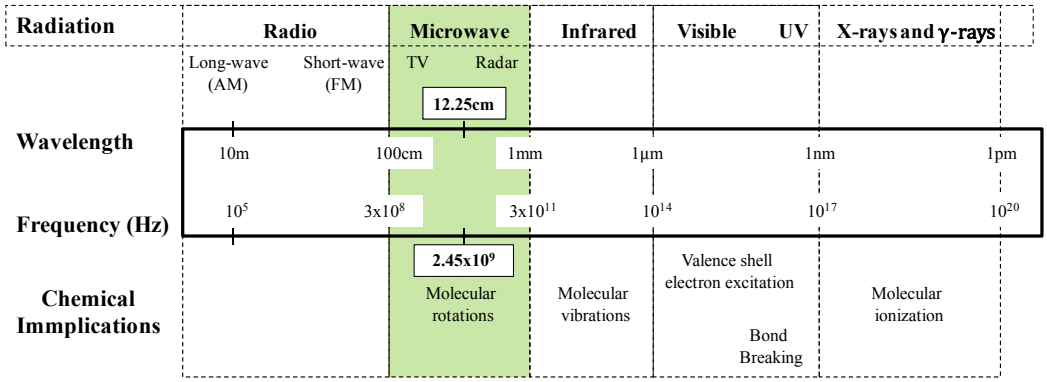


Figure 3.2 Regions of the electromagnetic spectrum with approximate scale, wavelengths, frequencies and chemical implications (adapted from[197])

Microwaves consist of electric and magnetic field components. The heating mechanism of microwave radiation is based on an effective absorption of the electric component of microwaves by the medium that is irradiated. The magnetic component might have an influence just on interactions with transition metal oxides, but this has not been explored in the literature so far[198]. More precisely, absorption of microwave radiation is called dielectric heating[199] and it is achieved through microwave-material interactions which can be explained by two mechanisms:

- dielectric polarization[200];
- ionic conduction[198].

Dielectric polarization is a complex phenomenon which involves three different types of polarizations:

- electronic – realignment of electrons around nuclei;
- atomic – relative displacement of nuclei because of the unequal distribution of charges inside molecules;
- dipolar – orientation of permanent molecular dipoles.

The specific contribution of each type of polarization is strictly dependent on the comparison of the time scales of polarization-depolarization cycles on the one hand and inverse values of the radiation frequencies on the other hand. In the case of microwave radiation, the first two mechanisms (electronic and atomic polarizations) act on a much smaller time scale than the frequency of microwaves. Therefore, they are usually neglected[200].

Dipolar polarization defines interactions of microwaves with molecules which have permanent or induced dipole moments. The main principle is to align dipoles with oscillations of the electromagnetic field. Therefore, if dipoles do not have enough time to align themselves (high frequencies of incoming radiation), or if molecules reorient themselves too quickly (low frequencies of incoming radiation), the heating process does not happen. Furthermore, dipoles do not follow an alternating field so precisely, which means that the electric field changes during the aligning process and generates a phase difference between the orientation of the field and the orientation of the dipole. Consequently, the phase difference causes that dipoles lose their energy through molecular frictions and collisions which enables more efficient dielectric heating. Hence, gases cannot be heated by microwave radiation because of too large distances between the molecules[198]. Focusing on reactions in the liquid phase, it is important to emphasize that polar solvents, such as dimethyl-sulfoxide (DMSO), dimethyl-formamide (DMF), ethanol, water, and so on, are heated very fast whereas non-polar solvents (toluene, hexane...) are only heated very slowly using microwaves[197].

The second mechanism is called ionic conduction and it is based on the collision of dissolved charged particles (ions) with their neighboring atoms and molecules. In particular, microwave radiation causes ions to move back and forth, and in that way the ions collide with molecules and atoms and create heat. This mechanism usually occurs when ionic liquids are used. It is defined as a stronger effect than the dipolar polarization[198].

3.3.2 Microwave radiation in the forms of equations

Description of the microwave radiation in the form of equations has been a major research topic in recent years. There are two mathematical approaches which could be applied to this phenomenon:

- average relaxation time, τ;
- loss tangent angle, tanδ[201].

3.3.2.1 Average relaxation time

The average relaxation time is the inverse average rotational frequency. The definition of τ was firstly proposed by Debye and it combines molecular properties (radius of molecule) with macro-physical properties, such as dynamic viscosity. The definition is depicted in Equation 3.1

$$\tau = \frac{4\pi r^3 \eta}{k\,T} \qquad 3.1$$

where

τ - Average relaxation time (s);
r - Radius of a molecule (m);
η - Dynamic viscosity ($\frac{N\,s}{m^2}$);
k - Rate constant (units depend to the order of chemical reaction);
T - Absolute Temperature (K).

If τ is low enough (range of ps), solvents effectively couple with microwave radiation. It is important to note that an increase of the temperature could lead to a significant decrease of the relaxation time which implies that some solvents could absorb dielectric heating rapidly under those conditions. Furthermore, dynamic viscosity is very dependent on the intermolecular interactions meaning that temperature, as well as dipole-dipole and induced dipole-dipole interactions have a huge influence on the values of the dynamic viscosity[201]. Therefore, investigations of the exact influence of temperature on the average relaxation time should be performed.

3.3.2.2 Loss tangent angle

This parameter is a more common approach to compare the influence of microwave radiation on different substances. It describes the ability to absorb electromagnetic radiation and convert it into heat. There are two approaches to define the loss tangent angle. The first one is based on the penetration phenomenon where tanδ is represented as the reciprocal value of the penetration depth. It is important to note that the penetration depth is the point where 37% of the initially irradiated microwave power is still present[196]. Nevertheless, the second definition is more useful in modern

organic synthesis. It states that tanδ is a ratio between dielectric loss and dielectric constant[202]. The expression is depicted in Equation 3.2

$$\tan\delta = \frac{\varepsilon''}{\varepsilon'} \qquad 3.2$$

where

$\tan\delta$ - Loss tangent (dissipation factor);

ε'' - Dielectric loss (-);

ε' - Dielectric constant (-).

More precisely, the dielectric loss is the ability of molecules to convert electromagnetic radiation into kinetic energy[202]. It depends on the dielectric conductivity and also on the frequency, as depicted in Equation 3.3

$$\varepsilon'' = \frac{\sigma}{2\,\pi\,f} \qquad 3.3$$

where

σ - Dielectric conductivity ($\frac{1}{s}$);

f - Frequency (Hz).

This parameter has tabulated values for plenty of organic and inorganic compounds, then plastics, ceramics, waxes and food products[202]. However, those values are usually dependent on the temperature, and therefore investigations about the dependence of dielectric loss on the temperature have been performed[198].

Apart from the dielectric loss, the definition of the loss tangent angle involves an additional parameter called the dielectric constant. The latter parameter explains the polarizability of molecules in the microwave field and implies on a better compatibility of polar molecules and ionic liquids with microwaves[202].

Nevertheless, ε' and ε'' are parts of a permittivity (ε) which is defined as a complex number shown in Equation 3.4. The dielectric constant is a real part whereas the dielectric loss represents an imaginary part[189]:

$$\varepsilon = \varepsilon' + i\varepsilon'' \qquad 3.4$$

Hence, if the dielectric loss is high, then the loss tangent angle also has a high value and absorption of microwave radiation is very good. Perfect absorption refers to the situation where tanδ=∞, whereas tanδ=0 refers to a totally transparent material. From a practical point of view, very good absorbers have tanδ values around 1[197]. The list of the most commonly used solvents in organic synthesis together with their tanδ values is provided in Table 3.3 (values are specified for 20^{0}C and 2.45 GHz).

Table 3.3 Loss factor (tanδ) for different solvents at 2.45 GHz and 20^{0}C[203, 204]

Solvent	**tanδ**	**Solvent**	**tanδ**
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	1,2-dichloroethane	0.127
DMSO	0.8525	Water	0.123
2-propanol	0.799	Chlorobenzene	0.101
Formic acid	0.722	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Ethyl acetate	0.059
1-butanol	0.571	Acetone	0.054
2-butanol	0.447	Tetrahydrofuran	0.047
1,2-dichlorobenzene	0.280	Dichloromethane	0.042
NMP	0.275	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

It is important to note that the loss tangent angle can over- or underestimate the ability of a solvent to absorb electromagnetic radiation. Hence, a special attention should be given to other parameters as well, such as: heat capacity, heat of vaporization, temperature, pressure, etc[**197**]. For instance, it is very easy to heat up water to 100^{0}C in a microwave atmosphere. However, further heating involves plenty of difficulties (such as heating from 100^{0}C till 200^{0}C)[**198**].

3.3.3 Advantages compared to the conventional heating

The main difference between dielectric and conventional heating is the different heating rate of the medium. In particular, if the medium is capable to couple with microwaves, its heating rate is usually in the range from 2 to 5^0C/s. Conventional heating methods, such as oil or water baths, reach much lower heating rates. The main reason for such differences is associated to the heating principles. More precisely, dielectric heating is based on energetic coupling which is on the molecular level, whereas conventional heating relies on superficial conduction and convection[205]. It is actually assumed that putting reactor tubes into very hot furnaces (more than 1000^0C) can achieve the heating rates obtained in a reactor irradiated with microwaves[201].

Comparison of temperature profiles between conventional methods on the one hand and microwave irradiated reactors on the other hand points towards some additional differences. The first is that a uniform temperature distribution is achieved if microwaves are applied which leads to plenty of benefits in organic synthesis. Conventional heating methods include negative temperature gradients starting from reactor walls and towards the central symmetric axis of reactors[203]. Secondly, dielectric heating has a big disadvantage – it is very selective regarding polar compounds whereas conventional heating is more generic, i.e. heating all reaction mediums[205].

Nevertheless, a detailed insight into the advantages of MAOS can be obtained by understanding two different microwave effects:

- thermal effects;
- non-thermal microwave effects[203].

3.3.3.1 Thermal kinetic theory

The thermal theory is mainly based on the energy of the microwave photon (0.0016 eV). In general, this energy is too low and thereby it cannot cause breakage of chemical bonds. In addition, the energy of the microwave photon is also lower than the energy of Brownian motion[206, 207] and it can therefore be concluded that microwave radiation cannot initiate chemical reactions[203].

However, some unusual effects could be observed during microwave irradiation. One interesting example is that solvents can potentially achieve higher boiling points compared to values at the atmospheric pressure. This phenomenon is called the “superheating effect” and could be caused by the very steep heating rate of a solvent. This heating behavior enables accumulation of energy in the liquid phase and reaching temperatures above normal boiling points. More precisely, energy provided with the microwave radiation surpasses energy dissipated by evaporation at the boiling point conditions. Therefore, temperatures up to 40^0C higher than normal boiling points have been observed in some particular cases[208]. The exact increase is still dependent on several factors, such as power dissipation, reactor geometry, solvent properties, and so on[209-211].

Despite the superheating effects, there is a chance that microwaves could initiate increased diffusion of polar molecules and anions within solid materials. More precisely, several different

intermolecular interactions, as well as disruption of hydrogen bonds could be achieved due to the oscillating field[212]. Leskovsek and coworkers[213] noticed increased reactivity in a system consisting of soybean oil-water-catalyst when hydrogenation of the soybean oil was performed while irradiating with microwaves.

Furthermore, successful applications of MOAS for non-polar solvents have been performed, as well. Although this reaction medium is in theory not suited for microwave radiation, there is anyhow a number of interesting approaches for enhancing absorption of this type of energy in non-polar solvents. Hence, additions of heterogeneous catalysts and reagents suited for microwave absorption could be a good choice for such reaction mixtures[214-219]. Adding such compounds to the non-polar solvent is also called formation of "molecular radiators" in the reaction mixture[216].

Dielectric heating is not always that perfect. Several authors have noticed inhomogeneity inside the reactor vessel which leads to the formation of undesired hot-spots[220, 221]. Such inhomogeneity can be explained by several reasons:

- different dielectric properties of the materials used in the reaction mixture;
- a consequence of uneven distribution of the electromagnetic field strength;
- volumetric dielectric heating;
- overheating might appear as an undesired effect due to the "inverted heat transfer" (from irradiated medium to the exterior)[222, 223].

In addition, there is a chance that inverted temperature gradients could appear in reaction mixtures irradiated with microwaves. However, the gradients are not supposed to be that high, and thereby their influence should not be that significant (unless used in applications of very temperature sensitive chemical reactions)[224-228].

3.3.3.2 Non-thermal microwave theory

The non-thermal microwave theory[203] is based on interactions of the electric field with specific molecules which are present in the reaction medium. The electric field leads to the orientation effects of dipolar molecules, and thereby the pre-exponential factor in the Arrhenius equation might be changed[229-231]. More precisely, efficiency of the molecular collisions could be increased. Binner and coworkers[232] performed experiments that seem to support this theory whereas Miklavc[233] approached to the same conclusions based on theoretical studies.

Furthermore, several authors claim that changes in thermodynamic parameters occur due to microwave radiation. For instance, Berlan and coworkers[234] implied on the occurrence of changes of the Gibbs free energy due to the increased polarity initiated by moving from the ground state to the transition states. In this way, the reactivity could be increased because of the lower activation energy[231]. Lewis and coworkers[235] confirmed this theory by performing imidization of polyamic acids, whereas similar conclusions were obtained for the decomposition of sodium hydrogen carbonate in water[236].

3.3.4 Process-engineering perspective of the MAOS applications

Acceleration of slow chemical reactions from days or hours towards just a few minutes or seconds is the main advantage of the microwave radiation. Furthermore, increased selectivity[203], improved reproducibility, easier discovery of new chemical reactions, easy scalability, broad temperature ranges, rapid reaction optimisation, and so on[237], are just some of the reasons why significant attention was given to the MAOS.

Focusing on the pharmaceutical industry, it is important to note that initial applications of MAOS were strictly linked to medicinal chemistry departments. The main focus was on reducing long reaction times, which significantly influence the work on drug discovery. Furthermore, applications of conventional heating methods were usually connected to plenty of issues related to the formation of heterocyclic compounds, for instance[176, 177]. A strategic approach to the MAOS applications in medicinial chemistry was proposed by David Rudge in AstraZeneca[68] whereas Biotage[238] announced the time prediction chart which is depicted in Table 3.4. It could be seen that if a chemical reaction lasts 96 hours at 20^0C in the conventional heating treatment, the same reaction would last 45 min in a microwave oven at 90^0C whereas increase of temperature up to 150^0C would result in a reaction time of just 42 s. As a consequence, dozens of accelerated chemical reactions have been tested, and published in the literature[176, 177].

From the process engineering perspective, applications of MAOS could be divided in three modes:

- batch;
- stop-and-flow;
- continuous.

The main purpose of batch mode operation supported with microwave irradiation is associated with applications in the area of discovery chemistry. It is important to note that glass reactors with volumes up to 5 ml are usually applied for discovery chemistry purposes[176, 177]. However, from the manufacturing point of view, batch applications are the least interesting. The analysis of the reactor content in such a batch process is usually based on rather old-fashioned principle of stopping chemical reactions, then allowing reaction mixtures to cool down and subsequently applying at- or even off-line analyses[239]. Nevertheless, several tests have been performed in order to implement in- and on-line process monitoring. Such attempts were based on NIR spectroscopy in the early beginning and introducing a U-turn bend fibre inside the reactor vessel. It is important to note that the optical fibers were completely inert to the microwave radiation[240]. Apart from NIR, applications of in-situ Raman spectroscopy have been successfully tested by using fiber optic probe for monitoring Suzuki coupling reactions[239].

A step forward in combining microwave radiation and batch processes is "stop-and-flow principle"[241]. It is based on sequences which include introduction of substrates in a batch reactor, then stopping flows in order to allow chemical reactions to occur and lastly with flushing products and other materials from the reactor. This approach is useful in cases when reasonably slow chemical reactions are applied[242].

Table 3.4 Acceleration of slow chemical reactions by applying microwave radiated organic synthesis (if a chemical reaction lasts 96 hr at 20^{0}C in the conventional heating, the same reaction would last 45 min in a microwave oven at 90^{0}C or 42 s at 150^{0}C) [68, 238]

T [^{0}C]	Reaction time									
20	1	2	4	6	8	12	24	48	96	172
30	30	1	2	3	4	6	12	24	48	86
40	15	30	1	1.5	2	3	6	12	24	43
50	8	15	30	45	1	1.5	3	6	12	22
60	4	8	15	23	30	45	1.5	3	6	11
70	2	4	8	11	15	23	45	1.5	3	5
80	56	2	4	6	8	11	23	45	1.5	3
90	28	56	2	3	4	6	11	23	45	1
100	14	28	56	1	2	3	6	11	23	40
110	7	14	28	42	56	1	3	6	11	20
120	4	7	14	21	28	42	1	3	6	10
130	2	4	7	11	14	21	42	1	3	5
140	53	2	4	5	7	11	21	42	1	3
150	26	53	2	3	4	5	11	21	42	1
160	13	26	53	1	2	3	5	11	21	38
170	7	13	26	40	53	1	3	5	11	19
180	3	7	13	20	26	40	1	3	5	9
190	2	3	7	10	13	20	40	1	3	5
200	1	2	3	5	7	10	20	40	1	2
210		1	2	2	3	5	10	20	40	1
220			1	1	2	2	5	10	20	35
230					1	1	2	5	10	18
240						1	1	2	5	9
250								1	2	4

The best choice is to apply continuous manufacturing modes[243] even there are still considerable issues when working with heterogeneous mixtures[244] and viscous liquids[245]. Several small-scale applications have been announced[187], such as work done by Benali and coworkers[246, 247] who tested mesoscale coiled reactors for C-N and C-C cross-coupling reactions, as well as for synthesis of triazoles. They achieved significant accelerations together with better selectivity and increased yields of desired products. Furthermore, Smith and coworkers[248] performed synthesis of aminopyrazolopyramidines in the packed bed coiled reactor with subsequent scavenger applications. They achieved very high yields of desired products, as well as very high purities. Despite coiled reactors, continuous manufacturing modes have been successfully applied in the "U-shaped" mesoscale tubular reactors. Baxendale and coworkers[249] obtained promising results in applying this reactor setup for a C-C coupling reaction (Suzuki couplings). Moreover, Shore and coworkers[250] used capillary reactors with thin metal films and achieved extremely high temperatures – up to 900^0C. The capillary approach was additionally applied for alkyne cyclotrimerization reactions without any metals as chemical catalysis[251].

However, small scale manufacturing is often not that suitable for industrial production and therefore scale up/out should be performed. Here, specifically, an important issue is that standard magnetrons at 2.45 GHz work with an efficiency between 50-72%. Hence, the electricity costs should be lowered in order to justify capital investment for establishing MAOS[252]. Apart from the relatively low efficiency, magnetrons also face issues with the penetration of microwave radiation inside the reaction media. The penetration depth is usually just a few centimetres[253] which leads to plenty of difficulties for processing larger volumes. One of the consequences is that the price of a product should be high in order to justify such huge investments[252].

Nevertheless, further investigations have been performed in order to adapt MAOS for larger scale applications. Plenty of companies have come up with interesting solutions. One idea is to put several closed vessels in parallel and achieve up to 1 L of effective reaction volume. However, this could be considered as a numbering up of batch reactors. Furthermore, an additional option might be to use a slim and specially designed teflon vessel with a reaction volume up to 350 ml. This is a step forward because of the increased volume of the reactor vessel, but with very bulky microwave ovens. However, if chemical reactions are supposed to be performed at temperatures below normal boiling points of solvents, then open vessels with volumes up to 5 L could be successfully applied[254].

Besides those applications with closed (batch mode) and open vessels (stop-and-flow), enlarged continuous flow apparatus has been developed as well. One of the successful applications was based on a tubular reactor which was able to have up to 200 ml of reaction volume, resulting in kilograms of products per day. However, this approach is just suited for homogeneous applications and further improvements are needed. An additional idea was to use a large reactor as a reservoir, and then to have a loop which would be irradiated with microwaves[254].

3.4 Microprocess technology

Microdevices have become important part of our daily life due to plenty of applications as mechanical, optical, thermal and fluidic devices. For instance, laser heads for CD players, read/write heads for hard disks, micro-sensors in automobiles are just some of good examples[255]. Miniaturization of equipment has also been attempted in the chemical process industry. The earliest trials go back to the last decade of the 20th century when a miniaturized "total chemical analysis system" (TAS) was firstly applied[256], such as pioneered microsized equipment with different unit operations developed by DuPont[257, 258].

Increased interests in microsized devices caused development of a new field called Microprocess technology. It involves integration of devices that are in a range from sub-micrometer to sub-millimetre into plant architectures with the main goal to establish continuous processing. Despite the focus on such devices, capillary and tubular reactors with small inner dimensions, then mini fixed-bed and small size foam reactors also belong to the Microprocess technology concept[259, 260].

3.4.1 Microprocess technology in the form of equations

Specific physical effects are dominant in the microscale dimensions (from 100 μm up to 1 mm):

- intensified mass transfer;
- intensified heat transfer;
- intensified surface phenomena due to high surface area-to-volume ratios[261].

The intensified mass transfer is mostly connected to the improved mixing in such small scale devices. More precisely, stirring in batch reactors is based on convection and usually involves chaotic mixing and turbulence. As a result, inhomogeneous mixing and undesirable formation of concentration gradients are characteristic for batch reactors. These conditions cause decreased productivity which leads to increased reaction times, as well as to economic disadvantages. Furthermore, problems with selectivity and yield could appear if reaction times are increased due to potential by-product formation[262].

One of the reasons for intensified mixing is a laminar flow which is dominant in such small devices. The most common approach to evaluate the flow type is to use the Reynolds number (Re). This dimensionless number is depicted in Equation 3.5

$$Re = \frac{u\rho L}{\eta} \qquad 3.5$$

where

u - Velocity ($\frac{m}{s}$);

ρ - Density ($\frac{kg}{m^3}$);

L - Traveled length – diameter (m);

η - Dynamic viscosity ($\frac{kg}{m\,s}$).

In the microscale, the usual range of values for Re is between 2 and 200 which is far from the turbulent and transitional regions (>2300). Therefore, only laminar flows and intensified molecular diffusion should be present in such small scale devices. As a consequence, mixing is intensified considerably and could be more than 1000 times faster compared to the macroscale batch reactors, for instance[263, 264].

An additional dimensionless number useful for evaluating mixing in the microscale is the Peclet number (Pe). It is defined as a ratio between mass transport caused by convection on the one hand and by diffusion on the other hand[265]. This parameter is mathematically expressed in Equation 3.6

$$Pe = \frac{ud}{D} \qquad 3.6$$

where

d - Hydraulic diameter of microchannel (m);

D - Diffusion coefficient ($\frac{m^2}{s}$).

Moreover, the same number can also be related to the Re number, as shown in Equation 3.7.

$$Pe = Re\frac{\eta}{\rho D} \qquad 3.7$$

It is important to note that if Pe<100, then a complete mixing based on diffusion could be accomplished within several cm[266]. Nevertheless, Hartman and coworkers[267] claim that micro-scaled devices would only benefit if Pe is smaller than unity.

Furthermore, micromixing could be additionally evaluated by calculating the diffusion timescale ($t_{D)}$ as shown in Equation 3.8

$$t_D = \frac{L_D^2}{D} \qquad 3.8$$

where

L_D - Length over which diffusion must occur (m).

Obtaining mixing in a timeframe of milliseconds is the final goal and therefore the lamination concept was developed. It involves an increased contact area between reagents based on splitting the flows in two layers and subsequently joining them together in order to allow higher diffusive mixing at the point of confluence[268]. Mixing time is significantly decreased in this way which leads to plenty of advantages in case of very fast chemical reactions.

Apart from Re, Pe and t_D, the Damköhler number (Da) is also very important. It is defined as a ratio between reaction rate and mass transport rate, as shown in Equation 3.9

$$Da = \frac{k_r C_o^{n-1}}{2} t_D \qquad 3.9$$

where

k_r - Specific reaction rate (units depends to the order of reactions);

C_o - Molar concentration of a reagent (M);

n - Order of a chemical reaction (-).

If the value of Da is smaller than 1, then chemical transformations are reaction rate limited. Quite the opposite, if Da>1, then reaction rates are controlled by mass transport. Hence, if the Da value is close to unity, chemical transformations are influenced by both factors[267].

A second important advantage of microreactors is intensified heat transfer. It should also be connected with significantly improved mixing properties. For instance, formation of temperature gradients and hot spots is avoided due to smaller diameters of tubular reactors. Furthermore, better heat exchange coefficients (up to 25 $\frac{kW}{m^2\,K}$) additionally result in better temperature control inside microreactors. More precisely, constant temperatures and rapid temperature changes can be easily managed[262].

Furthermore, a typical criterion for describing heat transfer in laminar flow of fluids is the Nusselt number (Nu). One of the simplest definitions is depicted in Equation 3.10

$$Nu = \frac{\alpha L}{\kappa} \qquad 3.10$$

where

α - Heat transfer coefficient ($\frac{W}{m^2 K}$);

κ - Thermal conductivity ($\frac{W}{m\,K}$).

In addition, influence of surface forces could be easily estimated by using Bond number (Bo). It is defined as depicted in Equation 3.11

$$Bo = \frac{\rho g L^2}{\gamma} \qquad 3.11$$

where

g - Gravitational acceleration ($\frac{m}{s^2}$);

γ - Surface tension at interface ($\frac{N}{m}$).

It is very common that values for Bo are very low in microscale equipment. If Bo<1, surface forces are assumed to be dominant, whereas Bo>1 indicates that gravitational forces are mostly dominant. When Bo is close to 1, the influence of both forces is important[269].

A third important advantage of microscale devices is the very high surface-to-volume ratio (up to 50000 $\frac{m^2}{m^3}$). If compared to the values in batch reactors (range from 100 - 4 $\frac{m^2}{m^3}$), it is clear that significant improvements are achieved by downsizing of the equipment[262].

3.4.2 Process-engineering perspective of applications of microscaled reactors

Chemistry in micro-structured devices does not differ drastically from the batch chemistry. Both "types of chemistries" have to be considered as bulk chemistries which means that the interference of the surfaces into chemistry is low even for the microchannels. Hence, the assumption is that the chemical reaction mechanisms and the product spectra should be the same[270].

However, in the fine chemical and pharmaceutical industry not all types of chemical reactions are suitable for micro-structured devices. Roberge and coworkers[270] claim that chemical reactions with a half life higher than 10 min should preferably be operated in batch manufacturing modes.

Nevertheless, downsizing the equipment to the microscale could indicate acceleration of such reactions[271]. Furthermore, chemical reactions with very reactive components (Grignard exchange reactions and reactions with chloride, bromide and amine species) are all very suitable for flow chemistry applications. These reactions that have typical half lives below 1 second, could therefore be completed in the mixing zone alone[272, 273]. Finally, chemical reactions with half lives from 1 second up to 10 min could also benefit from the micro-scale devices[274].

Applications of Microprocess technology could lead to plenty of advantages. Some of the benefits which are usually connected with those small devices are:

- increased efficiency due to decreased amounts of waste and input materials;
- easier optimization of experiments;
- possibilities to introduce easier multiple transformations by using lab-on-a-chip approach and continuous operating modes;
- safer synthesis of dangerous compounds;
- isolation of air and moisture sensitive chemistry;
- reduction of formation of hazardous wastes;
- faster transfer of research results into production;
- earlier start of production at lower costs;
- easier scale-up of production capacity;
- smaller plants for production at distributed sites;
- lower costs for transport, materials and energy;
- more flexible reaction to market demands[259, 262, 265, 275].

However, a major issue in the Microprocess technology is related to the type of reaction mixtures that are used. For instance, homogeneous reactions with suitable reaction times could result in plenty of benefits when implemented at microscale. Condensation reactions, acid- and base-promoted reactions, as well as photo- and electro-chemical reactions are just some examples[276]. Apart from homogenous reactions, a more complicated medium containing solid and liquid constituents has also been tested successfully in microscale. Therefore, reactions such as cross couplings, reductions and oxidations, as well as heterocyclic and on-bead synthesis, etc., have shown plenty of benefits when performed in micro-scale equipment[277]. Biphasic systems consisting of two immiscible liquid phases have also been used successfully in microscale due to improved diffusive properties[278]. In addition, gas-liquid reactions[276] and bioorganic reactions[279] have been successfully applied, as well.

From the process engineering perspective, microscale devices are facing issues in the modern organic synthesis because of difficulties associated with fast implementation of real-time process monitoring and control. There are several good examples based on at-line monitoring, such as applications of mass spectrometry (MS)[280] and combined liquid chromatography-ultraviolet spectroscopy-mass spectrometry system (LC-UV-MS)[281], or even on-line high performance liquids chromatography (HPLC)[282]. However, the delay times for data analysis in such analytical tools are

in the range of minutes or longer. Therefore, further development of fast spectroscopic tools is needed in order to establish in-line analysis of reaction mixtures.

McMullen and coworkers[178] published an excellent review about the usage of different analytical tools in Microprocess technology. According to them, laser induced fluorescence showed great advantages due to its high sensitivity and very low amount of sample material needed. More particularly, great applications have been reported specifically for enzymatic reactions[283, 284]. In addition, UV detection has been successfully tested for in-line analysis of a Berhelot reaction[285]. Furthermore, an on-line NIR flow cell was tested for toluene nitration[286], whereas in-line NIR measurements have also been used for ozonolysis (in the flow stream following the microreactor)[287]. A reflectance NIR approach has been applied as well by using a NIR probe combined with golden deposits on the back side of a microreactor which served as a reflecting layer[288]. Finally, application of inverted Raman microscopic spectroscopy has shown to be very useful for the synthesis of ethyl acetate. More specifically, in situ process monitoring was established via chemical imaging in micro-channels[289]. Usage of the non-contact fibre optic Raman probe for monitoring the photo-polymerization of methacrylate monomer droplets has been tested[290], as well as for heterogeneously catalyzed gas-liquid reactions[291].

Plenty of advantages related to performing organic chemistry in such microscale devices were recognized and consequently implemented in the industrial sector successfully[274]. Considering the pharmaceutical sector, most investigations have been done by Novartis Pharma Ltd[292, 293], then GlaxoSmith Kline Pharmaceuticals[294], Johnson & Johnson[295], Lonza Ltd.[296], Bayer[297] and Eli Lilly and Company[298]. Applications have moreover been extended to the chemical industry, such as BASF[299], DOW[300], Clariant GmbH[301], SK-Chemicals, Ampac Fine Chemicals, Phoenix Chemicals, as well as DSM and Alfa Laval[187]. A comprehensive review about industrial applications of microreactors was recently published by Denčić and coworkers[302].

3.5 Meso-flow chemistry in organic synthesis

Meso-flow chemistry, or more general Meso-science, is receiving significant attention in the chemical process industry. There is plenty of research in this area, mostly in the direction of Virtual Process Engineering (VPE)[303], which is based on the Energy Minimization Multiscale Models (EMMS)[304]. The main idea is to simplify scaling up procedures by increasing understanding of chemical processes on different levels and scales. Hence, the mesoscale is considered a bridge between micro- and macro-scales, and thereby plays a very important role in the EMMS paradigm.

Meso-flow reactors could be defined as tubular or capillary devices with dimensions in the range from half[194] or 1 mm[305] up to a few mm in inner diameter (mostly up till 3 mm). Larger dimensions are applied compared to the Microprocess technology which leads to a slightly decreased performance potential[306], but still a much better performance than in batch reactors. In fact, introduction of meso-flow chemistry could be understood as the act of avoiding some of the

disadvantages which are usually faced in the micro-scaled devices, while still keeping some good features which are dominant in the micro-scale (but in a weaker form).

Focusing on the pharmaceutical sector, this bridge between micro- and macro-scale synthesss is usually applied in the drug discovery research. More precisely, the main focus is on medicinial chemistry and preclinical development sectors due to relatively low amounts of synthesized products[307]. However, production in the pharmaceutical industry might be occasionally based on small-scale production equipment as well. It would yield plenty of benefits if meso-flow chemistry would be applied. Nevertheless, a general illustration of applications of different sizes of equipment is shown in Figure 3.3. It can be seen there that mesoscale equipment could also be applied in the preclinical development, such as Fit for Purpose (FFP) development.

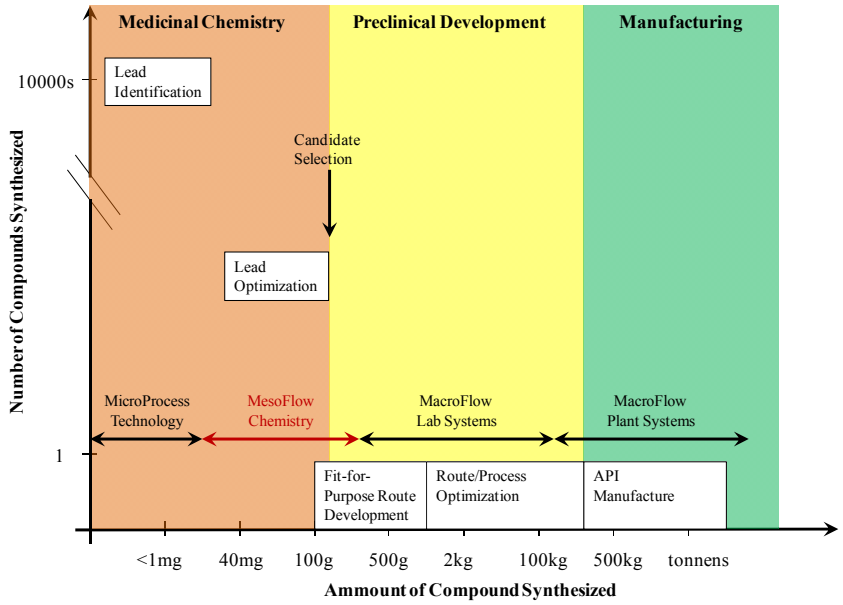


Figure 3.3 Equipment used in the different phases of drug development[307]

3.5.1 Comparison to Microprocess technology

One of the biggest issues in Microprocess technology is to avoid blockages of the narrow flow channels. The state of the art approach was established by Hartman and coworkers[308] who actually used acoustic radiation or periodical flushing in order to avoid bridging and constriction of solid materials in the microchannels. Nevertheless, applications of heterogeneous mixtures in meso-flow chemical devices would significantly decrease the risk of clogging. Along this line of thinking, Cervera-Padrell and coworkers[309] used a mesoscale side entry reactor for completing a Grignard alkylation reaction. In addition, they incorporated manometers in the plant architecture with the main purpose to use them as clogging indicators.

An additional issue in microscale devices is the considerable pressure drop along the channels caused by friction forces between fluids and reactor walls[310]. Applications of increased inner tube diameters in reactor devices – i.e. adopting meso-scale instead of microscale devices – could significantly reduce the pressure drop along reactor channels. However, Wu and Little[311] emphasized that pressure drops could even be significantly higher than the predicted values if gas is used as the reaction medium. Furthermore, Pfahler and coworkers[312] confirmed that flows of liquids led to similar conclusions. It is therefore important to pay special attention to the pressure drop phenomenon in meso- and also micro-scaled devices.

A significantly lower risk of clogging, as well as smaller pressure changes inside reactors are some of the good features related to upscaling of microscale devices. It is however important to note that those issues are not completely avoided in meso-flow chemistry, but their influence is drastically decreased.

Furthermore, there are additional issues present in such mesoscale devices. Wegner and coworkers[194] published a review highlighting ten challenges in meso-flow chemistry. They emphasized that flow capacitates in mesoscale channels play an important role for the further development and implementation of such devices. Indeed, the increased dimensions cause higher flow capacitaties compared to Microprocess technology and consequently increase the amount of synthesized products. Nevertheless, a large scale production in this type of devices would still need scale-up or scale-out activities.

Surface-to-volume ratios in meso-flow chemistry could cause small issues with heat transfer and precise temperature control. The surface-to-volume ratio values typical for meso-flow chemisty could be as low as 10000 $\frac{m^2}{m^3}$, which is around 5 times lower compared to microscale equipment. Nevertheless, mesoscale equipment still shows a significantly better performance than batch chemical processes. For instance, surface-to-volume ratios could go down to 5 $\frac{m^2}{m^3}$, if batch chemistry is applied[194, 262].

The dimensionless numbers for the evaluation of heat and mass transfer inside meso-flow channels are the same as in the microscale devices. Laminar flows are still desired due to all advantages which they bring. Moreover, mixing performances are usually lowered by switching from micro- to meso-scaled equipment, but they could be improved by using additional equipment, such as static mixers[313].

3.5.2 Applications of meso-flow chemistry

Plenty of practical examples of mesoscale equipment have been published in the literature. Wegner and coworkers[194] collected different applications in modern organic synthesis and classified them in five different categories:

- chemical reactions with reactive intermediates (fluorinated compounds, ozonolysis, monolithiation);
- chemical reactions with supported reagents (scavenger and monolithic applications);
- chemical reactions with supported chemical catalysts;
- multicomponent chemical reactions (Petasis reaction);
- photochemistry.

However, scale-out of such manufacturing processes is important if increased production volume is the main goal. As depicted in Figure 3.3, macro-flow lab and plant systems are the further steps. Therefore, a very common approach to increase production volume is to design shell-and-tube systems with adequate mesoscale chemical reactors. In addition, suitable static mixers for improved mass and heat transfer in the channels could be applied. This scale-out approach leads to plenty of economic benefits, as nicely explained by Nauman and coworkers[314]. One of the good examples was published by Styring and coworkers[315] who successfully performed cross coupling reactions. More precisely, they used a fixed-bed meso-flow reactor in parallel for Kumada reactions. An additional example process was implemented by Bonfils and coworkers[316] who tested Michael reactions in tubular reactors with a fluid-bed of beads. This is an interesting approach because avoidance of clogging was successfully demonstrated.

3.6 Ultrasounds in organic synthesis

Since the discovery of ultrasounds in the late 19th century, they have been receiving increased attention in everyday life and industry. They are labeled as a versatile tool which has been applied for plenty of different purposes – from the underwater sonar for submarines[317] to sterilization of water, for improving electroplating, for production of face creams and so on[189].

The ultrasound frequency region is in the area of frequencies which are too high for the human ear (Figure 3.4). Conventional power ultrasound is a sub-region in the interval of frequencies that spans from 20 kHz to 100 kHz. It has the highest importance for scientific applications because it is used in organic chemistry and additionally in cleaning procedures. Furthermore, higher frequencies (above 1 MHz and more) are typically used for medical applications, such as echocardiography, or for treating cancers, and so on[189]. The main focus here is on the conventional power ultrasound and its recent use in organic synthesis, with emphasis on applications in the pharmaceutical industry.

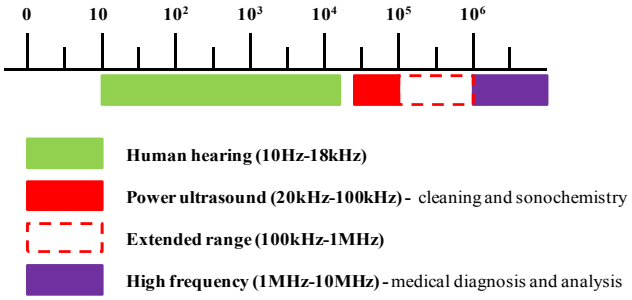


Figure 3.4 Frequencies of sound with defined subgroups and potential applications[318]

3.6.1 Theoretical background

In order to generate ultrasounds, it is necessary to perform mechanical work on the propagation medium. Hence, there are two different possibilities which are usually applied:

- magnetostriction:
- usage of the piezoelectric properties of some materials.

Magnetostriction is based on metal contraction activities. Hence, an electric current is passing through a wire which is rolled around a nickel cylinder and thereby induces a magnetic field. Besides nickel, other magnetostrictive materials could be used – such as oxides of iron, nickel, lead and zinc. A major issue in working with all of the mentioned materials is that they face issues at ultrasonic frequencies due to Foucault induced currents (loss of energy in the form of heat). However, this problem is avoided by using oxide slices as voltage transformers and consequently acoustic frequencies up to 120 kHz can be emitted.

The second phenomenon is called piezoelectricity. In the early beginnings it was based on direct effects caused by mechanical stresses of quartz which was becoming electrically polarized. Nowadays, a reciprocal process is used because of the significant enhancement of oscillations. Pioneering work was based on putting a quartz crystal between two steel slices and using resonance frequencies. Those attempts were further explored and quartz was replaced with other materials, such as: ferroelectric ceramics, then barium titanate ($BaTiO_3$), synthetic crystals of lithium niobiate ($LiNbO_4$) or lead zirconate titanat ($PbTiZrO_3$). Applications of this method have shown great benefits in modern organic synthesis[319].

Hence, acoustic waves are actually pressure waves made by compression and rarefaction. They are able to break intermolecular van der Waals forces and maintain cohesion of liquids. More precisely, gas-filled microbubbles start to grow in the closeness of inhomogenities and afterwards big bubbles collapse under the actions of destabilizing Laplace forces[320]. This phenomenon is called cavitation.

Cavitation could be divided in two different types:

- stable cavitation;
- transient cavitation.

There are no major differences between both. More precisely, stable cavitation occurs when micro-bubbles contain gas and their mean life is much longer than a cycle of the ultrasound. As long as the microbubble grows, its resonance frequency is higher than the frequency of the ultrasound. Consequently, they are driven into pressure antinodes where chemical reactions are actually induced. On the other hand, transient cavitation has a shorter duration because a cavity is rapidly formed containing mainly the vapor of the liquid. The cavity vigorously collapses after a few cycles leading to plenty of released energy[318]. Transient cavitation is very common in organic synthesis.

It is important to note that there are several factors which have a strong influence on the cavitation phenomenon. They are:

- properties of solvents, such as viscosity, volatility, surface tensions, as well as ability to generate radicals;
- ultrasonic frequency whose increase causes a decrease of the cavitation effect;
- acoustic power – during the power supply to the reaction medium, reaction rates increase up to a certain level and then rapidly decrease;
- gas type and content – gases with higher specific heat ratio and thermal conductivity give better cavitational effect;
- external temperature – the sonochemical effect is usually decreased if temperature is increased;
- external pressure – if pressure is increased, then the cavitational effect is also increased[317, 320].

Chemical effects of ultrasounds are based on the thermal theory, or so called “hot-spot” formation. More particularly, formation of “hot-spots” occurs during the collapse when temperatures up to 5000 K and pressures up to 1700 bars can be achieved. Hence, a huge amount of energy is usually released and consequently generation and stabilization of reactive species is obtained[320]. A schematic representation of this phenomenon is depicted in Figure 3.5.

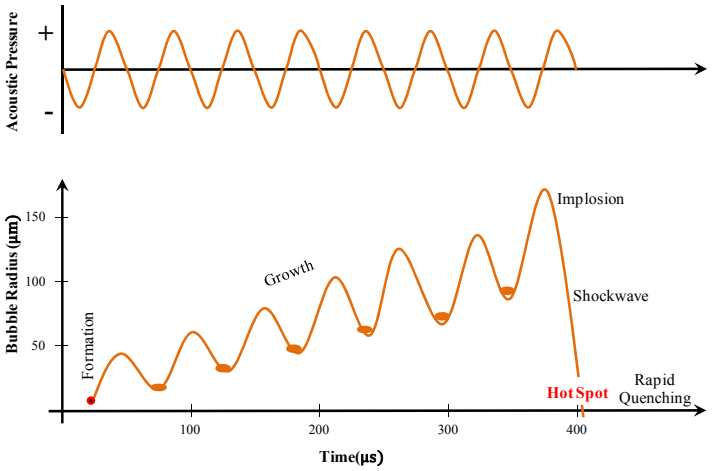


Figure 3.5 Schematic description of the transient cavitation phenomenon[321]

It can be seen that growth of microbubbles and afterwards the explosion of a big bubble take place in a time range of microseconds. Hence, a considerable amount of energy can be released very fast, leading to continuous delivery of energy.

It is important to emphasize that the influence of the ultrasounds should be separated as following:

- mechanical effects;
- sonochemcial effects.

In the first category, it could be enough just to implement ultrasonic pre-treatment and afterwards conventional chemical reaction would be performed. One of the interesting examples was realized by Roberge and coworkers[322] who used ultrasounds in order to avoid plugging of a continuous reaction channel system, and additionally to avoid clogging of microreactors. Hence, ultrasounds seem to be a very suitable tool for work with slurries.

If the effect is sonochemical, then ultrasounds have to be supplied in order to perform chemical reaction. The main principle is based on the diffusion of volatile compounds inside the formed bubble which breaks and causes breakage of bonds of molecules in a homolytic manner. The formed radicals are then sent in the bulk phase where they react further. This is typical for homogeneous mixtures. However, if heterogeneous systems are present, the sonochemical activation is a consequence of the mechanical effects of cavitation. More precisely, a liquid jet propagates in the phase boundary with a speed of several hundred meters per second. It hits the surface violently and causes very intensive mass transport. Hence, emulsification usually occurs if liquid-liquid systems are present whereas particle breakages occur if the reaction medium is a liquid-solid system[320].

3.6.2 Applications of ultrasounds in organic synthesis

The first clues about the chemical effects of ultrasounds were discovered by Richards and Loomis[323] at the end of the first quarter of the 20th century. However, further investigations were performed by Renaud and coworkers[324] in the 1950s who applied ultrasounds in organometallic chemistry. More precisely, they performed synthesis of several organic compounds with magnesium. After this discovery, plenty of additional applications have been discovered.

The main reasons for the increased application of ultrasounds in modern organic synthesis are related to the many advantages that can be achieved. Some of the advantages are:

- decrease of reaction time and/or increase of yield;
- lower reaction temperatures;
- chances to change reaction pathways;
- avoidance or decreasing phase transfer catalysis;
- usage of crude or technical reagents;
- metal activations;
- reduction of induction products;
- enhancement of substrate reactivation;
- formation of usful reaction species[325]

As described in section 3.6.1, it is important to clarify the influence of ultrasounds on chemical reactions. Hence, if the effect is just mechanical, then usually some physical issues are the main aim, such as: avoiding clogging, establishing easier flows, better mass transport in heterogeneous mixtures, and so on. However, if the sonochemical influence is important, then the presence of ultrasounds is essential for further reaction processing. Some of the common examples are within electrochemistry, enzyme activations and polymer synthesis[326]. Plenty of applications have been published in the literature with the main focus on the organometallic chemical reactions. Moreover, catalytic reactions, then sonoelectrochemistry, cycloadditions, reactions with biphasic systems etc., have been widely applied, as well[319].

From the process-engineering perspective, it is interesting to investigate how ultrasounds could be implemented in manufacturing modes. There are many different equipment designs which could be used[179]. Nevertheless, one of the cheapest and simplest approaches is to apply cleaning baths. However, they usually have insufficient intensity for sonochemical applications, but they are useful if just mechanical influence is desired. The most common approach is when liquid-solid reactions are carried out together with passivated and reactive solids[327].

Furthermore, more sophisticated designs have been tested. An ultrasonic titanium horn driven with a piezoelectric transducer could be used as a source of ultrasounds. It is usually immersed in stirred glass reactors with inlets and outlets[328]. One of the published examples is the synthesis of nanostructured materials[327]. Furthermore, there is a possibility to put several transducers in a continuous stirred tank reactor and obtain larger scales. More precisely, at least six ultrasonic transducers could be placed inside the reactor wall whereas three or less could be at the bottom of

the CSTR. Such a design was made by Berger and coworkers[329] who succesfully tested ultrasounds with different inorganic and organic chemical reactions on larger scales[330].

The main focus here is to perform manufacturing in the continuous mode. One of the first ideas was actually similar to the large scale microwaves – usage of specifically designed external loops. The main approach is to use big reactors as reservoirs, whereas mounted transducer[331] or probe systems[332] were applied in the flow loop in order to generate ultrasounds.

Such apparatus with a loop could be considered as the pioneering work for continuous flow applications. However, different and more sophisticated designs were developed for tubular reactors. One of them is based on the probe system and was suited for multiphase reactions[188] whereas several approaches with mounted transducers were reported as well[179].

3.7. Chemical catalysis and biocatalysis in organic synthesis

Chemical approaches are mostly based on chemical catalysis and biocatalysis. The first operational tool is usually applied for acceleration of slow chemical reactions and consequently easier adaptation to continuous manufacturing modes. However, there are plenty of disadvantages in such chemistries due to the very challenging downstream processing (expensive and times consuming procedures for removing transition metals). Furthermore, biocatalysis is one of the more environmentally friendly approaches, but still in a development phase. As a consequence, usage of very expensive reagents is demanded which is considered an obvious drawback.

The main focus here is to give a brief overview about applications of chemical catalysis and biocatalysis in organic synthesis emphasizing their influence on pharmaceutical production. It is important to note here that a full implementation of the PAT concepts could be achieved if those chemical approaches are combined with the physical approaches described in the previous sections.

3.7.1 Chemical catalysis in organic synthesis

Chemical catalysts are defined as "substances that when present in reaction mixtures increase reaction rates without itself being consumed"[180]. Their main purpose is to decrease the activation energy in chemical reactions and to increase atom efficiency. As a consequence, the E-factor is decreased also due to significantly decreased amounts of waste[333].

The main focus here is on transition metals and their applications in organic synthesis. Focusing on the pharmaceutical industry, there are hundreds of chemical reactions catalyzed by those metals. Many comprehensive reviews have been published in the literature[180], however there is still plenty of research on this topic, especially in the drug discovery area[334].

The exact number of chemical catalysts based on transition metals is unknown, but it is certainly very high. They could be classified in many different categories according to many different

criteria. However, the most basic classification is to distinguish between homogeneous and heterogeneous catalysis. The latter is usually preferred due to easier downstream processing or even total avoidance of the downstream processing. Moreover, there are nowadays several immobilization procedures known and widely applied in organic synthesis with the main purpose to "heterogenize" homogeneous catalysis[335, 336].

Furthermore, there are many new chemical reactions with very sophisticated organometalic catalysts which cannot be immobilized that easily. Good examples are cross-coupling reactions which are playing a prominent role in the pharmaceutical industry. Besides chemical catalysts, they usually involve sophisticated organic or organometallic ligands and therefore cause plenty of difficulties during the immobilization. A detailed overview about practical applications of several types of cross-coupling reactions was recently published by Nishihara and coworkers[182].

Heterogeneous catalysis is additionally a good initial point for establishing cleaner technologies, especially if leaching of transition metals is completely avoided[337]. This is one of the steps in fulfilling the requirements that have to be met for a green chemistry approach, something that is receiving increased attention in the pharmaceutical industry[338]. Besides the use of heterogeneous catalysis, there are additional approaches to fulfill the green chemistry requirements, such as a good solvent selection[339-342], better analytical instrumentation[343], and so on[344].

3.7.2 Biocatalysis in organic synthesis

Biochemical reactions are defined as providers of the metabolism of all living cells. They are usually catalyzed with enzymes which are defined as "protein molecules that have evolved to perform efficiently under the mild conditions required to preserve the functionality and integrity of the biological systems"[345]. In addition, their applications involve several advantages and usually are labeled as a "green technologies". Nevertheless, there are still some challenges which have to be solved in order to further expand applications of such reaction promoters. A brief overview about benefits and challenges of biocatalysis is provided in Table 3.5.

Table 3.5 Advantages and disadvantages of enzyme applications[345, 346]

Advantages	**Challenges**
High regio-, stereo- and chemo-control	High molecular complexity
High activity under moderate reaction conditions	High production costs
High turnover numbers	Intrinsic fragility
Highly biodegradable	
Considered as natural products	

Enzymes are naturally made to work under physiological conditions, i.e. at moderate temperature, pH, pressure and ionic strength. However, there are many research project nowadays whose main purpose is to adapt them to process applications (artificial conditions – in vitro), especially to harsh reaction conditions common in the chemical process industry[345]. In order to resolve those problems, there are different approaches under investigation:

- chemical modifications of enzymes;
- immobilization on solid matrices;
- crystallization and aggregation;
- site-directed mutagenesis and tandem mutagenesis;
- polymerization assisted gene-shuffling;
- ligase assisted recombinations[345].

There are plenty of successful attempts to establish industrial applications of biocatalytic processes. High fructose corn syrup processes, production of semi-synthetic penicillins, L-amino acids are just some of the examples. Major challenges for future applications could be related to the increase of the molar concentrations of reaction constituents in order to perform comparably to traditional organic syntheses, as well as to increase applications in production of effect chemicals (surfactants), biopharmaceuticals and biofuels[347, 348].

3.8. Change or modification of synthetic routes in organic synthesis

Although the 12 principles of green chemistry[344] emphasize that catalysis is a desired choice to be applied, there are many influential factors pushing towards a change of current transition-metal catalyzed synthetic routes to obtain desired products. The main reasons are linked to the high toxicity of transition metals and thereby their undesired appearance in pharmaceutical products[184]. In addition, very expensive and time consuming purification processes should be avoided leading to economic benefits for the overall production process.

Avoidance of transition metals would therefore be a desired choice, but keeping good atom efficiency, as well as good E-factor values in the absence of chemical catalysts is a very challenging approach. Good examples are mentioned in section 3.2 where a switch from transition metal chemistry into Grignard chemistry was indicated[185, 186]. This last approach is still not very environmentally friendly, but it includes of economic and process-engineering benefits. More precisely, reaction mixtures are simpler and therefore real-time process monitoring is easier. Furthermore, chemical reactions are transformed from being very endothermic into very fast and exothermic reactions with comparable yields. The latest would certainly have plenty of economic advantages due to simpler downstream processing and the use of cheaper reagents. Besides changing the chemistry, a good approach is also to use suitable solvents as reaction promoters when relevant. An example was published by Bolliger and coworkers[349] who accelerated C-N cross coupling reactions without using any transition metals. However, a very environmentally unfriendly solvent was applied (dioxane) in very clean reaction conditions (glovebox).

Nevertheless, the main purpose of changing synthetic routes is to try to adapt new approaches to the issues typical for the chemical-process engineers. Hence, short reaction times, then simpler reaction mixtures for easier real-time process monitoring, avoidance of complicated downstream processes, are just some of the main goals for changing synthetic routes.

3.9. Development of the PI strategy

The PI strategy for adaptation of slow chemical reactions to continuous manufacturing modes is shown in Figure 3.6 and it is mostly suited for the applications on lab scale. It is important to note that homogeneous chemical reactons are mostly considered (liquid phase preferably), but liquid-solid, liquid-gas and solid-gas systems could also be involved in such a decision making procedure.

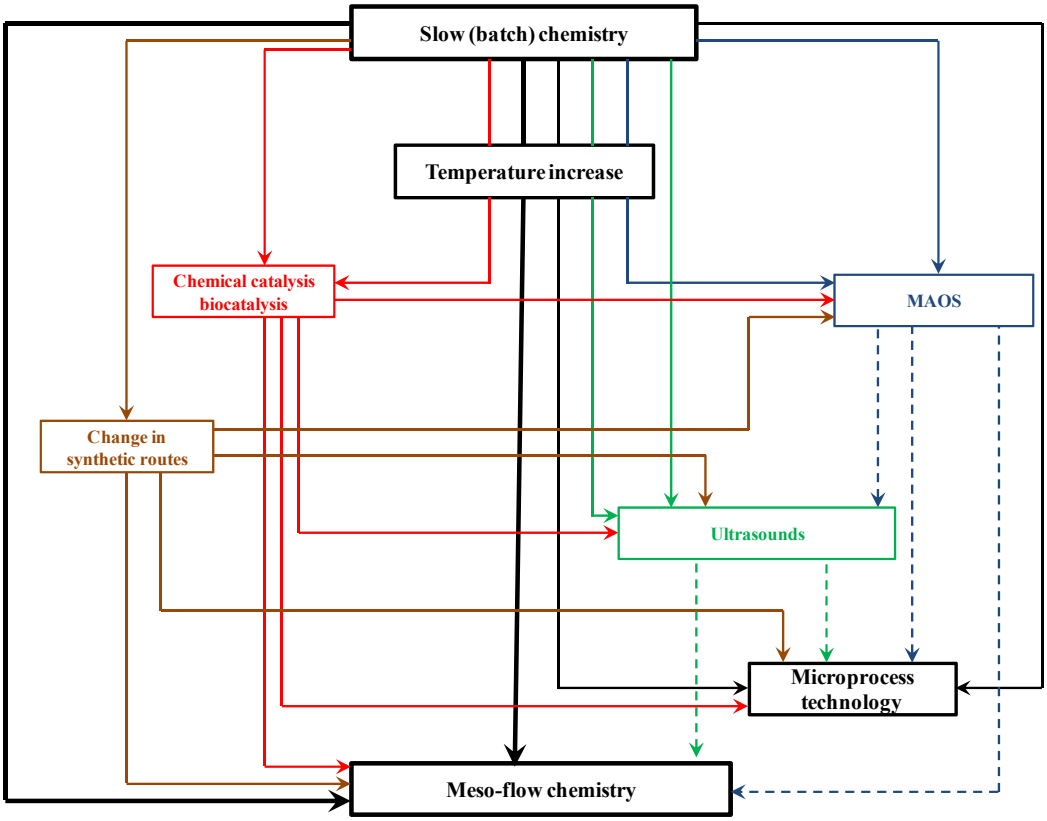


Figure 3.6 PI strategy for accelerating slow chemical reactions. Each colour represents an operational tool suitable for performing acceleration. Chemical approaches are depicted on the left hand side whereas physical approaches are on the right side. Suitable combinations are depicted with solid and dashed lines.

The most desired and at the same time the simplest approach is to perform a direct transformation of batch processes into meso-flow chemistry. The main purpose is to increase production process performance due to intensified mixing capabilities and improved heat transfer due to higher surface-to-volume ratios. At the same time, successful implementation of the PAT requirements could be accomplished, as well as easier scale-out and larger production capacity. This path is depicted with the thickest black line in Figure 3.6 connecting slow (batch) chemistry to Meso-flow chemistry.

Despite the relatively simple and straightforward transition to meso-flow chemistry, it is also possible to achieve additional improvements by applying some specific changes. For instance, further accelerations are possible on the basis of the Arrhenius equation. More precisely, a rise of the reaction temperature would probably lead to an increase of reaction rates and lower reaction times. However, it is important to pay special attention to side reactions, as well as to the stability of final products. This path is also coloured with a black thick line in Figure 3.6 and passes through the field "Temperature increase". A practical example of such a process intensification path is described in section 5 of the thesis.

Furthermore, if mass and heat transfer achieved with meso-flow chemistry are not good enough, the application of Microprocess technology, then MAOS or ultrasounds are good choices. These choices are coloured black (thinner), blue and green lines in Figure 3.6, respectively.

Application of Microprocess technology is very suitable for exothermic chemical reactions when heat removal should be done efficiently. Moreover, endothermic reactions could also benefit from microscale devices if sensitivity to temperature changes is present or if requirements for intensified mixing operations are demanded. The best way to evaluate the suitability of Microprocess technology for applications in organic flow chemistry is to check values for the following criteria: Bo, Re, Pe, τ_D and Da which values typical for Microprocess Technology applications are depicted in Table 3.6.

Table 3.6 Parameters for Microprocess technology applications

No.	Requirement	Explanation	Ref.
1.	Bo<1	Domination of surface forces	Kumacheva and Garstecki[269]
2.	2<Re<200 1<Re<1000	Presence of laminar flows	Taghavi-Moghadam and coworkers[263] Jähnisch and coworkers[264]
3.	Pe<1	Intensified micromixing	Hartman and coworkers[267]
4.	τ_D~ms	Very good micromixing	Bessoth and coworkers[268]
5.	Da>1	Dominant mass transport	Hartman and coworkers[267]

A very nice methodological approach was developed by Hartman and coworkers[267] who proposed three different levels in order to evaluate suitability of the Microprocess technology for process chemistry purposes. Their checklist includes mass transport at the first place. If it is a phenomenon which leads a chemical reaction to the completion, then a condition depicted in Table 3.6 entry 5 has to be satisfied. However, if the chemical reaction is not limited with the mass transfer, then heat removal is taking an important role. If none of the mentioned criteria are important, influence of dispersion on kinetics should be analized. Hence, entries 1 and 3 in Table 3.6 should be in the main focus. Therefore, if none of those criteira has influence on reaction kinetics, chemical reactions would not achieve any benefits in the microscale equipment. Consequently, focus on different colours in Figure 3.6 should be done.

The next operational tool to be considered is MAOS. This is a very popular approach in modern organic synthesis. The most important criterion is the loss tangent angle which requires values around unity or higher for good practical applications. In this way a successful absorption of the microwave energy would be performed. Nevertheless, if such criterion is not satisfied, trials with using "microwave radiators" could be done. This approach should be considered with special caution due to possible reactivity of additives with reaction mixtures. MAOS applications in the organic synthesis follow almost the same path as the previous two operational tools – either a direct transition from batch chemistry to MAOS could be applied or with included temperature rise as a middle stop (solid blue lines in Figure 3.6).

Last operational tool based on physical effects is applications of ultrasounds. This tool is very practical for working with slurries and viscous liquids in flow regimes. A type of reaction medium is important for the implementation of such operational tool. However, additional advantages in the sonochemical manner should be taken into account, as well. Nevertheless, applications of ultrasounds are coloured green in Figure 3.6 and could follow the same path as the previous three operational tools (direct transition or with the increase of reaction temperature).

Avoiding disadvantages related to the use of certain operational tools independently could be achieved by making suitable combinations between the tools. It is important to note that the main aim of the PI implementation strategy here is to fulfil requirements defined in the PAT Initiative. Hence, MAOS and application of ultrasounds might not be considered as the final steps due to the fact that there are plenty of potential difficulties from a PAT point of view (fast real-time process monitoring and control, for instance).

The first example of the combined tools is the combination of MAOS and meso-flow chemistry. In this particular case, it is crucial that reaction media fulfill the criteria for applying MAOS successfully. Hence, values for tanδ should be around unity or higher. There are several potential applications, mainly through coiled, U-tube or just simple tubular reactors in the mesoscale dimensions. The main reasons for the implementation of such a combination might be linked to the improved temperature profiles inside reactors, as well as to easier establishment of in-line process monitoring. This combination is depicted in Figure 3.6 as blue dashed line which starts from the MAOS box and point to the meso-flow chemistry.

Furthermore, it should be noticed that an additional blue dashed line could go from MAOS to the ultrasound text box. This combination involves three or more physical approaches and should use advantages of all of them. More precisely, green dashed lines connectes the ultrasound field with Meso-flow chemistry and Microprocess technology. Hence, combinations of MAOS, ultrasounds and either meso- or micro- sized devices is possible.

Combinations of MAOS and Microprocess technology are also possible. They are not that common in the modern organic synthesis because of the more supported attitude that MAOS and microsize equipment have the same effects on the reaction mixtures (no temperature gradients). Nevertheless, certain examples are present if capillary tubes are used as chemical reactors, such as described in the section referring to the MAOS applications (section 3.3.4). It is important to note that this combination is colured blue in Figure 3.6 which goes directly to the Microprocess technology box.

Combinations of ultrasounds with either meso-flow chemistry or Microprocess technology are also possible. They are colured green in Figure 3.6 and lead from the ultrasound text box to either meso-flow chemistry or Microprocess technology text boxes.

The left hand side of Figure 3.6 describes chemical approaches useful in modern organic synthesis. Chemical catalysis and biocatalysis are colured red whereas the brown colour refers to changes or modifications in synthetic routes. It can be seen that those approaches could be combined with different physical tools (end of red and brown lines) or with more than one physical tool (end of dashed lines). It is important to note that chemical approaches could be applied in batch mode as well, but if that is the case, the implementation of PAT would faces plenty of challenges.

Many chemical reactions are very dependent on application of chemical catalysts and biocatalysts. Hence, several examples are mentioned in section 3.6 whereas many practical applications of MAOS, Microprocess technology, meso-flow chemistry and ultrasounds were given that also involve chemical catalysts in either homogeneous or heterogeneous forms.

Changes in synthetic routes are mostly linked to finding more suitable reaction pathways with respect to reaction rates, yields of desired products and additionally PAT requirements. Hence, switching from C-S and C-N cross-coupling reactions into Grignard chemistries is a great example of such chemical tools. In this way, chemical reactions are accelerated from hours to milliseconds making them very suitable for meso-flow chemistry, for instance. Those examples are described in section 3.2 and 3.8.

3.10 Conclusions and future perspectives

The PI Strategy is a major driver in further development of the pharmaceutical production with the main focus on MAOS, Microprocess technology, meso-flow chemistry and ultrasounds as operational tools. All those "physical approaches" are very applicable in the modern organic synthesis because of their capability to accelerate slow batch chemistries and adapt those to continuous manufacturing modes. Furthermore, chemical catalysis and biocatalyis, as well as modifications or changes of the synthetic route to the final products, are additional tools which have been widely applied and are often used in combination with "physical approaches".

Dimensionless numbers, such as Bo, Re, Pe, and Da on the one hand, as well as tanδ on the other hand, are good indicators for making choices about which operational tool to apply. The application of ultrasounds is also considered as very important because of its good influence on processing very heterogeneous or viscous reaction mixtures. It is important to note that modern organic synthesis often deals with the mentioned reaction mixtures and thereby mechanical effects of ultrasounds are receiving more attention.

However, the state of the art understanding of "physical approaches" still has a lot of space for expansion. For instance, the influence of the MAOS on chemical reactions is still not clear enough due to the two completely different mainstream theories about microwave effects on chemical reactions. Furthermore, the loss tangent angle is not the best way to compare different reaction mixtures because of its unstable values if reaction conditions are changed (temperature, pressure, and so on). Hence, development of more stable mathematical expression should be one of the priorities in the MAOS.

Focusing on Microprocess technology, it is important to note that a lot of work has been done in this field. However, there are still major issues in establishing long lasting and stable processes with heterogeneous mixtures. Despite clogging issues, a good approach might be to focus on easier scale-out of such equipment. One idea is to perform scale-up and use meso-flow chemistry, but some of the good features dominant in the micro-scaled devices might be lost or have weaker influence.

Furthermore, different combinations of operational tools have shown to be a great choice for avoiding the disadvantages of specific operational tools. However, economic evaluations of such combinations put certain limitations to application for large scale productions.

4. Implementation of the Lean Production System and Process Intensification strategy on the case studies

Abstract

Acceleration of slow chemical reactions is a desired approach in the modern pharmaceutical industry. Implementation of the process intensification or process optimization tools is a suitable approach for adapting slow chemical reactions to continuous manufacturing modes. In addition, a considerable number of supportive activities could be excluded in case of achieving the desired reaction rates and selectivities in the crucial steps of the production. For instance, storing intermediates, crystallization steps, distillation steps, filtration steps, and so on, could be avoided. The main focus here is to summarize PI and PO tools used in the manufacturing of two different products: Clopenthixol and (2-Bromophenyl)(phenyl)sulfane. A rough analysis from the LPS perspective is additionally included with the main focus on using "Manufacturing Flow" and "Process Control" elements of the LPS. Hence, elimination of non-value added activities is performed as a consequence of achieving acceleration and increased selectivities in the crucial manufacturing steps.

4. Implementation of the Lean Production System and Process Intensification strategy on the case studies

4.1. Introduction

The pharmaceutical industry is constantly facing issues with long reaction sequences, slurries, by-products, undesired impurities, and so on. It is therefore necessary to include purification steps, storage of intermediates and additional non-value added activities in the overall process flow scheme. Such approaches are usually time consuming and represent additional capital investments.

Implementation of the PI and PO tools could significantly decrease the number of undesired activities in pharmaceutical manufacturing. Plenty of improvements could be achieved by using microwave assisted organic synthesis, ultrasounds, mesoscale flow chemistry and microscale equipment. Furthermore, slight modifications of the traditional equipment, such as introducing extensions to CSTRs in the form of tubular reactors, then applications of external or recycle loops, could bring several benefits as well. As a consequence, supportive actions could be considered as non-value added activities, and thus they could be excluded from the overall process flow schemes. In this way, two segments of the Lean Production System would be implemented – "Manufacturing Flow" and partly "Process Control".

The main focus of this chapter is on describing traditional and new manufacturing routes to two different products: Clopenthixol and (2-Bromophenyl)(phenyl)sulfane. The main aim is to implement PI and PO tools from the LPS perspective. Hence, process flow schemes should involve a minimized number of unnecessary non-value added activities. Plenty of economic benefits would be achieved in this way combined with smoother manufacturing of the desired APIs and API intermediates.

4.2 Clopenthixol production

Clopenthixol or 4-[3-(2-Chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol is a thioxanthene compound which appears as a mixture of two stereo-isomers. The cis-isomer of Clopenthixol is the desired API because of its high medical activity in the central nervous system. It is additionally named Zuclopenthixol and it is an internationally well-known product of H. Lundbeck A/S. The most common use of this API is to treat schizophrenia and mania[350]. Its chemical formula is depicted in Figure 4.1 (a) whereas the trans-isomer of Clopenthixol is depicted in Figure 4.1 (b). The trans-isomer is considered as a by-product.

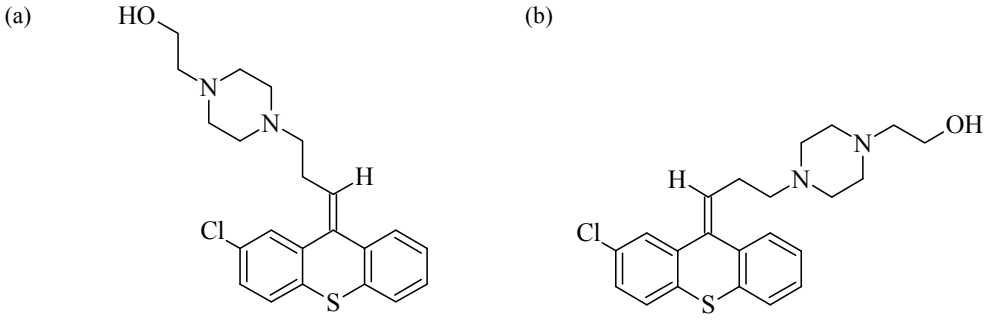


Figure 4.1 Clopenthixol or 4-[3-(2-Chlorothioxanthen-9-ylidene)propyl]-1-piperazineethanol isomers: (a) medically active cis-isomer (Zuclopenthixol) and (b) medically inactive trans-isomer

4.2.1 Synthetic route towards Clopenthixol

Tue synthetic route to Clopenthixol involves four chemical reactions which are grouped in two different sections. The first section is exothermic and it includes fast and exothermic chemical reactions which are usually difficult to control and optimize. These chemical reactions occur already in the mixing zones and can potentially cause formation of by-products. The second section includes slow and endothermic chemical reactions which should be accelerated without using any transition metals.

4.2.1.1. Exothermic section

Exothermic section is the initial part in the Clopenthixol synthesis. It involves Grignard alkylation and hydrolysis which are both performed in tetrahydrofuran (THF).

Substrates in the Grignard alkylation are 2-Chlorothioxanthene-9-one (CTX) and Allylmagnesium chloride. Titration of the carbonyl compound with the Grignard reagent is performed at 25-30^{0}C. It leads to the API intermediate called "Alkoxide". This product is rather unstable under the mentioned reaction conditions and should therefore immediately undergo the next synthetic step. Hence, hydrolysis with aqueous acetic acid is performed which leads to 9-Allyl-2-Chlorothioxanthen-9-Ol ("N714-Allylcarbinol") and magnesium salts as by-products. The chemical reactions are shown in Figure 4.2.

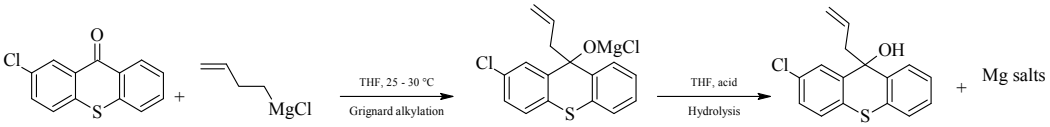


Figure 4.2 Exothermic chemical reactions in the Clopenthixol synthesis: Grignard alkylation between CTX and Allylmagnesiumchloride and consequent hydrolysis of the intermediate product into "N714-Allylcarbinol"

Production of "N714-Allylcarbinol" is the last chemical reaction in the exothermic section. Liquid-liquid separation should be performed after the hydrolysis in order to prepare the intermediate for the second phase of the synthesis (endothermic section).

4.2.1.2 Endothermic section

The endothermic section begins with the dehydration of "N714-Allylcarbinol" to cis/trans - 9H-Thioxanthene, 2-chloro-9-(2-propenylidene)-(9CI) or "N746-Butadienes". The chemical reaction is performed in toluene by using acetic acid anhydride and acetyl chloride, or in THF by using cheap Brøndsted acids (hydrochloric or sulphuric acid). The chemical reaction is shown in Figure 4.3.

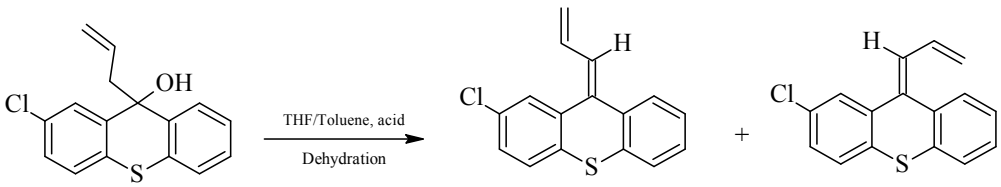


Figure 4.3 Dehydration of "N714-Allylcarbinol" into two stereo-isomers (cis/trans) of "N746-Butadiene"

This step is considered as the crucial step in the overall synthesis of Clopenthixol due to the undesired stereo-selectivity. More precisely, the chemical reaction is more selective towards the trans-isomer of "N746-Butadiene" and consequently big losses of Zuclopenthixol are experienced. A better stereoselectivity is therefore desired in order to increase the overall yield of the desired API.

After dehydration, the last synthetic step involves a very slow hydroamination reaction between "N746-Butadienes" and 1-(2-hydroxyethyl)piperazine (HEP). The chemical reaction is depicted in Figure 4.4 (a) for the cis-isomer (Zuclopenthixol) and in Figure 4.4 (b) for the trans-isomer. The recommended synthetic way excludes the usage of solvents. The final API appears in a black box in the figure.

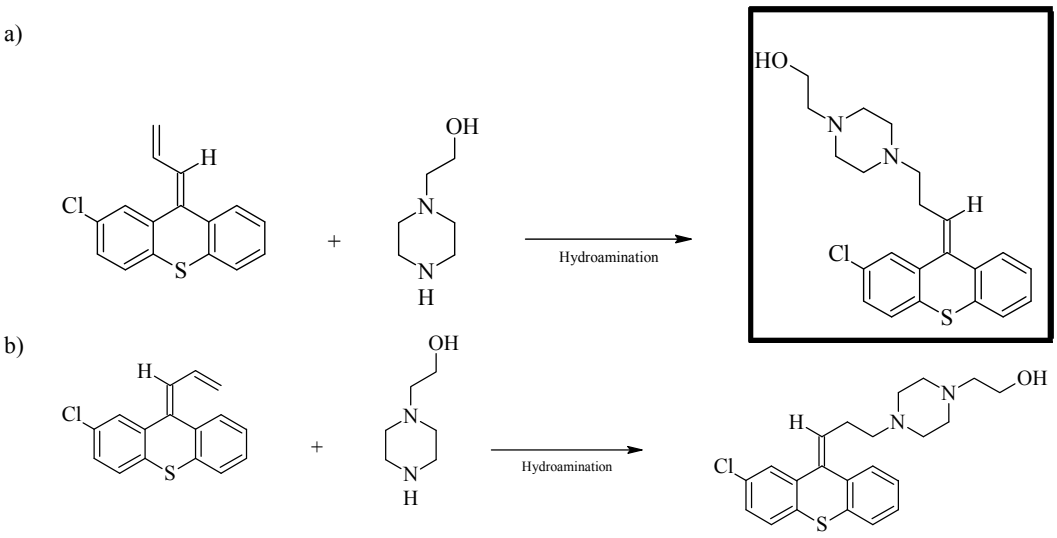


Figure 4.4 Hydroamination reaction between (a) cis-"N746-Butadiene" and (b) trans – "N746-Butadiene" with HEP leading to (a) cis-Clopenthixol (Zuclopenthixol) and (b) trans-Clopenthixol

The endothermic section is completed after the hydroamination reaction. The consequent steps include the purification of the desired API.

4.2.2 Implementation of LPS in the Clopenthixol production

The main focus is to exclude all NVAs from the process flow schemes by implementing PA and PO tools. Hence, "Manufacturing Flow" and partly "Process Control" elements of the overall LPS are implemented in order to modify the traditional batch approach and achieve a continuous manufacturing mode. Economic and more environmentally friendly manufacturing of Clopenthixol is obtained in this way.

Traditional manufacturing is based on using batch reactors with plenty of supportive operations. The overall process flow scheme is divided in two stages, such as depicted in Figure 4.5. It can be noticed that 8 manufacturing steps are needed in order to produce Clopenthixol. Furthemore, storage of intermediates was applied after each step (excluded from the figure).

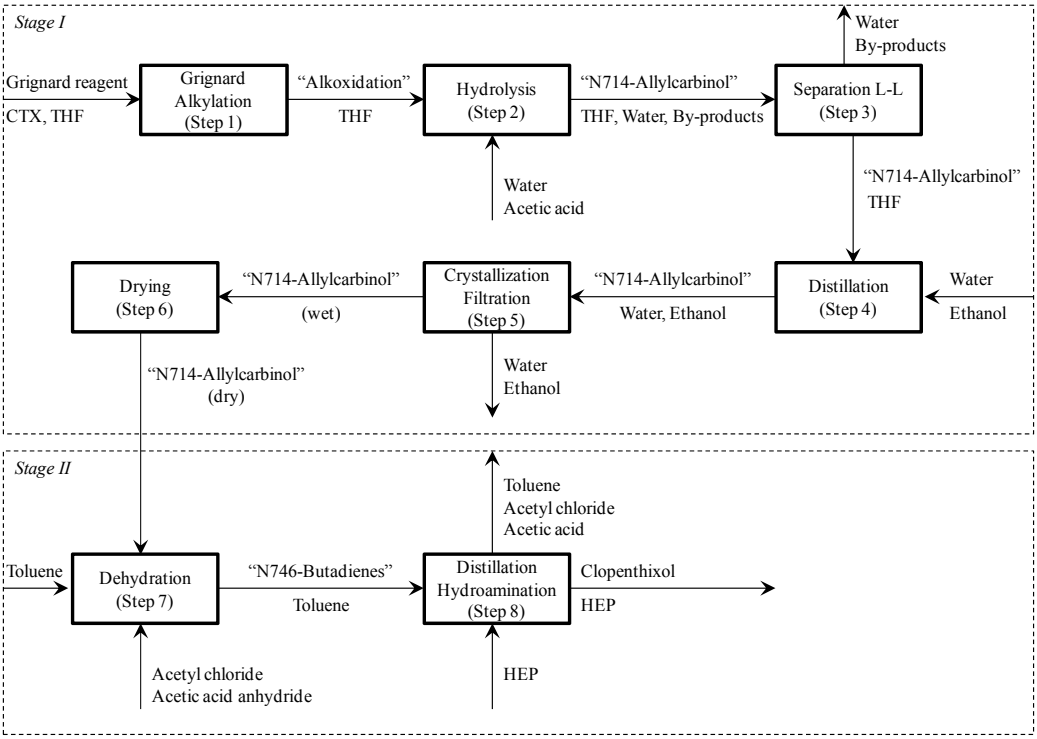


Figure 4.5 Traditional batch manufacturing of Clopenthixol involving two stages and 8 production steps. CTX-, THF-Tetrahydrofuran, HEP

Stage I is focused on the exothermic section. The Grignard alkylation (Step 1) and hydrolysis (Step 2) are performed here together with the purification steps of the obtained API intermediate – "N714-Allylcarbinol" (Steps 3, 4, 5 and 6). The main purpose of the Step 3 is to perform separation

of two partially mixed liquid phases. Hence, aqueous media together with all inorganic impurities is removed by using centrifugal forces. The consequent steps include purification of "N714-Allylcarbinol" in order to remove all organic impurities. The main aim of such sophisticated purification procedure is to decrease the formation of by-products in Stage II. Hence, distillation is performed in order to remove THF (Step 4), as well as crystallization (Step 5) and drying of "N714-Allylcarbinol" (Step 6). In this way, the API intermediate is purified and prepared for Stage II.

Stage II is the endothermic section of the Clopenthixol production. Dissolution of the "N714-Allylcarbinol" in toluene and the dehydration reaction are the initial actions in this stage (Step 7). Acetic acid anhydride and acetyl chloride are used as chemical catalysts in the dehydration reaction, such as indicated previously. After this manufacturing step, a reactive distillation is performed where toluene, acetic acid and acetyl chloride are removed from the reaction mixture whereas "N746-Butadienes" and HEP are used as substrates. The role of the solvent is then taken by the second substrate introduced in this step. As a result, Clopenthixol is produced, but high excess of HEP is usually used. It is important to note that the last two manufacturing steps (Steps 7 and 8) include long reactions times, 2 hours and 24 hours, respectively.

Introduction of the PI and PO tools in the traditional production of Clopenthixol should result in the elimination of several NVAs. First of all, a higher selectivity in Step 1 should be achieved because organic impurities could easily cause the formation of by-products in Stage II. Hence, a CSTR with additional side-entry tubular reactor was introduced. The main aim of the side entry reactor was to implement an improved dosage of the Grignard reagent and additionally to achieve better removal of the heat which was released by this exothermic reaction[309]. As a consequence, the formation of by products was completely avoided in the Step 1.

A further bottleneck in the traditional approach was Step 3. More precisely, continuous separation of THF and water was shown to be a very challenging approach. The main reasons are associated with similarities in the densities of the mentioned solvents and therefore very time consuming separation processes (based just on gravitational forces). Hence, usage of surface forces in a microscale system was applied instead of using traditional gravitational or centrifugal forces. The PTFE membrane separator has been tested successfully[351].

Introduction of the CSTR with a tubular side entry reactor could be considered as a PO tool whereas usage of the PTFE membrane separator is clearly an implementation of the PI approach. These two modifications in the traditional Clopenthixol production caused the elimination of all intermediate storages in Stage I. In addition, elimination of the purification steps 4, 5 and 6 could be done because desired purity of the "N714-Allylcarbinol" was achieved in Step 1.

See from the LPS perspective, it is important to note that the impact of several NVAs was decreased significantly due to the elimination of the intermediate storage in Stage I. Hence, waiting, transportation and excess inventory were eliminated as unnecessary activities. In addition, reduction of defects should also be considered as advantageous because the instability of "N714-Allylcarbinol" in case of long term storages was also avoided. Furthermore, a high reactivity of the

Grignard reagent could also be considered as a defect due to the potential losses when the Grignard reagent is in contact with moisture and air.

Apart from storage of intermediates, a high excess of inventory is present in the purification steps 4, 5 and 6. Elimination of the distillation (Step 4), the crystallization/filtration (Step 5) and the drying (Step 6) was a desired approach. In this way, additional reductions in the time needed for waiting, transportation and motion are achieved. Furthermore, the solvent swap from THF to toluene in Step 7 should be excluded, and also cheap Brøndsted acids should be used for the dehydration step (instead of acetic acid anhydride and acetyl chloride). Therefore, the excess of inventory will be reduced as well. The last production step in the Clopenthixol production would still be based on reactive distillation, but with THF as the solvent which would be removed.

All mentioned modifications lead to the new process flow scheme. This version of the Clopenthixol production route is depicted in Figure 4.6 and named "New Process Flow Scheme I".

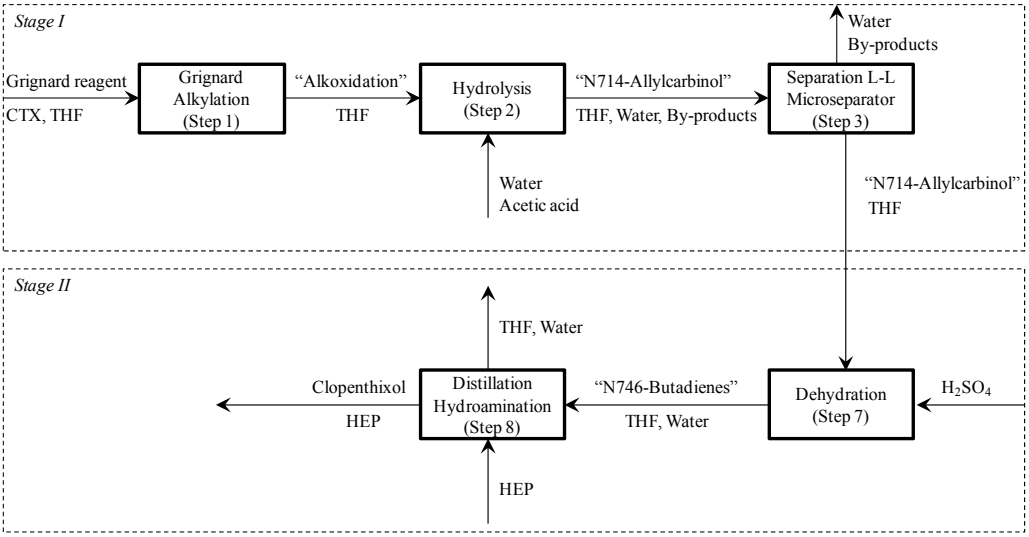


Figure 4.6 "New Process Flow Scheme I " of the Clopenthixol production. The numbers of the different steps in this figure refer to the numbers used in the original flow scheme

Avoidance of NVAs in the Stage I was performed succesfuly[352]. However, Stage II needed further improvements with the main focus on accelerating slow chemical reactions involved in the second part of the synthesis. Therefore, Steps 7 and 8 were still performed in batch modes with the intermediate storage of "N746-Butadienes".

The second round of the LPS implementation involved development of the "New Process Flow Scheme II". The main goal was to accelerate slow chemical reactions and to reduce waiting and transportation as unnecessary NVAs. Furthermore, defects influenced by the intermediate storage of

"N746-Butadienes" should be avoided. In addition, defects might result from the hydroamination step due to the long reaction sequences.

The decison was made to perform dehydration of "N714-Allylcarbinol" at temperatures above the normal boiling point of THF. Hence, increased pressures were applied in Step 7 together with the implementation of a tubular laminar reactor. As a result, acceleration from 2 hours to just 3 minutes was achieved with this PI approach. Furthermore, the hydroamination step included one more PI tool – MAOS. An acceleration of the reaction from 24 h common for reactive distillation towards just 2 h was reached. The resulting flow scheme is shown in Figure 4.7 and is called "New Process Flow Scheme II".

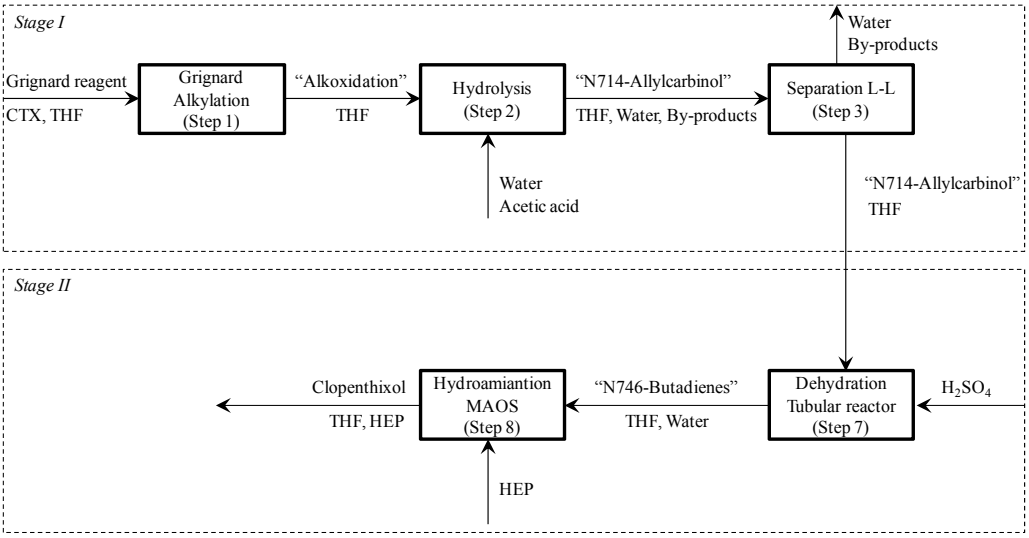


Figure 4.7 "New Process Flow Scheme II " of the Clopenthixol production. The numbers of the different steps in this figure refer to the numbers used in the original flow scheme

However, the "New Process Flow Scheme II" has its own disadvantages. The presence of competitive chemical reactions in the dehydration step together with a high price of the microwave equipment put significant limitations to the practical implementation of such a process flow scheme. Hence, the "New Process Flow Scheme III" is therefore suggested which excludes MAOS but includes neutralization of the Brøndsted acid (Step 9), as well as an additional L-L separation (Step 10). This approach represents a step backward from the LPS perspective due to the increased inventory and waiting time, but the increased yields of the desire API that can be achieved justify this approach. Detailed investigations about side reactions are performed in chapter 5. The "New Process Flow Scheme III" is depicted in Figure 4.8.

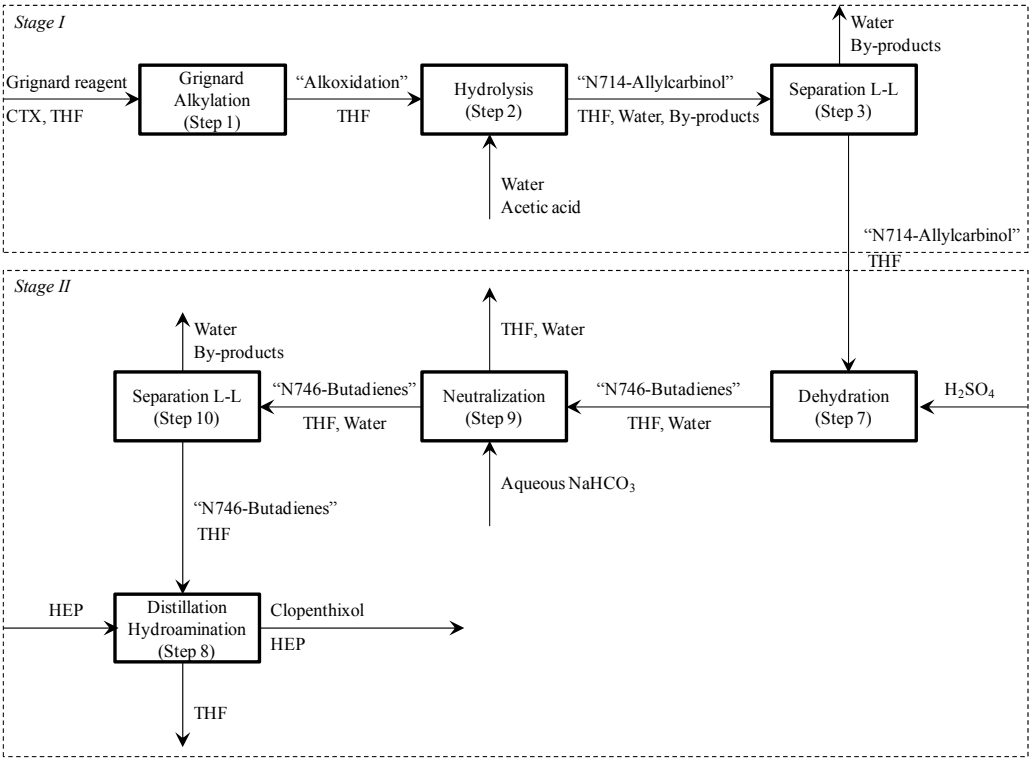


Figure 4.8 "New Process Flow Scheme III " of the clopenthixol production. The numbers of the different steps in this figure refer to the numbers used in the original flow scheme.

In this way, the overall Clopenthixol production is significantly accelerated compared to the traditional batch process. Furthermore, process monitoring, controllability and automation could be applied easier in the continuous manufacturing modes. Different PI and PO tools resulted in a significantly decreased number of NVAs, as well as a faster production of the final API. Space for the additional improvements is always left, of course.

4.3 Production of (2-Bromophenyl)(phenyl)sulfane

(2-Bromophenyl)(phenyl)sulfane is usually synthesized in batch modes by using a Carbon-Sulfur cross coupling mechanism. Application of chemical catalysts based on transition metals, then chemical ligands which could be with or without transition metals and finally very strong bases are considered as a necessity in such nucleophilic substitution reactions[353]. Nevertheless, applications of chlorinating agents and Grignard reagents could be additionally used for producing (2-Bromophenyl)(phenyl)sulfane.[185]

4.3.1 Synthetic route towards (2-Bromophenyl)(phenyl)sulfane

The Synthetic route towards (2-Bromophenyl)(phenyl)sulfane therefore includes two different possibilities. The most common pathway is based on the cross coupling between iodobenzene and 2-bromobenzenethiol, such as depicted in Figure 4.9.

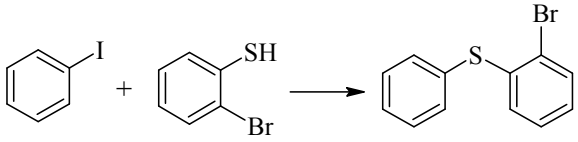


Figure 4.9 Synthesis of (2-Bromophenyl)(phenyl)sulfane by using iodobenzene and 2-bromobenzenethiol as substrates

This chemical reaction is performed by applying chemical catalysts based on either Pd[354, 355] or Cu[356, 357], then variety of chemical ligands and bases. It is important to note that long reaction sequences are usually faced[353].

Apart from the transition metal based approach, there is a chance to use chlorinating agents and Grignard reagents in order to synthesize this API intermediate. More precisely, the chemical reaction between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione would cause the synthesis of 2-bromophenyl hypochlorothioite (Figure 4.10) which would react with phenylmagnesium bromide in order to produce (2-Bromophenyl)(phenyl)sulfane (Figure 4.11).

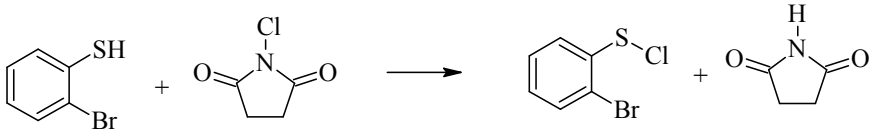


Figure 4.10 Chemical reaction between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione

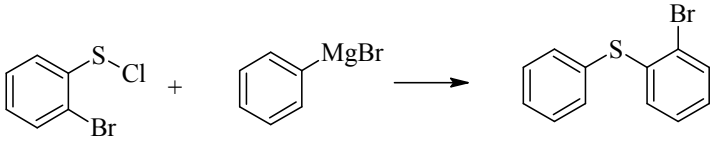


Figure 4.11 Chemical reaction between 2-bromophenyl hypochlorothioite and phenylmagnesium bromide

Synthesis of (2-Bromophenyl)(phenyl)sulfane would therefore be completed without using any transition metals, which would consequently result in cheaper downstream processing (mostly referring to the removal of transition metals from the final product).

4.3.2 Implementation of LPS in the production of (2-Bromophenyl)(phenyl)sulfane

Production of (2-Bromophenyl)(phenyl)sulfane could be achieved by applying batch manufacturing modes regardless which of the synthetic routes is applied. Focusing on the transition-metal based approaches, it is important to note that long reaction times (several hours) make this chemical reaction unsuitable for direct implementation in continuous manufacturing modes. It is therefore suggested that the traditional synthesis approach would be carried out in batch mode with consequent removal of transition metals. The initial process flow scheme is depicted in Figure 4.12 and it includes the recommended purification activity with suitable scavenging techniques (adsorption is widely applied[358]).

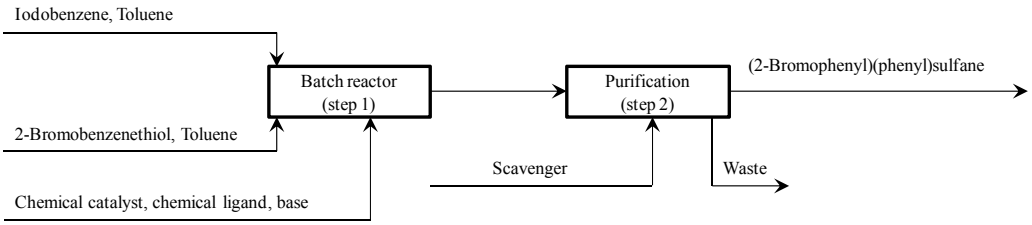


Figure 4.12 Traditional process flow scheme for producing C-S compounds with desired purity

Long reaction times, as well as time consuming purification procedures make this traditional approach as undesired process flow scheme for manufacturing (2-Bromophenyl)(phenyl)sulfane. One potential improvement consists addition of microwave irradiation to the process flow scheme[355]. This PI tool accelerates the chemical reaction significantly, but with an additional increase in the loading of chemical catalyst, chemical ligands and bases. An acceleration from 72 h reaction time (best batch mode)[354] to just 1 h was achieved with MAOS combined with Pd-based catalysts and Fe based chemical ligands. Hence, applications of coiled reactors with consequent scavenger techniques could be a suitable solution for such process flow scheme. However, the time frames of the mentioned two steps (MAOS step and purification step) are different, and therefore intermediate storage is needed. Nevertheless, additional process design could be performed to change the capacities of the mentioned steps, and then NVA (intermediate storage) could be avoided. The process flow scheme of such design is depicted in Figure 4.13.

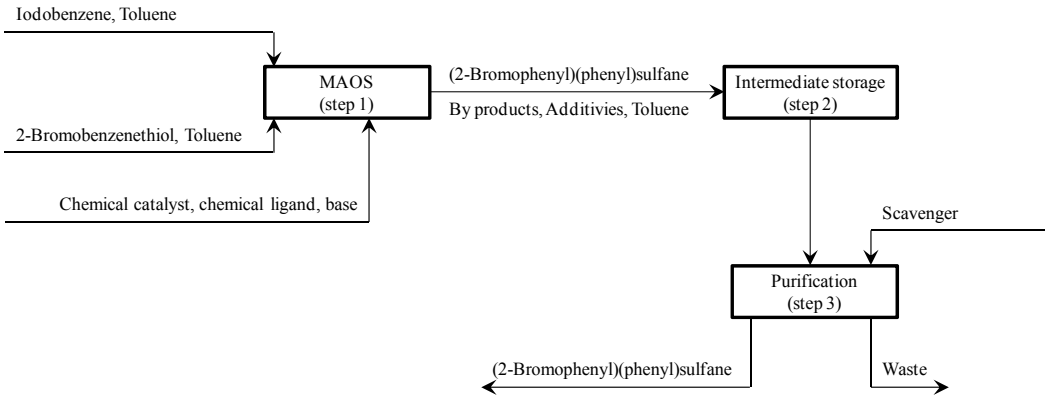


Figure 4.13 Implementation of MAOS in the process flow scheme for producing C-S compounds with desired purity

Apart from achieving significant improvements by using MAOS in the synthesis of (2-Bromophenyl)(phenyl)sulfane, it is important to note that still rather expensive materials are needed, as well as a time consuming processes. In order to simplify and accelerate such manufacturing route further, a change in the synthetic route is therefore proposed (Figures 4.14). The suggested flow scheme includes a five-step process with 2 chemical reactors (Step 1 and 2) and three purification steps (Steps 3, 4 and 5). It is important to note that Step 1 represents a CSTR where the chemical reaction between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione would be performed. The main reason for such approach is the extremely low solubility of 1-chloropyrrolidine-2,5-dione in THF, which is used as a solvent. Furthermore, 2-bromophenyl hypochlorothioite and pyrrolidine-2,5-dione (by-product) are introduced in Step 2 where the Grignard reaction is performed. This manufacturing step could be performed in a tubular reactor due to the very short reaction times of the Grignard reaction (in the range of ms)[273]. Hence, Steps 1 and 2 would be performed smoothly without any intermediate storage between them. Furthermore, continuous hydrolysis and L-L separation could be performed as well(Steps 3 and 4)[351], and finally the evaporation of THF and water from the desired API intermediate (Step 5)[359, 360].

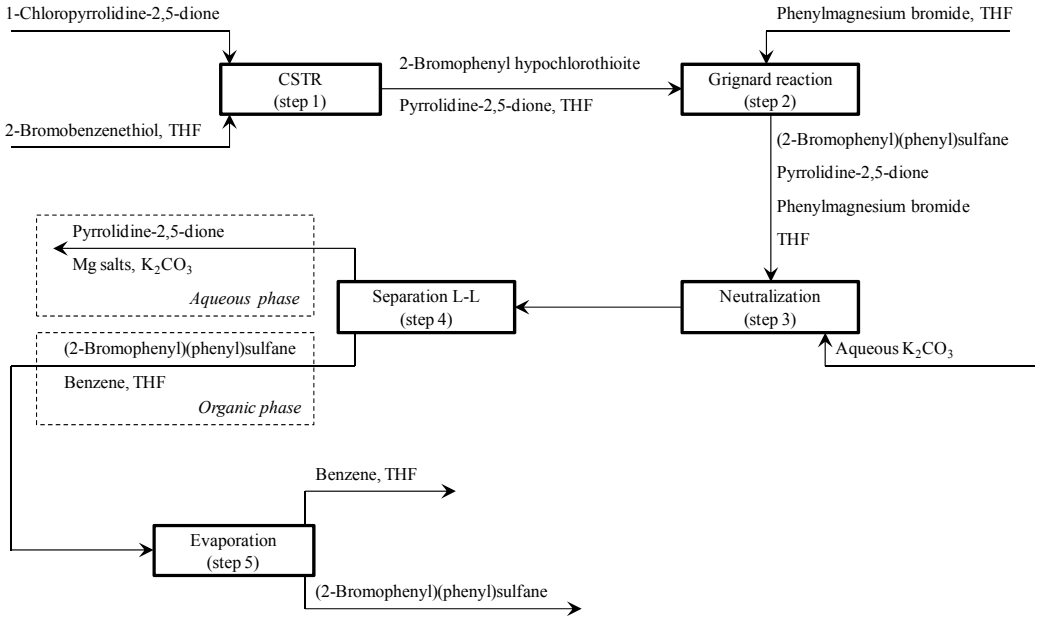


Figure 4.14 New Process Flow Scheme for producing compounds consisting C-S bonds

It can be easily noticed that the process flow scheme (Figure 4.14) is more complicated compared to the previously suggested processes. However, the entire process could be performed faster and smoother than the previously mentioned flow schemes (Figures 4.13 and 4.12). Furthermore, intermediate storages would be avoided which means that NVAs in the forms of waiting, transportation, defects and excess inventory would be completely avoided. Finally, unnecessary transportation and motion would be minimized which leads to a very good implementation of the "Manufacturing flow" element of the Lean Production System.

4.4 Conclusions and future work

Manufacturing of Clopenthixol was successfully transferred from batch towards continuous production. The crucial bottleneck in the Stage I (exothermic part) was to implement a better dosage of the Grignard reagent into the CTX (THF solution) and to minimize production of by-products. Hence, purification steps including distillation, crystallization/filtration and drying were considered as NVAs together with intermediate storages between the mentioned steps.

Implentation of the PI and PO tools in the Stage II (endothermic parts) of the Clopenthixol production resulted in significant accelerations of the manufacturing steps, but with several obstacles. More precisely, dehydration of "N714-Allylcarbinol" resulted in high amounts of undesired by-products and it was therefore important to perform a detailed analysis of the

polymerization reaction. Hence, the formation of poly-THF and additional polymers in this manufacturing step need to be excluded. The easiest approach was to introduce neutralization of H_3O^+ ions and consequent L-L separation, but applications of inhibitors of the polymerization should be additionally considered. Furthermore, a solvent swap step might be introduced as a suitable choice and therefore decrease the total number of steps in the manufacturing route. A change from THF to toluene could be considered as a suitable approach. Furthermore, the hydroamination reaction was accelerated significantly and adapted to the continuous manufacturing mode by either performing evaporation of THF or by introducing microwave irradiation in the overall process flow scheme.

Besides Clopenthixol, continuous production of (2-Bromophenyl)(phenyl)sulfane was labeled as a challenging approach. Long reaction times combined with significant loadings of transition metals implied severe difficulties to implement such a reaction in the continuous manufacturing mode. Applications of MAOS resulted in significant accelerations, but with very high capital investmens and with clear difficulties to perform scale up (toluene does not absorb microwave irradiation that well). Hence, application of molecular radiators might be beneficial, but the influence of such additives on the reaction kinetics should be explored. It is important to note that chemical catalysts and chemical ligands might be inactive in the presence of some specific compounds.

Nevertheless, the best choice was to implement a different synthetic route towards (2-Bromophenyl)(phenyl)sulfane. Hence, implementation of two very fast chemical reactions with consequent purification steps could be performed smoothly and without any intermediate storage. Cost of materials, labor and capital investments are minimized in this way together with reduced reaction times. Implementation of the “Manufacturing Flow” element of the LPS was therefore successfully performed.

5. Implementation of the PI Strategy to the Dehydration of "N-714 Allylcarbinol" to "N746-Butadienes"

Abstract

Dehydration of "N714-Allylcarbinol" to the mixture of "N746-Butadienes" is an elimination reaction which was performed in batch modes at the start of the project. It represents an intermediate step in the overall Zuclopenthixol production. Hence, intermediate storage of substrates and products, as well as a solvent swap process from THF to toluene needed to be performed as supportive operations. The main goal in this chapter is therefore to exclude non-value added activities and additionally to accelerate this chemical reaction by using the same solvent as in the previous steps of the synthesis (THF). Successfull applications of a mesoscale laminar tubular reactor together with in-line process monitoring were obtained. However, presence of side reactions caused by the polymerization of THF has been observed

It is important to note that the process design was done by Albert Emili Cervera Padrell, whereas initial experiments were performed by Asmus Ringlebjerg Mortensen. The polymerization analysis was done by Irakli Javakhishvili from the Danish Polymer Center (DTU Chemical Engineering). They are all greatly acknowledged for their help, as well as the people in CERE (DTU Chemical Engineering) who allowed me to use some of their laboratory equipment.

5. Implementation the Proposed PI Strategy to the Dehydration of "N-714 Allylcarbinol" to "N746-Butadienes"

5.1 Introduction

Production of unsaturated hydrocarbons is a very important chemical reaction in the modern organic synthesis. There are different types of chemical reactions which could lead to these organic compounds. However, dehydration of alcohols is the most commonly used and easiest approach. Acidic catalysts are usually applied amongst whom sulphuric, hydrochloric and phosphoric acids are most frequently applied[361].

Dehydration of "N714-Allylcarbinol" into "N746-Butadienes" is one of the manufacturing steps in the Zuclopenthixol production. So far, the reaction is performed in batch mode with quite long reaction times and plenty of difficulties for successful implementation of the PAT requirements. It is therefore important to introduce several modifications and achieve better performance of this manufacturing step.

The main aim of this chapter is to apply the process intensification approach to this manufacturing step. A careful look in the overall Zuclopenthioxol production route is needed, because storage of intermediates, then solvent swap procedures and all additional unnecessary production steps should be avoided as much as possible. As a consequence, the dehydration reaction is here carried out in THF together with stronger chemical catalysts. In this way, an acceleration of the reaction rate up to the values suitable for continuous manufacturing mode is achieved. Moreover, in-line process monitoring has been applied successfully to the reaction.

However, the introduction of THF as the reaction medium caused production of undesired by-products. Therefore, a careful analysis of such reaction mixture is performed including a detailed analysis of impurities present in the product flow of the API intermediate leaving the reactor.

5.2 Reaction pathway towards "N746-Butadiene"

Dehydration of alcohols can be performed via three different mechanisms: E1, E2 and E1cB. Primary alcohols undergo the E2 type of reaction, whereas secondary and tertiary alcohols react easier and follow the E1 mechanism. Lastly, the E1cB elimination is common for β-hydroxy-carbonyl compounds and basic reaction conditions[361].

"N714-Allylcarbinol" is a tertiary alcohol and it follows the E1 elimination mechanism for acidic reaction conditions. It dehydrates to "N746-Butadienes" through the carbocation intermediate. The overall chemical reaction route is depicted in Figure 5.1.

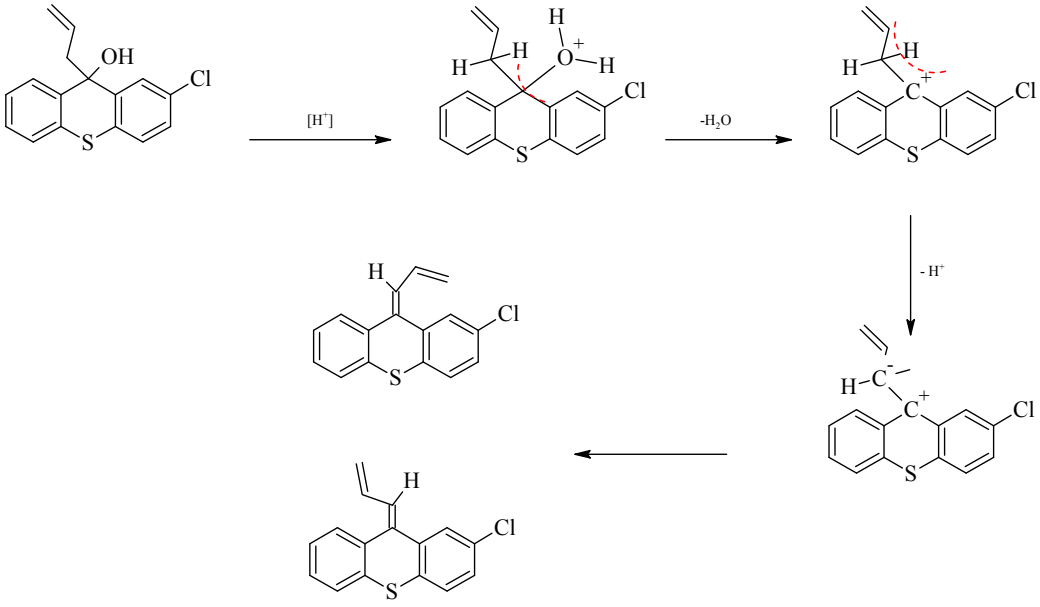


Figure 5.1 Dehydration of "N714-Allylcarbinol" to "N746-Butadiene" via the E1 elimination mechanism

It is important to note that the dehydration of this tertiary alcohol causes the production of two geometrical isomers. A detailed look in the chemical structures of such isomers implies the high level of similarity between them. Consequently, the expected molar ratio of the synthesized isomers is 1:1. However, the trans isomers are known as the more stable compounds due to the electronic repulsions between lone electron pairs placed at the same side of the double bond. Potential options to avoid such a high production of the trans isomer are described in chapter 6.

5.3 Process intensification strategy

As noticed in chapter 4, the traditional approach for dehydration of "N714-Allylcarbinol" into "N746-Butadienes" was performed in batch mode. Toluene was used as the reaction medium, whereas a mixture of acetic acid anhydride and acetyl chloride was used as the chemical catalyst. However, apart from being performed in batch mode, this approach also required additional operations, such as a solvent swap from THF to toluene, storage of the intermediate, removal of acetic acid and acetyl chloride after completing the dehydration step, cleaning procedures....

Implementation of the PI strategy described in chapter 3 could have plenty of benefits. Focusing on this particular chemical reaction, the PI implementation procedure applied to this case study is depicted in Figure 5.2 through the red line. It connects slow batch chemistry with the meso-flow chemistry via temperature increase and chemical catalysis/biocatalysis process options. The main focus here is on using THF and Brøndsted acids.

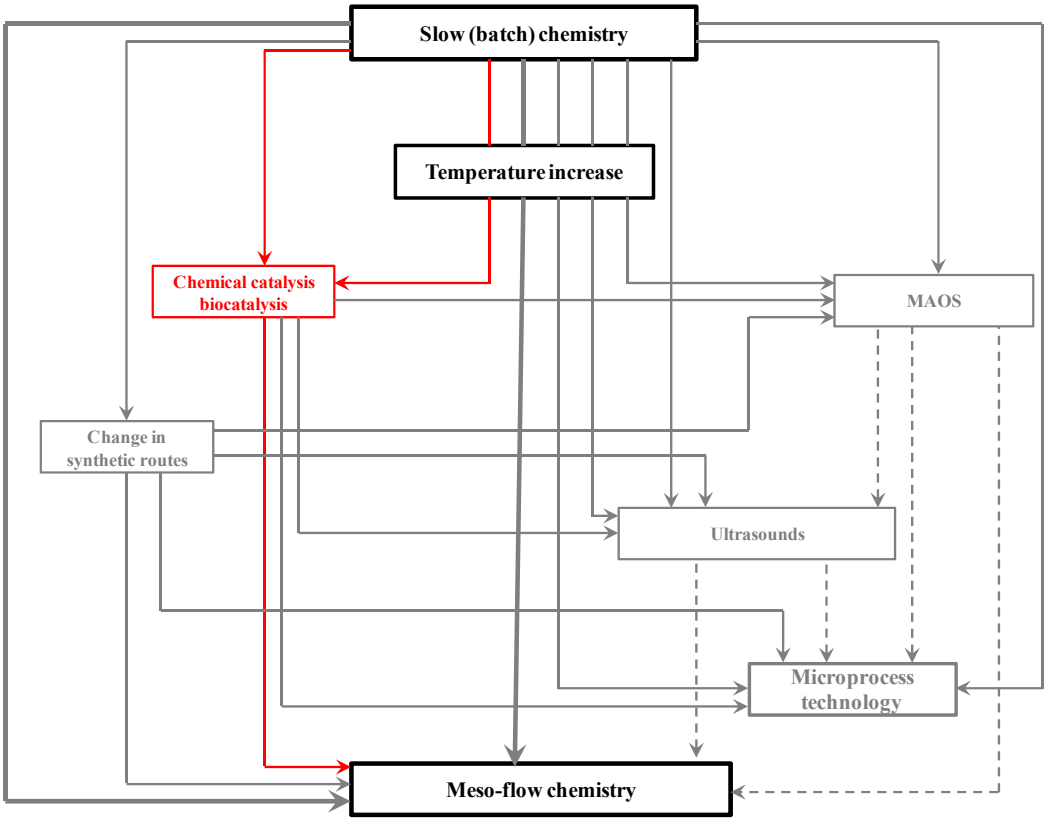


Figure 5.2 PI approach implemented to the dehydration of "N714-Allylcarbinol" with the main aim to accelerate this production step and make it suitable for PAT implementation

A switch towards meso-flow chemistry includes several practical issues in this particular reaction system. They are:

- quite low boiling point of THF does not allow reaction temperatures above 66^0C;
- very high concentrations of Brøndsted acids could cause a huge amount of impurities;
- the limited solubility of water in THF could cause issues with the real-time process monitoring applications.

Therefore, suitable solutions to these practical issues should be found. The main focus is to operate within the range which would include optimal amounts of water, as well as a suitable molar concentration of the Brøndsted acid. Therefore, the only way to accelerate such a slow chemical reaction is to increase temperature above the normal boiling point of the used solvent.

Operations above the normal boiling point of THF could be performed if the pressure is increased in the system. Such reaction condiditons are possible if the setup is equipped with suitable backpressure regulators. The dependence of the THF boiling point on pressure is depicted in Figure 5.3.

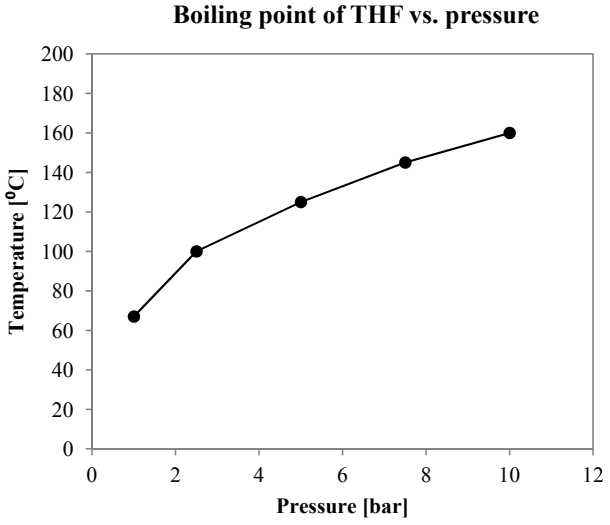


Figure 5.3 Dependance of boiling point of THF with the pressure increase

Despite all advantages which could be achieved, it is important to note that a combination of concentrated Brønstead acids and THF causes polymerization of the solvent. This undesired side reaction is performed either independently to the dehydration reaction or together with the intermediate carbocation which is formed during the dehydration process. Detailed analysis should be performed in order to check if this approach would lead to significant improvements of this production step.

5.4 Materials and methods

5.4.1 Preparation of samples for process calibration

A solution of "N714-Allylcarbinol" in THF was received directly from the manufacturing sites in H. Lundbeck A/S (Lumsås, Denmark) with unknown accurate molar concentration and with increased amounts of water. It was therefore necessary to apply suitable purification operations together with subsequent analyses of the purified material. Instrumental methods of analysis, such as NMR, HPLC and FT-NIR were used for validating the quality of the purified "N714-Allylcarbinol. The step-by-step procedure is depicted in Figure 5.4.

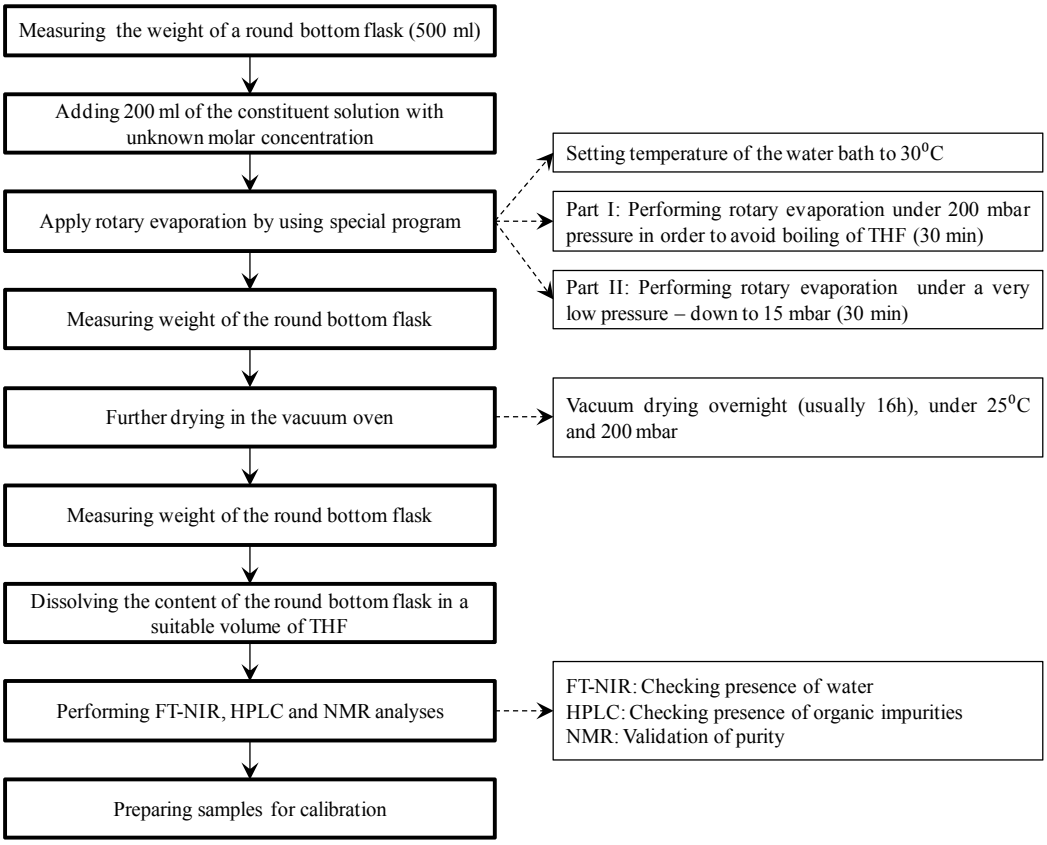


Figure 5.4 Step-by-step purification procedure in order to obtain accurate molar concentrations of "N714-Allylcarbinol"for calibration purposes

Despite purifying the "N714-Allylcarbinol", it was necessary to prepare the "N746-Butadienes" as clean as possible, and consequently to apply the same purification procedure. The importance of

having this unsaturated hydrocarbon in a clean form was very high due to significant overlaps of the NIR spectra of these two constituents.

Hence, the dehydration reaction involved three different constituents: “N714-Allylcarbinol”, “N746-Butadienes” and water as a by-product. The calibration set is depicted in Table 5.1 (a) whereas a validation set is written down in Table 5.1 (b).

Table 5.1 Data Sets for (a) calibration and (b) validation

a)

No.	$C_{\_N714\text{-}Allylcarbinol}$ [M]	$C_{\_N746\text{-}Butadiene}$ [M]	$C_{\_Water}$ [M]
1.	0.3000	1.4000	0
2.	0	1.1000	0.5000
3.	0.6000	0.9000	0.3000
4.	0.8000	0	0.2000
5.	0.9000	0.6000	1.3000
6.	1.1000	0.5000	0.9000
7.	1.2000	0	1.2000
8.	1.4000	0.2000	1.1000
9.	0.1000	0	0
10.	0.4000	0	0
11.	0.7000	0	0
12.	1.000	0	0
13.	0	0.1000	0
14.	0	0.4000	0
15.	0	1.000	0
16.	0	0	0.1000
17.	0	0	0.4000
18.	0	0	0.7000
19.	0	0	1.000
20.	0	0	1.3000

b)

No.	$C_{\_N714\text{-}Allylcarbinol}$ [M]	$C_{\_N746\text{-}Butadiene}$ [M]	$C_{\_Water}$ [M]
1.	0.2500	0.3500	1.050
2.	0.7500	0.1500	0
3.	0.5500	0	0.5500
4.	0	0.7500	0.1500

It is important to note that the purity of the "N746-Butadienes" was not very high because of the considerable amounts of impurities produced during the dehydration reaction. Those compounds were invisible if only FT-NIR and HPLC analyses were performed. However, applications of the NMR analysis confirmed their presence.

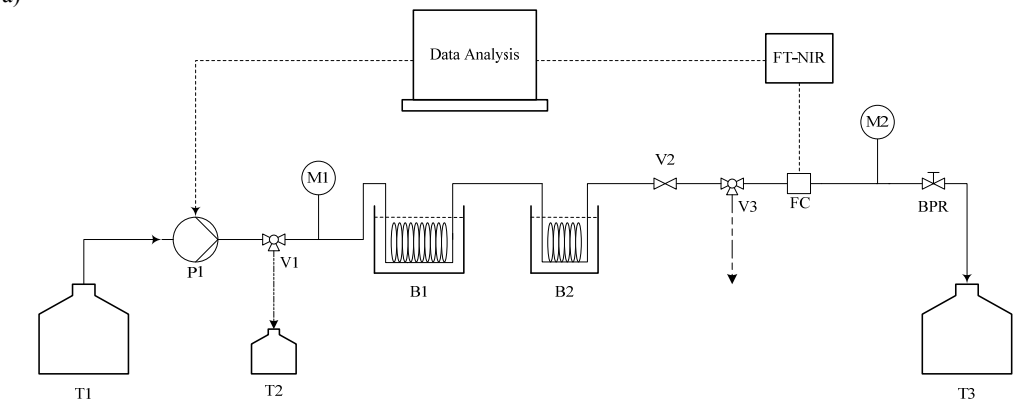
5.4.2 Experimental setup for the dehydration reaction

The main part was a 3m laminar tubular reactor which is basically a PFA tube with the outer/inner diameters of 0.125 inch (3.175mm) and 0.065 inch (1.65mm), respectively. It was placed in the oil bath (B1) whose temperature could be maintained up to 300^0C. However, the applied temperatures were in the range from 25 to 120^0C. After the reactor, a 1 m extension of the PFA tube was added and placed in the cooling bath (B2). The main purpose of this part was to significantly decrease reaction rates and get precise kinetic data. The cooling bath consisted of ice cubes with the temperature maintained down to 0^0C.

Furthermore, flow was regulated by using a Masterflex peristaltic pump (P1) with a PTFE tubing. The operation range was from 0-7.634 ml/min and usually 1.5 ml/min were applied in the kinetic investigations. The experiments were carried out under increased pressure which was achieved by using backpressure regulators (BPR). In addition, two different manometers were also applied (M1 and M2) for visual control of the pressure in the experimental setup. The first manometer (M1) was placed close to the pump in order to protect the pumphead (it does not tolerate pressures above 6 bars). Hence, over-pressure was regulated by using pressure relief valve V1. The second manometer (M2) was placed before the back-pressure regulator in order to maintain the desired value of the pressure which was 5 bars. All the connections were established by using PFA connectors suitable for the working conditions applied in the reaction system. All the valves in the system were made from stainless steel. It is additionally important to note that tanks T1 and T3 were used for storing reactants and products, respectively, whereas tank T2 was used just in case if the pressure relief valve (V1) would open. Valves V2 and V3 were used for collecting samples for at- and off-line analyses (closing V2 and opening V3). Moreover, in-line process monitoring was performed by using an Ocean Optics flow cell (FC) together with FT-NIR and the relevant supporting software.

Continuous dehydration of "N714-Allylcarbinol" to "N746-Butadienes" was performed in the experimental setup depicted in Figure 5.5. The upper part of the figure labelled with a) gives insight about the process flow scheme, whereas b) is the image of the setup.

a)



b)

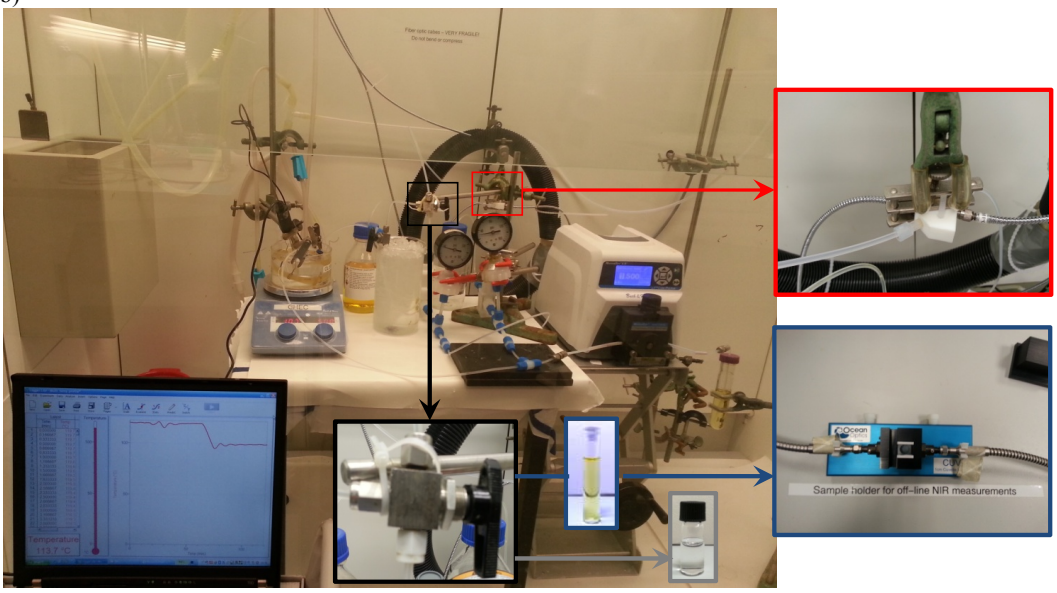


Figure 5.5 Experimental setup for performing the dehydration of "N714-Allylcarbinol" to "N746-Butadienes". a) Process Flow sheet including: T1, T2, T3 – tanks; P1 – pump; V1, V2, V3 – valves, B1, B2 – oil and ice baths, respectively; FC – flow cell; M1, M2 – manometers; BPR – back pressure regulator. b) Photo of the setup.

Major part of the equipment was purchased from Swagelok (PFA tubes, PFA unions, stainless steel valves) whereas the rest was bought from Parker (backpressure regulators, PFA protectors for manometers and manometers themselves). The peristaltic pump was obtained from Buch & Holm.

5.4.3 Sampling Procedure

Analysis of the reaction mixture was performed by using two different instruments and three different modes of analysis. An FT-NIR process analyzer (Networkir, Q-Interline/ABB) and LaChrome Elite HPLC equipment were used for performing in-/at-line and off-line analyses, respectively. It is noteworthy that the main focus was on the in-line FT-NIR analysis whereas at-line FT-NIR and off-line HPLC analyses were used for external validations.

5.4.3.1 At- and In-line FT-NIR Analysis

At- and in-line spectroscopic measurements were performed with FT-NIR process analyzer which was equipped with two InGaAs detectors. The detector 1 was applied for at-line analysis, whereas the second one was used for the in-line mode.

The at-line analysis was performed with the InGaAs suited for the wavenumber range from 12500 down to 3846.15 cm^{-1}. Furthermore, two 500 µm optical cables were applied in order to connect the CUV-UV holder with the light source on the one side and the detector on the other side. The holder was purchased from Ocean Optics and was optimized for 1 cm cuvettes. It is important to note that borosilicate glass vials from Kimble were used instead of using expensive borosilicate cuvettes. The Kimble vials were cheap and disposable with a diameter of 8 mm. It was therefore necessary to make a PTFE vial holder and put it inside the CUV-UV holder, such as depicted in Figure 5.5 b.

Furthermore, the in-line analysis was performed with the second InGaAs detector. It measures the wavenumber range from 12500-4761.90 cm^{-1} and was connected to the FIA-Z-SMA-TEF flow cell with 1 cm pathlength (Figure 5.5 b)). To this purpose, 300 µm optic cables were used wih a length of 15 m. The flow cell was purchased from Ocean Optics. Incorporation of the flow cell in the experimental setup was achieved by using 1/4-28 Upchurch fittings from Swagelok.

The kinetic studies were performed by using GRAMS/AI 7.0 Software (Thermo Electron Corporation) and its adds-on tool called PLSplus/IQ.

5.4.3.2 Off-line HPLC Analysis

Besides the fast FT-NIR analyses, molar concentrations of “N714-Allylcarbinol” and “N746-Butadienes” were quantified by using LaChrome Elite HPLC equipment. This device includes the Diode Array Detector (DAD) and a Phenomenex Gemini C6-Phenyl Column which is generally suited for reversed phase HPLC. It is additionally tolerant to a wide range of pH values. A 23-min gradient method was applied by using two mobile phases. The mobile phase one consists of a 10% buffer solution with pH=9, then 10% of acetonitrile and 80% of water whereas the mobile phase B had 10% of the buffer solution and 90% of acetonitrile. All of the percentages were based on volumetric calculations. The aqueous buffer was prepared by using 50 mM aqueous solution of

ammonium formate (NH_4HCO_2) and several drops of ammonium-hydroxide (NH_4OH) in order to adjust a desired pH.

The sampling procedure was based on using 1 ml of ethyl-acetate (EtOAc) as the HPLC diluent. This non-polar solvent was chosen due to its high versatility for different applications. Furthermore, its low UV absorption in the range of higher wavelengths allows easier and more precise analysis of the analyzed compounds. The applied wavelength here was 254 nm.

It is important to note that the high UV absorptions of "N714-Allylcarbinol" and the isomers of "N746-Butadiene" implied the necessity of performing the necessary dilutions of the analyzed solutions. A molar concentration range from 0-2 M was usually applied in the experimental procedures and it was therefore necessary to usewo different dilutions. The first dilution with a dilution factor (DF) of 20 was applied by taking 50 µl of the original sample and diluting it in 1950 µl of THF. Furthermore, 50 µl of the diluted samples were transferred to disposable HPLC vials where 1 ml of the HPLC diluent was placed. Hence, the second dilution with the DF=21 was additionally applied leading to the total dilution of DF=420.

All the chemicals were purchased from Sigma-Aldrich whereas disposable HPLC vials and caps were bought from VWR International.

5.4.4 Nuclear Magnetic Resonance (NMR) analysis

NMR analysis was performed as a validation procedure for the calibration models. Therefore, samples consisting "N714-Allylcarbinol", as well as samples with "N746-Butadiene" were analyzed.

The most common procedure for preparing samples was followed. More precisely, the samples with "N714-Allylcarbinol" were firstly evaporated in the rotary evaporator in order to remove THF from the NMR spectrum. The following step was to dissolve the residue in chloroform-d and to run the NMR analsys.

The sample preparation procedure for "N746-Butadienes" was slightly different. First of all, this constituent needed to be produced as pure as possible. After confirming the purity with HPLC and FT-NIR, it was necessary to neutralize the excess of sulphuric acid. For that purpose, a sodium bicarbonate solution was used. After the neutralization, two phases needed to be separated and consequently the organic phase needed to be evaporated. The latest steps were the same as in the case of "N714-Allylcarbinol".

These qualitative analyses were performed by using a Bruker Avance 300 MHz spectrometer. The chemical shifts are given in ppm.

5.4.5 Size Exclusion Chromatography (SEC) analsysis

Qualitative analysis of polymers was performed with Size Exclusion Chromatography (SEC). The main purpose of implementing this analytical technique was to detect the presence of polymers, as well as to estimate average molecular weights of such cTry oompounds.

A Viscotek GPCmax VE-2001 equipped with two PLgel mixed-D columns from Polymer Laboratories was used. Furthermore, a Knauer K-2501 UV detector and a Viscotek TriSec Model 302 tripple detecter array were used. The triple detector consisted of the refractive index detector, viscometer detector, and a laser light scattering detector at the light wavelength of 670 nm, and measuring angles of 90^0 and 7^0. All the samples were done in THF and at room temperature with a flow rate of $1\frac{\mathrm{ml}}{\mathrm{min}}$. Molecular weights were detected using polystyrene standards from Polymer Laboratories.

It is important to note that samples were prepared carefully due to the very high sensitivity of the chromatographic columns to acidic mediums. Therefore, washing with aqeous sodium bicarbonate solution was performed three times with consequent precise separation of the layers by using a separation funnel.

5.5 Results and discussions

5.5.1 Multivariate calibration development

Successful implementation of the real-time process monitoring involves good calibration of process analyzers. Multivariate calibration of the FT-NIR analyzer involves a process chemometrics approach. This procedure is described in chapter 2, section 2.5.2 where a step-by-step strategy is additionally depicted in Figure 2.11.

Three different types of analyses were performed in this particular process with the main aim to achieve a high level of data accuracy. At- and in-line analyses were performed as explained in section 5.4.2.1, whereas off-line HPLC analysis was done by following the procedure described in section 5.4.2.2. The calibration data set included 20 different samples, as described in section 5.4.1. It is important to note that the "N746-Butadienes" involved small amounts of by-products.

Focusing on in- and at-line modes of analyses, it is important to note that the first step was to define spectral regions which would give information about the constituents of interest. "N714-Allylcarbinol" and "N746-Butadiene" could be indentified and quantified by analyzing regions from 6220-5925 cm^{-1} and 4900-4560 cm^{-1}. The first region corresponds to allyl, vinyl and aromatic group absorptions whereas the second region shows combinations bands of allyl, vinyl and aromatic groups. For practical reasons, the second region was extended up to 5370cm^{-1} because the third constituent (water) has a strong absorption in that region. In addition, THF was used as a

background. Raw NIR spectrums including all three constituents are shown in Figure 5.6 together with the selected regions (in between the red or the black dashed lines, respectively).

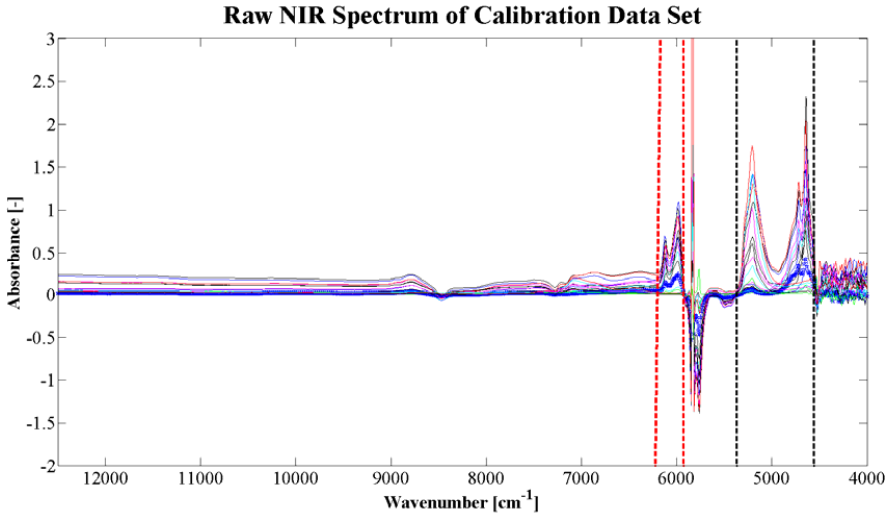


Figure 5.6 Raw NIR spectrums of all 20 samples used in the at-line calibration procedure together with the defined spectral regions used for process chemometrics

The second step in this procedure included testing different mathematical pre-treatments. Therefore, removing scattering, doing baseline corrections, smoothing, and so on, was performed by using four different mathematical techniques: baseline correction (BLC), mean centering (MC), then Savitzky-Golay first derivative (SG1) and Savitzky-Golay second derivative (SG2) derivations. These techniques were emphasized as the most comprehensive ones for covering a wide range of potential corrective actions[128]. All of these techniques were implemented independently, as well as in suitable combinations.

The obtained results are described in Table 5.2 for all three constituents and for both analytical modes used for acquiring data. Furthermore, numbers of applied latent variables (f), then RMSECV, RMSEC and RMSEP are also depicted in Table 5.2. The best pre-treatments are coloured with yellow and ocker yellow colours for at- and in-line modes of analyses, respectively.

Table 5.2 At- and in-Line process calibration of FT-NIR for (a) "N714-Allylcarbinol", (b) "N746-Butadiene" and (c) water including number of latent vatriables (F), root mean squared error of cross validation (RMSECV), root mean squared error of calibration (RMSEC), root mean squared error of prediction (RMSEP) and mathematical pre-treatments: baseline correction (BLC), mean centering (MC), Savitzky-Golay first derivative (SG1), Savitzky-Golay second derivative (SG2) and defined number of points (p) for SG1 and SG2

a) "N714-Allylcarbinol"

No.	Pre-treatment	At-Line				In-Line			
		f	RMSECV	RMSEC	RMSEP	F	RMSECV	RMSEC	RMSEP
1.	-	4	0.0250	0.0237	0.0430	4	0.0196	0.0198	0.0161
2.	BLC	4	0.0370	0.0345	0.0340	4	0.0197	0.0199	0.0154
3.	MC	4	0.0253	0.0225	0.0409	4	0.0206	0.0197	0.0159
4.	SG1+7p	2	0.0967	0.0950	0.0785	3	0.0620	0.0634	0.0696
5.	SG1+11p	3	0.0571	0.0667	0.0697	3	0.0924	0.0668	0.0920
6.	SG1+15p	4	0.0552	0.0667	0.0697	5	0.0438	0.0668	0.0920
7.	SG2+7p	2	0.0664	0.0760	0.0944	4	0.0245	0.0228	0.0226
8.	SG2+11p	4	0.0572	0.0477	0.0426	5	0.0272	0.0211	0.0377
9.	SG2+15p	4	0.0381	0.034	0.0148	7	0.0770	0.0313	0.0755
10.	MC+SG1+15p	3	0.0473	0.0508	0.0411	7	0.0235	0.0134	0.0351
11.	MC+SG2+15p	3	0.0892	0.0921	0.0895	7	0.0865	0.0308	0.0873
12.	MC+BLC	3	0.0385	0.0392	0.0312	3	0.0239	0.0244	0.0085

b) "N746-Butadiene"

No.	Pre-treatment	At-Line				In-Line			
		f	RMSECV	RMSEC	RMSEP	F	RMSECV	RMSEC	RMSEP
1.	-	4	0.0291	0.0288	0.0274	4	0.0108	0.0109	0.0147
2.	BLC	4	0.0443	0.0404	0.0514	4	0.0162	0.0167	0.0135
3.	MC	3	0.0299	0.0269	0.0303	4	0.0103	0.0098	0.0143
4.	SG1+7p	3	0.0654	0.0687	0.0449	3	0.0858	0.0762	0.0903
5.	SG1+11p	3	0.0560	0.0600	0.0499	4	0.0746	0.0557	0.0572
6.	SG1+15p	4	0.0434	0.060	0.0499	4	0.0590	0.0557	0.0572
7.	SG2+7p	3	0.0772	0.0870	0.0590	4	0.0461	0.0477	0.0350
8.	SG2+11p	3	0.0658	0.0728	0.0624	5	0.0335	0.0230	0.0325
9.	SG2+15p	4	0.0705	0.0799	0.0678	5	0.0787	0.0349	0.0675
10.	MC+SG1+15p	3	0.0522	0.0533	0.0423	5	0.0495	0.0277	0.0451
11.	MC+SG2+15p	3	0.0675	0.0721	0.0555	5	0.0793	0.0280	0.0621
12.	MC+BLC	3	0.0438	0.0433	0.0504	3	0.0170	0.0170	0.0139

c) Water

No.	Pre-treatment	At-Line				In-Line			
		f	RMSECV	RMSEC	RMSEP	F	RMSECV	RMSEC	RMSEP
1.	-	3	0.0402	0.0396	0.0250	4	0.0161	0.0171	0.0099
2.	BLC	4	0.0429	0.0467	0.0087	5	0.0122	0.0117	0.0092
3.	MC	4	0.0309	0.0313	0.0206	4	0.0159	0.0149	0.0094
4.	SG1+7p	3	0.1175	0.1196	0.0747	5	0.0602	0.0532	0.0207
5.	SG1+11p	4	0.0331	0.0309	0.0221	4	0.0693	0.0687	0.0731
6.	SG1+15p	4	0.0282	0.0309	0.0221	4	0.0710	0.0687	0.0710
7.	SG2+7p	3	0.1825	0.1919	0.1290	4	0.1374	0.1168	0.0759
8.	SG2+11p	4	0.0728	0.0362	0.0362	5	0.1326	0.0968	0.0968
9.	SG2+15p	5	0.0229	0.0251	0.0084	7	0.0766	0.0283	0.0873
10.	MC+SG1+15p	3	0.0420	0.0427	0.0133	7	0.0255	0.0095	0.0251
11.	MC+SG2+15p	3	0.0864	0.0913	0.0685	3	0.1753	0.1585	0.1442
12.	MC+BLC	4	0.0146	0.0133	0.0079	4	0.0225	0.0216	0.0091

Building PLS models for both modes of analyses included the leave-one-out cross validation procedure. Therefore, just one sample was usually excluded from the calibration data set and used for cross-validation. In addition, the starting number of latent variables was assumed to be 10 what was equal to half of the number of the calibration samples. This approach was recommended by the PLS guide[128]. The optimization procedure was performed by following two conditions:

1. RMSECV needed to reach the minimum or to be around the minimized value;
2. difference between RMSECV and RMSEC should be less than 20% in order to avoid overfitting according to Shenk and coworkers[136,]
3. RMSEP should have an acceptable low value.

Following the mentioned criteria, it was decided that the best pre-treatment for the in-line analysis of "N714-Allylcarbinol", "N746-Butadienes" and water was BLC with additional MC (such as depicted in Table 5.2 under entries 12 – colour occer yellow). Optimization of the latent variables is depicted in Figure 5.7 for (a) "N714-Allylcarbinol", (b) "N746-Butadienes" and (c) water.

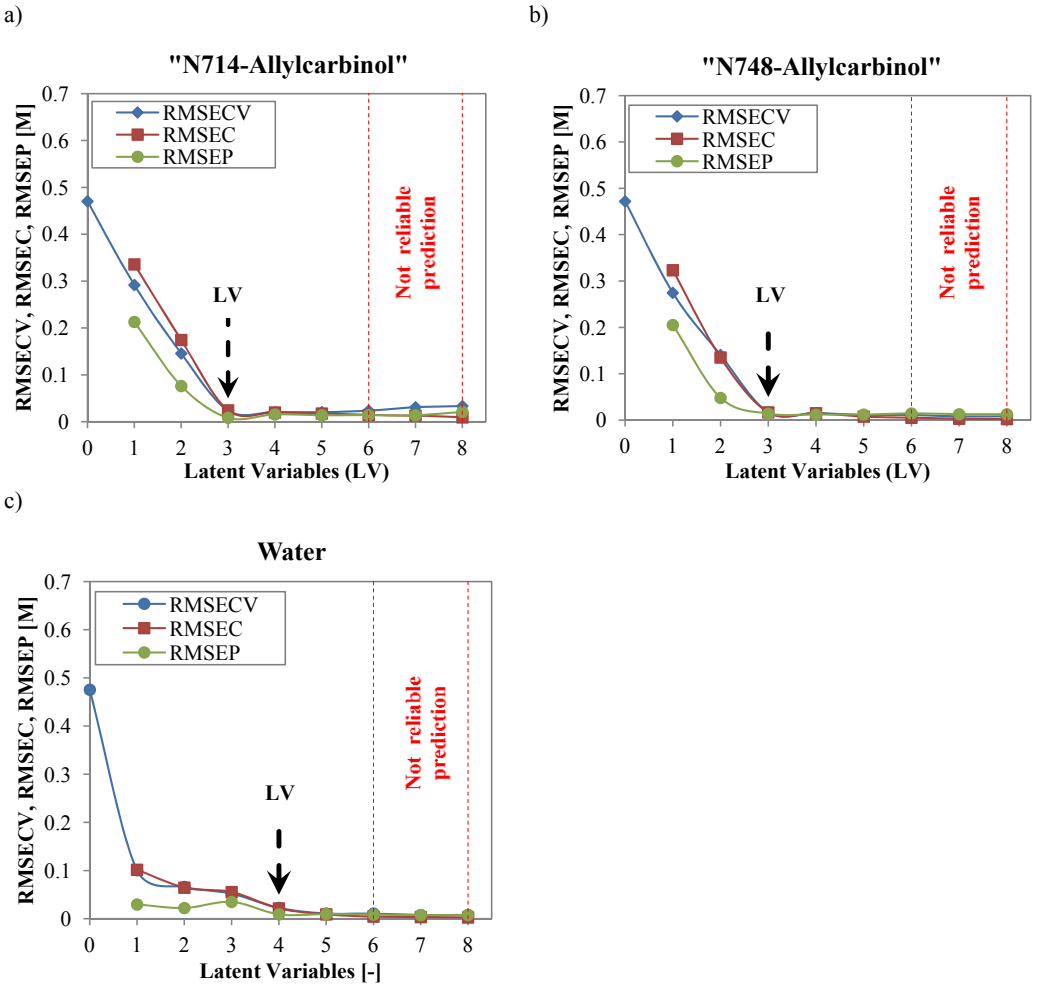


Figure 5.7 Optimization of the number of latent variables during building PLS calibration model for in-line mode of analysis: (a) "N714-Allylcarbinol", (b) "N746-Butadienes and (c) water

It could be easily noticed that the criterion 1 was satisfied for all three constituents. Hence, the chosen numbers for latent variables were 3, 3 and 4 for "N714-Allylcarbinol", "N746-Butadienes" and water, respectively. In case of water, there was an option that 2 LV could be used. However, in that case the RMSEP would be three times higher than the value obtained when 4 LV were applied. It was therefore decided that the latest number of latent variables should be used for the third constituent in the reaction system. Further increase of the latent variables initiated unreliable

predictions of molar concentrations for all three constituents. These regions are marked with red dashed lines in Figure 5.7.

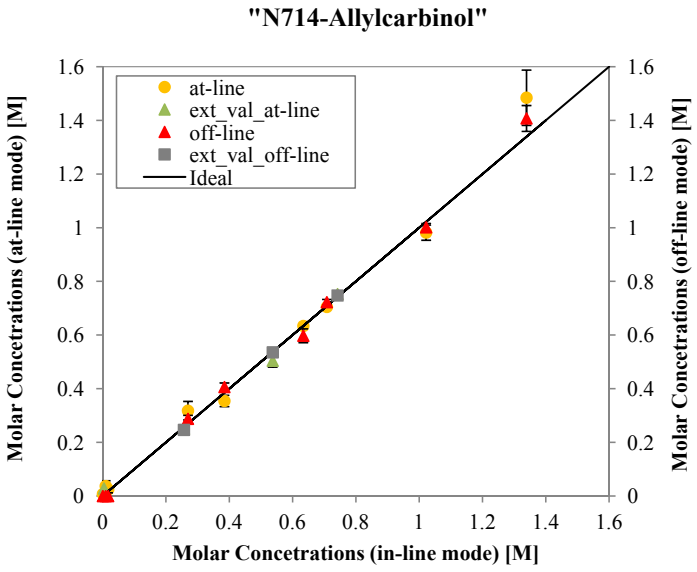
Furthermore, the difference between RMSECV and RMSEC for "N714-Allylcarbinol" was 2%, for "N746-Butadienes" was 0.01% whereas for water it went up to 4%. It was therefore concluded that the criterion 2 was satisfied, as well.

The same procedure was repeated for evaluating the best calibration models for at-line analysis. It is important to note that three different mathematical pre-treatments were chosen here in order to precisely predict the molar concentrations of the constituents. Raw spectra of "N714-Allylcarbinol" showed best results if SG2 and 15 points were applied as mathematical pretreatment whereas spectrums for "N746-Butadienes" and water were treated with MC and MC with additional BLC, respectively. The main reason for the selection of different pretreatments might be associated to the practical errors, such as inappropriate placing of the borosilicate vial in the sample holder, inadequate cleaning of the vials, and so on. Results are depicted in Table 5.2 and coloured occer yellow.

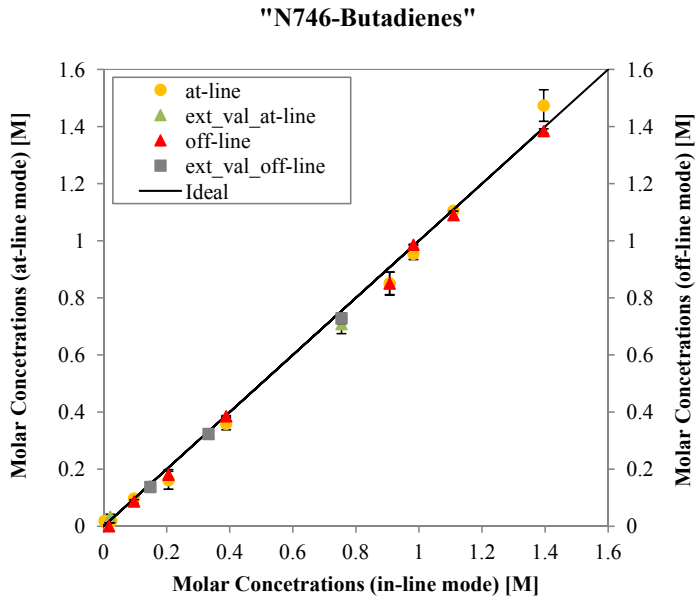
It is important to note that very good calibration models were developed for both modes of analysis. Comparison of predicted and actual molar concentrations resulted in high values for the correlation coefficients (R^2). More precisely, the in-line mode resulted with the value of 0.998 for "N714-Allylcarbinol" whereas the at-line mode showed a slightly decreased value (0.993). Furthermore, "N746-Butadienes" resulted in 0.999 and 0.995 for in- and at-line modes respectively whereas the R^2 for water was 0.998 for in-line and 0.999 for the at-line mode.

The last step in successful implementation of the multivariate calibration was to implement additional validation of the obtained calibration models. Hence, a comparison between predicted molar concentrations obtained by using the in-line mode with the at-line mode on the one side and off-line mode (HPLC) on the other side was done. The obtained results are depicted in Figure 5.8 (a) for "N714-Allylcarbinol", (b) for "N746-Butadienes" and (c) for water. All the plots show correlations between data predicted with in-line mode on x-axes, as well as data predicted with at- and off-line modes on primary and secondary y-axes, respectively. External samples for validations are additionally plotted together with the graphs, then standard deviations of all the points and finally an ideal case when all the predicted values would be identical (black diagonal line in the graphs). In case of water, the secondary y-axis was excluded.

a)


"N714-Allylcarbinol"
at-line
ext_val_at-line
off-line
ext_val_off-line
Ideal
Molar Concetrations (at-line mode) [M]
Molar Concetrations (off-line mode) [M]
Molar Concetrations (in-line mode) [M]
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6

b)


"N746-Butadienes"
at-line
ext_val_at-line
off-line
ext_val_off-line
Ideal
Molar Concetrations (at-line mode) [M]
Molar Concetrations (off-line mode) [M]
Molar Concetrations (in-line mode) [M]
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6

c)

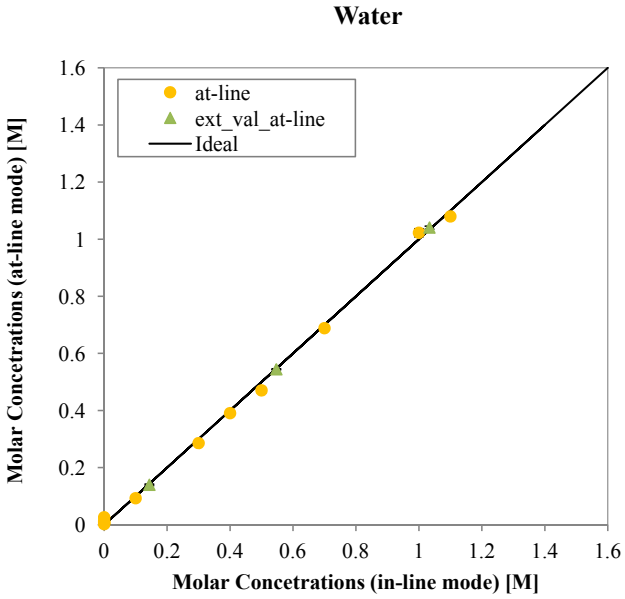


Figure 5.8 External validation of the experimental data obtained with in-line monitoring during the calibration procedure

It can be seen that different modes of analyses show very good correlations. More precesslly, the correlation coefficients (R^2) between in- and at-line modes are 0.992, 0.996 and 0.998 for "N714-Allylcarbinol", N746-Butadienes" and water, respectively. Furthermore, the R^2 for off- and in-line modes resulted with 0.997 for the alcohol and 0.999 for butadiene.

A few outliers could be noticed and might imply little uncertainties in specific operating regions. More precisely, it was noticed that quite high molar concentrations of "N714-Allylcarbinol" could cause a decreased correlation between at- and in-line modes. The specific example is depicted in Figure 5.8 (a) if a 1.4 M solution was applied. A similar behavior could be noticed in the case of "N746-Butadienes", however with lower standard deviation. Nevertheless, these values for the molar concentrations are outside of the range of interest because 1.05 M was the maximum value used in the manufacturing of "N746 Butadienes".

The general impression is that good calibration models were achieved for all three modes of analysis and for all constituents involved in the reaction mixture (excluding solvent). The main focus was on the in-line mode because of its further implementation on the real-time process monitoring and control of the manufacturing process. It is additionally important to note that small

errors might be included due to the usage of THF as a blank sample instead of air, but these errors are neglected in this work.

5.5.2 Development of the kinetic model

5.5.2.1 Assumption of isothermic conditions inside the reactor

Successful development of the kinetic model involved several assumptions. Firstly, isothermic reaction conditions were assumed in the tubular reactor and therefore simulations of the temperarue profiles along the length and radius of the reactor were performed. The initial step in such investigations was to explore the temperature profiles just in the axial direction (z-coordinate), such as depicted in Figure 5.9. It is furthermore important to note that cylindrical coordinates were used in simulating temperature profiles.

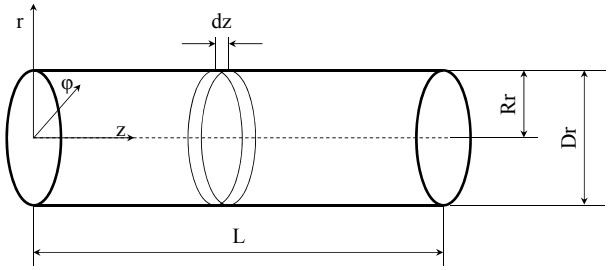


Figure 5.9 Schematic presentation of the reactor tube with coordinate systems and elements included in conservation equations. r,φ,z – spherical coordinates, L-length of the tubular reactor, dz – discretization element of the tubular reactor; Rr – Radius, D - Diameter

Furthermore, the velocity in the central area of the tubular reactor was assumed identical to the velocity at the entrance, such as suggested by Coker[362]. The same author recommended Equation 5.1 for the velocity distribution in the r-direction of the cylindrical coordinate system. The equation is depicted below:

$$w(r) = w_o \left[1 - \left(\frac{r}{R_r}\right)^2\right] \qquad 5.1$$

where

$w(r)$ - Velocity at the r distance from the middle of reactor ($\frac{m}{s}$);

w_o - Velocity at the entrance of the reactor ($\frac{m}{s}$);

r - Distance in the r direction (m);

R_r - Radius of the reactor (m).

In addition, Coker[362] claimed that the velocity in the centerline of the tube reactor (w_o) is equal to the double of the average entering velocity in the tubular reactor. Therefore, the average velocity applied during the calibration procedures (w) should be doubled for the centerline area.

Furthermore, additional assumptions were needed in order to perform successful preidiction of the temperature profile along the z-direction. They are:

- constant physical properties;
- pressure drop is negligible along the reactor;
- laminar flow;
- enthalpy of chemical reaction is excluded from the balance equation;
- convection is not neglected;
- cylindrical coordinates will be used where the z-axis is put as the axial direction;
- no changes in the φ-direction.

The following step in exploring temperature profiles was to implement defragmentation of the tubular reactor. Schematic view on such a small element was to study is depicted in Figure 5.10 together with the conservation equations important for evaluating the temperature profile.

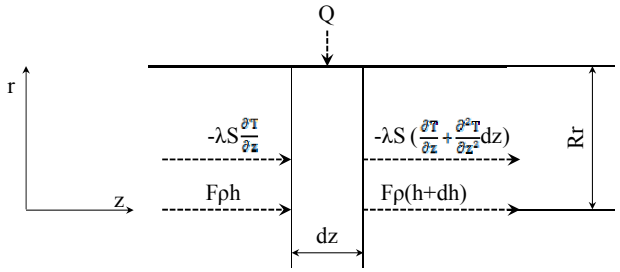


Figure 5.10 Fragment of the tubular laminar reactor. r,z – spherical coordinates, λ – thermal conductivity, S – cross-section area, T – temperature, F – flow rate, ρ – density, h – molar enthalpy, dz – discretization element, Q – heating energy rate per area, Rr – Radius of the reactor

Therefore, the energy balance could be written in the following form

$$\rho c_p \frac{\partial T}{\partial t} Sdz = -\rho c_p w \frac{\partial T}{\partial z} Sdz + \lambda \frac{\partial^2 T}{\partial z^2} Sdz + Q 2\pi R_r dz \quad 5.2$$

where

$$S = R_r^2 \pi \quad 5.3$$

$$w = \frac{2\,F}{S} \quad 5.4$$

$$Q = K_T(T_f - T) \quad 5.5$$

Further development of the energy balance included dividing both sides with $\rho c_p Sdz$ and rewriting the balance as Equation 5.6

$$\frac{\partial T}{\partial t} = -w \frac{\partial T}{\partial z} + \frac{\lambda}{\rho\, c_p} \frac{\partial^2 T}{\partial z^2} + \frac{2}{\rho\, c_p} \frac{Q}{R_r} \quad 5.6$$

Lastly, the discretization of Equation 5.6 was applied and the following expression was achieved:

$$T_{i+1,j} = T_{i,j} + dt\left[-\frac{w}{dz}\left(T_{i,j} - T_{i,j-1}\right) + \frac{1}{d_z^2} \frac{\lambda}{\rho\, c_p} \left(T_{i,j+1} - 2T_{i,j} + T_{i,j-1}\right) + \frac{2}{\rho\, c_p} \frac{K_T\left(T_f - T_{i,j}\right)}{R_r}\right] \quad 5.7$$

where i represents changes of the time variable, whereas j implies changes in the axial z-direction. All the parameters and variables are shown in Table 5.5 whereas the MATLAB code for solving the model is shown in Appendix A1.

The necessary parameters and variables are explained in Table 5.3.

Table 5.3 Parameters and variables used in for estimating temperature profiles alond the axial direction of the tubular laminar reactor

No.			Parameters/Variables	Unit	Value	Ref.
1.	ρ	-	Density	$(\frac{kg}{m^3})$	889	[363]
2.	c_p	-	Specific heat capacity	$(\frac{J}{kg\,K})$	1705	[364]
3.	λ	-	Thermal conductivity	$(\frac{J}{s\,m\,K})$	0.15	[365]
4.	K_T	-	Heat transfer coefficient	$(\frac{J}{m^2 K\,s})$	283.58	[366]
5.	T_f	-	Temperature of the heating fluid	(K)	393.15	-
6.	R_r	-	Radius of reactor	(m)	0.0032	-
7.	F	-	Volumetric flow rate	$(\frac{m^3}{s})$	$2.5 \cdot 10^{-8}$	-
8.	S	-	Cross sectional area	(m^2)	Eq. 5.3	-
9.	w	-	Average velocity (speed) of the fluid	$(\frac{m}{s})$	Eq. 5.4	-
10.	Q	-	Heating energy rate per area	$(\frac{J}{m^2 s})$	Eq. 5.5	-
11	T	-	Temperature	(K)	-	-

Results of the simulation pointed towards a very fast heating of THF along the central area in the axial direction of the tubular reactor. Figure 5.11 shows the results obtained by applying the discretization shown in Equation 5.7 combined with the parameter/variable values depicted in Table 5.3. It can be concluded easily that quite a uniform temperature profile is established after just 5 cm along the z-axis, i.e. almost immediately after the entrance to the reactor. In addition, it is important to emphasize that this temperature profile refers to the positions in the reactor that are furthest away from the reactor walls.

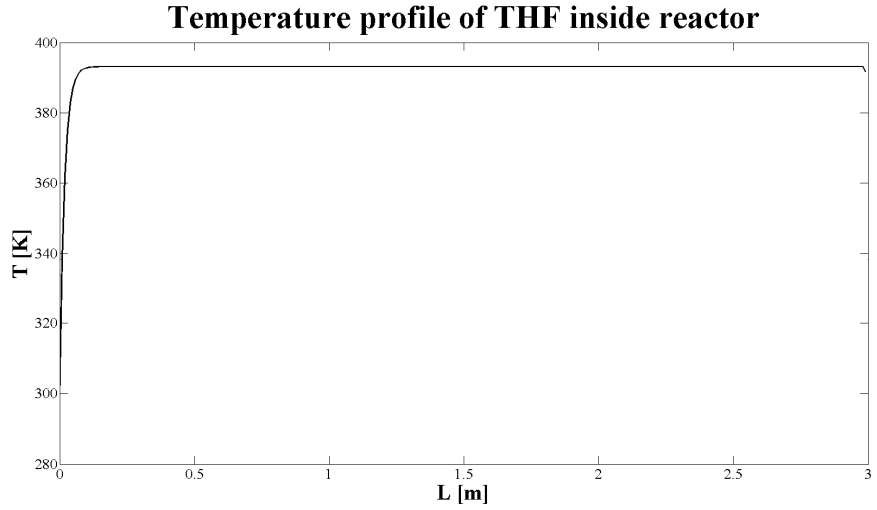


Figure 5.11 Steady state temperature profile of the solvent along the axial direction of the laminar tubular reactor

Besides the above analysis for r = 0, additional analyses were performed for different r values. More precisely, the values which are equal to 0.25 Rr, then 0.5 Rr, 0.75 Rr and Rr, were analyzed. Results are depicted in Figure 5.12 where it can be seen that the fastest heating to the desired temperature was achieved at the reactor walls (r=Rr). In this particular case, the energy transfer based on convection was neglected due to the absence of flow at the walls in laminar tubular reactors.

Furthermore, the slowest heating was observed in the middle of the tubular reactor because it is the point furthest away from the reactor walls. This behavior is depicted as a black line in Figure 5.12. Nevertheless, the desired temperature was achieved very fast and consequently the assumption about isothermic reaction conditions was confirmed.

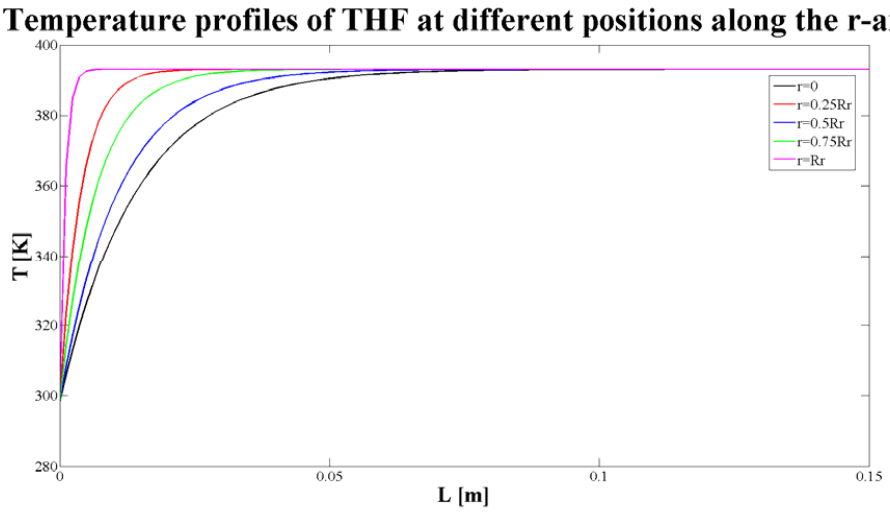


Figure 5.12 Steady state temperature profile of the solvent along the axial direction of the laminar tubular reactor for different values of the r-axis

It is important to note that three additional lines in Figure 5.12 represent different distances from the wall in the r-direction. An interesting behavior was observed referring to the switch between the lines describing temperature profile at 0.25Rr, 0.5Rr and 0.75Rr (red, blue and green lines, respectively). The expected order was according to the increase of the flow rate along the r-direction, however the obtained results implied a different behavior. More precisely, it can be concluded that thermal conductivity and heat transfer have a significant influence on the temperature profile in the r-direction.

Nevertheless, temperatures at all distances from the wall reach the maximum possible values over a distance which is less than 10 cm. This is an important conclusion supporting our assumption that isothermic reaction conditions are present in the tubular laminar reactor used for the dehydration reaction. This value is low compared to the total length of the reactor (3 m).

5.5.2.2 Kinetic model development

Development of the kinetic model was based on a set of 5 different samples carried out at 6 different temperatures. The starting molar concentration of "N714-Allylcarbinol" was 1.06 M and the value remained the same in all experimental runs. Furthermore, the molar concentration of H_3O^+ ions was varied from 0.02 M to 0.1 M. The applied temperatures were in the range from 25-120^{0}C with a step increase of 20^{0}C (only the T step corresponding to the first increase was different, from 25-40^{0}C).

Specifically for "N714-Allylcarbinol", a relationship between in-line data on the one hand and at-line and off-line data on the other hand was investigated. Figure 5.13 shows the molar concentrations that were obtained if the in-line mode was applied, whereas the primary and secondary y-axis refer to at-line and off-line molar concentrations, respectively. Standard deviations are additionally included as an indicator of the error between the different modes of analysis.

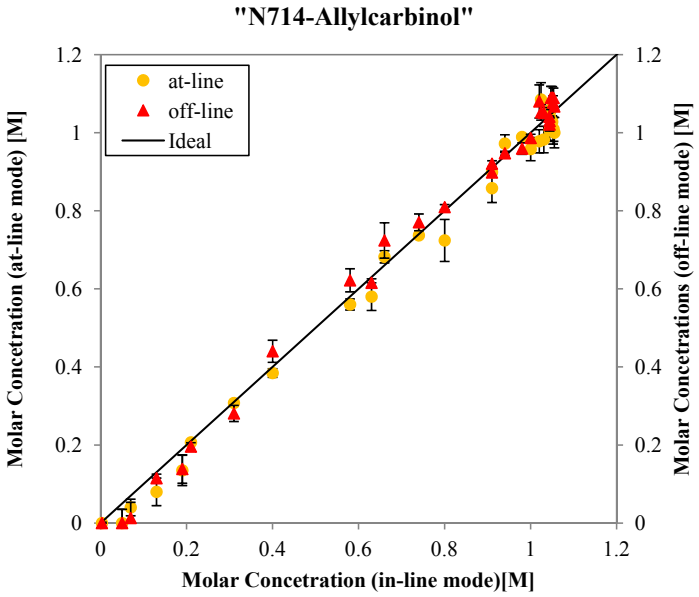


Figure 5.13 External validation of the experimental data obtained with in-line monitoring during development of the kinetic model for the dehydration reaction of "N714-Allylcarbinol"

It could be easily noticed that a very good correlation between in- and at-line experimental data was achieved, resulting in an R^2 = 0.993. Furthermore, off- and in-line data showed an excellent correlation as well (R^2 = 0.995), meaning that a very high accuracy was achieved. Therefore, it can be concluded that a good starting point for the kinetic model development was achieved. The good correlations also serve as a confirmation that the calibration models are quite good. It is important to note that building of the kinetic model was just based on the results obtained from the in-line FT-NIR data.

One of the starting assumptions in the kinetic model development procedure was that the chemical reaction is elementary and that it follows first order kinetics. Hence, the assumed kinetic model is shown in equation 5.8

$$r_r = -\frac{dC_A}{d\tau_r} = kC_A \quad 5.8$$

where

r_r - Reaction rate ($\frac{mol}{dm^3 s}$);

C_A - Molar concentration of "N714-Allylcarbinol" (M);

k - Reaction rate constant ($\frac{1}{s}$);

τ_r - Average residence time (s).

Solving the differential equation 5.8 with the following initial conditions: 1.06 M (C_{Ao}) and 0 s (τ_o), as well as with the following boundary conditions: C_A and τ = 256.2 s, lead to the expression depicted in Equation 5.9.

$$\frac{\ln\left(\frac{C_{Ao}}{C_A}\right)}{\tau_r} = k \quad 5.9$$

The latest equation resulted in a set of values for the reaction rate constant which varies as a function of the changes of the molar concentration of sulphuric acid as well as with temperature, of course. Further analysis was therefore performed in order to calculate all the constituents describing the reaction rate constant, such as depicted in the Arrhenius equation below:

$$k = k_o e^{-\frac{E_A}{RT}} \quad 5.10$$

where

k_o - Arrhenius pre-exponential factor ($\frac{1}{s}$);

E_A - Energy of activation ($\frac{kJ}{mol}$);

R - Universal gas constant ($\frac{kJ}{mol\ K}$);

T - Temperature (K).

The logarithmic version of Equation 5.10 is shown in Equation 5.11. Hence, determining the values of k and Ea would include plotting values for ln(k) as a function of inverse temperature.

$$\ln(k) = \ln(k_o) - \frac{E_A}{R}\frac{1}{T} \quad 5.11$$

As a result, a straight line is expected with good linear fitting. The results are depicted in Figure 5.14.

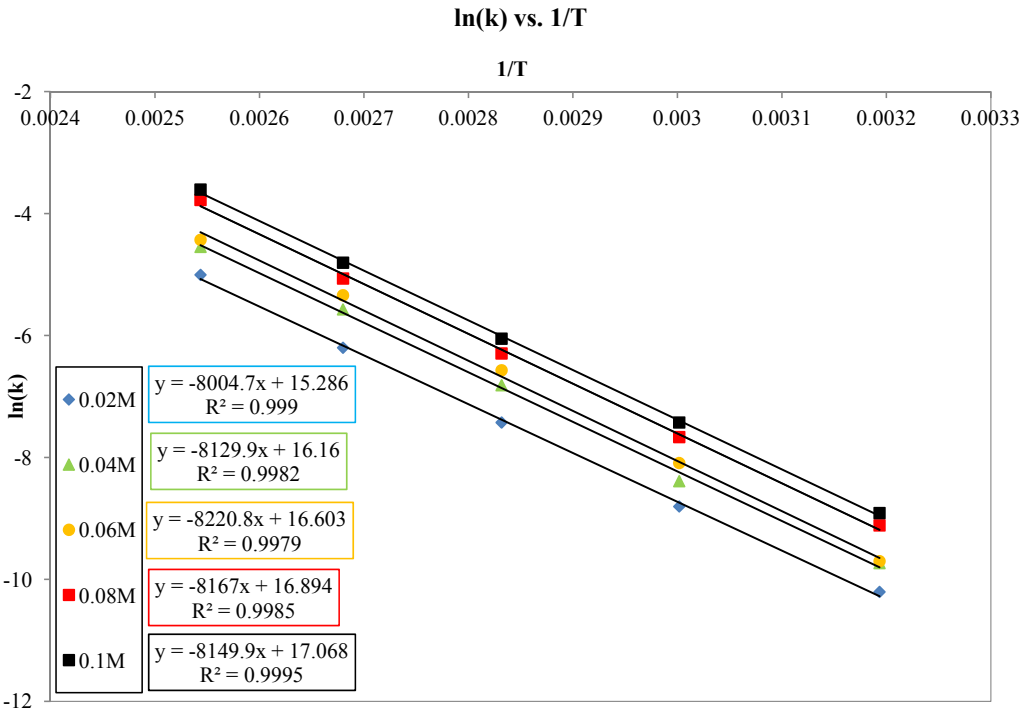


Figure 5.14 Relationship between ln(k) and inverse values of temperature with the main purpose to find values for the Energy of activation (E_A) and the pre-exponential factor in the Arrhenius equation (k_o). M – molar concentration of the chemical catalyst

It could be seen that the assumed kinetic model was actually correct because a very good fit was achieved (Figure 5.14). Furthermore, 5 different values of the molar concentrations of sulphuric acid resulted in different values for $\ln(k_o)$ and thereby influenced further investigations in the kinetic model development studies. However, the value for E_A was calculated from Figure 5.14 and is equal to 67792.86 $\frac{J}{mol}$.

Furthermore, a graph which would plot values for k_o obtained from Figure 5.14 versus values of the molar concentrations of hydronium ions present in the final solution is shown in Figure 5.15. A very good linear fitting was achieved thus confirming the linear dependence between pre-exponential factor and molar concentration of hydronium ions.

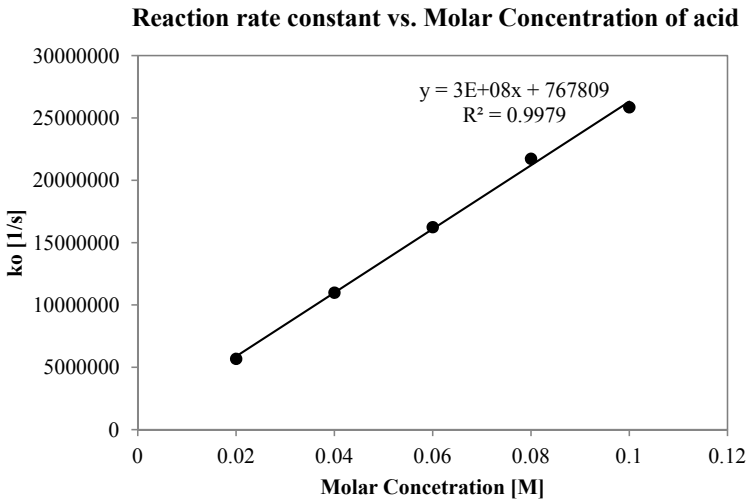


Figure 5.15 Relationship between Arrhenius pre-exponential factor (k_o) and molar concentration of hydronium ions [H^+] present in the reaction medium

More detailed analysis showed that the pre-exponential factor could be expressed as written below

$$k_o = k_1[H^+] + k_2 \qquad 5.12$$

where $k_1 = 2.55 \times 10^8 \frac{dm^3}{mol\,s}$ and $k_2 = 7.68 \times 10^5 \frac{1}{s}$.

Therefore, the final version of the kinetic model which describes the conversion of "N714-Allylcarbinol" during the dehydration reaction could be described as Equation 5.13.

$$-\frac{dC_A}{d\tau} = (k_1[H^+] + k_2)\, e^{-\frac{E_A}{RT}} C_A \qquad 5.13$$

Comparison between the model values for the molar concentration of "N714-Allylcarbinol" and experimental data points was done, as shown in Figure 5.16. A very good prediction of the alcohol conversion was achieved for all molar concentrations of the hydrogen ions present in the reaction mixture.

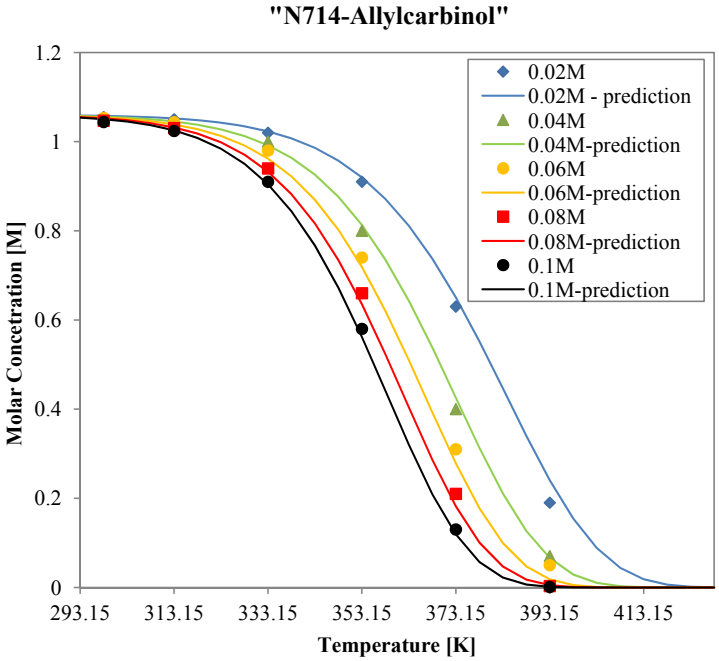


Figure 5.16 Conversion of "N714-Allylcarbinol" during the dehydration reaction. Lines show the predicted values whereas the points show the experimental data. Different molar concentrations of the chemical catalyst are coloured with different colours.

It is just additionally important to note that small prediction errors might be present in the areas with very low molar concentrations of alcohol, such as the concentration ragne below 0.1 M. The main reason for such behaviour might be a lack of calibration data points in that region (Figure 5.8 a). Nevertheless, a general impression conclusion is that a very good kinetic model was achieved

Furthermore, prediction of the molar concentrations of "N746-Butadienes" was done. In case of the perfect conversion, 1 mol of the alcohol would give the same amount of the butadiene at the end of the chemical reaction due to the equal stochiometry present in the chemical reaction. Hence, the modeled values for "N746-Butadienes" were calculated by subtracting the reacted amounts of "N714-Allylcarbinol" from the initial molar concentration of the same constituent.

Figure 5.17 depicts the difference between predicted and experimental data. It is important to note that standard deviations calculated between in-line, at-line and off-line measurements are also included. The main reason for such approach was to emphasize the impact of the experimental errors when calculating values for "N746-Butadienes".

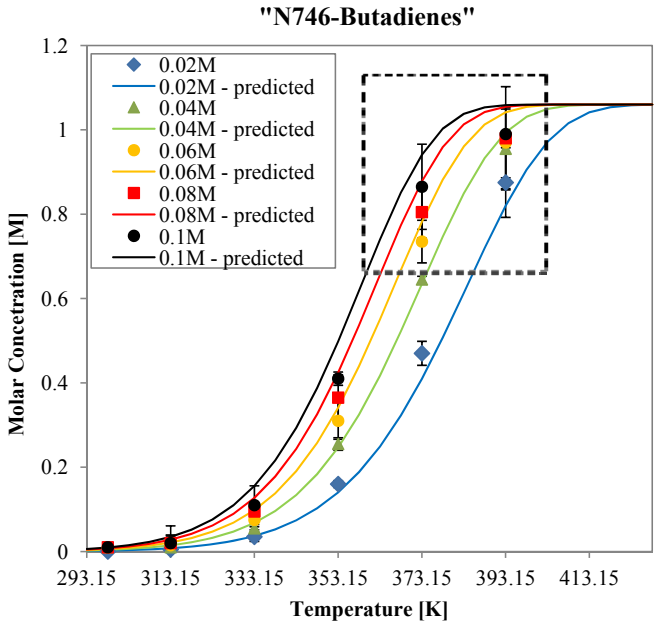


Figure 5.17 Synthesis of "N746-Butadienes" during the dehydration reaction. Lines refer to the predicted values whereas points represent the experimental data. Different molar concentrations of chemical catalyst are coloured with different colours.

Plotting predicted and experimental data for "N746-Butadienes" hints towards several undesired effects in the reaction system. As an initial conclusion, it could be noticed that the increase of the load of chemical catalyst indicates a decreased formation of the desired product. More precisely, 0.1 M solutions of hydronium ions result in significant over-predictions of the amount of synthesized butadiene. This behaviour is depicted as a black line in Figure 5.17.

Furthermore, it is easy to notice that quite high standard deviations are observed in the regions with high molar concentrations of "N746-Butadienes". This is caused by the significantly different results obtained when in-/at- and off-line analyses were applied. The main reason for such behaviour might be due to practical approaches during the sampling procedures. More precisely, in-line monitoring was performed almost immediately after the reaction, whereas the at-line and off-line modes included time delays. Hence a possibility that side reactions were not stopped is therefore very high although instrumental methods of analysis (HPLC and FT-NIR) did not imply on the presence of any impurities.

5.5.3 Polymerization tests

Applications of sulphuric acid as a chemical catalyst caused a very fast conversion of "N714-Allylcarbinol" during the dehydration reaction. However, it was noticed that certain amounts of the desired product disappear, and therefore the predicted and the experimental values did not show a good fit. One indication about potential side reactions was very-well known behaviour of THF in the presence of strong Brøndsted acids[367]. More precisely, opening the THF ring usually occurs together with the oligo- and polymerization of the obtained alkyl chains. The best chemical catalyst for such reactions is boron trifluoride[368]. However, the presence of the hydronium ion is always a very good initiator[369]. Therefore, any strong Brøndsted acid would influence the synthesis of poly-THF.

Furthermore, HPLC and FT-NIR did not indicate the formation of any additional components in the reaction system. It was therefore decided that NMR and SEC analyses should be performed. As a result, a significant number of peaks were observed in the NMR spectrum in the aromatic and alkyl regions, which is illustrated in more detail in Appendix A2.

The presence of polymers was not confirmed with the NMR analysis, and therefore it was necessary to perform SEC analysis. The obtained results implied the presence of compounds with very high molecular weight, thus confirming the presence of polymers in the reaction medium. However, it might be concluded that besides the polymerization of THF, certain amounts of polymers were also formed as a chemical reaction between the open THF rings and the intermediate products in the dehydration reaction (carbocation). Qualitative results are depicted in Figure 5.18, whereas the complete detailed report can be found in Appendix A2. Peaks at retention volumes 21 and 19 ml indicate the presence of compounds with high molecular weigths.

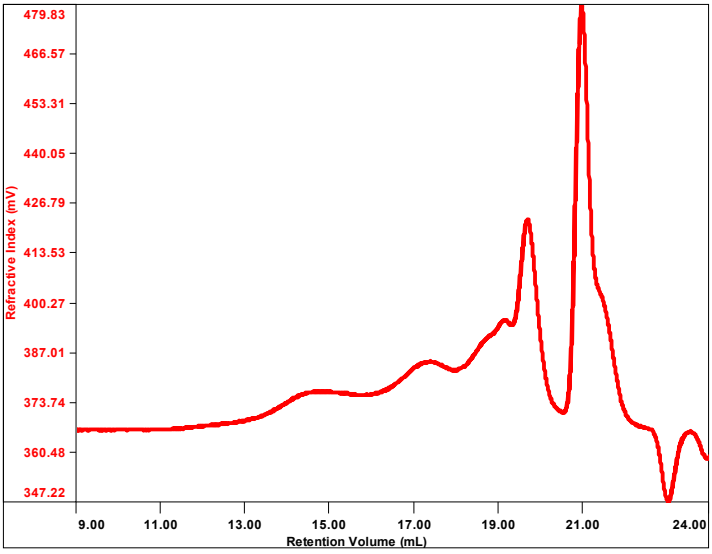


Figure 5.18 Identification of the polymers formed during the dehydration reaction

5.5.4 Process control

Development of the transfer function for process control purposes is based on the mass balance of this tubular reactor. The main reason for such an approach is the exothermic reaction conditions which were assumed in the section 5.3.1. Furthermore, some additional assumptions are needed in order to implement the conservation equation. More precisely, it is necessary to assume:

- constant physical properties;
- molar concentrations of components are changing just in the axial direction;
- the pressure drop is negligible along the reactor;
- cylindrical coordinates will be used where the z-axis represents the axial direction.

According to these assumptions, changes of the molar concentration will just occur in the z-direction. A further step in the evaluation of the material balance is to implement a discretization of the laminar tubular reactor. A scheme which represents inputs and outputs inside one of the segments is shown in Figure 5.19. It is important to note that F is the inlet volumetric flow rate, dz is the segment width, D is the effective diffusion coefficient and S is the cross-sectional area.

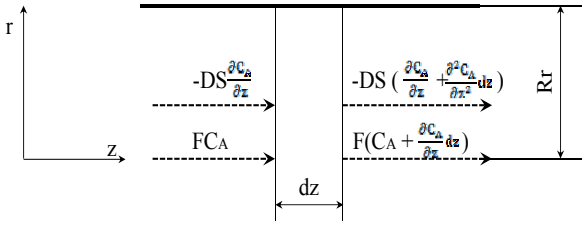


Figure 5.19 Schematic presentation of a segment of a tubular reactor with the contributions needed for calculating a component material balance

Hence, the component material balance could be written in the following form

$$\frac{\partial C_A}{\partial t} Sdz = -F\frac{\partial C_A}{\partial z}dz + D\frac{\partial^2 C_A}{\partial z^2}Sdz + \nu_A r_r Sdz \qquad 5.14$$

which becomes equation 5.15 after dividing by Sdz.

$$\frac{\partial C_A}{\partial t} = -w\frac{\partial C_A}{\partial z} + D\frac{\partial^2 C_A}{\partial z^2} + \nu_A r_r \qquad 5.15$$

Hence, Equation 5.15 could therefore be modified in the following form

$$\frac{\partial C_A}{\partial t} + w\frac{\partial C_A}{\partial z} + (k_1[H^+] + k_2)e^{\left(-\frac{E_a}{RT}\right)}C_A = 0 \qquad 5.16$$

Further work was based on evaluating dominant forces in the meso-scaled devices. Hence, indicators such as Re, Pe and τ_D were calculated in order to evaluate which phenomena are major drivers in our particular system. The results are summarized in Table 5.4. It is important to note that that a value of $1 \cdot 10^{-9}$ $\frac{m^2}{s}$ was used as a diffusion coefficient[266] whereas additional parameters are listed in Table 5.3.

Table 5.4 Calculating Re, Pe and τ_D for evaluating dominant forces in the tubular laminar reactor

No.	Parameters	Eq.	Conclusion
1.	Re = 79	3.5	laminar flow
2.	Pe = 5015	3.6	advection is dominant
3.	τ_D = 672.04 min	3.8	Very slow mixing based on diffusion

Table 5.4 indicates that Pe>>1, which directly emphasizes that mixing is mainly based on the advection mechanism. Therefore, the equation 5.15 could be simplified by simply excluding the diffusion part, and the simplified equation can be processed further in the suitable transfer function for evaluation of the process dynamics.

After introducing a perturbation and rewriting equation 5.16 in the form of deviation variables, the Laplace transformation is performed. As a result, the equation in the Laplace domain was obtained, as depicted below:

$$\frac{dC_A(z,s)}{dz} = -\frac{\left(s + (k_1[H^+] + k_2)e^{\left(-\frac{E_a}{RT}\right)}\right)z}{w}C_A(z,s) \qquad 5.17$$

Integration of the ordinary differential equation 5.17 for the desired length of the tubular reactor (z) and knowing the molar concentration of "N714-Allylcarbinol" at the reactor inlet led to the following expression:

$$C_A(z,s) = C_A(0,s)e^{-\frac{\left(s+(k_1[H^+]+k_2)e^{\left(-\frac{E_a}{RT}\right)}\right)z}{w}} \qquad 5.18$$

Hence, assuming that we now have two tubular reactors in series, and assuming that the length of the first reactor is L and the second one is L_2, the obtained transfer function for our system could be the following

$$G_s = \frac{C_A(L + L_2, s)}{C_A(0, s)} = K * e^{-\frac{s(L+L_2)}{w}} \quad 5.19$$

where

$$K = e^{-\frac{(k_1[H^+]+k_2)e^{\left(-\frac{E_a}{RT}\right)}(L+L_2)}{w}} \quad 5.20$$

Implementation of the classical feedback control loop by using either P, PI or PID controller did not result with reasonable results. Experimental runs including individual or combined step changes in molar concentrations of "N714-Allylcarbinol", then molar concentrations of hydronium ions, temperatures and volumetric flow rates. Constant adaptation of the controller was required due to the changes in the process gain. Hence, applications of the adaptable controller is demanded in order to predict process dynamics of such tubular laminar reactor[370-375].

5.6 Conclusions and future perspectives

Dehydration of "N714-Allylcarbonol" to the mixture of "N746-Butadienes" was significalty accelerated by applying a transfer from batch towards meso-scaled tubular laminar reactor. Increase from 2 h to just 3 minutes was obtained by increasing reaction temperature from the normal boling ponit of THF to 120^0C. For this purpose, a back-pressure system was used in order to allow higher boling points of THF.

Multivariate calibration was developed greatly with the main aim to implement in-line process monitoring. Hence, acquiring data was achieved in a very fast mode. In addition, external versifications of the obtained results were performed with off-line HPLC analysis and additionally at-line FT-NIR analysis by using second detector of the instrument. It is important to note that results obtained by using in-line mode were even more accurate that the at-line results due to the absence of human errors due to the inappropriate placing of cuvetes in the sample holder.

A very successful kinetic model development was obtained based on the data achieved with the in-line process montirong. Very good heat transfer through the reactor wall influenced on almost complete absence of the temperature gradients along the radius of reactor. Hence, an isothermic reaction conditions in the reactor were assumed in a justified manner.

However, complete conversion of "N714-Allylcarbinol" did not lead to the desired products. More precisely, side reactions based on the polymerization mechanism were present in the reaction system due to the presence of the hydronium ion and THF. Hence, formations of poly-THF and

additional polymers were performed. It was therefore decided that futre work includes either neutralization of the hydronium ions with aqueous $NaHCO_3$ or to perform this step in the another solvent, such as toluene.

Lastly, process control simulations were performed. A step change in the inlet concentrations was considered, however fluctuations in flow rates, then molecular concentrations of acids and additionally changes of temperatures might be considered as potential disturbances in such system. This approach would require an adaptable controller and therefore it could be a future work.

6. Stereo-selective Synthesys of cis “N746-Butadiene”

Abstract

Stereo-selective synthesis of “cis-N746 Butadiene” is a bottleneck in the overall Zuclopenthixol production. Undesired stereoselectivity in the dehydration of “N714-Allylcarbinol” is caused by higher stability of the “trans-N746-Butadiene” and therefore big losses are usually faced. Side reactions additionally lead to the production of significant amounts of by-products. Furthermore, the similarity of the geometrical isomers causes complicated downstream processing and consequently plenty of economic disadvantages. Hence, screening of different Brøndsted and Lewis acids, as well as combinations of Lewis acids and Lewis bases, is performed in this chapter in order to increase stereoselective synthesis of “cis-N746 Butadiene”. Increases from 42% up to 62% are obtained, however with significantly modified reaction conditions.

6. Stereo-selective Synthesis of cis "N746-Butadiene"

6.1 Introduction

Formation of carbon-carbon double bonds is a very important synthetic pathway in modern organic synthesis. It is usually performed via dehydration of alcohols whose reactivity is dependent on their chemical structure. More precisely, the reactivity is increasing starting from primary towards tertiary alcohols[361]. It is additionally also important to note that plenty of practical applications have been realized in the pharmaceutical industry, as well as in the manufacturing of fine chemicals[376].

Despite just performing the dehydration reaction, it is usually required to produce particular geometrical isomers of unsatured hydrocarbons. The main reasons to prefer only one particular isomer are associated with the medical activities of different isomers. Therefore, it is very common that just one of the isomers can be applied as API whereas the second isomer is considered as a by-product. In some cases it is possible to perform isomerisation afterwards; however one has to realize that the isomerisation procedure could be a very demanding operation in case of similar structures of the geometrical isomers.

It is important to note that synthesis of cis isomers is a challenging approach due to the presence of electronic repulsions between atoms placed on the same side of the double bond. This phenomenon has been investigated in the literature and several different synthetic pathways have been found. For instance, different Brøndsted and Lewis acids could be used to dehydrate different types of alcohols selectively. In addition, chemical reactions such as the Peterson olefination[377], the Tebbe olefination[378] and the Wittig reaction[361] could lead to cis-alkenes or cis-dienes starting from the carbonyl compounds.

The main focus here is to increase stereoselectivity towards the cis isomer of "N746-Butadiene" and therefore to avoid production of undesired by-products. Special attention is given to this production step because it is might be defined as a bottleneck in the overall Zuclopenthixol synthesis. One of the main reasons to focus on this step is the fact that significant economic benefits could be achieved with increasing stereo-selectivity. In addition, a brief overview about potential chemical catalysts is provided in the beginning of this chapter, whereas practical screening of chosen Brønsted and Lewis acids is additionally performed.

6.2 Brief overview of the dehydration agents

Dehydration of alcohols is a usual synthetic route to unsaturated hydrocarbons. It is based on the β-elimination principle where a hydroxyl group is modified into an OH_2^+ leaving group. To this purpose, the protonation principle is used by applying acidic media[379], such as described in chapter 5. Brøndsted acids are usually used amongst whome sulphuric and phosphoric acids have found a wide range of applications[380]. Considering organic compounds, a very important role is givent to toluensulfonic acid (TsOH) which might lead to the increased synthesis of cis isomers[381].

Besides the Brønsted acids, a significant role is given to Lewis acids in such elimininations reactions. For instance, Wattley and coworkers[382] tested several combinations of Lewis acids/Lewis bases and obtained excellent results regarding stereo-selectivity. Applications of trifluoroacetic acid anhydride (TFAA) and trimethyl amine (Me_3N) at significantly lowered temperature (down to -78^{0}C) resulted exclusively with the formation of cis-products. Furthermore, combinations of TFAA and triethyl-amine (Et_3N), as well as thionyl chloride ($SOCl_2$) and Et_3N resulted with 98% and 65% of cis-isomers, respectively. In addition, Clark and coworkers[383] added p-(dimethylamino)pyridine (DMAP) to the combination of TFAA and Et_3N and consequently achieved 75% of the desired cis-isomer at room temperature. It is important to note that dichloromethane (DCM) was used as a solvent in all the examples, which has a disadvantage of being undesired solvent in the pharmaceutical industry[341].

It is important to note that it is also possible to apply an integrated version of Lewis acid and bases. One of the examples is N-(triethylammoniumsulfonyl)carbamate or in other words the Burgess reagent. It was developed almost three decades ago by Edward M. Burgess[384] and has found plenty of applications in modern organic synthesis. Some of them are:

- dehydration of alcohols into unsaturated hydrocarbons (mostly alkenes)[385-389] under neutral conditions and at low temperatures[390];
- dehydration of amides to nitriles[391];
- conversion of alcohols to carbamates[392, 393].

Heterogeneous versions of Lewis acids are researched intensively, as well. The major drivers towards heterogenization of Lewis acids are potentially higher activity and higher stability of the heterogenized acids, as well as easier downstream processing. Dabbagh and coworkers[394], tested TiO_2, Ga_2O_3, Al_2O_3 and WO_3 and achieved high cis-selective dehydrations of secondary alcohols (2-octanol in particular). Furthermore, Bernal and coworkers[395] extended the list by adding La_2O_3, CeO_2, Pr_6O_{11}, Sm_2O_3, Eu_2O_3, Dy_2O_3 and Yb_2O_3 and achieved very cis-selective dehydrations of butanols[395]. Nevertheless, the best results were achieved with applying alumina as a dehydrating agent[395, 396], especially if the acidic version was used[397].

It is also important to note that plenty of research is going on in the field of dehydrating biomass, which is focused on developing catalysts with both Lewis and Brønsted centres. In this way, the advantages of both types of centres could be achieved simultaneously. A very comprehensive review on this topic was written by Rinaldi and coworkers[398].

6.3 Materials and methods

Screening of different chemical catalysts for stereo-selective synthesis of "cis-N746-Butadiene" could be performed by using exothermic and endothermic reaction conditions. Depending on the catalysts which are applied (or combinations of catalysts), two different experimental setups were used:

- experiemental setup for endothermic chemical reactions;
- experimental setup for exothermic chemical reactions.

The same column and HPLC equipment were used as described in chapter 5, however with different method and sampling procedures.

6.3.1 Experimental setup for endothermic reactions

Endothermic synthesis of "cis-N746 Butadiene" was performed in batch mode. To this purpose, disposable 4 ml glass vials were used as reactor vessels and were sealed with polypropylene screw caps. It is important to note that 12 mm teflon septums were added in order to increase the stability of the caps against aggressive solvents. These reactor vessels were placed in the HLC Biotech thermomixer (model MHR11) which was used as a heating medium. A rack with 16 places was found very suitable for the screening purposes.

Experiments were carried out by applying 1 M solutions of "N714 Allylcarbinol". To this purpose, a crystallized version of the alcohol was used. More particularly, 1 mmole of the alcohol was measured on the analytical balance and carefully distributed in a 4 ml glass vial. After this step, 1 ml of a desired solvent was added and mixing on the IKA® MS 3 basic vortex device was applied. In order to have consistent preparation conditions, every reactor vessel was mixed 5 s with the vortex which was long enough to achieve total dissolution of "N714-Allylcarbinol" in each of the solvents used for screening. The tested solvents were toluene (TOL), benzene (BEN), dimethyl-formamide (DMF) and THF.

The second phase of preparing reaction media was focused on measuring the desired amounts of chemical catalysts. The same analytical balance was applied because the tested chemical catalysts were all in solid form. After measuring 1 mmole of a desired catalyst, the powder was added into a reactor vessel and mixing with the vortex was applied again. It is important to note that a 5 s mixing procedure was used here which was long enough to dissolve Burgess reagent and TsOH into each of the four solvents tested in this screening procedure.

The applied experimental condiditions were constant for all experimental runs. Temperatures of 40^0C, then a stirring rate of 500 rpm and an overall reaction time of 20 hours were applied. These reaction conditions were chosen due to the low boiling point of THF. Furthermore, from a literature survey it was concluded that room temperature or slightly higher values were preferred due to the better stereo-selectivity at lower temperatures[382]. Samples were taken after 0, 2.5 h, 5 h and 20 h,

and were then analyzed by HPLC. The analytical and sampling procedures are described in section 6.3.3.

Lastly, disposable experimental equipment was purchased from VWR International (vials, septums and caps) whereas the HLC Biotech Thermomixer was bought from TG Instrument AB. Solvents and chemical catalysts were bought from SIGMA-ALDRICH whereas crystallized "N714-Alllylcarbinol" was obtained from the manufacturing sites of H. Lundbeck A/S (Lumsås).

6.3.2 Experimental setup for exothermic reactions

Exothermic chemical reactions were performed in the fume hood in a more sophisticated experimental setup as well. The main reasons for performing reactions in this setup are the very low reaction temperatures (-68^{0}C), as well as the potential formation of toxic gasses as by-products. Therefore, some caution was exercised in performing such experimental runs.

A three-neck round bottom glass flask with an overall volume of 25 ml was used as a batch reactor vessel. Each neck had the same dimensions and was used for a different purpose. As depicted in Figure 6.1, one entry was accommodated for inserting a nitrogen supply in order to work under a nitrogen atmosphere, whereas the second and the third were used for entering the Lewis acid and for monitoring the reaction temperature, respectively.

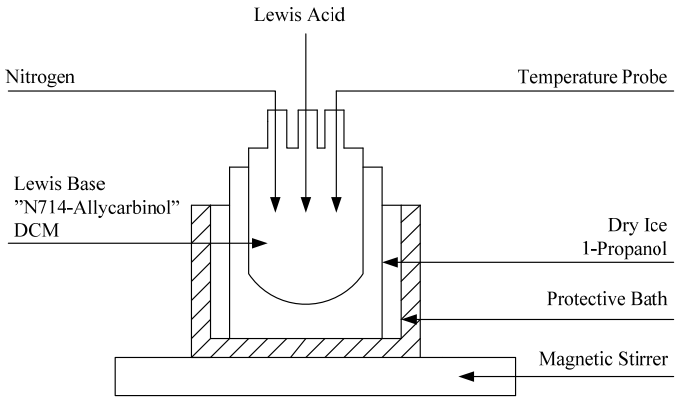


Figure 6.1 Scheme of the experimental setup used for performing exothermic stereo-selective synthesis of "N746-Butadiene"

The batch reactor was placed in a dry ice bath. The required temperature for such chemical reactions was very low (-78^{0}C) and therefore a mixture of 2-propanol with dry ice was used for this purpose. Such a low temperature caused very easy freezing of the moisture present around the

equipment and therefore the reactor was placed in the dry ice bath which was then put in the larger glass vessel. The last one was just filled with air and was packed in aluminium foil. In this way, freezing of the moisture inside the fume hood was minimized, as well as a good protection of IKA® RCT basic magnetic stirrer was achieved. A stirring rate of 500 rpm was applied without any problems.

Experimental runs were carried out by applying 0.2 M solutions of "N714-Allylcarbinol" in DCM. More precielly, the analytical balance was used for measuring 1 mmole of the crystallized "N714-Allylcarbinol" which was afterwards transferred to the three-neck bottom flask. The next step was to add 5 ml of DCM and to perform careful shaking by hand till the dissolution of the alcohol. Furthermore, 3 mmole of a desired Lewis base were added and shaking was performed again.

After dissolving the alcohol and the Lewis base in the reactor vessel, it was necessary to connect the reactor with the rest of the equipment. Besides the dry ice bath and the larger protective glass around the reactor, it was necessary to introduce a nitrogen atmosphere through one of the inlets. This was done by using two needles – one for introducing nitrogen and another one for removing the inert gas. Both needles were placed in one of the inlets/outlets by piercing the polyproline caps. Furthemore, the Vernier temperature probe was introduced through the polyprolene cap in the second inlet/outlet. The last inlet was closed with the third polyproline cup and occasionally opened in order to perform sequential additions of the Lewis acid.

It is important to note that 1 equivalent of Lewis acid was added by applying 5 equal portions. More precisely, the acid was added every 10 min and the addition was completed after 50 min. Nevertheless, the chemical reaction was allowed to proceed up to 135 minutes, which was the recommended time for the completition of this elimination reaction[382]. The reaction temperature was monitored in the middle of the chemical reactor and a value of -68^0C was usually recorded. Temperature gradients within the batch reactor, as well as the heat release after adding the Lewis acid, could be potential reasons for such temperature increase compared to the dry ice bath temperature.

After the necessary reaction time was passed, the reaction mixture was quenched with a 4 M aqueous solution of potassium-hydroxide (KOH). It is important to note that such quenching was performed slowly, and following the removal of the batch reactor from the dry ice bath.

The following step was to separate liquid layers and perform successful sampling and HPLC analysis. DCM and water are immiscible liquids, and it was therefore easy to separate both layers by using an extraction funnel afterwards.

6.3.3 Sampling procedure and HPLC analysis

The sample preparation procedure includes the addition of 1 ml of ethyl-acetate as a diluent and 5 µl of a desired reaction mixture if an endothermic reaction was studied, or 10 µl in case of exothermic chemical reactions. In this way, dilution factors of 201 and 101 were applied, respectively. All of the samples were analyzed with the same HPLC equipment as described in section 5.3.2.2. Therefore, the LaChrome Elite HPLC equipment with the Diode Array Detector (DAD) and Phenomenex Gemini C6-Phenyl Column were used.

However, a new HPLC method was applied in order to separate peaks of the geometrical isomers. More precisely, a 25-min isocratic method was used with the mobile phase consisting 78% v/v of methanol and 22% v/v of the buffer solution with pH = 9. The aqueous buffer was prepared by using a 50 mM aqueous solution of ammonium formate (NH_4HCO_2) and several drops of ammonium-hydroxide (NH_4OH) in order to adjust to the desired pH.

It is important to note that an assumption was made regarding the UV absorptivities of the gemometrical isomers. Hence, due to their very similar chemical structures, it was assumed that the absorptions of the UV-light for both isomers were the same. The applied wavelength was 254 nm. In addition, a derivatization technique was applied in order to confirm this theory, as well as to identify retention times of the geometrical isomers. Hence, the hydroamination reaction (chapter 7) was performed involving a huge excess of 1-(2-hydroxyethyl) piperazine (HEP). In this way, cis/trans Clopenthixols were obtained in the same ratios as assumed cis/trans "N746-Butadienes" and therefore a connection between peaks in chromatograms was established. It is important to note that just a few samples were treated with the derivatization technique.

Internal Lundbeck compounds were provided from the manufacturing site in Lumsås whereas all additional chemicals were purchased from SIGMA ALDRICH. Disposable HPLC vials and caps were bought from VWR International.

6.4 Results and discussions

6.4.1 Endothermic chemical reactions

Applications of strong Brøndsted acids resulted in just 42% of the desired "N746-Butadiene" (see chapter 5). Hence, tests to increase the stereo-selectivity were performed here by using two different chemical catalysts. The Burgess reagent and Toluensulfonic acid were tested in the screening procedure, as well as four different solvents: benzene, toluene, dimethyl-formamide and THF. The first three were recommended from the literature (chapter 6.2) whereas THF was tested because it is the most desired choice for our particular system. In addition, the consequent step, the hydroamination reaction, is also supposed to be performed in THF (section 7).

Focusing on the Burgess reagent, it is important to note that elimination of the hydroxyl group resulted with above average conversions of "N714-Allylcarbinol". Complete conversion was only achieved if THF was used as a solvent, such as depicted in Figure 6.2 a). This approach would imply on a significant simplication of the overall manufacturing setup in the Zuclopenthixol synthesis because it would allow the use of THF throughout the synthesis. However, a significant increase in stereoselectivity was not achieved. More precisely, just 48% of the cis "N746-Butadiene" was obtained leading to an increase with just 6% compared to the usage of cheap Brønsted acids. The results regarding steroselectivity are depicted with the blue bar in Figure 6.2 b).

a) b)

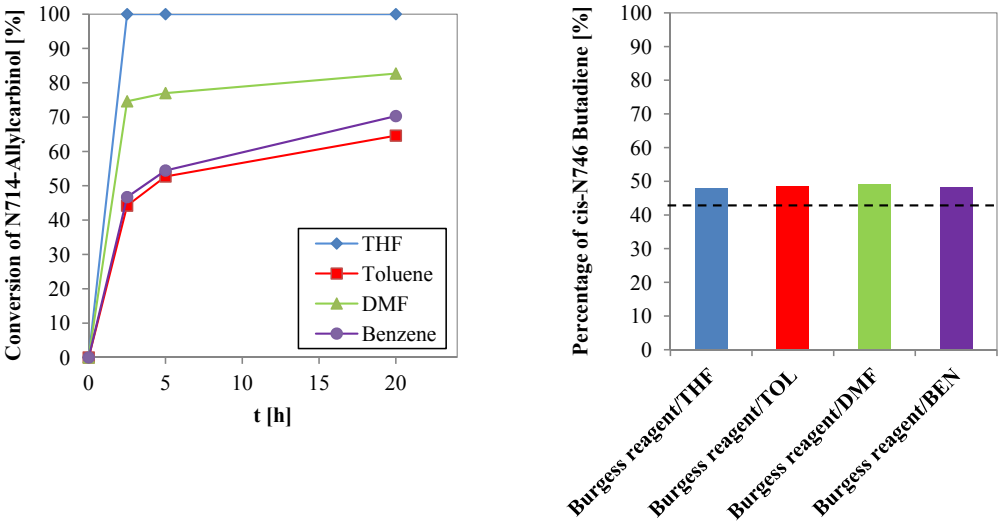


Figure 6.2 Single runs in the stereo-selective synthesis of cis "N746-Butadiene" if the Burgess reagent was applied as a chemical catalyst: (a) conversion of "N714-Allylcarbinol" during the elimination reaction and (b) stereo-selectivity when different solvents were applied with additional dashed black line implying on the stereo-selectivity achieved in case of using sulphuric acid as a chemical catalyst and THF as a solvent

The usage of DMF also showed above average conversion of the tertiary alcohol. As shown in Figure 6.2 a), the overall conversion went up to 83% with DMF. However, rather long reaction times together with a relatively low stereo-selectivity (green bar in Figure 6.2 b)) actually did not bring any improvements. Furthermore, application of toluene and benzene resulted in slightly above average conversions of "N714-Allylcarbinol", as shown in Figure 6.2 a) with red and purple lines respectively. In addition, these two solvents did not give significant improvements in the stereo-selectivity of the reaction, as depicted in the bar chart in Figure 6.2 b).

It can be concluded that applications of the Burgess reagent did not bring expected improvements in the stereo-selectivity. Relatively long reaction times are not a big issue because they could be avoided by applying the methodological approach described in chapter 3. Hence, accelerations and adaptation of such chemical reactions to continuous manufacturing modes might be performed just by increasing the temperature, i.e. on the basis of the predicted effect of the Arrhenius equation on the reaction rate. However, none of the approaches resulted in significant improvements, and therefore further tests for achieving improved stereo-selectivity were performed.

The second chemical catalyst of choice for the endothermic elimination of the hydroxyl group was toluensulfonic acid. The same group of solvents as before was tested, and results are summarized in Figure 6.3 a) and b).

a) b)

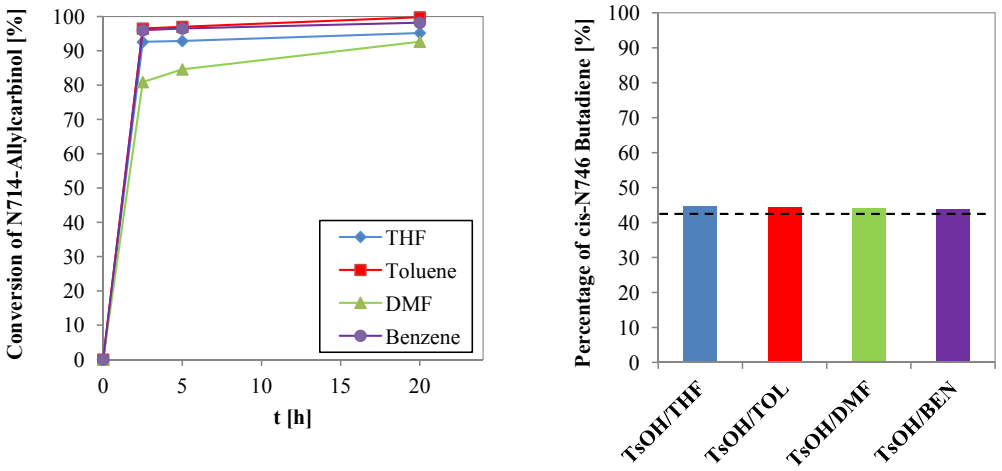


Figure 6.3 Single runs in the stereo-selective synthesis of cis "N746-Butadiene" if Toluensulfonic acid was applied as a chemical catalyst: (a) conversion of "N714-Allylcarbinol" during the elimination reaction and (b) stereo-selectivity when different solvents were applied with additional dashed black line implying on the stereo-selectivity achieved in case of using sulphuric acid as a chemical catalyst and THF as a solvent

It can be seen that toluene and benzene showed impressive conversions of "N714-Allylcarbinol" if TsOH was used. The results are shown as red and purple lines in Figure 6.3 a), respectively. However, despite the fact that total conversion was not achieved for both solvents, it is important to note that these results are totally different compared to the tested application of the Burgess reagent, when the mentioned solvents had the worst conversions. Furthermore, DMF and THF resulted in a high conversion (above 90%) as well, as depicted with green and blue colour in the same Figure.

Nevertheless, the relatively high conversions achieved with all the mentioned solvents did not result in increased stereo-selectivity. As shown in Figure 6.3 b) applications of TsOH represent a step backward compared to the usage of the Burgess reagent because of the lowered stereoselectivity. Hence, a new approach needs to be tested.

6.4.2 Exothermic chemical reactions

Exothermic elimination of hydroxyl groups from tertiary alcohols could be performed by applying suitable combinations of Lewis acids and Lewis bases. Focusing on "N714-Allylcarbinol" and its stereo-selective elimination reaction, it is important to note that just a few combinations were tested. All of them were recommended by the literature survey, which is summarized in section 6.2.

Preliminary results about the stereo-selective synthesis of "cis-N746 Butadiene" are depicted in Figure 6.4. As could be seen, seven different combinations were tested amongst whom the best results were obtained if the combination of TFAA and Et_3N in DCM was used. Applying this catalytic mixture resulted in 61% of the desired "cis-N746 Butadiene". However, repeatability of such approach showed that it was difficult to achieve identical results. The main reasons for this might be linked to the potential effect of impurities that are left behind when using the standardized washing procedures. Hence, it was decided that the combination consisting of TFAA/Et_3N/DCM was not the main point of focus for future research.

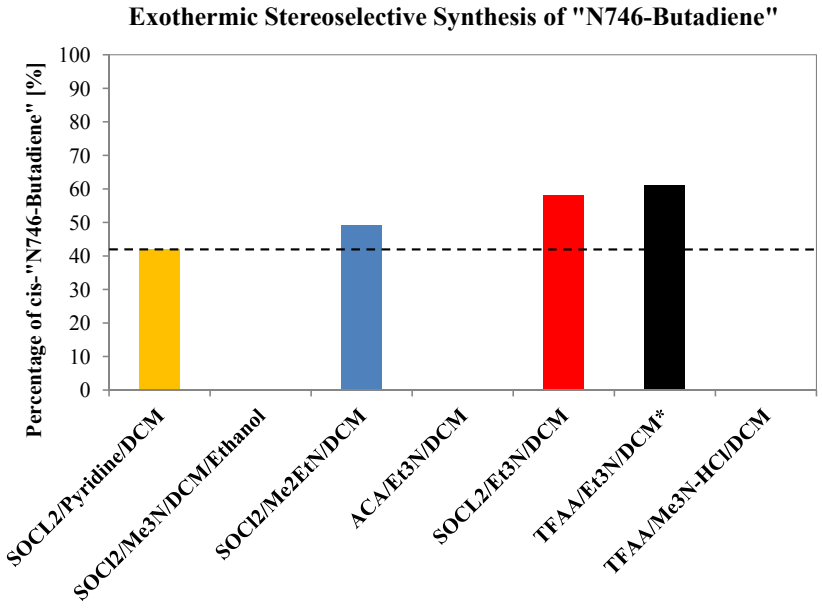


Figure 6.4 Stereo-selective synthesis of "cis-N746 Butadiene" by applying Lewis acids and bases via exothermic reaction pathway

Furthermore, the combination of $SOCl_2$/Et_3N/DCM showed increased stereo-selectivity compared to the values achieved when concentrated sulphuric acid was applied. More precisely, an increase from 42% to 58% was achieved. However, the reaction time was significantly prolonged. This combination is depicted in Figure 6.4 as a red coloured bar. It could be noticed that it is the second best combination, however also here it was concluded that this approach is not good enough to justify further investigations in this direction.

Besides testing combinations of Lewis acids with Et_3N, different Lewis bases were additionaly tested. Applications of $SOCl_2$ with pyridine and dinethylethylamine (Me_2EtN) resulted in 42% and 49% of the cis isomer, respectively. The results are depicted as yellow and blue coloured bars in Figure 6.4. Hence, the application of pyridine as a Lewis base was more suited for producing the trans isomer due to the repulsion forces between lone electrons on the chlorine atom and electronic clouds present in the molecular structure of pyridine.

Applications of Me_3N and its hypochlorite version, then followed by addition of ethanol in the reaction mixture, as well as a combination of acetic acid anhydride (ACA) with Et_3N, did not give any results under the mentioned reaction conditions. Furthermore, applications of other solvents except DCM did not give any conversion of "N714-Allylcarbinol". The tested solvents were THF, Me-THF and toluene.

Reagrding the conversions, the application of Lewis acids and bases did not lead to the complete conversions of "N714-Allylcarbinol". The results are depicted in Figure 6.5. It can be seen that applications of $SOCl_2$ and Me_2EtN showed the highest conversion within the 135 min reaction time. Moreover, a significant conversion in the reaction system consisting of TFAA and Et_3N was achieved, but again problems with repeatability occurred. The obtained conversions were 78% and 68%, respectively. However, the conversion does not really allow to directly calculate the yield of the desired butadiene due to formation of small amounts of by-products. The name and the structure of the by-product is unknown, but according to the HPLC analysis, the by-product appears at the retention time 6.68s. Therefore, it was called RT 6.68.

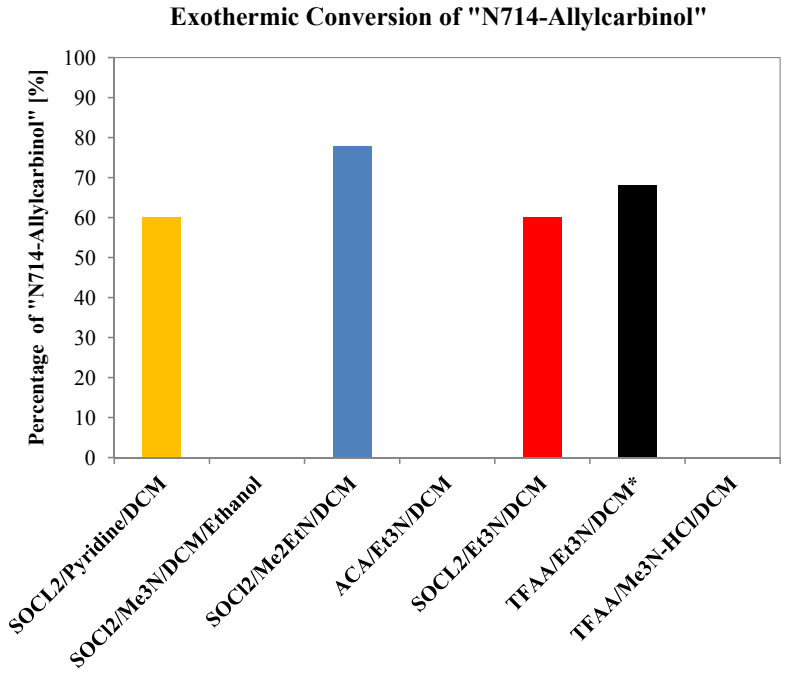


Figure 6.5 Conversion of "N714-Allylcarbinol" during the exothermic stereo-selective synthesis of "cis-N746 Butadiene"

6.5 Conclusions and future work

Improvements in the stereo-selective synthesis of "cis-N746 Butadiene" were achieved when combinations of Lewis acids and Lewis bases were applied. Applications of the combinations involving TFAA/Et_3N/DCM resulted in a significant increase of the amount of the synthesized cis isomer. More precisely, an increase from 42% to 61% was achieved, however at the expense of longer reaction times and more harsh reaction conditions. Further improvements in using this catalytic system might involve introduction of more adequate dosage of the Lewis acid. The desired way is to use a dropwise manner in a larger batch reactor (up to 0.5 l).

Application of the endothermic reactions did not show significant improvements. The expensive Burgess reagent resulted in a slightly increased stereo-selectivity, but that increase was insignificant to justify further investigations in this area. In addition, solvents used in such screening are labelled as dangerous and therefore not desired in the modern pharmaceutical industry.

Lastly, potential applications of enzymes should be considered, as enzymes are known to be very stereospecific. However, the changes required in the overall process flow scheme to adopt enzymatic catalysis (biocatalysis) put this approach in another perspective.

7. Implementation of the Proposed PI Strategy in the Hydroamination of "N746-Butadienes" to Clopenthixol

Abstract

The hydroamination reaction between unsaturated hydrocarbons and amines is a big challenge in modern organic synthesis. Applications of different chemical catalysts, together with suitable ligands, solvents and additional additives have been investigated in the last decade. The main focus here is on the chemical reaction between "N746-Butadienes" and HEP. It is based on the intermolecular and anti-Markovnikov hydroamination which is known as a slow and unselective chemical reaction. Nevertheless, speeding up of the reaction from 24 h down to 4 h is achieved by switching from batch operation mode with toluene to either solvent-free batch mode or microwave assisted hydroamination with THF as a solvent. It is important to note that comparable conversions of "N746-Butadienes" are achieved together with above average yields of Clopenthixol.

Microwave assisted experiments were performed at the Medicinal Chemistry department of H. Lundbeck A/S in Valby (Denmark). Andreas Ritzen and Trine Puggaard Petersen are greatly acknowledged for their assistance and help.

7. Implementation of the Proposed PI Strategy to the Hydroamination of "N746-Butadienes" to Clopenthixol

7.1 Introduction

The hydroamination reaction is the desired synthetic way to produce amines because current manufacturing modes are facing plenty of economic disadvantages. More precisely, reactions of alcohols with ammonia or simpler amines, as well as reductive aminations of carbonyl compounds with ammonia (or simpler amines, as well)[399-402] have an unsuitable atom-efficiency. Nucleophilic substitutions of halides followed by reduction, then reductions of nitro compounds and hydroaminatomethylation of alkenes are facing the same problem[403]. It is therefore preferred to implement hydroamination as a synthetic way in order to apply better ratios of substrates, as well as to decrease by-product formation.

The significance of the hydroamination reaction is high due to the very broad application spectrum of amines. For instance, production of dyes, dispersing agents, emulsifiers, corrosion inhibitors, wetting and surface-active agents and petroleum additives are just some of the examples[400-402, 404-406]. Furthermore, amines have showed a very high medical activity and therefore plenty of applications have been found for amines in the pharmaceutical industry[407, 408]. One particular example is Zuclopenthixol, a product of H. Lundbeck A/S.

Hence, the main focus here is on the chemical reaction between "N746-Butadienes" and 1-(2-hydroxyethyl)piperazine (HEP). This is the last step in the Clopenthixol manufacturing and it is labelled as additional bottleneck in the overall production. More precisely, very long reaction times (up to 24 h in batch mode), as well as several side reactions should be avoided in the hydroamination reaction. Therefore, implementation of the process intensification approach will be performed with the main aim to emphasize advantages of applying microwave assisted organic synthesis.

7.2 Synthetic pathway to Clopenthixol

Hydroamination is defined as a direct addition of a N-H bond from primary, secondary or tertiary amines, imines and enamines, to C=C unsaturated bonds of alkenes, alkynes and dienes. It is considered as an exergonic and exothermic chemical reaction at standard reaction conditions[409], but its performance involves a high activation energy barrier due to strong repulsive electrostatic interactions between the lone pair of the amine and the π system of the unsaturated hydrocarbon[410, 411]. Nevertheless, activated multiple bonds which are present in 1,3-dienes, vinyl arenes, allenes or ring-strained alkenes enable smoother performance of the hydroamination reaction[403]. In addition, electron-deficient π-systems with neighboring functional groups should perform nucleophilic addition of amines even easier[412-414].

Considering cyclisation of the product, hydroamination could be performed in two possible pathways: intramolecular and intermolecular. Apart from the cyclisation, there are two possible regio-selective synthetic paths: Markovnikov and anti-Markovnikov[415, 416]. Focusing on Clopenthixol, it is important to note that the chemical reaction between "N746-Butadienes" and HEP is based on the intermolecular hydroamination with anti-Markovnikov regioselectivity. The chemical reaction is shown in Figure 7.1.

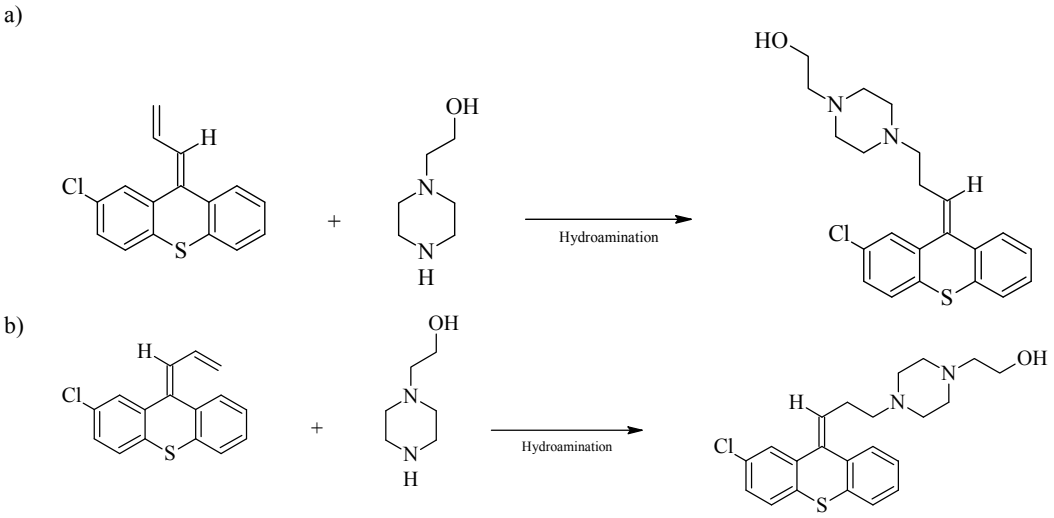


Figure 7.1 Hydroamination reaction between (a) cis – "N746-Butadiene" and HEP and (b) trans – "N746-Butadiene" and HEP

The presence of several aromatic rings together with additional functional groups (hydroxyl and clorine) allow to perform the hydroamination reaction between "N746-Butadienes" and HEP in the absence of any chemical catalysts. However, when performing the hydromamination in this way, very long reaction times are required and plenty of undesired by-products are formed. It is therefore necessary to accelerate this chemical reaction and increase its selectivity.

7.3 Brief overview of the catalytic approaches

Catalytic approaches have received more attention in the last two decades because of the desire to achieve a 100% atom-efficiency[417]. Several different catalytic approaches have been found, but there is still no efficient and universal methodology which could be applied in this chemical reaction[418, 419]. It is additionally important to note that catalytic anti-Markovnikov addition of alkenes to amines is part of the concept: "Ten Challenges for catalysis"[420].

Metals from I and II groups of the PSE have shown great activity in intermolecular hydroamination reactions producing exclusively anti-Markovnikov products. A detailed review was written by Seayad and coworkers[403] who implied on wide applications of n-BuLi. Furthermore, applications of sec-BuLi, Na and KOtBu were registered, but their activity is limited only to several examples. Elemental alkali metals[421] or alkali metal amides[422, 423] have additionally been used in catalytic hydroaminations. Moreover, $LiN(SiMe_3)_2$ together with TMEDA showed good results in the hydroamination of aryl amines. However, the presence of different functional groups (such as halogens) significantly decreases the yields of desired products. Experiments to replace $LiN(SiMe_3)_2$/TMEDA with $KN(SiMe_3)_2$/TMEDA improved catalytic activity and consequently reactions could be run under milder conditions, but the disadvantage is that the amounts of by-products were increased[424].

Besides alkali metals, transition metals have been tested successfully. Horrilo-Martines and coworkers[424] performed transition-metal catalyzed hydroamination of aryl alkenes and achieved intermolecular hydroamination and anti-Markovnikov products. With the main focus on alkenes, allenes, and aromatic alkenes, rhodium[415, 425-429] and ruthenium[430-432] complexes have shown the best results. However, quite long reaction times, as well as the usage of different ligands labeled those approaches as very expensive. Furthermore, iridium[433], zirconium[434], titanium[435, 436] and palladium[437, 438] have been used, as well. Lastly, organolanthanide catalyzed hydroamination by using neodymium, mendelevium and samarium showed good potential based on computational studies[439, 440].

Furthermore, heterogeneous catalysis has been tested by using zeolites as chemical supports. Great results have been achieved by using Cu(I)/H-BEA, Rh(I)/H-BRA and Zn/H-BEA for the intermolecular hydroamination of methyl acrylate with aniline[441]. In addition, palladium immobilized on ionic liquids has shown noticeable results, as well[442, 443].

Lastly, a couple of enzymatic approaches have been performed. The best results were achieved by a scientist in BASF who used Phenylalanine ammonia lyase (PAL) obtained from *Petroselinum crispum*[444]. Nevertheless, applications of enzymes in this chemical reaction are still unexplored although the use of biocatalysis in modern synthetic methodologies is increasing[445]

7.4 Implementation of the process intensification strategy

Acceleration of the hydroamination reaction between "N746-Butadienes" and HEP was performed by applying the process intensification approach depicted in Figure 7.2. Three different modes of intensification were tested, as depicted with red, black and blue colours in the figure. Grey boxes and lines are just parts of the general PI scheme described in chapter 3, but not used in this particular example.

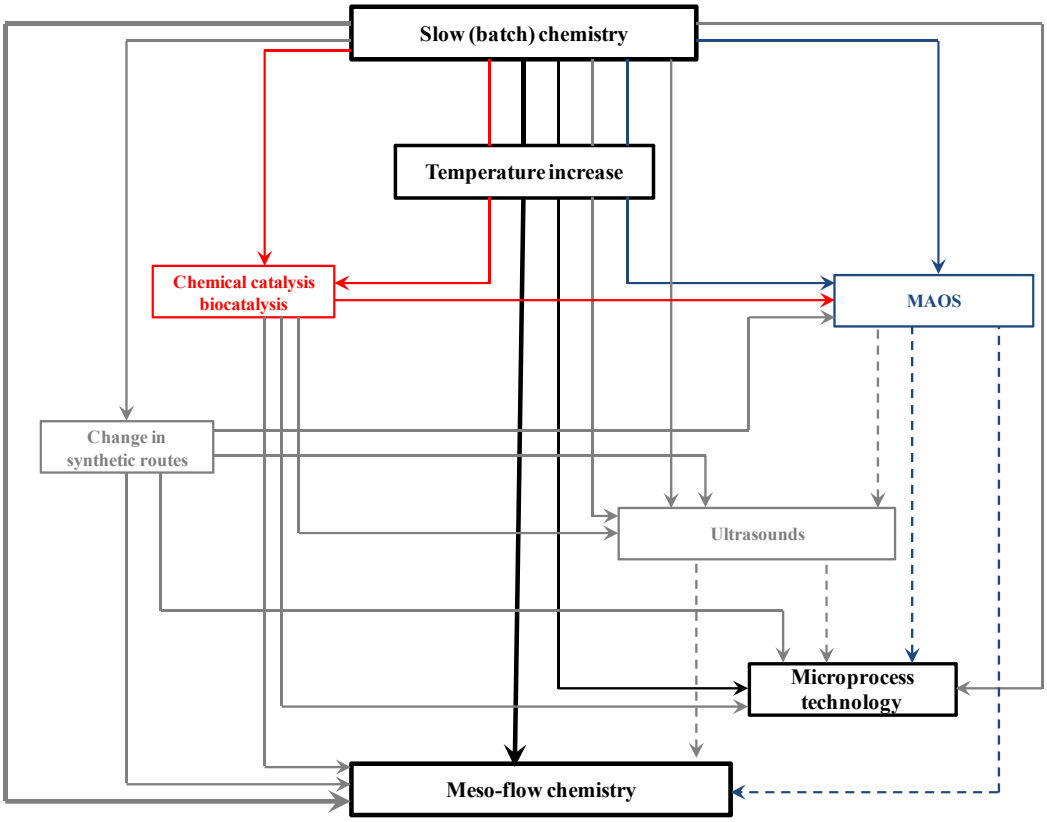


Figure 7.2 PI approach implemented in the synthesis of Clopenthixol

The most desired path was to implement direct transition from batch towards either meso-scaled flow chemistry or Microprocess technology. Both trials were performed in H. Lundbeck A/S, however the obtained results were not great. Therefore, the main focus in this work will be on applications of either chemical catalysts or MAOS.

Applications of chemical catalysts could imply accelerations and better selectivity. The main aim is to activate one or both reaction partners in order to reduce effects of the negative entropy present in the reaction system[416, 425, 439]. Hence, different chemical catalysts could be used for this purpose, as

summarized in chapter 7.3. Nevertheless, the biggest problems are usually faced if unactivated unsaturated hydrocarbons are used, such as alkenes[446]. Applications of aromatic hydrocarbons with additional functional groups in their chemical structures reduce obstacles in successful performance of the hydroamination reaction[412-414].

Apart from catalytic approaches, applications of microwave assisted organic synthesis would be tested. The main reason to select such an approach was to use just physical effects for acceleration and consequently to simplify downstream processes (such as avoiding the need for removal of transition metals from the final products). In addition, the extension in Figure 7.2 is shown in the form of blue dashed lines implying the potential combinations of MAOS with either Microprocess technology or Mesoflow chemistry. In this way, better satisfaction of the PAT requirements would be achieved, such as capability for on-line process monitoring, control and automation.

7.5 Materials and methods

7.5.1 Traditional batch experiments

Batch experiments were carried out in disposable 4 ml glass vials which were closed with polypropylene screw caps. These reactor vessels were placed in the HLC Biotech thermomixer (model MHR11) which was used as a heating medium. A rack with 16 places was very suitable for screening purposes. Temperatures up to 120^0C were easily achieved.

Collecting kinetic data was performed by applying 4 different molar concentrations of "N746-Butadienes". More precisely, the molar concentrations of 1.63 M, 0.81 M, 0.54 M and 0.41 M of "N746-Butadienes" in HEP were used for this purpose. It is important to emphasize that the main focus here was on molar ratios between "N746-Butadienes" and HEP. Hence, the ratios of 1:5, 1:10, 1:15 and 1:20 correspond to the mentioned molar concentrations of the butadiene.

Sample preparations were done by using gravimetric techniques. More precisely, desired amounts of butadienes and HEP were measured on the analytical balance and then transferred to a 4 ml vial. The main reason for such approach was associated with high viscosity of both substrates. The following step was to perform a short pre-heating of the samples in order to decrease viscosities of substrates. Furthemore, additional mixing was performed by using an IKA® MS 3 basic vortex device with the main purpose to dissolve all amounts of butadienes in HEP.

Temperatures of 60^0C, 80^0C, 100^0C, and 120^0C were applied together with a stirring rate of 500 rpm. Applications of higher temperatures were avoided due to the thermal instability of the final API – Clopenthixol. Samples for HPLC analysis were taken every 30 min during the first 2 h, and in the last 2 h sampling was performed every 60 min. The main reason for such approach was linked to the formation of solid by-products which caused difficulties in the sampling.

All the samples were analyzed by using HPLC equipment described in the section 7.5.4.

Lastly, it is important to note that disposable experimental equipment was mostly purchase from VWR International (vials, septums and caps) whereas the HLC Biotech Thermomixer was bought from TG Instrument AB. "N746-Butadienes" were synthesized by using the dehydration step (chapter 5). It is important to note that neutralization of the sulphuric acid was performed immediately after the reaction in order to decrease formation of by-products and polymers. Nevertheless, the purity of the substrate was never 100%. Furthermore, HEP was provided from the manufacturing sites of H. Lundbeck A/S.

7.5.2 Microwave assisted experiments

Besides traditional batch experiments, applications of microwave irradiation were performed with the main goal to acclerate this synthetic step. For this purpose, the Biotage Initiator was used whose image is shown in Figure 7.3 together with its performance properties.

Temperature	40-250 °C (104-482 °F)
Temperature increase	2-5 °C/sec (3.6-9 °F/sec)
Pressure range	0-20 bar (2 MPa, 290 PSI)
Power range	0-400 W at 2.45 GHz
Reaction vials	4 sizes: 0.2-0.5, 0.5-2, 2-5, 10-20 mL
Vial volume range	0.2-20 mL (EXP) 0.5-5 mL
Agitation	Variable magnetic stirrer (300-900 RPM)

Figure 7.3 Image of Biotage Initiator and its performance properties

Small scale batch experiments were performed under microwave irradiation. More precisely, 0.5-2 ml borosilicate glass vials were used as batch reactors together with a magnetic stirrer. Furthermore, special septums were added in order to increase safety. It is important to note that a special device for closing the vials was used in order to improve sealing of the batch reactors. Air was used as the reaction atmosphere.

Solutions with 1M concentration of "N746-Butadienes" in THF were used with the main purpose to avoid evaporation of the solvent in the overall production of Clopenthixol. Hence, preparation of samples included measuring desired weights of HEP and afterwards addition of the desired volumes of the "N746-Butadienes" solutions. The exact weight of HEP was measured on the analytical balance.

The ratio between "N746-Butadienes" and HEP was 1:15 whereas a temperature range from 80^0C to 250^0C was tested. The chemical reactions proceed rather slow, leading to prolonged reaction times, for example from 20 minutes up to 5 hours.

All the samples were analyzed by using LC-MS, such as described in section 7.5.5.

It is important to emphasize that microwave assisted experiments were performed in Research & Development section of H. Lundbeck A/S in Valby, Denmark.

7.5.3 Batch experiments with chemical catalysts

Screening of different chemical catalysts was additionally performed. Following the literature survey in section 7.3, two examples were chosen as the most desired options. Hence, tests with n-BuLi in toluene, as well as a combination of tris(triphenylphosphine)rhodium(I) carbonyl hydride ($([C_6H_5)_3P]_3Rh(CO)H$) and 6,6′-[(3,3′-Di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin) (BiPhePhos) were done. The main purpose of using chemical catalysts was to increase the atom efficiency in the hydroamination reaction. Hence, the applied molar ratios between "N746-Butadiene" and HEP were kept at 1:1 in all experimental runs.

Aplications of n-BuLi were performed by applying equipment used in the traditional batch experiments (section 7.5.1). It is however important to note that different techniques in preparing samples were applied. Therefore, the gravimetric technique for measuring "N746-Butadienes" and HEP was used, but addition of 1.4 M solutions of n-BuLi in toluene required special working conditions. More precisely, a very high reactivity of this Grignard reagent with moisture and air demanded an inert atmosphere. For this purpose, a nitrogen atmosphere was used during the addition of the n-BuLi solution in the reaction mixture.

Focusing on the experimental details, it is important to note that the ratios between "N746-Butadienes" and n-BuLi were 1:0.5, 1:1, 1:1.5 and 1:2. All the experiments were performed in 2 ml of toluene and at a reaction temperature of 60^0C. The chosen reaction time was 1 h in this screening procedure. It is additionally important to note that the results were analyzed by applying HPLC, as described in the section 7.5.4.

Additionally, tests with transition metals were performed together with the assistance of microwave radiation. Equipment described in section 7.5.2 was also used here. Loadings of 4% and 16% were used for $([C_6H_5)_3P]_3Rh(CO)H$ and BiPhePhos, respectively. The molar percentages were calculated with respect to the amount of "N746-Butadienes" which was chosen to be the limited substrate. The reaction conditions involved the recommended 150^0C and 40 min[447].

It is important to emphasize that results obtained by using transition metals were analyzed with LC-MS. The detailed description of the sampling procedure, as well as of the equipment is described in section 7.5.5.

7.5.4 HPLC analysis

Molar concentrations of "N746-Butadienes" were quantified by using LaChrome Elite HPLC equipment. This device includes the Diode Array Detector (DAD) and Phenomenex Gemini C6-Phenyl Column which is generally suited for reversed phase HPLC. It is additionally tolerant to a wide range of pH values. A 23-min gradient method was applied by using two mobile phases. The mobile phase one consisted of 10% of aqueous buffer solution with pH=9, then 10% of acetonitrile and 80% of water whereas the mobile phase B contained 10% of the buffer solution and 90% of acetonitrile. The aqueous buffer was prepared by using 50 mM aqueous solution of ammonium formate (NH_4HCO_2) and several drops of ammonium-hydroxide (NH_4OH) in order to adjust to a desired pH. It is important to note that all of the percentages were based on volumetric calculations.

The sampling procedure was based on using 1 ml of ethyl-acetate (EtOAc) as the HPLC diluent. This non-polar solvent was chosen as a desired option due to its high versatility for different applications. Furthermore, its low UV absorption in the range of higher wavelengths allows easier and more precise analysis of the analyzed compounds. The applied wavelength here was 254 nm.

It is important to note that high UV absorptions of "N746-Butadienes" caused dilutions of the analyzed solutions. A molar concentration range from 0-2 M was usually applied in the experimental procedures and it was therefore necessary to apply two different dilutions. The first dilution with a dilution factor (DF) of 20 was applied by taking 50 µl of the original sample and diluting it in 1950 µl of THF. Furthermore, 50 µl of the diluted samples were transferred to disposable HPLC vials where 1 ml of the HPLC diluent was placed. Hence, the second dilution with a DF of 21 was additionally applied leading to a total DF of 420.

All the chemicals used in the HPLC analyses were purchased from Sigma-Aldrich whereas disposable HPLC vials and caps were bought from VWR International.

7.5.5 LC-MS analysis

Analyses of the results obtained by using microwave radiation were analyzed by using LC-MS. The samples were prepared by dissolving 5 µl of the reaction medium in 1 ml of DMSO – HPLC grade. This approach was recommended in the medicinal chemistry lab (H. Lundbeck A/S) because plenty of analyses are usually done in this way. The LC-MS samples were placed in 2 ml HPLC vials.

LC-MS were run on Waters Acquity UPLC-MS consisting of Waters Acquity with the column manager, binary solvent manager, sample organizer, PDA detector (operating at 254 nM), ELS detector, and SQ-MS equipped with APPI-source operating in positive ion mode. The column was an Acquity UPLC BEH C18 1.7 µm; 2.1x50mm operating at 60°C with 1.2 ml/min of a binary gradient consisting of water + 0.05 % trifluoroacetic acic (A) and acetonitrile + 5% water + 0.035 % trifluoroacetic acid.

7.6 Results and discussions

Three different ways of analysis were performed in the hydroamination manufacturing step. Traditional batch experiments were performed first with the main purpose to become familiar with the kinetics of the chemical reaction. Secondly, acceleration of the chemical reaction was performed by using microwave assisted organic synthesis. Despite quite good results, difficulties to implement microwaves in the overall process infrastructure influenced additional trials with chemical catalysts. Hence, usage of n-BuLi and Rh based catalysts was tested.

7.6.1 Traditional batch experiments

Small scale batch experiments were used for the kinetic model development. According to the previous experiences in performing this chemical reaction in H. Lundbeck A/S, it was known that toluene decreases the reaction rate significantly. Therefore, avoidance of toluene in the reaction mixture was desired. On the other hand, presence of THF would cause quite low reaction temperatures because of its low normal boiling point. It was therefore decided to perform a solvent-free procedure where HEP would have a double role – as a substrate and as a solvent.

Initial experiments involved a very small ratio between "N746-Butadienes" and HEP. More precisely, the ratio of 1:5 was applied indicating quite a high molar concentration of "N746-Butadienes" (1.63 M). The obtained results are depicted in Figure 7.4 where it can be seen that the temperature increase had a significant influence and resulted in faster conversion of "N746-Butadienes". More precisely, conversions of 94.5%, 83.4%, 53.4% and 43.8% were achieved after 4 hours of operation at 120^0C, 100^0C, 80^0C and 60^0C, respectively.

Although almost a complete conversion of "N746-Butadienes" was achieved at 120^0C, the yield of the desired product was not so high. Hence, plenty of the converted diene did not lead to the desired product, such as confirmed in Figure 7.5. More precisely, 94.5% of the converted "N746-Butadienes" lead to just 42.2% of Clopenthixol at 120^0C. In addition, lower temperatures caused even lower yields of the desired product, such as 23.47%, 3.16% and less than 1% of Clopenthixol when 100^0C, 80^0C and 60^0C were used, respectively. It can be concluded that around 45-50% of the converted "N746-Butadienes" were converted into by-products.

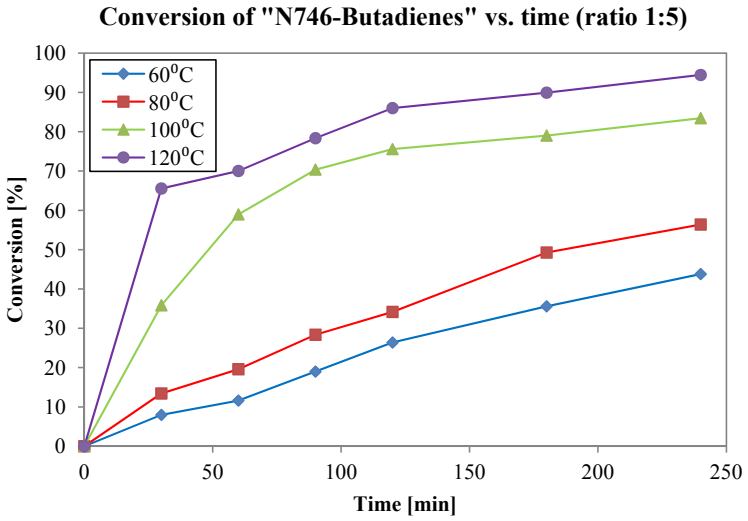


Figure 7.4 Conversion of "N746-Butadienes" as function of time when the molar ratio of 1:5 between substrates is applied

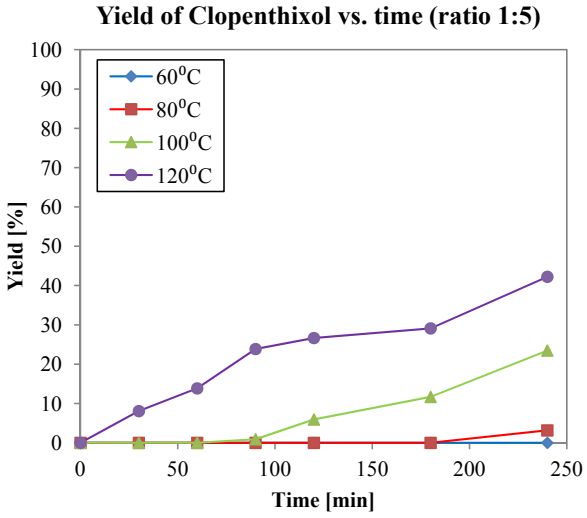


Figure 7.5 Yield of Clopenthixol versus time when a molar ratio of 1:5 between substrates is applied

It is important to emphasize that the stereo-selectivity leads to even lower amounts of the final API – Zuclopenthixol. More precisely, the stereo-selectivity of "N746-Butadienes" was 42% to 58% (cis to trans) which would theoretically lead to the same ratio between Zuclopenthixol and trans-

Clopenthixol. Incorporation of such conclusions in the results achieved here would lead to just 17.7% of Zuclopenthixol which is very low.

Despite the polymerization reaction which occurs in the dehydration reaction, there are high chances for the same type of chemical reaction to happen in the hydroamination step. More precisely, the chemical reaction between the double bond at the end of the functional group pf "N746-Butadienes" could cause polymerization between the same substrate. Furthermore, HPLC analyses implied the presence of simpler organic compounds in the reaction mixture, as well. Hence, big losses could be caused by additional side reactions and it was therefore necessary to introduce some changes in the reaction mixture. Hence, further increase of the ratio between substrates was applied as an initial option. The first approach included an increase from 1:5 to 1:10 between substrates (molar equivalents) which leads to the decrease of the molar concentrations of "N746-Butadienes" from 1.63 M to 0.81 M. The results describing the conversion of "N746-Butadienes" are shown in Figure 7.6.

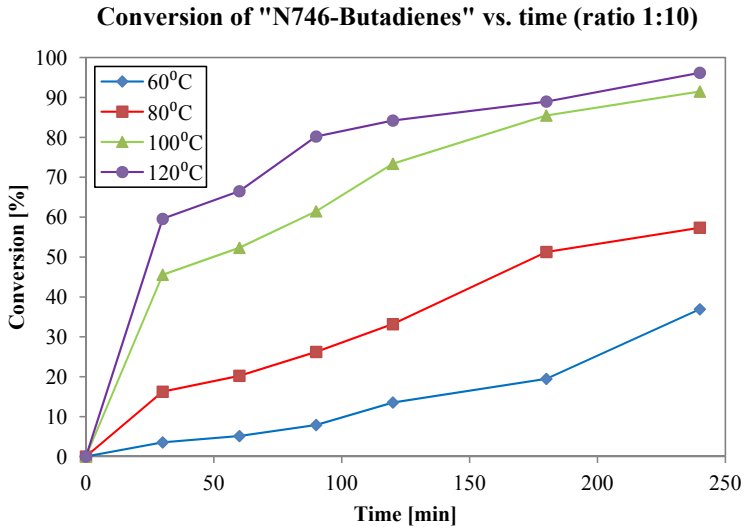


Figure 7.6 Conversion of "N746-Butadienes" versus time when a molar ratio between substrates of 1:10 is applied

It can be noticed that almost complete conversion was achieved at 120^{0}C. More precisely, a conversion of 96.2% was obtained which is an increase by almost 2%. However, it is important to note that conversions at 60^{0}C and 80^{0}C were even lower compared to the results obtained when the previous ratio between the substrates was used. More precisely, 7% less of "N746-Butadienes" was converted at the lowest tested temperature.

Focusing on the Clopenthixol yield, it is important to note that significant improvements were achieved by applying increased ratios of the substrates. More precisely, usage of the ratio 1:10 resulted in 58.9% of Clopenthixol at 120^{0}C which is an increase of 16.2% compared to the previously obtained results. Furthermore, yields of Clopenthixol were higher at the other temperatures also. For instance, increases of 4% were recorded when temperatures of 80^{0}C and 100^{0}C were obtained.

Applications of lower molar concentrations of "N746-Butadienes" in the hydroamination reaction resulted in decreased by-product formations. More precisely, losses of 45-50% which were present in the previous experimental approach actually decreased now to approximately 15%. Focusing on the highest used temperature, the losses of converted "N746-Butadienes" were 37.3%. This is a significant step forward in reducing the formation of undesired by-products. Yields of the Clopenthixol versus time for all tested temperatures are depicted in Figure 7.7.

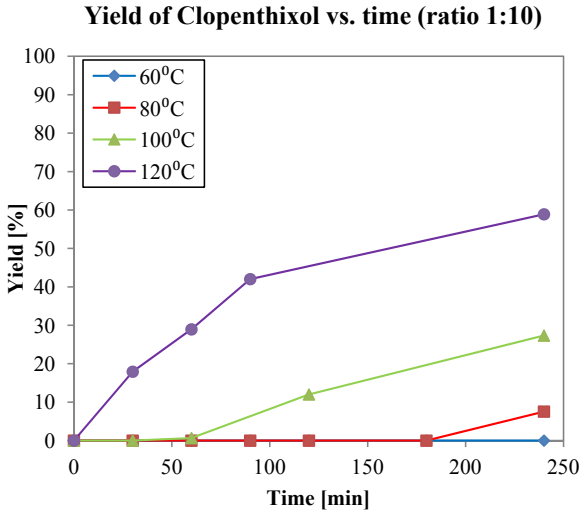


Figure 7.7 Yield of Clopenthixol versus time when a molar ratio of 1:10 between substrates is applied

A clue that the increase of ratio between substrates might cause a significant decrease of the formation of by-products had a big influence on the planning of further work. Hence, the following investigations were based on exploring the reaction behaviour when the ratio 1:15 was applied. Applications of such a high ratio led to significantly decreased initial molar concentration of "N746-Butadienes" – down to 0.54 M.

The obtained results which depict conversions of "N746-Butadienes" and yields of Clopenthixol are shown in Figure 7.8 and Figure 7.9, respectively. Although conversions of "N746-Butadienes" were quite similar to the previously tested ratios, the yields for Clopenthixol improved significantly.

More precisely, the conversion of 98.2% achieved at 120^{0}C led to 61.3% of Clopenthixol. In this way, an above average yield of the desired product was achieved which would theoretically lead to 25.75% of Zuclopenthixol. This amount represents an increase for almost 10% compared to the test applied with the ratio of substrates equal to 1:5.

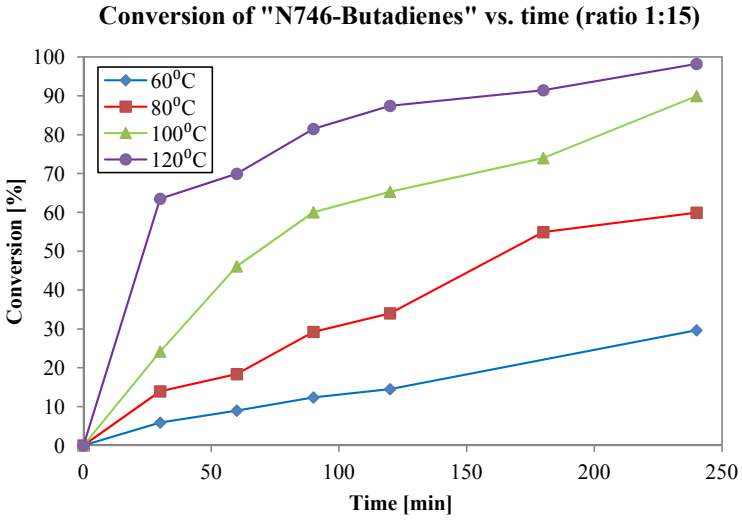


Figure 7.8 Conversion of "N746-Butadienes" versus time when the molar ratio between substrates of 1:15 is applied

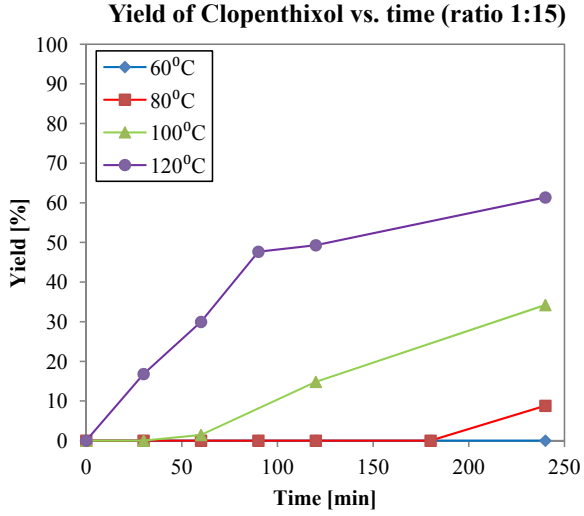


Figure 7.9 Yield of Clopenthixol versus time when a molar ratio of 1:15 between substrates is applied

A significant increase of the Clopenthixol yield, as well as improved conversion of "N746-Butadienes" initiated one more test with an increased ratio of substrates. More precisely, the ratio of 1:20 was applied in order to minimize side reactions. A very low initial molar concentration of "N746-Butadienes" was therefore applied in this case– just 0.42 M. The results are shown in Figure 7.10.

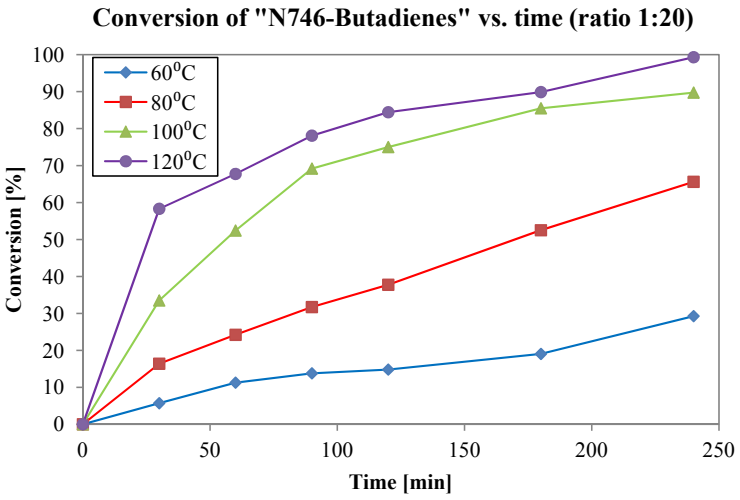


Figure 7.10 Conversion of "N746-Butadienes" versus time when a molar ratio between substrates of 1:20 is applied

The latest applied ratio caused the highest possible conversions of "N746-Butadienes". They were 29.27%, 65.6%, 89.73% and 99.3% for the temperatures 60^0C, 80^0C, 100^0C and 120^0C, respectively. Comparing to the previously tested molar ratios between substrates, the highest conversion was achieved if a ratio of 1:20 was applied. This was also the expected behaviour due to the very low molar concentration of "N746-Butadienes".

However, in this screening procedure the main focus was on improving the yields of Clopenthixol. Hence, a decrease of the by-product formation together with an increase of the ratio between substrates was additionally confirmed. More precisely, synthesis of 72.7% of Clopenthixol was registered at 120^0C whereas 66% of the desired product was produced if a reaction temperature of 100^0C was applied. In this way, significant improvements of the Clopenthixol synthesis were achieved. Yields of Clopenthixol are depicted in Figure 7.11.

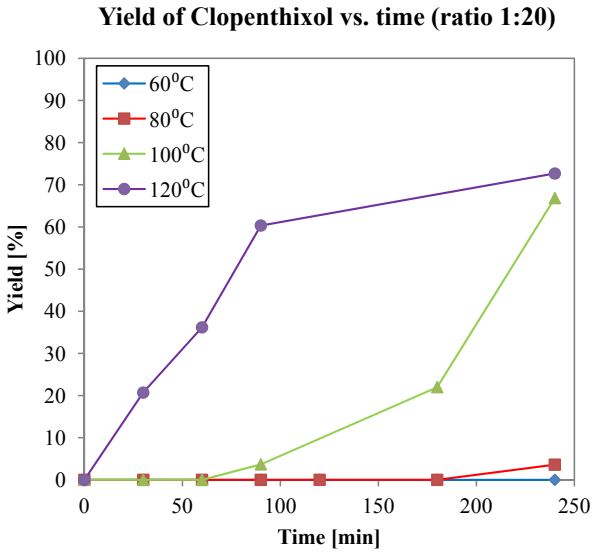


Figure 7.11 Yield of Clopenthixol versus time when a molar ratio between substrates of 1:20 is applied

Focusing on the Zuclopethixol synthesis, it is important to note that quite high theoretical yields were achieved if the ratio 1:20 was applied. So, assuming the same stereo-selectivity between Clopenthixol isomers as it was in case of "N746-Butadienes", this result would lead to 30.53% of Zuclopenthixol at 120^{0}C whereas 27.72% would be synthesized at 100^{0}C. Quite high yields of the desired API would be achieved in this way, however with significantly higher amounts of HEP used in the chemical synthesis. A further increase might lead to increased production of Zuclopenthixol, but the very low molar concentrations of "N746-Butadienes" might be an obstacle from an economic point of view.

7.6.2 Kinetic model development

Development of the kinetic model was based on the integral method, such as already applied in chapter 5. Hence, the starting assumption was identical as in the dehydration of "N714-Allylcarbinol" assuming that the chemical reaction is elementary. Furthermore, it is important to note that Figures 7.4, 7.6, 7.8 and 7.10 imply the same conversion manner of "N746-Butadienes" and consequently lead to the conclusion that the presence of a high amount of HEP could actually cause pseudo-first or pseudo-second order kinetics. Therefore, the starting assumption was pseudo-first order, such as depicted in Equation 7.1.

$$r_{HYD} = -\frac{dC_{BUT}}{dt} = k^* C_{BUT} \quad 7.1$$

where

r_{HYD} - Reaction rate of the hydroamination reaction($\frac{mol}{dm^3 s}$);

C_{BUT} - Molar concentration of "N746-Butadiene" (M);

k^* - Reaction rate constant for the pseudo-first order kinetics ($\frac{1}{s}$);

t - Residence time (s).

General solution of the Equation 7.1 with the initial conditions C_{BUTo} and t = 0 min, as well as corresponding C_{BUT} at the desired temperature and desired time, would lead to the general expression depicted in Equation 7.2.

$$\frac{\ln\left(\frac{C_{BUTo}}{C_{BUT}}\right)}{t} = k^* \quad 7.2$$

Furthermore, following the Arrhenius equation, the reaction rate constant would be expressed as a function of temperature as depicted in Equation 7.3:

$$k^* = k_o e^{-\frac{E_A}{RT}} \quad 7.3$$

The next step is to make a logarithmic version of the Equation 7.3, shown bellow

$$\ln(k^*) = \ln(k_o) - \frac{E_A}{R}\frac{1}{T} \quad 7.4$$

The obtained results for $\ln(k_o)$ and E_A are shown in Figure 7.12. It can be seen that the assumed kinetic model was correct, i.e. a very good fit was achieved. There is just one line labeled with "30 min" which showed a slightly decreased correlation coefficient, but its influence was not very significant due to the availability of plenty of additional experimental points, as shown also in the graph. Therefore, the calculated values for E_A and k_o are $4.62 \times 10^4 \frac{kJ}{mol}$ and $2.68 \times 10^4 \frac{1}{s}$, respectively.

In addition, the graph showing the predicted conversions of "N746-Butadienes" and the experimentally obtained values is shown in Figure 7.13. The main focus was on the ratio between substrates of 1:20 due to the lowest formation of by-products if such molar concentration of "N746-Butadienes" was applied.

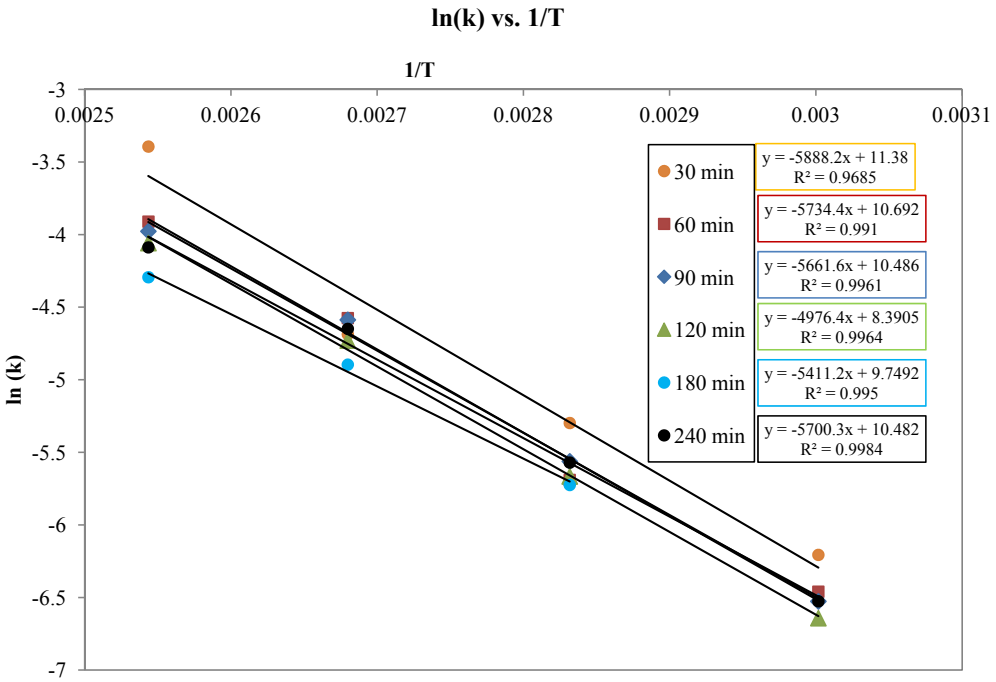


Figure 7.12 Relationship between ln(k) and inverse values for Temperature with the main purspoe to find values for Energy of activation (E_A) and pre-exponential factor in the Arrhenius equation (k_o)

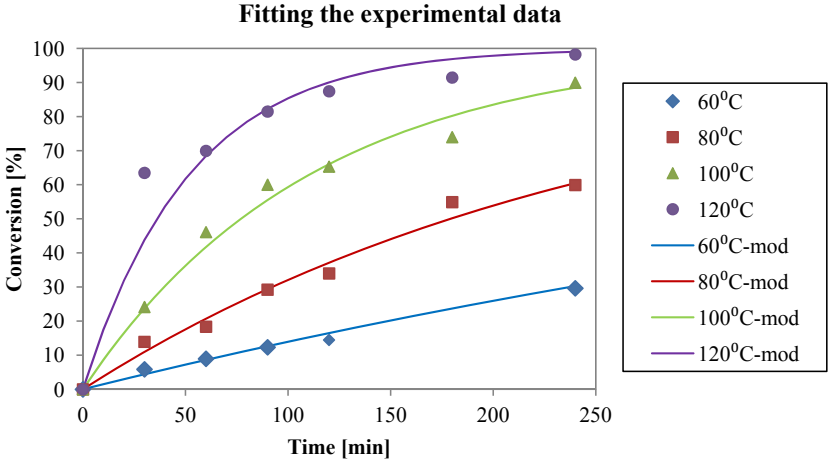


Figure 7.13 Conversion of "N746-Butadiene" at four different temperatures as a fuinction of time

Figure 7.13 indicates quite a good fit between the predicted and experimental values for conversion of "N746-Butadienes". It could be noticed that a few outliers are present in the chart. The main reason for such outliers is associated to changes of HEP viscosity with temperature. Hence, a slight inaccuracy is present in the fitting of the experimental data, but a general impression is that a good kinetic model was developed which would be useful for further investigations of the hydroamination reaction between "N746-Butadienes" and HEP.

7.6.3 Applications of microwave assisted organic synthesis in the hydroamination reaction

Advantages of microwave assisted organic synthesis were tested and compared with the results obtained in the batch mode. It is very important to note that experiments performed with the assistance of microwave irradiation included solutions of "N746-Butadienes" in THF whereas a great polarity of HEP influenced a terrific absorption of the microwave irradiance. Hence, it was easy to achieve very high temperatures, such as even 250^{0}C.

The initial conditions included ratios between substrates of 1:15 and a reaction temperature of 120^{0}C. This ratio was chosen as a desired option due to the quite high yields of Clopenthixol obtained in the solvent-free batch mode, as well as due to the reasonably high molar concentration of "N746-Butadienes" in HEP. The results are depicted in Figure 7.14 and compared with the traditional batch experiments which were solvent-free.

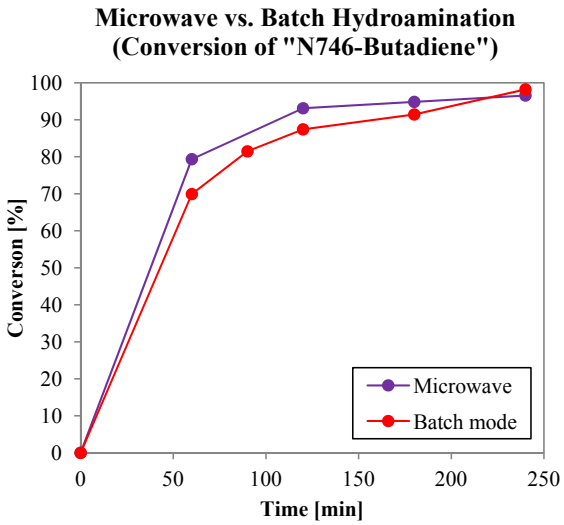


Figure 7.14 Comparison of the "N746-Butadiene" conversions achieved if microwave assisted organic synthesis and traditional batch experimentation are applied at 120^{0}C

It can be noticed that quite similar "N746-Butadiene" conversions were achieved. However, a slightly faster conversion was achieved if MAOS was applied, although THF was present in the reaction medium. Hence, quite a good conversion could be achieved within reasonable short reaction times even if THF was used.

Furthermore, the results for Clopenthixol yields are plotted in Figure 7.15 together with the comparison to the yields obtained when a solvent-free batch mode was applied. It can be noticed that 66% of Clopenthixol were synthesized if MAOS was applied whereas batch experiments resulted in 61.34%. Small differences between the obtained values are unexpected and are probably due to lower temperature gradients if MAOS was applied. The conclusions might imply a polymerization of the substrate as well.

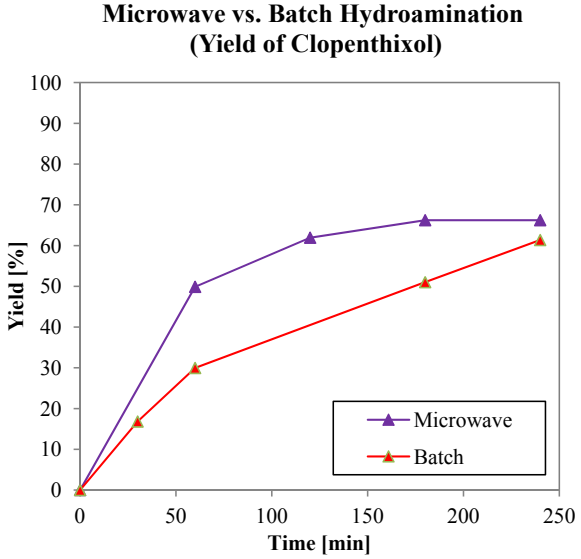


Figure 7.15 Comparison of the Clopenthixol yields achieved if microwave assisted organic synthesis and traditional batch experimentation are applied at 120^0C

Further investigations about the MAOS applications were focused on the temperature increase with the main aim to accelerate the hydroamination reaction as much as possible. Hence, 5 additional temperatures were tested with reaction times equal to 1 h. Results are presented in Figure 7.16. It could be noticed that very fast conversion of "N746-Butadienes" was achieved with the increase of temperature. Almost complete conversion of the substrate was obtained within 20 min if 250^0C was applied.

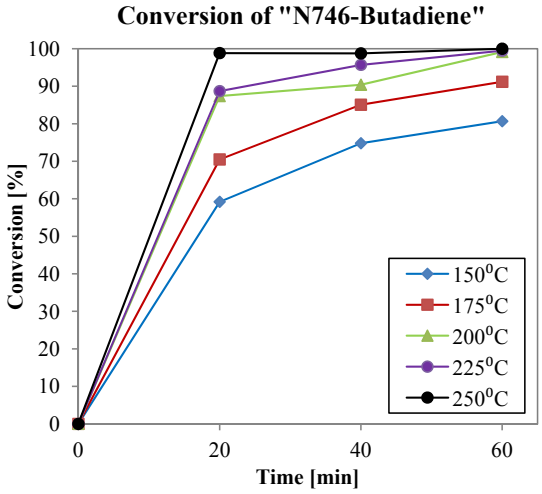


Figure 7.16 Conversion of "N746-Butadienes" at temperatures above 120^{0}C and under microwave irradiation

Apart from very rapid conversion of "N746-Butadienes", yields of Clopenthixol showed an unexpected behaviour. More precisely, the quite sophisticated structure of Clopenthixol had a significant temperature instability which was confirmed by plotting Clopenthixol yields against time at temperatures above 120^{0}C (Figure 7.17).

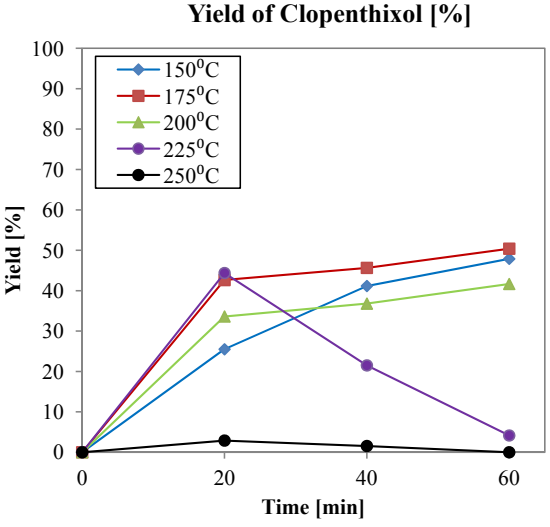


Figure 7.17 Yields of Clopenthixol at temperatures above 120^{0}C and under microwave irradiation

It can be easily noticed that if temperature goes higher than 175^{0}C, then a significant decrease of the Clopenthixol concentrationis obtained. This is also easily confirmed with the LC-MS results leading to the conclusion that the main reason for such behaviour was probably the decomposition of Clopenthixol. Plenty of organic compounds with lower molecular weights were noticed.

Therefore, the most optimal conditions for such chemical reactions could go up to 120^{0}C. It is also important to note that very long reaction times might cause increased amounts of by-product formation. Therefore, the best conditions for applying microwave irradiation were 1:15 molar ratios between "N746-Butadienes" and HEP, wheres the reaction time should not be longer than 180 min due to the established equilibrium between substrates and products.

7.6.4 Applications of chemical catalysts in the hydroamination reaction

Hydroamination reactions catalyzed by alkali metals are strongly dependent on the pKa of the used amine[448]. According to Seayad and coworkers[403], the most favorable conditions would be:

- high concentration of catalyst;
- high pKa of amine or low acidity;
- high nucleophilicity of the metal amide complex which could be achieved by choosing appropriate metal precursors[449], solvents[449] and additives[450].

The literature survey described in section 7.3 pointed towards n-BuLi and toluene as a suitable combination of chemical catalyst and solvent. Experiences with the usage of toluene led to conclusions that this solvent significantly decreases the reaction rate of the hydroamination reaction between "N746-Butadienes" and HEP. However, its combination with a desired chemical catalyst should overcome the mentioned issues. Trials with different molar concentrations of n-BuLi in toluene were performed. More precisely, the molar ratio between "N746-Butadienes" and HEP was 1:1, wereas the ratios to n-BuLi were 1:0.5, 1:1, 1:1.5 and 1:2. Applications of the alkali metals in this particular hydroamination reaction resulted in minor yields of the Clopenthixol (<1%). Furthermore, total conversion of "N746-Butadienes" was not observed if smaller ratios of n-BuLi were applied whereas higher ratios resulted in plenty of by-products.

Besides alkali metals, tests with transition metals were performed as well. More particularly, a precatalyst, $([C_6H_5)_3P]_3Rh(CO)H$ together with the ligand, BiPhePhos were tested. Catalyst loadings of 4% and 16% were used together with microwave radiation. The reaction conditions involved the recommended 150^{0}C and 40 min reaction time[447], however the obtained result demonstrated that the the used catalytic complex was unsuitable. On the other hand, from an economic point of view, thevery high cost of this catalytic complex would not be justified for industrial use.

Applications of additional chemical catalysts were excluded although some further screening might lead to the desired atom efficiency and increased yields of Clopenthixol. For instance, quite good practice in synthesis of Cinnarizine has been recently published by Beck and coworkers[451].

7.7 Conclusons and future perspectives

Acceleration of the hydroamination reaction was successfully performed by using two different approaches: solvent-free batch mode and microwave assisted organic synthesis.

The solvent free batch approach resulted with almost complete conversion of "N746-Butadienes" at 120^0C and within 4 h. The applied ratio between "N746-Butadienes" and HEP was 1:20. Besides the good conversion, quite a high selectivity to Clopenthixol was achieved – up to 73%. Nevertheless, presence of by-products consisting of simpler organic compounds was noticed. Furthermore, the presence of polymer byproducts is also considered a possibility.

MAOS applications significantly reduced the presence of simpler organic compounds as by-products. The applied ratio between substrates was 1:15 and it resulted in high conversion of "N746-Butadienes" into Clopenthixol. More precisely, a conversion of 96.6% resulted with formation of 66% of Clopenthixol, and the presence of by-products was not noticed with LC-MS analyses. The main reasons explaining such results could be the polymerization of "N746-Butadienes" or even some intermediate products which are formed in the hydroamination reaction.

Quite high capital costs of the microwave equipment would put this approach as a second option in the overall process development of the Zuclopenthixol synthesis. The main reasons might be that quite similar results can be achieved by using solvent free batch modes. Hence, the overall process flow scheme could have an additional step with the solvent evaporation before the hydroamination reaction – in this particular case it would be THF although applications of additional solvents should be considered.

Furthermore, applications of chemical catalysts did not bring significant improvements. Very low yields of the desired products were achieved eventhough the literature survey emphasized significant roles of the used catalysts. It might be possible to apply better combinations of solvents, ligands and addititives in order to achieve a full selective conversion of "N746-Butadienes" into Clopenthixol.

The future work would therefore be based on the development of a meso-scaled tubular reactor system with the previously established removal of THF and its aezotrop with water. Hence, a solvent-free hydroamination should be transferred from batch towards meso-scaled flow chemistry. In addition, applications of in-line process monitoring with successful process control and automation would satisfy plenty of the requirements defined with the PAT Initiative.

8. Implementation of the Proposed PI Strategy to the C-S cross coupling reactions

Abstract

Carbon-sulphur cross coupling reactions are taking significant attention in the modern organic synthesis and thereby in the pharmaceutical industry. Difficulties to establish this kind of C-heteroatom bonds were avoided by using transition metals as chemical catalysts together with special additives, such as chemical ligands and bases. It is however important to note that these synthetic routes include long reaction times, expensive catalysts and additives, complicated and time consuming downstream processes, as well as environmental unfriendly solvents in majority of cases. One interesting example is synthesis of (2-bromophenyl)(phenyl)sulfane which is assisted with Pd and Fe salts, as well as toluene as a solvent. Acceleration in producing this product is performed in this work by applying free radical mechanism. Reaction times are decreased down to just 20 min compared to 72h in case of batch modes or 1h if MAOS were applied. In addition, continuous manufacturing mode is developed together with the economic evaluations of all the mentioned processes.

8. Implementation of the Proposed PI Strategy to the C-S cross coupling reactions

8.1 Introduction

Carbon-sulphur and carbon-heteroatom bond formations are a big challenge in the modern organic synthesis and in the modern pharmaceutical industry. Plenty of new APIs include these bonds in their chemical structures and therefore cheaper, faster and more environmentally friendly approaches to synthesize those APIs are desired.

Focusing just on the C-S bonds, it is important to note that several practical examples of processes leading to C-S bonds are already known and used for APIs that are available on the pharmaceutical market. Some of the known examples are: medicines for treating Chigas disease[452], drugs for asthma and chronic obstructive pulmonary disease[453], drugs for treating HIV (AIDS)[454], antitumor reagents[455], reagents important for tubulin assembly inhibitions[456, 457], inhibitors of MAP Kinase p38[458], as well as APIs playing a role in treatment of inflammatory processes and immune diseases[459, 460].

The highly inert behavior of aryl halides usually requires chemical catalysts for the synthesis of C-S compounds based on the cross coupling reactions[461]. Hence, applications of different alkali and transition metals are a well-known approach[462]. Nevertheless, new synthetic routes which would lead to the desired products could be used, such as applications of chlorinating agents and Grignard reagents[186].

The main focus in this chapter is to perform transition-metal free synthesis of (2-bromophenyl)(phenyl)sulfane. This compound is an important API intermediate and its production is mainly based on using transition metal salts as chemical catalysts, then chemical ligands, bases and environmentally unfriendly solvents. However, a suitable application of chlorinating agents and Grignard reagents could lead to the desired product and forms a promising approach for reducing the production costs.

8.2 Overview of the catalytic approaches for performing C-S cross-coupling reactions

Carbon-sulphur bonds are usually established by using transition metals as chemical catalyst. The role of transition metals in such chemical reactions is manifold and includes the following:

- metals may form a σ-complex with the lone electron pair of the halogen atom and thereby cause polarization of the bond between the carbon and the halogen atoms (the attack of a nucleophile would be performed easily)[461];
- metals could act either as electron donor[463] or electron acceptor[464, 465] and consequently initiate the radical mechanism of the cross coupling reactions;
- oxidative addition of an aryl halide followed by reductive elimination of the exchanged product could be initiated by different types of metals[466];
- if an electron withdrawing group is present (nitro group, cyano groups, sulfonates, and so on), the metal may form a π-complex and become equivalent to the electron withdrawing group in the aryl ring[467-469] leading to easier performance of the nucleophilic substitutions.

However, applications of transition metals in the formation of C-S bonds involve several issues related to the difficulties involved in the substitutions at the sp^2-carbon atom. It is also noteworthy to mention that poisoning of the catalysts might potentially occur because of the strong coordinating and adsorptive properties of C-S compounds[470]. Furthermore, thiols pretend to undergo oxidative coupling reactions, and thereby undesired disulfides are synthesized[471]. Nevertheless, all of the issues could be minimized if a suitable combination of transition metal salts, then ligands, bases and solvents is applied.

Many different transition metals have been tested in order to enable successful performance of this type of chemical reactions. However, it is extremely important to note that significant attention is paid to secure providers of the chemical catalysts. The main reasons are associated with the potential presence of impurities in chemical catalysts, which consequently might lead to decreased activity[472]. It is important to note that it is possible to exclude the use of chemical catalysts for some particular examples – such as substrates with electron withdrawing groups[473].

Depending on the type of aryl halide, different catalytic mixtures could be applied. Considering aryl iodides, the majority of the investigations have been done with copper salts, such as: CuI[356, 474-489] at the first place, then CuBr[490-494], Cu_2O[495, 496], CuCl[497, 498] and $Cu(OTf)_2$[499]. It is important to note that all of these salts are usually combined with suitable chemical ligands, then bases and solvents. The catalytic activity of the copper salts is usually decreased if aryl bromides are applied, and even more with aryl-chlorides and aryl-fluorides. Hence, salts based on different transition metals have been tested, as well. The most promising results have been achieved by using palladium[500-511] salts which have shown increased catalytic activities in reactions with aryl bromides. Furthermore, salts based on nickel[512-515], iron[516-518], cobalt[519, 520], indium[521] and lanthanum[522] have been successfully tested.

The current way of performing C-S cross coupling reactions involves catalytic mixtures which include several different compounds. In order to simplify this approach, some research groups decided to synthesize catalytic complexes which would involve chemical ligands and transition

metal salts together. A couple of examples have been found in the literature, such as [(IPr)Ni(allyl)Cl][523], [2,6-$(Ph_2PO)_2C_6H_3$]NiCl[524], [Cu(phen)$(PPh_3)_2$]NO_3[525] and (SIPr)Pd(Py)Cl_2[526] which all achieved high yields of the desired sulfides.

Nevertheless, quite long reaction times could be faced together with difficulties in introducing continuous manufacturing modes. In order to solve these major issues, microwave irradiation has been tested. For instance, Ku and coworkers[527] were able to accelerate C-S cross coupling reactions down to 10 minutes. They used a combination of Fe_2O_3 and $Cu(OAc)_2$ as chemical catalysts, then TMEDA as a chemical ligand, Cs_2CO_3 as a base and DMF as a solvent. The above average yields were obtained when aryl-iodides and aryl-bromides were tested, whereas aryl-chlorides resulted in average, or even below average yields of the desired products. However, some applications of microwave irradiantion resulted in quite long reaction times which lead to the conclusion that it is extremely important to find a suitable catalytic system[528-530].

When performing C-S coupling reactions for synthesis of pharmaceutical intermediates, very low concentrations of transition metals in the final products are desired[531]. Therefore, the use of transition metal catalysts usually involves complicated, expensive and time consuming procedures for removing the transition metals again[532]. As a consequence, all of the mentioned approaches with homogeneous catalysis are not desired options from an economical point of view, and therefore immobilized catalysts have been tested. The majority of heterogeneous catalytic approaches have been based on CuO[357, 533, 534] and CuI[535] nanoparticles, then CuO immobilized on mesoporous silica[536], copper on iron powder[537], palladium on charcoal[538], iron on graphite[539], In_2O_3[540] and NiO-ZrO_2[541]. All of the mentioned heterogeneous approaches do not involve the usage of ligands, and reuse of the catalyst was achieved up to a couple of times. Some application examples were based just on metallic Cu without any solvent, base and ligand. However, very harsh reaction conditions were typically applied in such systems[542].

Heterogeneous approaches have led to many advantages compared to homogeneous catalysis, but the reaction times were still high when considering continuous manufacturing. Experiments to accelerate such reactions without increasing the loading of chemical catalysts have led to the idea of immobilizing ligands and transition metals together on a solid support. One interesting example is nickel combined with suitable ligands on silica-coated magnetic nanoparticles[543]. However, reaction times did not decrease significantly, and therefore microwave irradiantion has been tested as well. Usage of CuI nanoparticles[544], as well as copper on metal nanoparticles[545] resulted in acceleration of cross coupling reactions down to a reaction time of about 5 minutes. However, despite these achievements, leaching of transition metals was not completely avoided.

Nevertheless, the cheapest way to perform C-S cross coupling reactions is to avoid using any transition metals. So far, the usage of DMF and Cs_2CO_3 showed good results in reactions of aryl-iodides[499], whereas reactions of aryl-bromides needed KOtBu and DMSO[491]. The presence of electron withdrawing groups caused easy couplings of aryl-fluorides in DMF by using NaH as a chemical catalyst[546]. In addition, KOH and DMF or PEGs showed great potential, as well[547].

Despite the typical chemical reactions between aryl-halides and thiols, a couple of additional approaches have been published. For instance, transition-metal free reactions of aryl-halides and thiolate ions in HPMA resulted in quite high yields[548]. Furthermore, reactions of aryl-halides with aromatic disulfides catalyzed by Cu_2S[549] or Ni[550] gave quite high yields of the desired sulfides, as well. Nickel nanoparticles catalyzed reactions of thiols and phenols gave results that implied high yields of aromatic sulfides in reasonably short reactions times[551]. In addition, reactions of tributylstannyl alkyl or aryl sulfide with aryl halides assisted by Pd salts resulted in quite high yields of the desired sulfides[552]. Moreover, reactions between aryl halides and indium-tri(organothiolate) catalyzed by Pd salts resulted in quite good yields of the desired products as well[553]. Lastly, a very successful usage of chlorination agents and Grignard reagents was tested[185].

8.3 Brief overview of the synthetic ways to (2-bromophenyl)(phenyl)sulfane

The main aim in this section is to find the most suitable way to synthesize (2-bromophenyl)(phenyl)sulfane. A literature survey indicated the existence of several different approaches to synthesize this product. One of the most common synthetic ways is a chemical reaction between iodobenzene and 2-bromobenzenethiol, which is depicted in Figure 8.1.

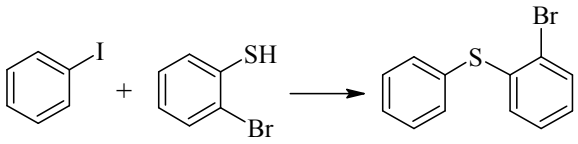


Figure 8.1 Chemical reaction between iodobenzene and 2-bromobenzenethiol

This chemical reaction is usually catalyzed by using transition metals based on Pd and Cu. The overview of the applied chemical catalysts, ligands, bases and solvents is shown in Table 8.1.

Table 8.1 Brief overview of catalytic system used for the chemical reaction between iodobenzene and 2-bromobenzenethiol

No.	R-SH (eq.)	Catalyst (eq.)	Ligand (eq.)	T (^{0}C)	t (h)	Yield (%)	Ref
		Base (eq.)	Solvent (ml)				
1.	1	$Pd(dba)_2$ (0.01-0.1)	DPPF (0.01-0.1)	50	72	97	[354]
		KOtBu (1)	Toluene (5)				
2.	0.91	CuI (0.01)	TBAB (1)	80	10	96	[356]
		KOH (1.5)	water (1)				
3.$^{\mu W}$	1	$Pd_2(dba)_3$ (0.05)	DPPF (0.1-0.2)	100	1	94	[355]
		NaOtBu (4)	Toluene (2)				
4.	0.91	CuO-nanop (0.0126)	-	80	9	90	[357]
		KOH (1.5)	DMSO (1)				

The main focus was just on achieving high yields because this product is just an intermediate compound. It can be noticed that very long reaction times are required for performing this chemical reaction. The fastest approach is shown in the entry 3 where synthesis was performed in a reasonable short reaction time. Hence, 94% of the desired API intermediate was produced within 1 hour. It is however important to note that microwave assisted organic synthesis was applied in this case together with quite high amounts of $Pd_2(dba)_3$, as well as DPPF and NaOtBu. All of the additional entries in Table 8.1 include reaction times which are too high for performing continuous manufacturing in tubular laminar reactors.

Furthermore, the chemical reaction between 1-iodo-2-bromobenzene and benzenethiol is a suitable synthetic route to the desired product as well. The chemical reaction is depicted in Figure 8.2.

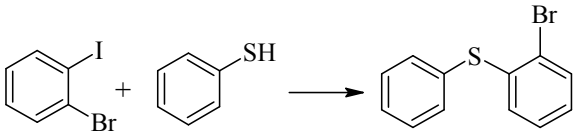


Figure 8.2 Chemical reaction between 1-iodo-2-bromobenzene and benzenethiol

This synthetic route has been less investigated in the literature probably because of the potentially higher deactivation of dihalogenated aromatic compounds. Nevertheless, the results which have been collected from the literature are summarized in Table 8.2.

Table 8.2 Brief overview of catalytic system used for the chemical reaction between 1-iodo-2-bromobenzene and benzenethiol

No.	R-SH (eq.)	Catalyst (eq.)	Ligand (eq.)	T (^{0}C)	t (h)	Yield (%)	Ref
		Base (eq.)	Solvent (ml)				
1.	0.6	CuI (0.1)	L-Proline (0.2)	80	40	92	[494]
		K_2CO_3 (2)	DME (3)				
2.	0.67	CuBr (0.1)	1,2,3,4-Tetrahydroquinolin-8-ol (0.2)	80	24	91	[491]
		K_2CO_3 (2)	DMSO (1L)				

It can be seen that very long reaction times are usually needed for completing the C-S cross coupling reaction between 1-iodo-2-bromobenzene and benzenethiol. In addition, quite high loadings of chemical catalysts and chemical ligands are needed, as shown in Table 8.2.

Furthermore, the chemical reaction between 2-bromophenyl boronic acid and benzenethiol (Figure 8.3) has shown above average results. More precisely, Xu and coworkers[554] achieved a 82% yield of (2-bromophenyl)(phenyl)sulfane at room temperature after 8 h of the reaction. As a catalytic

system, they used 5% of $CuSO_4$, then 5% of 1,10-Phenyl·H_2O and 40% of aqueous n-Bu_4NOH in ethanol.

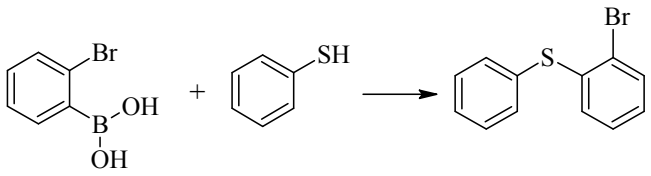


Figure 8.3 Chemical reaction between 2-bromophenyl boronic acid and thiophenol

Finally, the chemical reaction between aryl-iodides and diaryl disulfides has been performed. Wang and coworkers[549] tested 1-iodo-2-bromobenzene and (phenyldisulfanyl)benzene (Figure 8.4).

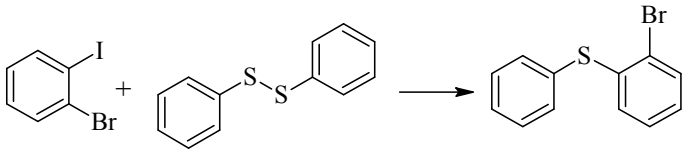


Figure 8.4 Chemical reaction between 1-iodo-2-bromobenzene and (phenyldisulfanyl)benzene

They obtained above average yields of (2-bromophenyl)(phenyl)sulfane (89%) after 18 h and at a temperature of 90^0C. As a catalytic system, they used 1% of Cu_2S, then 0.6 equivalents of Fe as a ligand and 1 equvalent of K_2CO_3 as a base. The ratio between the aryl dihalogenide and the diaryl-disulfide was 1:2. Chemical reactions were performed in DMSO (1 ml) leading to a 1 M concentration of aryl halide. However, similar problems as before are noticed with the long reaction times.

8.4 Suggested synthetic pathway to (2-bromophenyl)(phenyl)sulfane

Application of different transition metals for the synthesis of 2-bromo-1-phenylsulfanyl-benzene resulted in quite high yields, however with reaction times unsuitable for establishing continuous manufacturing modes in tubular laminar reactors.

Therefore, further acceleration of the reaction is needed in order to achieve a sufficiently reduced reaction time. One of the potential choices is to implement an increase of the reaction temperature. However, it has been reported that transition metal catalysts start to lose their activity at temperatures above 90^0C[555]. The second approach might be to increase the loading of catalytic complexes at the applied reaction conditions, but this has the disadvantage that it would cause a need for more expensive and more sophisticated downstream processes. On the other hand, the

usage of the microwave irradiation might be a good choice, as for example shown in Table 8.1, entry 3. However, it might be an economically unjustified approach (especially if larger scales are considered)[556].

It is therefore important to find a more suitable synthetic way to the desired API intermediate. A very fast approach to obtain C-S compounds was discovered by Cheng and coworkers[185] who divided this synthesis in 2 steps. The first step involves synthesis of sulfenylchlorides by applying the desired thiol and 1-chloropyrrolidine-2,5-dione as substrates. Adapted to our example, the chemical reaction including 2-bromobenzenethiol could be performed as depicted in Figure 8.5.

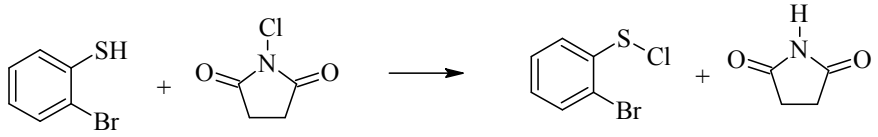


Figure 8.5 Chemical reaction between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione

The chemical reaction is usually completed within 20 minutes at the room temperature. These reagents were chosen due to the possible formation of disulfide if 1-bromopyrrolidine-2,5-dione is used. In addition, 1-iodopyrrolidine-2,5-dione could react even faster, but with undesired stereo-selectivity.

After the formation of sulfenylchloride, the second step is performed (Figure 8.6). This step includes sulfenylchloride and phenylmagnesium bromide as substrates. It is a very fast and exothermic chemical reaction at room temperature which selectively leads to the desired API intermediate. It is important to note that an inert atmosphere is required due to the high reactivity of Grignard reagents with air.

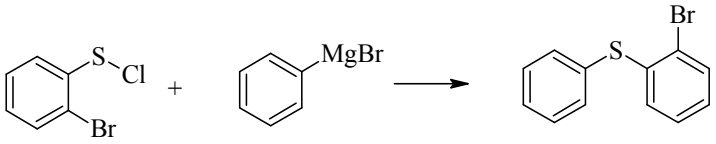


Figure 8.6 Chemical reaction between 2-bromophenyl hypochlorothioite and phenylmagnesium bromide

After this step, it is necessary to neutralize the excess of Grignard reagent. More precisely, 1.5 equivalents of the reagent are recommended for the second step. Hence, high amounts of the Grignard reagent would still be present in the solution after the second step of the synthesis. The overall chemical reaction is supposed to be carried out in toluene whereas neutralization is performed by using a saturated aqueous solution of K_2CO_3.

8.5 Proposed PI Strategy to (2-bromophenyl)(phenyl)sulfane

As noticed in sections 8.3 and 8.4, the synthesis of (2-bromophenyl)(phenyl)sulfane could be performed in several different ways. Different solvents, as well as different catalytic mixtures could be applied in order to complete chemical reactions which would produce higher amounts of the desired product.

Implementation of the PI guideline described in section 3 could lead to several benefits for this synthesis. The main focus is of course on finding an economic, eco-friendly and especially also a fastest approach to synthesize (2-bromophenyl)(phenyl)sulfane. The suggested PI strategy for this case study is depicted in Figure 8.7 which includes two different chemical approaches combined with three different physical assisting effects.

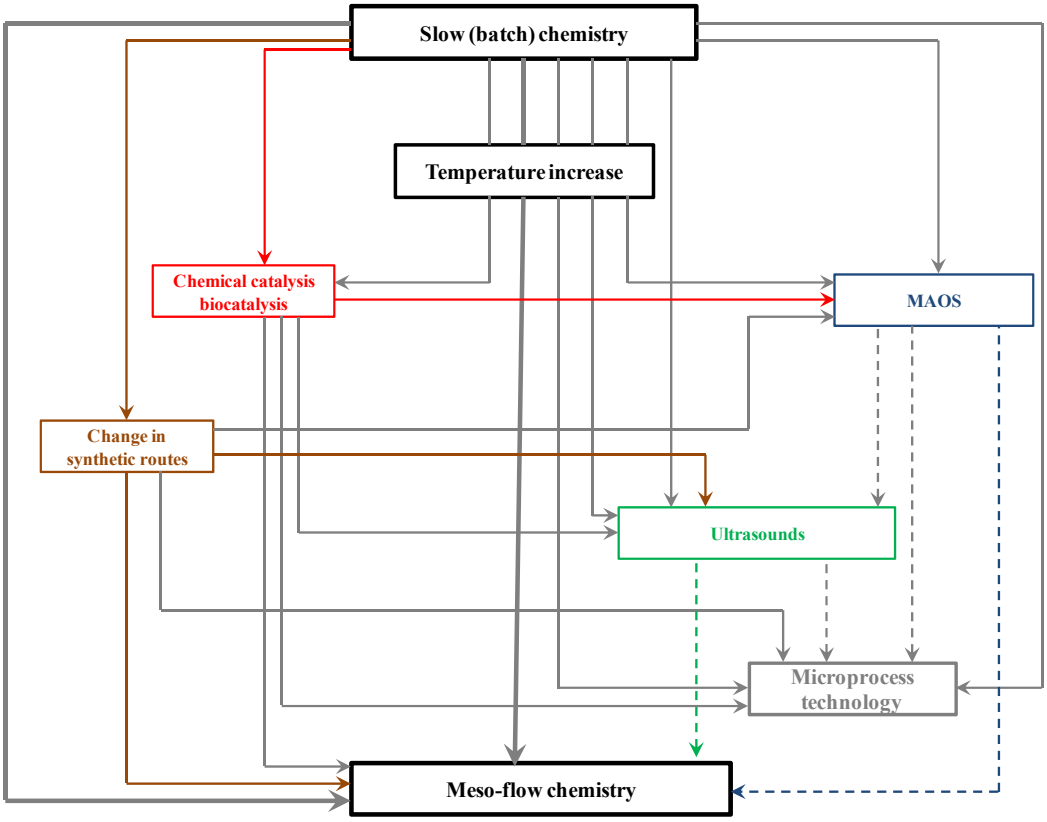


Figure 8.7 PI strategy implemented in the synthesis of 2-bromo-1-phenylsulfanyl-benzene with the main aim to accelerate this production step and make it suitable for PAT implementation

The main focus is on the approaches which would enable the synthesis of the desired product with high yields in a short reaction time, so that the synthesis can be performed in continuous manufacturing modes. Considering applications described in section 8.3, the chemical reaction between iodobenzene and 2-bromobenzenthiol catalyzed with Pd_2dba_3, DPPF and NaOtBu and assisted with microwave irradiation satisfies the criteria[355]. Hence, yields of 94% are achieved together with reasonably short reaction times (1 h). The reaction conditions are depicted in Table 8.1, entry 3, whereas an idea for successful lab-scale production is depicted in Figure 8.7 combining fields involving chemical catalysis/biocatalysis, MAOS and Mesoflow chemistry. In this way, a very fast production of the desired product can be achieved, however with very high capital investments and additionally very expensive downstream processing.

Therefore, the main focus here was on finding a cheaper and faster approach to the desired product. As a result, the synthetic pathway described in section 8.4 was investigated in more detail. It involves a switch of the synthetic route from the chemical reaction depicted in Figure 8.1 to the set of two chemical reactions described in Figures 8.5 and 8.6. Continuous manufacturing applied to such chemical reactions is depicted in Figure 8.7 with brown lines including the connection of slow batch chemistry to Mesoflow chemistry through the field named “Change in Synthetic Routes”. This is typical for the first step whereas the second step involves the usage of ultrasounds in order to avoid clogging of mesoscale tubular reactors.

8.6 Materials and methods

The equipment used in this chapter is divided in three different categories. More particularly, batch experiments in 4-ml vials were performed, as well as meso-scale flow chemistry.

8.6.1 Traditional batch experiments

Traditional batch experiments were used for performing two different sets of experiments. Chemical reactions between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione, as well as between 2-bromobenzenethiol and bromobenzene were performed in 4 ml glass vials. It is important to note that 12 mm teflon septums were added to the polypropylene screw caps in order to increase the stability of the caps against toluene and THF. These reactor vessels were placed in the HLC Biotech thermomixer (model MHR11) which was used as a heating medium. A rack with 16 places was very suitable for screening purposes.

Both sets of experiments were carried out by applying 1 M solutions of 2-bromobenzenethiol. Hence, 1 mmole of the substrate was measured by using an analytical pipette and was carefully transferred to a 4ml glass vial where 1 ml of the solvent was placed. Toluene was used in case of Pd-catalyzed experiments whereas THF was applied for transition metal free experimental runs. It is addiitionally important to note that errors achieved in calculating molar concentrations were neglected (changes of volumes after adding substrates).

The second step in preparing samples was dependent on the type of experiments which were performed. In case of Pd catalyzed experimental runs, it was necessary to measure 1 mmole of bromobenzene and distribute it in the reactor vessel. The substrate is in liquid form and therefore an analytical pipette was used for such addition. Furthermore, the desired amounts of Pd_2dba_3, BINAP and NaOtBu were measured on the analytical balance and carefully distributed in the vials. After this step, vials were placed in the HLC Biotech thermomixer whose temperature was maintained at 80^0C. Furthermore, slow mixing was used (200 rpm) because vigorous mixing would increase the probability to remove chemical catalysts from the reaction mixture (they might get stuck to the upper parts of the reactor wall).

Preparing samples for transition metal free approaches was relatively simple. After adding 2-bromobenzenethiol, it was necessary to add 1.1 equivalent of 1-chloropyrrolidine-2,5-dione. This substrate was in solid form and therefore the desired weight was measured on the analytical balance. The following step was to perform mixing on the IKA® MS 3 basic vortex device. Three different reaction times were applied (20, 40 and 60 min) with three different reaction temperatures 20^0C, 30^0C and 40^0C.

Furthermore, the second step in the transition metal free approach included the addition of 1.5 equvalents of phenyl magnesium bromide under a nitrogen atmosphere. For this purpose, a suitable syringe and needle were used. After this action, the excess of the Grignard reagent was neutralized with an aqueous solution of K_2CO_3 and separation of the phases was easily performed by using a separation funnel.

All the chemicals were bought from Sigma-Aldrich whereas analyses of the results were done by using the HPLC method described in section 8.6.3. It is additionally important to note that HPLC analyses were performed before and after every step in the synthetic routes. Hence, conversion of 2-bromobenzenethiol was followed in both types of experiments, whereas conversion of 2-bromophenyl hypochlorothioite was additionally followed in the transition metal free experimental runs.

8.6.2 Meso-scale flow chemistry experiments

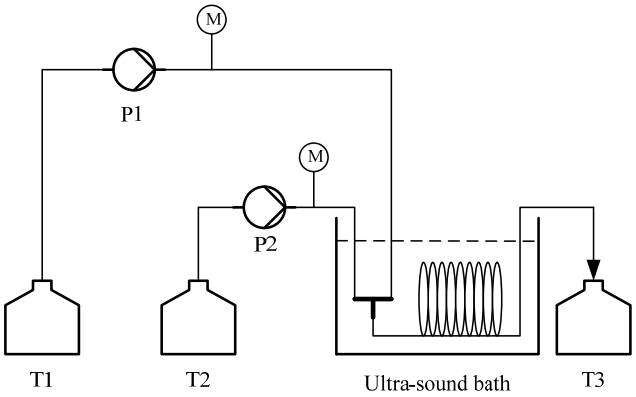
Synthesis of (2-bromophenyl)(phenyl)sulfane in continuous mode was performed in a laminar tubular reactor. The main part was a 30 cm laminar tubular reactor which is a PFA tube with outer and inner diameters of 0.125 inch (3.175mm) and 0.065 inch (1.65mm), respectively. It was placed in an ultrasound bath whose temperature was kept in the range between 20^0C and 30^0C. Neutralization of the Grignard reagent was performed in the tank (T3) which was filled with a saturated aqueous solution of K_2CO_3.

The flow of phenyl-magnesium bromide was regulated by using a Masterflex peristaltic pump (P1) with a PTFE tubing head. The operation range was from 0-7.634 ml/min and flow rates between 1 and 2 ml/min were applied. Furthermore, an Omega PHP-212B-T diaphragm pump (P2) was used

for dosing the flow of 2-bromophenyl hypochlorothioite. The pump operated at a fixed flow rate of 1.625 ml/min which was the lowest flow rate possible to establish with the desired accuracy. In addition, two different manometers were also applied (M) for visual control of the pressure in the experimental setup. All the connections were established by using stainless steel Swagelok connectors.

A continuous Grignard reaction was performed in the experimental setup depicted in Figure 8.8. The upper part of the figure labelled with a) gives insight about the process flow scheme whereas part b) is an image of the setup in the laboratory.

a)



b)

Figure 8.8 Experimental setup for performing the chemical reaction between 2-bromophenyl hypochlorothioite and phenylmagnesium bromide in continuous mode. a) Process flow sheet including: T1, T2, T3 – tanks; P1 and P2 – pump; M – manometers. b) Photo of the setup

8.6.3 Sampling procedure and HPLC analysis

The sample preparation procedure includes 1 ml of ethyl-acetate as a diluent and 10 µl of the desired reaction mixture. In this way, a dilution factor of 101 was applied. All samples were analyzed with the same HPLC device consisting of LaChrome Elite HPLC equipment with a Diode Array Detector (DAD) and a Phenomenex Gemini C6-Phenyl Column. A 25-min isocratic method was used with the mobile phase made by mixing 70% v/v of methanol and 30% v/v of ultra-pure water. The applied wavelength in the DAD was 254 nm. All the retention times in the HPLC chromatograms were identical compared to the reference samples.

All the chemicals were purchased from Sigma Aldrich whereas disposable HPLC vials and caps were bought from VWR International. It is important to note that the lack of a very high purity in all of the used chemicals might influence the accuracy of the obtained results.

8.7 Results and discussions

Results are classified in three different sections because three different sets of experiments were performed in this chapter. Hence, Pd-catalyzed cross coupling reactions are analyzed as the first point. Furthermore, transition metal free experiments in batch modes are explained and discussed and lastly mesoscale flow chemistry experiments are presented and analyzed.

8.7.1 Batch experiments with transition metals

From the literature survey in sections 8.2 and 8.3 it is clear that using transition metals in C-S cross coupling reactions is a widely applied approach. The majority of the cases include Pd and Cu based salts, but the obtained results are usually linked to long reaction times and high loadings of chemical catalysts, chemical ligands and bases. Focusing on (2-bromophenyl)(phenyl)sulfane**,** the best approach is to use $Pd_2(dba)_3$, CuI and CuO as chemical catalysts, as shown in Table 8.1.

The main aim of this section is to find a cheaper approach with a reasonably high conversion of substrates to the desired product. It was therefore decided to perform the chemical reaction between bromobenzene and 2-bromobenzenethiol, as shown in Figure 8.9.

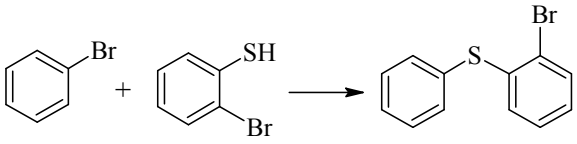


Figure 8.9 Chemical reaction between bromobenzene and 2-bromobenzenethiol

This is a typical cross coupling reaction whose mechanism includes the oxidative addition of aryl-halide to Pd^0, then thiol coordination, deprotonation with halide abstraction, and lastly reductive elimination when the final product is synthesized and the covalent number of Pd is reduced from 2 to 0 again. This is a circular process developed mostly for Buchwald-Hartwig amination reactions[557]. Detailed insight into the synthetic route is shown in Figure 8.10.

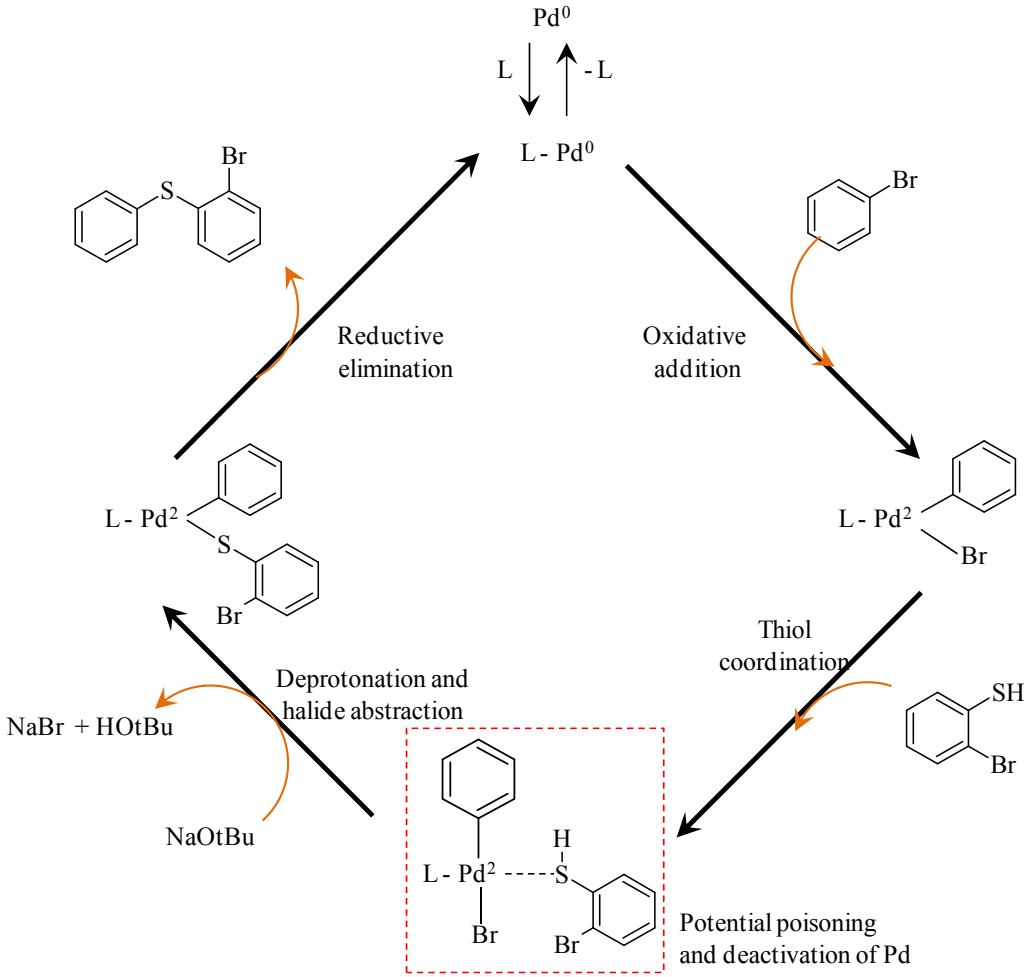


Figure 8.10 Detailed steps in the synthetic route towards (2-bromophenyl)(phenyl)sulfane. L = chemical ligand, Pd = palladium

The very strong coordinative and adsorptive properties of sulfur containing compounds might cause a deactivation of Pd^2 before performing the deprotonation and halide abstraction[470]. This step is depicted inside a red dashed frame in Figure 8.10. Furthermore, the presence of the bromine functional group in the ortho position might cause problems due to steric effects. It would therefore

cause difficulties in establishing bonds between Pd^2-S and decrease the yield of the final product. In addition, Rout and coworkers[357] confirmed that the activity decreases as follows: I > Br > Cl > F. However, the extent of this decrease might be considered as rather surprising due to the significantly lowered yields in the case of using bromo- and chloro-aryl halides.

The experiment performed in this section is identical to the chemical reaction between iodobenzene and 2-bromobenzenethiol (Figure 8.1 and Table 8.1). However, a cheaper substrate is applied together with increased loadings of the Pd_2dba_3 (from 1 % to 5 %) and the chemical ligand – from 10 % to 15 %. A switch from DPPF to BINAP was introduced for this particular occasion with the main aim to avoid presence of additional transition metals in the final product. BINAP and DPPF usually have similar effects in the synthetic routes if Buchwald-Hartwig aminations are applied[462]. In addition, a base was switched from KOtBu towards NaOtBu combined with the increase of the amount added from 1 to 2 equivalents. Lastly, 5 times less solvent was applied in this particular example (1 ml instead of the recommended 5 ml of toluene). Decisions for using 80^0C as reaction temperature were made due to the potential loss of activity of chemical catalysts and chemical ligands if higher temperatures are applied. The recommended range was between 80-90^0C, such as announced by Björn and coworkers[555].

Initial experimental results are depicted in Figure 8.11. It can be easily noticed that a maximum conversion of 2-bromobenzenethiol was achieved after 5 hours, implying to a slow deactivation of the chemical catalyst used in this experimental run. The final conversion was 73% and remained at that value in the consequent 4 h. Yields of (2-bromophenyl)(phenyl)sulfane were not determined.

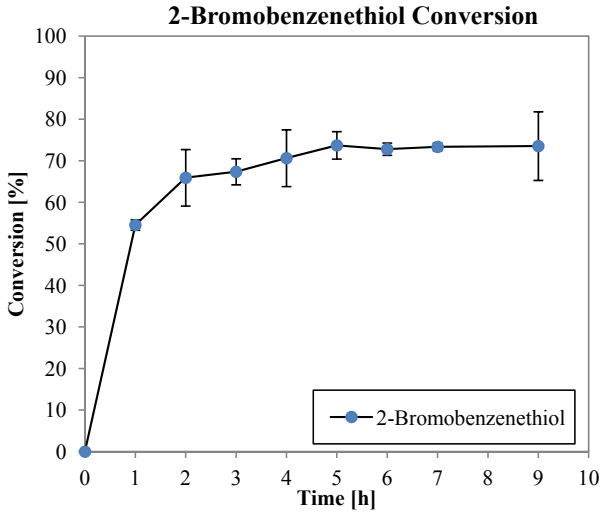


Figure 8.11 Conversion of 2-bromobenzenethiol during the C-S cross coupling reaction with bromobenzene

Applications of bromobenzene with increased amounts of chemical catalysts, chemical ligands and bases did not result in significant improvements in the synthesis of (2-bromophenyl)(phenyl)sulfane. It was therefore decided to implement new synthetic routes which would exclude transition metals, but achieve lower reaction times and higher yields of the desired product.

8.7.2 Batch experiments without transition metals

The main focus of the initial experiments in this section was to investigate the possibility to synthesize the desired product without any transition metals involved. More precisely, the chemical reaction between benzenethiols and 1-chloropyrrolidine-2,5-dione was announced as slightly endothermic and not always selective towards sulfenyl chlorides. Cheng and coworkers[185] claim that selectivity towards disulfides is a big obstacle in performing such chemical reactions. In addition, the same group of authors indicated relatively low yields of the desired products when using THF as a solvent. They tested 20^0C as the reaction temperature and 20 min as reaction time.

It was therefore decided to perform 1-mmole scale experiments at the start. Hence, temperatures of 20^0C, 30^0C and 40^0C were tested, as well as reaction times of 20 min, 40 min and 60 min. The obtained results implied the complete conversion of 2-bromobenzenthiol, regardless which of the mentioned reaction conditions were applied.

Further investigations were focused on exploring this chemical reaction in more details. The first sign about a potential reaction behavior was a significant change of colour when addition of 1-chloropyrrolidine-2,5-dione was performed. More precisely, the change from the transparent sample into an orange colour was performed within a few minutes. Figure 8.12 a) describes the colour change and probably the completiton of the chemical reaction after just a few min. A very fast and short yellow transition state is also noticed and shown in Figure 8.12 a) with a yellow arrow.

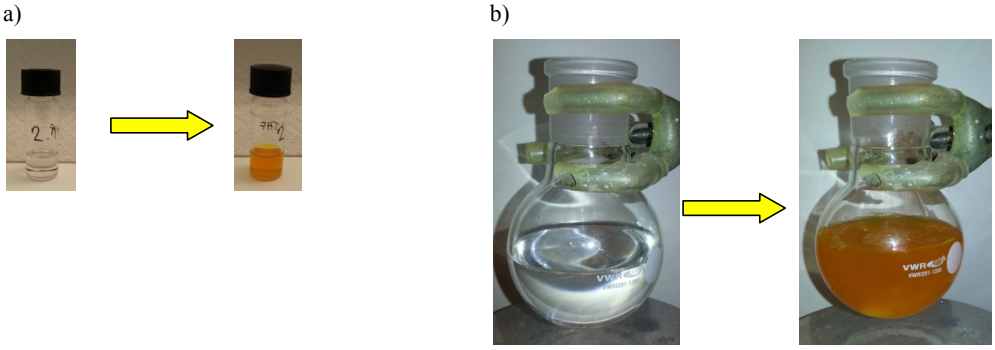


Figure 8.12 Changes in colour when the chemical reaction between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione is performed if (a) 1 ml and (b) 50 ml of the reaction solutions are tested

Furthermore, a larger batch scale experiment was performed. Hence, upscaling from 1 ml solutions up to 50 ml solutions was performed. A completely identical behaviour was noticed compared to the 1-mmole scale experiments and in an identical time frame. Hence, after addition of 1.1 equivalents of 1-chloropyrrolidine-2,5-dione, the reaction mixture changed its colour from transparent to orange via a short yellow transition state, as shown in Figure 8.12 b) as well.

It is important to note that heat release was noticed during the colour change which implies the possibility that the chemical reaction is exothermic at room temperature. More precisely, a free radical reaction is probably performed[558] which is even smoother due to the presence of a C-heteroatom-hydrogen bond in the chemical structure of 2-bromobenzenethiol[559]. The assumed synthetic pathway is depicted in Figure 8.13.

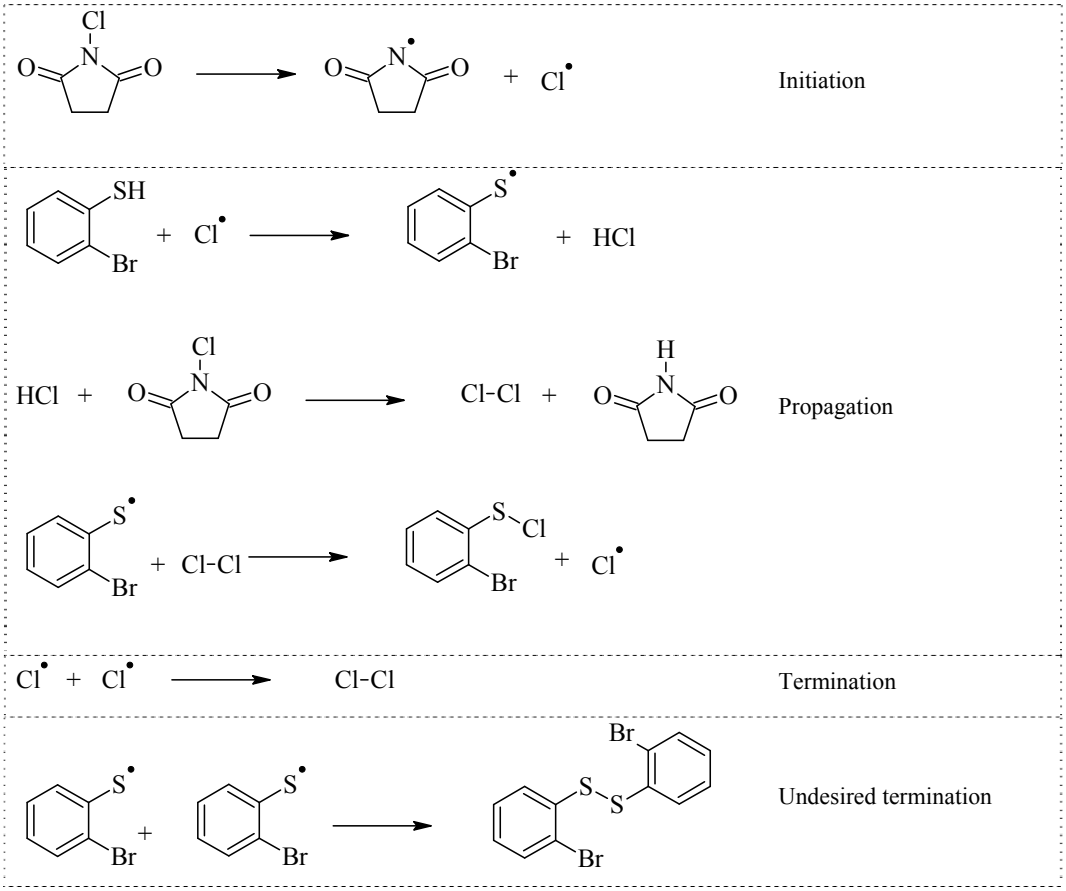


Figure 8.13 Suggested synthetic pathway towards 2-bromophenyl-sulfenylchloride

The heat which is necessary for the initiation of the reaction was probably added by applying stirring of the substrates. Hence, the free chlorine radical was formed easily and therefore propagation was performed with medium heat release. The last step includes reactions between free radicals. It is important to note that disulfides could be formed in this step. However, HPLC analysis did not show any additional by-products. In addition, Cheng and coworkers[185] tested more reactive agents, such as 1-bromopyrrolidine-2,5-dione and 1-iodopyrrolidine-2,5-dione, which resulted in increased by-product formations. It could be concluded that the less reactive 1-chloro-pyrrolidine2,5-dione initiated the 100% conversion of 2-bromobenzenethiol, and this with a very high selectivity (assumed to be 100% in this work according to HPLC analysis).

The second step in the synthesis of (2-bromophenyl)(phenyl)sulfane was to add Grignard reagent to the synthesized 2-bromophenyl hypochlorothioite Hence, 1.5 equivalents of phenylmagnesium bromide solution in THF were used under a nitrogen atmosphere. The basic principle was just to purge the batch reactor with nitrogen during the addition procedure. This reaction is usually completed within milliseconds, and therefore quenching with aqueous K_2CO_3 was performed almost immediately.

Synthesis of (2-bromophenyl)(phenyl)sulfane was completed in this way. HPLC analyses pointed towards the presence of just two components in the final mixture. According to the reference solutions, the desired product was present in the mixture whereas the second component was assumed to be benzene, a by-product obtained after the neutralization of the excess of the Grignard reagent. In addition, substrates from the first and second chemical reactions were not detected with the HPLC analysis at the end of the overall experimental process. It implies on the complete conversion of the mentioned components.

It is important to add that both steps were performed in THF due to its lower toxicity compared to toluene and diethyl ether[341] which were the recommended choices for such chemistry[185].

8.7.3 Meso-scale flow chemistry application

The next step towards successful implementation of such approach was to implement meso-scale flow chemistry. More precisely, both chemical reactions cause a heat release and additonaly they require very low reaction times. This makes the production of (2-bromophenyl)(phenyl)sulfane smoother and suited for flow chemistry applications.

The chemical reaction between 2-bromobenzenethiol and 1-chloropyrrolidine-2,5-dione includes solid particles. Hence, a very low solubility of 1-chloropyrrolidine-2,5-dione in THF is a major obstacle in the implementation of such approach in mesoscale flow devices. It was therefore decided that the first step will be performed in batch mode whereas the second step would include a mesoscale flow reactor. The batch reactor would be converted into CSTR in the ideal case, such is depicted in Figure 8.14. It is important to note that the physical connection between the first and the second step was not established in the work reported here, and therefore a dashed line was used in

the figure in order to represent the connection between the CSTR and the pump P1. More precisely, the eqvuivalence between CSTR in the Figure 8.14 and the tank T1 in Figure 8.8 could be made.

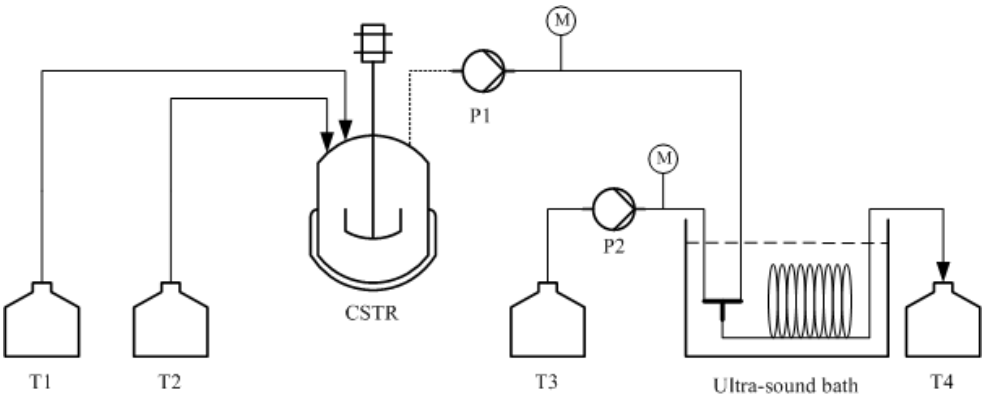


Figure 8.14 Schematic presentation of the integrated setup for producing (2-bromophenyl)(phenyl)sulfane. CSTR – continous stirred tank reactor for the synthesis of 2-bromophenyl hypochlororhioite; T1, T2, T3 and T4 – tanks for storing 2-bromobenzenethiol, 1-chloropyrrolidine-2,5-dione, phenylmagnesium bromide and (2-bromophenyl)(phenyl)sulfane; P1, P2 – pumps; M-manometers. The dashed line implies that no physical connection was established between both reaction steps.

Previous experiences in working with Grignard reagents were done in tubular laminar reactors with a few mm in diameter. More precisely, the Grignard reaction between 2-chlorothioxanthene-9-one and allyl-magnesiumchloride was partly performed in laminar tubular reactors with an inner diameter of 1/16 of an inch[309]. The main reason for adopting such an approach was to avoid clogging of tubular reactors. In addition, in-line process monitoring and control should be established easier in the mesoscale equipment compared to microscale reactors.

Focusing on the experimental part, it is important to note that different flow rates, as well as different molar concentrations of substrates were used in the second step. The main aim was to investigate potential impurity formation, as well as to evaluate whether potential clogging of the equipment is an issue that should be considered seriously. The results are presented in Table 8.3.

Table 8.3 Experimental runs performed in the synthesis of (2-bromophenyl)(phenyl)sulfane the by using mesoscale flow chemistry

No.	2-Bromophenyl hypochlorothioite	Phenylmagnesium bromide	**Conversion [%]**
	Flow rate [ml/min] / (C [M])	**Flow rate [ml/min] / (C [M])**	
1.	1.625 (1 M)	2.43 (1 M)	100
2.	1.625 (1 M)	1.7 (1 M)	100
3.	1.625 (0.5 M)	1.7 (1 M)	100
4.	1.625 (0.5 M)	1 (1 M)	100
5.	1.625 (0.5 M)	2 (1 M)	100

It was easy to notice that the chemical reaction was occurring due to the different colours in all three streams (yellow for 2-bromophenyl hypochlorothioite, light brown for phenylmagnesium bromide and dark green for (2-bromophenyl)(phenyl)sulfane). Furthermore, small amounts of solids particles were observerd, but did not cause any clogging of the tubular reactor. The main reasons for such a smooth flow are associated with the mechanic effects of the ultrasounds. The production was simulated for 30 min without any practical problems

After performing the second step, it was necessary to neutralize the obtained mixture and perform HPLC analysis. The obtained results indicated the complete conversion of 2-bromophenyl hypochlorothioite. HPLC analyses just showed different amounts of benzene in the product mixture due to the different initial molar concentrations of 2-bromophenyl hypochlorothioite, as well as due to different flow rates of phenylmagnesium bromide which were used in the screening procedure. It can therefore be concluded that a very cheap synthetic way towards (2-bromophenyl)(phenyl)sulfane was achieved together with suitable conditions for applying mesoscale flow chemistry.

8.8 Economic evaluation of the production process

The main purpose of performing an economic analysis is to compare the material costs of different synthetic routes towards (2-bromophenyl)(phenyl)sulfane. Two different types of analyses are performed: excluding and including purification processes. Three different examples are analyzed and compared by using prices from the Sigma-Aldrich official website[363]. It is important to note that relative comparisions are additionally performed in order to give a general impression about the usefulness of specific processes. Energy and labor costs are assumed to be the same for all process alternatives, whereas capital investments are excluded from the economic evaluation.

The first example process is named “Experiment 1” and it was previously illustrated in Table 8.1, entry 1. It involves usage of 1 % of $Pd(dba)_2$, then 1 % of DPPF as chemical catalyst and chemical ligand, respectively. In addition, 1 equivalent of KOtBu was applied as a base whereas 5 ml of toluene were used as the reaction medium. The chemical reaction was completed after 72 h with a yield of 97 %[354].

The second example process (“Experiment 2”) is shown in Table 8.1 as entry 3. It includes usage of microwave irradiation together with increased loads of chemical catalysts, chemical ligands and base. More precisely, 5% of $Pd_2(dba)_3$ were applied together with 10 % of DPPF and 4 equivalents of NaOtBu. The reaction was performed in 2 ml of toluene[355].

Finally, the “Experiment 3” represents the new synthetic approach described in section 8.4 (chemical reactions are shown in Figures 8.5 and 8.6). It is important to note that the usage of chemical catalysts, chemical ligands and base is excluded in this approach. Chemical reactions were peformed in THF, and the total volume used was 2.5 ml for both steps.

The implementation of the economic analyses includes evaluation of prices for all constituents involved in “Experiments 1, 2 and 3”. Hence, prices in € per gram and per mmole are shown in Table 8.4 a) for substrates, then b) for additives (chemical catalysts, ligands and bases) and finally c) for solvents. The prices for solvents were calculated in € per ml.

Table 8.4 Prices per gram and mmole of (a) substrates, (b) additives and (c) solvents used in synthetic routes to (2-bromophenyl)(phenyl)sulfane

a)

No.	Substrates	Mw ($\frac{g}{mol}$)	Price (€/g)	Price (€/mmol)
1.	Iodobenzene	204.01	5.82	1.187
2.	2-Bromobenzenethiol	189.07	15.41	2.913
3.	1-Chloropyrrolidine-2,5-dione	133.53	0.21	0.028
4.	Phenylmagnesium bromide	181.31	4.08	0.739

b)

No.	Additivies	Mw ($\frac{g}{mol}$)	Price (€/g)	Price (€/mmol)
1.	$Pd_2(dba)_3$	915.72	53.28	48.789
2.	$Pddba_2$	575.00	46.94	26.993
3.	DPPF	554.38	46.18	25.599
4.	NaOtBu	96.10	4.76	0.458
5.	KOtBu	112.21	4.40	0.493

c)

No.	Solvent	Mw ($\frac{g}{mol}$)	Price (€/ml)
1.	Toluene	-	0.058
2.	THF	-	0.121

Economic evaluation was based on calculating amounts (mmole) of constituents and summarizing their price in every particular "Experiment". For instance, "Experiment 1" included 1 mmole of iodobenzene, then 1 equivalent of 2-bromobenzenethiol, 1 equivalent of KOtBu, 0.01 equivalents of the chemical catalyst, 0.01 equivalents of the chemical ligand and 5 ml of toluene. Hence, the total price per experimental run was 7.714 €. However, the yield was 97% and therefore the total price for producing 1 mmole of the product was 7.953 €. Recalculating this price in terms of €/g results in 2.108 € for 1 g of the final product. The same procedure was followed for calculating costs of production in "Experiments 2 and 3". All the results comparing costs of production in €/g and space-time-yields (STY) are provided in Table 8.5. In addition, relative costs and relative STY with respect to the "Experiment 1" are additionally shown in the table. The main reason for adopting such an approach was to give a rough approximation about the costs regardless the size of the

equipment. The assumption was made that changes in prices for bulk orders follow the same trend for every chemical used in the economic evaluation.

Table 8.5 Comparison of costs of production, Space-Time-Yields, relative costs related to "Experiment 1" and relative space time yield relted to "Experiment 1"

No.	Synthetic route	Cost (€/g)	STY ($\frac{g}{h\ ml}$)	Rel. Cost	Rel. STY
1.	Experiment 1 (batch mode) [354]	2.108	0.0007	1	1
2.	Experiment 2 (microwave) [355]	3.114	0.1245	1.477	174.433
3.	Experiment 3 (new approach)	1.155	0.3183 (verified by HPLC)	0.548	445.807

It could be noticed that "Experiment 2" is 1.477 times more expensive than "Experiment 1", but with 174.433 times higher STY. The latter will probably mean that the capital cost for "Experiment 2" is much lower compared to "Experiment 1". One step further towards a more efficient process is "Experiment 3" which would have the lowest costs per produced gram of the final product, as well as the higher STY. More precisely, the cost is almost halved whereas STY is almost 500 times higher compared to the "Experiment 1". Furthermore, comparison between "Experiments 2 and 3" was performed, resulting in a 2.7 times cheaper process and a 2.56 times higher STY if "Experiment 3" is used.

Despite just producing (2-bromophenyl)(phenyl)sulfane, a very important role should be given to the purification process both in terms of time consumption and additional costs caused by such downstream processes. The choice of a suitable purification method depends on the composition of the mixture which is used in the synthetic route. For instance, "Experiments 1 and 2" involve two different types of transition metals whereas "Experiment 3" includes just an excess of the Grignard reagent.

Focusing on the first two "Experiments", it is important to note that a suitable purification technique should include effective removal of Pd (allowed concentration is 5 ppm) and Fe (allowed concentration is 20 ppm). A comprehensive review about adsorbents was made by Welch and coworkers[358] with main focus on removing Pd, Fe, Ru and Rh from the mixtures that are commonly used in the pharmaceutical process research. The main goal was to perform screening of different candidates in a 35-minute purification process. Hence, the desired limits of the mentioned transition metals were not achieved, but a good indication about suitable scavengers was provided. It is important to note that additional techniques could also be used for scavenging transition metals, such as the techniques explained by Garrett and coworkers[531] whose main focus was on removing Pd from a variety of APIs.

The main focus here was to find suitable scavengers/adsorbents which are specialized for removing Pd and Fe down to the allowed concentration. The best choice for $Pd_2(dba)_3$ and $Pd(dba)_2$ is

Silia*Bond* Thiol which would enable just 2.5 ppm of Pd in the final product. The desired amount of the scavenger is 4 equivalents of the amount of $Pd_2(dba)_3$ (or $Pd(dba)_2$) in the initial mixture), whereas process conditions are 16 hours and 80^0C. In addition, this scavenger showed good removal possibilities for Fe when using DPPF[560]. A detailed analysis was performed by Silicycle Inc.[561] indicating possibilities to achieve 32 ppm of Fe in the final product after operating the purification process for just 4 hours (4 equivalents of Silia*Bond* Thiol were used). It is therefore assumed that prolongation of the scavenging time up to 16 hours would allow reaching the limit of 20 ppm for Fe, as well. The cost of the chosen adsorbent was 4.8852 €/g[561].

Focusing on the "Experiment 3", the purification procedure was based on the neutralization of the excess of Grignard reagent followed by immediate separation of two immiscible liquids. Both processes are very fast and should not have a big influence on the overall processing time. Nevertheless, an addition of 10 min is used in the economic evaluations with additional costs of 0.031 €/g[363] of product.

Incorporation of the purification processes in the overall economical analysis results insignificant changes in the relative costs and relative space times yields. More precisely, the costs of the adsorbent are included in the total costs for producing 1 mmole of (2-bromophenyl)(phenyl)sulfane, whereas the purification time was added to the overall processing time in the STY calculations. The results are summarized in Table 8.6.

Table 8.6 Comparison of costs of production, Space-Time-Yields, relative costs related to "Experiment 1" and relative space time yield related to "Experiment 1" with purification costs included

No.	Synthetic route	Cost (€/g)	STY ($\frac{g}{h\ ml}$)	Rel. Cost	Rel. STY
1.	Experiment 1 (batch mode) [354]	2.395	0.00058	1	1
2.	Experiment 2 (microwave) [355]	3.401	0.0073	1.420	12.54
3.	Experiment 3 (new approach)	1.160	0.53 (verified by HPLC)	0.484	907.217

It can be noticed that differences between "Experiments 1 and 2" are now smaller from the STY point of view, when compared to the results in Table 8.5. A significant decrease of the relative STY from 174.433 to 12.54 is obtained as well for "Experiment 2" which confirms that purification processes play a very significant role in obtaining final products. In addition, "Experiment 3" now showed significant further improvements due to the absence of long-lasting purification steps. Hence, the relative STY was increased from 445.807 up to 907.217 (compared to "Experiment 1"). If the comparison is done relative to "Experiment 2", the increase in STY was from 2.56 to 72.34 relative units. Changes in costs were not significant, but the fact is that "Experiment 3" approached a cheaper price – from 0.548 to 0.484 compared to the "Experiment 1" whereas the same ratio was kept compared to the "Experiment 2".

Finally it is important to note that capital costs would have an additional and significant impact on "Experiment 2". Prices of the microwave ovens are considerable, but the exact values depend on the equipment manufacturers. In addition, scaling-up is not a recommended approach for "Experiment 2" because toluene is labeled as a reaction medium with low absorption for microwave irradiation. Hence, it is expected that the effectiveness of the microwave would not be very high when scaling up the equipment. A suitable approach might be to use coiled tubular reactors, such as described in section 3.3.4.

The economic evaluation convincingly showed many potential benefits if the new synthetic route would be applied. More detailed analyses should be performed for achieving a more accurate economic evaluation of all three "Experiments". Hence, energy costs, capital investments, labor costs and material costs should be recalculated with more precise and realistic values. Nevertheless, application of the new synthetic route would lead to plenty of benefits from an economic point of view.

8.9 Conclusions and future work

Transition metal based chemistry is a commonly applied method for producing carbon-sulfur containing compounds. Plenty of different chemical catalysts and chemical ligands have been developed and they showed good efficiency. However, the economic aspects of using Pd, Cu, Ni, and so on, and additionally chemical ligands and suitable bases label this approach as very expensive.

Synthesis of 2-bromo-1-phenylsulfanyl-benzene was performed in two different modes including $Pd_2(dba)_3$, BINAP and NaOtBu in the first approach and radical free with consequent Grignard reaction as the second approach. The obtained results demonstrated significantly lower reaction temperatures (from 80^0C to just 20^0C), as well as significantly lowered reaction times (from 5 h to 20 min), and also demonstrating the use of much cheaper reagents for the new synthetic route. In addition, increased conversion of 2-bromobenzenthiol from 73 % to 100 % was achieved as an additional benefit.

The practical realization of the mesoscale flow chemistry example implied easy and smooth production of (2-bromophenyl)(phenyl)sulfane using the new synthetic route. The production was performed for 30 min, and was assisted by the mechanic effects of ultrasounds. In this way, a successful implementation of the PI strategy (see Chapter 3) was achieved by using one chemical and two physical approaches. More precisely, a change in the synthetic route from nucleophilic substitution reactions towards free radical mechanism combined with subsequent Grignard reactions was successfully performed.

Further work would include evaluating the performance of in-line process monitoring, process control and automation. Integration of both synthetic steps in the new production route is a desired approach, and therefore a suitable performance evaluation of working with slurries should be done.

The most desired approach would be to use peristaltic pumps with continuous mixing of the 1-chloropyrrolidine-2,5-dione solution in THF.

Finally, an economic analysis illustrated several benefits if the new synthetic route would be applied. A more detailed analysis would provide a better economic basis if larger scales are to be considered in the future. Nevertheless, a 907 times better space time yield was achieved with the new synthetic route compared to the best batch mode operation published in the literatue. Furthermore, 72 times increased space time yields were obtained compared to the results of microwave assisted experiments (from the literature). Besides the increased STY, the costs for producing (2-bromophenyl)(phenyl)sulfane are halved compared to the batch operating mode, or even almost three times cheaper if MAOS were applied. It is important to note that the economic values are focused on obtaining products with the desired purity.

9. Conclusions and Future Perspecives

9. Conclusions and future perspectives

The required high quality of pharmaceutical products is in many production processes a very challenging goal to be achieved. In order to satisfy all necessary criteria, new trends have emerged in the pharmaceutical industry, such as cGMP along with the PAT Initiative, Knowledge space and QbD approach. Apart from quality, additional goals need to be achieved as well for future pharmaceutical manufacturing processes, such as improved economic performance, environmentally friendly processes, and so on. Hence, implementation of different continuous improvement methodologies/technologies has been performed. More precisely, applications of Lean Production Systems, then Six Sigma, Lean Sigma, Theory of Constrains, and so on, have led to plenty of advantages in the pharmaceutical industry.

Implementation of the "Manufacturing Flow" and partly "Process Control" elements of the LPS to the manufacturing of different APIs requires additional improvements of the crucial steps in the production routes. Different tools for process intensification and process optimization have been developed and were afterwards implemented for faster production of the API. Focusing on the PI tools, modern approaches include applications of microwave assisted organic synthesis, meso-scale flow chemistry, microreactor technology and ultrasounds with its mechanical or sonochemical effects. All of these physical effects could be combined with chemical catalysis or biocatalysis in order to accelerate chemical reactions and make them suitable for the continuous manufacturing modes. In addition, a change of synthetic routes to desired products might be desired in case all the previous acceleration tools do not result in the required rate of production.

Focusing on the Clopenthixol production, it is important to note that traditional batch production was successfully transferred to the continuous manufacturing mode (lab-scale purposes). Application of the PI tools in the endothermic part of the production resulted in significant acceleration of slow chemical reactions and consequently lead to easier adaptability of the process to the PAT requirements. More precisely, the dehydration of "N714-Allylcarbinol" was successfully transferred to a continuous tubular laminar reactor with increased reaction temperature and pressure. Furthermore, applications of MAOS resulted in a significant acceleration of the hydroamination step where "N746-Butadienes" reacted with HEP.

A move from classical batch towards continuous mode in the dehydration step was performed by applying a tubular laminar reactor with back-pressure regulators and in-/at- and off-line analyses. Application of temperatures up to 120^0C resulted in a decrease of the reaction time from 2 hours to just 3 minutes. Furthermore, the usage of FT-NIR together with multivariate calibration showed very promising results for future real-time process monitoring purposes. However, issues in the dehydration step included low selectivity of the desired cis-isomer (cis-"N746-Butadiene"), as well as a significant formation of by-products. Trials to increase the stereo-selectivity were performed by using Lewis acids and Lewis bases in combination with dichloromethane as a suitable solvent. Average increases of the stereoselectivity were achieved in case of using TFAA and Et_3N (from 42 % up to 62 %), but such increases are insignificant for the introduction of such an approach in the overall process flow sheme. In addition, issues associated with the formation of poly-THF and

additional polymers were faced because of the high molar concentrations of hydronium ions in the reaction system. This obstacle could be avoided by using either a solvent swap from THF to preferably toluene or by introducing polymerization inhibitors in the overall process flow scheme. This last approach would influence the new impurity profile in the final product and therefore it is not a desired choice for the future work.

The last step in the Clopenthixol manufacturing is the hydroamination reaction. Microwave radiation was implemented as a PI tool in this particular step and therefore significant acceleration of the reaction was achieved. More precisely, an acceleration from 24 hours reaction time towards just 2 hours was achieved with comparable yields. In addition, a solvent removal procedure was introduced before performing the hydroamination reaction. The solvent free batch modes resulted in similar yields as achieved in the case of using MAOS. It is therefore possible that THF has a significant influence on the reaction rate of the hydroamination reaction. Hence, aiming at a further decrease in the reaction time would include the removal of THF from the reaction mixture before applying MAOS. Quite a good absorption of the microwave irraditon by HEP would not cause obstacles in achieving high temperatures. Nevertheless, the stability of the final product decreases significantly at temperatures above 120^0C and therefore this value should be used as the upper limit. As a future work, completion of the continuous manufacturing could be accomplished by implementing MAOS and coiled reactors in the hydroamination step. Significant accelerations would be obtained with easier implementation of real time process monitoring, control and preferably automation.

Additional focus in this work was on accelerating processes for production of compounds containing Carbon-Sulfur bonds. More precisely, the main aim was to establish continuous production of (2-Bromophenyl)(phenyl)sulfane which is becoming an important API intermediate. Two different approaches were performed with significantly different results. The recommended way to perform this synthesis was to use chemical catalysts, chemical ligands and strong bases. Hence, application of high quantities of transition metals and environmentally unfriendly solvents were needed, but resulting in a process that is unsuitable for continuous manufacturing modes. More precisely, the applications of 5% of $Pd_2(dba)_3$, then 15% of BIINAP and 2 equvalents of NaOtBu in 1 ml of toluene resulted in conversion of 73% of the substrate. Applications of MAOS could be very beneficial here, but performing scale up might cause obstacles because toluene does not absorb microwave irradiation that well. For this process alternative, a very expensive batch operating mode will result in this way together with long reaction times and time consuming purification procedures.

Therefore, a new synthetic route was suggested which included a free radical mechanism as the first step and afterwards a Grignard reaction. A less harmful solvent was applied in this particular synthetic route (THF) with significantly cheaper material costs. Hence, long reaction sequences were replaced by two exothermic reactions carried out at room temperature, and therefore easier and smoother processing was achieved. The economic analysis based on approximations of the material costs implied 50% reduction of the material costs of the new process, and about 900 times higher space time yields. Meso-scale flow chemistry was additionally performed combined with

exploiting the mechanistic effects of ultrasounds. Conversions of 100% were achieved in both steps leading to very high yields of the desired API intermediate. For a complete confirmation of the results, it will be necessary to perform additional analysis, such as NMR. Future work will include the development of suitable in-line process monitoring, process control and automation of this continuous process. According to the literature study, the best choices would be either IR or Raman spectroscopies.

The PI strategy developed in this work was implemented in the manufacturing of several compounds. As a result, chemical reactions were significantly accelerated and therefore adapted to continuous manufacturing modes. Better selectivities were achieved as an additional benefit and resulted in the removal of several purification steps combined with elimination of the intermediate storages in the overall process flow scheme. Hence, it can be confirmed that “Manufacturing Flow“ and “Process Control” elements of the LPS were successfully implemented in the production process of two different API intermediates and one API.

10. References

10. References

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A. Appendix

A1. MATLAB® Code for performing simulations of the temperature gradients along the length of a tubular reactor

```
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% Teperature profile of THF inside the reactor
% Aleksandar Mitic 03/01/2014

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%


% tubular reactor
Diameter = 0.635e-2; % m
Rad = Diameter/2; % m
L = 3; % m
time = 256.2; % s

% flow rate
fiv = 2*1.5e-6/60; % m^3/s (1.5 ml/min)
A = pi*Rad^2; % m
w = fiv/A; % m/s (convection)
S = 2/Rad; % m-1 surface to volume

% parameters
dens = 889; % kg/m^3 (THF)
cp = 1705; % J/kg K (THF)
lamb = 0.15; % J/K m s (THF)
Tent = 25+273.15; % K entrance temp
Toil = 120+273.15; % K oil bath
Kb=244; %kcal/h m^2 C (PFA)
Kt=Kb*4.184*1000/3600; %J/m^2 s K
Diff = 0.09e-4; % m^2/s (THF in air)

% preallocation / domain
Nz = 300;
Nt = 2500;

c = zeros(Nt,Nz+1); % with room for dc/dz=0 boundary condition
T = zeros(Nt,Nz+1); % with room for dT/dz=0 boundary condition

% boundary condition
T(:,1) = Tent;
T(1,:) = Tent;

% discretization
dz = L/Nz;
dt = time/Nt;
L_vec = 0:dz:L-dz;
%t_vec=[0:dt:Nt-dt 0:dt:Nt-dt];

for t=1:Nt-1

    for z=2:Nz
```

```
        T(t+1,z) = T(t,z) + dt * ( -w/dz * (T(t,z)-T(t,z-1)) + lamb/dens/cp/dz^2
* (T(t,z+1)-2*T(t,z)+T(t,z-1))...
                 + 1/dens/cp * Kt*S*(Toil-T(t,z)) );

    end
end

% remove exit boundary
T = T(1:end,1:end-1);

figure
plot(L_vec,T(end,:),'k','linewidth',2)
ylabel('T [K]','FontName','Times New Roman','FontSize',30,'FontWeight','bold')
xlabel('L [m]','FontName','Times New Roman','FontSize',30,'FontWeight','bold')
title ('Temperature profile of THF inside reactor','FontName','Times New
Roman','FontSize',45,'FontWeight','bold')
set(gca,'FontName', 'Times New Roman')
set(gca,'FontSize',20)
```

A2. NMR Data for evaluating purity of substrates and products in the dehydration reaction

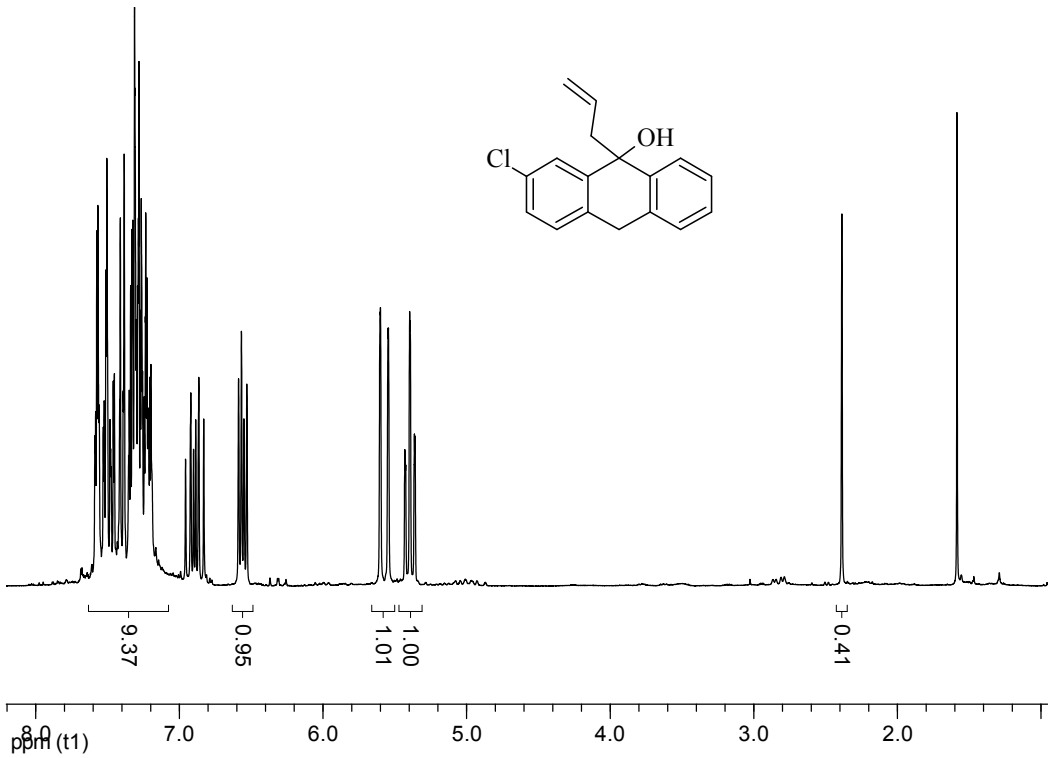


Figure A1 NMR Spectrum of "N714-Allylcarbinol"

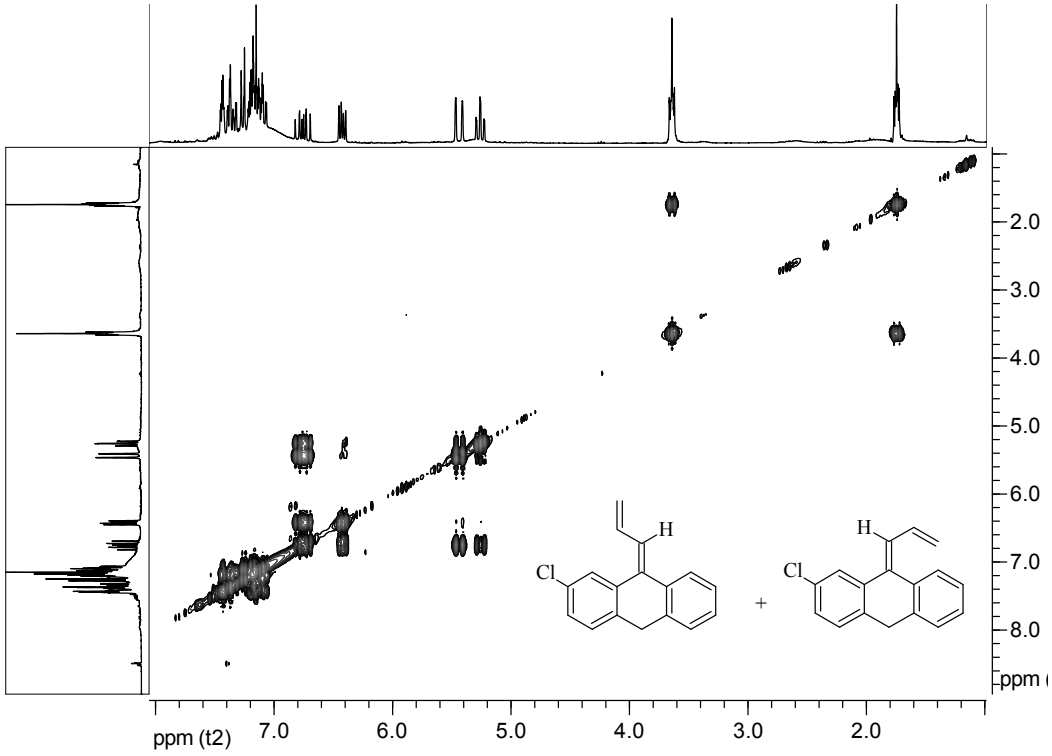
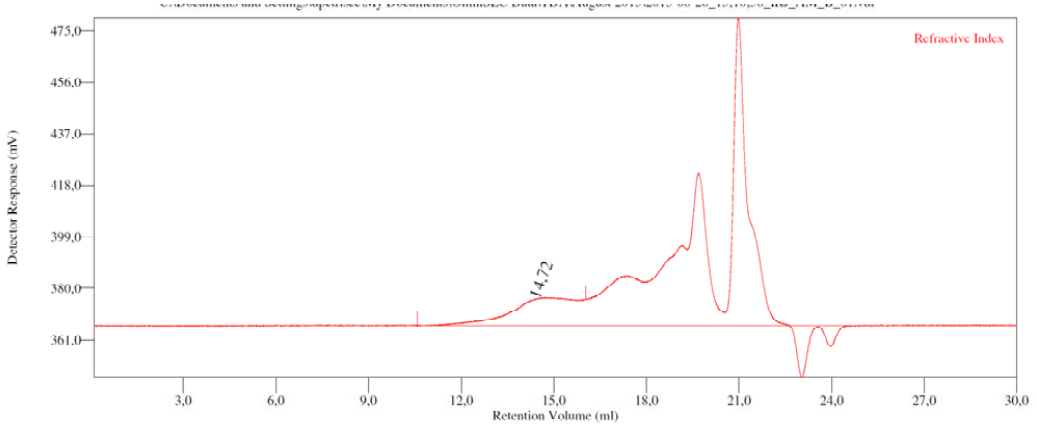


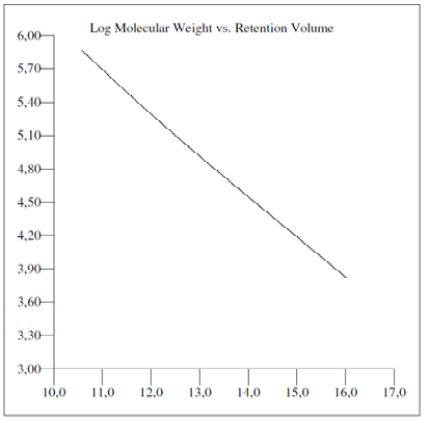
Figure A2 NMR Spectrum of "N746-Butadienes" with impurities



Conventional Calibration - Homopolymers : Results

Peak RV - (ml)	14,720
Mn - (Daltons)	16.928
Mw - (Daltons)	35.815
Mz - (Daltons)	113.991
Mp - (Daltons)	19.446
Mw / Mn	2,116
Percent Above Mw: 0	0,000
Percent Below Mw: 0	0,125
Mw 10.0% Low	7.322
Mw 10.0% High	148.225
RI Area - (mvml)	26,16
UV Area - (mvml)	0,00

Annotation	
Method File	PS-EasiCal-July 2013-0003.vcm
Limits File	6_IRJ_AM_B_01-PS-EasiCal-July 2013-0003-0000.lim
Date Acquired	Aug 26, 2013 - 15:10:36
Solvent	THF
Acquisition Operator	admin : Administrator
Calculation Operator	admin : Administrator
Column Set	Mixed D
System	TDA
Flow Rate - (ml/min)	1,000
Inj Volume - (ul)	100,0
Volume Increment - (ml)	0,00333
Detector Temp. - (deg C)	30,0
Column Temp. - (deg C)	30,0
OmniSEC Build Number	257



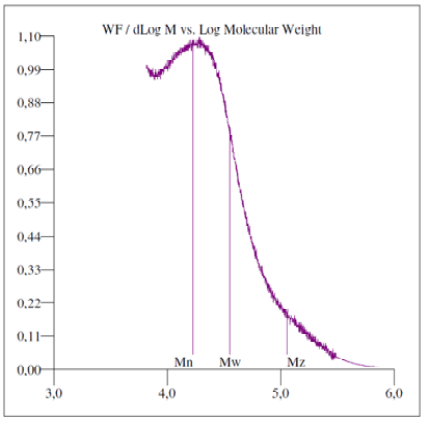


Figure A3 SEC report implying in polymers in the analyzed sample of "N746-Butadienes"

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