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INTRODUCTION

Organic synthesis is essential for the production of an important class of pharmaceuticals. However, once a production route has been established in the development lab, the subsequent implementation of organic synthesis on an industrial scale is still a great challenge. Traditionally, pharmaceutical manufacturing is mainly based on batch and semi-batch processes. However, besides flexibility and versatility of batch vessels, there are also many disadvantages connected with batch production. Furthermore, Process Analytical Technology (PAT) cannot reach the full benefits in this type of production system. Moving from batch to continuous production mode might offer a solution to those problems. Considering the relatively low production volumes in the pharmaceutical industry, the focus in a continuous production system is automatically directed towards small scale or even micro-scale equipment for reaction, separation etc.

PROCESS DESCRIPTION

The synthesis of *cis*-zuclopenthixol – a product of H. Lundbeck A/S – is studied. The manufacturing process consists of the process steps described in Figure 1. The paper will have focus on the experience gained with some of those steps, and will illustrate how a batch production system was converted into a continuous system.

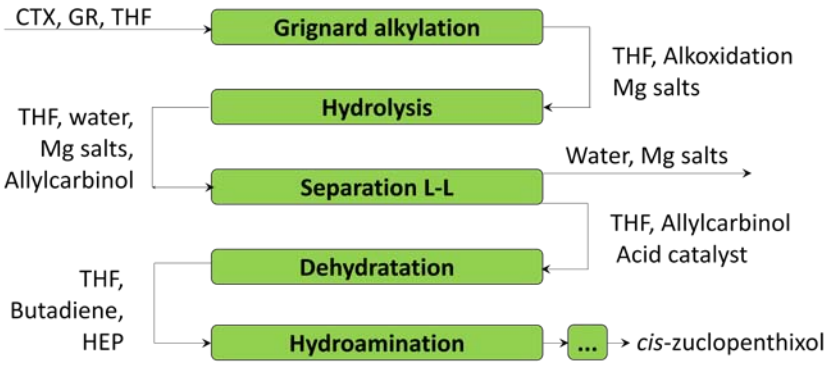

Figure 1: Schematic description of the production process (CTX - 2-Chlorthioxanthen-9-one; GR - Allyl magnesium chloride; THF - Tetrahydrofuran; Alkoxidation – intermediate; Allylcarbinol - 9-Allyl-2-Chlorothioxanthen-9-Ol-9H-thioxanthen-9-ol-2-chloro-9-(2-propenyl)-(9CI); Butadiene - 9H-Thioxanthene-2-chloro-9-(2-propenylidene)-(9CI) ; HEP - 2-(1-piperazinyl)ethanol)

Grignard alkylation

A mini-reactor is used to perform the Grignard alkylation of CTX. Impurity formation in this step was kept low due to the development of a feedback controller that uses on-line near infrared (NIR) spectroscopy data to titrate the CTX with Grignard reagent. Thanks to an improvement of mass and heat transfer in the mini-reactor, combined with more accurate dosing of the Grignard reagent, formation of by-products has been drastically decreased.

Liquid-liquid separation

After hydrolysis of the product obtained in the alkylation reaction, it is necessary to separate the organic (THF-allylcarbinol) and aqueous phases (water containing Mg salts). The presence of inorganic salts significantly affects the solubility of THF in water due to the salting-out effect. The two solvents, which under normal circumstances are totally miscible, separate into an aqueous and an organic phase. The salting-out effect is further increased by the addition of acid which dissolves the basic magnesium salts in the solution. In our case study the phases have similar densities, and therefore a PTFE membrane mini-separator based on capillarity and surface tension differences [1] has been developed and tested. Different immiscible liquid mixtures have been examined and the efficiency achieved with this separation method is very high.

Hydroamination reaction

One of the major practical problems when switching an organic synthesis-based process from batch to continuous operation is that not all reactions are suited to be operated in continuous mode. Hence, in the example process the slow hydroamination step has to be accelerated. Possible solutions could be chemical catalysts for intermolecular anti-Markovnikov hydroamination [2-3]. Hence, different catalysts are to be tested. Furthermore, micro-scale technology as well as microwave heating will be investigated, too.

CONCLUSIONS

Micro-scale technology can be extremely helpful when establishing a continuous pharmaceutical production process, as illustrated here for the zuclopenthixol synthesis process. However, not all reactions can be operated in a straightforward way at micro-scale. As illustrated for the case study efficient process development might result in a combination of unit operations at the micro-scale on the one hand, and liter scale reactors on the other hand.

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