

# An Integrated Systematic Framework to Assist the Development of Pharmaceutical Processes

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# An integrated systematic framework to assist the development of pharmaceutical processes.

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The pharmaceutical industries are dominated by batch wise processes, which have served well the pharmaceutical industries as well as the regulatory bodies. Batch vessels provide the flexibility of handling different unit operations in a multipurpose plant. However, batch processes may not be very efficient for product quality assurance and may have drawbacks. Over the last decade the regulatory bodies required the pharmaceutical companies to demonstrate more process understanding. Continuous pharmaceutical manufacturing (CPM) has become an attractive option, which naturally eliminates some of the drawbacks of the batch processing while maintaining the flexibility [1].

Pharmaceutical industries are therefore looking for opportunities to evaluate the feasibility to apply continuous manufacturing. Methods and tools, which have been applied to other industries (such as chemical and petrochemical) may not be directly applicable for pharmaceutical processes. Therefore Process Systems Engineering (PSE) tools and methods tailor-made for pharmaceutical applications can have an important role in the transition from batch to continuous manufacturing in the pharmaceutical industries [2].

An integrated computer-aided framework for the development of pharmaceutical processes has been developed. The objective of the framework is to assist the pharmaceutical companies to facilitate the move from batch to continuous manufacturing and the development of batch or continuous pharmaceutical processes. The integrated framework consists of four parts: (Part A) identification of the reaction mechanism, (Part B) reaction analysis, (Part C) separation analysis and (Part D) evaluation of the developed process. Identification of the reaction mechanism is the first part and it consists of two steps. Step A.1 is the selection of the active pharmaceutical ingredient (API) or the intermediate to be produced and step A.2 the identification of the reaction pathway. The reaction analysis (part B) consists of six steps and it aims to identify all the relevant information for the reactor design. Step B.1 is the general analysis of the reaction, in this step the basic information for the reaction (such as reactants, solvent, kind of reaction, catalyst, properties and by-product) are collected (if available). In step B.2 the kinetic analysis is performed and the reaction limitations are identified. In the next step (Step B.3) the reaction variables are evaluated with respect the reaction performance. Based on the information which have been collected (or predicted through reliable models), a decision (Step B.4) whether continuous operation is beneficial or not for the system is taken. In the step B.5 decision on the reactor design is taken considering the collected information and finally, if separation of the reaction stream is needed (step B.6), the separation analysis (part C) is performed. The separation analysis consists of seven steps, in the beginning the objective of the separation is defined. In the Step C.1 the mixture to be separated is analyzed and the separation tasks are defined. In the step C.2 the alternatives of the separation are generated and in step C.3 they are evaluated in order to minimize the number of alternatives. Finally, in the steps C.4-C.7 the separation process is designed (unit operation design parameters and operation mode). The final part of the framework (part D) is the evaluation of the developed process and consists of two steps, simulation/evaluation of the process (Step D.1) and optimization, control and monitoring of the developed process (Step D.2).

Development of the framework requires the development and the use of model-data based computer aided methods and tools such as a knowledge database, a model library, modeling tools, solvent selection tools, process analytical technology (PAT) and quality by design (QbD) approaches. The knowledge library should provide all the relevant information for pharmaceutical product/process development such as reaction mechanisms, reactants (substrates, catalysts, and solvents), reaction conditions, and process efficiency. The model library should contain information to describe many unit operations involved in pharmaceutical processes, reaction kinetic models and properties prediction models. The modeling tools must assist in the development of new models and model-based simulations. Solvent selection tools must assist for the selection

of an appropriate solvent when needed and to optimize the use of solvents in pharmaceutical development. PAT and QbD approaches are needed to improve and ensure high the quality of the product.

The application of the proposed integrated framework is highlighted through the BHC (Boots and Hoechst-Celanese) patented synthesis pathway for ibuprofen. The improved BHC synthesis of ibuprofen consists of three reaction steps [3] and it is used to verify the proposed integrated framework. The objective here is to demonstrate that the framework plus the methods and tools can be applied for new products (and their processing paths) as well as validate or retrofit existing ones.

References:

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