Operational Aspects of Continuous Pharmaceutical Production

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 Intensification (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-Chlorothioxanthene-9-Ol ("N714-Allylcarbinol") to the mixture of cis and trans 9H-thioxanthene,2-chloro-9-(2-propenylidene) (9CI) ("N746-Butadienes"). Both components are in 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-situ 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-Chlorothioxanthene -9-ylidene)propyl] - 1 - piperezineethanol (Clopenthixol). This chemical reaction is well-known as very slow and difficult to be accelerated by applying chemical catalysts. vi 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 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.