Active pharmaceutical ingredient (API) production involving continuous processes – A process system engineering (PSE)-assisted design framework - DTU Orbit (28/01/2019)

**Active pharmaceutical ingredient (API) production involving continuous processes – A process system engineering (PSE)-assisted design framework**

A systematic framework is proposed for the design of continuous pharmaceutical manufacturing processes. Specifically, the design framework focuses on organic chemistry based, active pharmaceutical ingredient (API) synthetic processes, but could potentially be extended to biocatalytic and fermentation-based products. The method exploits the synergic combination of continuous flow technologies (e.g., microfluidic techniques) and process systems engineering (PSE) methods and tools for faster process design and increased process understanding throughout the whole drug product and process development cycle. The design framework structures the many different and challenging design problems (e.g., solvent selection, reactor design, and design of separation and purification operations), driving the user from the initial drug discovery steps – where process knowledge is very limited – toward the detailed design and analysis. Examples from the literature of PSE methods and tools applied to pharmaceutical process design and novel pharmaceutical production technologies are provided along the text, assisting in the accumulation and interpretation of process knowledge. Different criteria are suggested for the selection of batch and continuous processes so that the whole design results in low capital and operational costs as well as low environmental footprint. The design framework has been applied to the retrofit of an existing batch-wise process used by H. Lundbeck A/S to produce an API: zuclopenthixol. Some of its batch operations were successfully converted into continuous mode, obtaining higher yields that allowed a significant simplification of the whole process. The material and environmental footprint of the process – evaluated through the process mass intensity index, that is, kg of material used per kg of product – was reduced to half of its initial value, with potential for further reduction. The case-study includes reaction steps typically used by the pharmaceutical industry featuring different characteristic reaction times, as well as L–L separation and distillation-based solvent exchange steps, and thus constitutes a good example of how the design framework can be useful to efficiently design novel or already existing API manufacturing processes taking advantage of continuous processes.

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