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Systematic retrofitting methodology for pharmaceutical drug purification processes

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ABSTRACT

A systematic retrofitting methodology supported by real data implementation was developed to facilitate the optimization of pharmaceutical drug purification processes. The methodology consists of five tasks: (I) understand the plant through measurements, (II) create a process model, (III) adapt the model for optimization, (IV) optimize the process model, and (V) interpret the outcome of the task. A novelty of this methodology is the use of path-flow decomposition as a tool to provide a visual representation of the process, thus facilitating its understanding and the creation of the process model. Furthermore, a decision-tree diagram furnishes detailed and specific support during the creation of the process model, in particular for a dissolution–filtration–crystallization process. Identification of constraints and optimization variables ensure the applicability of the methodology to pharmaceutics. Incorporation of measured process data improves the reliability of the methodology, making it applicable in real case studies. The methodology was applied to an industrial case study.

1. Introduction

Process optimization is becoming an increasingly important subject in the pharmaceutical industry. Expiration of patents protecting companies from competition and increases in R&D expenses causes economic issues for pharmaceutical companies (Duff, 2011). To cover the research costs and to reduce the time required for commercialization of a drug, a pharmaceutical plant must be operational as soon as possible after the approval of a new product (Hughes et al., 2011), which may result in low efficiencies. The strong competition forces the realization of feasible solutions in a short time, frequently leading to suboptimal designs.

The pharmaceutical industry could profit more from engineering-based analyses, including computer simulations. Modeling and problem-solving skills are crucial for the success of an optimization (Reklaitis et al., 2010; Troup and Georgakis, 2013), leading to time and cost reductions. However, in current practice, simulation and process modeling are of secondary importance because of the prevalent use of more pragmatic methodologies. In fact, in the pharmaceutical industry, well-established experiment-based approaches limit the need for process systems engineering in drug synthesis. The high value of the products, especially in pharmaceutical manufacturing, furthermore justifies insufficient optimizations in the first steps of creating a new production line. In addition, regulations for maintaining product quality, known as Good Manufacturing Practices (GMP), must be respected and complied with simulating, optimizing, and changing manufacturing processes.

In recent years, many studies have contributed to the simulation-based optimization of pharmaceutical production processes. A common topic is scheduling. Wu and Ierapetritou (2003) developed a decomposition-based methodology for solving short-term scheduling optimization problems. Subsequently, Papavasileiou et al. (2007) proposed the use of production scheduling tools available on the market and process simulation as means for commercializing pharmaceutical products. Systematic bottleneck removal methods were developed as auxiliary tools for computer model simulators working on batch simulation problems (Koulouris et al., 2000). Another area is the improvement of general process capability and performance, including yield improvements. Srinivasan et al. (2002) offered an overview of analytical and numerical techniques for the optimization of general batch

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List of symbols

Greek letters

α	empirical parameter [kg]
β	empirical parameter [kg^{-1}]
θ	dimensionless initial heating medium temperature [–]
λ	dimensionless process stream flow rate [–]
ρ	crystal density [$kg\,m^{-3}$]

Roman letters

B	crystal aspect ratio [–]
c	concentration in the bulk of the API [$mol\,m^{-3}$]
c_A	concentration of the API [$mol\,m^{-3}$]
$c_{p,s}$	specific heat capacity of the shell medium [$J\,kg^{-1}\,K^{-1}$]
$c_{p,t}$	specific heat capacity of the tube medium [$J\,kg^{-1}\,K^{-1}$]
c_s	saturation concentration of the API [$mol\,m^{-3}$]
D	molecular diffusion coefficient of the API in water [$m^2\,s^{-1}$]
d_o	outside tube diameter [m]
d_i	inside tube diameter [m]
F	normalized process stream flow rate [–]
F_{max}	maximal flow rate [$kg\,s^{-1}$]
F_s	flux inside the shell [$kg\,s^{-1}$]
F_t	flux inside the tube [$kg\,s^{-1}$]
l	crystal height [m]
L_{HEX}	heat exchanger length [m]
L_{pore}	filter pore size [m]
m	API crystal mass [kg]
m_{byprod}	mass of by-product [kg]
m_{cryst}	sterile crystal mass [kg]
m_{crude}	crude API crystal mass [kg]
M_W	molar weight of the API [$kg\,mol^{-1}$]
k	mass transfer coefficient [$m\,s^{-1}$]
k_{deg}	reaction rate constant [s^{-1}]
k_w	material thermal conductivity [$W\,m^{-1}\,K^{-1}$]
r	crystal radius [m]
r_A	reaction rate [$mol\,m^{-3}\,s^{-1}$]
Re_D	particle Reynolds number [–]
S	crystal surface area [m^2]
Sc	Schmidt number [–]
t	time variable [s]
T_H	normalized inlet temperature of the heating medium [–]
$T_{H,max}$	maximum heating medium temperature [K]
T_{in}	inlet temperature of the process stream [K]
t_R	unit specific residence time [s]
T_s	shell temperature [K]
T_t	tube temperature [K]
T_w	wall temperature [K]
U_s	overall heat transfer coefficient of the shell medium [$W\,m^{-2}\,K^{-1}$]
U_t	overall heat transfer coefficient of the tube medium [$W\,m^{-2}\,K^{-1}$]
V	batch volume [m^3]
v_f	liquid velocity [$m\,s^{-1}$]
x	length variable [m]

processes. In a second study, Srinivasan et al. (2003) discussed the role of measurements and their application in the creation, validation and implementation of process models. Uerdingen et al. (2003) proposed a three-stage systematic methodology for screening retrofit options in chemical processes, comprising path flow decomposition and impact potentials, e.g., energy and material costs, as objective functions. The systematic retrofit method proposed by Simon et al. (2008) is a combination of multiple process evaluation techniques, e.g., indicators, heuristics and process models, and its applicability for batch processes was shown in an industrial case study. The application of path-flow decomposition for batch processes were also shown by Carvalho et al. (2008), with the aim of identifying design alternatives. The same method was further investigated in the optimization of batch process retrofitting of a specialty chemical production plant (Bumann et al., 2011). Cervera-Padrell et al. (2012) developed a process systems engineering (PSE)-assisted framework for the design of continous pharmaceutical manufacturing processes, focusing on the chemical synthesis of Active Pharmaceutical Ingredients (APIs) and its costs evaluation. Similar retrofitting frameworks are also presented in other recent works, e.g., Lapkin et al. (2011) and Shah et al. (2012). However, all these contributions describe particular steps to be followed in applying the methodologies, and none provides an overall strategy for retrofitting, considering the needs and the constraints of the pharmaceutical manufacturing, e.g., GMP, highly complex unit operations and lack of measured data.

In this work, we aim to develop a systematic methodology that can assist the retrofitting of pharmaceutical processes. The method consists of five tasks: (I) acquire process understanding and data, (II) create a process model, (III) adapt the process model for optimization, (IV) optimize the process model, and (V) interpret the outcome of the task. Although the entire procedure is structured in a general manner, the second task is the most prominent and specialized for the purification of the crude APIs in crystalline form.

Among other sterilization techniques such as radiation (Maquille et al., 2008), heat (Boca et al., 2002), and ethylene oxide gas (Shull, 1963) treatments, this work focuses on sterilization by particle filtration techniques (WHO, 2014). Filtration coupled with recrystallization is a common purification and crystal-shaping technique for thermally unstable APIs. Recently, Nagy et al. (2013) discussed the importance of the crystallization, its modeling and control in pharmaceutical manifacturing. In this publication Nagy elucidated the work of Snyder et al. (2008), who studied the evolution of crystal shape of an organic substance during dissolution with a prediction model and experimental studies. The control and monitoring of the crystallization in pharmaceutical processes was widely discussed by Simon et al. (2015), as well in several other works, e.g., Samad et al. (2010, 2011, 2013).

The process considered in this work involves the dissolution of the crude organic material, the filtration of impurities, and the crystallization of the final product. This process will be called the DFC process in this paper. The methodology is applied to an industrial case study to prove its effectiveness.

2. Methodology

The flowchart (Fig. 1) shows the sequence of tasks to be followed.

It is necessary to gain understanding of the plant and its behavior (Task I) in order to create a viable process model in Task II. Measurements coupled with path-flow decomposition help in this task. In Task II, all the processes are reproduced as mathematical models with the aim of imitating the plant. In Task III, the created model is adapted—i.e., transformed to a model that relates optimization parameters to an objective function—so that the optimization can be performed in Task IV. In Task V, the outcomes of each task are interpreted and the process models as well as the assumptions made during model formulation are validated or invalidated. Iteration of the previous tasks could be requested as a result.