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RESEARCH ARTICLE

Surrogate-Based Optimization of Expensive Flowsheet Modeling for Continuous Pharmaceutical Manufacturing

Fani Boukouvala · Marianthi G. Ierapetritou

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Abstract Simulation-based optimization is a research area that is currently attracting a lot of attention in many industrial applications, where expensive simulators are used to approximate, design, and optimize real systems. Pharmaceuticals are typical examples of high-cost products which involve expensive processes and raw materials while at the same time must satisfy strict quality regulatory specifications, leading to the formulation of challenging and expensive optimization problems. The main purpose of this work was to develop an efficient strategy for simulation-based design and optimization using surrogates for a pharmaceutical tablet manufacturing process. The proposed approach features surrogate-based optimization using kriging response surface modeling combined with black-box feasibility analysis in order to solve constrained and noisy optimization problems in less computational time. The proposed methodology is used to optimize a direct compaction tablet manufacturing process, where the objective is the minimization of the variability of the final product properties while the constraints ensure that process operation and product quality are within the predefined ranges set by the Food and Drug Administration.

Keywords Surrogate-based optimization · Simulation-based optimization · Kriging · Pharmaceutical manufacturing · Flowsheet simulation

Introduction

Downstream pharmaceutical manufacturing involves a sequence of processing steps necessary to transform a mixture of powders into a final product such as tablet or capsule. Specifically, based on the properties of the main ingredient, the active pharmaceutical ingredient (API), as well as the process constraints and objectives, critical decision-making steps include the choice of the necessary additives (excipients) and the appropriate processing route, ranging from direct compaction to dry and wet granulation, in order to produce pharmaceuticals within specifications [11, 25, 26, 40]. The application of optimization to downstream pharmaceutical manufacturing engineering problems involves many challenges, such as the need to rely on expensive simulation-based process models, the uncertainty and variability introduced by the powder material properties, and, in certain cases, the lack of process understanding which leads to dependency on noisy experimental data-based correlations. In addition, optimizing the production of pharmaceuticals requires the overcoming of another challenge, namely, the identification of clear economical objectives, which can be attributed to the hitherto atypical manufacturing practices employed in the industry compared to other industrial processes such as petrochemicals, specialty chemicals, and foods. In fact, engineers in other industries started relying on computational tools for designing their processes since the early 1900s, minimizing the need to physically experiment or rely on heuristics and empirical knowledge [55]. Specifically, recent advances in the optimization literature are not only limited to profit-based optimization but also incorporate supplementary aspects to integrated process design, such as systems to improve environmental impact, simultaneous process and product design, and process intensification combining multiple operations into fewer components and multi-plant integration. In opposition, even though pharmaceutical tablets are products which are highly regulated in terms of their physical properties, consistency, appearance, and taste, their manufacturing procedure has been predominantly designed empirically due to the lack of process knowledge.

The pharmaceutical industry relies predominantly on batch processes, which may not be operated at optimal operating conditions. Their economic inefficiency increases

F. Boukouvala · M. G. Ierapetritou (✉)
Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ 08854, USA
e-mail: marianth@soemail.rutgers.edu