chemistry proceedings

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Proceeding Paper

Techno-Economic Evaluation and Optimization of Batch, Fed-Batch and Multistage Continuous Crystallization Processes †

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† Presented at the 3rd International Online Conference on Crystals, 15–30 January 2022; Available online: https://iocc_2022.sciforum.net.

Abstract: Over the last decade, continuous manufacturing techniques have been increasingly used in the pharmaceutical manufacturing industry. However, despite the outstanding performance associated with the steady-state operation, continuous processes face common and important challenges of low efficiency and high material wastes during the start-up and shutdown. Considering that most pharmaceutical manufacturing campaigns are accomplished in a short operation window, an optimal start-up and shut down strategy will have a significant impact on the economic and environmental performance of the continuous pharmaceutical process. In this study, a combined start-up, steady-state, and shutdown optimization of a three-stage mixed suspension mixed product removal (MSMPR) crystallizer was compared against optimized batch and fed-batch crystallizers. The crystallization of Aspirin (acetylsalicylic acid, ASA) in ethanol (solvent) and water (antisolvent) was used as a case study. The optimization problems were solved using a hybrid method, which combines a genetic algorithm and a sequential quadratic programming (SQP) method. The multistage continuous crystallizer was designed and optimized to maximize on-spec production over a total operating window of 800 min. It was shown that a maximum on-spec production of 5510 g can be achieved with the continuous process. A batch and a fed-batch crystallizer were designed and optimized to achieve the same production rate to help establish a reliable basis for rigorous techno-economic analysis and comparison.

Keywords: crystallization; dynamic optimization; continuous crystallization; fed-batch; decision making

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Citation: Liu, J.; Benyahia, B. Techno-Economic Evaluation and Optimization of Batch, Fed-Batch and Multistage Continuous Crystallization Processes. *Chem. Proc.* **2022**, *9*, 6. https://doi.org/10.3390/IOCC_2022-12144

Academic Editor: Gianluca Di Profio

Published: 12 January 2022

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1. Introduction

Over the past decade, the pharmaceutical industry has witnessed a clear trend towards the adoption of continuous manufacturing instead the traditional batch processing which is commonly adopted in the pharmaceutical and biopharmaceutical industries. Compared to the traditional batch operation, continuous processing shows several advantages such enhanced flexibility, efficiency, and higher product quality. Moreover, there is an expectation that moving from batch to continuous will reduce scale-up efforts and costs and prevent the risks of out of specification products due to batch-to-batch variations.

Crystallization is a critical purification unit in most pharmaceutical manufacturing processes. The successful development of continuous crystallization is an essential step when moving from batch to continuous process due its significant impact on the product quality of the drug safety and efficacy which can be determined by crystal size distribution and purity. In addition, these critical properties have a clear impact on downstream processability such filterability. To achieve the targeted quality performance, a typical optimization objective in crystallization is to maximize the mean crystal size [1,2]. The driving force of the crystallization is supersaturation, which can be generated by cooling, solvent evaporation or antisolvent addiction. Various approaches have been adopted to design and control

batch crystallization processes in the literature. For continuous process, most literature focused on three mean types of continuous crystallizers (MSMPR, Plug flow reactor and continuous oscillatory baffled crystallizers). The most popular crystallizers in the pharma industry are based on stirred tank design and as such. many experimental and modelling efforts have been devoted to the continuous MSMPR crystallizers, in the recent years. Several studies were particularly devoted to the optimization of single, multistage MSMPR, crystallization network and integrated end-to-end continuous pharmaceutical plant with a series of MSMPR crystallizers [3–5].

Most recently, a systematic optimization of a multistage continuous crystallization, which combines start-up, steady-state and shut down process, has been developed in the case of Aspirin (ASA) antisolvent crystallization [6]. With the optimized start-up and shut down strategies, 5510.2 g (417 µm) of ASA crystals are produced. To compare the performance of the continuous process against the batch or fed batch process, a series of batch process optimization were developed in this study to produce the same product with the same mean crystal size. Several alternative batch capacities and batch times were evaluated and discussed to provide precious insights to the decision maker to help identify the most effective and viable crystallization technology.

2. Method

The crystallization of ASA in a mixture of ethanol and water is considered in this work. The dynamic mathematical model of a fed-batch process was built based on several assumptions, including:

- All vessels are assumed to be well mixing
- Crystal breakage and agglomeration are negligible
- Mixing solvent and antisolvent and crystallization do not affect the total volume

The fed-batch process setup and a three-stage MSMPR crystallizer are illustrated in Figure 1.

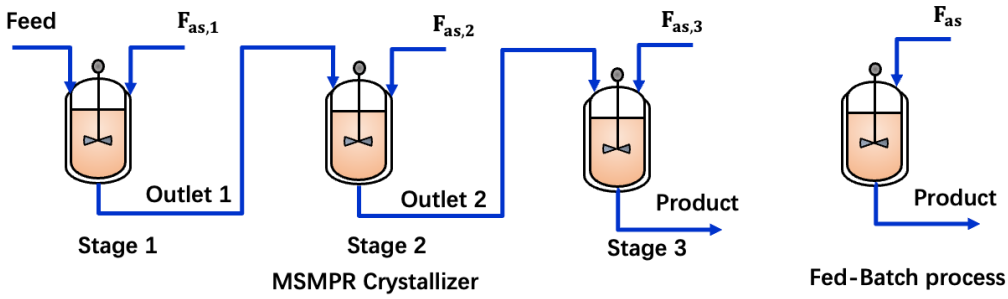

Figure 1. The setup of fed-batch crystallizer and multistage MSMPR crystallizer.

The model of the ASA crystallization process is developed including a population balanced model solved using the standard method of moments. The details of the continuous process with a three-stage MSMPR have been thoroughly discussed in the previous work [6,7]. For the batch process, with the standard method of moments, the moments of the fed-batch process are shown in Equations (1) and (2).

$$\frac{d\mu_0}{dt} = B \tag{1}$$

$$V\frac{d\mu_j}{dt} = Gj\mu_{j-1}V - \mu_j F_{AS},\ j = 1,2,3 \tag{2}$$

where B is the nucleation rate, and G is the growth rate. Both are adopted from the literature [8–10]. The V is the volume of the solution. The F_{AS} is the addiction antisolvent flow rate.

The fed-batch process is first prepared with prefilled solution, which is saturated at 40 °C with 25% antisolvent (water) and 75% solvent (ethanol) in mass. When the

crystallization starts, the additional antisolvent is added to the vessel, and the temperature of the jacket is controlled to generate supersaturation, which is the driving force for the crystallization process. As such, the mass balance in the liquid phase can be expressed as follow (Equations (3) and (4)):

$$\frac{dM_{ASA}}{dt} = -3\rho_c k_v G \mu_2 V \tag{3}$$

$$\frac{dM_{AS}}{dt} = F_{AS} \tag{4}$$

M_{ASA} and M_{AS} are the mass of ASA and antisolvent in the vessel. As the solvent is not added its will remain constant during the process. The ρ_c is the density of crystals and k_v is the shape factor.

Besides, the energy balance is also considered in this work. The energy balance equation is shown below:

$$\frac{dT}{dt} = \left(UA\left(T_J - T\right) - 3\Delta H k_v \rho_c \mu_2 G\right) / \left(C_{p,mix} M_T\right) \tag{5}$$

$$C_{p,mix} = \frac{M_S C_{p,S} + M_{AS} C_{p,AS} + M_{ASA} C_{p,ASA}}{M_S + M_{AS} + M_{ASA}} \tag{6}$$

where U is the overall heat transfer coefficient, and A is the heat transfer surface area. T_J is the jacket temperature and T is the temperature of the solution. $C_{p,S}$, $C_{p,AS}$ and $C_{p,ASA}$ are the heat capacity of the solution, antisolvent and ASA respectively.

With the mathematical models (i.e. continuous and fed-batch), several optimization scenarios were developed. The mathematical formulation of the optimization problem aimed at minimization of the batch time (t_f) is shown below:

$$\begin{aligned}
&\underset{T_{J,i}, F_{AS,i}, t_i}{Min} \; t_f \\
s.t. \quad & \dot{x} = f(x, y, u, p, t), \; x_{t=0} = x_0 \\
& 0 = g(x, y, u, p, t) \\
& C1 : 25 \leq T_{J,i} \leq 40 \\
& C2 : 0 \leq F_{AS,i} \leq 20 \\
& C3 : 0.5 \leq t_i \leq 10 \\
& C4 : \; T_{J,i+1} \leq T_{J,i} \\
& C5 : \sum_{i=1}^{5} F_{AS,i} \times t_i = 555 \\
& C6 : \; Yield \geq 75\% \\
& C7 : \; \frac{|d_b - d_c|}{d_c} \leq 1\%
\end{aligned} \tag{7}$$

In this scenario, the batch time is discretised into 6 intervals, and the jacket temperature, antisolvent flow rate and time interval length of the first five-time intervals are regarded as decision variables to minimize the manufacturing batch time. The temperature is cooled linearly in each time interval, and the corresponding decision variable is the jacket temperature at the endpoint of each time interval.

C1 to C3 are the upper bound and lower bound of the decision variables. C4 is a linear constraint used to ensure cooling and avoid heating at any time. C5 is a nonlinear constraint that is used to force the antisolvent ratio to stay within 70%. Both C4 and C5 come from the requirement of the solubility polynomial [8]. C6 is also the nonlinear constraint, which is used to ensure a final yield over 75%. C7 is used to ensure that the difference of the product quality form fed batch is within 1% variation of the targeted quality also obtained with the continuous process. With these settings, the whole process manufacturing time is minimized either one single batch or multiple batches are considered.

3. Results and Discussion

The optimization problem is solved using a hybrid optimization method, which combines a genetic algorithm (ga function in MATLAB) and SQP (fmincon function in MATLAB). With the optimal operation profile, the manufacturing time is minimized to 28.26 min. In the continuous process, 5510.2 g on-spec product is collected when combined optimal start-up and shut down of the multistage MSMPR crystallizer are considered. The same throughput can be obtained with several batches with different volumes. Assuming that the draining, cleaning and refilling of vessels will take 20 min, the batch capacities and manufacturing batch times are shown in Table 1.

Table 1. Optimized batch number, Manufacturing time and batch capacity.

Scenario	Manufacturing Time (Mins)	Volume (L)
1 batch	28.26	50
2 batches	76.51	25
4 batches	173.03	10
9 batches	414.31	5
14 batches	655.60	2.5
20 batches	945.14	2
Continuous process	800	0.2/0.5/0.5

Based on the optimized results, a short-cut evaluation of the different fed-batch alternatives and continuous process was developed. The costs, including equipment, material cost, maintenance, environmental footprint, and labor, were used to evaluate the overall score and rank all possible alternatives [1].

In Table 2, the equipment and maintenance costs received the largest weighting factor. The score associated with the equipment and maintenance is determined by the vessel capacity and the number of batches. For example, the continuous process consists in three MSMPR vessels. Although the total volume is only around 1.2 L, three vessels generated lower scores than the scenarios with 20 batches. Material cost and environmental footprints are largely determined by the yield, whereas the direct labor cost is inherent to the total manufacturing time. It is worth mentioning that the labor cost in a continuous process is significantly lower than the fed-batch process due the limited operator intervention. Based on the methodology outlined above, the continuous process outperforms all batch scenarios.

Table 2. Performance indicators of different fed-batch scenarios vs. a 3-stage continuous process.

	Weighting Factor	1	2	4	9	12	20	Continuous
Equipment and Maintenance	20	0	1	2	3	5	6	4
Material	8	1	1	1	1	1	1	0
Direct labor cost	6	5	4	3	2	1	0	7
Energy	2.5	1	1	1	1	1	1	0
Environmental Footprint	2.5	0	0	0	0	0	0	1
Cleaning	6	6	5	4	3	2	1	4
Score		76.5	84.5	92.5	100.5	128.5	136.5	148.5
Rank		7	6	5	4	3	2	1

4. Conclusions

Several optimization scenarios of a fed-batch and multistage continuous crystallization of ASA in ethanol and water were developed and solved to establish a technoeconomic analysis. The fed-batch systems were designed to achieve the same targeted product quality, here the mean crystal size, with minimum operation time by manipulating the jacket temperature, antisolvent flow rate and by using different discretization methods. The techno-economic analysis and comparison were developed based on the batch capacity and the batch operation time to help allocated score and rank the optimized fed-batch process and optimized continuous process including its systematic start-up and shut down

optimization. Based on this method, the continuous process outperformed the batch alternatives particularly on the costs of labor, material, and cleaning.

Author Contributions: Conceptualization, B.B.; methodology, B.B. and J.L.; validation, J.L. and B.B.; formal analysis, J.L. and B.B.; investigation, J.L.; resources, B.B.; data curation, J.L.; writing—original draft preparation, J.L.; writing—review and editing, B.B. and J.L.; supervision, B.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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