Stochastic Technoeconomic Analysis and Optimization of Batch and Continuous Crystallization for Sustainable Pharmaceutical Manufacturing under Supply Delays

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Abstract

To better understand the trade-offs between batch and continuous production, a robust technoeconomic cost model to serve as a predictive decision-making tool is necessary. Thus, this study has simulated the annual production cycle for a given active pharmaceutical ingredient (API) at various production volumes for both a batch system and a continuous mixed suspension, mixed product removal (MSMPR) crystallization layout. This was done using PharmaPy, a Python-based modelling tool that was custom-made for pharmaceutical flowsheet analysis. The batch and continuous crystallization configurations are optimized, and the capital expenses (CAPEX) and operational expenses (OPEX) are compared between the two systems. In addition, the environmental sustainability of each system, through the process mass intensity metric (PMI) is analysed. We observed from the results that while the batch system is lower in overall costs, the continuous system shows more potential for expansion. Finally, to better understand each system under stochastic disruption, the optimal results are then simulated in a Monte-Carlo simulation with stochastic delivery delays of varying likelihood and length. With the added decision variable of overstocking considered, we can see that the continuous system, less overstocking is necessary, showing it can serve as a more robust manufacturing option.

**Keywords**: Technoeconomic Analysis, Industry 4.0, Process Design, Stochastic Optimization, Continuous Manufacturing

* 1. Introduction

As the field of pharmaceutical manufacturing develops, the application of continuous crystallization techniques as a process intensification method grows more important as it allows for more flexibility and efficiency in drug production, driving a revolution in the pharmaceutical industry (Diab and Gerogiorgis, 2020). However, for new technologies to be successfully implemented, a robust technoeconomic cost analysis is necessary to serve as a decision-making tool for manufacturers. Thus, this paper aims to conduct a preliminary investigation for the comparison of conventional batch crystallizers and mixed suspension, mixed product removal (MSMPR) continuous crystallizers. Additionally, the effect that stochastic disruptions in the form of supply chain delays have on each system are also investigated. For both layouts, the common active pharmaceutical ingredient (API) of paracetamol (PCM), a common analgesic drug, has been selected as the model system. The comparative analysis between the conventional batch crystallization and the MSMPR process is conducted through simulating the annual performance for both systems using PharmaPy, a Python-based simulation tool designed for pharmaceutical flowsheet analysis (Casas-Orozco et al., 2021). The simulation-optimization is conducted with three different annual production volumes and mean crystal size as the key critical quality attribute (CQA). Furthermore, both systems were optimized for minimal costs and environmental impact. This impact was quantified using the process mass intensity (PMI) value of the systems as a quantified metric of environmental sustainability. Then, using the value acquired from the optimized cost case, a simulation of annual production with stochastic delivery delays is optimized for the number of planned deliveries and the required percentage of overstock.

* 1. Methodology
		1. Modeled Flowsheets

In this study, the simulation was conducted for just the crystallizer unit operations. The selected API is paracetamol (PCM) and the kinetic parameters for the API have been adapted from Szilagyi et al. (2020). For the batch system, a single unit was set as the default, but extra parallel processes were set as a decision variable, thus allowing for the numbering-up of the batch system as well as scaling-up. For the continuous system, the setup consists of two chained MSMPR crystallizer units to allow for better control of the process. The optimization is conducted with an adaptive Nelder-Mead derivative-free algorithm. For the stochastic analysis, the parameters from the simulation optimized for cost are then applied for a day-by-day simulation of the annual production. For each simulation, the number of deliveries in the year and the percentage of overstocking was selected as a decision variable. Then, for various delivery delay chances and delay amounts, the Monte-Carlo simulation is optimized for minimal costs and minimal stockout with a genetic algorithm 50 times. The summary of the layout is shown in Figure 1. In all cases, crystallizers were modeled with PharmaPy while the optimization algorithms were provided by the SciPy Python library.

* + 1. Optimization Formulation

The optimization problem for this study can be written as a nonlinear constrained design problem with the objective function being either the total cost of manufacturing or the sustainability metric, PMI. The mathematical formulation with the constraints can be seen in Equation (1). It should also be noted that to improve the optimizer performance, both the objective function and the constraints were nondimensionalized. Finally, the decision variables of the problem for both the batch and continuous systems are summarized in Table 1.

Figure 1 – Schematic summary of the two different setups as well as the stochastic simulation.



|  |  |
| --- | --- |
| $$\min\_{x}J(x,y,z)$$$s.t. g\_{i}\left(x,y,z,u\right)\leq 0,$ $∀i\in I,$$x\_{lb}\leq x\leq x\_{ub}$ | (1) |

Table 1 - Description of decision variables for the optimization problems and their bounds.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **System** | **Description** | **Bounds** |
| $V\_{CR}$  | Batch | Crystallizer Volume | 0.1 ~ 7.5 [m³] |
| $t\_{CR}$  | Batch | Cycle Time | 10 ~ 720 [min] |
| $n\_{CR}$  | Batch | No. of parallel process lines | 1 ~ 3 [lines] |
| $T\_{CR,i}$  | Batch | Crystallizer $i$th Temp. Point | 273 ~ 330 [K] |
| $V\_{CR01}, V\_{CR02}$  | Cont. | Crystallizer Volume | 0.1 ~ 7.5 [m³] |
| $T\_{CR01},T\_{CR02}$  | Cont. | Crystallizer Temp. | 273 ~ 330 [K] |
| $H\_{ss}$  | Cont. | Steady state multiplier | 1 ~ 100,000 |
| $n\_{d}$  | Stochastic | Number of deliveries per year | 1 ~ 24 |
| $OS\_{\%}$  | Stochastic | Percentage of material overstocking per delivery | 0 ~ 100 [%] |

For the initial simulation-optimization, there were 5 constraints that were summarized in $g\_{i}$: mean crystal size, production volume, overall yield, decreasing temperature, and total time. These constraints are summarized in Table 2.

Table 2 - Description of the constraints considered in the problem.

|  |  |  |
| --- | --- | --- |
| **Variable** | **Description** | **Constraint** |
| $$g\_{1}$$ | Mean Crystal Size | $$40 \left[μm\right]< \overbar{L}$$ |
| $$g\_{2}$$ | Production Volume | $$PV\_{target}<PV\_{actual}$$ |
| $$g\_{3}$$ | Overall Yield | $$0.9Y\_{max}<Y\_{actual}$$ |
| $$g\_{4}$$ | Decreasing Temp. | $$T\_{i+1}\leq T\_{i}$$ |
| $$g\_{5}$$ | Total Time | $$t\_{total} < 260 \left[days\right]$$ |

* + 1. Cost Calculations

The costs of manufacturing the API in this study can be categorized as capital expenses (CAPEX) and operational expenses (OPEX). While there are many different methods of estimating these costs, most of the calculations are adapted from Diab et al. (2020). However, it should be noted that for CAPEX, this study uses the equivalent uniform annual cost (EUAC) of the battery limit installation cost. This EUAC equation can be found in literature (Gurnani, 1983). The equation can be seen in Equations (2). Additionally, while there are many different cost drivers for OPEX, for this study, only the material and waste costs are considered. Finally, for the stochastic day-to-day simulation, a daily inventory cost of $0.01 per kilogram of material was implemented.

|  |  |
| --- | --- |
| $$EUAC=BLIC\left(\frac{i\_{rate}\left(1+i\_{rate}\right)^{t\_{PL}}}{\left(1+i\_{rate}\right)^{t\_{PL}}-1}\right)$$ | (2) |

* + 1. Sustainability Metric Calculations

Finally, as previously mentioned, other than cost, the other objective function that was considered was the sustainability of the entire system. While there are many metrics that can be used for this, the metric for this study was the process mass intensity (PMI) (Jimenez-Gonzalez et al., 2011). This metric was chosen over the standard E-factor metric as the PMI metric, which is a ratio of the API produced and the total material used, as that provides a fuller picture as to what material inputs are for a process and not just the waste. The equations for PMI can be seen in Equation (3).

|  |  |
| --- | --- |
| $$PMI=\frac{total mass from a process  [kg]}{total mass of product [kg]}$$ | (3) |

* 1. Results and Discussion
		1. Batch vs. Continuous Comparison

From the optimization problem that was described in the previous section, we can then compare the differences in performance as well as cost between the batch and continuous systems. In Figure 2, the CAPEX and OPEX cost drivers have been shown for the different annual production volumes and the different systems. Furthermore, the numerical values from the simulation for the batch and continuous systems can be seen in Table 3 and Table 4, respectively.

From Figure 2, several observations can be made. First, we can see that the CAPEX for the continuous systems is consistently less than the batch counterparts. This is due to the fact that the optimal volume for the MSMPRs are less than the batch crystallizers, even though the batch system always requires two lines. It is important to note that the purpose of the cost model is to serve as a decision-making tool for manufacturers. Thus, from this observation, we can see that a continuous system may be more flexible for a manufacturing line from scratch. However, despite this difference, the overall cost of batch systems is still lower than for continuous production due to lower OPEX costs. However, simply comparing the total cost of the systems does not provide a holistic comparison. While the overall cost may be higher, for all production volume targets, the MSMPR systems were able to produce target volumes in less time, resulting in consistently higher throughput rates. This is reflected in the availability of the crystallizers. In the context of this paper, availability is the ratio of a systems operational period to the total planned production time. As the continuous crystallizers require only a single startup and shutdown period, we can see in Tables 3 and 4 that the continuous systems have higher availability percentage than the batch systems. Thus, from these simulation results, we can see that while batch systems are currently more versatile in existing systems, continuous crystallization systems have potential for scaling up and providing an agile manufacturing alternative. This potential can also be observed when comparing PMI. While the PMI values for the continuous system is generally higher than the batch system, we can see on Table 3 and Table 4 that when optimizing for PMI, the cost difference greatly differs. We can see that while for all cases, the improvement to PMI is less than 1%, the increased cost for the batch system is much higher than that for the continuous system. This can be interpreted as the fact that while the overall PMI for the continuous system may be higher, the cost of improving the system for PMI would be less prohibitive for the continuous system. It should be noted that while the significance of lowering the PMI would be different for each industry on a case-by-case basis, we can observe that for the problem in this study, it is possible for continuous system to show a greater potential for improvement in sustainability.



Figure 2 - Annual CAPEX and OPEX comparison for different annual production volumes and objective functions between batch and continuous crystallization units.

Table 3 – Numerical results of the batch crystallization setup simulation

|  |  |  |  |
| --- | --- | --- | --- |
|   | **2M kg / yr** | **1.5M kg / yr** | **1M kg / yr** |
| **Cost Obj.** | **PMI Obj.** | **Cost Obj.** | **PMI Obj.** | **Cost Obj.** | **PMI Obj.** |
| **Total** |  $30,299,710.70  |  $35,025,675.04  |  $22,811,463.81  |  $23,629,527.52  |  $15,403,923.91  |  $15,900,095.91  |
| **API Made** | 1999977.11 kg | 2328427.96 kg | 1500006.076 | 1556340.47 kg | 999996.73 kg | 1034675.34 kg |
| **Solvent Used** | 7313845.94 kg | 8479547.28 kg | 5472862.24 kg | 5674079.24 kg | 3654758.21 kg | 3773681.50 kg |
| **API Used** | 2974363.67 kg | 3448426.11 kg | 2225680.27 kg | 2307510.34 kg | 1486301.48 kg | 1534664.70 kg |
| **Total Time** | 260.26 days | 260.08 days | 260.09 days | 260.00 days | 260.02 days | 260.02 days |
| **Throughput**  | 320.187 kg/h | 373.024 kg/h | 240.304 kg/h | 249.409 kg/h | 160.246 kg/h | 165.798 kg/h |
| **Availability** | 68.85% | 65.65% | 73.21% | 73.33% | 78.59% | 78.50% |
| **Cost/Kg** | $15.15 /kg | $15.04 /kg | $15.21 /kg | $15.18 /kg | $15.40 /kg | $15.37 /kg |
| **PMI** | 5.144164E+00 | 5.122758E+00 | 5.132341E+00 | 5.128434E+00 | 5.141077E+00 | 5.130446E+00 |
| **Cost Change** |  | 15.597% |  | 3.586% |  | 3.221% |
| **PMI Change** |  | -0.416% |  | -0.076% |  | -0.207% |
|  | **Optimal Decision Variables** |
| $V\_{CR}$ | 5.893 m³ | 6.201 m³ | 5.132 m³ | 5.209 m³ | 4.289 m³ | 4.469 m³ |
| $t\_{CR}$ | 19510.616 s | 17362.060 s | 23279.987 s | 22704.940 s | 30030.870 s | 30336.715 s |
| $n\_{CR}$ | 2 lines | 2 lines | 2 lines | 2 lines | 2 lines | 2 lines |
| $T\_{CR,1}$ | 306.69 K | 295.87 K | 297.02 K | 300.98 K | 294.70 K | 305.84 K |
| $T\_{CR,2}$ | 292.24 K | 295.87 K | 296.19 K | 300.95 K | 290.49 K | 298.39 K |
| $T\_{CR,3}$ | 273.13 K | 273.14 K | 273.15 K | 273.15 K | 273.15 K | 273.15 K |

Table 4 - Numerical results of the continuous crystallization setup simulation.

|  |  |  |  |
| --- | --- | --- | --- |
|   | **2M kg / yr** | **1.5M kg / yr** | **1M kg / yr** |
| **Cost Obj.** | **PMI Obj.** | **Cost Obj.** | **PMI Obj.** | **Cost Obj.** | **PMI Obj.** |
| **Total** |  $ 33,546,963.84  |  $ 33,859,805.92  |  $ 25,146,755.02  |  $ 25,717,103.73  |  $ 16,896,477.54  |  $ 16,959,178.60  |
| **API Made** | 2000003.58 kg | 2020834.54 kg | 1500045.79 kg | 1534693.85 kg | 1001400.91 kg | 1006269.14 kg |
| **Solvent Used** | 8389101.80 kg | 8468226.21 kg | 6271905.36 kg | 6416700.08 kg | 4184063.43 kg | 4200663.35 kg |
| **API Used** | 3160355.06 kg | 3189758.55 kg | 2361312.90 kg | 2415827.35 kg | 1574916.38 kg | 1580915.61 kg |
| **Total Time** | 210.29 days | 258.41 days | 226.41 days | 231.63 days | 163.70 days | 174.56 days |
| **Throughput**  | 396.285 kg/h | 325.840 kg/h | 276.058 kg/h | 276.062 kg/h | 254.888 kg/h | 240.195 kg/h |
| **Availability** | 99.93% | 99.94% | 99.93% | 99.93% | 99.91% | 99.91% |
| **Cost/Kg** | $16.77 /kg | $16.76 /kg | $16.76 /kg | $16.76 /kg | $16.87 /kg | $16.85 /kg |
| **PMI** | 5.774718E+00 | 5.768896E+00 | 5.755303E+00 | 5.755237E+00 | 5.750923E+00 | 5.745559E+00 |
| **Cost Change** |   | 0.933% |   | 2.268% |   | 0.371% |
| **PMI Change** |   | -0.101% |   | -0.001% |   | -0.093% |
|  | **Optimal Decision Variables** |
| $V\_{CR01}$ | 2.020 m³ | 1.653 m³ | 1.396 m³ | 1.531 m³ | 1.288 m³ | 1.213 m³ |
| $V\_{CR02}$ | 4.123 m³ | 3.833 m³ | 3.068 m³ | 3.332 m³ | 2.752 m³ | 2.821 m³ |
| $T\_{CR01}$ | 273.00 K | 273.00 K | 273.00 K | 273.00 K | 273.00 K | 273.00 K |
| $T\_{CR02}$ | 273.00 K | 273.00 K | 273.00 K | 273.00 K | 273.00 K | 273.00 K |
| $H\_{ss}$ | 9078.73 | 11156.65 | 9774.24 | 8940.25 | 7065.28 | 7534.09 |

* + 1. Stochastic Batch vs. Continuous Comparison

Finally, we simulated the day-to-day operation of batch and continuous process with the obtained optimal parameters. The simulation was then optimized for minimizing cost as well as minimizing the stockouts. From the results in Table 5, we can see that as the chance of delivery delays increased, there was an expected increase in optimal overstocking and less frequent deliveries. However, this was balanced by the inventory cost, thus preventing too much material to be stored. Furthermore, as more and more deliveries delays occurred, the amount of API that could be manufactured for both systems were decreased.

Additionally, we could observe that while both systems required more overstocking, the percentage of overstocking needed for continuous systems was less than for batch systems, demonstrating a potential for a more robust manufacturing process. The percentage difference of overstocking between the two systems can become a significant cost driver as the manufacturing scale increases.

Table 5 - Numerical results for stochastic simulation of batch and continuous processes.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Delay | 14 days | 21 days |
|  | Delay % | 10% | 50% | 10% | 50% |
|  |  | Value | STD | Value | STD | Value | STD | Value | STD |
| Batch | $n\_{d}$  | 21.86 | 2.44 | 11.64 | 3.13 | 21.66 | 2.89 | 11.04 | 2.96 |
| $OS\_{\%}$  | 0.230% | 0.49% | 3.202% | 5.87% | 0.168% | 0.48% | 3.529% | 10.95% |
| API Made | 2.50E+06 kg | 3.61E+04 kg | 2.34E+06 kg | 1.37E+05 kg | 2.48E+06 kg | 5.85E+04 kg | 2.22E+06 kg | 2.16E+05 kg |
| **Cost / Kg** | $16.51 /kg | $2.98 /kg | $18.02 /kg | $1.21 /kg | $16.22 /kg | $0.66 /kg | $18.29 /kg | $1.37 /kg |
|  |  |  |  |  |  |  |  |  |
|  |  | Value | STD | Value | STD | Value | STD | Value | STD |
| Cont. | $n\_{d}$  | 21.78 | 3.13 | 12.22 | 2.48 | 21.72 | 2.84 | 12.06 | 2.71 |
| $OS\_{\%}$  | 0.016% | 0.03% | 1.939% | 6.00% | 0.132% | 0.39% | 2.567% | 9.85% |
| API Made | 3.34E+06 kg | 5.18E+04 kg | 3.10E+06 kg | 1.32E+05 kg | 3.34E+06 kg | 7.30E+04 kg | 2.98E+06 kg | 3.40E+05 kg |
| Cost / Kg | $17.76 /kg | $0.42 /kg | $19.91 /kg | $1.05 /kg | $17.80 /kg | $0.62 /kg | $20.06 /kg | $1.79 /kg |

* 1. Conclusions

This study defined and solved a simulation-optimization problem for a representative API manufacturing plant. The comparison of batch crystallizers and continuous crystallizers showed the subtle differences the two different methods could have. While the batch method was overall lower in cost and PMI, the continuous method showed better potential for expansion. Additionally, when simulating the systems with the supply chain disruption in a Monte-Carlo simulation, it was shown that while both systems suffered loss in efficiency due to unpredictable delivery delays, the continuous system proved to require less overall material overstocking to prevent stockouts in production. However, it should be noted that these results are with arbitrary parameters and serve as a representative example of a technoeconomic cost model method. The purpose of this study is to show the capabilities of the cost model as a decision-making tool and that it can be applied for any setup and API.

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