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Technoeconomic and Sustainability Analysis of Batch and Continuous Crystallization for Pharmaceutical Manufacturing

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ABSTRACT

Continuous manufacturing in pharmaceutical industries has shown great promise to achieve process intensification. To better understand and justify such changes to the current status quo, a technoeconomic analysis of a continuous production must be conducted to serve as a predictive decision-making tool for manufacturers. This paper uses PharmaPy, a custom-made Python-based library developed for pharmaceutical flowsheet analysis, to simulate an annual production cycle for a given active pharmaceutical ingredient (API) of varying production volumes for a batch crystallization system and a continuous mixed suspension, mixed product removal (MSMPR) crystallizer. After each system is optimized, the generalized cost drivers, categorized as capital expenses (CAPEX) or operational expenses (OPEX), are compared. Then, a technoeconomic and sustainability cost analysis is done with the process mass intensity (PMI) as a green metric. The results indicate that while the batch system does have an overall lower cost and better PMI metric at smaller manufacturing scales in comparison with the continuous system, the latter system showed more potential for scaling-up for larger production volumes.

Keywords: Technoeconomic Analysis, Industry 4.0, Process Design, Modelling and Simulations, Optimization

INTRODUCTION

As technology develops and industries advance into the "Industry 4.0" era, the sector of chemical and pharmaceutical manufacturing is no exception. As such, the pharmaceutical industry has been working tirelessly to discover and apply innovations to the field [1]. In particular, the concept of Quality-by-design (QbD), which was first adopted by the FDA as a means to ensure quality in the development, manufacturing, and regulation of drugs [2], has been augmented by the Quality-by-Control (QbC) framework, which employs real-time process observation and control [3]. The paradigm of QbC has notably been applied to concept of continuous crystallizers [3,4]. Continuous manufacturing has been accepted as a promising technology to achieve process intensification in pharmaceutical manufacturing [4,5]. Such methods are important as it promises flexibility and efficiency for both high volume products as well as personalized medicine [4-6]. However, before the entire industry can adopt a new method of production, technoeconomic cost analyses of continuous production are necessary as a predictive decision-making tool for manufacturers. This is because an intimate understanding of the cost drivers and performance of continuous crystallizers is necessary for manufacturers to adopt change in an already batch system dominated industry [7]. But beyond the importance of technoeconomic analyses in industry, the issue of sustainable processes has also become more pressing. The importance of coupling technoeconomic models with sustainable metrics for a technoeconomic sustainability analysis, not just chemical processes, but for process design in general has been noted [8]. Thus, the application of sustainability metrics, either in forms of life cycle assessment or simple quantitative standards is important for chemical manufacturing [9].

In this paper, a preliminary investigation on the comparison of conventional batch crystallizers and mixed

suspension, mixed product removal (MSMPR) continuous crystallizers is conducted. First, simulated models of the annual performance of both types of systems are constructed using PharmaPy, a custom-made library for pharmaceutical flowsheet analysis [10]. For both layouts, the common active pharmaceutical ingredient (API) of paracetamol (PCM), a common analgesic drug, has been selected. Then, given three different fixed annual production volumes, operational parameters, and desired critical quality attributes (CQAs), each system is optimized for both overall cost as well as sustainability, using the process mass intensity (PMI) as a quantitative metric. For each case, a derivative-free optimizer was used.

METHODOLOGY

Modeled Flowsheets

For this study, the analyses were conducted on the crystallizer unit operation. For both batch and continuous crystallizer layouts, the selected API for simulation was paracetamol. The kinetic parameters for the API have been adapted from Szilagyi et al. [11]. Additionally, an arbitrary number of annual workdays were selected wherein the system was set to produce three different annual production volumes. For the batch cooling crystallizer setup, a single unit is set as the default. However, as part of the decision variables, up to three parallel units are considered, thus allowing for the batch crystallizer to be optimized for numbering-up as well as scaling-up. In comparison, the continuous crystallizer setup is comprised of two chained MSMPR crystallizer units. The reason for this setup is because while a single batch cooling crystallizer has the flexibility to operate with a dynamic cooling profile, each MSMPR unit can only be operated under a static temperature value. Thus, by setting up two MSMPR units, the optimizer can affect the process with two different crystallizer dimensions, residence times, and operating temperatures, which enable to manipulate both throughput and critical quality attributes (CQAs), thus allowing for sufficient control and complexity for comparison with the batch process.

For the batch layout, the API is produced in batch, wherein the number of total batches are calculated from the optimal cycle time, which factors in a static one-hour ramp-down/cleanup time. However, for the continuous crystallizer, API is produced continuously in a singular campaign duration. This optimal campaign duration is calculated by multiplying the residence time of the secondary MSMPR, τ_{CR02}, by the optimal steady state horizon multiplier, H_{ss}. This determines the duration at which the MSMPR system operates at steady state and continuously produces API. Additionally, the optimal value for τ_{CR02} was obtained from a preliminary optimization sequence prior. Like the batch system, the MSMPR system also has a ramp-down/cleanup time, but it is only initiated once after the campaign. However, the MSMPR also has ramp-up time wherein it must reach steady state, which was estimated for the temperature decision variables of the MSMPR units.

Finally, for each setup, an inlet of feed slurry is defined. This feed slurry serves to represent an input from a reactor unit. However, as the focus of this work is to analyze the performance of the crystallizer unit, the reactor unit has been omitted. Then, the output of each crystallizer is run through a filtration process step. However, like the reactor, the filtration unit operation has been omitted. A schematic summary of the two setups can be seen in Figure 1.

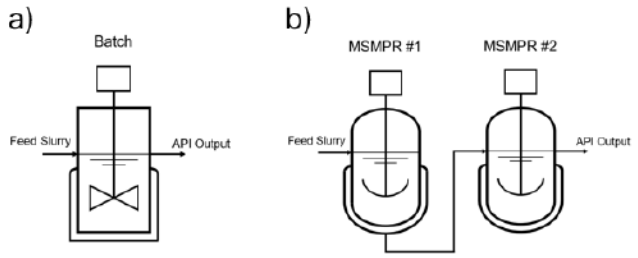

Figure 1. Schematic summary of the two different crystallization unit operations, a) batch crystallization and b) continuous crystallization.

Both crystallization configurations were simulated using PharmaPy. As previously mentioned, PharmaPy is a custom-made Python-based library for the analysis of pharmaceutical flowsheets. Using this tool, the defined unit operations can have operational parameters, such as inlet flows, initial conditions, and pharmacokinetic parameters assigned to in an object-orient software structure [10]. Then, once the unit operations are defined as such, a simulation object of the flowsheet is created. This coupled with a callback function, decision variables can be set as inputs and PharmaPy operations as outputs allows for an optimization framework to be established.

Optimization Formulation

For this study, the optimization problem is expressed as a non-linear constrained design problem wherein the objective is to minimize either the total cost of the manufacturing the API or the sustainability metric, PMI. The proper definition can be seen in Equation (1) [12].

$$\min_{\boldsymbol{x}} J(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{z}) \tag{1}$$

$$\text{s.t.} \frac{d\boldsymbol{y}}{dt} = f_1\big(t, \boldsymbol{y}, \boldsymbol{z}, \boldsymbol{u}(t)\big),$$

$$f_1\big(t, \boldsymbol{y}, \boldsymbol{z}, \boldsymbol{u}(t)\big) = \boldsymbol{0}, \tag{2}$$

$$\boldsymbol{y}(t=0) = \boldsymbol{y_0}, \boldsymbol{z}(t=0) = \boldsymbol{z_0},$$

and

$$g_i(x,y,z,u) \le 0, \qquad \forall i \in I, \tag{3}$$

$$\boldsymbol{x_{lb}} \le \boldsymbol{x} \le \boldsymbol{x_{ub}}$$

The equations in Equation (2), adapted from Casas-Orozco *et al.* [12], correspond to the process model of a differential-algebraic equation (DAE) system, with $\boldsymbol{y} \in \{y_1, \dots, y_j, \dots, y_{n_y}\}$ being the set of differential states and $\boldsymbol{z} \in \{z_1, \dots, z_{n_z}\}$ being the set of algebraic states, and $\boldsymbol{y_0}$ and $\boldsymbol{z_0}$ being their respective initial values. Additionally, the model inputs are represented by the variables, $u(t) \in \{\mathrm{u}_1(t), \dots \mathrm{u}_{n_u}(t)\}$. The entirety of the DAE system is represented by the PharmaPy simulation. Finally, Equation (3) shows the nonlinear constraints and decision variable bounds for the problem.

For this study, the decision variables are dependent on the type of crystallizer that is being simulated. Consequently, the lower and upper bounds represented in Equation (3) vary by the system. Thus, the decision variables that are considered as well as their bounds are listed in Table 1.

Table 1: Description of decision variables considered in the optimization problem along with their bounds.

Variable	System	Description	Bounds
V_{CR}	Batch	Cryst. 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	Cryst. ith Temp. Point	273 ~ 330 [K]
V_{CR01}, V_{CR02}	Cont.	Cryst. Volume	0.1 ~ 7.5 [m³]
T_{CR01}, T_{CR02}	Cont.	Cryst. Temp.	273 ~ 330 [K]
H_{ss}	Cont.	Steady state multiplier	1 ~ 100,000

Finally, the function $g_i(x,y,z,u)$ represent the nonlinear constraints that are being applied to the problem. These constraints are representative of CQAs or standards that would be an important metric for determining the success of the system. The first constraint is that the API produced in a system must be at least a certain diameter. This an important CQA for a crystallization unit as the mean size of the crystals, and to an extent the crystal size distribution (CSD) can determine the flowability and filterability of the API produced [13]. This then has large implications for how easily the API is handled, or even how effective the drug is. The second constraint is the production volume. This is simply to ensure that the optimal results always at least produce enough API product to meet the fixed annual production volume. The third constraint is the yield constraint, which is in place to make sure that the optimal results would produce a certain percentage of the theoretical maximum yield, thus ensuring a certain level of efficiency. The fourth constraint is an operational constraint to make sure that the temperature profile for the batch and the temperatures in the consecutive MSMPRs are monotonically decreasing. Finally, the fifth and final constraint are implemented to make sure that the total calculated time for manufacturing does not exceed the allotted annual workdays. This is in place because while the total time for the batch system is divided into distinct batches, the continuous system simply has a single campaign to continuously create API. These constraints are summarized in Table 2. In addition, Table 2 also lists the weights for each constraint. These weights were then applied to a penalty function for the constraints to ensure that the optimal solution wasn't trivial or impractical.

Table 2: Description of the constraints considered in the optimization problem and their respective weights.

Variable	Description	Weight	Constraint
g_1	Mean Crystal Size	$w_1 = 10^2$	$40\ [\mu m] < \bar{L}$
g_2	Production Volume	$w_2 = 10^3$	$PV_{target} < PV_{actual}$
g_3	Overall Yield	$w_3 = 10^2$	$0.9Y_{max} < Y_{actual}$
g_4	Decreasing Temp.	$w_4 = 10^0$	$T_{i+1} \le T_i$
g_5	Total Time	$w_5 = 10^1$	$260\ [\text{days}] > t_{total}$

For this simulation, the defined optimization problem was then solved with the adaptive Nelder-Mead algorithm included in the SciPy library. Thus, to translate the problem to an unconstrainted optimization problem for the derivative-free Nelder-Mead algorithm, the nonlinear constraints were reformulated into an augmented objective function. It should be noted that given the non-convexity of the problem and due to the challenges of employing a gradient-based method in a simulation-optimization approach to the problem, a derivative-free algorithm was preferred. Furthermore, to improve optimizer performance, the objective function and constraint values were normalized. Thus, the objective function was transformed to Equation (4) and the constraints were transformed to Equations (5).

$$J_{norm}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z}) = \left[\frac{J(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z}) - J_{min}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})}{J_{min}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})}\right]^2 \tag{4}$$

$$g_{norm,i} = \begin{cases} i \in [1,4], & 1 - \frac{g_{i,target}}{g_i} \\ i = 5, & \frac{g_{i,target}}{g_i} - 1 \end{cases} \tag{5}$$

where $J_{min}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z})$ is the overall lowest function evaluation the optimizer found and $g_{i,target}$ is the constraint value for g_i. Thus, the final augmented and normalized objective function is shown in Equation (6).

$$\min_{\boldsymbol{x}} J_{norm}(\boldsymbol{x},\boldsymbol{y},\boldsymbol{z}) + \Sigma_{i\in[1,5]}\left[\max\left(0, w_i \cdot g_{norm,i}\right)\right]^2 \tag{6}$$

Cost Calculation

As previously mentioned, one of the objective functions used to evaluate the simulation is the overall cost of the system. The cost of the system can be broken down into two categories, capital expense (CAPEX) and operational expense (OPEX).

CAPEX Calculation

CAPEX involves all the terms that are related to the purchase of equipment. However, while the volume of the crystallizers as a decision variable are not discrete values, in reality, equipment are usually made and sold at discrete capacities. Thus, to account for this, a cost-capacity correlation equation is from Diab *et al.* [6] is used:

$$C_B = f C_A \left(\frac{S_B}{S_A}\right)^n \tag{7}$$

Wherein, the C_i is the cost of the equipment and S_i is the capacity of the given equipment. Next, f are equipment-dependent coefficients to account for indirect costs that may be involved for certain equipment. Finally, n is a value is the cost exponent to represent the exponential increase in cost of equipment as capacity increases. The index of A in Equation (7) represent existing equipment while the index of B refer to the equipment selected for the simulation. The specific values for base equipment values in Equation (7) are based on the Chemical Engineering Plant Cost Indices (CEPCIs) [14]. However, for this study, the values are identical as the ones used by Diab *et al.* [6].

Furthermore, to provide a more realistic estimation for the technoeconomic cost model, rather than taking the flat equipment cost, a battery limit installed cost (BLIC) is calculated. Thus, the additional indirect costs associated with installing the equipment are considered. To calculate the BLIC, the Chilton method is employed [6]. In summary, the BLIC is a factor of the total physical plant cost (TPPC), which is the sum of the installed equipment cost (IEC) and the process piping and instrumentation (PPI) cost. The PPI is a percentage of the IEC while the IEC is a factor of the previously calculated equipment cost. The exact coefficients and factors for these calculations are the same as the ones used by Diab *et al.* [6].

Finally, once the BLIC was calculated, rather than apply the flat equipment cost, an equivalent uniform annual cost (EUAC) was calculated. This is to reflect the fact that while it is not unheard of for a company to outright purchase all the required equipment for a new setup, it is more customary for the annual equipment cost of a production line to be expressed as an annuity [15]. The calculation can be seen in Equation (8). An interest rate, i_{rate} of 5% and a project timeline, t_{PL} of 20 years is taken from literature [6].

$$EUAC = BLIC\left(\frac{i_{rate}(1+i_{rate})^{t_{PL}}}{(1+i_{rate})^{t_{PL}}-1}\right) \tag{8}$$

In addition to the equipment cost, the CAPEX for this simulation also takes into consideration for the working capital (WC) and the contingency costs (CC) of the plant. The WC and CC are set to be 3.5% of the annual material costs and 20% of the total BLIC, respectively. These values can be found in literature [16].

Summary of the total CAPEX calculation is summarized in Equation (9).

$$CAPEX_{total} = EUAC + WC + CC \tag{9}$$

OPEX Calculation

As opposed to CAPEX, which represented expenses that are investments that need to be made prior to establishing a setup, OPEX represents all expenses that are incurred during the hours of plant operation. The major cost drivers here are the cost of the materials that serve as inputs for the pharmaceutical process and the cost involved with dealing with the waste material of a process. The material cost, $C_{material}$, can be straightforwardly calculated as the product of the total mass of each chemical species m_i and their respective cost per mass, C_i. Finally, the waste cost, C_{waste}, can be calculated as a certain percentage of the total cost of solvents, C_{solv}, involved in the process. The exact percentage, while it may vary on a plant-by-plant basis, was set as 35%. The summary of these calculations as well as the final total OPEX calculation can be seen in Equations (10-12).

$$C_{material} = \sum_i C_i m_i \tag{10}$$

$$C_{waste} = 0.35 \sum_i C_{solv,i} \tag{11}$$

$$OPEX_{total} = C_{material} + C_{waste} \tag{12}$$

Thus, the objective function when calculating for minimal costs can be seen in Equation (13).

$$\min_{\boldsymbol{x}} J_{cost}(\boldsymbol{x}, \boldsymbol{y}, \boldsymbol{z}) = CAPEX_{total} + OPEX_{total} \tag{13}$$

Sustainability Calculation

In the previous section, the method of calculating the cost of a crystallization unit operation has been outlined. However, while cost is an important metric for a technoeconomic model, sustainability, or "green processing", is an ever-growing concern for the future of the sustainable pharmaceutical industry [17]. Thus, optimizing the manufacturing system in regard to a sustainability metric in addition to the cost is a necessary perspective to take. Over time, many different metrics for sustainability have emerged. Notably, the E factor, seen in Equation (14), has often been used in studies as a metric for efficiency of pharmaceutical manufacturing [17].

$$\text{E factor} = \frac{total\ mass\ of\ waste\ from\ a\ process\ [kg]}{total\ mass\ of\ product\ [kg]} \tag{14}$$

However, as the E factor serves as a ratio of the API produced and the waste material produced from the entire process, the E factor can be a misleading metric as it only represents the waste material, thus not guaranteeing the efficiency or lack thereof in regard to the other materials involved in the process [18]. Thus, as a correction, the process mass intensity (PMI) metric has been introduced. The PMI, shown in Equation (15), serves a ratio of the total API produced with the mass of all chemical species that was involved in the process [18].

$$\text{PMI} = \frac{total\ mass\ from\ a\ process\ [kg]}{total\ mass\ of\ product\ [kg]} \tag{15}$$

Thus, with PMI as a secondary objective function, the manufacturing system can also be investigated regarding sustainability as well as minimized costs.

RESULTS AND DISCUSSION

With the optimization problem defined in the previous section as well as the layout of the batch and continuous crystallization manufacturing units, we can then compare the differences in performance and cost for the systems. For both batch and continuous systems, the simulation was optimized for minimal total cost, which was the sum of the CAPEX and OPEX, and for minimal PMI The results of the optimization for both systems with the two different objective functions and at three different target annual production volumes can be seen in Figure 2. Additionally, it is important to note that the CAPEX and OPEX have been graphed separately on different axes. This is because while the technoeconomic cost model was created to provide a holistic view of the unit operations, the inclusion of CAPEX is not always relevant for some industries, for example where the equipment is already in place. Also, the numerical values of the simulations, optimal decision variables as well as some additional performance metrics for the batch system and the continuous system can be seen in Table 3 and Table 4, respectively.

When first observing the results of the simulation, it is important to note that from Figure 2, we can observe that the overall OPEX for the continuous system, regardless of annual production volume, is higher than that for the batch system. This is a logical outcome as one of the drawbacks of MSMPR crystallizers is that a constant feed of slurry needs to be input. However, it should also be noted that the CAPEX values for continuous systems are always lower than their batch counterparts across the board. This is even with the consideration that a single production line of continuous crystallization requires two MSMPR units in cascade. This is reflective of the result that, due to the higher throughput of the continuous systems, a smaller crystallizer unit is sufficient to meet the annual production targets. However, this result comes with the caveat that the inclusion of CAPEX may not be significant for manufacturers who are not looking to create a new manufacturing line from scratch, thus making the difference in CAPEX irrelevant.

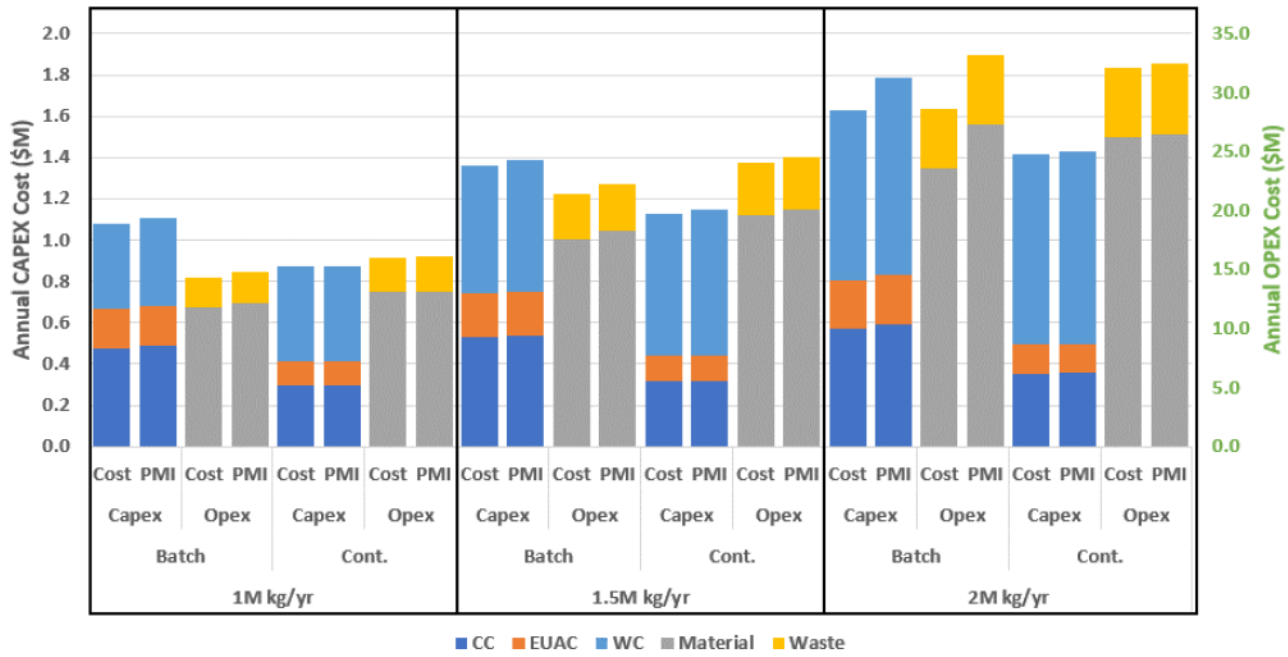

Figure 2: Annual CAPEX and OPEX comparison for different annual production volumes between batch and continuous crystallization units. In addition, the differing values on whether the optimizer prioritized minimal cost or minimal PMI have been presented next to each other.

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.
Material	$23,550,782.88	$27,304,372.89	$17,622,765.28	$18,270,689.49	$11,768,420.85	$12,151,357.09
Waste	$5,119,692.16	$5,935,683.09	$3,831,003.57	$3,971,855.47	$2,558,330.75	$2,641,577.05
EUAC	$230,485.79	$237,646.32	$212,143.30	$214,036.03	$190,490.66	$195,239.96
WC	$824,277.40	$955,653.05	$616,796.78	$639,474.13	$411,894.73	$425,297.50
CC	$574,472.47	$592,319.69	$528,754.88	$533,472.40	$474,786.93	$486,624.30
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.
Material	$ 26,259,268.76	$ 26,505,728.06	$ 19,627,749.43	$ 20,080,882.20	$ 13,092,875.99	$ 13,144,073.54
Waste	$ 5,872,371.26	$ 5,927,758.35	$ 4,390,333.75	$ 4,491,690.05	$ 2,928,844.40	$ 2,940,464.34
EUAC	$ 142,092.38	$ 142,770.88	$ 126,473.28	$ 126,473.28	$ 119,259.38	$ 118,712.96
WC	$ 919,074.41	$ 927,700.48	$ 686,971.23	$ 702,830.88	$ 458,250.66	$ 460,042.57
CC	$ 354,157.04	$ 355,848.15	$ 315,227.32	$ 315,227.32	$ 297,247.11	$ 295,885.18
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

In addition to this observation, we can see from Table 3 and Table 4 that despite the differences in CAPEX, the overall cost for the batch system is lower than their continuous counterparts. However, that comparison does not provide a full view of the comparison. An important aspect of continuous crystallization is the efficiency in terms of throughput and availability. This is observed in the simulation results in Table 4. The results show that for all annual production volumes, the continuous system resulted in a more consistent throughput rate while Table 3 indicates that the batch system has a steeper drop in throughput. This is also reflected in the fact that for all three annual production volumes, the batch system needed to use all 260 days for all cases, even though the batch cases have already optimized for 2 parallel lines.

Additionally, we can see that for the continuous system, the overall optimized crystallizer volume is lower than for the batch scenario. In conjunction with this, we can see that the total availability, which is the percentage of time in which the system is actually running and not ramping up, ramping down or cleaning, the continuous system predictably has a higher percentage. With all these observations, we can see that the MSMPR setup, while for the selected parameters may have an overall higher cost, shows a better potential for scaling up and provides a more agile manufacturing alternative.

Finally, the previously made observations can also be seen when considering the PMI. From the same tables, we when we see the results for optimizing for PMI rather than cost, we can compare the sustainable nature of both setups. As expected, the continuous system has a higher PMI value due to the necessity for a continuous input of slurry. However, when comparisons with cost in mind, we can see that while optimizing for PMI decreases the resultant PMI by less than 1%, the cost in continuous systems increases less significantly than the batch systems. Thus, while the significance of decreasing PMI would be different on a case-by-case basis, we can observe that the continuous system has a lower cost necessary for improving the overall sustainability of the process.

CONCLUSION

This study was an example to show the capabilities of the technoeconomic cost model simulation to serve as a decision-making tool for manufacturers. By employing a simulation-optimization strategy with the annual production of paracetamol as a generic representative API and applying CAPEX and OPEX calculations that have been standardized in literature, a good first simulation result was achieved. Furthermore, with the simulation, other than directly comparing cost, the potential capabilities of continuous production methods in the pharmaceutical industry could be explored. While the overall costs of continuous systems may higher than the existing batch production setup, the potential for continuous systems to scale up and maintain efficiency in both availability and throughput shows promise. Furthermore, in the light of sustainability for pharmaceutical processes, we could see that the trade-off in cost for improving PMI metrics would be much less than that for batch processes, thus additionally showing how continuous systems could be more easily adapted to be more sustainable and embody the idea of “green chemistry”.

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