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Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study

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ABSTRACT: The capital, operating, and overall costs of a dedicated continuous manufacturing process to synthesize an active pharmaceutical ingredient (API) and formulate it into tablets are estimated for a production scale of 2000 t of tablets per year, with raw material cost, production yield, and API loading varied over broad ranges. Costs are compared to batch production in a dedicated facility. Synthesis begins with a key organic intermediate three synthetic steps before the final API; results are given for key intermediate (KI) costs of \$100 to \$3000/kg, with drug loadings in the tablet of 10 and 50 wt %. The novel continuous process described here is being developed by an interdisciplinary team of 20 researchers. Since yields are not yet well-known, and continuous processes typically have better yields than batch ones, the overall yields of the continuous processes with recycling were set equal to that of the batch process. Without recycling, yields are 10% lower, but less equipment is required. The continuous process has not been built at large scale, so Wroth factors and other assumptions were used to estimate costs. Capital expenditures for continuous production were estimated to be 20 to 76% lower, depending on the drug loading, KI cost, and process chosen; operating expenditures were estimated to be between 40% lower and 9% higher. The novel continuous process with recycling coupled to a novel direct tablet formation process yields the best overall cost savings in each drug loading/KI price scenario: estimated savings range from 9 to 40%. Overall cost savings are also given assuming the yield in the continuous case is 10% above and 10% below that of the batch process. Even when yields in the continuous case are lower than in the batch case, savings can still be achieved because the labor, materials handling, CapEx, and other savings compensate.

INTRODUCTION

Continuous manufacturing (CM) is attracting increasing attention within the pharmaceutical industry today because it could lead to significant decreases in production costs while improving product quality.^{1,2} Historically, production costs were seen as a small enough part of the overall industry expenses that major cost reductions were not needed. Regulations also drove production toward the batch mode, since processes were required to be run in exactly the same way for the lifetime of the therapy. Also, batch production allows verification of quality of each batch from each process before further processing, whereas a “batch” in a continuous process is not contained in the same way.^{3,4} Today, however, it is becoming more difficult for pharmaceutical companies to meet profit expectations, due to increasing research and development (R&D) costs and competition from generics manufacturers.⁵ At the same time, regulatory bodies are shifting the emphasis toward process understanding and giving more freedom when such understanding is demonstrated.⁶ For sufficiently large production scales, continuous processes tend to have lower production costs; CM would also allow manufacturers to use the increased process understanding for online process control, yielding consistently high-quality product and less material wasted as off-spec product.^{7,8}

A review of the fine and commodity chemical industries demonstrates that CM could offer both operating expenditure (OpEx) and capital expenditure (CapEx) savings for the pharmaceutical industry. Labor for transporting material between batch units, labor for quality assurance/quality control (QA/QC), and in-process inventory (working capital) can all be significantly reduced in continuous

processing.^{1,9} Processing equipment for fine chemical synthesis can be made much smaller by moving to continuous processing, as well as having larger surface area to volume ratios, which implies a safer plant (a smaller holdup of solvents in reactors and enhanced heat transfer for safe handling of highly exothermic reactions), a smaller investment in reactors, and faster change over in multipurpose plants.^{7,8,10} More rapid mixing, reaction, and quenching are possible in continuous flow,¹¹ enabling reactions that would produce significantly more impurities if run in batch mode, such as in the first reaction in the novel continuous process presented in this work. Plant footprint can also be reduced due to smaller processing equipment, with commensurate energy savings for heating, ventilation, and air conditioning.¹²

Pharmaceutical processes often contain continuous or semi-continuous processing steps, such as milling and tablet compression, but the processes are started and stopped to mirror the batch processing in other steps. These steps can be more naturally run in a continuous manner, potentially yielding more consistent product quality.^{1,4} Scaleup of batch granulation can be difficult, and is sometimes easier in continuous mode, so development of a needed granulation process could begin on continuous equipment, easing scaleup for production.³ Recently, the lack of continuous tablet coating equipment was a bottleneck for

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Table 2. Raw Materials Costs for All Processes at 50 wt % API Loading and \$3000/kg KI^a

materials	Bx	CM1R/DTF	CM1/DTF	CM1R/RC	CM1/RC
organic reagents	3,394,145,000	3,375,898,000	3,899,888,000	3,375,898,000	3,899,888,000
inorganic reagents	2,674,000	4,784,000	4,784,000	4,784,000	4,784,000
organic solvents	92,356,000	22,864,000	27,263,000	22,864,000	27,263,000
water	2,182,000	780,000	996,000	780,000	996,000
excipients and coatings	15,936,000	15,893,000	15,893,000	15,893,000	15,893,000
total	3,507,293,000	3,420,219,000	3,948,824,000	3,420,219,000	3,948,824,000

^a All values in \$/year. DTF, direct tablet formation; RC, roller compaction.

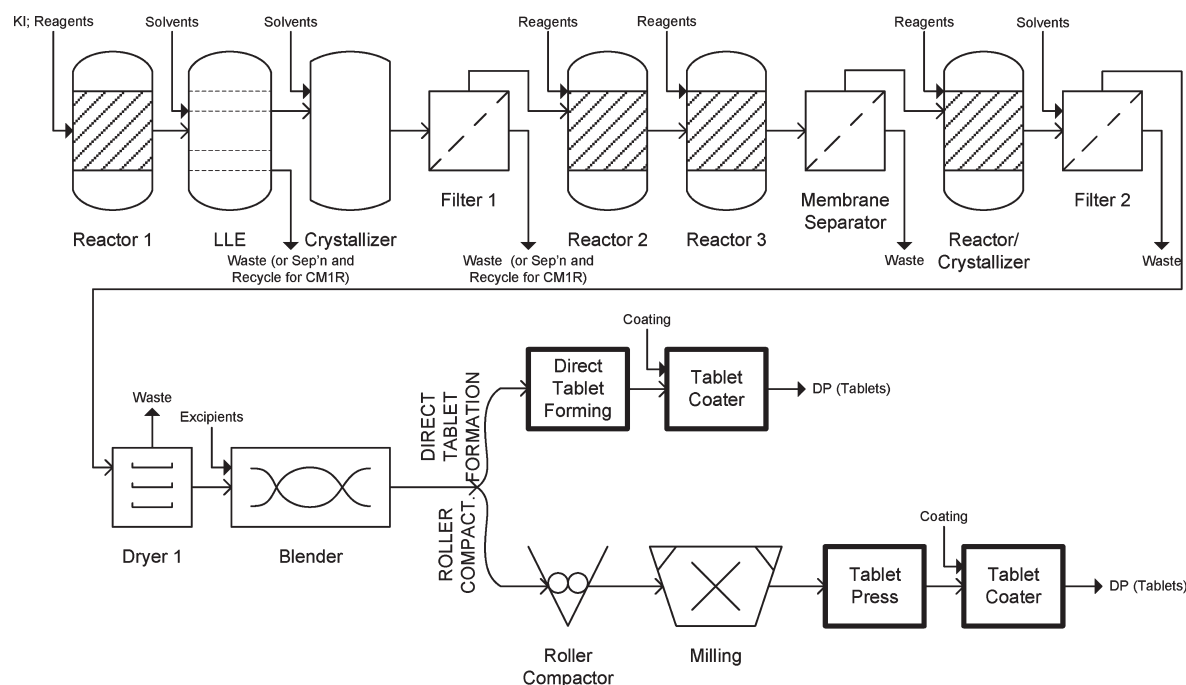


Figure 2. Process flow diagram for continuous manufacturing route CM1, showing both options for forming tablets.

Novel CM Route (CM1). The CCM team developed a new synthetic route (CM1; Figure 2) that utilizes pathways that are not feasible in a batch process. For example, processing in a continuous-flow reactor enables a much more rapid deprotection reaction than batch reaction; translating the CM1 route into a standard batch process would result in significant degradation of the product because the required rate of reagent addition cannot be achieved in batch mode. Also, the continuous processes save an average of 61% of the annual water usage and 21 wt % of the annual solvent usage compared to batch. Reactors 1, 2, and 3 are plug-flow reactors. The crystallizer and combined reactor/crystallizer are agitated tanks. The API synthesis is coupled with two downstream process options: roller compaction (RC) and a novel direct tablet formation (DTF) process. RC is a well-established pharmaceutical technology; a patent application is being prepared for the novel direct tablet formation process, so it is not described in detail here. Since the yields for the final continuous processes are not known precisely, yields have been set such that the overall yield for the continuous process with recycling for the first reaction (CM1R) is equal to that of the batch process, and the overall yield of the continuous process without recycling (CM1) is 10% below that of the batch process. Overall cost savings are also given for the case where overall yield

for process CM1R is 10% below and 10% above that of the batch case. In each case, the overall yield for process CM1 is 10% below the corresponding overall yield for process CM1R. The actual yields that have been demonstrated in bench-scale continuous reactions are bracketed by these scenarios; it is believed that a mature continuous process will have yields equal to or better than the batch yields, since the continuous process already has competitive yields despite being developed for fewer than half as many years, at a much smaller scale, and by fewer people.

Continuous reactions scale up very predictably and in an economically favorable way.⁸ One issue currently limiting the savings is microreactor plugging or fouling, which can be observed as an increasing pressure drop across the reactor.^{7,8} The methods for using microreactors with heterogeneous catalysts or severe precipitation are not mature.⁷ However, several workarounds to the plugging and fouling issue are possible, based on including strategic solvent choice, flow velocity, temperature, and device geometry.⁷ Microreactors have been successfully used to produce hundreds of kilograms of product in a few weeks.⁸

Novel CM Route with Recycle (CM1R). Process CM1R is identical to CM1, except that a single recycle loop and appropriate separation equipment are added to increase the effective yield (from 86.4% to 98.5%) in the first step (Reactor 1) of the

API synthesis from the KI. Separation equipment and recycle are essential in order to reduce formation of the primary impurity. Without the separation step, the primary product of the reaction can undergo a subsequent reaction to form an impurity. The overall yields (mol drug substance/mol KI) of processes CM1 and CM1R are 69% and 79%, respectively; that of the batch process is 79%. Even without recycling, significant savings overall are estimated, due to savings in CapEx, working capital, quality assurance and control, labor, materials handling, waste handling, and utilities.

Material Balances. Material requirements and costs for all processes are given in Table 1. For Table 2, the cost of the KI (one of the organic reagents) is \$3000 kg/year, whereas costs for other raw materials are from vendor quotes, and are typically much less than \$3000/kg.

COST ANALYSIS METHODS

Green-field construction of a new, dedicated plant was considered in all cases. A 335-day working year was considered, with 30 days left for maintenance, cleaning, and startup/shutdown. One production line per plant was assumed. Batch process effective utilization time was assumed to be 85% for upstream processes and 55% for downstream processes; 95% was assumed for all continuous processes. This is the percentage of time when the process equipment is actually processing material. The remaining time is spent filling, emptying, and cleaning the batch processing unit, or simply waiting for material to be processed. These assumptions are optimistic for batch production, representing lean batch operations in dedicated production: According to Vervaeke and Remon,⁴ the overall equipment effectiveness (OEE), a related metric, takes a typical value in

batch pharmaceutical production of 30%, with good processes having 74% and “best-in-class” production lines reaching 92%.

Capital Expenditures (CapEx). *Equipment Size and Cost Estimation.* Vendor price quotations for all process equipment were obtained for both batch and continuous equipment over a wide range of sizes, and the smallest unit of sufficiently large size was selected. When price quotations were only available for batch equipment, a 10% price premium was assumed for continuous units relative to a batch unit of the same size, to account for the increased process engineering (CapEx) required to operate a process continuously with feedback control, as compared to batch processes which are typically operated in an open-loop manner. Scaling of cost could be approximated well ($R^2 \geq 0.98$) by a power law in the following cases: plug-flow reactor, exponent 0.42; filtration equipment, exponent 0.33; agitated vessel/CSTR/crystallizer, exponent 0.20; dryer, exponent 0.21.

Calculation of Overall CapEx from Individual Process Equipment Costs. The total cost of processing equipment excluding any ancillary equipment, delivery, electrical, engineering, or piping expenses is termed the FOB (free on board) cost. From delivered equipment cost ($1.05 \times \text{FOB cost}$), Wroth factors (Table 3) were used to calculate delivered installed equipment cost, which includes ancillary equipment, delivery, electrical, engineering, and piping costs.¹⁴ Wroth factors allow quick estimation of installation and other necessary equipment costs, and are commonly used at this stage of an economic analysis.

$$\begin{aligned} & (\text{delivered installed equipment cost}) \\ &= (\text{Wroth factor}) \times (\text{delivered equipment cost}) \end{aligned} \quad (1)$$

Additional CapEx heuristics used in the present analysis are summarized in Table 4. Since pharmaceutical production scales are smaller than typical commodity chemical production scales, and must adhere to stricter hygiene regulations, the additional expenses are expected to comprise a larger fraction of the CapEx. Thus, the values used were the upper bounds of the ranges given by Couper et al.

Operating Expenditures (OpEx). Operating expenditures were calculated for KI prices of \$100, \$500, and \$3000/kg. The heuristics used are summarized in Table 5. The continuous plant has not been built at large scale, so the values for labor, materials handling, and QA/QC savings represent our best estimates at this time. For example, OpEx savings are expected in QA/QC since some manual sampling and analysis can be replaced by online analysis.

Table 3. Selected Wroth Factors¹⁴

unit	Wroth factor
distillation tower and internals	4.0
instrument	4.1
process tank	4.1
reactor	(factor into appropriate process tanks and other equipment)
storage tank	3.5
all other equipment	3.5

Table 4. Summary of CapEx Heuristics Used

item	cost
(1) FOB cost	sum of processing equipment units ¹⁴
(2) delivery	5% of FOB cost ¹⁴
(3) installation: ancillary equipment, automation, electrical, piping, and engineering	$[(\text{Wroth factor}) - 1] \times (\text{delivered equipment cost})^{14}$
(4) battery-limits installed cost (BLIC)	sum of items (1) to (3) ¹⁴
(5) buildings and structures	20% of BLIC ¹⁴
(6) contingency	20% of BLIC ¹⁴
(7) offsite capital (for a grass-roots plant)	150% of BLIC ¹⁴
(8) service facilities	20% of BLIC ¹⁴
(9) waste disposal	not included in CapEx; assumed to be treated at a nominal cost indicated in Table 5
(10) working capital	35% of annual sales ¹⁴ $\Rightarrow$ used 35% of annual materials costs for batch; 3.5% for continuous, since throughput times are expected to be 10x lower in continuous processing
(11) total CapEx	sum of items (4) to (10)

Table 5. Summary of OpEx Heuristics Used

item	cost
(1) labor and supervision	\$160,000/year per operator; ¹⁵ number of operators estimated as in Ulrich; ¹⁶ twice as many operators required for batch processes as for continuous
(2) materials handling and storage	continuous is estimated at 40% of batch
(3) off-spec product	0% for batch and continuous
(4) quality assurance and control (QA/QC)	continuous is estimated at 50% of batch
(5) utilities	\$1.50/kg material input
(6) waste disposal	\$2.50/gallon for water and organic solvents; \$15.00/gallon for all other material ¹⁷
(7) total OpEx	sum of items (1) to (6) plus raw material costs

Table 6. CapEx (Including Working Capital) Differences for All Process Options, Relative to Batch Case, For Upstream and Downstream^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
Batch (basis for differences)	Tot: [\$315M] U: [\$73M] D: [\$242M]	Tot: [\$346M] U: [\$105M] D: [\$242M]	Tot: [\$542M] U: [\$300M] D: [\$242M]	Tot: [\$429M] U: [\$173M] D: [\$256M]	Tot: [\$585M] U: [\$329M] D: [\$256M]	Tot: [\$1565M] U: [\$1308M] D: [\$256M]
CM1R with direct tablet formation	Tot: −28% U: −31% D: −27%	Tot: −33% U: −49% D: −27%	Tot: −54% U: −76% D: −27%	Tot: −39% U: −52% D: −31%	Tot: −53% U: −70% D: −31%	Tot: −76% U: −85% D: −31%
CM1 with direct tablet formation	Tot: −31% U: −43% D: −27%	Tot: −36% U: −57% D: −27%	Tot: −55% U: −78% D: −27%	Tot: −42% U: −59% D: −31%	Tot: −55% U: −73% D: −31%	Tot: −76% U: −85% D: −31%
CM1R with roller compaction	Tot: −20% U: −31% D: −17%	Tot: −26% U: −49% D: −17%	Tot: −49% U: −76% D: −17%	Tot: −34% U: −52% D: −21%	Tot: −49% U: −70% D: −21%	Tot: −75% U: −85% D: −21%
CM1 with roller compaction	Tot: −23% U: −43% D: −17%	Tot: −29% U: −57% D: −17%	Tot: −50% U: −78% D: −17%	Tot: −36% U: −59% D: −21%	Tot: −50% U: −73% D: −21%	Tot: −74% U: −85% D: −21%

^a Abbreviations: Tot, total CapEx; U, upstream CapEx; D, downstream CapEx. CapEx dollar amounts are provided in square brackets for the base case of a batch process.

Overall Cost of Production. To quantify overall cost differences accounting for both CapEx and OpEx, present cost of the project (eq 2) was calculated for each processing option. This is the discounted total cost of the project, excluding any revenue. Present cost of the project is similar to net present value (NPV, eq 3), but does not include revenue. This figure of merit was chosen because we are comparing costs, not NPV.

$$(\text{present cost}) = (\text{CapEx}) + \sum_{i=1}^{\tau} \frac{(\text{OpEx})}{(1 + r_d)^i} \quad (2)$$

$$(\text{NPV}) = -(\text{CapEx}) + \sum_{i=1}^{\tau} \left\{ \frac{-(\text{OpEx})}{(1 + r_d)^i} + \frac{(\text{revenue})}{(1 + r_d)^i} \right\} \quad (3)$$

Discount rate (r_d) was 7%, construction period was 1 year, and project lifetime (τ) was 15 years.

Contributors to Overall Cost Savings. To quantify the contributions of different expenses to the cost differences for

CM relative to batch, the following quantity was defined:

$$\begin{aligned} & (\text{contribution to present cost difference}) \\ &= ((\text{present cost of contributor for Bx process}) \\ &\quad - (\text{present cost of contributor for CM process})) \\ &\quad / (\text{present cost of Bx process}) \end{aligned} \quad (4)$$

To clarify the above definition, note that

$$\begin{aligned} & \sum_{(\text{contributors})} (\text{contribution to present cost difference}) \\ &= (\text{percentage present cost difference vs batch}) \end{aligned} \quad (5)$$

RESULTS

Capital Expenditures (CapEx). Process CM1 with direct tablet formation has the largest CapEx savings (31–76% savings vs batch processing). At the highest KI price, the working capital, especially for the KI, dominates CapEx, so savings are similar for

Table 7. Summary of CapEx Differences for All Process Options, Relative to Batch Case^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
batch (basis for differences)	[\$315M]	[\$346M]	[\$542M]	[\$429M]	[\$585M]	[\$1565M]
CM1R with direct tablet formation	−28%	−33%	−54%	−39%	−53%	−76%
CM1 with direct tablet formation	−31%	−36%	−55%	−42%	−55%	−76%
CM1R with roller compaction	−20%	−26%	−49%	−34%	−49%	−75%
CM1 with roller compaction	−23%	−29%	−50%	−36%	−50%	−74%

^a Total CapEx dollar amounts are provided in square brackets for the base case of a batch process.

Table 8. Annual OpEx Differences for All Process Options, Relative to Batch Case^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
Batch (basis for differences)	Tot: [\$136M]	Tot: [\$226M]	Tot: [\$785M]	Tot: [\$531M]	Tot: [\$979M]	Tot: [\$3777M]
	URM: [\$49M]	URM: [\$139M]	URM: [\$698M]	URM: [\$246M]	URM: [\$693M]	URM: [\$3491M]
	DRM: [\$25M]	DRM: [\$25M]	DRM: [\$25M]	DRM: [\$16M]	DRM: [\$16M]	DRM: [\$16M]
	Oth: [\$62M]	Oth: [\$62M]	Oth: [\$62M]	Oth: [\$269M]	Oth: [\$269M]	Oth: [\$269M]
CM1R with direct tablet formation	Tot: −33%	Tot: −20%	Tot: −6%	Tot: −40%	Tot: −22%	Tot: −6%
	URM: −36%	URM: −13%	URM: −2%	URM: −36%	URM: −13%	URM: −2%
	DRM: 0%	DRM: 0%	DRM: 0%	DRM: −1%	DRM: −1%	DRM: −1%
	Oth: −45%	Oth: −45%	Oth: −45%	Oth: −47%	Oth: −47%	Oth: −47%
CM1 with direct tablet formation	Tot: −19%	Tot: −6%	Tot: 8%	Tot: −22%	Tot: −6%	Tot: 9%
	URM: −6%	URM: 7%	URM: 13%	URM: −6%	URM: 7%	URM: 13%
	DRM: 0%	DRM: 0%	DRM: 0%	DRM: −1%	DRM: −1%	DRM: −1%
	Oth: −36%	Oth: −36%	Oth: −36%	Oth: −38%	Oth: −38%	Oth: −38%
CM1R with roller compaction	Tot: −33%	Tot: −20%	Tot: −6%	Tot: −40%	Tot: −22%	Tot: −6%
	URM: −36%	URM: −13%	URM: −2%	URM: −36%	URM: −13%	URM: −2%
	DRM: 0%	DRM: 0%	DRM: 0%	DRM: −1%	DRM: −1%	DRM: −1%
	Oth: −45%	Oth: −45%	Oth: −45%	Oth: −47%	Oth: −47%	Oth: −47%
CM1 with roller compaction	Tot: −19%	Tot: −6%	Tot: 8%	Tot: −22%	Tot: −6%	Tot: 9%
	URM: −6%	URM: 7%	URM: 13%	URM: −6%	URM: 7%	URM: 13%
	DRM: 0%	DRM: 0%	DRM: 0%	DRM: −1%	DRM: −1%	DRM: −1%
	Oth: −36%	Oth: −36%	Oth: −36%	Oth: −38%	Oth: −38%	Oth: −38%

^a Abbreviations: Tot, total OpEx; URM, upstream raw materials OpEx; DRM, downstream raw materials OpEx; Oth, all other OpEx. OpEx dollar amounts are provided in square brackets for the base case of a batch process.

all processes. Detailed results are given in Table 6; summarized results are given in Table 7.

Operating Expenditures (OpEx). Process CM1R with either direct tablet formation or roller compaction has the lowest annual OpEx of any process option (6–40% savings); process CM1 options show slightly less savings, due to the lower overall yield without recycling. Detailed results are given in Table 8; summarized results are given in Table 9.

Overall Cost of Production. Process CM1R with direct tablet formation has the lowest present cost (9–40% savings). CM1R with roller compaction is the next best option, with very similar savings. See Table 10.

If the overall yield of process CM1R is 10% below that of the batch process (Table 11), the overall costs of continuous processing are between 4% higher and 35% lower than batch processing if the best process is chosen for each API loading/KI price scenario. At \$3000/kg for the KI, all continuous processes are estimated to be more expensive than the batch process. If the overall yield is 10% higher for CM1R than for the batch process

(Table 12), 19–35% savings can be achieved versus batch in all low API loading cases by choosing process CM1R with direct tablet formation.

Contributors to Overall Cost Savings. In Table 13, the present cost of the project for the baseline case in which CM1R yield is equal to batch yield is broken down into contributions for each category (cf. eq 4). The values are for the novel continuous process with recycling with direct tablet formation (CM1R/DTF) and are similar to those for the other novel CM options (not published).

The expenditures for the KI and for excipients are the same for CM1R/DTF and batch, since equally priced excipients are used and the overall yield of drug substance from KI is assumed equal in CM1R and batch. The cost of the other organic reagents needed in the novel continuous process are lower, reducing OpEx in the “other” raw materials category. The novel continuous process also has lower solvent usage, reducing costs of other raw materials and waste handling. Moving toward higher KI price in the table means the KI makes up a higher fraction of the

Table 9. Summary of Annual OpEx Differences for All Process Options, Relative to Batch Case^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
batch (basis for differences)	[\$136M]	[\$226M]	[\$785M]	[\$531M]	[\$979M]	[\$3777M]
CM1R with direct tablet formation	−33%	−20%	−6%	−40%	−22%	−6%
CM1 with direct tablet formation	−19%	−6%	8%	−22%	−6%	9%
CM1R with roller compaction	−33%	−20%	−6%	−40%	−22%	−6%
CM1 with roller compaction	−19%	−6%	8%	−22%	−6%	9%

^a Annual OpEx dollar amounts are provided in square brackets for the base case of a batch process.

Table 10. Summary of Present Cost Differences for All Process Options, Relative to Batch Case^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
batch (basis for differences)	[\$1515M]	[\$2337M]	[\$7472M]	[\$5117M]	[\$9225M]	[\$34902M]
CM1R with direct tablet formation	−32%	−22%	−9%	−40%	−24%	−9%
CM1 with direct tablet formation	−21%	−10%	4%	−24%	−9%	5%
CM1R with roller compaction	−30%	−21%	−9%	−40%	−23%	−9%
CM1 with roller compaction	−20%	−9%	4%	−23%	−8%	5%

^a Present cost is the total discounted cost of the project, excluding any revenue, for the 15-year project lifetime. Present cost dollar amount is provided in square brackets for the base case of a batch process.

Table 11. Summary of Present Cost Differences if CM1R Yield is 10% below Batch Yield^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
batch (basis for differences)	[\$1515M]	[\$2337M]	[\$7472M]	[\$5117M]	[\$9225M]	[\$34902M]
CM1R with direct tablet formation	−28%	−15%	3%	−35%	−14%	4%
CM1 with direct tablet formation	−16%	−1%	18%	−16%	3%	20%
CM1R with roller compaction	−27%	−13%	3%	−34%	−14%	4%
CM1 with roller compaction	−14%	0%	18%	−15%	3%	20%

^a Present cost is the total discounted cost of the project, excluding any revenue, for the 15-year project lifetime. Present cost dollar amount is provided in square brackets for the base case of a batch process.

expenses, so percentage savings are reduced. However, the working capital (in-process inventory) savings measured in dollars are increased moving toward higher KI price, since the batch process has 10 times more in-process inventory. For a given KI price, the percentage savings due to working capital is similar for high and low loadings. This may initially seem counterintuitive since the high-loading processes require five times more KI, the most expensive raw material. However, the high-loading cases also have about four times greater overall cost than the corresponding low-loading cases, so the percentage savings are similar.

In the low API loading scenarios, the largest savings consistently come from (first) other raw materials, (second) utilities, (third) waste handling, (fourth) CapEx excluding working capital, (fifth) labor and materials handling, (sixth) QA/QC, and (seventh) other organic reagents. The significance of working capital varies depending on the KI price; it is the first, sixth, or eighth contributor to cost savings for KI prices of \$3000/kg, \$500/kg, and \$100/kg, respectively.

In the high API loading scenarios, the largest savings consistently come from (first) other raw materials, (second) utilities,

(third) labor and materials handling, (fourth) waste handling, (fifth) QA/QC, (sixth) other organic reagents, (seventh) CapEx excluding working capital. The significance of working capital again depends on the KI price; it is the first, fifth, or seventh most significant contributor to cost savings for KI prices of \$3000/kg, \$500/kg, and \$100/kg, respectively.

DISCUSSION

Batch and continuous production of a very large-scale pharmaceutical product produced in dedicated batch or continuous plants was analyzed. This is one of the first market segments in which continuous pharmaceutical manufacturing may be implemented. Overall cost savings of 9 to 40% are predicted if the appropriate process is selected for the API loading/KI price scenario at hand. The novel process with recycling (CM1R) with direct tablet formation is consistently one of the most favorable processes, with the same or slightly more savings than CM1 with roller compaction. Percentage savings are greatest when KI prices are lower. This is because the expenditure for the KI is the same in batch and CM1R, that expenditure is proportional to KI price, and all other expenses

Table 12. Summary of Present Cost Differences if CM1R Yield is 10% above Batch Yield^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
batch (basis for differences)	[\$1515M]	[\$2337M]	[\$7472M]	[\$5117M]	[\$9225M]	[\$34902M]
CM1R with direct tablet formation	−35%	−28%	−19%	−44%	−31%	−19%
CM1 with direct tablet formation	−25%	−17%	−7%	−30%	−18%	−6%
CM1R with roller compaction	−33%	−27%	−18%	−44%	−31%	−19%
CM1 with roller compaction	−24%	−16%	−7%	−29%	−17%	−6%

^a Present cost is the total discounted cost of the project, excluding any revenue, for the 15-year project lifetime. Present cost dollar amount is provided in square brackets for the base case of a batch process.

Table 13. Contributions to Present Cost Difference Relative to Batch for Novel Continuous Process with Recycling (CM1R) with Direct Tablet Formation^a

cost of KI :	API mass loading = 10%			API mass loading = 50%		
	\$100/kg	\$500/kg	\$3000/kg	\$100/kg	\$500/kg	\$3000/kg
organic reagents	−2.2%	−1.4%	−0.4%	−3.2%	−1.8%	−0.5%
KI	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
other raw materials	−8.0%	−5.2%	−1.6%	−11.9%	−6.6%	−1.7%
excipients	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
labor and materials handling	−4.1%	−2.6%	−0.8%	−5.3%	−3.0%	−0.8%
waste handling	−4.4%	−2.8%	−0.9%	−5.0%	−2.8%	−0.7%
utilities	−4.7%	−3.0%	−0.9%	−6.9%	−3.8%	−1.0%
QA/QC	−2.9%	−1.9%	−0.6%	−4.3%	−2.4%	−0.6%
CapEx excluding working capital	−4.2%	−2.7%	−0.8%	−1.6%	−0.9%	−0.2%
working capital/in-process inventory	−1.6%	−2.2%	−3.1%	−1.7%	−2.5%	−3.2%
total:	−32%	−22%	−9%	−40%	−24%	−9%
	=[−\$485M]	=[−\$513M]	=[−\$689M]	=[−\$2048M]	=[−\$2188M]	=[−\$3066M]

^a Difference in present cost relative to batch case is provided in square brackets. Contribution to present cost difference relative to batch is defined by eq 4. Since the continuous yield is identical to the batch yield, the contribution of KI cost to overall savings is identically zero in all cases.

except working capital are insensitive to KI price. That is, as KI price approaches infinity, present cost savings approach the working capital savings from the reduced in-process inventory.

The process development costs will tend to be greater for continuous manufacturing processes as opposed to batch processes, because the pharmaceutical industry has less experience with continuous processing and the absence of conventional batches in the highly regulated industry demands more process understanding and online instrumentation (i.e., PAT). This was accounted for as a 10% price premium for continuous processing equipment at the same scale as an equivalent batch process. With the current trend toward smaller continuous processes (e.g., microreactors), however, more process understanding will be obtained at early stages of the process development, making scaleup easier and less expensive over time. Furthermore, the smaller scale required for each unit in a continuous process (due to greater effective utilization time) usually offsets the additional process understanding and control required. Some unit operations are easier to characterize in continuous mode: Dhenge et al.¹⁸ claims that continuous granulation processes can be developed more quickly, with associated savings in API material during development. Once the process is operational, labor costs are typically lower as well.

The capital expenditure for the novel direct tablet formation process was based on a vendor quotation, but since it has not

been used in the pharmaceutical industry, the equipment cost is subject to more uncertainty than most of the other costs. A typical Wroth factor for the process under consideration in other industries is about 2.0, but the standard value for “other equipment” of 3.5 has been assumed (cf. Table 3). This assumption allows for cost increases specific to the pharmaceutical industry and may be unnecessarily high, meaning that the realized cost savings for the direct tablet formation process may be greater than those estimated here. The novel direct tablet formation process should also be more broadly applicable than roller compaction and eliminate other costs related to powder handling that are not considered in this study. In addition to the direct tablet formation approach reported here, we are developing another novel tablet formation process (not yet published) that should have significantly better yields than roller compaction.

Although different aspects of continuous pharmaceutical production have been analyzed,^{1,8,9,12} no articles have been published comparing the overall economics of batch and continuous pharmaceutical processes producing drug product (tablets) from an organic key intermediate. A presentation at the American Association of Pharmaceutical Scientists meeting on Drug Product Manufacturing claimed 58% CapEx savings and 67% annual OpEx savings for a continuous pharmaceutical processing facility versus a batch processing facility.¹⁹ A study on production of ethanol

estimated 57% CapEx savings by shifting the process from batch to continuous mode.²⁰ A study on production of cell culture media estimated overall cost savings at 34% for switching from batch to continuous production at 100 000 L/year capacity.²¹ A study on production of fine chemicals on dedicated batch versus continuous equipment found that continuous production is economically favorable at all production levels studied (as low as 200 t/year).²² Thus, this case study of a specific pharmaceutical product found results similar to those found in other industries.

Some areas of continuous processing in pharmaceuticals are well understood, whereas others require further study. Microreactors and other continuous-flow reactors have received quite a lot of study;^{7–9,23,24} however, efficient chemistry for the particular product being produced is absolutely crucial. Particularly in the case of high KI price, a 10% yield difference can shift a continuous process from providing cost savings to providing cost increases (see Tables 11 and 12). Continuous granulation processes have also been widely studied.^{4,18,25–30} On the contrary, studies on continuous crystallization for pharmaceuticals has been lacking until recently.³¹ The recent research is promising: one study found that the purification of an API using a continuous oscillatory baffled crystallizer is much more predictable to scale up than batch crystallization, as well as having a lower residence time: the continuous process took 12 min as opposed to 9 h and 40 min using the batch process.³¹ The easy scaleup in this type of continuous crystallizer compares favorably with the 10 different schemes for scaling-up batch crystallization enumerated by Lawton et al.^{31–43} Despite recent promising results on continuous crystallization of pharmaceuticals, appropriate solvents and conditions must be chosen for each specific purification step in each particular manufacturing process. Other effective separations technologies may become more promising under continuous mode as well.^{44–47} Vervaet and Remon⁴ wrote a review article on six different methods of continuous granulation. The best-studied method for continuous granulation is extrusion, on which the first papers for pharmaceutical applications were published in 1986,²⁵ and much subsequent work has been completed.^{18,26–30} Commercial equipment for creating the final dosage form such as continuous tableting and coating is already available; alternative methods for doing so may prove even more efficient.

Apart from considerations of continuous pharmaceutical manufacturing unit operations, more economic analysis and system-level research is also required, specifically, analysis of smaller-scale production and the considerations of a multipurpose continuous production line rather than a line dedicated to a single product. For example, how much time is needed to change between products, and how much waste material is generated during startup and shutdown, when the production line has not reached steady state, as well as the economic implications thereof. Plantwide dynamic models are essential for this task.⁴⁸

CONCLUSION

An integrated cost estimation of the production of a final drug product from a key organic intermediate was performed, using a batch process and four continuous processes. To make the analysis applicable to a wider range of products, the analysis was performed with two API loading levels in the final drug product, three prices for the most expensive KI organic feedstock, three continuous API synthesis processes, and two continuous drug product formation processes. The overall cost of production can be reduced most by changing to the continuous

process with recycling (CM1R) with the novel direct tablet formation process in all scenarios tested if overall yields for the continuous process meet or exceed those of the batch process; in those two yield scenarios, the savings are 9 to 40% and 19 to 44%, respectively. If the CM process with recycling has 10% lower yield than the batch plant, savings can be achieved for all scenarios except the highest KI price. The break-even KI price is \$1700/kg. Again, the maximal savings can be achieved by choosing process CM1R with the novel direct tablet formation process. When combining the economic advantage with more consistent product quality and greater regulatory freedom, continuous manufacturing of pharmaceuticals is a viable way for the pharmaceutical industry to achieve substantial cost savings. Many opportunities for further study exist: developing more efficient chemical routes, separations technologies, final dosage form production, and plantwide modeling are all expected to lead to more economical processes.

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ABBREVIATIONS

API = active pharmaceutical ingredient
BLIC = battery-limits installed cost, US\$
Bx = batch manufacturing process
CapEx = capital expenditures, US\$
CCM = Novartis-MIT Center for Continuous Manufacturing
CM1 = novel continuous manufacturing process
CM1R = novel continuous manufacturing process with recycle
DP = drug product (final dosage form)
DTF = direct tablet formation
FOB = free on board (cost of equipment before delivery), US\$
KI = key intermediate
LLE = liquid–liquid extraction
NPV = net present value
OEE = overall equipment effectiveness
OpEx = operating expenditures, US\$
PAT = process analytical technology
QA/QC = quality assurance/quality control
RC = roller compaction

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