Continuous pharmaceutical process engineering and economics

Citation for published version:

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
Chemistry Today

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Abstract
Continuous Pharmaceutical Manufacturing (CPM) emerges as a ground-breaking technology which can invigorate the global pharmaceutical industry by sustainably fostering its agility and the affordability of healthcare for large populations. Continuous production methods feature numerous significant technical advantages, which however need to be ensured by robust, scaleable chemistry, systematic process design and efficient Process Analytical Technology (PAT) for control. Quality by Design (QbD) must be achieved by a relentless pursuit of efficiency in energy and solvent use, but above all the business case for a product must be strong enough to cover both synthesis and process R&D against competition. Remarkable corporate investments in production-scale CPM facilities illustrate the value and promise of this paradigm. This paper focuses on applications of process systems engineering methodologies (flowsheet modelling and simulation) toward evaluating the technical efficiency, environmental impact and economic viability of two continuous processes. Original final upstream separation results for ibuprofen and recent ones for plantwide CPM economics are discussed.

INTRODUCTION
Pharmaceutical processes are broadly distinguished in batch (the overwhelming majority) and continuous (a growing minority): in either case, a process comprises a primary (upstream) and a secondary (downstream) part: the first addresses production of the Active Pharmaceutical Ingredient (API or Drug Substance, DS), while the latter focuses on mixing the API with excipients to manufacture the final marketed formulation (Drug Product, DP).

The incentive for technically sound and economically viable CPM (1) depends on each business case, but also on technical advances in organic synthesis, multiphase flow units and process automation (2). The business aspect has paramount importance for deciding if a CPM process should even be evaluated (3). The economic viability is determined using several factors: the total manufacturing cost comprising capital (CapEx) and operating (OpEx) expenditures, the product selling price, marketing costs, and often product and/or technology licensing costs (4).

Batch organic synthesis of API molecules at laboratory and production scale is an arduous procedure, in which long sequences of separate reactions are performed in large reactors, with purification steps conducted between successive stages. This normally effective procedure is also extremely wasteful: the E-factor (waste-to-product ratio) is as high as 25-100 for APIs, indicating that 25-100 kg of waste are generated for every 1 kg of API produced (petrochemical industries have E << 1). Reducing the manufacturing cost is possible via fewer reactions, fewer separations and more efficient unit operations. Disruptive microreactor technology enables previously unattainable syntheses, which are now possible via dramatic intensification (much higher concentration, pressure, temperature) and/or drastic reaction time reduction (flash chemistry), in which hazardous reactions can be safely performed and highly unstable intermediates can be used in flow (5-6). Precise reaction time control (< 1s) yields higher selectivity, economising on unit size (lower CapEx) and materials (lower OpEx). Microreactors facilitate rapid and efficient scaling up of flow syntheses, unleashing CPM potential due to several key advantages (7). Several continuous flow microreactors can accommodate catalyst immobilisation, gas handling and multiphase reactions, ensuring process intensification due to their high mixing efficiency, effective heat removal and low process inventories (8-10). Common pharmaceutical syntheses include hydrogenations, nitrations, fluorinations, oxidations and organometallic reactions.

The most important contributions which hold the promise to revolutionise the global pharmaceutical industry by facilitating the advent of CPM processes can thus be summarised in synthetic chemistry and process engineering, as:
**CONTINUOUS FLOW SYNTHESSES**

A rapidly growing body of literature details the quest for organic synthesis routes to replace batch with CPM processes. Continuous synthesis studies illustrate the production of ibuprofen (15), artemisinin (16) and 6-quinolone (17), and an extensive review covers a wide range of APIs (6). Process modelling, simulation (18-19) and optimisation (20) are key in CPM process analysis.

The flowsheet presented in Figure 1 considers a series of 3 plug flow reactors (PFRs) toward producing ibuprofen (15). Isobutylbenzene (IBB) is mixed with propanoic acid and neat triflic acid (TfOH); the mixture enters the first reactor (150 °C), where IBB undergoes Friedel-Crafts acylation to produce a ketone (2). The outlet stream is cooled (0 °C) and then reacts with a cold (0 °C) solution of diacetoxycetyloobenzene, PhI(OAc)₂, in a mixture of trimethyl orthoformate (TMOF) and methanol (MeOH). The combined stream is fed to the second reactor (50 °C), where intermediate 2 undergoes PhI(OAc)₂-mediated 1,2-aryl migration to produce an ester (3). The outlet stream is mixed with a methanol-water KOH solution and fed into the third reactor, where 3 undergoes base hydrolysis and is converted to the salt form of the API, K-ibuprofen.

**ENVIRONMENTALLY BENIGN, EFFICIENT SEPARATIONS**

Efficient continuous separations which can achieve high API recovery and low waste generation are essential for CPM. Reactor effluent streams often carry large excess reagent quantities for recycling and by-products for elimination. Ensuring that a high-purity API stream can be fed to downstream processing is critical toward final dosage formation. Successful separation design must satisfy technical, regulatory but also environmental constraints, and the E-factor (ratio of API mass produced over total waste generated) is a convenient metric for evaluating how benign a process is.

Systematic unit operation modelling and simulation is very useful in designing and operating efficient separations: one of the several choices available is Liquid-Liquid Extraction (LLE), here explored in the context of ibuprofen CPM. Judicious selection of LLE solvents is key from a technical (efficiency) as well as an environmental (waste) viewpoint. For LLE design, stream F20 is assumed to be a binary (water-methanol) mixture which carries several solutes, and multicomponent thermodynamics (the UNIFAC method) have been used to compute effluent compositions upon solvent addition and phase separation at ambient (25 °C) as well as effluent (65 °C) temperature, to facilitate comparisons (18). Thermodynamic equilibrium between the aqueous and the organic phase is taken to be rapidly established in the unit, with crystallisation and precipitation phenomena negligible. The API distribution in effluent (organic/O, water/W) streams relies on assuming that the ibuprofen partition coefficient is equal to the ratio of corresponding solubilities in each phase. Technical (recovery) and environmental (E-factor) metrics for two solvents n-hexane and toluene are depicted in Figure 2.

Increasing solvent feed is technically and environmentally detrimental, inducing lower recoveries and higher E-factors.

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- New, robust and more efficient chemical pathways are discovered and demonstrated for many APIs (5, 6, 11, 12).
- New miniaturised, multi-purpose reactors are developed and effective for a wide spectrum of conditions (8-10).
- New miniaturised separators are integrated in several pilot- and production-scale plant demonstrations (13-14). Moreover, plantwide process modelling and simulation are instrumental toward CPM design, optimisation and control.
but to this day very few peer-reviewed publications have quantitatively evaluated the projected economic performance benefits. Envisaging that the promise of higher yields and selectivities will result in lower capital (CapEx) and operating (OpEx) costs as a result of continuous operation is plausible, but very few comparative evaluations of options have appeared. Roberge et al. (21) published a techno-economic analysis of process alternatives for an annual capacity of 700 kg, identifying clear economic benefits (albeit without analysing the entire process, from raw materials to final product formulation).

Schaber et al. (22) investigated the economic impact of operating an integrated CPM plant using an organic key intermediate (KI) and three organic reactions to derive the API, toward subsequent tablet formation, at an annual blockbuster drug production scale (2000 tons) and for several design parameters. The batch process has been evaluated for a set of four key CPM process variants (roller compaction/RC or direct tablet formation/DTF, with/without recycle). Three pivotal sensitivity variables (Key Intermediate/KI cost, 100-3000 USD/kg; production yield, ±10% vs. batch; tablet API load, 10 and 50 wt%) are employed for each variant, indicating a strong incentive for CPM implementation. Process flow diagrams for both pharmaceutical processes considered are illustrated in Figures 3 and 4, respectively. Seifert et al. (23) conducted an economic analysis of modular CPM in comparison to multi-product batch manufacturing plants, identifying that the former results in a 30% Net Present Value (NPV) increase over the latter: a further 35% NPV increase was obtained under the assumption that construction can be completed within one year.

The summary of CapEx, OpEx and total cost comparisons for all CPM cases considered by Schaber et al. (2011) is presented in Figure 5. The highest production cost reduction is obtained for a switch from batch to CPM with recycle (R) and tablet formation (TF), options; the alternative technology of roller compaction (RC) is also advantageous, but not in all cases without a recycle stream. Depending on KI production cost, total (CapEx+OpEx) cost savings range between 9-40% when batch and CPM yields coincide, but increase considerably (19-44%) if the latter exceeds the former. Total cost savings remain noteworthy even for a CPM yield lower than the corresponding batch, due to the enormous CapEx savings achieved when using smaller, cheaper units. OpEx savings are due to lower labour and water/solvent costs (61% and 21%, respectively), but they illustrate higher KI price sensitivity. Another detailed techno-economic analysis for ibuprofen and artemisinin further corroborates the strong incentive for CPM processes due to the remarkable cost savings attainable by continuous flow synthesis and efficient separations (24).

Hexane is superior to toluene in terms of LLE operability, due to a wider immiscibility window at low solvent feed ratios; it also achieves higher, less wasteful API recovery than toluene in the entire solvent feed range at ambient temperature. Nevertheless, the trend is reversed for the higher (PFR3 effluent) temperature (65 °C), in which toluene is clearly more advantageous, as it offers consistently higher and marginally less wasteful API recovery, as long as phase immiscibility is ensured: the most technically efficient and environmentally benign LLE operation is achieved for ratios below 1 (0.75).

COST SAVINGS AND ECONOMIC BENEFITS

Numerous research studies highlight the incontrovertible technical advantages of CPM over batch processes,
CONCLUSIONS

The remarkable benefits of continuous over traditional batch processes for manufacturing APIs and organic intermediates are enormous and clearly documented, as the gradual adoption and industrial implementation of CPM concepts can result in significant technical as well as economic gains: CapEx savings are attainable via fewer unit operations and smaller footprint required, while OpEx savings emerge due to increased productivity (higher yield and selectivity), reduced materials, labour and waste. Microreactors improve heat and mass transfer rates spectacularly, enabling reaction intensification under reliable control. First-principles process modelling, simulation and optimisation (18-20) are pivotal enabling technologies toward rapid evaluation of process (flowsheet and unit operation topology) and operation (solvent selection) alternatives, and critical in accelerating R&D by systematic design of reactors and separators which demonstrably achieve optimal performance. Finally, this methodology can seamlessly accommodate detailed and comprehensive economic analyses (21-24) toward comparison with existing or potential batch counterparts, to investigate a priori the economic viability of CPM processes.

REFERENCES