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Design space investigation for development of continuous flow syntheses of active pharmaceutical ingredients

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Abstract

Continuous flow chemistry and synthesis have received significant attention over the past two decades for their potential for enhancing yields, selectivities, productivities, smaller operation and implementation of otherwise difficult/dangerous reactions. Recent demonstrations applied to a variety of different reaction types have highlighted the potential for continuous manufacturing technologies for fine and speciality chemical production, including many critical Active Pharmaceutical Ingredients (APIs) but also many biopharmaceuticals and therapeutics. This study discusses recent demonstrations from the literature on design space elucidation for continuous API production and further highlights attainable regions of recoveries, material efficiencies, flowsheet complexity and cost components for upstream (reaction + separation) via modelling, simulation and nonlinear optimisation studies, providing insight into optimal regions of operation.

Keywords: Continuous flow synthesis; Active Pharmaceutical Ingredients (APIs); pharmaceutical manufacturing; design space investigation; comparative evaluation.

1. Introduction

1.1 Continuous flow synthesis

The development of continuous flow technology and synthetic strategies by chemists and engineers has been the focus of significant research attention over the past two decades due to the wide variety of chemical processes whose performance can be improved or intensified by switching from batch to continuous flow operation. Operating continuously allows for smaller equipment dimensions, wherein mixing and heat transfer are significantly enhanced and thus improving yields, selectivities, productivities and allowing access to operating windows (e.g., high pressure/temperature, avoiding prolonged presence of hazardous intermediates, circumventing requirements for cryogenic conditions) that would be otherwise unsafe if implemented in batch mode.

1.2 Continuous manufacturing of active pharmaceutical ingredients

There has been significant research focus on continuous Active Pharmaceutical Ingredient (API) production due to pressure on the pharmaceutical industry to reduce drug development times, minimise product quality variation, process performance deviations, overall costs and environmental impact via lower capital and operating expenditures that are inherent of the smaller equipment and material usage reductions with continuous operations. The chemistry, chemical engineering and process systems engineering communities have approached both unit operation and plantwide Continuous

Pharmaceutical Manufacturing (CPM) processes from both experimental (lab-based and pilot plants) and theoretical (mathematical modelling, simulation and optimisation) perspectives to elucidate promising designs for optimal continuous API synthesis.

1.3 This work: Integrated upstream continuous pharmaceutical manufacturing

The majority of design space investigation studies in the literature focus on the attainment of optimal unit operation performance or specified product quality attributes. Consideration of technoeconomic and environmental impacts of different designs are also important for the selection of feasible and viable process operating regions. Modelling and simulation aids design space elucidation without labour-intensive experiments. In this study, we discuss design space investigation efforts for various upstream continuous reaction + separation processes for different APIs, encompassing both technoeconomic and material efficiency considerations of upstream CPM plantwide design considerations.

2. Relevant Literature

2.1 Design space investigation of flow reactors

The demonstration of continuous flow chemistry of an API is the foundation of any CPM process; however, subsequent purification, separation (upstream) and drug product formulation (downstream) unit operations are often challenging and expensive processes that must be considered in the comparative evaluation of different designs. Establishing feasible operating regions to the meet desired product quality and process performance targets is an important stage of design that has been implemented in various CPM studies.

Development of automated continuous flow systems for reaction optimisation has been a recent hot topic of research. Bédard et al. (2019) developed a continuous synthesis system composed of reagent/feedstocks and pumps and interchangeable reactor and separator modules with online analytics and a software interface for process control and reaction monitoring. The authors demonstrated a variety of pharmaceutically-relevant reactions in flow, elucidating optimal regions of operation regarding operating temperature, residence time, reagent ratios, catalyst and base loading. Wyvratt et al. (2019) characterised the design space of a Knoevenagel condensation by varying residence time and catalyst loading whilst minimising the number of experiments and material consumption required to adequately map the design space. Comparative evaluation of batch vs. continuous syntheses are also useful in quantifying technical and economic benefits of different production paradigms and flowsheet configurations. Ott et al. (2016) performed a Life Cycle Assessment (LCA) of different flowsheet configurations of batch vs. flow microreactor networks for rufinamide synthesis, considering various metrics related to plant material efficiencies and environmental impacts of different production options.

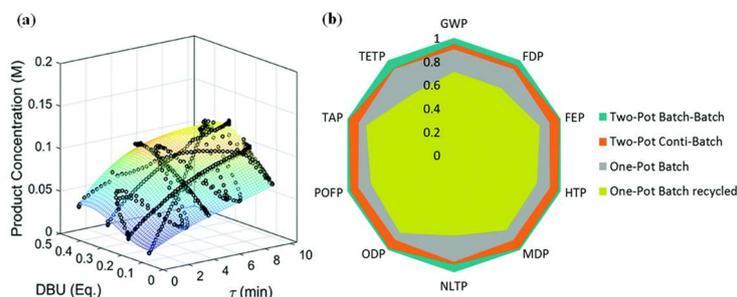


Figure 1: Flow synthesis design spaces: (a) Wyvratt et al., 2019, (b) Ott et al., 2016.

2.2 Design space investigation of separation processes

Design space investigation of separation options is also important when considering continuous API production. Gonzalez et al. (2019) used probabilistic modelling to establish the design space of a reaction and crystallisation to enhance process robustness and impurity control in the final product. The authors found a crystallisation combined with wet milling allowed greater robustness than a design without milling. Ridder et al. (2014) performed experiments and modelled the antisolvent crystallisation of flufenamic acid in a multisegment, multiaddition-plug flow crystalliser, where antisolvent feed rate to different tubular crystalliser segments was varied in order to either maximise the mean crystal size or minimise the product size distribution coefficient of variation. The authors presented Pareto fronts to show trade-offs between the two product quality attributes.

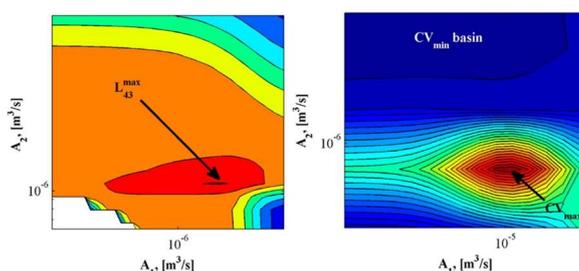


Figure 2: Design space of crystal quality vs. antisolvent addition (Ridder et al., 2014).

3. Plantwide design space investigation

In this study, we concentrate on upstream plantwide CPM studies we have previously done, encompassing both reaction (flow synthesis) and separation (continuous Liquid-Liquid Extraction (LLE) or antisolvent crystallisation) phenomena and unit operations as well as detailed Capital (CapEx) and Operating (OpEx) Expenditures cost components.

3.1 Upstream plantwide design case studies

Ibuprofen (analgaesic): three flow reactions followed by continuous Liquid-Liquid Extraction (LLE) with hexane (nHex) or toluene (PhMe) (Jolliffe and Gerogiorgis, 2016).

Artemisinin (antimalarial): two reactions and cooling-antisolvent crystallisation using ethanol (EtOH) or ethyl acetate (EtOAc) as antisolvents (Jolliffe and Gerogiorgis, 2016).

Diphenhydramine (antihistamine): one reaction followed by LLE with heptane (nHep), cyclohexane (CyHex) or methyl cyclohexane (MeCyHex) (Diab and Gerogiorgis, 2017).

Warfarin (anticoagulant): one reaction followed by continuous LLE with EtOAc, isopropyl acetate (iPrOAc) or isobutyl acetate (iBuOAc) (Diab and Gerogiorgis, 2018).

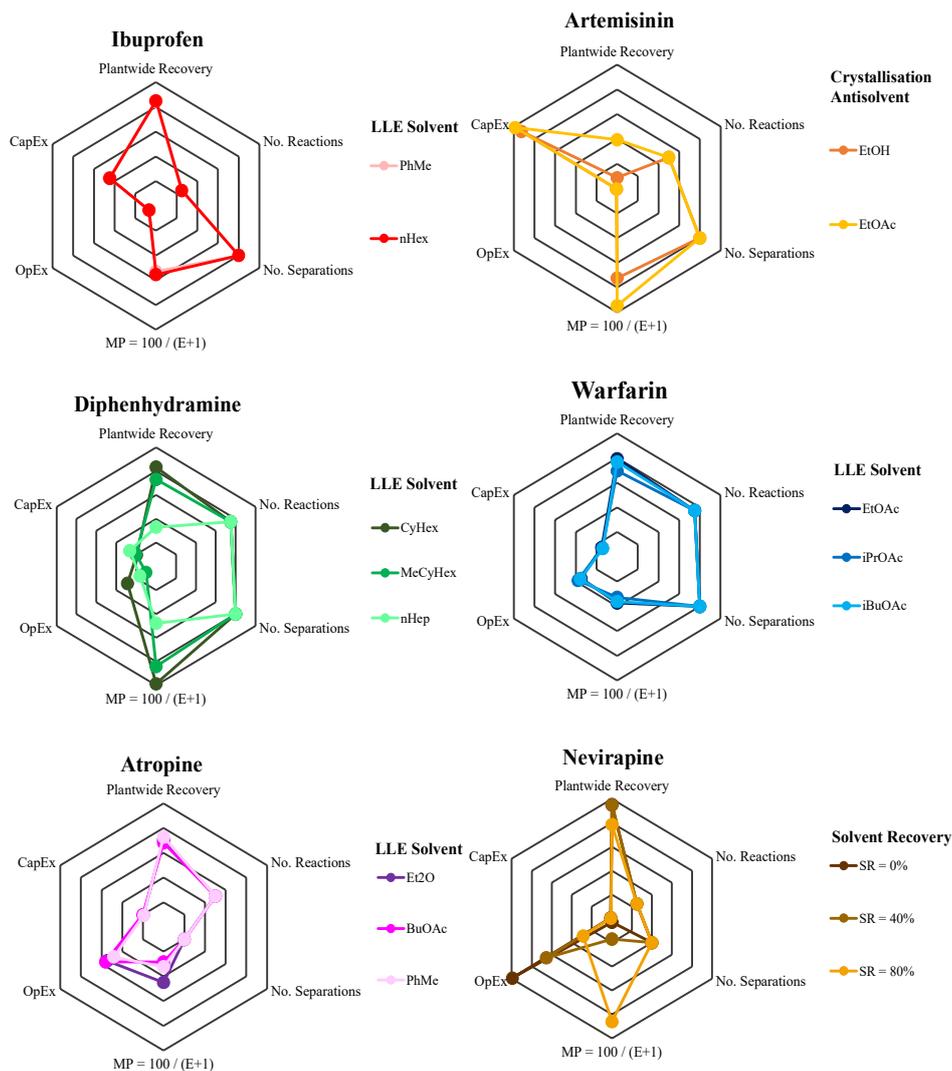
Atropine (nerve agent effects): three flow reactions followed by LLE utilising either diethyl ether (Et₂O), *n*-butyl acetate (nBuOAc) and PhMe (Diab and Gerogiorgis, 2019).

Nevirapine (HIV treatment): considers three flow reactions followed by crystallisation via pH change with different Solvent Recovery (SR) assumptions (Diab et al., 2019).

The extent of simulation/optimisation differs for each API case study. For ibuprofen, artemisinin and diphenhydramine, simulation studies are considered; for warfarin and nevirapine, nonlinear optimisation of the upstream plants have been implemented. Modelling, simulation and optimisation details are in the relevant literature references.

3.2 Technoeconomic analysis methodology

Process performance metrics encompassing technical performance, process intensity and costs are compared for different APIs and selected separation option. The process metrics considered are: plantwide API recovery, Mass Productivity (MP = 100 / E-factor, a measure of how efficiently material is used in a process), number of reaction and separation stages (a measure of process intensity) and CapEx and OpEx cost components per unit mass of API produced. Fig. 3 shows a radar plot of these metrics for each API.



	Plantwide Recovery (%)	MP (%)	Reactions (#)	Separations (#)	CapEx (10^3 GBP kg^{-1})	OpEx (10^3 GBP kg^{-1})
min	30	0.6	3	4	10	0
max	100	3.6	1	1	420	230

Figure 3: Performance metrics of various CPM processes for different APIs.

Each axis (process performance metric) in Fig. 3 bear different meaning depending on whether they have a high or low value. Clearly, high plantwide recoveries and MP but lower cost components are desirable. For the number of reaction and separation stages, reverse-ordered axes are used to illustrate that lower values are preferable (i.e., fewer unit operations equate to lower process complexity). The maximum and minimum values of each axis in these axes are also provided in Fig. 3. For each API, the number of reactions and separation stages have the same coordinates for each different separation option.

3.3 Separation process design option selection

For ibuprofen, the different separation options (LLE solvent = {nHex, PhMe}) give similar results and thus the LLE solvent with the lower environmental/EHS impact (i.e., PhMe) is preferable (Jolliffe and Gerogiorgis, 2016). Similarly, for warfarin and atropine, each considered LLE solvent performs similarly, however, each also have similar EHS characteristics; solvent selection should thus be informed by subsequent crystallisation process design (Diab and Gerogiorgis, 2018; 2019). For artemisinin and diphenhydramine, plantwide techno-economic performance varies more drastically with separation solvent choice; for artemisinin, EtOH as antisolvent allows for lower costs and is more environmentally friendly than EtOAc (Jolliffe and Gerogiorgis, 2016), and for diphenhydramine, nHep has both poorer EHS characteristics than either CyHex or MeCyHex as well as incurring higher costs (Diab and Gerogiorgis, 2017). For nevirapine CPM, various values of solvent recovery are considered (SR); whilst high SR (= 80%) is attainable in lab-scale conditions, lower values are likely to be possible at larger scale operation. The assumed SR drastically affects OpEx, thus inducing the significant contribution of the latter towards total costs: here, OpEx >> CapEx (Diab et al., 2019).

3.4 Comparative evaluation and discussion

While comparing different APIs for their performance on a detailed level may not be considered so valuable given the widely varying process phenomena, highlighting typical regions of operation for different processes is useful. For example, the CPM designs for the considered APIs in this study have typical plantwide recoveries = 70–80%; although total cost components and material efficiencies vary, this highlights that beyond this API recovery, cost benefits are incremental at best and not worth the extra effort with respect to material consumption and increased equipment volumes required for higher flow rates. Quantification of dimensionless numbers for different continuous processes for different APIs may also provide valuable insight into the most promising regions of operation.

Total cost components (i.e., CapEx and OpEx) have been scaled per unit mass of API produced in the product streams of each upstream CPM plant for fair comparison where different plant capacities are considered. Each case study considered upstream plant total costs as the economic metric for comparative evaluation of different process designs. Comparison of optimal Net Present Values (NPVs) can also provide valuable insight and alternative process designs for different APIs, but are subject to API sales price variation, which may be quite significant for certain drugs (e.g., artemisinin). Ultimately, when choosing whether to switch to continuous operation, clear operational and economic benefits must be clear over traditional / current manufacturing methods for the API.

4. Conclusions

Demonstrated continuous flow synthesis of APIs pave the way for the design of CPM processes for lean and efficient production. Various demonstrations in the literature have elucidated operating regions and mapped design spaces on a technical basis at unit operation level. We have conducted technoeconomic plantwide analyses for upstream CPM (reaction + separation) for various APIs. Separation design is informed by technical, economic and EHS criteria. Currently, strategic pharma decisions on whether to design (or adopt) continuous operation are made on a case-by-case basis. Elucidating operating regions for demonstrated CPM for different APIs is an important step towards more systematic selection and screening of promising candidates for continuous production.

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