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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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INTRODUCTION

Batch manufacturing methods have historically dominated the pharmaceutical industry, with benefits of versatile equipment usage, specific batch recall, and well-established regulatory protocol (2). However, batch manufacturing necessitates large equipment, intensive labour (3), limited automation and frequent plant reconfiguration (4). Additionally, costs associated with R&D and bringing new drug products to market have drastically increased over previous decades (5). Increasing competition from new drug products to market have drastically increased the pharmaceutical industry, with benefits of versatile enterprises (6).

Continuous Pharmaceutical Manufacturing (CPM) is a new production paradigm receiving attention from the highest regulatory levels due to its potential for reduced costs, lower material requirements and waste handling and smaller footprints (7). CPM offers enhanced mixing and heat transfer efficiencies, safer operation under hazardous conditions and improved yields (8). However, CPM is yet to demonstrate the feasibility and viability of continuous separations in pharmaceutical manufacturing. Here, we present and discuss the steady-state process modeling results of the CPM for two APIs: diphenhydramine (this work) and artemisinin (17), whose conceptual continuous separations show improvements over the batch methods. API recoveries and material efficiencies are quantified for batch and continuous separation options. In both cases, a plant capacity of 100 kg API per annum and 8000 h of annual operation are assumed. Figure 1 shows conceptual flowsheets and demonstrated reaction pathways for the CPM of both APIs. Both APIs are produced in flow using plug flow reactors (PFRs), in accordance with experimental studies (24).

ATTAINABLE RECOVERIES AND MATERIAL EFFICIENCIES

API recoveries and material efficiencies for batch and continuous separations are compared. Material efficiencies are quantified by the environmental (E)-factor, the mass ratio of waste-to-product, and the mass productivity (MP), quantifying how efficiently material is used (12). Continuous separations are modelled as single-stage ideal processes. Efficiencies versus thermodynamic equilibrium (80, 90 and 90%) are compared for batch and continuous separation options. Material efficiencies for solvent removal are required to meet the desired feed concentration of the mixture at 5 °C. A flash evaporation in the toluene-antisolvent mixture at 40 °C, and the continuous crystalliser is considered at 90% API saturation in the toluene-antisolvent mixture at 40 °C, and the target mother liquor composition is the API saturation concentration at 5 °C. A flash evaporation for solvent removal is required to meet the desired feed composition. The API recovery is calculated as the thermodynamically possible crystallisation yield from these respective conditions.

ARTEMISININ

Artemisinin is traditionally produced by extensive downstream processes and extraction (27). A recently demonstrated continuous flow synthesis of the API utilizes antimalarial from the three-stage flow model of the continuously implemented batch separation, as a feedstock (26, 28). Toluene is the carrier solvent for the process (Figure 1). The demonstrated batch separation comprises 17 stages (including neutralisation, evaporation, drying, washing, crystallisations and filtrations) to obtain the API at 70.1% yield (26). Here, we consider continuous antisolvent crystallisation of artemisinin (similar to recent efforts for artemisinin crystallisation (21)), comparing ethyl acetate (EIOAc) and acetone (ACN) as candidate antisolvents (Figure 2). 5F ratios of 2.3 and 4 are considered for EIOAc and ACN, respectively. In both cases, the feed to the continuous crystalliser is considered at 90% API saturation in the toluene-antisolvent mixture at 40 °C, and the target mother liquor composition is the API saturation concentration at 5 °C. A flash evaporation for solvent removal is required to meet the desired feed composition. The API recovery is calculated as the thermodynamically possible crystallisation yield from these respective conditions.
For the continuous crystallisation of artemisinin from the ethyl acetate rinse, EIOAC achieves higher API recoveries (45.8–57.2%) than ACN (42.1–52.6%) as shown in Figure 3. The batch separation system attains an API recovery of 70.1% due to its extensive nature (23). EIOAC is the most promising antisolvent for CPM, attaining API recoveries comparable to ACN (Figure 3). A broader antisolvent consideration also includes safety, ecotoxicity and lifecycle assessment (31). Process Analytical Technology (PAT), high-fidelity instrumentation and (preferably model-based) automatic control strategies (28) are essential to ensure the optimal control of the process, and the minimisation of inevitable start-up and shut-down times.

Economic benefits of continuous separations

Demonstrating the cost savings benefits available via CPM is imperative in order to make a convincing business case. Our economic analysis compares the cost benefits available by implementing continuous thermally operated CPM (90% efficiency) versus thermodynamic equilibrium. EtOAc usage allows greater total cost savings than ACN compared to EtOAc. Total costs savings of 5.8–22.5% are attainable using EtOAc. For ACN, total costs savings of 6.5% and 14.5% are attainable for 90 and 100% efficiencies, respectively (23). In the designed continuous processes, an increase in total costs of 3.3% is incurred for 80% efficiency versus thermodynamic equilibrium. CPM usage allows greater total cost savings for all efficiencies than ACN. Its usage for continuous crystallisation of artemisinin is preferred. The present techno-economic analysis of both CPM processes indicates that continuous separation allows greater material efficiency and cost savings over batch separation methods. Process modelling for planarisation and economic analysis employed an essential assumption, and the scaling up of CPM processes can induce cost saving variations, as we have already demonstrated (18). Life-Cycle Analysis (LCA) investigations of plant operation and capacity effects are thus encouraged.

Conclusions

Continuous Pharmaceutical Manufacturing (CPM) has been established as a promising alternative to the currently implemented batch methods in the pharmaceutical industry. Process modelling and simulation facilitates the screening of candidate unit operations for purification of active pharmaceutical ingredients (APIs). The CPM case studies discussed here for two critical APIs, dihydroartemisinin and arteether (7), depict the benefit of material efficiency and cost savings attainable via continuous separation and the importance of separation solvent selection. A more detailed techno-economic analysis which highlights methodological background details has also been published elsewhere (34). Systematic process modelling and simulation approaches facilitate the quantification of enhanced process performance and the design of efficient, cost-effective separations, towards meaningful transitions to continuous manufacturing in the pharmaceutical industry.

Economic analysis of a CPM vs. batch separation process.

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REFERENCES