Process modelling, simulation and technoeconomic evaluation of separation solvents for the Continuous Pharmaceutical Manufacturing (CPM) of diphenhydramine

Technoeconomic Analysis of Separation Processes for Continuous Pharmaceutical Manufacturing:
Assessing Process Performance, Material Efficiency and Economic Viability

Samir Diab, Dimitrios I. Gerogiorgis*

Institute for Materials and Processes (IMP), School of Engineering, University of Edinburgh, The King's Buildings, Edinburgh, EH9 3FB, United Kingdom

Corresponding Author: D.Gerogiorgis@ed.ac.uk (+44 131 6517072)

Abstract
The pharmaceutical industry is currently dominated by the traditionally implemented, yet wasteful and inefficient, batch production paradigm. Continuous Pharmaceutical Manufacturing (CPM) shows potential to bring technological innovation, cost savings and environmental benefits to pharmaceutical firms. This paper describes the process modelling and simulation of CPM of two active pharmaceutical ingredient (API) cases: diphenhydramine (a globally-marketed antishistamine) and artemisinin (an important antimalarial drug), with focus on implementing a continuous separation process for each. The continuous liquid-liquid extraction of diphenhydramine and crystallisation of artemisinin are compared to the batch methods, in order to demonstrate the benefits of material efficiency and economic viability of continuous separations in pharmaceutical manufacturing.

1. Introduction
Batch manufacturing methods have historically dominated the pharmaceutical industry, with benefits of versatile equipment usage, specific batch recall, long residence times for exploring different reaction pathways (1), 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 generics manufacturers also poses a significant threat to pharmaceutical firm profitability. Technological innovation is required to ensure sustainability for pharmaceutical 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 input and waste handling and reduced footprints (7). CPM offers enhanced mixing and heat transfer efficiencies, safer operation under hazardous conditions and improved yields (8). However, CPM is yet to be widely adopted due to significant investments in batch infrastructures (2) and legislative constraints (9). Furthermore, challenges in scaleup and solids handling are critical issues to be addressed (10). To facilitate the transition from batch manufacturing, CPM benefits must be conclusively illustrated for active substances of societal importance and high global demand (11).

Pharmaceutical manufacturing is one of the most wasteful industrial sectors, producing 200 times more waste than petroleum manufacturing (12). Approximately 56% of this waste is attributed to solvent usage (13). Separations in upstream pharmaceutical manufacturing is particularly wasteful due to strict product purity requirements (14). To elucidate CPM waste reduction and economic benefits, continuous separation process alternatives must be investigated.

Candidate separation process screening via process modelling and simulation is critical prior to financial investments in experimentation and scaleup (15-16) as detailed in recent studies (11, 17-18). This work demonstrates the benefits of continuous separations by examining two API case studies: diphenhydramine, a popular antihistamine, and artemisinin (17), an important antimalarial drug. Theoretical modelling of conceptual continuous separations illustrates the importance of conducting technoeconomic analyses in the early stages of design to identify promising candidate CPM processes.

2. Green Continuous Flow Syntheses and Separations

To demonstrate the feasibility and viability of continuous separations in pharmaceutical manufacturing, promising unit operations must be investigated for integration into fully continuous CPM flowsheets. Continuous flow syntheses of a wide range of APIs and the development of continuous downstream processes is documented in the literature (19-23). Here, we present and discuss the steady-state process modelling 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 compared 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).

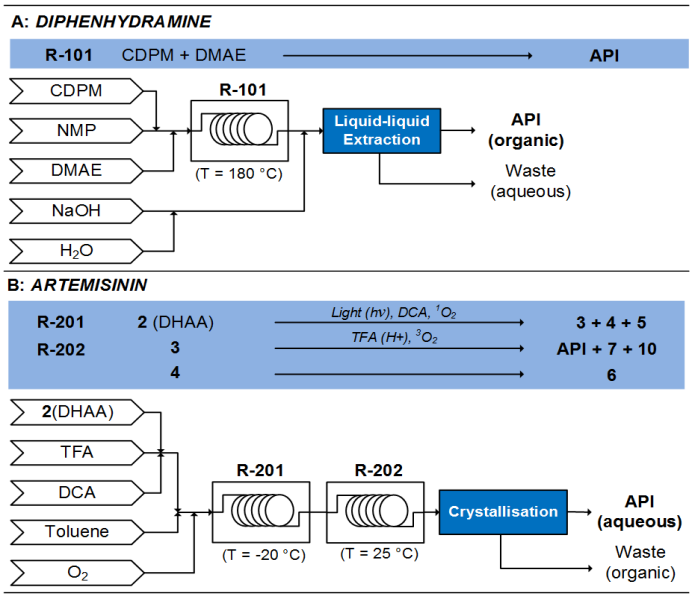

Figure 1: Conceptual flowsheets for continuous production of A. Diphenhydramine, adapted from Snead and Jamison, 2013 (25), B. Artemisinin (17), adapted from Kopetzki et al., 2013 (26).

2.1 Diphenhydramine

Diphenhydramine is most commonly used as a first-generation antihistamine and is globally marketed in various brand formulations (Benadryl®, Unisom®, Tylenol®, Zzzquil®). The continuous flow synthesis of diphenhydramine (25) features a single-step synthesis at 180 °C (Figure 1) between chlorodiphenylmethane (CDPM) and dimethylaminoethanol (DMAE) in carrier solvent, *N*-methylpyrrolidone (NMP). The demonstrated batch separation of diphenhydramine employs a three-stage liquid-liquid extraction (LLE) with diethyl ether, attaining an API recovery of 80% (25). We compare a single-stage continuous LLE separation (Figure 2) to the batch separation. Cyclohexane (CyHex) and methylcyclohexane (MeCyHex) are compared as continuous LLE solvents, considering an operating temperature of 20 °C and a solvent-to-feed ratio (S:F, mass basis) of 5.

Modelling of continuous LLE of diphenhydramine requires estimation of the composition of each liquid phase in the process and of the API solubility in each phase. Liquid-liquid and solid-liquid equilibria are estimated via the UNIFAC and NRTL models. The partition coefficient of API between liquid phases is assumed to equal the ratio of API solubilities in each phase.

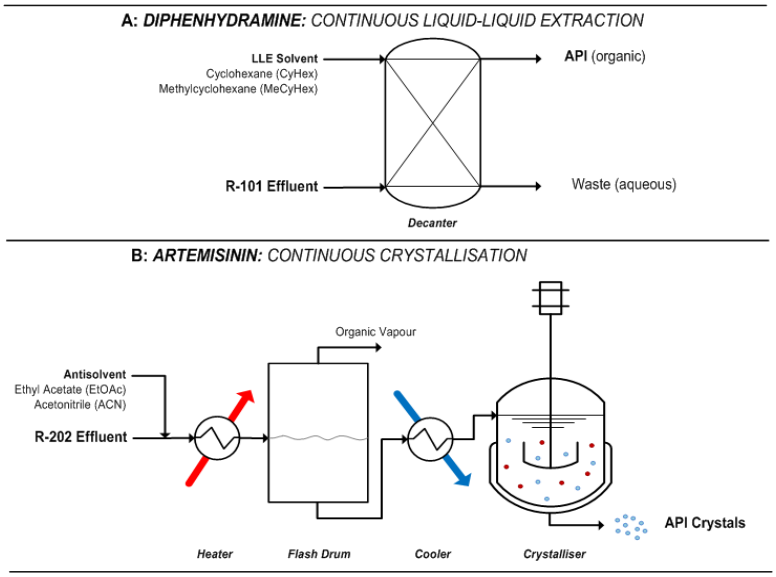

Figure 2: Continuous separation: A. Diphenhydramine (liquid-liquid extraction), B. Artemisinin (crystallisation) (17).

2.2 Artemisinin

Artemisinin is traditionally produced by extensive batch cultivation and extraction (27). A recently demonstrated continuous flow synthesis of the API uses dihydroartemisinic acid (DHAA), a waste component of the currently 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, washes, 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 (29)), comparing ethyl acetate (EtOAc) and acetonitrile (ACN) as candidate antisolvents (Figure 2). S:F ratios of 2.33 and 4 are considered for EtOAc 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 of the mixture at 5 °C. A flash evaporation for solvent removal is required to meet the required feed composition. The API recovery is calculated as the thermodynamically possible crystallisation yield from these respective conditions.

3. Attainable Recoveries and Material Efficiencies

API recoveries and material efficiencies for batch and continuous separations are compared. Material efficiences 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 100%) are considered to account for continuous stage inefficiencies.

3.1 API Recoveries

The continuous LLE of diphenhydramine attains API recoveries of 70.6−88.3% for CyHex and 64.9−81.1% for MeCyHex (Figure 3). Improved recoveries relative to the batch separation (25) are only attainable when 100% efficiency versus thermodynamic equilibria is assumed. This highlights the importance of considering stage efficiencies of continuous separation processes.

For the continuous crystallisation of artemisinin from the toluene-antisolvent mixture, EtOAc attains 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 (26). EtOAc is the most promising antisolvent for CPM, attaining a higher API recovery compared to ACN (Table 1). A broader antisolvent consideration must also include safety, ecotoxicity and life cycle assessment (31). Process

Analytical Technology (PAT), high-fidelity instrumentation and (preferably model-based) automatic control strategies (28) are essential to ensure the intended continuity of the process, and the minimisation of inevitable start-up and shut-down times.

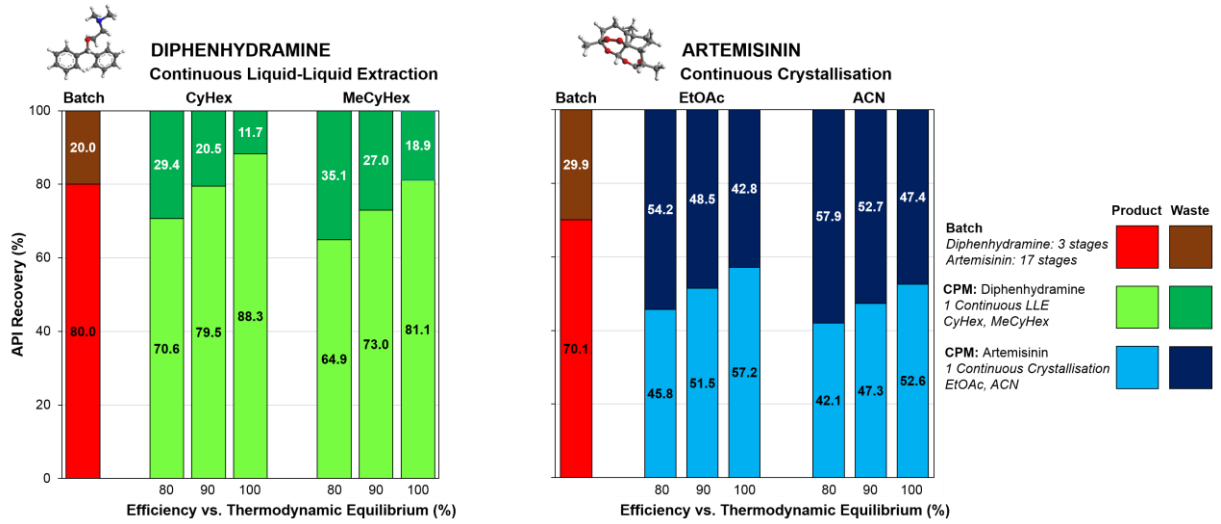

Figure 3: Comparison of performances of continuous separation schemes vs. batch separation methods (17).

3.2 Material Efficiencies: E-Factors and Mass Productivities

The continuous LLE of diphenhydramine incurs poorer material efficiencies (higher E-factors, lower MPs) than the batch separation for both LLE solvents (Table 1) due to the large volumes of LLE solvent required to attain comparable API recoveries. Nevertheless, computed E-factors and MPs are still acceptably low for pharmaceutical processes (30).

The continuous crystallisation of artemisinin is significantly more efficient is terms of material usage than the batch separation (26), as shown in Table 1. This is due to the greater number of unit operations and material requirements for the batch separation (26) compared to our conceptual continuous separation process (17-18).

Table 1: Environmental (E)-factors and mass productivities (MPs).

	DIPHENHYDRAMINE					ARTEMISININ				
	Batch	Efficiency vs. Thermodynamic Equilibria (%)	Continuous Liquid-Liquid Extraction (LLE)			Batch	Efficiency vs. Thermodynamic Equilibria (%)	Continuous Crystallisation	
			CyHex	MeCyHex				EtOAc	ACN
		80	34.3	39.0			80	21.8	27.7
E (—)	10.2	90	30.3	34.5	**E** (—)	65.3	90	19.3	24.6
		100	27.2	31.1			100	17.4	22.1
		80	2.8	2.5			80	4.4	3.5
MP (%)	8.9	90	3.2	2.8	**MP** (%)	1.5	90	4.9	3.9
		100	3.5	3.1			100	5.4	4.3

4. 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 separations. Capital (CapEx) and operating (OpEx) expenditures and total costs (adjusted for inflation) for a 20-year lifetime and a 5% discount rate have been calculated. The designed CPM plants are considered at an existing pharmaceutical manufacturing site, with essential auxiliary infrastructure available. Plant throughputs and unit size modelling consider reported reaction and projected separation efficiencies to meet the required plant capacity. Calculation of CapEx, OpEx and

total costs follow the methodology of a published CPM economic analysis (32). CapEx comprises battery limits installed costs and working capital and construction. OpEx comprises materials, utilities and waste handling requirements. Equipment and material prices are quoted from various vendors. Equipment costs have been scaled for varying unit size and year of purchase. Cost savings of continuous separation options relative to the batch separations are shown in Figure 4.

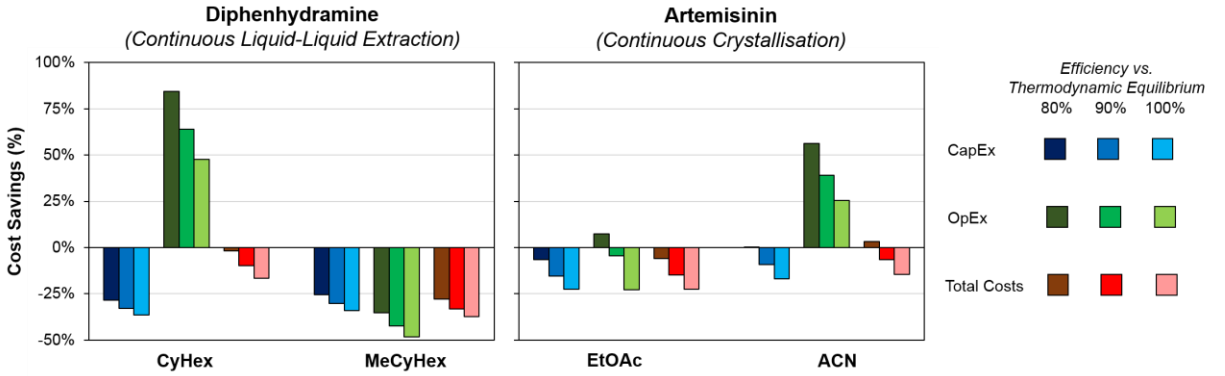

Figure 4: A comparative illustration of CapEx, OpEx and Total Cost of continuous separations (18).

Continuous LLE of diphenhydramine allows significant CapEx savings: 28.5−36.3% savings are available using CyHex, and 25.6−34.0% savings are available using MeCyHex (Figure 4). Such cost savings are attainable due to the reduced equipment dimensions via CPM (33). Using CyHex leads to 47.6−84.5% increase in OpEx due to the large solvent quantity (S:F = 5) required to meet the calculated API recovery and the high price of CyHex. Meanwhile, OpEx savings of 35.2−48.1% using MeCyHex are available, due to the lower material price compared to CyHex. The total costs savings benefits of implementing MeCyHex (27.9−37.4%) are significantly greater than for CyHex (1.7−16.4%). MeCyHex is the best candidate LLE solvent for CPM of diphenhydramine based upon the economics presented.

For the continuous crystallisation of artemisinin, CapEx savings of 6.6−22.4% are available for EtOAc usage. A slight increase in CapEx (0.3%) is incurred when assuming 80% efficiency versus thermodynamic equilibrium for ACN usage; CapEx savings of 9.2% and 16.9% are attainable when considering 90% and 100% efficiencies versus thermodynamic equilibrium, respectively. Such savings are mainly due to the significant reduction in equipment requirements for the continuous separation in comparison to the 17-step batch route (26). OpEx savings of 4.4% and 22.5% are attainable using EtOAc (for 90 and 100% efficiencies versus thermodynamic equilibrium, respectively), whilst an OpEx increase of 7.3% is incurred for 80% efficiency versus thermodynamic equilibrium. ACN usage leads to an OpEx increase of 25.5−56.2%. This difference is due to the poorer API recovery and high S:F required for 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 versus thermodynamic equilibrium, respectively), whilst an increase in total costs of 3.3% is incurred for 80% efficiency versus thermodynamic equilibrium. EtOAc usage allows greater total costs savings for all efficiencies considered; thus, its usage for continuous crystallisation of artemisinin is preferred.

The present technoeconomic analysis of both CPM processes indicates that continuous separation allows for significant material efficiency and cost savings over batch separation methods. Process modelling for plantwide simulation and economic analysis employ essential assumptions, 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.

4. 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 described here for two critical APIs, diphenhydramine and artemisinin (17), demonstrate the benefits of enhanced material efficiency and cost savings attainable via continuous separation and the importance of separation solvent selection. 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.

5. References

1. Hartman, R.L., McMullen, J.P., Jensen, K.F., "Deciding whether to go with the flow: evaluating the merits of flow reactors for synthesis", *Angew. Chemie-International Ed.* 50(33): 7502–7519 (2011).
2. Lee, S.L. *et al.*, "Modernizing pharmaceutical manufacturing: from batch to continuous production", *J. Pharm. Innov.* 10(3): 191–199 (2015).
3. Plumb, K., "Continuous processing in the pharmaceutical industry - changing the mind set", *Chem. Eng. Res. Des.* 83(A6): 730–738 (2005).
4. Behr, A. *et al.*, "New developments in chemical engineering for the production of drug substances", *Eng. Life Sci.* 4(1): 15–24 (2004).
5. Morgan, S. *et al.*, "The cost of drug development: a systematic review", *Health Policy (New. York)* 100(1): 4–17 (2011).
6. Yoshida, J., Nagaki, A., Yamada, D., "Continuous flow synthesis", *Drug Discov. Today. Technol.* 10(1): e53-9 (2013).
7. Jiménez-González, C. *et al.*, "Key green engineering research areas for sustainable manufacturing: a perspective from pharmaceutical and fine chemicals manufacturers", *Org. Process Res. Dev.* 15(4): 900–911 (2011).
8. Gutmann, B., Cantillo, D., Kappe, C.O., "Continuous-flow technology: a tool for the safe manufacturing of active pharmaceutical ingredients", *Angew. Chemie-International Ed.* 54(23): 6688–6728 (2015).
9. Federsel, H.-J., "En route to full implementation: driving the green chemistry agenda in the pharmaceutical industry", *Green Chem.* 15(11): 3105–3115 (2013).
10. Rogers, A., Ierapetritou, M., "Challenges and opportunities in pharmaceutical manufacturing modelling and optimization", *Comput. Aided Chem. Eng.* 34: 144–149 (2014).
11. Jolliffe, H.G., Gerogiorgis, D.I., "Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen", *Chem. Eng. Res. Des.* 97: 175–191 (2015).
12. Sheldon, R.A., "Fundamentals of green chemistry: efficiency in reaction design", *Chem. Soc. Rev.* 41(4): 1437–1451 (2012).
13. Constable, D.J.C., Jimenez-Gonzalez, C., Henderson, R. K., "Perspective on solvent use in the pharmaceutical industry", *Org. Process Res. Dev.* 11(1): 133–137 (2007).
14. Raymond, M.J., Slater, C.S., Savelski, M.J., "LCA approach to the analysis of solvent waste issues in the pharmaceutical industry", *Green Chem.* 12(10): 1826–1834 (2010).
15. Teoh, S.K., Rathi, C., Sharratt, P., "Practical assessment methodology for converting fine chemicals processes from batch to continuous", *Org. Process Res. Dev.* 20(2): 414–431 (2015).
16. Rossetti, I., Compagnoni, M., "Chemical reaction engineering, process design and scale-up issues at the frontier of synthesis: flow chemistry", *Chem. Eng. J.* 296: 56–70 (2016).
17. Jolliffe, H.G., Gerogiorgis, D.I., "Process modelling and simulation for continuous pharmaceutical manufacturing of artemisinin", *Chem. Eng. Res. Des.* 112: 310–325 (2016).
18. Jolliffe, H.G., Gerogiorgis, D.I., "Plantwide design and economic evaluation of two continuous pharmaceutical manufacturing (CPM) cases: ibuprofen and artemisinin", *Comput. Chem. Eng.* 91(1): 269–288 (2016).
19. Malet-Sanz, L., Susanne, F, "Continuous flow synthesis. A pharma perspective", *J. Med. Chem.* 55(9): 4062–4098 (2012).
20. Baumann, M., Baxendale, I.R., "The synthesis of active pharmaceutical ingredients (APIs) using continuous flow chemistry", *Beilstein J. Org. Chem.* 11: 1194–1219 (2015).

21. Porta, R., Benaglia, M., Puglisi, A., “Flow chemistry: recent developments in the synthesis of pharmaceutical products”, *Org. Process Res. Dev.* 20(1): 2–25 (2016).
22. Poechlauer, P., Manley, J., Broxterman, R., Gregertsen, B., Ridemark, M., “Continuous processing in the manufacture of active pharmaceutical ingredients and finished dosage forms: an industry perspective”, *Org. Process Res. Dev.* 16(10): 1586–1590 (2012).
23. Sen, M., Chaudhury, A., Singh, R., John, J., Ramachandran, R., “Multi-scale flowsheet simulation of an integrated continuous purification–downstream pharmaceutical manufacturing process”, *Int. J. Pharm.* 445(1–2): 29–38 (2013).
24. Mascia, S. *et al.*, “End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation”, *Angew. Chemie-International Ed.* 52(47): 12359–12363 (2013).
25. Snead, D.R., Jamison, T.F., “End-to-end continuous flow synthesis and purification of diphenhydramine hydrochloride featuring atom economy, in-line separation, and flow of molten ammonium salts”, *Chem. Sci.* 4(7): 2822–2827 (2013).
26. Kopetzki, D., Levesque, F., Seeberger, P.H., “A continuous-flow process for the synthesis of artemisinin”, *Chem. Eur. J.* 19(17): 5450–5456 (2013).
27. Hommel, M., “The future of artemisinins: natural, synthetic or recombinant?”, *J. Biol.* 7(10): 38 (2008).
28. Gilmore, K. *et al.*, “Continuous synthesis of artemisinin-derived medicines”, *Chem. Commun.* 50(84): 12652–12655 (2014).
29. Malwade, C. R. *et al.*, “Crystallization of artemisinin from chromatography fractions of artemisia annua extract”, *Org. Process Res. Dev.* 20(3): 646–652 (2016).
30. Ritter, S.K., “Reducing environmental impact of organic synthesis”, *Chem. Eng. News* 91: 22–23 (2013).
31. Henderson, R.K. *et al.*, “Expanding GSK’s solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry”, *Green Chem.* 13(4): 854–862 (2011).
32. Schaber, S.D. *et al.*, “Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study”, *Ind. Eng. Chem. Res.* 50(17): 10083–10092 (2011).
33. Ashe, R., “From batch to continuous processing”, *Chem. Eng.* 119(10): 34–40 (2012).