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Process modelling and simulation for continuous pharmaceutical manufacturing of artemisinin

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ABSTRACT

Recent advances in pharmaceutical manufacturing technologies are showing the promise of continuous production: pharmaceutical firms currently rely on mature batch technology but increasingly evaluate the potential of Continuous Pharmaceutical Manufacturing (CPM). Continuous production methods have efficiency, cost, reliability and quality advantages: in this paper we evaluate and quantify these for the case of CPM of artemisinin, a key antimalarial Active Pharmaceutical Ingredient (API). Published reaction and unit operation data are analysed, static models are developed, and continuous plug flow reactors are designed for a reference case producing 100 kg of API per year. The small reactor volumes computed (19.72 mL and 78.72 mL) illustrate the capital expenditure and small footprint benefits of continuous manufacturing. Alternative CPM cases are also developed, whereby different continuous API recovery operations are evaluated in comparison to the base case; the latter employs a reported batch product recovery. Employing published solubility data as well as data estimated using the UNIFAC method, our systematic evaluation identifies ethanol (EtOH) and ethyl acetate (EtOAc) as promising candidate antisolvents for continuous crystallisation. For the same 100 kg per year production level of API, designs using continuous separation techniques can achieve significantly improved E-factor values (22.52 average) compared to the batch process (65.28), implying enhanced sustainability through reduced waste generation. This API of critical societal importance is a very promising candidate for CPM, with the future benefits of performing full analysis and technoeconomic optimisation evident.

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1. Introduction

The pharmaceutical industry faces escalated pressure from market and technological drivers, including increasing R&D costs and competition from generic manufacturers (Behr et al., 2004; Jolliffe and Gerogiorgis, 2015a; Gerogiorgis and Jolliffe, 2015). The currently prevalent paradigm of batch manufacturing (the predominant method of pharmaceutical production) is thus challenged by Continuous Pharmaceutical Manufacturing (CPM), a new research field which has gained support at the highest regulatory levels (Plumb, 2005; Lee et al., 2015). Batch process efficiency can be very low, with high rates

of waste production and solvent use, while inherently poor heat and mass transfer lead to difficulties in process scale-up (Anderson, 2012; Germaey et al., 2012). In contrast, continuous production methods offer higher yields, smaller equipment, more efficient solvent and energy use, and safer, more reliable operation (Roberge et al., 2008; Anderson, 2012); the petrochemical, energy (Liu et al., 2007) and materials (Balomenos et al., 2014; Gerogiorgis et al., 2014) industries have benefited from the advantages of continuous processing for numerous decades, and the implementation of continuous manufacturing in the pharmaceutical industry appears exceptionally promising (Schaber et al., 2011; Jolliffe and Gerogiorgis, 2016b).

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Nomenclature

Latin letters

A'	interfacial area (m^2)
a^s	pure solid component activity
C_A	concentration of molecule A (mol L^{-1})
C_A^*	equilibrium concentration of molecule A (mol L^{-1})
$C_{A,0}$	initial concentration of molecule A (mol L^{-1})
$C_{A,W}$	aqueous phase concentration of molecule A (mol L^{-1})
C_p	specific heat capacity at constant pressure ($\text{J mol}^{-1} \text{K}^{-1}$)
d_{32}	Sauter mean droplet diameter (m)
$D_{A,O/W}$	diffusivity of molecule A in organic/aqueous phase ($\text{m}^2 \text{h}^{-1}$)
D_i	impeller diameter (m)
D_t	tank diameter (m)
E	environmental factor, dimensionless
E_o	Eotvos number, dimensionless
Fr_W	aqueous (continuous) phase Froude number, dimensionless
ID	internal diameter (mm)
k'	pseudo-first-order reaction rate constant (h^{-1})
k_i	rate constant of reaction i ($\text{L mol}^{-1} \text{h}^{-1}$) (second-order reaction)
k_O	organic phase film mass transfer coefficient (m h^{-1})
k_W	aqueous phase film mass transfer coefficient (m h^{-1})
K_W	overall mass transfer coefficient (m h^{-1})
L_i	UNIFAC compound parameter of r , q and z
m_{API}	mass of recovered API
m_{bpd}	mass of byproducts
m_{ur}	mass of unconverted reactants
m_{ws}	mass of waste solvent
m_{uAPI}	mass of unrecovered API
MW	molecular weight (g mol^{-1})
m_{waste}	mass of waste
$\dot{N}_{TFA}$	molar rate of trifluoroacetic acid transfer (mmol h^{-1})
Q_k	UNIFAC surface area parameter for functional group k
q_i	UNIFAC parameter for molecule i , a measure of van der Waals molecular surface area
R	universal gas constant ($8.3144 \text{ J mol}^{-1} \text{K}^{-1}$)
Re_i	impeller Reynolds number, dimensionless
R_k	UNIFAC volume parameter for functional group k
r_A	rate of reaction of molecule A ($\text{mol L}^{-1} \text{s}^{-1}$)
r_i	UNIFAC parameter for molecule i , a measure of van der Waals volume
S_i	selectivity of species i
Sc_W	aqueous (continuous) phase Schmidt number, dimensionless
Sh_d	organic (dispersed) phase Sherwood number, dimensionless
Sh_W	aqueous (continuous) phase Sherwood number, dimensionless
T	temperature (K)
T_{fus}	melting (fusion) point temperature (K)
t	time (h)

U_{mn}	UNIFAC energy interaction between groups m and n
X_A	conversion of molecule A at time t
$X_{A,f}$	final conversion of molecule A
x_i	mole fraction of molecule i
x_m	UNIFAC mole fraction of group m
x_i^{sat}	mole fraction at saturation (solubility)
Y_i	yield of species i
z	UNIFAC system coordination number (default value: 10)

Greek letters

Γ_k	UNIFAC residual group activity coefficient for group k
$\Gamma_k^{(i)}$	UNIFAC residual group activity coefficient in a reference solution of 100% i molecules
γ_i	Activity coefficient of component i
γ_i^C	UNIFAC combinatorial component of γ_i
γ_i^R	UNIFAC residual component of γ_i
γ_i^{sat}	Activity coefficient of component i at saturation
ΔH_{fus}	Enthalpy of fusion (J mol^{-1})
θ_i	UNIFAC molar-weighted area fractional component for molecule i
θ_m	UNIFAC summation of area fraction of group m over all different groups
$v_k^{(i)}$	UNIFAC number of occurrences of functional group k in molecule i
φ	Dispersed phase volume fraction
τ_i	Residence time in reactor i (h)
ϕ_i	UNIFAC molar-weighted segment fractional component molecule i
ψ_{mn}	UNIFAC group energy interaction parameter

Investigating the feasibility and viability of CPM processes via process modelling and simulation is a rapid and cost-efficient methodology which can quantitatively evaluate the potential benefits of continuous processes for pharmaceutical production (Gerogiorgis and Ydstie, 2005; Gerogiorgis and Barton, 2009; Jolliffe and Gerogiorgis, 2016a; Teoh et al., 2016). Furthermore, elaborate design and optimisation of multiphase unit operations are also possible, given the vast computational power and robust software now available for high-fidelity simulations (Gerogiorgis and Ydstie, 2003; Gerogiorgis et al., 2003); high-resolution model-based control studies can thus further advance the state of the art (Nayhouse et al., 2015).

We have previously shown how systematic analysis can identify good candidates for CPM, and have performed initial technoeconomic comparisons of the CPM of two key Active Pharmaceutical Ingredients (API), ibuprofen and artemisinin (1) (Jolliffe and Gerogiorgis, 2015a, 2015b; Gerogiorgis and Jolliffe, 2015, 2016a,b). Here, we present a detailed process model for steady-state simulation of the continuous production of artemisinin, one of the most effective anti-malarial APIs available today. The flowsheet used is adapted from published continuous chemical synthesis routes, the kinetics of which have been hereby analysed and used for parameter estimation and systematic reactor design (Kopetzki et al., 2013).

Malaria is a disease of extreme and global societal importance. There are an estimated 225 to 500 million annual cases of malaria from *Plasmodium falciparum* (the main strain of malaria-causing parasite), resulting in approximately one

Fig. 1 – Historic and projected artemisinin market trends (The Boston Consulting Group (BCG), 2009; Bionexx, 2014).

million deaths, while *Plasmodium vivax* (a strain inducing marginally more benign but still potentially fatal symptoms) causes 70 to 390 million cases a year. Malaria disproportionately affects low-income regions and young children, and has significant detrimental effects on economies through lost productivity (Davis et al., 2011). Endemic mainly in tropical regions, it is also frequently reported in Central and South America, large areas of Asia and Africa, the Caribbean, and the Middle East.

Artemisinin and its medicinal and therapeutic properties (White, 2008) have been known for a very long time. The natural source of artemisinin, the plant sweet wormwood (*Artemisia annua*), has featured in traditional Chinese medicine for at least two millennia, and an early reference to its use in treating malaria can be found in a medical text from 1596 (Tu, 2011; Henry, 2014). Known in Chinese as *qinghao*, artemisinin was first isolated and identified as a result of a project to find cures and treatments for malaria (Tu et al., 1981, 1982). The 2015 Nobel Prize in Physiology or Medicine has been awarded to Youyou Tu for her discovery of artemisinin (The Nobel Assembly, 2015).

Artemisia annua is native to temperate regions of Asia, but can now be found in various other locations with suitable climatic conditions; the main cultivation and production centres are China (180–200 t of artemisinin in 2011), Vietnam (23–26 t), Madagascar (16 t projected for 2013) and East Africa (Kenya and Uganda, 14 t projected for 2013) (Cutler, 2013). Other minor producers include India, Australia, Papua New Guinea, West Africa, Brazil, Argentina, UK, USA and Switzerland (Ellmann, 2010). Current production methods predominantly rely on plant cultivation and subsequent batch extraction, a process which has long lead times, between 12 and 14 months (from seed planting to API extraction) (Hommel, 2008). In conjunction with the fluctuating and unpredictable artemisinin demand (malaria is transmitted by mosquitos, the population levels of which can be significantly affected by weather), this leads to highly variable prices: from 2007 to 2011 it has fluctuated between 200 and 400 USD per kilogram, rising to 900 USD at the end of 2011 (due to shortages from poor harvests) before dropping again to 400 USD in 2012, and to 360 USD at the start of 2013 (Cutler, 2013). Indeed, comparisons of global monthly artemisinin prices and production levels illustrate periods of excessive production (2007, 2014) which can be attributed to respective prior price peaks (2005, 2012) (Fig. 1).

In anti-malaria medications, artemisinin derivatives are frequently used to enhance bioavailability, and this often happens in conjunction with other antimalarial substances in Artemisinin Combination Therapies (ACT): the latter actually constitute the majority of commercially available formulations. The artemisinin derivative targets the bulk of the parasitic infection within the first three days, with the partner substance targeting residual parasite levels (World Health Organisation, 2015). Examples of derivatives include artesunate (water-soluble), artemether (lipid-soluble) and artemotil (Miller and Su, 2011), while partner anti-malarial substances they are often combined with include lumefantrine, amodiaquine, mefloquine, piperaquine and pyronaridine.

The Global Fund to Fight AIDS, Tuberculosis and Malaria reports that the anti-malarial market has been estimated at 340 million USD (2008–2014), with two categories of ACTs – artemether–lumefantrine (AL) and artesunate–amodiaquine (ASAQ) – constituting a combined 87% of the total market size. There are five pharmaceutical firms involved in ACT production: Novartis and Ajanta producing AL, Sanofi Aventis producing ASAQ, and Ipca and Cipla producing both forms (Bionexx, 2014).

Demand for ACTs varies enormously (The Boston Consulting Group (BCG), 2009), yet artemisinin API price fluctuations have a rather limited impact on ACT manufacturing cost and consequent selling price. For eight major ACT formulations (four AL, four ASAQ) accounting for 354 million treatments at a total cost of 292 million USD (average ACT price: 0.82 USD per dose), artemisinin constitutes between 20 and 23% of the cost for AL formulations and between 10 and 29% for ASAQ formulations, an average of 21%, which illustrates the extent of the API price influence on the total cost to end purchasers (Bionexx, 2014).

In recent years, there have been attempts to produce both synthetic (Zhu and Cook, 2012) and semi-synthetic (Paddon et al., 2013; Peplow, 2013; Paddon and Keasling, 2014; Turconi et al., 2014) artemisinin by a variety of methods, including the use of biotechnology (Hommel, 2008; Wang et al., 2014; Abidin and Alam, 2015; Corsello and Garg, 2015). The recent demonstration of the continuous synthesis of artemisinin from the waste material of the current batch extraction processes is of particular interest (Lévesque and Seiberger, 2012; Kopetzki et al., 2013). Dihydroartemisinic acid (DHAA, 2) is normally

Fig. 2 – Conceptual flowsheet for continuous production of artemisinin (adapted from Kopetzki et al., 2013).

discarded as waste: in the process developed by Kopetzki et al. (2013), on which this work is based, photo-oxidation with the subsequent use of an acid catalyst is used to transform 2 via several intermediates to artemisinin. Further developments of this process have been reported to produce various artemisinin derivatives, and there are plans to commercialise the process (Extance, 2012; Gilmore et al., 2014; Seeberger et al., 2014). Other groups are also pursuing similar routes: strategies applying Green Chemistry principles to continuous artemisinin synthesis involving liquid CO_2 solvent with catalysts, as well as synthesis using benign, simple solvents (ethanol and water), are being explored (Amara et al., 2015).

Product recovery via crystallisation is a well-established operation used in many industries, in both batch and continuous operation; the latter is predominantly used for the largest scale processes (Ward et al., 2011). In recent years, there have been advances in the study of the continuous crystallisation of APIs using both well-mixed (Kwon et al., 2014a) and plug-flow (Kwon et al., 2014b) crystallisers. Although few in number at

this stage, there have been demonstrations of continuous API crystallisation in pilot plants (Zhang et al., 2014).

Process control in continuous pharmaceutical operations is of paramount importance. For continuous crystallisation control, key process parameters include crystal size and shape, and high-resolution process modelling has been successful in addressing such technical challenges (Griffin et al., 2010; Kwon et al., 2013). Plantwide model-based control for a CPM process has been recently demonstrated, also incorporating crystallisation (Lakerveld et al., 2015). Moreover, a model-based control study for a novel dropwise additive manufacturing process for pharmaceutical products (DAMPP) has also been published (İçten et al., 2015).

This paper is organized in the following manner: first, the process flowsheets and reactions are introduced, before kinetic data analysis and parameter estimation is covered along with process mass balances and the plug flow design methodology. The systematic design of continuous separations follows, and original results for mass balances, reactor

Fig. 3 – Reaction scheme detailing synthesis path from feed material (2) to product API (1) and side products via intermediates (Kopetzki et al., 2013).

Table 1 – Main component molar and mass flow changes due to all three continuous flow reactions.

Component	Stoichiometric coefficient	Selectivity (%)	Flow in		Flow change		Flow out	
			(mmol h ⁻¹)	(g h ⁻¹)	(mmol h ⁻¹)	(g h ⁻¹)	(mmol h ⁻¹)	(g h ⁻¹)
PFR 1								
2 (DHAA)	−1		98.59	23.30	−96.62	−22.84	1.97	0.47
O ₂	−1		318.18	10.18	−96.62	−3.09	221.56	7.09
3	+1	86.6 ^a	0	0	+83.67	+22.45	83.67	22.45
4	+1	10.3 ^a	0	0	+9.96	+2.67	9.96	2.67
5	+1	3.1 ^a	0	0	+2.99	+0.80	2.99	0.80
PFR 2								
2 (DHAA)	−	−	1.97	0.47	−	−	1.97	0.47
O ₂	−1	−	221.56	7.09	−62.56	−2.00	158.99	5.09
3	−1	−	83.67	22.45	−69.87	−18.75	13.81	3.70
4	−1	−	9.96	2.67	−6.10	−1.64	3.86	1.04
5	−	−	2.99	0.80	−	−	2.99	0.80
6	+1	100.0 ^c	0	0	+6.10	+1.53	6.10	1.53
7	+1	6.7 ^b	0	0	+4.66	+1.09	4.66	1.09
10	+1	3.8 ^b	0	0	+2.65	+0.66	2.65	0.66
1(API)	+1	89.5 ^b	0	0	+62.56	+17.66	62.56	17.66

designs and separations are evaluated in relation to typical performances for pharmaceutical processes. Detailed models for the calculation of API solubilities by the UNIFAC method are given in the Appendix.

2. Flowsheet and process modelling

The process flowsheet is based on a recently demonstrated continuous synthesis route (Fig. 2) (Kopetzki et al., 2013). Artemisinin is produced in a series of two plug flow reactors, the first reactor being a chilled photo-oxidation reactor operating at –20 °C. Here, raw material 2 (DHAA) is photo-oxidised (Schenck ene reaction) to key intermediate 3. DCA (9,10-dicyanoanthracene) is a photosensitiser, essential to allow the production of the singlet oxygen necessary for the photooxidation reaction; light is provided by a suitable source such as a high-power mercury lamp (Kopetzki et al., 2013). Intermediate 4 and byproduct 5 are also produced (Fig. 3).

Subsequently, a multitude of reactions and transformations occur in PFR 2. Intermediate 3 (with trifluoroacetic acid, TFA, acting as acid catalyst) produces side product 7 by proximal protonation; terminal protonation results in a Hock rearrangement leading to 9, which in turn either transforms into byproduct 10 via isomerisation or reacts with triplet oxygen to produce the API artemisinin (1). Other minor

byproducts include hydrogen peroxide (H₂O₂, the loss of which leads to 7) and water (the loss of which leads to 6, 10 and 1) (Gilmore et al., 2013). A dehydrating cyclisation of 4 produces byproduct 6; in some conditions, 5 may further react, but negligible amounts are present under the operating conditions studied here (Kopetzki et al., 2013).

PFR reactor design requires the calculation of the process mass balances (Tables 1 and 2). The starting point is a recent synthesis study (Kopetzki et al., 2013), with the following assumptions: (1) reactions occur only inside the reactors and not in any of the lines connecting them, (2) isothermal operation is ensured in all reactors via suitable heat exchange media, (3) temperature changes cause no phase transformation or precipitation affecting the flow, (4) reactions shown in Fig. 3 are the only ones which occur, (5) gas-to-liquid mass transfer in the reactors is not the rate-limiting step and does not impede the reactions in any way.

3. Kinetic parameter estimation and reactor design

The reactions for the CPM of artemisinin have been assumed to be first order, considering the nature and structure of chemical compounds (large organic molecules reacting with excess of smaller reagents, e.g. O₂) for which reaction kinetic data

Table 2 – Process mass balance (g h⁻¹).

Component	Stream									
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	F ₁₀
2 (DHAA)	23.30	0	0	23.30	0	23.30	0	23.30	0.47	0.47
1 (API)	0	0	0	0	0	0	0	0	0	17.66
DCA	0	0.11	0	0.11	0	0.11	0	0.11	0.11	0.11
TFA	0	0	5.62	5.62	0	5.62	0	5.62	5.62	5.62
O ₂	0	0	0	0	0	0	10.18	10.18	7.09	5.09
3	0	0	0	0	0	0	0	0	22.45	3.70
4	0	0	0	0	0	0	0	0	2.67	1.04
5	0	0	0	0	0	0	0	0	0.80	0.80
6	0	0	0	0	0	0	0	0	0	1.53
7	0	0	0	0	0	0	0	0	0	1.09
10	0	0	0	0	0	0	0	0	0	0.66
H ₂ O ₂	0	0	0	0	0	0	0	0	0	0.16
H ₂ O	0	0	0	0	0	0	0	0	0	1.28
Toluene	0	0	0	0	168.27	168.27	0	168.27	168.27	168.27
Total	23.30	0.11	5.62	29.04	168.27	197.30	10.18	207.48	207.48	207.48

Table 3 – Temperature–conversion–selectivity data for photo-oxidation of 2 (DHAA) into intermediates 3, 4 and 5 (Seeberger et al., 2014).

Temperature (°C)	Conversion (%)	Selectivities (%)				
		X ₂	S ₃	S ₄	S ₅	S _{other}
–18	86	82	10	3	5	
0	93	79	11	3	7	
20	92	77	11	5	7	
40	99	73	12	5	10	
75	86	62	10	5	24	

Table 4 – Temperature–yield (based on initial DHAA) data for reaction of 3 into byproducts and API 1 (a: estimated) (Seeberger et al., 2014).

Temperature (°C)	Conversion ^a (%)	Yield (%)				
		X ₂	Y _{1(API)}	Y ₆	Y ₇	Y ₁₀
–15	49	18.0	1.6	2.1	21.3	
0	63	33.4	3.7	2.1	17.8	
25	78	59.1	6.1	4.4	2.5	
50	67	47.0	7.2	5.5	4.7	
75	55	31.2	7.5	6.1	9.6	

are available (Kopetzki et al., 2013; Seeberger et al., 2014). Kopetzki et al. (2013) employed pure oxygen supplied at 10 bar with a volumetric flow at the inlet of 5 mL min^{–1}, corresponding to 3.2 equivalents with respect to feed DHAA, reducing to 1.9 mL min^{–1} (at 10 bar) after all reactions are complete, implying a feed oxygen excess of 61.2%. Experimental measurements of oxygen solubility in toluene indicate saturated O₂ concentrations of 0.65% and 0.84% at –20 °C and 25 °C, respectively, at 10 bar (corresponding to Henry's constant values of 154.8 MPa and 118.4 MPa—determined from literature) (Li et al., 2007; Wu et al., 2014). Good mixing that is achievable with small process line and reactor dimensions, and high interfacial area (up to 25,300 m² m^{–3}), can ensure that the reaction is not impeded and thus the first-order assumption holds (Seeberger et al., 2014).

Reaction rate constants have been estimated based on reported conversions and lab-scale reaction line volumes, with mathematical programming used to find rate constant values. Reciprocals of instantaneous reaction rates can be plotted against conversion (assuming a given value of the rate constant), and necessary reactor volumes can be determined from the area under the curve, as this corresponds to reactor volume over the product of volumetric flow and inlet reactant concentration. Nonlinear optimisation allows the determination of rate constant values in order to ensure that calculated reactor designs match the experimental reactor volumes reported.

In the first PFR, the photo-oxidation reaction can achieve 98% conversion of 2 (DHAA), with product selectivities of 86.6% (3), 10.3% (4) and 3.1% (5) (Table 1), with the aforementioned kinetic data analysis implying a rate constant of 39.12 h^{–1}; this is for the reaction conducted at –20 °C (Kopetzki et al., 2013). This agrees well with additional data (Fig. 4A), with a value of 38.8 h^{–1} for the same reaction at –18 °C (Table 4, Seeberger et al., 2014). The rate constant has very non-monotonic behaviour and high variability with respect to temperature: this is because experimental data indicates highly variable non-monotonic conversions with respect to temperature, although desired product selectivity is monotonic, as increasing with decreasing temperature (see page

32, Table 4 in Seeberger et al., 2014). The continuous line is a linear best fit of data with conversions explicitly given for different reaction times (see page 32, Table 3 in Seeberger et al., 2014), with the rate constant (65.5 h^{–1}) determined from the slope. An outlying data point at t=0.051 h (not shown) has been discounted: this fell significantly below the trend, implying higher reactant consumption than expected. A possible explanation is that the higher reaction time allowed sufficient temperature increases for higher conversions (cooling is required to maintain temperatures) (Seeberger et al., 2014).

For the dashed lines in Fig. 4A, the rate constants have been determined using nonlinear optimisation. Although a different solvent (dichloromethane, DCM) and photosensitizer (tetraphenyl porphyrin, TPP) have been used in these cases, similar yet better conversions and selectivities can be achieved using toluene and DCA, respectively, ensuring that the use of kinetic parameters determined from the DCM and TPP data will give marginally over-designed reactors (Seeberger et al., 2014).

For the second reaction (multiple transformations beginning with intermediate 3 and resulting in 1, artemisinin), a conversion has been calculated based on batch reactor data at small scale (5 mL total volume) for a duration of 20 min (Fig. 4B) (Kopetzki et al., 2013; Seeberger et al., 2014). The reported yields (based on the original quantity of 2) of 1, 7, and 10 are 59.1%, 4.4%, and 2.5%, respectively. In conjunction with data for the conversion of 2 (DHAA) in the first PFR, a 78% conversion of 3 in the second PFR can be estimated from these values, with product selectivities of 89.5%, 6.7%, and 3.8% (for 1, 7 and 10, respectively). Employing a similar analysis as for the photooxidation reaction gives a value of 4.502 h^{–1} for the rate constant, which again shows significant variability and non-monotonicity. Subsequently applying this value for the stated reaction time in continuous flow (24 min, 0.4 h in the 25 °C reactor) increases the conversion of 3 to 83.5% (Seeberger et al., 2014).

The conversion of intermediate 4 (67.0%) has been similarly calculated using the overall yield of byproduct 6 (6.1%, based on initial DHAA amount) (Kopetzki et al., 2013). Byproduct 6 is not of commercial interest here, but must be taken into account in determining by-product and impurity levels, because those are key in evaluating final API separation operations against final product quality and purity requirements.

Kopetzki et al. (2013) report small quantities of unspecified byproduct from the photo-oxidation reaction. At less than 1% (molar fraction), these have been assumed negligible, and the values for selectivity given here have been adjusted to account for the difference. For the reactions occurring in the second PFR, the balance of yield based on initial DHAA is assumed to be unreacted species 3. For PFR design, small internal diameters of 5 mm have been studied to ensure adequate heat transfer; proven CPM systems with designs at this length scale have been reported (Mascia et al., 2013).

The PFRs presented here have been designed using the standard plug flow reactor performance equation for a first-order reaction:

$$\tau_i = C_{A,0} \int_0^{X_{A,f}} \frac{dX_A}{-r_A} \quad (1)$$

The static model assumes homogeneous mixtures and ideal solutions with isothermal operation. The PFRs are assumed to be submerged in suitable circulating heat transfer

Fig. 4 – Determination of reaction rate constants for reactor design. (A) DHAA photooxidation (Table 3) (Seeberger et al., 2014). (B) Reaction of intermediate 3 (Table 4) (Seeberger et al., 2014).

media which ensure that there are no temperature gradients, with specific heat capacities and reaction enthalpies remaining constant; phase change phenomena do not occur under the considered conditions. There are also no radial concentration gradients, and mass transfer between the gaseous O₂ component and the liquid stream is assumed to not be the rate-limiting step of the process. The small PFR dimensions considered ensure that the assumptions of excellent heat and mass transfer remain valid.

4. Final separation

The continuous synthesis route shown here will produce a range of organic intermediates and byproducts which must be removed in the final purification separation step. In the lab-scale demonstration of this continuous synthesis, multiple batch operations were used, including extraction, evaporation, filtration, recrystallisation, and washing stages (Kopetzki et al., 2013; Seeberger et al., 2014). Suitable continuous separation alternatives must be found to fully capitalize on and demonstrate the benefits of CPM. Furthermore, for further processing the product API is required in pure solid form for downstream operations and final formulation (unless it will be used to produce artemisinin derivatives).

The reported efficiencies of the batch separation scheme used by Kopetzki et al. (2013) have been used to determine potential base-case process efficiencies such as product recovery and solvent use.

For this conceptual continuous flowsheet, continuous extraction operations have been investigated for trifluoroacetic acid (TFA) removal. First, the use of counter-current extraction has been considered; however, the low initial amounts of TFA (approximately 2.5 mol%) and thermodynamic behaviour (as per the calculated TFA–toluene–water ternary phase diagram) imply that this is impractical. Instead, the potential of a continuous two-phase agitated tank with subsequent phase settling and separation has been investigated. In this idealised design, the dispersed organic phase (toluene) is injected into the continuous phase (water–NaHCO₃ solution) with constant agitation achieved using an impeller. As acid–base reactions are effectively instantaneous, with rate constants over the order of 10⁸ s⁻¹ reported (Pines et al., 1997), given sufficient bulk mixing the reaction should only be limited by the rate of mass transfer of TFA from the dispersed organic (toluene) droplets to the

continuous water phase, which can be represented using the following equation:

$$\dot{N}_{\text{TFA}} = K_W A' (C_{\text{TFA,W}}^* - C_{\text{TFA,W}}) \quad (2)$$

where $\dot{N}_{\text{TFA}}$ is the molar transfer rate of TFA, A' is the interfacial area (between dispersed organic drops and bulk aqueous phase), $C_{\text{TFA,W}}$ is the concentration of TFA in the aqueous phase, and $C_{\text{TFA,W}}^*$ is $C_{\text{TFA,W}}$ at equilibrium. The overall mass transfer coefficient K_W is calculated from the organic- and water-side film transfer coefficients k_O (from dispersed phase Sherwood number Sh_d) and k_W (from the continuous phase Sherwood number, using the Skelland–Moeti correlation) (Skelland and Moeti, 1990):

$$\frac{1}{K_W} = \frac{1}{mk_O} + \frac{1}{k_W} \quad (3)$$

$$Sh_d = \frac{k_O d_{32}}{D_{\text{TFA,O}}} = 6.6 \quad (4)$$

$$Sh_W = \frac{k_W d_{32}}{D_{\text{TFA,W}}} = 1.27 \times 10^{-5} Sc_W^{1/3} Fr_W^{5/12} Eo^{5/4} \varphi^{-1/2} Re_i^{2/3} \left(\frac{D_i}{d_{32}} \right)^2 \left(\frac{d_{32}}{D_t} \right)^{1/2} \quad (5)$$

here $D_{\text{TFA,O/W}}$ is the diffusivity of TFA in toluene (O) or water (W), d_{32} is the Sauter mean droplet diameter (of the dispersed toluene droplets), Sc_W and Fr_W are, respectively, the Schmidt and Froude numbers of the continuous phase, Eo is the Eotvos number, φ is the dispersed phase volume fraction, Re_i is the impeller Reynolds number, and D_i and D_t are the impeller and tank diameters, respectively. As TFA is miscible in both toluene and water, the partition coefficient m is unity. Eq. (1) can then be used to estimate the potential for TFA extraction by varying vessel dimensions and operational parameters (dispersed phase volume fraction, impeller rotation speed).

In published studies, following batch acid extraction, toluene is removed by evaporation under reduced pressure, with the resultant solid dissolved in acetonitrile and then refluxed with activated carbon, which is then filtered off; this procedure removes DCA. The solvent is then again evaporated

Fig. 5 – Mass balance of key flowsheet streams (g h⁻¹).

under reduced pressure; the solid proceeds to recrystallisation using cyclohexane and ethanol.

Although effective in recovering and purifying the API in the lab, alternatives to this procedure are highly preferred and sought for efficient CPM at industrial production scale. In batch pharmaceutical production, solvent swaps are frequent due to their suitability for a wide spectrum of applications; the best solvent for a reaction may not be suitable for a subsequent operation. However, solvent swaps are costly in terms of energy and material waste, and also take time. Another benefit of continuous production is that, almost exclusively, a single primary solvent is used (except where separations are required, e.g. liquid–liquid extraction, or antisolvents for crystallisation). Here, we systematically investigate the potential for toluene to be kept as a solvent, with the simultaneous introduction of an antisolvent intended to replace the batch recrystallisation procedures which rely on cyclohexane and ethanol. The UNIFAC method for estimating activity coefficients has been used toward calculating artemisinin solubilities (see Appendix) (Gracin et al., 2002).

5. Results and discussion

5.1. Mass balance and reactor design

The continuous design presented here produces artemisinin at a rate of 17.66 g h⁻¹, corresponding to 141.28 kg of annual production (prior to separation) for 8000 annual operating hours. A summary of key flowsheet stream mass balances is illustrated in Fig. 5. The mass balances are based on published kinetics and conversions for the reactions (Kopetzki et al., 2013; Seeberger et al., 2014).

The experimental demonstration achieved recoveries of 87.7% and 80.7% in the recrystallisation stages, for an overall product recovery of 70.8% (although it is reported that marginally higher recoveries are attainable) (Seeberger et al., 2014). Assuming that similar performance can be achieved by scaling up the batch scheme to mass flows used here, this

recovers 12.5 g h⁻¹, or 100.0 kg per year of API. The mass flow to this point has been used as a preliminary level to produce this benchmark annual quantity of API, allowing subsequent evaluation of continuous separation operations with regards to mass flows required.

Toluene (C₇H₈) is the organic solvent. The key species are feedstock 2 (DHAA), intermediate 3, and 1 (artemisinin, the API product). In addition to these key organic molecules, various byproducts are present: species 4 and 5 are produced alongside 3 (although at far lower selectivity), while 7 and 10 also originate from 3. TFA acts as acid catalyst here, and so is never consumed. DCA, the photosensitizer, is present in quantities too low to display in Fig. 5.

Small sizes have been calculated for the two reactors, with 19.722 mL for PFR 1 and 78.923 mL for PFR 2 (Table 5). Small internal diameters of 5.0 mm have been studied to ensure excellent heat and mass transfer. CPM pilot plant systems have been successfully demonstrated at this scale, with heat transfer ID = 1.6 mm and reactor ID = 11.7 to 40 mm, respectively (Mascia et al., 2013). Process simulations have also been performed here at the reported capacity and compared to the published reactor dimensions implemented in the laboratory-scale experimental system (Kopetzki et al., 2013). These reactor sizes are for the production capacity presented in Fig. 5: larger capacities will require larger reactors, assuming only one system is used.

Kopetzki et al. (2013) report an overall yield of 65% for artemisinin, which is close to the value calculated here (63.5%). More detailed experimental investigations for the full continuous process will elucidate the contributing factors to this small variation. In the full experimental demonstration, toluene is used as a solvent with DCA as photosensitizer, while the value of 63.5% has been computed on the basis of the marginally lower performance of DCM and TPP (solvent and photosensitizer, respectively). Moreover, the extent to which reactions may occur in the process lines between reactors is not taken into consideration here. While this is expected to be minimal, Kopetzki et al. (2013) do have an additional small pre-heating line at 10 °C between the two reactors.

Table 5 – PFR design results.

PFR # (reaction)	Temperature (°C)	Flowrate (g h ⁻¹)	Conversion (%)	ID (mm)	Volume (mL)	Length (mm)
PFR 1 (2 → 3)	–20	207.48	98.0	5.0	19.722	1005
PFR 2 (3 → API)	25	207.48	83.5	5.0	78.923	4020
(4 → 6)	25	207.48	67.0	5.0	78.923	4020

Fig. 6 – Batch separation scheme for artemisinin purification according to the original flow synthesis method considered (Kopetzki et al., 2013).

This novel continuous synthesis of artemisinin employs a reaction line coiled around a transparent plate and placed near a mercury lamp (Kopetzki et al., 2013). The optimal configuration for maximum energy efficiency could be different, and multiple options are possible, including wrapping the reaction line in a coil with the lamp down the centre (Peplow, 2013). Here, the lamp and the exact reactor configuration reported by the authors are assumed to provide the necessary light for successful completion of the photooxidation reaction.

5.2. Final separation

The product stream F_{10} requires separation and purification of the API product, artemisinin (1). The batch scheme utilised in the demonstration of the continuous chemical synthesis is illustrated in Fig. 6, where flows SF_1 – SF_{18} are not true streams but illustrate the use and movement of material to and from stages; SF_1 corresponds to the effluent stream of PFR 2, which is CPM flowsheet stream F_{10} . An extraction with aqueous sodium bicarbonate first removes trifluoroacetic acid (TFA); this is followed by washing with brine and water. The organic phase then proceeds to a solvent removal stage where toluene is removed: this consists of drying with sodium sulfate, concentration using reduced pressure, followed by acetonitrile addition and subsequent evaporation and then vacuum drying. The resulting solid is then dissolved in acetonitrile with added activated carbon (which captures poorly soluble DCA) and filtered, which removes the carbon (along with DCA). The filtration product is then recrystallised using cyclohexane and ethanol in multiple steps, resulting in the API product in solid form (Kopetzki et al., 2013; Seeberger et al., 2014). These operations are suitable for lab-scale purification (where such steps are known as workup), but implementation of the continuous scheme in production scale requires continuous alternatives.

For the continuous extraction of TFA from the organic phase, the use of an agitated tank has been investigated,

where the organic phase (toluene) is dispersed into the aqueous phase. Sodium bicarbonate (NaHCO_3), saturated in the aqueous phase, neutralises the TFA. Oxygen and any other gaseous components are assumed removed prior to this by simple venting, with the process now at atmospheric pressure. Adjustable parameters affecting the estimation of TFA molar mass transfer from the toluene to the water include the impeller speed (at a high but attainable 15 s^{-1}), impeller diameter, tank diameter (typically equal to 2–3 times the size of the impeller diameter) and dispersed phase volume fraction (set with an upper limit of 0.2).

The inlet flow of TFA at this point in the flowsheet (entering an agitated tank) is 49.3 mmol h^{-1} (Fig. 7, black dashed line). As illustrated by Fig. 7, mass transfer of TFA is favoured by higher dispersed phase volume fractions and impeller sizes (illustrated here by tank volumes, which are tied to impeller dimensions). Naturally, there are practical limits to both these parameters, particularly for volume fractions. Furthermore, higher ratios of impeller diameter to tank diameter (Fig. 7B) result in higher required volumes for a given mass transfer rate; however, smaller impellers tend to achieve higher energy efficiency.

Eight common solvents, several of which are classified as desirable (with the lowest toxicity and environmental impact), have initially been investigated as potential antisolvents for use in a continuous crystallisation operation. These eight solvents are ethanol (EtOH), acetone, ethyl acetate (EtOAc), methanol (MeOH), 2-propanol (2-PrOH), *n*-butanol (*n*-BuOH), butanone (methyl ethyl ketone, MEK) and acetonitrile (ACN). The generalised separation system design considered here is illustrated in Fig. 8. Artemisinin solubilities have been evaluated for a temperature range of 0 to 40°C , for toluene-to-antisolvent ratios of 50:50, 30:70, and 20:80 by weight (Fig. 9).

Solubility increases with temperature in each case, while some candidate antisolvents (acetone, EtOAc, MEK) show little solubility variation between different solvent-to-antisolvent

Fig. 7 – Variation of potential mass transfer of TFA with tank volume and dispersed phase (organic) volume fraction (ϕ). (A) Tank diameter (D_t) 2 times the impeller diameter (D_i). (B) Tank diameter (D_t) 3 times the impeller diameter (D_i).

ratios. Additional ratios with toluene in the majority have also been studied, however in these cases antisolvent addition increased predicted artemisinin solubilities, possibly because toluene is a non-polar solvent (results not shown). The use of ethyl acetate (EtOAc) is predicted to produce the lowest artemisinin solubilities. Recently published experimental solubility data for the toluene–ethanol system imply that the values computed through UNIFAC here may induce overestimation (Horváth et al., 2015). The complex molecular structure of artemisinin, along with the unavailability of some group interaction parameters, are plausible explanations for this discrepancy. For further design, the experimental solubility data from Horváth et al. (2015) have been used, employing ethanol as antisolvent with suitable feed API concentrations studied for each case of antisolvent amount at 90% of saturation (26.8%, 18.9%, and 14.1% by mass for 50:50, 30:70 and 20:80 of toluene:EtOH, respectively) (Fig. 10). This has been compared with the use of ethyl acetate (EtOAc) as antisolvent, studying similar feed API concentrations at 90% of saturation (26.2%, 25.2% and 24.4% by mass for 50:50, 30:70 and 20:80 of toluene:EtOAc, respectively), with the use of solubility data calculated via the UNIFAC method (Fig. 11).

Stream concentration (in order to reduce its solvent content) is required for efficient crystallisation: antisolvent addition without API concentration results in low feed API mass fractions, with which crystallisation cannot be efficiently

performed (concentration is below the solubility that would be reached at the bottom of the temperature range). In order to achieve the desired feed API concentrations, antisolvent must first be added, as toluene evaporation alone will exceed API saturation (Liu et al., 2009). The required antisolvent quantities to be added in each case have been calculated by performing isothermal flash calculations via the UniSim® software suite (Honeywell, 2014). The predicted solubilities achieved for ethyl acetate (Fig. 11) are higher than experimental solubilities for ethanol use (Fig. 10), however there is less variation with quantity of antisolvent.

The API recovery that could be achieved has been assumed to be the thermodynamically possible yield for each system, and on this basis the three continuous separation schemes (varying antisolvent use, for a temperature drop from 40 °C in the feed to 5 °C) for each antisolvent (ethanol or ethyl acetate) have been compared with the experimentally employed batch scheme (Tables 6 and 7, respectively). Annual operation has again been considered to last 8000 h.

Maximum product recoveries improve with increasing antisolvent use in the case of ethanol (between 53.7% to 65.2%), in contrast to ethyl acetate, for which they remain relatively constant (between 57.2% and 58.8%) (Fig. 12); this is predominantly due to the solubility behaviour of the API in the antisolvent–solvent mixture. While ethanol is preferable (based on product recoveries), taking into account additional

Fig. 8 – Generalised conceptual design of the continuous separation system.

Fig. 9 – Artemisinin solubility evaluation of potential antisolvents for continuous crystallisation using the UNIFAC method. Solvents appear in order of decreasing API solubility (mole fraction units).

metrics, particularly those related to environmental impact and safety, can significantly affect antisolvent preferability (Jolliffe and Gerogiorgis, 2016a).

Product recoveries which vary as a function of antisolvent mass used in crystallisation also offer a clear potential for efficient process control. API productivity could be increased or maintained by adjusting the antisolvent injection flowrate, in order to address potential mass throughput bottlenecks elsewhere in the process.

5.3. Environmental impact (E-factor)

A useful metric for quantifying environmental impact is the E-factor (Sheldon, 2012). It is versatile with multiple definitions, the simplest of which is the mass of waste generated (excluding water) per unit mass of product. Sustainability metrics (Balomenos et al., 2014) and systematic model-based sensitivity analyses (Angelopoulos et al., 2013, 2014) acquire ever-increasing importance in the entire spectrum of chemical

Fig. 10 – Conceptual crystallisation operating parameters; empirical solubility data has been used (Horváth et al., 2015). The system studied comprises solute (API), solvent (toluene), and antisolvent (EtOH) only.

process industries, in order to assess profitability in tandem with environmental acceptability and societal responsibility. Highly efficient industries relying almost completely on continuous production methods (such as petrochemical processes) have E-factors in the order of 0.1, while batch-reliant processes (such as pharmaceutical production) generate significant relative amounts of waste, with high E-factors of 200 not uncommon (Ritter, 2013). Here, the E-factor is computed where the product is (pure) recovered API, while the waste consists of byproducts (bpd), unconverted reactants (ur), waste solvent (ws, all assumed unrecovered), and unrecovered API (uAPI):

$$E = \frac{m_{\text{waste}}}{m_{\text{API}}} = \frac{m_{\text{bpd}} + m_{\text{ur}} + m_{\text{ws}} + m_{\text{uAPI}}}{m_{\text{API}}} \quad (6)$$

Material requirements for TFA removal have not been included in E-factor calculations as water is the main

Fig. 11 – Conceptual crystallisation operating parameters; calculated using the UNIFAC method—see Fig. 8 (EtOAc). The system studied comprises solute (API), solvent (toluene), and antisolvent (EtOAc) only.

component in this stage, and due to its negligible environmental impact cost is commonly excluded (Sheldon, 2012). Moreover, this operation is upstream of the subsequent API separation and general E-factor trends would remain unaffected. The solvents have been assumed to be unrecovered, while unused O₂ has been assumed to have been recovered via simple phase separation after exiting the last reactor.

For the batch scheme outlined in Fig. 6, the calculated E-factor is 65.28: for every kilogram of pure API obtained, 65.28 kilograms of waste are generated. This is very likely an underestimation, as specific quantities of chemicals used have not been reported for all of the operations detailed in Fig. 6 (Seeberger et al., 2014). Solvents form the bulk of the waste (794.5 g h⁻¹).

Based on the assumed feed concentrations (post-solvent evaporation), calculated E-factor values are better (lower) for the six studied CPM scenarios in comparison to the batch

Table 6 – Comparison of batch vs. continuous API recovery: EtOH antisolvent.

		Batch	CPM		
			1	2	3
Production capacity (kg year ⁻¹)		100	100	100	100
PFR outflow (g h ⁻¹)	2 (DHAA)	0.47	0.61	0.51	0.51
	3	17.66	23.30	19.49	19.17
	1 (API)	5.62	7.41	6.20	6.10
	TFA	5.09	6.71	5.61	5.52
	O ₂	3.70	4.89	4.09	4.02
	4	1.04	1.37	1.14	1.13
	5	0.80	1.06	0.88	0.87
	6	1.53	2.01	1.68	1.66
	7	1.09	1.44	1.20	1.18
	10	0.66	0.87	0.73	0.72
Solvent (g h ⁻¹)	H ₂ O ₂	0.16	0.21	0.17	0.17
	H ₂ O	1.28	1.69	1.42	1.39
	Toluene	168.27	221.95	185.65	182.61
	Solvent: antisolvent (weight:weight)	–	50:50	30:70	20:80
Separation (g h ⁻¹)	ACN	19.80	–	–	–
	Cyclohexane	587.80	–	–	–
Antisolvent (g h ⁻¹)	EtOH	18.60	56.65	107.02	189.53
	EtOAc	–	–	–	–
Thermodynamic API recovery (%)		70.1	53.7	64.1	65.2
Waste (g h ⁻¹)	API	5.16	10.80	6.99	6.67
	Unrecovered solvents	794.51	253.84	244.11	276.17
	Others (excl. O ₂)	16.35	21.57	18.04	17.75
	Total	816.03	286.21	269.14	300.58
E-factor		65.28	22.90	21.53	24.05

Table 7 – Comparison of batch vs. continuous API recovery: EtOAc antisolvent.

		Batch	CPM		
			4	5	6
Production capacity (kg year ⁻¹)		100	100	100	100
PFR outflow (g h ⁻¹)	2 (DHAA)	0.47	0.58	0.57	0.56
	3	17.66	21.86	21.65	21.27
	1 (API)	5.62	6.95	6.89	6.77
	TFA	5.09	6.30	6.24	6.13
	O ₂	3.70	4.58	4.54	4.46
	4	1.04	1.28	1.27	1.25
	5	0.80	0.99	0.98	0.97
	6	1.53	1.89	1.87	1.84
	7	1.09	1.35	1.34	1.31
	10	0.66	0.82	0.81	0.80
	H ₂ O ₂	0.16	0.20	0.19	0.19
	H ₂ O	1.28	1.59	1.57	1.55
Solvent (g h ⁻¹)	Toluene	168.27	208.21	206.25	202.65
Solvent: antisolvent (weight:weight)		–	50:50	30:70	20:80
Separation (g h ⁻¹)	ACN	19.80	–	–	–
	Cyclohexane	587.80	–	–	–
Antisolvent (g h ⁻¹)	EtOH	18.60			
	EtOAc		30.72	44.90	52.84
Thermodynamic API recovery (%)		70.1	57.2	57.7	58.8
Waste (g h ⁻¹)	API	5.16	9.36	9.15	8.77
	Unrecovered solvents	794.51	238.92	251.15	255.49
	Others (excl. O ₂)	16.35	20.24	20.04	19.69
	Total	816.03	268.51	280.34	283.96
E-factor		65.28	21.48	22.43	22.72

case, ranging from 21.48 to 24.05 (Tables 6 and 7, Fig. 12). This implies that for each unit mass of API produced, the CPM schemes generate on average 66.2% less waste than the batch process. While high compared to industries exclusively using continuous processes, these values are acceptably low given that typical pharmaceutical processes have significantly higher values. Although product recoveries are lower for the CPM cases than the batch case (CPM: 53.7–64.1%, batch: 70.1%), this is offset by the significant reduction in waste. Moreover, it must be noted that the separation scheme employed would not be implemented industrially without prerequisite adjustments: while high recoveries are achieved, the required timescale of the batch operations and the full technoeconomic evaluation (Jolliffe and Gerogiorgis, 2016b) has not been the focus of the present study, which only addresses the technical objective of API product recovery maximisation. In addition, although material requirements are likely to change and E-factors worsen with more detailed design of CPM separation cases, they nevertheless show promise, and there is clear

potential to employ multiple crystallisation stages, possibly combined with other separation technologies in order to further enhance process performance (Horváth et al., 2015).

The differences between E-factors calculated for the use of ethanol (Table 6) versus ethyl acetate (Table 7) are small, in the range of 21.43–24.05 and 21.48–22.72, respectively, an average difference of only 2.7%. The use of ethanol results in higher API recoveries, with the exception of 50:50 (toluene:ethanol) use. Product recoveries increase with antisolvent mass used: for both antisolvents, recovery is lowest for the 50:50 (toluene:antisolvent) and highest for the 20:80 ratio. Due to the smaller influence of antisolvent quantity on API solubility (Fig. 10), there is less variation in recovery when ethyl acetate is used.

Given the similar API recovery performance of the two antisolvents discussed here, additional factors such as compatibility with subsequent (or additional prior) separation operations require investigation for accurate evaluation. Nevertheless, on the basis of the calculations and analysis

Fig. 12 – Evaluation of batch and continuous separation schemes: API recovery and E-factor.

presented here, the use of ethanol in a 20:80 ratio with toluene by weight (CPM case 3, Fig. 12) is to be favoured: it results in the highest API recoveries, while the E-factor (i.e. waste generated) is only marginally higher than in other CPM cases, but significantly lower than the batch case.

6. Conclusions

The Continuous Pharmaceutical Manufacturing (CPM) of the key antimalarial substance artemisinin has been presented in this paper. Multiple designs with different continuous product recoveries have been compared with a batch reference case, with all designs producing 100 kg of API per year. The continuous flow chemistry considered in this study is of particular interest, because the feedstock is a high-volume waste product of current artemisinin production: significant added value is possible from implementing this continuous manufacturing design toward integrating this concept and improving the sustainability of established artemisinin production plants.

A novel kinetic parameter estimation analysis has been performed using published data, enabling systematic continuous flow reactor design. The computation of small reactor volumes (19.72 mL and 78.72 mL) clearly indicates the anticipated capital cost and space advantages, which are established strong benefits of continuous production.

An environmental (E-) factor of 65.28 has been estimated for a reference batch design case which considers the reported performance of a batch separation scheme, an acceptable value for a process employing some batch operations. Evaluations of potential continuous alternatives, using published solubility data as well as the UNIFAC method, indicate a significantly improved, environmentally superior performance, with improved E-factors ranging from 21.48 to 24.05: ethanol and ethyl acetate emerge as strong candidate antisolvents for the crystallisation process. The small decrease in product recovery for continuous separation (70.1% for batch, up to 65.2% for continuous designs) is offset by a significant reduction in waste generation compared to the batch process. Investigation of a continuous alternative for acid neutralisation illustrates the scope for using continuous agitated tanks.

Artemisinin is a substance of critical importance. An effective anti-malarial itself, it is the precursor to many anti-malarial derivatives which are widely used to combat a disease of incessantly devastating impact. The use of a currently unexploited waste material as viable feedstock gives significant added value to the implementation of this design, which is an excellent opportunity for demonstrating CPM benefits. The potential use of a widely employed solvent of low toxicity and environmental impact in a continuous alternative separation illustrates how green processing ideals can be met with systematic design. To further demonstrate the industrial potential of this design, a full investigation of an integrated continuous separation process is required; this is of particular importance for downstream processing. Furthermore, a systematic technoeconomic evaluation and optimisation methodology with high-fidelity experimental data will be of paramount importance in order to build a solid business case for CPM implementation (Jolliffe and Gerogiorgis, 2016b).

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Appendix A.

A.1. Solubility

The solubilities (saturation mole fractions, x_i^{sat}) of components in solvent mixtures are calculated using the following equation (Gracin et al., 2002):

$$a_i^s = x_i^{\text{sat}} \gamma_i^{\text{sat}} = \exp \left[\frac{\Delta H_{\text{fus}}}{R} \left(\frac{1}{T_{\text{fus}}} - \frac{1}{T} \right) \right] \quad (\text{A1})$$

where H_{fus} is the enthalpy of fusion and T_{fus} is pure solid solute i melting point. Solid activity (a_i^s) is first estimated via the exponential portion of Eq. (A1). Activity coefficient γ_i^{sat} is obtained from Eq. (A2) when then allows the calculation of x_i^{sat} via Eq. (A1). An iterative process is required for Eq. (A1), as the activity coefficient γ_i^{sat} also depends on mole fraction x_i^{sat} .

In the UNIFAC method the activity coefficient for molecule i (γ_i) is the sum of a combinatorial and residual components γ_i^c and γ_i^r , respectively (Fredenslund et al., 1975):

$$\ln \gamma_i = \ln \gamma_i^c + \ln \gamma_i^r \quad (\text{A2})$$

The UNIQUAC model is used to compute γ_i^c (Abrams and Prausnitz, 1975):

$$\ln \gamma_i^c = \ln \frac{\phi_i}{x_i} + \frac{z}{2} q_i \ln \frac{\theta_i}{\phi_i} + L_i - \frac{\phi_i}{x_i} \sum_j x_j L_j \quad (\text{A3})$$

In Eq. (A2) ϕ_i is the molar weighted segment fractional component and θ_i is the area fractional component:

$$\phi_i = \frac{x_i r_i}{\sum_j x_j r_j} \quad (\text{A4})$$

$$\theta_i = \frac{x_i q_i}{\sum_j x_j q_j} \quad (\text{A5})$$

The UNIFAC compound parameter L_i is defined by r_i , q_i and z :

$$L_i = \frac{z}{2} (r_i - q_i) - (r_i - 1), \quad (z = 10) \quad (\text{A6})$$

Parameters r_i and q_i , also used in computing ϕ_i , θ_i , are calculated from volume (R) and surface area (Q) parameter contributions from functional groups:

$$r_i = \sum_k \nu_k^{(i)} R_k \quad (\text{A7})$$

$$q_i = \sum_k \nu_k^{(i)} Q_k \quad (\text{A8})$$

where ν_k is the number of occurrences of group k on a molecule.

The residual component γ_i^r is calculated from Γ_k and $\Gamma_k^{(i)}$, the residual group activity coefficient of group k in reality and in a reference solution of pure substance i , respectively:

$$\ln \gamma_i^r = \sum_k v_k^{(i)} \left[\ln \Gamma_k - \ln \Gamma_k^{(i)} \right] \quad (\text{A9})$$

Both Γ_k and $\Gamma_k^{(i)}$ are calculated via the following equation:

$$\ln \Gamma_k = Q_k \left[1 - \ln \sum_m \theta_m \psi_{mk} - \sum_m \frac{\theta_m \psi_{km}}{\sum_n \theta_n \psi_{nm}} \right] \quad (\text{A10})$$

where parameters θ_m and x_m (summation of the area fraction of group m over all different groups, and the mole fraction of group m , respectively) are defined as follows:

$$\theta_m = \frac{Q_m x_m}{\sum_n Q_n x_n} \quad (\text{A11})$$

$$x_m = \frac{\sum_j v_m^j x_j}{\sum_j \sum_n v_n^j x_j} \quad (\text{A12})$$

A modified Arrhenius equation is used to calculate ψ_{mn} (a measure of interaction energy between groups):

$$\psi_{mn} = \exp \left[-\frac{U_{mn} - U_{nm}}{RT} \right] \quad (\text{A13})$$

Tables for group interactions and other parameters are widely available in literature (Wittig et al., 2003).

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