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# Plantwide design and economic evaluation of two Continuous Pharmaceutical Manufacturing (CPM) cases: Ibuprofen and artemisinin

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ABSTRACT

Increasing Research and Development (R&D) costs, growing competition from generic manufacturers and dwindling market introduction rates for novel drug products bolster the efforts of pharmaceutical firms to secure competitiveness by investigating Continuous Pharmaceutical Manufacturing (CPM). The present paper explores the CPM of two key Active Pharmaceutical Ingredients (APIs), ibuprofen and artemisinin: cost savings and material efficiency benefits are evaluated for CPM vs. batch processing, with two continuous options for each API. Capital Expenditure (CapEx) savings of up to 57.0% and 19.6% and corresponding Operating Expenditure (OpEx) savings of up to 51.6% and 29.3% have been determined for ibuprofen and artemisinin, respectively. Total projected cost savings for a 20-year plant lifetime can reach 54.5% and 20.1%, respectively. Environmental (E)-factors (mass of waste generated per unit mass of product) of 43.4 (for ibuprofen) and 12.2 (for artemisinin) have been computed, indicating environmental and material efficiency advantages for these conceptual continuous pharmaceutical processes.



## 1. Introduction

Due to the increasing cost of pharmaceutical product R&D and competition from generic manufacturers, current research focuses on more efficient, cost-saving production methods which are superior in several aspects compared to batch production, the currently prevalent paradigm in the pharmaceutical industry (Behr et al., 2004; Ashe, 2012). Batch production processes have multiple advantages including equipment flexibility, the option to buy process vessels 'off-the-shelf', high-fidelity offline quality control and the possibility to recall specific batches. However, improvements in batch production are rare, as this is a mature technology; its limitations include large storage volume requirements, poor heat and mass transfer scaling, and inefficient solvent and energy use (Anderson, 2012; Gernaey et al., 2012). Attention is turned to Continuous Pharmaceutical Manufacturing (CPM) which has the potential to revolutionise drug production quality, safety, yields, efficiency (of equipment, energy and material use) and cost (Plumb, 2005; Roberge et al., 2008; Mascia et al., 2013). However, as pharmaceutical firms have significant investments in batch plants, and as production licenses are legally tied to the specified (batch) production method according to regulatory legislation, research conclusively elucidating the benefits of CPM is required in order to first delineate its applicability limits and then facilitate this paradigm shift in drug production (Lee et al., 2015).

Rapid, low-cost methodologies for evaluating the benefits of continuous processing in the production of pharmaceuticals are essential toward investigating the technical feasibility and economic viability (Douglas, 1988) of CPM processes, a task greatly facilitated via process modelling and simulation (Gerogiorgis and Barton, 2009; Teoh et al., 2016). Moreover, extensions to cost estimation allow the determination and quantification of potential CPM economic benefits (Schaber et al., 2011; Gerogiorgis and Jolliffe, 2015). Previous publications have systematically identified promising candidates for CPM and performed an initial comparative technoeconomic assessment of two of these: ibuprofen and artemisinin (Jolliffe and Gerogiorgis, 2015a,b).

Ibuprofen (2-(4-isobutylphenyl) propanoic acid) is a widely used analgaesic which is considered essential by the World Health Organisation, with significant market presence in many differ-

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**Nomenclature**

| | |
|---|---|
| API | Active Pharmaceutical Ingredient |
| BLIC | Battery Limits Installed Cost of all equipment in a process, part of CapEx, £ |
| BX | Batch |
| C | Cost of reference item A, £ |
| CapEx | Capital Expenditure, £ |
| $C_{B,1C}$ | Calculated cost of design item B at 100 kg/year API production scale, £ |
| $C_{B,1K}$ | Calculated cost of design item B at 1000 kg/year API production scale, £ |
| CPM | Continuous Pharmaceutical Manufacturing |
| E-factor | Environmental factor, a measure of material efficiency, kg (waste)/kg (product API) |
| $f$ | Product of adjustment factors, used in cost-capacity power equation (1) |
| KI | Key ingredient |
| KI5 | Sensitivity case with KI at £5/kg |
| KI10 | Sensitivity case with KI at £10/kg |
| $m_{API}$ | Mass of API produced after separation, kg/year |
| $m_{bpd}$ | Mass of by-product waste, kg/year |
| $m_{uAPI}$ | Mass of unrecovered API, kg/year |
| $m_{ur}$ | Mass of unreacted reagent waste, kg/year |
| $m_{waste}$ | Total mass of waste, kg/year |
| $m_{ws}$ | Mass of solvent waste, kg/year |
| $n$ | Dimensionless exponent used in cost-capacity equation (1) |
| NPV | Net Present Value, the total costs over a certain plant lifetime, adjusted to the present |
| OpEx | Operating Expenditure, £ |
| $r$ | Discount rate, the correction factor for adjusting costs to the present |
| $S_A$ | Capacity of reference item A, units vary with item type |
| $S_{B,1C}$ | Required capacity of design item B at 100 kg/year API production scale, units vary with item type |
| $S_{B,1K}$ | Required capacity of design item B at 1000 kg/year API production scale, units vary with item type |
| SR | Solvent recovery |
| SR50 | Sensitivity case with SR at 50% |
| SR70 | Sensitivity case with SR at 70% |
| $\tau$ | Plant lifetime, years |
| U/W | Utilities and waste handling costs, part of OpEx, £ |
| WCC | Sum of Working Capital and Contingency, part of CapEx, £ |

ent commercial formulations. First synthesised in the 1960s, the first industrial six-step Boots synthesis method has been largely replaced by a more efficient, less complex route (Adams, 1992). In a recent landmark study, the continuous synthesis of ibuprofen has been demonstrated by employing novel flow reaction routes, producing ibuprofen in high yield using three plug flow reactors (Bogdan et al., 2009).

Artemisinin has been used medicinally for a long time, especially in traditional Chinese remedies, as a natural product of its source plant, the sweet wormwood (*Artemisia annua*); it has been identified and isolated as a potent API only recently (Tu, 2011). The currently prevalent production method relies on batch extraction of artemisinin with the use of a wide variety of solvents. Taking into account cultivation times, this results in a long lead time from seed planting to final dosage formulation: combined with unpredictable demand, this technological shortcoming results in highly fluctuating prices (Hommel, 2008; Cutler, 2013). There have been numerous published attempts to produce synthetic and semi-synthetic artemisinin in recent years (Zhu and Cook, 2012; Peplow, 2013; Paddon and Keasling, 2014; Turconi et al., 2014). Biotechnology has also been explored in this regard (Wang et al., 2014; Abdin and Alam, 2015; Corsello and Garg, 2015). Recent publications which focus on the semi-synthetic production of artemisinin from the waste of current batch extraction methods (Lévesque and Seeberger, 2012; Kopetzki et al., 2013; Gilmore et al., 2014; Horváth et al., 2015) are of particular interest in the context of the present study. In these novel processes, dihydroartemisinic acid (DHAA), which is normally discarded as extraction waste, undergoes photo-oxidation (with the subsequent use of an acid catalyst) and is transformed via several intermediates to artemisinin.

The present detailed technoeconomic study aims to determine the economic benefits (cost savings) of continuous product generation and separation for ibuprofen and artemisinin in comparison to the respective batch processes, with the use of original process models based on published continuous synthesis routes (Bogdan et al., 2009; Kopetzki et al., 2013). Two continuous separation alternatives have been studied for each API (a total of six process instances, including a batch reference design case for each API). Capital Expenditure (CapEx), Operating Expenditure (OpEx) and total cost savings have been determined over a typical pharmaceutical plant lifetime with the use of systematic cost estimation methods. Furthermore, the material efficiency of each process has been evaluated using the Environmental (E) factor (Sheldon, 2012). To further elucidate the potential cost savings, a simplified 'lean' modification of the batch processes has been studied in comparison to the continuous production flowsheets. Moreover, a plant capacity sensitivity analysis has considered the transition from 100 kg/year to 1000 kg/year of API production, in order to investigate how cost advantages vary as a function of throughput scale.

This paper is organized in the following manner: process descriptions, reaction schemes, synthesis and different (batch as well as continuous) separation sections of the two CPM flowsheets are first presented, with detailed operational descriptions and schematics of individual process instances and necessary equipment units. The cost analysis methods are comprehensively covered, along with a discussion of how process vessels and other equipment units have been sized. The results cover potential cost savings and technoeconomic comparisons of continuous and batch process options considered: in particular, tables and figures detail how Capital Expenditure (CapEx), Operating Expenditure (OpEx), total cost savings, and material efficiency (in terms of E-factor) vary, for two production capacities and two levels of reference batch case complexity, for each API. The results are then discussed in the wider context of this emerging field of research, in order to illustrate a systematic methodology for evaluating CPM potential and applicability.

## 2. Process description

### 2.1. Ibuprofen

The landmark continuous synthesis by Bogdan et al. (2009) forms the basis for the ibuprofen flowsheets studied here (Fig. 1). First, isobutyl benzene (IBB) reacts with propanoic acid in a Friedel-Crafts acylation reaction conducted in a plug flow reactor at 150 °C; neat triflic acid (TfOH) is used as acid catalyst as well as solvent. Species $\mathbf{2}_A$, 1-(4-isobutylphenyl)propan-1-one, is produced with reported conversions of 91%; the reactor effluent is then chilled to 0 °C (Bogdan et al., 2009). The effluent is mixed with additional reagents and solvents that have also been chilled to 0 °C. In the second reactor (50 °C) a diacetoxyiodobenzene-mediated 1,2-aryl migration converts $\mathbf{2}_A$ to $\mathbf{3}_A$, 2-(4-isobutylphenyl)propanoate, with

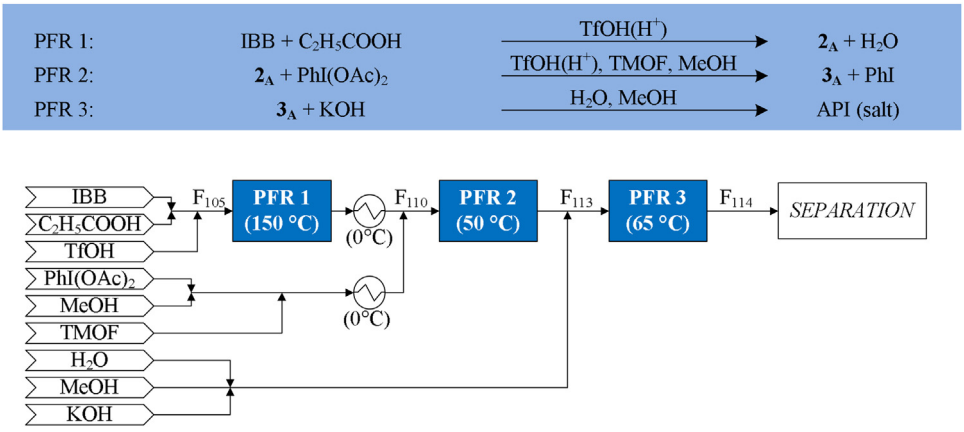


**Fig. 1.** Demonstrated process flowsheet for the CPM of ibuprofen (Bogdan et al., 2009).

98% conversion. The reactor products are combined with a water-methanol stream containing potassium hydroxide (KOH), and the resulting mixture enters the last reactor. The third reactor, operating at 65 °C, causes the saponification of $\mathbf{3}_A$ into the potassium salt form of ibuprofen. This is acidified with strong acid (reverting ibuprofen to its normal carboxylic acid form) during product recovery and separation (Bogdan et al., 2009).

### 2.1.1. Full ibuprofen batch separation ($Ibuprofen_{BX,F}$)

In the experimental demonstration, a comprehensive batch process has been used to recover ibuprofen (Bogdan et al., 2009). While it achieves ibuprofen in high purity, such a process can take a long time and require large quantities of feedstock and solvent materials (Andraos, 2011); the overall API product recovery is 57.8%. To estimate the capital costs required for such a process, a manufacturing procedure in which some batch vessels perform multiple functions of the Bogdan et al. (2009) scheme has been devised (Fig. 5). Batch vessel IB-BX-T1 is a mixing vessel which quenches the product of the last PFR; methanol is then evaporated by IB-BX-EV1. Batch vessel IB-BX-T2 performs an organic wash with diethyl ether and acidification with concentrated hydrochloric acid. In the next vessel, IB-BX-T3, three operations are performed. Discarding the aqueous phase in each case: extraction with diethyl ether, a wash with water, and a subsequent wash with brine. The material is then dried with sodium sulphate, mixed in IB-BX-T4 and filtered out by IB-BX-F1. The organic filtrate is concentrated and then dried in IB-BX-DR1, and subsequently solubilised in IB-BX-T5 with diethyl ether, with activated carbon also added; the latter is filtered out by IB-BX-F2. The filtrate is then concentrated in IBI-BX-DR2 prior to crystallisation in IB-BX-CR1. The crystals are filtered in IB-BX-F3 before being dried in IB-BX-DR3.

### 2.1.2. Ibuprofen continuous separation ($Ibuprofen_{CPM1}$, $Ibuprofen_{CPM2}$)

Continuous separation alternatives have significant promise in delivering cost and sustainability benefits, therefore we hereby economically evaluate two continuous liquid–liquid extraction (LLE) options we have previously published (Jolliffe and Gerogiorgis, 2015a,b). The first option (Ibuprofen CPM1) uses toluene as a waste-extracting solvent, operating at 65 °C, at a solvent mass injection rate equal to 75% of the incoming reactor effluent. The second option (Ibuprofen CPM2) uses *n*-hexane, also at 65 °C, but at a solvent mass injection rate equal to 50% of the incoming reactor effluent. The former option (Ibuprofen CPM1) has the advantages of lower environmental impact (toluene is less toxic and environmentally more acceptable than *n*-hexane), while *n*-hexane use requires less solvent for similar product recovery (Ibuprofen CPM1 can recover 89.2% of API, while CPM2 can recover 89.5%). Toluene use is thus strongly recommended here; nevertheless, *n*-hexane use is analysed in order to determine the difference in potential cost savings. An exemplary flowsheet of the above process is given in Fig. 5. In continuous contacting tank IB-CPMX-T101, the incoming reactor product stream is acidified. The resulting acidified stream then proceeds to liquid–liquid extraction in IB-CPMX-T102, where either toluene ($X=1$) or hexane ($X=2$) are used. Given the low

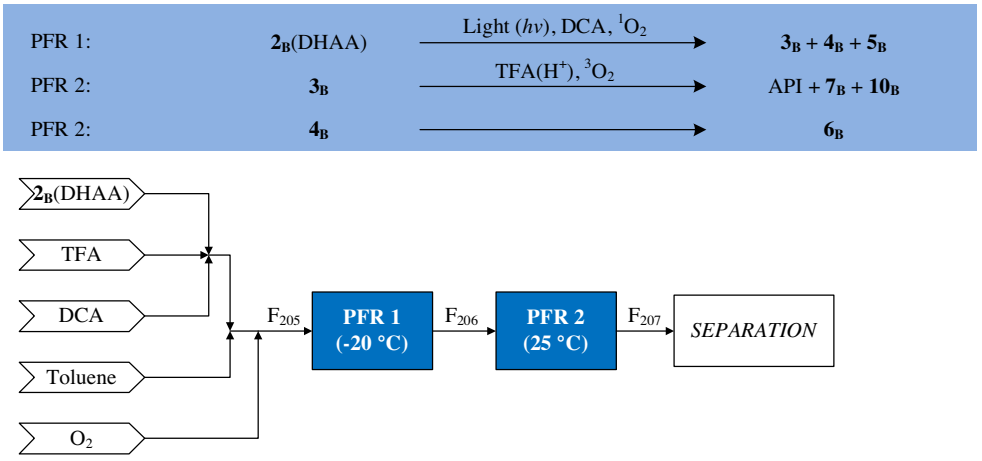


**Fig. 2.** Demonstrated process flowsheet for the CPM of artemisinin (Kopetzki et al., 2013).

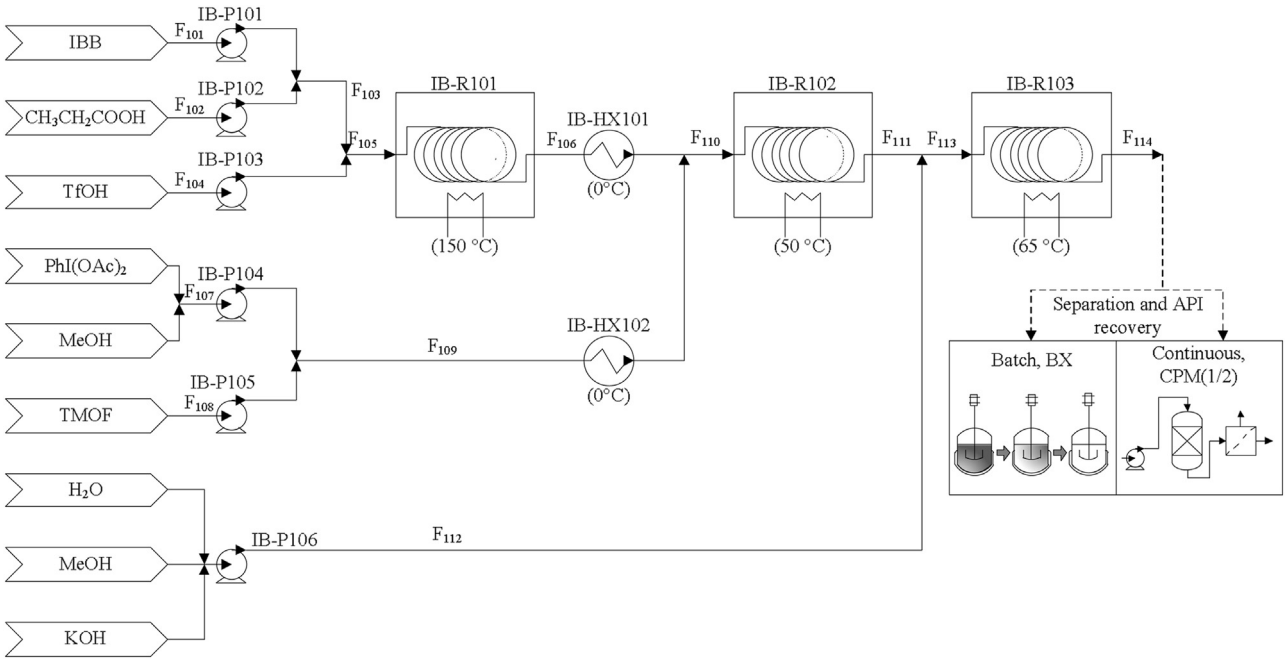


**Fig. 3.** Detailed process flowsheet including key unit operation equipment for CPM of ibuprofen (Bogdan et al., 2009).

quantities of solvent used in this extraction stage relative to the organic reactor effluent feed, considerable residence times may be required to ensure adequate inter-phase contact and mass transfer.

#### 2.1.3. Lean Ibuprofen batch separation ($Ibuprofen_{BX,L}$)

A more uniform basis for comparison to continuous separations is provided by considering a simplified batch separation scheme, based on the process used by Bogdan et al. (2009). In this simplified scheme (Fig. 5), the major unit operations (those which perform quenches, solvent swaps, acid neutralisation, and extraction) have been kept, while those which remove trace impurities or produce the API in solid form have been removed. A yield of 68% has been estimated for such a process, based on yields achieved after similar steps (Bogdan et al., 2009); this corresponds to a product recovery of 77%. The process vessel tags and purposes are exactly the same as described for the full ibuprofen batch separation.

### 2.2. Artemisinin

The second flowsheet studied here is based on research by Kopetzki et al. (2013). Dihydroartemisinic acid (DHAA, species $\mathbf{2}_B$) is a waste substance from the prevalent (batch) extraction of artemisinin from the plant *Artemisia annua*. It is mixed with trifluoro-acetic acid (acting as acid catalyst), 9,10-dicyanoanthracene (DCA, a photosensitizing dye), oxygen, and toluene solvent. The dye takes no direct part in the reaction, but promotes singlet oxygen ($^1O_2$) generation under a light source; a high intensity monochromatic light has been used by Kopetzki et al. (2013), and it is assumed that a similar device is available here. In the first plug flow reactor, which is chilled to $-20\,^{\circ}C$, $\mathbf{2}_B$ undergoes photooxidation toward the key organic intermediate $\mathbf{3}_B$ and by-products. The conversion attained in this reactor is 98% (Kopetzki et al., 2013; Seeberger et al., 2014). In the second reactor, several reactions take place. The key ones are a Hock rearrangement and oxidation with triplet oxygen ($^3O_2$), producing artemisinin (species $\mathbf{1}_B$); as previously, a variety of by-products are also produced. The conversion attained in the second reactor is estimated to be 83.5% (Jolliffe and Gerogiorgis, 2016).

#### 2.2.1. Full artemisinin batch separation ($Artemisinin_{BX}$)

An elaborate batch process has been used to recover artemisinin in the experimental demonstration, consisting of washes, drying, crystallisations, evaporations and filtrations; an overall product recovery of 70.8% is achieved with this method (Seeberger et al., 2014). A potential scheme with multi-role batch equipment has been devised to allow capital cost estimations (Fig. 6). The first vessel, AR-BX-T1 extracts and removes acid with sodium bicarbonate ($NaHCO_3$), washes the organic phase with water and brine, and then dries it with sodium sulphate ($Na_2SO_4$). The organic stream is then concentrated via reduced pressure evaporation in AR-BX-EV1. The resulting material is then dissolved in acetonitrile in AR-BX-T2 before all solvent is evaporated with AR-BX-DR1; this removes any remaining toluene (Seeberger et al., 2014). Acetonitrile is again added along with activated carbon, with the resulting mixture refluxed, in AR-BX-T3; the carbon is removed by filter AR-BX-F1. The filtrate is evaporated and dried with AR-BX-DR2 with the solids then recrystallized in AR-BX-CR1. The mother liquor (filtrate from AR-BX-F2) is washed, dried (AR-BX-DR3) and recrystallised again (AR-BX-CR2). The solids from the first crystalliser and the mother liquor are washed (in AR-BX-T4 and AR-BX-T5, respectively) before they are alternately dried by AR-BX-DR4. They are then combined and recrystallised again in AR-BX-CR3. The solids are filtered by AR-BX-F3 and finally washed in AR-BX-T5.

#### 2.2.2. Artemisinin continuous separation ($Artemisinin_{CPM1}$, $Artemisinin_{CPM2}$)

Here, we expand on a previous publication (Jolliffe and Gerogiorgis, 2015b) and evaluate the cost saving potential of continuous crystallisation for API recovery (Fig. 6). Using the reported product recovery achieved by means of the batch scheme outlined above as a reference case for comparison, two continuous crystallisation alternatives have been studied. The first ($Artemisinin_{CPM1}$) is analysed using published solubility data for the use of 30:70 toluene:ethanol antisolvent mixture (by weight), and the second ($Artemisinin_{CPM2}$) is evaluated using solubility data for the use of 30:70 toluene:ethyl acetate antisolvent mixture (by weight), with all solubilities estimated using the UNIFAC method. Ethyl acetate has been identified from among eight possible antisolvents as the most promising candidate for this process (Jolliffe and Gerogiorgis,

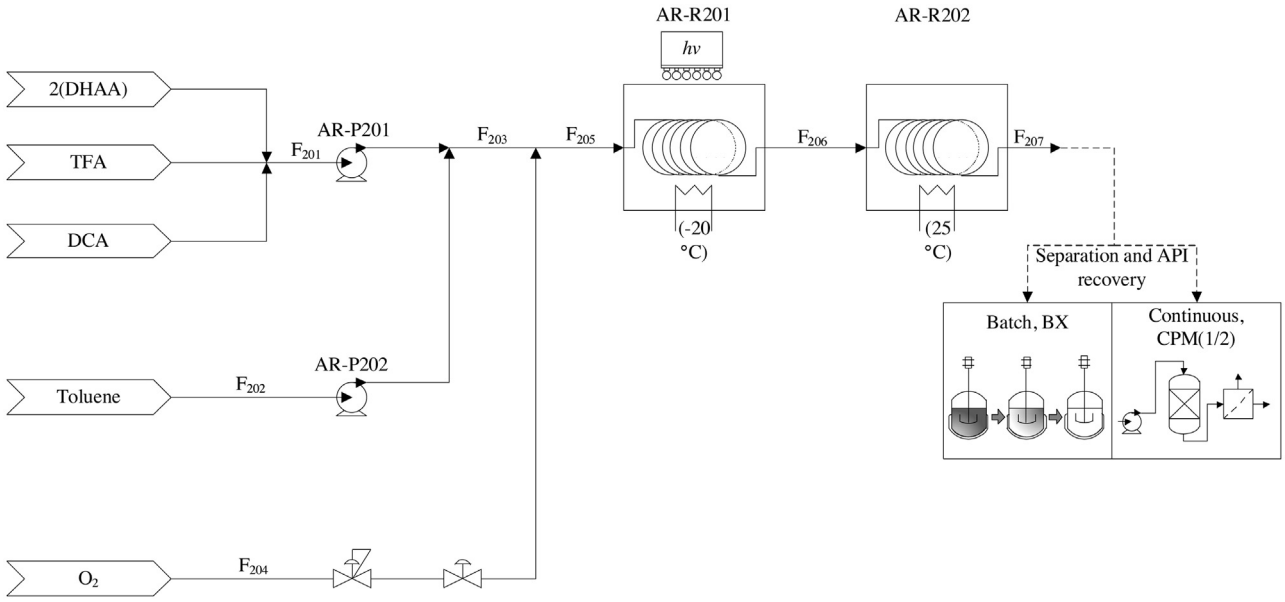


**Fig. 4.** Detailed process flowsheet including key unit operation equipment for CPM of artemisinin (Kopetzki et al., 2013).

2016). An agitated tank (AR-CPMX-T201) neutralises the acid; the residence time must here be sufficient to allow for adequate mass transfer between the two immiscible phases (toluene and an aqueous phase) (Jolliffe and Gerogiorgis, 2016). The resulting neutralised organic phase stream is heated with AR-CPMX-HX201 and some solvent is removed via evaporation in AR-CPMX-FC201, in order to sufficiently concentrate the stream for crystallisation. The stream is subsequently cooled to the required temperature with AR-CPMX-HX202 before proceeding to the crystalliser (AR-CPMX-CR201), where either ethanol or ethyl acetate is used as the essential anti-solvent.

#### 2.2.3. Lean artemisinin batch separation ($Artemisinin_{BX}$)

By removing unit operations not directly related to recovering artemisinin or producing it in dry solid form, we obtain an alternative batch separation scheme which is directly comparable to the continuous separation case. In this modified batch scheme (Fig. 6), the unit operations for swapping toluene for acetonitrile and for removing DCA with activated carbon are not included. The process proceeds from the quenching and washing of the incoming reactor effluent and subsequent removal of toluene to the crystallisation operations. The expected product recovery remains at 70.8%.

### 2.3. Higher production capacity (1000 kg/year)

The processes studied in the present technoeconomic study, for both APIs, produce 100 kg/year, which is markedly higher than the laboratory scale, but perhaps smaller than certain industrial implementations. The potential cost savings at 1000 kg/year have been evaluated with the same cost estimation methods.

### 2.4. Material requirements

A summary of the annual material input requirements for reagents, catalysts, solvents and other substances is given in Table 1. The material requirements for the higher plant capacity of 1000 kg/year API are an order of magnitude higher. Solvents and antisolvents used in the process toward product separation are considered to be recovered at a rate of 90%, a common assumption (Boodhoo and Harvey, 2013); input requirements and associated costs for these materials (ibuprofen: methanol, water/brine, ethyl acetate, toluene, hexane; artemisinin: toluene, cyclohexane, ethanol, ethyl acetate, acetonitrile) have been adjusted accordingly.

## 3. Cost estimation

The process configurations studied here have been assumed to be considered for implementation at an existing pharmaceutical manufacturing site, with much of the essential and auxiliary infrastructure already in place. An 8040-h working year (335 days) has been considered. A consistent combination of sourced vendor data and established economic prediction methods have been used to estimate both Capital Expenditure (CapEx) and Operating Expenditure (OpEx).

### 3.1. Capital Expenditure (CapEx)

Vendor prices have been sourced where possible for process vessels and equipment of suitable capacity. Wherever these are unavailable, cost-capacity correlations have been used (Woods, 2007). The correlations take the form of a power function:

$$C_B = C_A \left(\frac{S_B}{S_A}\right)^n f \quad (1)$$

Here, $C_B$ and $C_A$ are the costs of two identical pieces of equipment (B and A) which are at different capacities, given by $S_B$ and $S_A$. These capacities are of a dimension inherent to the equipment: examples include tank volume and filter area. The exponent $n$ is particular to the type of equipment, and typically ranges between 0.2–1.0. Other factors (summarised within $f$) can be applied to take into account design options such as construction material or operating conditions. Wherever there is a significant surplus in the applicable capacity range in comparison to the required capacity, these additional factors have not been used. To account for the greater cost of continuous equipment with regards to batch equipment of the same capacity, a factor of 0.9 has been applied to continuous equipment whenever there is no suitable batch equivalent cost-capacity relation available. Furthermore, wherever the determined price corresponds to the past, the Chemical Engineering Plant Cost Index (CEPCI) has been used in order to incorporate inflation effects

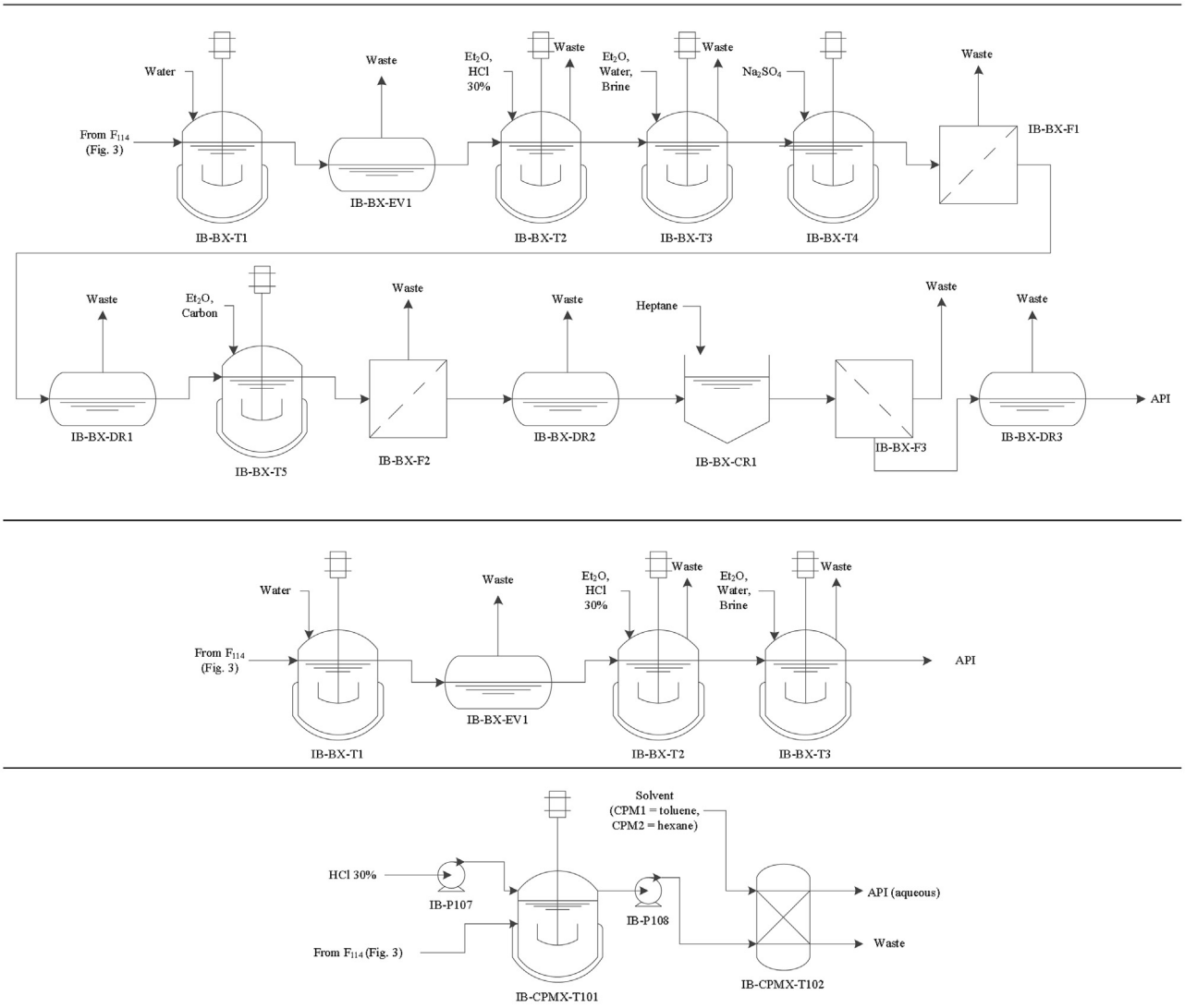


**Fig. 5.** Ibuprofen product recovery. Top: batch purification, method of Bogdan et al. (2009). Middle: simplified batch separation. Bottom: potential continuous ibuprofen purification; CPM1 uses toluene as solvent, CPM2 uses *n*-hexane (Jolliffe and Gerogiorgis, 2015a).

**Table 1**
Main annual material requirements (kg) for the production of 100 kg/year of API, for full batch (BX,F), lean batch (BX,L) and continuous (CPM) separations schemes.

| | Ibuprofen$_{SEP}$ | | | | | | Artemisinin$_{SEP}$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *SEP*= | BX,F (kg) | BX,L (kg) | CPM1 (kg) | CPM2 (kg) | Price (£/kg) | *SEP*= | BX,F (kg) | BX,L (kg) | CPM1 (kg) | CPM2 (kg) | Price (£/kg) |
| Process reagents, catalysts and solvents | | | | | | | | | | | |
| IBB | 128 | 96 | 83 | 82 | 1.13 | DHAA | 188 | 188 | 207 | 230 | – |
| $C_2H_5COOH$ | 70 | 53 | 46 | 45 | 1.81 | DCA | 1 | 1 | 1 | 1 | 108.65 |
| $PhI(OAc)_2$ | 311 | 233 | 201 | 201 | 67.70 | TFA | 45 | 45 | 50 | 55 | 15.43 |
| TMOF | 404 | 303 | 262 | 261 | 1.86 | O2 | 82 | 82 | 90 | 100 | 0.50 |
| Water | 657 | 493 | 426 | 424 | 0.60 | Toluene | 135 | 135 | 149 | 166 | 0.56 |
| TfOH | 710 | 532 | 460 | 458 | 21.64 | $NaHCO_{3(aq)}$ | 701 | 701 | 773 | 859 | 0.57 |
| KOH | 1,435 | 1,076 | 929 | 926 | 0.93 | | | | | | |
| MeOH | 299 | 224 | 193 | 193 | 0.25 | | | | | | |
| HCl 30% | 2,534 | 1,900 | 1,641 | 1,635 | 0.08 | | | | | | |
| Materials used in product separation and recovery | | | | | | | | | | | |
| Water/brine | 3,577 | 2,683 | 0 | 0 | 0.60 | Cyclohexane | 473 | 473 | 0 | 0 | 1.90 |
| $Et_2O$ | 3,138 | 2,353 | 0 | 0 | 1.59 | EtOH | 15 | 15 | 47 | 0 | 0.61 |
| Toluene | 0 | 0 | 326 | 0 | 0.56 | EtOAc | 0 | 0 | 0 | 24 | 0.56 |
| Hex | 0 | 0 | 0 | 216 | 0.49 | ACN | 16 | 0 | 0 | 0 | 1.56 |
| Total | 13,262 | 9,947 | 4,565 | 4,442 | | Total | 1,655 | 1,639 | 1,318 | 1,436 | |

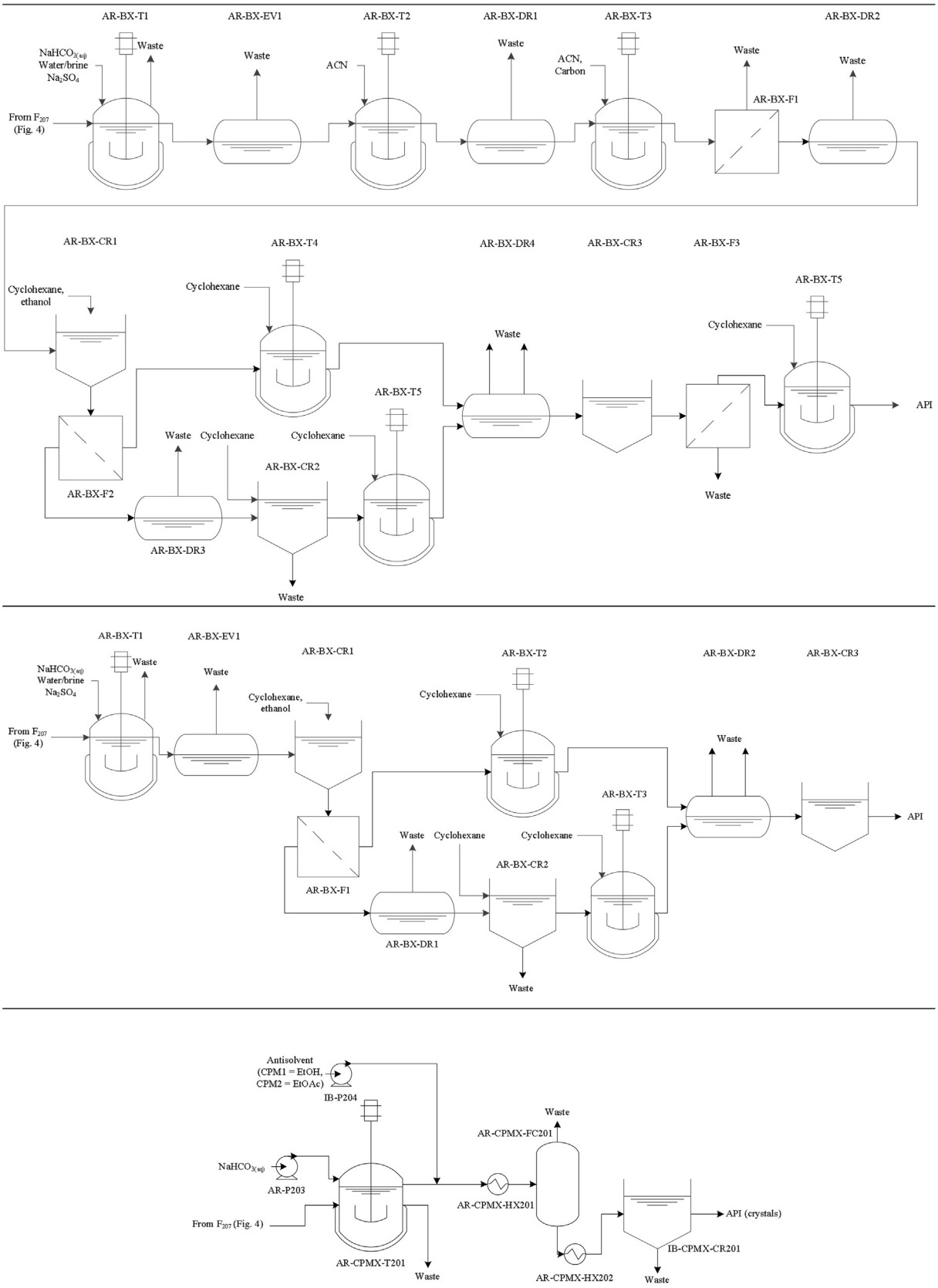


**Fig. 6.** Artemisinin product recovery. Top: batch purification, method of Kopetzki et al. (2013). Bottom: potential continuous ibuprofen purification; CPM1 uses ethanol as antisolvent, CPM2 uses ethyl acetate (Jolliffe and Gerogiorgis, 2016).

**Table 2**
Free-On-Board cost estimates for key process equipment for ibuprofen: batch (full, BX,F; lean, BX,L) and CPM options (CPM 1,2).

| Ibuprofen full batch production (BX,F) | | | | | | | | | 100 kg/year | | | 1000 kg/year | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| IB-R101 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 17.34 | 22,605 | 22,605 | – | – | – | (Corning, 2015) |
| IB-R102 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 5.44 | 7,094 | 7,094 | – | – | – | (Corning, 2015) |
| IB-R103 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 78.53 | 102,388 | 102,388 | – | – | – | (Corning, 2015) |
| IB-HX(101-102) | Cooler | 2015 | – | – | – | 2 | 3,454 | – | – | 3,454 | 6,907 | – | – | – | (Cole-Palmer, 2015) |
| IB-P(101-106) | Pump | 2015 | – | – | – | 6 | 958 | – | – | 958 | 5,748 | – | – | – | (ProMinent, 2015) |
| IB-BX-T(1-5) | Mixing tank | 2007 | 10.33 | Turbine power (kW) | 0.30 | 5 | 22,230 | 5.00 | 0.70 | 13,599 | 67,993 | – | – | – | (Woods, 2007) |
| IB-BX-EV1 | Evaporator | 2015 | – | – | – | 1 | 5,872 | – | – | 5,872 | 5,872 | – | – | – | (FischerSci, 2015) |
| IB-BX-DR(1-3) | Dryer | 2007 | 10.33 | Drying area ($m^2$) | 0.32 | 3 | 58,500 | 3.00 | 0.10 | 21,737 | 65,210 | – | – | – | (Woods, 2007) |
| IB-BX-F(1-2) | Filter | 2007 | 10.33 | Filter area ($m^2$) | 0.60 | 2 | 134,550 | 150.00 | 0.50 | 7,268 | 14,536 | – | – | – | (Woods, 2007) |
| IB-BX-CR1 | Crystalliser | 2007 | 10.33 | Volume ($m^3$) | 0.68 | 1 | 146,250 | 75.00 | 0.20 | 2,867 | 2,867 | – | – | – | (Woods, 2007) |
| | | | | | | | | | | | 301,220 | | | | |
| Ibuprofen lean batch production (BX,L) | | | | | | | | | | | | | | | |
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| IB-R101 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 13.01 | 16,958 | 16,958 | 129.95 | 169,431 | 169,431 | (Corning, 2015) |
| IB-R102 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 4.08 | 5,317 | 5,317 | 40.87 | 53,283 | 53,283 | (Corning, 2015) |
| IB-R103 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 58.90 | 76,791 | 76,791 | 588.96 | 767,903 | 767,903 | (Corning, 2015) |
| IB-HX(101-102) | Cooler | 2015 | – | – | – | 2 | 3,454 | – | – | 3,454 | 6,907 | – | 3,454 | 6,907 | (Cole-Palmer, 2015) |
| IB-P(101-106) | Pump | 2015 | – | – | – | 6 | 958 | – | – | 958 | 5,748 | – | 958 | 5,748 | (ProMinent, 2015) |
| IB-BX-T(1-3) | Mixing tank | 2007 | 10.33 | Turbine power (kW) | 0.30 | 3 | 22,230 | 5.00 | 0.70 | 13,599 | 40,796 | 7.00 | 27,133 | 81,398 | (Woods, 2007) |
| IB-BX-EV1 | Evaporator | 2015 | – | – | – | 1 | 5,872 | – | – | 5,872 | 5,872 | – | 5,872 | 5,872 | (FischerSci, 2015) |
| | | | | | | | | | | | 158,389 | | | 1,090,543 | |
| Ibuprofen continuous production 1 (CPM 1) | | | | | | | | | | | | | | | |
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| IB-R101 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 11.23 | 14,645 | 14,645 | 112.21 | 146,298 | 146,298 | (Corning, 2015) |
| IB-R102 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 3.52 | 4,589 | 4,589 | 35.28 | 46,005 | 46,005 | (Corning, 2015) |
| IB-R103 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 50.86 | 66,306 | 66,306 | 508.55 | 663,053 | 663,053 | (Corning, 2015) |
| IB-HX(101-102) | Cooler | 2015 | – | – | – | 2 | 3,454 | – | – | 3,454 | 6,907 | – | 3,454 | 6,907 | (Cole-Palmer, 2015) |
| IB-P(101-108) | Pump | 2015 | – | – | – | 8 | 958 | – | – | 958 | 7,664 | – | 958 | 7,664 | (ProMinent, 2015) |
| IB-CPM1-T101 | Mixing tank | 2007 | 10.33 | Turbine power (kW) | 0.30 | 1 | 24,700 | 5.00 | 0.70 | 15,109 | 15,109 | 7.00 | 30,147 | 30,147 | (Woods, 2007) |
| IB-CPM1-T102 | LLE | 2007 | 10.33 | Volumetric flow ($L s^{-1}$) | 0.22 | 1 | 19,500 | 10.00 | 5.00 | 18,472 | 18,472 | 50.00 | 30,656 | 30,656 | (Woods, 2007) |
| | | | | | | | | | | | 133,693 | | | 930,730 | |
| Ibuprofen continuous production 2 (CPM 2) | | | | | | | | | | | | | | | |
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| IB-R101 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 11.19 | 14,596 | 14,596 | 111.83 | 145,808 | 145,808 | (Corning, 2015) |
| IB-R102 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 3.51 | 4,574 | 4,574 | 35.17 | 45,851 | 45,851 | (Corning, 2015) |
| IB-R103 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 103,208 | 80.00 | 50.68 | 66,084 | 66,084 | 506.84 | 660,830 | 660,830 | (Corning, 2015) |
| IB-HX(101-102) | Cooler | 2015 | – | – | – | 2 | 3,454 | – | – | 3,454 | 6,907 | – | 3,454 | 6,907 | (Cole-Palmer, 2015) |
| IB-P(101-108) | Pump | 2015 | – | – | – | 8 | 958 | – | – | 958 | 7,664 | – | 958 | 7,664 | (ProMinent, 2015) |
| IB-CPM2-T101 | Mixing tank | 2007 | 10.33 | Turbine power (kW) | 0.30 | 1 | 24,700 | 5.00 | 0.70 | 15,109 | 15,109 | 7.00 | 30,147 | 30,147 | (Woods, 2007) |
| IB-CPM2-T102 | LLE | 2007 | 10.33 | Volumetric flow ($L s^{-1}$) | 0.22 | 1 | 19,500 | 10.00 | 5.00 | 18,472 | 18,472 | 50.00 | 30,656 | 30,656 | (Woods, 2007) |
| | | | | | | | | | | | 133,407 | | | 927,864 | |

**Table 3**
Free-On-Board cost estimates for key process equipment for artemisinin: batch (full, BX,F; lean, BX,L) and CPM options (CPM 1,2).

| Artemisinin full batch production (BX,F) | | | | | | | | | 100 kg/year | | | 1000 kg/year | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| AR-R201 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 19.72 | 28,286 | 28,286 | – | – | – | (Corning, 2015) |
| AR-R202 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 78.92 | 113,191 | 113,191 | – | – | – | (Corning, 2015) |
| AR-P(201-202) | Pump | 2015 | – | – | – | 2 | 958 | – | – | 958 | 1,916 | – | – | – | (ProMinent, 2015) |
| AR-BX-T(1-6) | Mixing tank | 2007 | 10.33 | Turbine power (kW) | 0.30 | 6 | 22,230 | 5.00 | 0.70 | 13,599 | 81,591 | – | – | – | (Woods, 2007) |
| AR-BX-EV1 | Evaporator | 2015 | – | – | – | 1 | 5,872 | – | – | 5,872 | 5,872 | – | – | – | (FischerSci, 2015) |
| AR-BX-DR(1-4) | Dryer | 2007 | 10.33 | Drying area ($m^2$) | 0.32 | 4 | 58,500 | 3.00 | 0.10 | 21,737 | 86,946 | – | – | – | (Woods, 2007) |
| AR-BX-F(1-3) | Filter | 2007 | 10.33 | Filter area ($m^2$) | 0.60 | 3 | 134,550 | 150.00 | 0.50 | 4,845 | 14,536 | – | – | – | (Woods, 2007) |
| AR-BX-CR(1-3) | Crystalliser | 2007 | 10.33 | Volume ($m^3$) | 0.68 | 3 | 146,250 | 75.00 | 0.20 | 2,867 | 8,602 | – | – | – | (Woods, 2007) |
| | | | | | | | | | | | 340,940 | | | | |

| Artemisinin lean batch production 1 (BX,L) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_B$ | $C_B$ (£) | Total (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| AR-R201 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 19.72 | 28,286 | 28,286 | 196.24 | 281,448 | 281,448 | (Corning, 2015) |
| AR-R202 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 78.92 | 113,191 | 113,191 | 785.30 | 1,126,282 | 1,126,282 | (Corning, 2015) |
| AR-P(201-202) | Pump | 2015 | – | – | – | 2 | 958 | – | – | 958 | 1,916 | – | 958 | 1,916 | (ProMinent, 2015) |
| AR-BX-T(1-3) | Mixing tank | 2007 | 10.33 | Turbine power (kW) | 0.30 | 3 | 22,230 | 5.00 | 0.70 | 13,599 | 40,796 | 7.00 | 27,133 | 81,398 | (Woods, 2007) |
| AR-BX-EV1 | Evaporator | 2015 | – | – | – | 1 | 5,872 | – | – | 5,872 | 5,872 | – | 5,872 | 5,872 | (FischerSci, 2015) |
| AR-BX-DR(1-2) | Dryer | 2007 | 10.33 | Drying area ($m^2$) | 0.32 | 2 | 58,500 | 3.00 | 0.10 | 21,737 | 43,473 | 1.00 | 45,414 | 90,828 | (Woods, 2007) |
| AR-BX-F(1-3) | Filter | 2007 | 10.33 | Filter area ($m^2$) | 0.60 | 3 | 134,550 | 150.00 | 0.50 | 4,845 | 14,536 | 5.00 | 19,290 | 19,290 | (Woods, 2007) |
| AR-BX-CR(1-3) | Crystalliser | 2007 | 10.33 | Volume ($m^3$) | 0.68 | 3 | 146,250 | 75.00 | 0.20 | 2,867 | 8,602 | 2.00 | 13,724 | 41,171 | (Woods, 2007) |
| | | | | | | | | | | | 246,981 | | | 1,648,204 | |

| Artemisinin continuous production 1 (CPM 1) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| AR-R201 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 21.76 | 31,208 | 31,208 | 217.62 | 312,109 | 312,109 | (Corning, 2015) |
| AR-R202 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 87.08 | 124,884 | 124,884 | 870.84 | 1,248,966 | 1,248,966 | (Corning, 2015) |
| AR-P(201-204) | Pump | 2015 | – | – | – | 4 | 958 | – | – | 958 | 3,832 | – | 958 | 3,832 | (ProMinent, 2015) |
| AR-CPM1-T201 | Mixing tank | 2007 | 10.33 | Volume ($m^3$) | 0.30 | 1 | 24,700 | 10.00 | 0.70 | 15,109 | 15,109 | 7.00 | 30,147 | 30,147 | (Woods, 2007) |
| AR-CPM1-EX201 | LLE | 2007 | 10.33 | Volumetric flow ($L s^{-1}$) | 0.22 | 1 | 19,500 | 10.00 | 5.00 | 18,472 | 18,472 | 50.00 | 30,656 | 30,656 | (Woods, 2007) |
| AR-CPM1-HX(201-202) | Heat exchangers | 2007 | 10.33 | Heat transfer area ($m^2$) | 0.71 | 2 | 45,500 | 100.00 | 20.00 | 16,012 | 32,025 | 200.00 | 82,121 | 164,243 | (Woods, 2007) |
| AR-CPM1-FC201 | Flash column | 2007 | 10.33 | Volume ($m^3$) | 0.52 | 1 | 65,000 | 20.00 | 1.00 | 37,760 | 37,760 | 10.00 | 125,035 | 125,035 | (Woods, 2007) |
| AR-CPM1-CR201 | Crystalliser | 2007 | 10.33 | Volume ($m^3$) | 0.68 | 1 | 162,500 | 75.00 | 0.20 | 3,186 | 3,186 | 2.00 | 15,248 | 15,248 | (Woods, 2007) |
| | | | | | | | | | | | 266,476 | | | 1,930,236 | |

| Artemisinin continuous production 2 (CPM 2) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Item | | Ref. year | $f$(%) | Capacity basis | $n$ | Units | $C_A$ (£) | $S_A$ | $S_{B,1C}$ | $C_{B,1C}$ (£) | $Tot_{1C}$ (£) | $S_{B,1K}$ | $C_{B,1K}$ (£) | $Tot_{1K}$ (£) | Ref. |
| AR-R201 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 24.17 | 34,671 | 34,671 | 241.77 | 346,752 | 346,752 | (Corning, 2015) |
| AR-R202 | Reactor | 2014 | 1.06 | Volume (mL) | 1.00 | 1 | 113,529 | 80.00 | 96.74 | 138,741 | 138,741 | 967.50 | 1,387,596 | 1,387,596 | (Corning, 2015) |
| AR-P(201-204) | Pump | 2015 | – | – | – | 4 | 958 | – | – | 958 | 3,832 | – | 9,580 | 38,320 | (ProMinent, 2015) |
| AR-CPM2-T201 | Mixing tank | 2007 | 10.33 | Volume ($m^3$) | 0.30 | 1 | 24,700 | 10.00 | 0.70 | 15,109 | 15,109 | 7.00 | 30,147 | 30,147 | (Woods, 2007) |
| AR-CPM2-EX201 | LLE | 2007 | 10.33 | Volumetric flow ($L s^{-1}$) | 0.22 | 1 | 19,500 | 10.00 | 5.00 | 18,472 | 18,472 | 50.00 | 30,656 | 30,656 | (Woods, 2007) |
| AR-CPM2-HX(201-202) | Heat exchangers | 2007 | 10.33 | Heat transfer area ($m^2$) | 0.71 | 2 | 45,500 | 100.00 | 20.00 | 16,012 | 32,025 | 200.00 | 82,121 | 164,243 | (Woods, 2007) |
| AR-CPM2-FC201 | Flash column | 2007 | 10.33 | Volume ($m^3$) | 0.52 | 1 | 65,000 | 20.00 | 1.00 | 37,760 | 37,760 | 10.00 | 125,035 | 125,035 | (Woods, 2007) |
| AR-CPM2-CR201 | Crystalliser | 2007 | 10.33 | Volume ($m^3$) | 0.68 | 1 | 162,500 | 75.00 | 0.20 | 3,186 | 3,186 | 2.00 | 15,248 | 15,248 | (Woods, 2007) |
| | | | | | | | | | | | 283,796 | | | 2,137,998 | |

and allow for appropriate cost adjustments to the present time. A summary of the equipment costing for all considered processes (batch and continuous separations for both APIs) is given in Table 2 (ibuprofen) and Table 3 (artemisinin).

The use of inflation-adjusted Eq. (1) produces the Free-on-Board (FOB) cost. The Chilton Method has then been used to estimate the Battery Limits Installed Cost (Couper, 2003). The installed equipment cost has been taken to be 1.43 times the FOB. Process piping and instrumentation have been taken to be 0.3 and 0.12 times the installed equipment costs, respectively; the sum of the installed, piping, and instrumentation costs then forms the total physical plant cost, to which a final factor for construction (0.3) is included, producing the BLIC.

The Working Capital and Contingency (WCC) is calculated with working capital considered at 35% and 3.5% of annual material costs for processes which are batch and continuous, respectively (Schaber et al., 2011). The contingency has been set at 20% of the BLIC. Finally, the total CapEx required is computed as the sum of the BLIC and the WCC.

### 3.2. Ibuprofen flowsheet equipment

The flowsheet for the production of ibuprofen consists of three reactors (with integrated heating), IB-R(101-103) (Fig. 3). For cost estimations, vendor quotes for a modular plug-flow microreactor system from Corning have been used (Corning, 2015). A silicon carbide (SiC) version of the G1 is also offered, which is suitable for use with triflic acid. Although lower exponents of 0.42 have been reported for continuous pharmaceutical production reactors (Schaber et al., 2011), there are very few cost estimation methods for microreactors available (Harmsen, 2012); an exponent of 1.0 has therefore been used here, a value suggested for tubular plug flow reactors (Woods, 2007). The design scalings are such that the process produces 100 kg/year or 1000 kg/year of ibuprofen after separation and product recovery. The two chillers (IB-HX101, IB-HX102) have been costed based on available price data for equipment with suitable cooling ranges and capacity. The pumps have been costed based on commercially available solenoid metering pumps with suitable volumetric flowrate ranges and pressures.

#### 3.2.1. Batch separation

The process vessels and unit operation equipment used in the exemplary batch separation scheme (Fig. 5) for ibuprofen, based on the process employed by Bogdan et al. (2009), have been costed using cost-capacity equations, with prices converted from U.S. dollars (USD) to pounds sterling (GBP) at a rate of 1:0.65 (Woods, 2007). The mixing tanks IB-BX-T(1-5) have been taken to be closed vessels with a single-turbine shaft (0.7 kW) operating at 50–100 rpm, with an alloy factor of 1.9 applied due to the use of corrosive substances (HCl 30%, brine), and a 0.9 factor due to the relatively lower cost of batch equipment. The evaporator IB-BX-EV1 has been costed based on commercial rotary evaporators of suitable capacity. Dryers IB-BX-DR(1-3) have been costed as batch agitated pan dryers under vacuum with heating via conduction. The filters IB-BX-F(1-3) have been costed as vacuum leaf filters; a batch factor of 0.9 has also been applied. Finally, the crystalliser IB-BX-CR1 has been costed as a batch cooling crystalliser including a mixer, scaled by internal volume; a batch factor of 0.9 has again been applied according to the foregoing procedure.

#### 3.2.2. Continuous separation

As an alternative to complex and lengthy batch separation processes, a continuous alternative has been envisaged and evaluated. The equipment costing performed here does not include batch cost adjustment factors applied. The mixing tanks IB-CPMX-T101 (toluene, $X = 1$, or $n$-hexane, $X = 2$) have been costed as closed vessels with a turbine, exactly as performed for the batch mixing tanks. The liquid–liquid extractor IB-CPMX-T102 has been costed as a mixer with a separate gravity phase separator, including drives and pumps.

### 3.3. Artemisinin flowsheet equipment

The reactors for artemisinin synthesis (Fig. 4) have been costed similarly to those considered for CPM of ibuprofen, based on a commercial modular flow reactor concept by Corning, which is also offered as a photoreactor; a 10% price premium has been considered in order to account for the photoreactor version. The pumps are solenoid metering pumps (commercially sourced prices), and the photoreactors have heat exchange functionality.

#### 3.3.1. Batch separation

The batch separation scheme employed by Kopetzki et al. (2013) has been used as a basis to allow for the essential comparison between batch and continuous process operation. The mixing vessels AR-BX-T(1-6) are closed turbine vessels, similar to the ones used for ibuprofen (single turbine, 50–100 rpm, alloy factor, and batch cost factor taken into account). A commercial rotary evaporator has been used to cost AR-BX-EV1, and vacuum agitated pan dryers with a cost-capacity relationship have been used for AR-BX-DR(1-4); a cost-capacity relationship has also been used for AR-BX-F(1-3), which have been costed as vacuum leaf filters, with a 0.9 batch factor applied. As with the crystalliser used in batch ibuprofen separation, batch cooling crystallisers (with a batch factor of 0.9) have been used as the cost-capacity basis for AR-BX-CR(1-3).

#### 3.3.2. Continuous separation

The continuous separation of artemisinin studied here (Fig. 6) consists of three main process units, with two heat exchangers and pumps. The acid neutralisation tank AR-CPMX-T201 has been costed as a single turbine mixing tank, exactly as for other mixing tanks studied. Flash column AR-CPMX-FC201 has been costed as a vertical pressure vessel that can operate at up to 1 MPa, including access holes and nozzles. The heater AR-CPMX-HX201 and cooler AR-CPMX-HX202 have been costed as shell-and-tube heat exchangers with fixed heads.

### 3.4. Operating Expenditure (OpEx)

The cost of material purchase (including reagents, catalysts and solvents) forms a significant portion of the OpEx. The prices have been sourced from vendors as well as official records of imports and exports to and from countries including France, Spain, Germany, Iran, Saudi Arabia, China, Bangladesh and India.

A subset of the established heuristics employed by Schaber et al. (2011) have been used to estimate the balance of the OpEx, which is utilities and waste disposal costs. Utilities costs have been estimated based on the total amount of material input: a figure of £0.96/kg has been used. Waste disposal costs have been estimated at £0.35/L for solvents, which constitute a significant majority of the waste.

These values represent the best estimates at the current time. Labour costs have not been included, because the processes considered are not at the highest of production capacities, and the batch separation schemes employed in each experimental demonstration did not take processing time into consideration; some operations have been reported to run overnight (Bogdan et al., 2009; Seeberger et al., 2014). Batch processes however require significant manual intervention (Plumb, 2005), and with the number of operations employed, labour costs are expected to be considerably high. Optimisation of the batch separations (with respect

**Table 4**
CapEx costs (£) and savings for batch (full) and continuous API separation and recovery ($10^2$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,F | CPM 1(Savings) | CPM 2(Savings) | BX,F | CPM 1(Savings) | CPM 2(Savings) |
| Base case | BLIC | 733,989 | 325,773(−55.6%) | 320,406(−56.3%) | 807,162 | 649,326(−19.6%) | 691,532(−14.3%) |
| | WCC | 163,093 | 66,055(−59.5%) | 64,976(−60.2%) | 162,218 | 129,917(−19.9%) | 138,363(−14.7%) |
| | Total | 897,082 | 391,828(−56.3%) | 385,381(−57.0%) | 969,380 | 779,243(−19.6%) | 829,895(−14.4%) |
| KI5 | BLIC | 733,989 | 325,773(−55.6%) | 320,406(−56.3%) | 807,162 | 649,326(−19.6%) | 691,532(−14.3%) |
| | WCC | 164,503 | 66,066(−59.8%) | 64,987(−60.5%) | 162,547 | 129,953(−20.1%) | 138,404(−14.9%) |
| | Total | 898,491 | 391,839(−56.4%) | 385,393(−57.1%) | 969,709 | 779,280(−19.6%) | 829,935(−14.4%) |
| KI10 | BLIC | 733,989 | 325,773(−55.6%) | 320,406(−56.3%) | 807,162 | 649,326(−19.6%) | 691,532(−14.3%) |
| | WCC | 164,726 | 66,080(−59.9%) | 65,001(−60.5%) | 162,875 | 129,990(−20.2%) | 138,444(−15.0%) |
| | Total | 898,715 | 391,854(−56.4%) | 385,407(−57.1%) | 970,038 | 779,316(−19.7%) | 829,975(−14.4%) |
| SR70 | BLIC | 733,989 | 325,773(−55.6%) | 320,406(−56.3%) | 807,162 | 649,326(−19.6%) | 691,532(−14.3%) |
| | WCC | 171,847 | 66,071(−61.6%) | 64,986(−62.2%) | 162,923 | 129,925(−20.3%) | 138,371(−15.1%) |
| | Total | 905,835 | 391,844(−56.7%) | 385,392(−57.5%) | 970,085 | 779,251(−19.7%) | 829,903(−14.5%) |
| SR50 | BLIC | 733,989 | 325,773(−55.6%) | 320,406(−56.3%) | 807,162 | 649,326(−19.6%) | 691,532(−14.3%) |
| | WCC | 179,363 | 66,087(−63.2%) | 64,997(−63.8%) | 163,629 | 129,933(−20.6%) | 138,379(−15.4%) |
| | Total | 913,352 | 391,860(−57.1%) | 385,403(−57.8%) | 970,791 | 779,259(−19.7%) | 829,911(−14.5%) |

**Table 5**
CapEx costs (£) and savings for batch (lean) and continuous API separation and recovery ($10^2$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,L | CPM 1(Savings) | CPM 2(Savings) | BX,L | CPM 1(Savings) | CPM 2(Savings) |
| Base case | BLIC | 385,950 | 325,773(−15.6%) | 320,406(−15.8%) | 601,823 | 649,326(7.9%) | 691,532(14.9%) |
| | WCC | 89,412 | 66,055(−26.1%) | 64,976(−26.3%) | 121,141 | 129,917(7.2%) | 138,363(14.2%) |
| | Total | 475,362 | 391,828(−17.6%) | 385,381(−17.8%) | 722,965 | 779,243(7.8%) | 829,895(14.8%) |
| KI5 | BLIC | 385,950 | 325,773(−15.6%) | 320,406(−15.8%) | 601,823 | 649,326(7.9%) | 691,532(14.9%) |
| | WCC | 89,541 | 66,066(−26.2%) | 64,987(−26.4%) | 121,470 | 129,953(7.0%) | 138,404(13.9%) |
| | Total | 475,492 | 391,839(−17.6%) | 385,393(−17.8%) | 723,294 | 779,280(7.7%) | 829,935(14.7%) |
| KI10 | BLIC | 385,950 | 325,773(−15.6%) | 320,406(−15.8%) | 601,823 | 649,326(7.9%) | 691,532(14.9%) |
| | WCC | 89,709 | 66,080(−26.3%) | 65,001(−26.5%) | 121,799 | 129,990(6.7%) | 138,444(13.7%) |
| | Total | 475,659 | 391,854(−17.6%) | 385,407(−17.8%) | 723,622 | 779,316(7.7%) | 829,975(14.7%) |
| SR70 | BLIC | 385,950 | 325,773(−15.6%) | 320,406(−15.8%) | 601,823 | 649,326(7.9%) | 691,532(14.9%) |
| | WCC | 93,194 | 66,071(−29.1%) | 64,986(−29.3%) | 122,109 | 129,925(6.4%) | 138,371(13.3%) |
| | Total | 479,144 | 391,844(−18.2%) | 385,392(−18.4%) | 723,932 | 779,251(7.6%) | 829,903(14.6%) |
| SR50 | BLIC | 385,950 | 325,773(−15.6%) | 320,406(−15.8%) | 601,823 | 649,326(7.9%) | 691,532(14.9%) |
| | WCC | 96,976 | 66,087(−31.9%) | 64,997(−32.0%) | 123,076 | 129,933(5.6%) | 138,379(12.5%) |
| | Total | 482,927 | 391,860(−18.9%) | 385,403(−19.0%) | 724,900 | 779,259(7.5%) | 829,911(14.5%) |

to batch sizes, number of vessels, and production scheduling) will help lower operating costs, but it is extremely unlikely that they will be on par with continuous alternatives in terms of Operational Asset Effectiveness (OAE).

The sensitivity of the cost savings with respect to changes in key ingredient (KI) price and solvent recovery (SR) have been studied in comparison to the reference case conditions, which consider a cost of £1.13/kg for isobutyl benzene (ibuprofen KI), a representative market price. For the artemisinin processes no KI (DHAA) purchase cost has been assumed, given the benefits of installing the artemisinin process alongside an existing traditional batch production plant (to make use of waste DHAA as feed). The reference case condition for solvent recovery is 90% (including process solvents and solvents used in product separation). The sensitivity of the cost savings with respect to KI prices of £5/kg and £10/kg (KI5 and KI10, respectively) has been studied, while for the effects of poorer solvent recovery on cost savings, recovery rates of 70% and 50% (SR70 and SR50, respectively) have been considered.

### 3.5. Total costs

To quantify the combined impact of both the CapEx and OpEx, a 20-year plant lifetime has been considered and the total cost of operation has been evaluated by determining the Net Present Value (NPV):

$$\mathrm{NPV} = \mathrm{CapEx} + \sum_{i=1}^{\tau} \left( \frac{\mathrm{OpEx}}{(1+r)^i} \right) \quad (2)$$

Here, $\tau$ is the plant lifetime, and $r$ is the discount rate (taken to be the annual interest rate; a value of 5% has been used). Eq. (2) calculates the total cost, in present-day terms, of running a given process for the designated timespan (in this case, $\tau$ = 20 years).

## 4. Results

A graphical summary of the CapEx, OpEx and total cost savings for all process alternatives considered for the production of both APIs is given in Figs. 7–9.

### 4.1. Capital Expenditure

Ibuprofen shows CapEx savings at between 56.3% and 57.8% with respect to the full batch separation, and between 17.6% and 19.0% with respect to the lean batch separation. For artemisinin, CapEx savings of between 14.4% and 19.7% are attainable with respect to the full batch separation, while the CapEx for continuous separations is in fact between 7.5% and 14.8% greater than the

lean batch separation. There is little variation across the sensitivity options KI5, KI10, SR70 and SR50, which is expected because these concern material prices and waste, rather than equipment directly; the limited variation is attributed to the different levels of working capital required. A summary of these values is given in Tables 4 and 5. At the higher process capacity of 1000 kg/year API production, the CapEx savings (Table 8) for ibuprofen are broadly similar to the 100 kg/year capacity. However, for artemisinin, the CapEx for performing product separation using continuous operations is again more costly at the higher capacity (Table 8).

### 4.2. Operating Expenditure

Contrary to the foregoing observed trends regarding CapEx variation, OpEx savings vary to a greater extent, and solvent recovery rates have a stronger impact on economic viability than KI prices (Tables 6 and 7). For ibuprofen, OpEx savings are between 51.2% and 54.0% for 90% solvent recovery, increasing to over 76% in the case of SR50, when continuous separation is compared to the full batch separation. When compared to the lean batch separation of ibuprofen, OpEx savings are between 34.5% and 65.0%. Both KI prices and solvent recovery rates have significant effects on OpEx for artemisinin, with savings varying between 8.9% and 44.9% compared to the full batch separation, and in a similarly wide range for the lean batch case. At the higher process capacity, OpEx savings for ibuprofen are similar to those determined for the lower plant capacity. For artemisinin, a higher OpEx is required for continuous separation relative to the lean batch case at the higher plant capacity of 1000 kg/year (Table 9).

### 4.3. Total cost

Summaries of the total cost savings are given in Tables 10 and 11. Full batch production of ibuprofen costs the most. The continuous separation schemes for ibuprofen achieve a spectacular total cost reduction between 53.9% and 71.0%, compared to the full batch separation, and a remarkable total cost reduction between 27.0% and 52.6% compared to the lean batch separation case. For artemisinin, the computed total cost savings range between 14.0% and 23.9% (full batch separation case) and shrink to a narrower range between 3.0% and 12.5% (lean batch separation case). The use of *n*-hexane as a solvent ($\text{Ibuprofen}_{\text{CPM2}}$) results in greater cost savings in comparison to toluene use for ibuprofen recovery ($\text{Ibuprofen}_{\text{CPM1}}$), however the difference is very small less than 1% in each case). Conversely, the advantages of ethanol use for continuous artemisinin separation ($\text{Artemisinin}_{\text{CPM1}}$) are clearer, with total cost savings of 5% higher than the case of ethyl acetate use ($\text{Artemisinin}_{\text{CPM2}}$). When compared to the lean batch case, the CPM of artemisinin gener-

**Table 6**
OpEx costs (£) and savings for batch (full) and continuous API separation and recovery ($10^2$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,F | CPM 1(Savings) | CPM 2(Savings) | BX,F | CPM 1(Savings) | CPM 2(Savings) |
| Base case | Material | 46,558 | 25,716(−44.8%) | 25,554(−45.1%) | 2,244 | 1,476(−34.2%) | 1,628(−27.4%) |
| | U/W | 12,732 | 4,383(−65.6%) | 4,264(−66.5%) | 2,096 | 1,594(−23.9%) | 1,735(−17.2%) |
| | Total | 62,762 | 30,657(−51.2%) | 30,374(−51.6%) | 4,340 | 3,070(−29.3%) | 3,363(−22.5%) |
| KI5 | Material | 50,585 | 26,035(−48.5%) | 25,873(−48.9%) | 3,183 | 2,513(−21.1%) | 2,780(−12.7%) |
| | U/W | 12,732 | 4,383(−65.6%) | 4,264(−66.5%) | 2,096 | 1,594(−23.9%) | 1,735(−17.2%) |
| | Total | 66,789 | 30,976(−53.6%) | 30,692(−54.0%) | 5,279 | 4,106(−22.2%) | 4,514(−14.5%) |
| KI10 | Material | 51,223 | 26,448(−48.4%) | 26,284(−48.7%) | 4,123 | 3,549(−13.9%) | 3,931(−4.7%) |
| | U/W | 12,732 | 4,383(−65.6%) | 4,264(−66.5%) | 2,096 | 1,594(−23.9%) | 1,735(−17.2%) |
| | Total | 67,427 | 31,389(−53.4%) | 31,104(−53.9%) | 6,218 | 5,143(−17.3%) | 5,665(−8.9%) |
| SR70 | Material | 71,568 | 26,177(−63.4%) | 25,863(−63.9%) | 4,259 | 1,700(−60.1%) | 1,854(−56.5%) |
| | U/W | 26,198 | 5,379(−79.5%) | 5,050(−80.7%) | 5,681 | 4,113(−27.6%) | 4,461(−21.5%) |
| | Total | 106,874 | 32,382(−69.7%) | 31,734(−70.3%) | 9,940 | 5,813(−41.5%) | 6,314(−36.5%) |
| SR50 | Material | 93,045 | 26,638(−71.4%) | 26,172(−71.9%) | 6,274 | 1,924(−69.3%) | 2,079(−66.9%) |
| | U/W | 39,665 | 6,376(−83.9%) | 5,835(−85.3%) | 9,266 | 6,631(−28.4%) | 7,187(−22.4%) |
| | Total | 147,452 | 34,107(−76.9%) | 33,094(−77.6%) | 15,540 | 8,556(−44.9%) | 9,266(−40.4%) |

**Table 7**
OpEx costs (£) and savings for batch (lean) and continuous API separation and recovery ($10^2$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,L | CPM 1(Savings) | CPM 2(Savings) | BX,L | CPM 1(Savings) | CPM 2(Savings) |
| Base case | Material | 34,919 | 25,716(−26.4%) | 25,554(−26.8%) | 2,219 | 1,476(−33.5%) | 1,628(−26.6%) |
| | U/W | 9,549 | 4,383(−54.1%) | 4,264(−55.3%) | 2,073 | 1,594(−23.1%) | 1,735(−16.3%) |
| | Total | 47,072 | 30,657(−34.9%) | 30,374(−35.5%) | 4,293 | 3,070(−28.5%) | 3,363(−21.7%) |
| KI5 | Material | 35,289 | 26,035(−26.2%) | 25,873(−26.7%) | 3,159 | 2,513(−20.5%) | 2,780(−12.0%) |
| | U/W | 9,549 | 4,383(−54.1%) | 4,264(−55.3%) | 2,073 | 1,594(−23.1%) | 1,735(−16.3%) |
| | Total | 47,442 | 30,976(−34.7%) | 30,692(−35.3%) | 5,232 | 4,106(−21.5%) | 4,514(−13.7%) |
| KI10 | Material | 35,767 | 26,448(−26.1%) | 26,284(−26.5%) | 4,098 | 3,549(−13.4%) | 3,931(−4.1%) |
| | U/W | 9,549 | 4,383(−54.1%) | 4,264(−55.3%) | 2,073 | 1,594(−23.1%) | 1,735(−16.3%) |
| | Total | 47,920 | 31,389(−34.5%) | 31,104(−35.1%) | 6,171 | 5,143(−16.7%) | 5,665(−8.2%) |
| SR70 | Material | 45,725 | 26,177(−42.8%) | 25,863(−43.4%) | 4,984 | 1,700(−48.2%) | 1,854(−43.2%) |
| | U/W | 19,649 | 5,379(−72.6%) | 5,050(−74.3%) | 5,614 | 4,113(−26.7%) | 4,461(−20.5%) |
| | Total | 72,204 | 32,382(−55.2%) | 31,734(−56.1%) | 10,597 | 5,813(−36.8%) | 6,314(−31.2%) |
| SR50 | Material | 56,532 | 26,638(−52.9%) | 26,172(−53.7%) | 7,748 | 1,924(−52.4%) | 2,079(−47.9%) |
| | U/W | 29,749 | 6,376(−78.6%) | 5,835(−80.4%) | 9,154 | 6,631(−27.6%) | 7,187(−21.5%) |
| | Total | 97,337 | 34,107(−65.0%) | 33,094(−66.0%) | 16,902 | 8,556(−39.0%) | 9,266(−33.6%) |

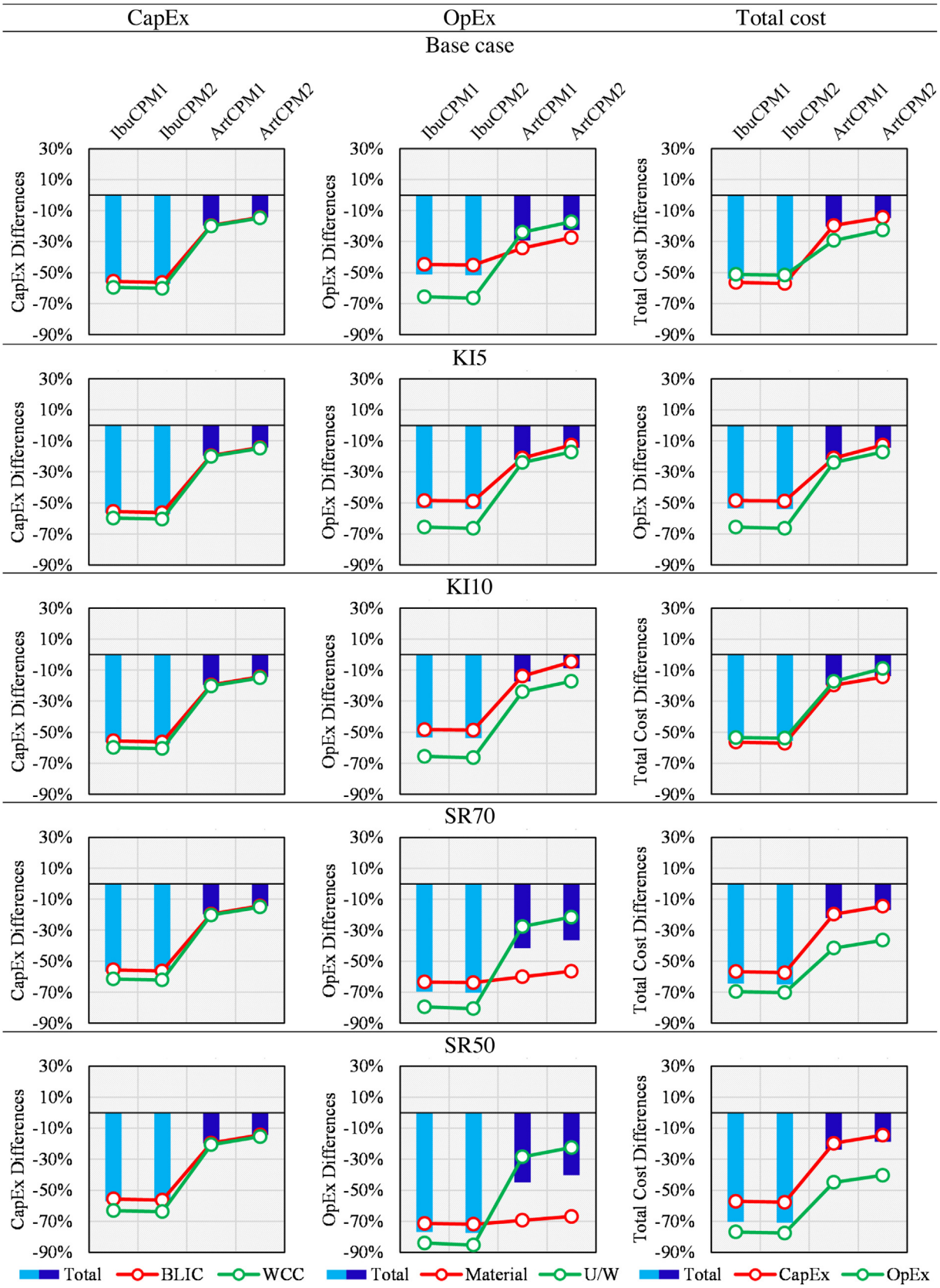


**Fig. 7.** Capital Expenditure (CapEx), Operating Expenditure (OpEx) and total cost differences for continuous product recovery for ibuprofen and artemisinin, with respect to the full reference batch separation in each case. Results illustrated include Battery Limits Installed Cost (BLIC), Working Capital and Contingency (WCC), raw material requirements, and Utilities and Waste management (U/W); API production capacity is 100 kg/year.

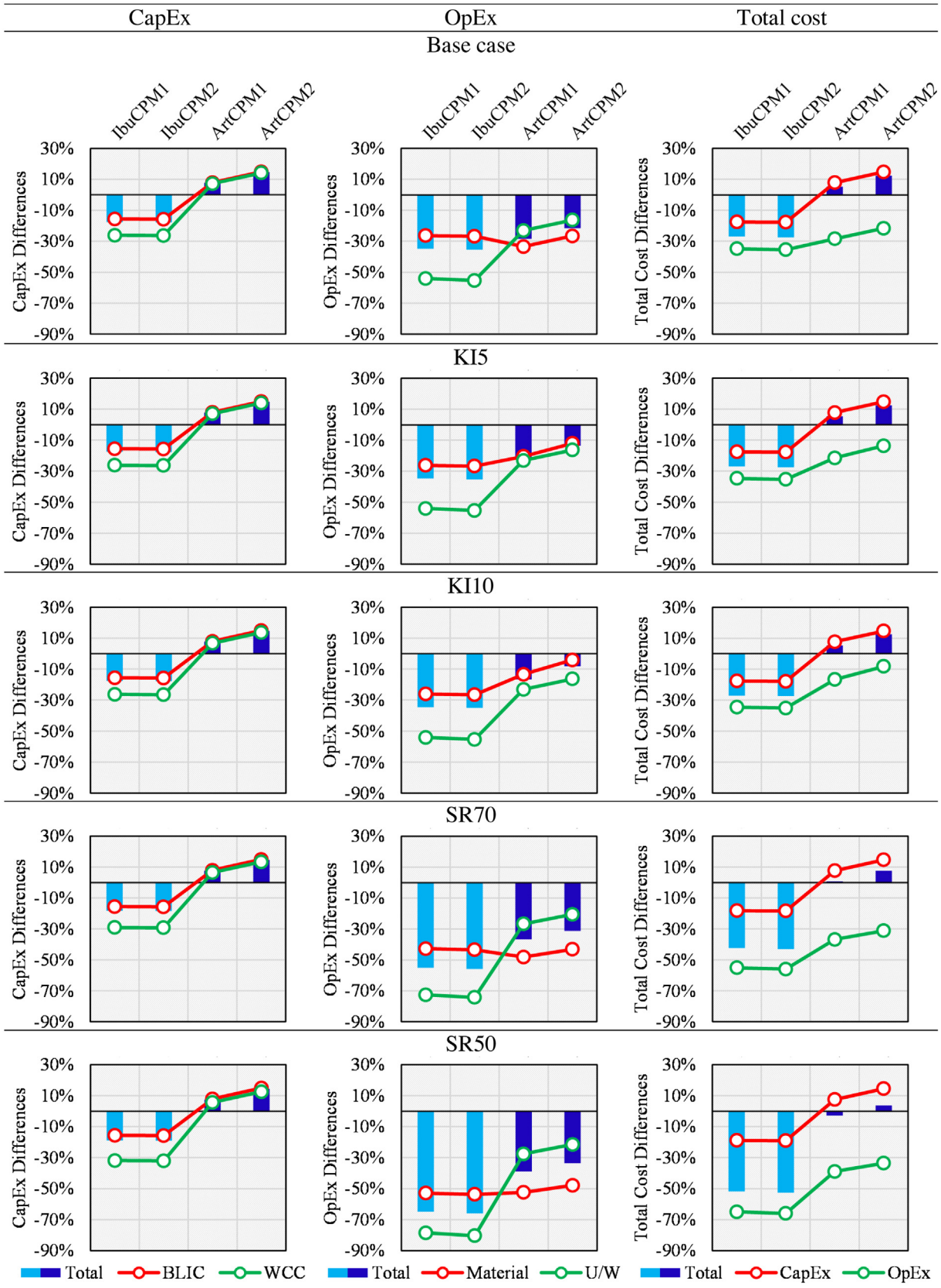


**Fig. 8.** Capital Expenditure (CapEx), Operating Expenditure (OpEx) and total cost differences for continuous product recovery for ibuprofen and artemisinin, with respect to the lean reference batch separation in each case. Results illustrated include Battery Limits Installed Cost (BLIC), Working Capital and Contingency (WCC), raw material requirements, and Utilities and Waste management (U/W); API production capacity is 100 kg/year.

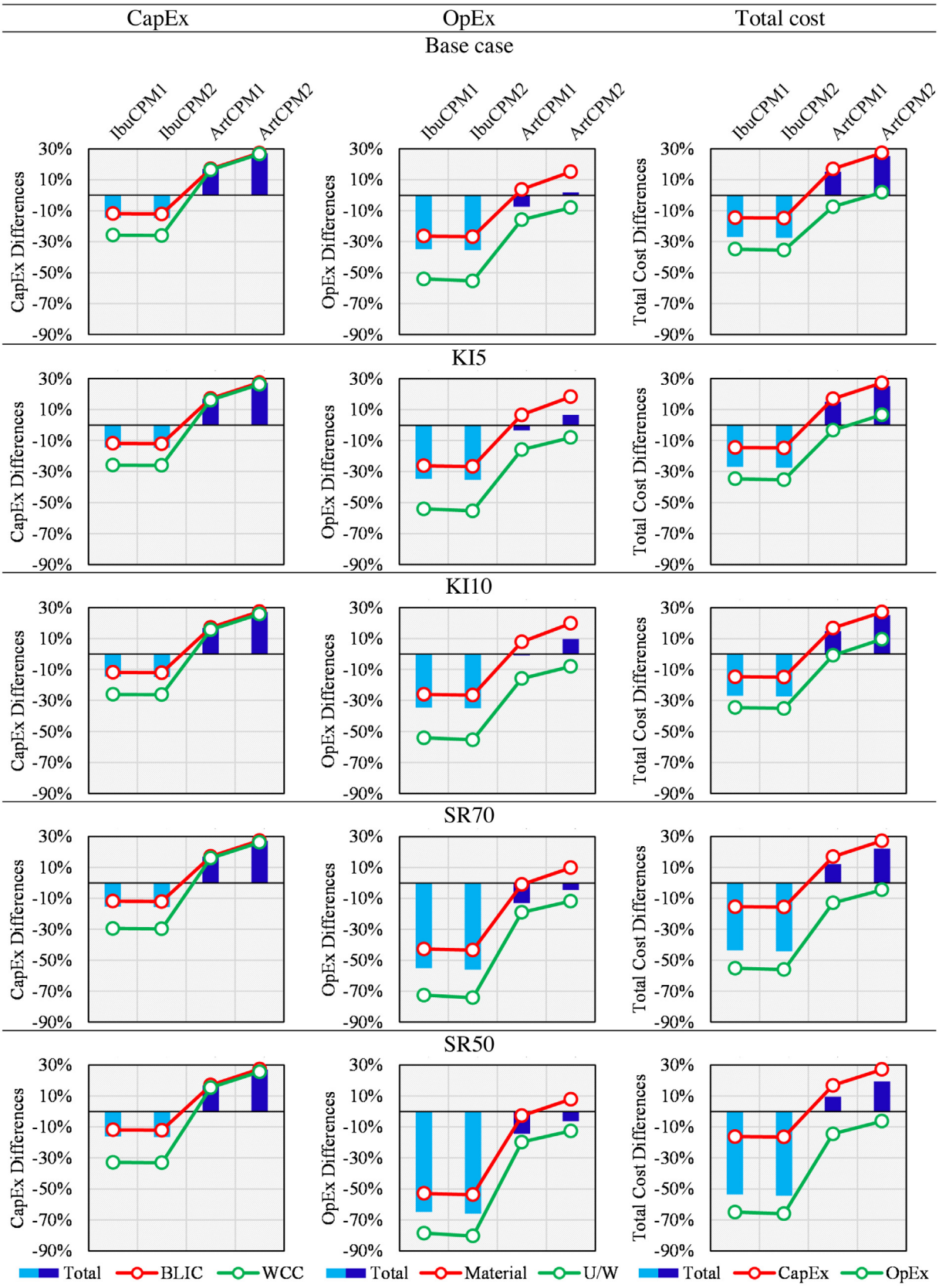


**Fig. 9.** Capital Expenditure (CapEx), Operating Expenditure (OpEx) and total cost differences for continuous product recovery for ibuprofen and artemisinin, with respect to the lean reference batch separation in each case. Results illustrated include Battery Limits Installed Cost (BLIC), Working Capital and Contingency (WCC), raw material requirements, and Utilities and Waste management U/W); API production capacity is 1000 kg/year.

**Table 8**
CapEx costs (£) and savings for batch (lean) and continuous API separation and recovery ($10^3$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,L | CPM 1(Savings) | CPM 2(Savings) | BX,L | CPM 1(Savings) | CPM 2(Savings) |
| Base case | BLIC | 2,934,882 | 2,587,483(−11.8%) | 2,580,497(−12.1%) | 4,089,169 | 4,787,483(17.1%) | 5,209,701(27.4%) |
| | WCC | 709,192 | 526,497(−25.8%) | 525,043(−26.0%) | 822,727 | 958,004(16.4%) | 1,042,504(26.7%) |
| | Total | 3,644,074 | 3,113,980(−14.5%) | 3,105,540(−14.8%) | 4,911,896 | 5,745,487(17.0%) | 6,252,205(27.3%) |
| KI5 | BLIC | 2,934,882 | 2,587,483(−11.8%) | 2,580,497(−12.1%) | 4,089,169 | 958,367(17.1%) | 5,209,701(27.4%) |
| | WCC | 710,487 | 526,609(−25.9%) | 525,155(−26.1%) | 825,998 | 5,745,850(16.0%) | 1,042,907(26.3%) |
| | Total | 3,645,369 | 3,114,092(−14.6%) | 3,105,652(−14.8%) | 4,915,167 | 4,787,483(16.9%) | 6,252,608(27.2%) |
| KI10 | BLIC | 2,934,882 | 2,587,483(−11.8%) | 2,580,497(−12.1%) | 4,089,169 | 4,787,483(17.1%) | 5,209,701(27.4%) |
| | WCC | 712,161 | 526,754(−26.0%) | 525,299(−26.2%) | 829,269 | 958,730(15.6%) | 1,043,310(25.8%) |
| | Total | 3,647,043 | 3,114,237(−14.6%) | 3,105,796(−14.8%) | 4,918,438 | 5,746,212(16.8%) | 6,253,011(27.1%) |
| SR70 | BLIC | 2,934,882 | 2,587,483(−11.8%) | 2,580,497(−12.1%) | 4,089,169 | 4,787,483(17.1%) | 5,209,701(27.4%) |
| | WCC | 747,015 | 526,658(−29.5%) | 525,151(−29.7%) | 826,683 | 958,373(15.9%) | 1,042,913(26.2%) |
| | Total | 3,681,897 | 3,114,142(−15.4%) | 3,105,648(−15.7%) | 4,915,852 | 5,745,856(16.9%) | 6,252,614(27.2%) |
| SR50 | BLIC | 2,934,882 | 2,587,483(−11.8%) | 2,580,497(−12.1%) | 4,089,169 | 4,787,483(17.1%) | 5,209,701(27.4%) |
| | WCC | 784,838 | 526,820(−32.9%) | 525,259(−33.1%) | 830,639 | 958,742(15.4%) | 1,043,321(25.6%) |
| | Total | 3,719,720 | 3,114,303(−16.3%) | 3,105,757(−16.5%) | 4,919,808 | 5,746,224(16.8%) | 6,253,023(27.1%) |

**Table 9**
OpEx costs (£) and savings for batch (lean) and continuous API separation and recovery ($10^3$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,L | CPM 1(Savings) | CPM 2(Savings) | BX,L | CPM 1(Savings) | CPM 2(Savings) |
| Base case | Material | 349,187 | 257,158(−26.4%) | 255,542(−26.8%) | 13,982 | 14,504(3.7%) | 16,102(15.2%) |
| | U/W | 95,489 | 43,828(−54.1%) | 42,643(−55.3%) | 18,713 | 15,750(−15.8%) | 17,218(−8.0%) |
| | Total | 470,717 | 306,510(−34.9%) | 303,690(−35.5%) | 32,695 | 30,254(−7.5%) | 33,320(1.9%) |
| KI5 | Material | 352,886 | 260,353(−26.2%) | 258,726(−26.7%) | 23,327 | 24,866(6.6%) | 27,614(18.4%) |
| | U/W | 95,489 | 43,828(−54.1%) | 42,643(−55.3%) | 18,713 | 15,750(−15.8%) | 17,218(−8.0%) |
| | Total | 474,416 | 309,704(−34.7%) | 306,873(−35.3%) | 42,040 | 40,616(−3.4%) | 44,832(6.6%) |
| KI10 | Material | 357,670 | 264,483(−26.1%) | 262,843(−26.5%) | 32,672 | 35,228(7.8%) | 39,126(19.8%) |
| | U/W | 95,489 | 43,828(−54.1%) | 42,643(−55.3%) | 18,713 | 15,750(−15.8%) | 17,218(−8.0%) |
| | Total | 479,200 | 313,835(−34.5%) | 310,990(−35.1%) | 51,385 | 50,978(−0.8%) | 56,344(9.7%) |
| SR70 | Material | 457,252 | 261,768(−42.8%) | 258,629(−43.4%) | 25,285 | 25,038(−1.0%) | 27,781(9.9%) |
| | U/W | 196,488 | 53,792(−72.6%) | 50,497(−74.3%) | 50,106 | 40,560(−19.1%) | 44,224(−11.7%) |
| | Total | 722,043 | 323,651(−55.2%) | 317,188(−56.1%) | 75,390 | 65,598(−13.0%) | 72,005(−4.5%) |
| SR50 | Material | 565,318 | 266,378(−52.9%) | 261,716(−53.7%) | 36,588 | 35,572(−2.8%) | 39,461(7.9%) |
| | U/W | 297,487 | 63,756(−78.6%) | 58,352(−80.4%) | 81,498 | 65,370(−19.8%) | 71,229(−12.6%) |
| | Total | 973,370 | 340,792(−65.0%) | 330,686(−66.0%) | 118,086 | 100,942(−14.5%) | 110,690(−6.3%) |

ally costs slightly more when using continuous separation. The cost trends for ibuprofen are broadly maintained when the process capacity is scaled up to 1000 kg/year of API production, but this is not the case for artemisinin, where the higher plant capacity produces greater cost disparities, in favour of the lean batch seperation process.

### 4.4. Process material efficiency

A useful metric for assessing process material efficiency and sustainability is the Environmental factor (E-factor) (Sheldon, 2012). It is attractive and widely used because it is intuitive to understand and can be applied to the widest variety of simple as well as complex processes, and is defined as the total quantity of waste (excluding water) produced per unit mass of product:

$$E = \frac{m_{\text{waste}}}{m_{\text{API}}} = \frac{m_{\text{bpd}} + m_{\text{ur}} + m_{\text{ws}} + m_{\text{uAPI}}}{m_{\text{API}}} \quad (3)$$

Here, waste comprises byproducts (bpd), unreacted reagents (ur), waste solvent (ws) and unrecovered API (uAPI); the denominator is the mass of API produced. Very favourably low E-factor values are straightforward to determine for industries exclusively using continuous production; the petrochemicals sector is a classic example, where values of as low as 0.1 are the de facto standard. For the pharmaceutical industry, where batch production is almost universal, values of 200 are not uncommon (Ritter, 2013). The present technoeconomic study considers E-factor values which have been computed to give an indication of the material efficiencies of all processes studied (Tables 10 and 11). For both process capacity levels, continuous separation has a clear advantage with superior E-factor values. Naturally, poorer solvent recovery (SR70, SR50) results in worse material efficiency (higher E-factor values), and there is no effect on material efficiency from KI cost. The leaner batch processes show improved E-factors, however they are still worse than the respective continuous manufacturing alternatives. Furthermore, the considered increase in process capacity from 100 to 1000 kg/year of API production did not discernibly impact E-factor values.

## 5. Discussion

The process units and auxiliary equipment have been costed by determining prices for items of suitable capacity where possible; remaining items have costed using cost-capacity relationships with typical reference cost values for the given type of equipment. In general, the required design capacities studied here are at the low end of the application range for the relationships, therefore some cost overestimation may have occurred. The most important equip-

**Table 10**
Total costs (£) and savings (percent difference) for batch (full) and continuous API separation and recovery ($10^2$ kg/year API production).

| | | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,F | CPM 1(Savings) | CPM 2(Savings) | BX,F | CPM 1(Savings) | CPM 2(Savings) |
| Base case | Total | 1,679,238 | 773,877(−53.9%) | 763,908(−54.5%) | 1,023,465 | 817,505(−20.1%) | 871,805(−14.8%) |
| | E-factor | 131.6 | 44.7 | 43.4 | 15.6 | 12.2 | 13.4 |
| KI5 | Total | 1,730,834 | 777,869(−55.1%) | 767,887(−55.6%) | 1,035,498 | 830,455(−19.8%) | 886,192(−14.4%) |
| | E-factor | 131.6 | 44.7 | 43.4 | 15.6 | 12.2 | 13.4 |
| KI10 | Total | 1,739,006 | 783,032(−55.0%) | 773,032(−55.5%) | 1,047,531 | 843,405(−19.5%) | 900,579(−14.0%) |
| | E-factor | 131.6 | 44.7 | 43.4 | 15.6 | 12.2 | 13.4 |
| SR70 | Total | 2,237,720 | 795,396(−64.5%) | 780,865(−65.1%) | 1,093,961 | 851,693(−22.1%) | 908,593(−16.9%) |
| | E-factor | 271.9 | 55.0 | 51.6 | 42.3 | 31.6 | 34.3 |
| SR50 | Total | 2,750,926 | 816,915(−70.3%) | 797,822(−71.0%) | 1,164,458 | 885,881(−23.9%) | 945,381(−18.8%) |
| | E-factor | 412.2 | 65.4 | 59.8 | 69.1 | 51.0 | 55.3 |

**Table 11**
Total costs (£) and savings (percent difference) for batch (lean) and continuous API separation and recovery, for both $10^2$ and $10^3$ kg/year API production capacities.

| | API (kg/year) | Ibuprofen | | | Artemisinin | | |
|---|---|---|---|---|---|---|---|
| | | BX,L | CPM 1(Savings) | CPM 2(Savings) | BX,L | CPM 1(Savings) | CPM 2(Savings) |
| Base case | $10^2$ | 1,061,979 | 773,877(−27.1%) | 769,511(−27.5%) | 776,460 | 817,505(5.3%) | 871,805(12.3%) |
| | $10^3$ | 9,510,245 | 6,933,768(−27.1%) | 6,890,184(−27.5%) | 5,319,345 | 6,122,516(15.1%) | 6,667,449(25.3%) |
| | E-factor | 98.5 | 44.7 | 43.4 | 15.4 | 12.2 | 13.4 |
| KI5 | $10^2$ | 1,066,719 | 777,869(−27.1%) | 773,489(−27.5%) | 788,493 | 830,455(5.3%) | 886,192(12.4%) |
| | $10^3$ | 9,557,643 | 6,973,688(−27.0%) | 6,929,970(−27.5%) | 5,439,079 | 6,252,014(14.9%) | 6,811,316(25.2%) |
| | E-factor | 98.5 | 44.7 | 43.4 | 15.4 | 12.2 | 13.4 |
| KI10 | $10^2$ | 1,072,848 | 783,032(−27.0%) | 778,634(−27.4%) | 800,527 | 843,405(5.4%) | 900,579(12.5%) |
| | $10^3$ | 9,618,938 | 7,025,313(−27.0%) | 6,981,422(−27.4%) | 5,558,812 | 6,381,512(14.8%) | 6,955,184(25.1%) |
| | E-factor | 98.5 | 44.7 | 43.4 | 15.4 | 12.2 | 13.4 |
| SR70 | $10^2$ | 1,378,970 | 795,396(−42.3%) | 786,468(−43.0%) | 855,995 | 862,707(0.8%) | 920,829(7.6%) |
| | $10^3$ | 12,680,155 | 7,147,544(−43.6%) | 7,058,509(−44.3%) | 5,855,382 | 6,563,350(12.1%) | 7,149,955(22.1%) |
| | E-factor | 203.7 | 55.0 | 51.6 | 41.9 | 31.6 | 34.3 |
| SR50 | $10^2$ | 1,695,961 | 816,915(−51.8%) | 803,425(−52.6%) | 935,530 | 907,910(−3.0%) | 969,854(3.7%) |
| | $10^3$ | 15,850,064 | 7,361,320(−53.6%) | 7,226,834(−54.4%) | 6,391,419 | 7,004,185(9.6%) | 7,632,462(19.4%) |
| | E-factor | 308.9 | 65.4 | 59.8 | 68.3 | 51.0 | 55.3 |

ment units which constitute the majority of the Capital Expenditure are the plug flow reactors, whose costing has been based on a commercial microreactor system. Due to the very few established cost estimation methods available for microreactors (Harmsen, 2012), it is expected that there is a greater margin of uncertainty in costing this unit operation compared to others, however this remains the best and most reliable cost estimation method available in the peer-reviewed literature. There are several heuristics that have been developed to estimate Battery Limits Installed Costs (BLIC). The Chilton Method has been employed, with two key considerations which must be noted regarding its implementation. The first is that at capacities of 100 kg/year and 1000 kg/year of API production, these CPM processes remain relatively small, and construction of dedicated facilities is an unlikely endeavour. The second is that in the case of artemisinin the key ingredient (DHAA) is a waste product from the currently prevalent process of artemisinin extraction from plant feedstock, which can be used directly without any pretreatment as feedstock in the continuous synthesis described by Kopetzki et al. (2013) and studied here. Significant value-adding benefits are expected in the case of installing CPM processes at existing artemisinin production plants, in order to capitalize on the potential to use waste directly as feedstock. Therefore, the present implementation of the Chilton Method considers a very limited need for building work, auxiliary services and outside process lines. Emphasis has been placed on the use and costing of Process Analytical Technology (PAT) and extensive high-fidelity instrumentation, because maximising the benefits of continuous production requires high-resolution, multi-point monitoring and efficient CPM process control.

The small variation in CapEx between the base cases and the sensitivity analysis cases (KI5, KI10, SR70, SR50) is expected, as these changes primarily affect ingredients and material use, and only impact the WCC; any effects are further attenuated by the dominance of contingency (based on BLIC) in the WCC. When comparing against the complete (not lean) batch separation, both ibuprofen CPM separations with either toluene (CPM1) or *n*-hexane (CPM2) indicate similar cost: product recoveries (hence material input requirements for 100 kg/year production) are similar, and solvent use rates and prices are also of similar magnitude. The KI cost also has little effect on OpEx savings, because it is quite lower than that of other reagents and catalysts (diacetoxyiodo-benzene, triflic acid), and it is also masked by the cost of solvent purchase and handling (in terms of utilities and waste costs). Consequently, the reduced rates of solvent recovery of 70% (SR70) and 50% (SR50) have a remarkable impact on OpEx costs and savings relative to the reference batch case: the seemingly counter-intuitive greater cost savings (70.0% average for SR70 and 77.2% average for SR50, compared to 51.4% average for the base case at 90% solvent recovery) result from this remarkably higher weight of solvent importance in the calculations, and absolute OpEx costs for SR70 and SR50 are higher than for the base case. The significant advantage of continuous operations is therefore more evident when revamping inherently more wasteful processes. The OpEx cost savings from CPM separation in artemisinin production range between 22.5% and 29.3%: the former (for CPM2, ethyl acetate use) has slightly poorer performance due to higher input material requirements compared to CPM1 (ethanol), which is therefore strongly preferable for further detailed CPM process design evaluation and implementation. The

effect of KI price is prominent as the other reagents are cheaper and the cost of KI purchase rapidly dominates the OpEx. Lower solvent recoveries lead to higher cost savings, yet poorer performance because absolute OpEx costs are higher than the base case; this trend is consistent for both APIs. Considering total costs and savings for the base case and permutations over a 20-year plant lifetime, similar trends are observed (Table 11). For both APIs, continuous separation costs less than batch, and KI price has relatively little impact, because the total cost is dominated by CapEx costs. Poorer solvent recoveries do however reduce performance: while costs are lower than the reference batch cases, and there are higher percentage savings (particularly for ibuprofen), absolute costs are nevertheless higher than the base case with good solvent recovery rates. This is further underlined by the worse material efficiency for SR70 and SR50. Base case E-factor values are 44.0 for ibuprofen and 12.8 for artemisinin (average values): these constitute clear improvements over the reference batch separation values of 131.6 and 15.6 for ibuprofen and artemisinin, respectively, which worsen further in cases of poorer solvent recovery. The CPM case E-factors calculated here are acceptable for a pharmaceutical process, in comparison to typical literature values (Ritter, 2013); other syntheses of ibuprofen over the years are reported to have E-factors between 50 and 10,000 (Andraos, 2011).

When the continuous separations (CPM1 and CPM2) for each API are compared against the modified, leaner batch separation configuration, the spectrum of cost savings changes considerably. The potential CapEx savings are expectably reduced, because there are fewer unit operations and equipment items in the batch separation flowsheets. Indeed, while there are still CapEx savings in the case of ibuprofen, for artemisinin the continuous separations cost more. This is chiefly due to the lower estimated product recoveries in the continuous crystallisation operations, which in turn require greater material input and larger reactors, thereby significantly contributing to CapEx costs. However, it should be noted that the time required to complete the batch separation process is not fully elucidated in the literature, and so the overall material processing rate may be lower than assumed here: this consequently induces a higher CapEx for the batch case, thus implying more favourable cost comparisons to the advantage of continuous separation cases. The potential OpEx savings, while still generally good, are diminished in the ibuprofen cases. For artemisinin, OpEx savings are relatively unchanged between comparisons to lean and exhaustive batch separations. This is chiefly due to the difference in unit operations removed after the simplification of the batch separations (with those omitted from the ibuprofen flowsheets requiring more auxiliary material), but also because of the increased material input requirements for the ibuprofen cases (which leads to increased costs for material purchase, handling and waste treatment). The diminished cost advantages for artemisinin continuous separation, arising from higher CapEx costs, carry over into total costs: for the majority of cases, total costs for continuous separation cases are marginally higher than the lean batch case.

Evaluating the processes (lean batch vs. continuous separation) at the higher plant capacity of 1000 kg/year underlined a diverging trend between the ibuprofen and artemisinin processes. At the higher plant capacity, cost savings are not readily apparent for artemisinin, while all cases studied for ibuprofen continuous separation yield clear total cost reductions. This highlights the great variability between different processes, their chemistries, separations and plantwide operational efficiency. The clear conclusion here is that specific and detailed technoeconomic investigations of candidate APIs is required in order to quantitatively and conclusively elucidate potential CPM savings. Nevertheless, the artemisinin synthesis route studied here does show significant promise: subject to more efficient separation design and optimisation, total cost can be drastically reduced, thus unleashing the potential for increased efficiency and profitability, as intended in the context of reported plans to commercialise this process (Extance, 2012).

Despite the multitude of peer-reviewed publications addressing essential technological developments in the field of CPM, there have been very few technoeconomic studies including direct comparisons of batch and continuous production for the same API. In one of the first such examples, an extensive comparison has been performed for a full end-to-end synthesis of an API: in certain cases therein, Capital Expenditure and total cost savings of up to 76% and 40%, respectively, can be attained by switching from batch to continuous production (Schaber et al., 2011). A more recent technoeconomic study comparing five continuous manufacturing process instances to a reference batch case for the production of a high-value, low-volume API (100 kg/year) determined potential Capital Expenditure reductions of up to 72% and total cost savings between 31% and 35% (Denčić et al., 2014).

With the exception of the reactors and some auxiliary items such as pumps, chillers and evaporators, the unit operations have been costed as standard continuous equipment items (Woods, 2007). There is a need for research into unit operations specifically for CPM use at the microscale (Schaber et al., 2011). Microreactors (Kockmann et al., 2008; Kockmann and Roberge, 2009; Hartman, 2012), tablet manufacturing and granulation (Fonteyne et al., 2014; Rogers et al., 2014; Järvinen et al., 2015) but also continuous crystallisation have been the focus of numerous technical publications: plug flow crystallisers and oscillatory baffled crystallisers show promise, with some designs achieving over 98% yield or a 97.9% reduction of required operating times (Lawton et al., 2009; Wong et al., 2012; Ferguson et al., 2014; Besenhard et al., 2015; Majumder and Nagy, 2015). Reliable cost estimation methods for these novel unit operations are yet to be developed, however, due to technical performance as well as market penetration uncertainty.

Systematic process modelling and simulation and detailed comparative economic analyses are invaluable tools for evaluating CPM process potential. Given the costly reagents used in the ibuprofen synthesis studied here, commercialisation is not envisaged without further development toward efficiency improvement, especially in the context of agile production platforms and distributed manufacturing. Nevertheless, the artemisinin design developed by Kopetzki et al. (2013) shows great promise and there are plans for industrial-scale versions (Extance, 2012) which have further encouraged the development of photoreactors for efficient semi-synthetic production (Amara et al., 2015). The recent FDA approval for a new drug produced exclusively via continuous production further highlights the intense industrial interest in continuous manufacturing, with several other CPM plants awaiting approval or already under construction (Armental and Burton, 2015; Palmer, 2015).

## 6. Conclusions

Continuous manufacturing promises numerous significant advantages over batch processing (the dominant method in pharmaceutical production), which is the very reason that comprehensive evaluation of potential benefits, technical feasibility and economic viability for specific pharmaceutical products is paramount. The potential cost savings of employing continuous product separation in comparison to batch manufacturing have been studied for two important Active Pharmaceutical Ingredients (APIs), ibuprofen and artemisinin. These pharmaceuticals of critical importance (ibuprofen is listed as an essential drug by the World Health Organisation, as are many formulations of artemisinin derivatives) are among those substances for which the use of CPM could add great societal as well as economic value (other examples include novel substances for which the chemistry can be developed

from the start with continuous production in mind). Continuous Pharmaceutical Manufacturing (CPM) offers a novel path to securing competitiveness for pharmaceutical firms challenged by the current economic and market environment. Preliminary studies estimating process efficiencies and economics are valuable tools for identifying and evaluating promising candidate APIs and processes for CPM.

Four processes have been evaluated for each API (eight process instances in total) with continuous upstream production: for each pharmaceutical product, the process portfolio includes the full batch product recovery reference case, the lean reference batch case, and two continuous separation cases which employ similar processes but different solvents, antisolvents or operating conditions. Two production capacities have been studied: one to produce 100 kg per year after product recovery, and the other to produce 1000 kg per year, with requisite material balances and reactor dimensions calculated for all process alternatives. A combination of vendor quotes, market data and cost estimation methods have been employed to calculate Capital Expenditure (CapEx), Operating Expenditure (OpEx), and total costs, along with the cost savings which conceptual continuous processes offer over the given reference batch case. Material efficiencies in the form of E-factors (mass of waste per unit mass of product) have also been calculated. CapEx savings has been determined as greater for ibuprofen, with savings attainable in all cases studied, while for artemisinin, CapEx savings have been reduced at higher production capacity. Conversely, OpEx savings have been determined as broadly similar for the two APIs except at the higher process capacity, where artemisinin OpEx savings are diminished. Finally, over a 20-year plant lifetime, CPM implementation for ibuprofen attains total cost savings in all cases studied, while the CPM process alternatives for artemisinin indicate a mixed landscape of projected cost savings, with the lower process capacity performing better. The CPM processes are significantly more materially efficient, as evidenced by the clearly lower E-factor values computed in comparison to the respective ones for the reference batch process cases: advantages are evident.

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