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Cost-optimal Solvent Selection for Batch Cooling Crystallisation of Flurbiprofen

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ABSTRACT

Choosing suitable solvents for crystallisation processes can be a challenging task when developing new pharmaceuticals, given the vast number of candidates available. To streamline this task, however, process modelling tools can be used to systematically probe the behaviour of different crystallisation setups entirely in-silico. In fact, it is possible to couple thermodynamic models with basic solid-liquid equilibria (SLE) principles to determine the impact of key process variables (e.g., temperature and solvent choice) on process performance, prior to conducting lab-scale experiments. In light of this, in this study we have used thermodynamic computational modelling tools (implemented within MATLAB®) to evaluate the cost and environmental impact of different batch crystallisation processes that may be used to manufacture flurbiprofen – a non-steroidal anti-inflammatory drug (NSAID) that can be used to treat various forms of arthritis. To complete this work, we have used the Apelblat equation to study the solubility of flurbiprofen in four (4) common solvents (n-octane, methyl tert-butyl ether, n-propanol, and isopropyl acetate) over a wide temperature range (283.15-323.15 K). Further to this, we have used green metrics (i.e., E-factor) and established costing methodologies to compare each process candidate; before evaluating their Scope 1 and 2 CO_2e emissions by considering their electricity usage and incineration activities.

Keywords: Non-Steroidal Anti-Inflammatory Drugs (NSAID), flurbiprofen, crystalliser, design, solvent selection

1. INTRODUCTION

In 2024, the global market for non-steroidal anti-inflammatory drugs (NSAIDs) reached 21.56 billion USD, and it is projected to grow at a Compound Annual Growth Rate (CAGR) of 5% over the next 8 years [1]. Consequently, cost-effective manufacturing processes must be developed for NSAIDs if we hope to satisfy future demand [2-3]. In light of this, we have used computational modelling to study the impact of solvent choice and process temperature on the batch cooling crystallisation of flurbiprofen – a generic NSAID (with global sales of 100 million USD per year [4]) which is used to treat rheumatoid arthritis, migraines and osteoarthritis [5]. To do this, we have used a purely thermodynamic approach, whereby the Apelblat equation is used to assess the solubility of flurbiprofen (Fig. 1) in four (4) pharmaceutical solvents (n-octane, methyl tert-butyl ether, n-propanol, and isopropyl acetate) [5] at different temperatures (T).

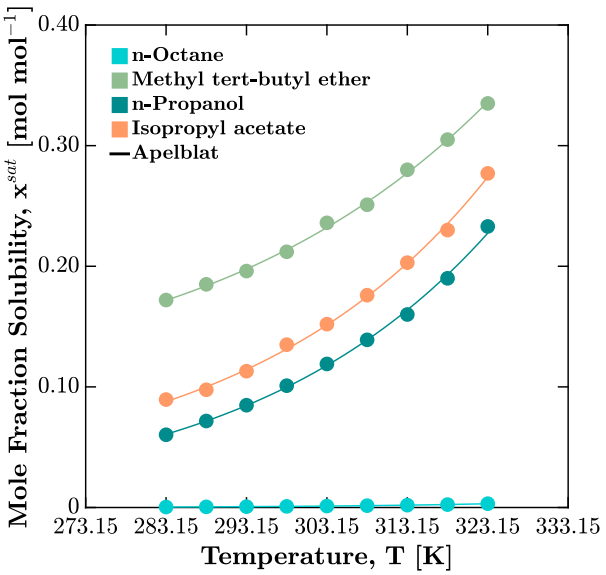

Figure 1. Flurbiprofen solubility in four solvents. Data [5].

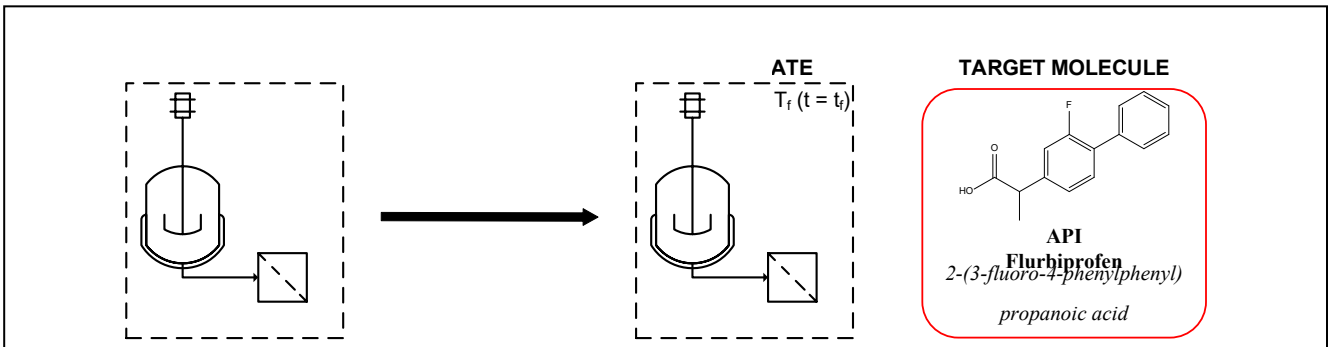

Figure 2: Batch cooling crystallisation using thermodynamic considerations alone.

Established green metrics and cost-estimation methods have then been used to identify the solvent and process conditions which afford the lowest cost solution whilst maintaining a reasonable carbon footprint.

2. PROCESS DESIGN & SIMULATION

As has been demonstrated by several authors [3, 6], it is possible to design crystallisers using thermodynamic principles alone (Fig. 2). The main benefit of this approach being that it allows promising solvent candidates to be identified prior to establishing their crystallisation kinetics; thereby reducing the number of experimental trials required to develop new processes.

In light of these observations, we have used the Apelblat equation (Eq. 1) alongside solid-liquid equilibrium (SLE) principles (Eqs. 2-5) to calculate the mass of flurbiprofen produced by each crystallisation batch cycle (m_{BC}) as we vary the initial and final temperatures (T_0, T_f) used. Meanwhile, we have used Eqs. 6-10 to determine any process volumes, operating times and production strategies required by each system; whilst Eqs. 11-12 have been used to determine product recoveries and cooling requirements.

Fig. 3 depicts the calculation sequence used to carry out this work, where basic physical properties (e.g., molecular weights, melting (T_{mp}) and boiling (T_{bp}) points) have been taken from the literature wherever possible [5, 7]. It is important to note, however, that the density and specific heat capacity of each solvent has been estimated using temperature-dependent empirical correlations when performing these calculations [8]. Meanwhile, only crystallisers of standard-size (1000, 2000, 5000, 10000, 20000 L) have been considered (70 v/v % fill capacity); whilst parallel production lines (N_{PT}) have been permitted whenever production targets could not be met using a single production line.

$$\ln x^{sat} = A + \frac{B}{T} + C\ ln(T) \quad (1)$$

$$n_{prod,0} = x_{prod,0}^{sat} n_S \quad (2)$$

$$n_{prod} = x_{prod}^{sat} n_S \quad (3)$$

$$n_{prod}^{cryst} = n_{prod,0} - n_{prod} \quad (4)$$

$$m_{prod}^{cryst} = M_{prod} n_{prod}^{cryst} \quad (5)$$

$$V_{cryst} = \frac{m_{prod}^{cryst}}{\rho_{prod}} \quad (6)$$

$$V_{liq} = \frac{M_S n_S}{\rho_S} \quad (7)$$

$$V_{sys} = V_{liq} + V_{cryst} \quad (8)$$

$$t_{BC} = t_{cryst} + t_{CIP} \quad (9)$$

$$m_{annual} = m_{BC} N_{BC} N_{PT} \quad (10)$$

$$r_T^{cryst} = \left(\frac{n_{prod,0} - n_{prod}}{n_{prod,0}}\right) \quad (11)$$

$$Q = \Delta T C_{P_S} n_S \quad (12)$$

$$\{T_0, T_f\} \geq \max \begin{Bmatrix} T_{min,Apel} \\ T_{mp_{solv}} + T_{os_1} \\ T_{min,phys} \end{Bmatrix} \quad (13)$$

$$\{T_0, T_f\} \leq \min \begin{Bmatrix} T_{max,Apel} \\ T_{bp_{solv}} - T_{os_2} \\ T_{max,phys} \end{Bmatrix} \quad (14)$$

In addition to this, we have also stipulated that the initial state of a crystalliser must have a temperature greater than that of the final state; all the while abiding by the constraints defined in Eqs. 13-14 ($T_{OS,1} = 5; T_{OS,2} = 10\ K$) so as to prevent any solvent phase changes from occurring during crystallisation [3, 6] (Fig. 3). Likewise, we have specified that each process must use a minimum of 4 mL of solvent per gram of solute so as to avoid high shear forces during mixing [3].

Using this approach, material balances have been constructed across each process by assuming that: (i) 100 metric tonnes of API are produced per year (m_{annual}); (ii) each process operates for a maximum of 6000 h annually (t_{op}); (iii) all mixtures are well-mixed, fully suspended and have uniform temperature and concentration profiles; (iv) vessel clean-in-place times (t_{CIP}) are 30 minutes between batches; and (v) each crystallisation batch takes 12 hours (t_{cryst}) [2]. It is important to note, however, that several unit operations are likely to precede the crystallisation steps studied in this work. Thus, each production line should only be allowed to complete

one full-process batch cycle per day – irrespective of an individual crystallisation unit's batch cycle time (t_{BC}). Otherwise, unrealistic manufacturing processes could be developed which demand infeasibly large numbers of batches to be produced each day.

Eqs. 1-14 introduce terms n_S, $n_{prod,0}$ and n_{prod} to represent the molar amount of solvent used in each process, as well as the initial and final amounts of drug product dissolved in this solvent (mol). Terms $x_{prod,0}^{sat}$, x_{prod}^{sat} and x^{sat} are also used to denote the mole fraction of dissolved product for a given process state (mol mol^{-1}). Meanwhile, A (–), B (K) and C (–) are used to denote Apelblat correlation coefficients. n_{prod}^{cryst} (mol) and m_{prod}^{cryst} (kg) are then used to describe the molar and mass amounts of product produced; whilst r_T^{cryst} (–) and Q (kJ) give the API recovery and heating requirements. M_{prod} and M_S are used to represent the molar mass (g mol^{-1}) of the drug-product and solvents, respectively; whilst ρ_{prod} and ρ_S denote their densities (kg m^{-3}). Terms V_{cryst}, V_{liq} and V_{sys} are then left to represent crystal, liquid (mother-liquor) and total system volumes (L) for each batch in a process; whilst C_{P_S} (J mol^{-1} K^{-1}) represents the specific heat capacity of a solvent and $T_{min,Apel}$, $T_{max,Apel}$, $T_{min,phys}$, $T_{max,phys}$ (K) denote the minimum and maximum temperatures for which the Apelblat and physical property correlations are applicable. N_{BC} gives the number of batch cycles per production line for a given throughput.

3. ENVIRONMENTAL IMPACT

Environmental (E_{factor}) and emission factors (i.e., the amount of CO_2e produced per kilogram of product, PCE) have been used to assess the environmental impact of each process (Eqs. 15-16). Consequently, any Scope 1 and 2 emissions expected to arise from each process (due to material and energy consumption) have been calculated assuming that: (i) 0.20705 kg CO_2e are produced per kWh of electricity used [9]; (ii) any emissions produced during waste incineration activities only occur due to the complete combustion of waste material; and (iii) on-site scrubbing and catalytic reduction facilities are available to completely abate any NO_x and SO_x gases which arise during these incineration activities (allowing their potential generation to be ignored).

$$E_{factor} = \frac{m_{total\ input} - m_{total\ prod}}{m_{total\ prod}} \quad (15)$$

$$PCE = \frac{m_{total\ CO_2e}}{m_{total\ prod}} \quad (16)$$

Eqs. 15-16 introduce terms $m_{total\ input}$, $m_{total\ prod}$ and $m_{total\ CO_2e}$ to represent total process material requirements, API production, and CO_2e emissions (kg).

4. ECONOMIC ANALYSIS

An established costing methodology [2, 10] has been used to assess the viability of each process. As part of this, the capital costs ($CapEx$) associated with each process have been calculated in USD by taking the sum of any fixed (FCC) and working (WCC) capital costs (Eq. 17). Consequently, any FCC costs have been calculated

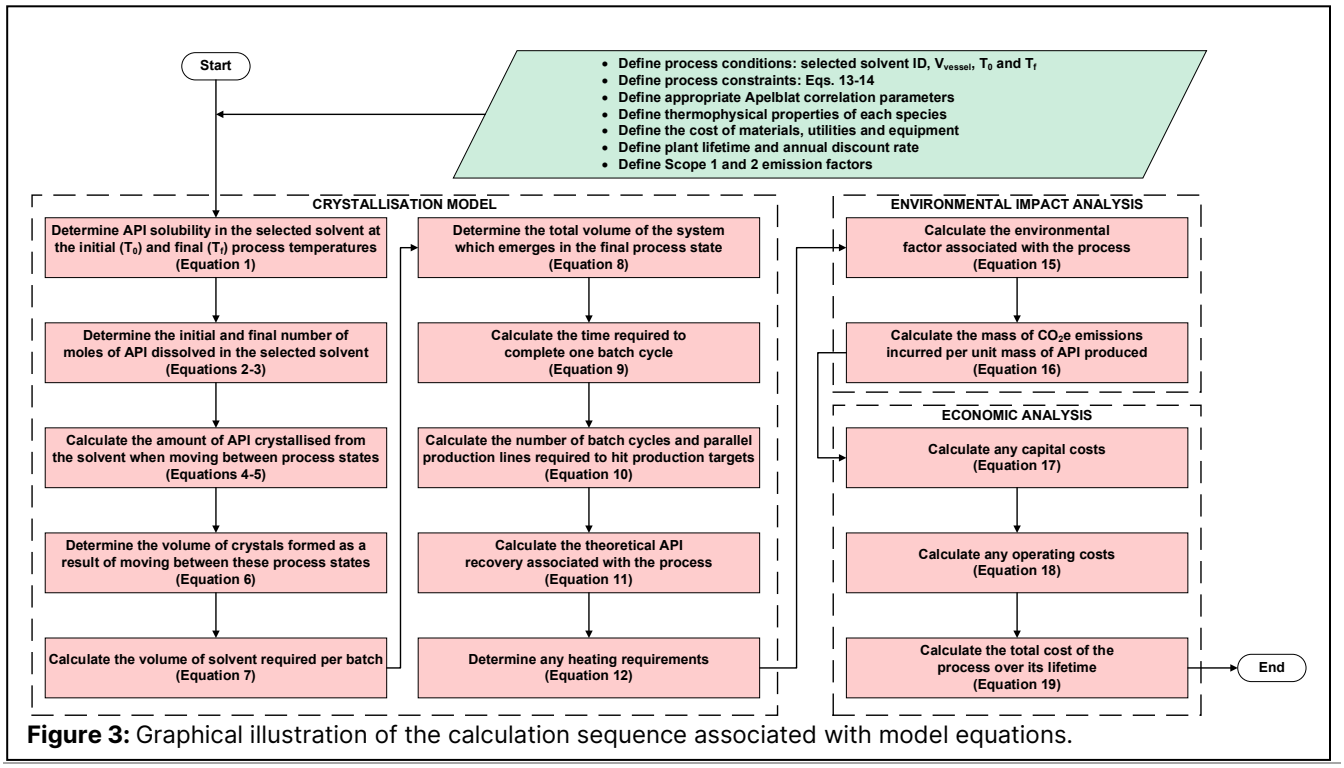

Figure 3: Graphical illustration of the calculation sequence associated with model equations.

as sum of the inside battery limits, outside battery limits, engineering and contingency costs (using Chemical Engineering Plant Cost Indices and Lang factors to account for the effects of inflation and equipment installation); whilst any WCC costs have been assumed equal to 15 % of the FCC costs. Likewise, any operating costs have been simply calculated as the sum of the fixed ($FCOP$) and variable ($VCOP$) costs of production (Eq. 18). Where, any $VCOP$ costs have been calculated as the sum of any raw material, waste disposal, and utility costs; whilst any $FCOP$ costs have been broken down into: (i) supervision and management costs; (ii) maintenance costs; (iii) renting of land/buildings; (iv) insurance premiums/property taxes; (v) direct salary overheads; and (vi) labour costs.

$$CapEx = FCC + WCC \tag{17}$$

$$OpEx = FCOP + VCOP \tag{18}$$

The total cost of each process (TPC) has then been determined via Eq. 19 – assuming all $CapEx$ occurs in year zero, whilst any $OpEx$ is incurred from year one onwards.

$$TPC = CapEx + \sum_{n=1}^{t_{LTP}} \frac{OpEx}{(1+I_{dr})^n} \tag{19}$$

Bulk prices used to calculate material costs have been calculated by averaging values published by known vendors and market research firms (i.e., the IMARC group) in the last year (2023-2024) wherever possible. However, import and export reports published for major markets have been used if this information was unavailable. Similarly, waste disposal costs have been estimated in-line with recommendations made by Jolliffe and Gerogiorgis (2017) [11] and the World Health Organization (1999) [12]. Meanwhile, a plant lifetime (t_{LTP}) of 20 years has been assumed, with an annual discount rate (I_{dr}) of 5.5 % [11]. An efficiency of 40 % has been assumed when converting electrical energy to crystalliser cooling duties.

5. RESULTS & DISCUSSION

Using the modelling framework presented in Sections 2-4, we have visualised the design space associated with each crystallisation process. From this, we observed that (regardless of the solvent used) it is wise to use the largest crystalliser available (20000 L) since this will reduce process costs, whilst also minimising the number of batches and parallel production lines required to achieve a given throughput (Fig. 4a). Alongside this, however, we also observed that it is also best to maximise the temperature difference between the initial and final states of a given process if we wish to minimise its production costs whilst maximising drug recovery. Fig. 4b provides findings from these investigations for two of the solvents studied in this work: n-octane (low API solubility) and n-propanol (moderate API solubility). Consequently, we could safely set the volume and temperature difference of each system to their maximum allowable values before studying the impact of solvent choice on: (i) process cost (Fig. 5a); (ii) material usage (Fig. 5b); (iii) CO_2e emissions (Fig. 5c); and (iv) API recovery (Fig. 5d).

Interestingly, however, from studying these trends, we found that simply choosing the solvent with the highest expected API solubility (i.e., methyl tert-butyl ether herein) will not necessarily result in a cost-optimal (Fig. 5a) or environmentally friendly (Figs. 5b-c) manufacturing process. Rather, we must take into account the cost of purchasing and disposing of any materials (as well as

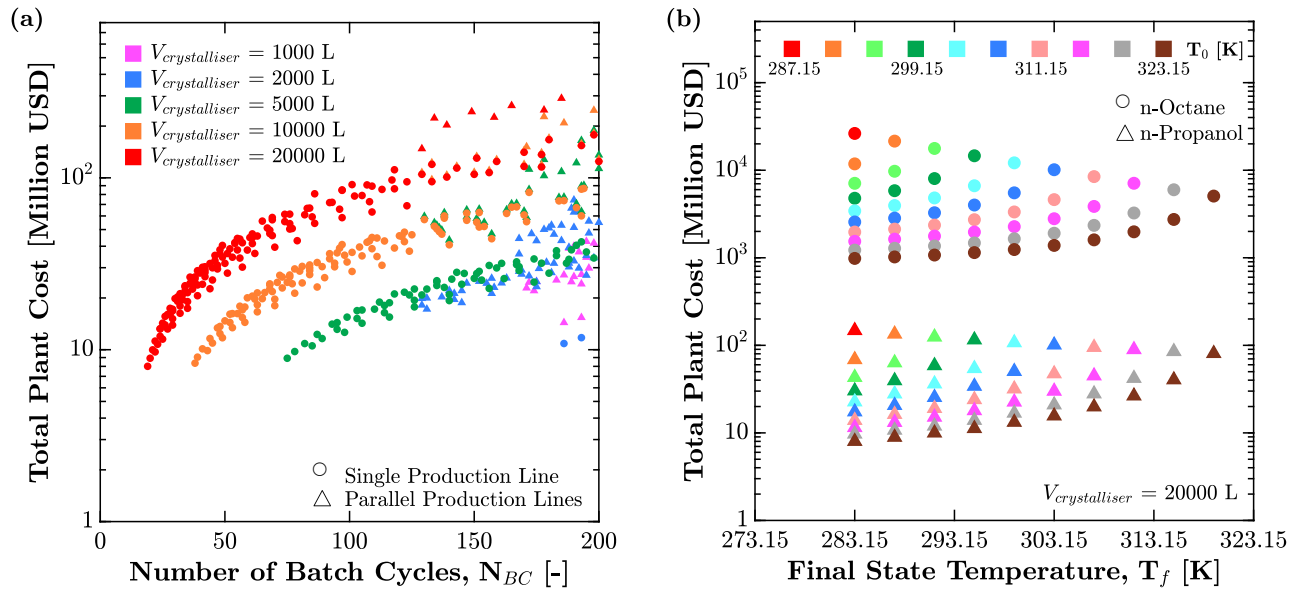

Figure 4: Impact of: (a) crystalliser volume (for all solvents, at various process conditions); and (b) process temperature (T_0, T_f) on process cost.

the volatility of any solvents used) if we wish to identify cost-optimal processes; since these variables can have a significant impact on the overall viability of a process. Consequently, in this work, n-propanol was identified as the best solvent available for flurbiprofen crystallisation ahead of methyl tert-butyl ether (Figs. 1 and 5); with the final optimised process exhibiting a total cost of 8.00 million USD, an API recovery of 73.31 w/w % and CO_2e emissions of only 4.23 kg_{CO_2e}/kg_{API}.

In light of these findings, it was worth examining the cost breakdown associated with this process to understand what aspects of process design influence the cost of batch crystallisation processes most. From this, it was found that an initial investment ($CapEx$) of only 0.10 million USD (FCC: 86.96 %; WCC 13.04 %) would be required to design and build the optimised n-propanol process; yet, it would cost around 0.66 million USD annually ($FCOP$: 4.95 %; $VCOP$: 95.05 %) to operate ($OpEx$). It is, therefore, abundantly clear that batch cooling crystallisation processes such as those studied in this work are dominated by operating costs rather than capital investment (with material acquisition, utility usage, and waste disposal costs making up 9.50, 37.76 and 52.74 % of any $VCOP$ costs incurred in this case).

In addition to these findings, however, it was also observed that simply targeting maximum product recoveries (or crystal yields) can be hazardous when optimising a new process. Especially, since doing so can result

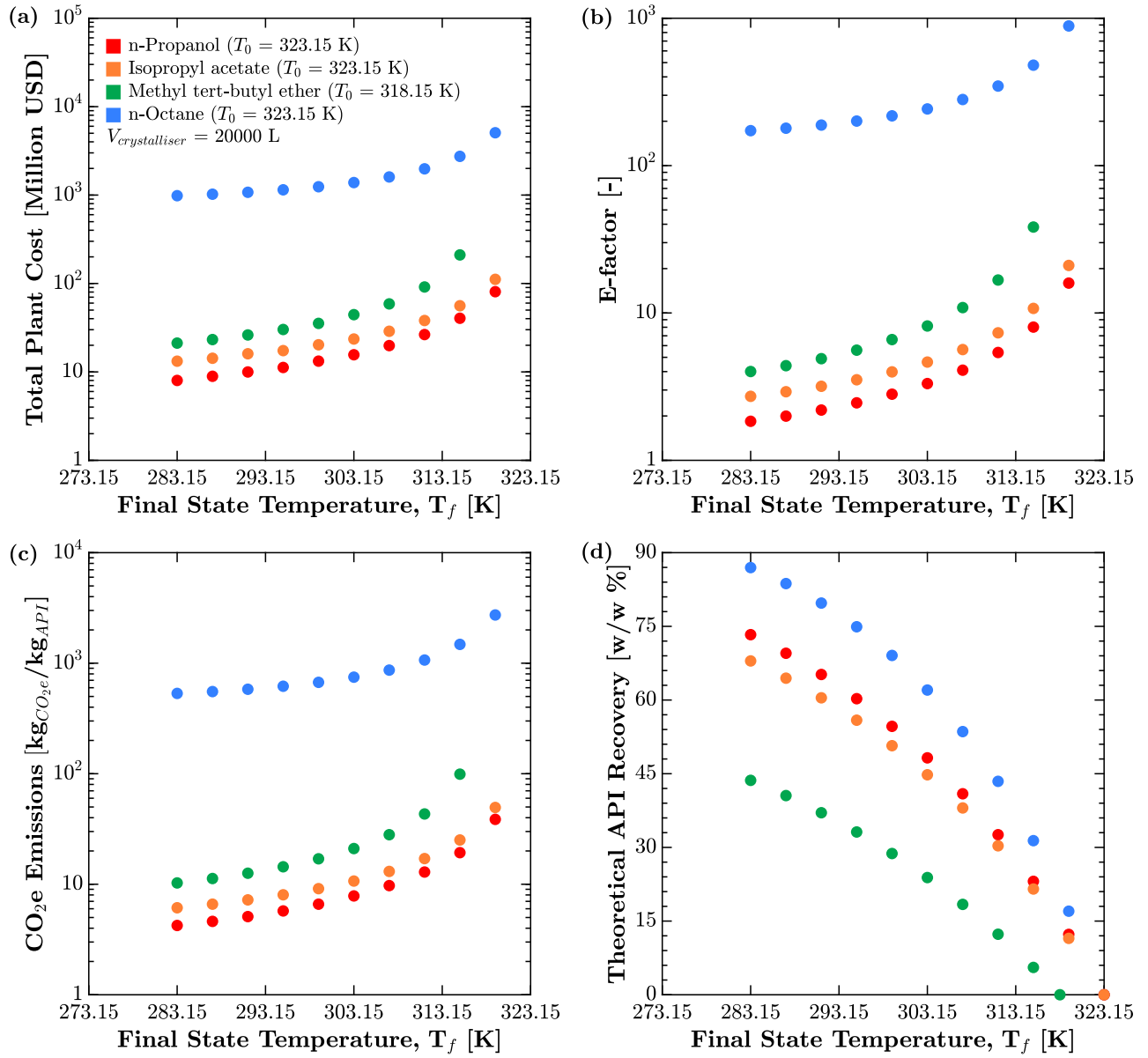

Figure 5: Impact of solvent choice on: (a) process cost; (b) E-factor; (c) CO_2e emissions; and (d) API recovery. T_0 set to maximum allowable value for each solvent.

in the selection of solvents which have extremely low drug solubilities (Fig. 1) even though this raises process costs on account of the larger volumes of solvent required in such scenarios (Fig. 5d). Hence, it is safer to evaluate processes in terms of their process costs and environmental impact, as has been done in this work.

6. CONCLUSIONS

In this work, we have presented a practical modelling framework for the visualisation and optimisation of design spaces associated with batch cooling crystallisation processes. Further to this, we have demonstrated how this framework can be used to identify cost-optimal process conditions for flurbiprofen production, whilst minimising carbon emissions. As part of this, we have successfully identified n-propanol as the most suitable solvent (of those tested) for the batch cooling crystallisation of flurbiprofen ($V_{crystalliser}$ = 20000 L; T_0 = 323.15 K; T_f = 283.15 K). Consequently, the systematic methods presented in this paper can also be used to explore the design space associated with a whole host of other small molecule APIs, since around 80% of all small molecule pharmaceuticals produced today require crystallisation at some point(s) during the manufacturing process [3].

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