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In silico solvent selection for green and cost-effective pregabalin crystallisation

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ABSTRACT

Identifying cost-optimal yet environmentally friendly crystallisation processes in the production of small molecule pharmaceuticals is a highly complex task, since multiple solvent systems often exist which could be used to purify a given drug to a similar standard. It is, however, rarely possible to test each of these solvent systems within a laboratory setting, since this would be time-consuming and incur large material costs. It has, therefore, been suggested that process modelling tools should be used to screen different crystallisation processes available to produce a new drug prior to studying them experimentally – essentially allowing a shortlist of promising process candidates to be created. Indeed, it has been shown by several authors that this sort of work can be conducted without any need to establish the crystallisation kinetics associated with each drug-and-solvent combination considered: the reason being that crystallisation processes may be defined as simple solid-liquid equilibria (SLE) problems using thermodynamic models alone. Considering this, the present work has used SLE modelling to assess the cost and environmental impact of different solvent systems available for the crystallisation of pregabalin – an anticonvulsant and anxiolytic drug used to treat epilepsy, anxiety and neuropathic pain. Moreover, it has used entirely data-led approaches to achieve this: leveraging established costing methodologies and green metrics (i.e., Scope 1 and 2 CO_2e emissions) to assess their economic viability and carbon footprint. This modelling framework can be used to identify viable crystallisation strategies for other small molecules.

Keywords: Pregabalin, technoeconomic analysis, crystallisation, environmental impact analysis, solvent selection.

1. INTRODUCTION

In 2024, pregabalin – a generic anticonvulsant drug and anxiolytic agent commonly used to treat epilepsy, anxiety and neuropathic pain [1-3] – had a global market of 1.8 billion USD, and it is expected that this market will continue to grow at a compound annual growth rate (CAGR) of 5.1 % between 2025 and 2034 [4]. Consequently, this work aims to identify technoeconomically optimal – and environmentally benign – manufacturing routes that can be used for its production. To achieve this, it has used in-silico technoeconomic analyses and environmental impact assessments to establish which solvents (of those commonly used in the crystallisation of small molecule pharmaceuticals) and process conditions allow cost-effective – yet green – pregabalin manufacturing.

2. PROCESS MODELLING STRATEGY

Designing crystallisation processes for pharmaceuticals can be an arduous process, since often several solvent systems will exist which could be used to perform the purification required by a given process – each of which will hold unique crystallisation kinetics. Recent studies [5, 6] have shown that promising crystallisation setups can be identified for new processes entirely in silico, without the need to establish kinetics (thereby greatly reducing the number of experiments required during process design). Thermodynamic modelling alone [5-7] can be used to achieve this by simply ranking each system based on their expected trends in process costs as API solubility varies under different operating conditions.

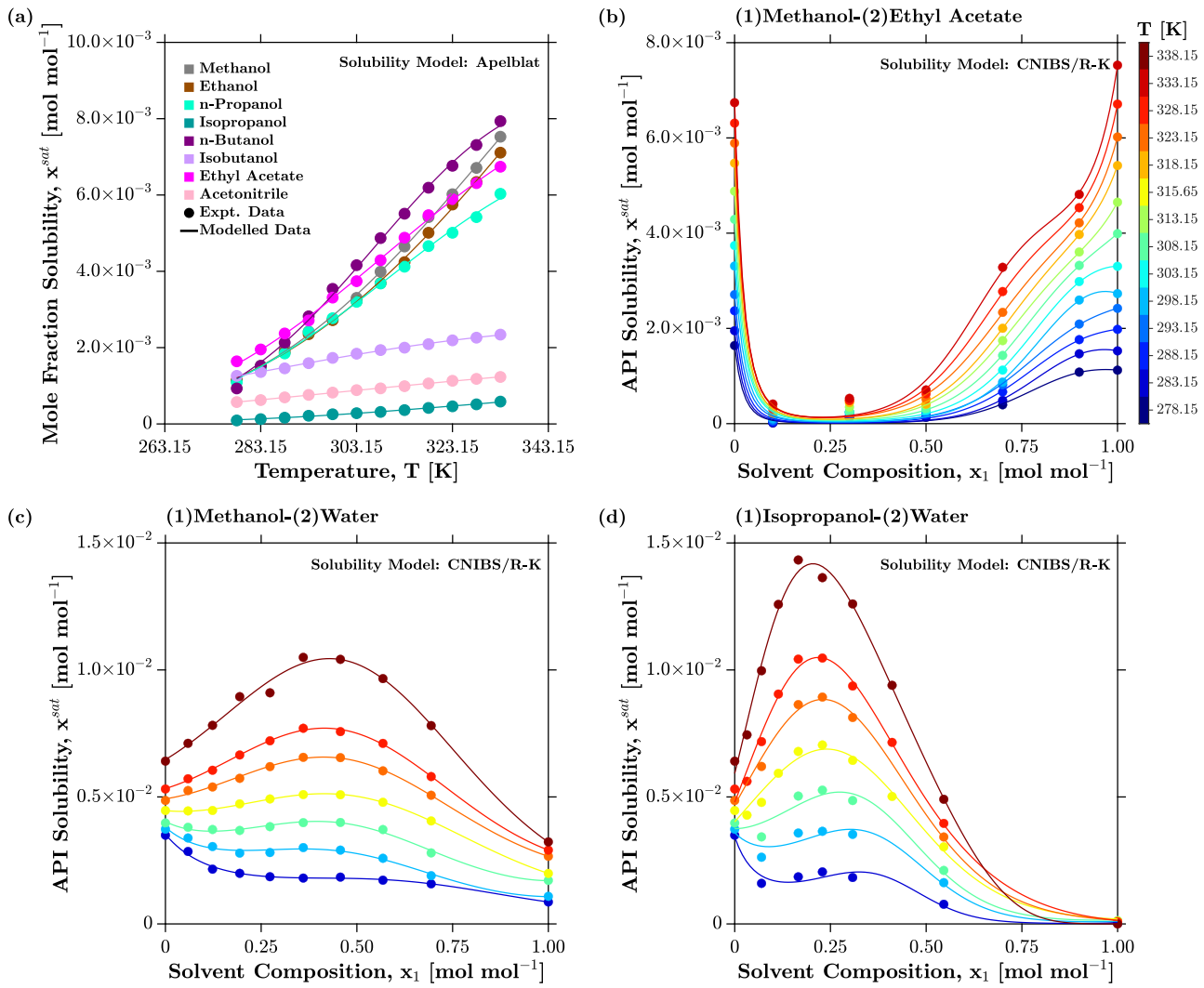

Figure 1. Pregabalin solubility in (a) pure and (b-d) mixed solvents [8-9].

This paper uses the modified Apelblat equation (Eq. 1) to model the temperature dependent solubility of pregabalin in pure solvents (methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, ethyl acetate, acetonitrile), whilst it has used the Combined Nearly Ideal Binary Solvent/Redlich-Kister (CNIBS/R-K) model (Eq. 2) to study its solubility in solvent mixtures (i.e., (1) methanol-(2) ethyl acetate, (1) methanol-(2) water, (1) isopropanol-(2) water) with varying molar compositions [8, 9] (Fig. 1).

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

$$\ln x^{sat} = B_0 + B_1 x_1 + B_2 x_1^2 + B_3 x_1^3 + B_4 x_1^4 \quad (2)$$

Material balances can be computed for all processes, assuming that they will produce 100 metric tonnes of pregabalin over an annual operating time of 6000 h (m_{annual}) – thus allowing solid-liquid equilibrium (SLE) principles (Eqs. 3-6) to be used to determine the mass of pregabalin that would be (theoretically) produced per each batch (m_{BC}) in each crystallisation process proposed under various different operating conditions (i.e., solvent mixture composition, T_0 and T_f) [5, 7].

$$n_{prod,0} = x_{prod,0}^{sat} n_{S_T,0} \quad (3)$$

$$n_{prod} = x_{prod}^{sat} n_{S_T} \quad (4)$$

$$n_{prod}^{cryst} = n_{prod}^{0} - n_{prod} \quad (5)$$

$$m_{prod}^{cryst} = M_{prod} n_{prod}^{cryst} \quad (6)$$

It is important to note, however, that it has been assumed in this work that all process mixtures considered are well-mixed, fully suspended, and have uniform temperature and concentration profiles. Moreover, it has been assumed that each crystallisation process takes 12 hours (t_{cryst}) – since the thermodynamic models used

herein (Eqs. 1-2) have no time element – whilst the clean-in-place requirements of any equipment has been set to 30 minutes (t_{CIP}) [7, 10, 11].

This framework may be used to model both pure and mixed solvent systems; however, when dealing with mixed solvent systems, it is important to note that the total amount of solvent in each system must also obey the relationships expressed in Eqs. 7-14. In other words, the total amount of solvent present in the initial and final states of each system will be the sum of any solvents and antisolvents present (Eqs. 7-8) – noting that the composition of the initial and final states will be different if an antisolvent is added throughout the crystallisation process (Eqs. 9-12). Hence, the solute-free compositions of each solvent system must be held between 0 and 1 in each state (Eq. 13), whilst also summing to 1 (Eq. 14).

$$n_{S_T,0} = n_{S_1,0} + n_{S_2,0} \tag{7}$$

$$n_{S_T} = n_{S_1} + n_{S_2} \tag{8}$$

$$n_{S_1} = n_{S_1,0} + n_{S_1,+} \tag{9}$$

$$n_{S_2} = n_{S_2,0} + n_{S_2,+} \tag{10}$$

$$n_{S_1}^{+} \geq 0 \tag{11}$$

$$n_{S_2}^{+} \geq 0 \tag{12}$$

$$0 \leq \{x_1, x_2\} \leq 1 \tag{13}$$

$$x_1 + x_2 = 1 \tag{14}$$

Eqs. 15-16 should be used to determine the size of any equipment required by each process – noting that only standard sizes of crystalliser (i.e., 5000, 10000, 20000 L) which have a 70 v/v % fill capacity may be used. Moreover, parallel production lines (N_{PT}) should be permitted whenever a single production line proves incapable of meeting throughput requirements for a specific process. It is important to note, however, that – since other unit operations (e.g., reactions, filtrations and liquid-liquid extractions) are likely to precede crystallisation steps in production processes – this work has also stipulated that each production line designed may only complete one batch cycle per day to prevent unrealistic manufacturing processes (i.e., those which require unreasonably large numbers of batches per day) from being developed. Eqs. 17-18 are used to determine the cycle time (t_{BC}) and heating requirements of each process, whilst Eq. 19 are used to compute theoretical product recovery.

$$V_{sys} = V_{liq} + V_{cryst} \tag{15}$$

$$m_{annual} = m_{BC} N_{BC} N_{PT} \tag{16}$$

$$t_{BC} = t_{cryst} + t_{CIP} \tag{17}$$

$$Q \approx \bar{C}_{P_{S_T}} \bar{n}_{S_T} \Delta T \tag{18}$$

$$r_{API} = 100 \left(\frac{n_{prod,0} - n_{prod}}{n_{prod,0}} \right) \tag{19}$$

Physical properties required to implement this model (e.g., the molecular weights, melting points and boiling points of pregabalin and any solvents) have been taken from the literature wherever possible [8, 9, 12]. Thus, established temperature dependent correlations have been used to assess the density and specific heat capacities of each solvent [13]. However, it should be noted that the initial temperature of each process should always be greater than or equal to its final temperature (Eq. 20), whilst respecting the limits specified in Eq. 21 ($T_{OS,1} = 5\,K; T_{OS,2} = 10\,K$) at all times, so as to make sure that: (i) crystallisation occurs, whilst (ii) the freezing and/or evaporation of any solvent does not [5, 6]. Likewise, it has been stipulated that (in order to avoid high shear forces during mixing) at least 4 mL of solvent should be used per gram of API being processed in each system [3].

$$T_0 \geq T_f \tag{20}$$

$$\max \left\{ \begin{matrix} T_{SM}^{\min} \\ T_{mp} + T_{os_1} \\ T_{phys}^{\min} \end{matrix} \right\} \leq \{T_0, T_f\} \leq \min \left\{ \begin{matrix} T_{SM}^{\max} \\ T_{bp} - T_{os_2} \\ T_{phys}^{\max} \end{matrix} \right\} \tag{21}$$

Each of the mathematical terms presented in Eqs. 1-21 are defined as described by the following statements. Term x^{sat} denotes the mole fraction (mol mol^{-1}) of API in a given solvent system when saturated, whilst terms $x_{prod,0}^{sat}$ and x_{prod}^{sat} denote the fraction of drug product dissolved in a system during the initial and final states of a crystallisation process (mol mol^{-1}). Terms x_1 and x_2 then denote the solute-free mole fraction of solvents 1 and 2 in each solvent mixture (mol mol^{-1}). A (–), B (K) and C (–) are correlation coefficients in the Apelblat equation, whilst B_0, B_1, B_2, B_3 and B_4 are CNIBS/R-K coefficients (–). Term T then denotes the temperature of each system, such that T_0 and T_f may be used to denote their initial and final temperatures. Meanwhile, terms T_{bp} and T_{mp} have been used to represent the boiling and melting point temperatures of each system. Terms $T_{SM}^{min}, T_{SM}^{max}, T_{phys}^{min}, T_{phys}^{max}$ then symbolise the minimum and maximum temperatures of the solubility (i.e., Apelblat, CNIBS/R-K) and physical property models used herein – leaving T_{os_1} and T_{os_2} to represent the temperature offsets applied to each system to prevent freezing and boiling, respectively. Term ΔT then represents the temperature difference between the initial and final states of a system. Meanwhile, terms n_{S_T} and $n_{S_T,0}$ denote the total moles of solvent used in the initial and final states of each process (mol); $n_{S_1,0}, n_{S_1}, n_{S_2,0}$ and n_{S_2}represent the initial and final amounts of any solvents and antisolvents in a system (mol); $n_{S_1,+}$ and $n_{S_2,+}$ signify the amount of solvent or antisolvent added to each

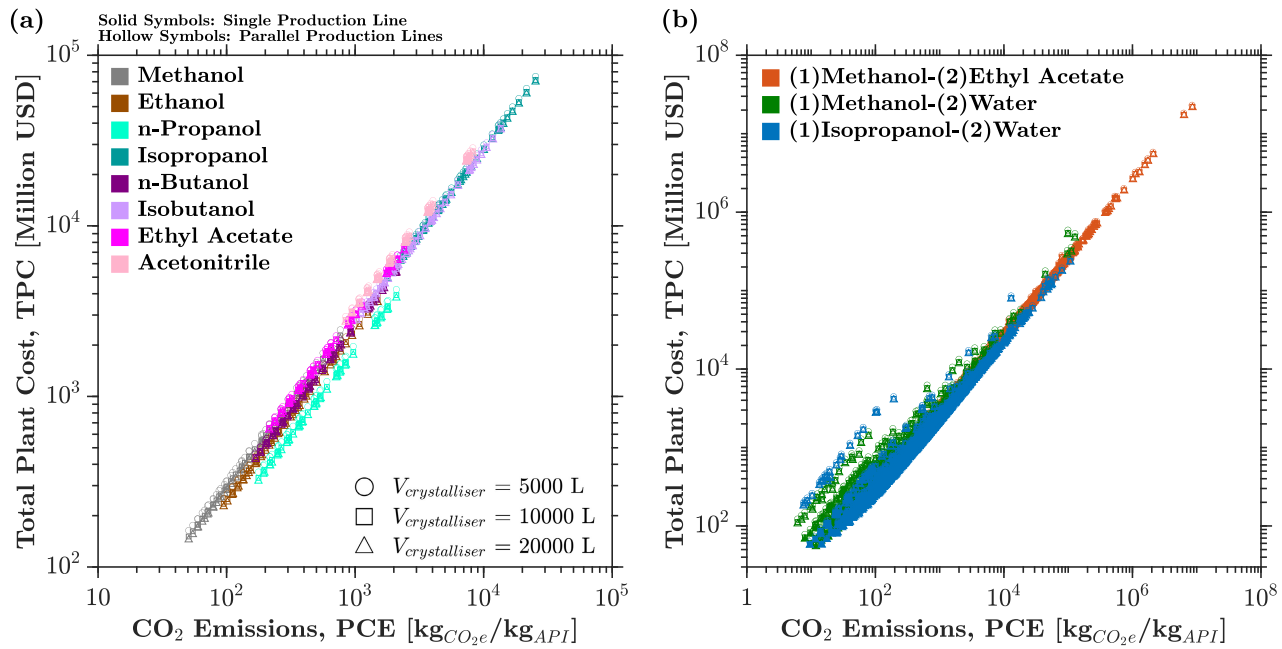

Figure 2. Relationship observed between the total cost and (scope 1 and 2) carbon emissions of each process.

system between the initial and final states (mol); $n_{prod,0}$ and n_{prod} give the amount of API product dissolved in this each system in each state (mol); and n_{prod}^{cryst} represents the amount of API crystallised during each process (mol). Meanwhile, $\bar{n}_{S_T}$ represents the average moles of solvent associated with a given system over its batch operating time. N_{BC} then denotes the annual number of batch cycles required by each production line. Symbols m_{prod}^{cryst} (kg) and M_{prod} (g mol^{-1}) then describe the mass and molar mass of the API product. Term V_{sys} then symbolises the total volume of a batch in a given process, whilst V_{liq} and V_{cryst} denote its liquid (mother-liquor) and crystal components (L). Q (kJ) then represents the heating requirements of each process, whilst r_{API} (%) gives the API recovery of each system. $\bar{C}_{P_{S_T}}$ (J mol^{-1} K^{-1}) then represents the average specific heat capacity of a system over its batch operating time.

3. CARBON EMISSIONS ANALYSIS

Carbon emission factors (PCE) have been used to assess the environmental impact of each process (Eq. 22) [7, 10] – assuming that any NO_x and SO_x generated by each process can be entirely abated by on-site scrubbing and catalytic conversion units. To allow this, it has been assumed that any waste will be incinerated and experience complete combustion, with every 1 kWh of electricity used producing 0.20705 kg of CO_2e [14].

$$PCE = \frac{m_{total\ CO_2e}}{m_{total\ prod}} \quad (22)$$

Terms $m_{total\ prod}$ and $m_{total\ CO_2e}$ in Eq. 22 denote total API production and CO_2e emissions (kg).

4. TECHNOECONOMIC ASSESSMENT

The cost of each process has been evaluated using an established costing methodology where: (i) capital costs ($CapEx$) are taken as the sum of any fixed (FCC) and working (WCC) capital costs (Eq. 23); whilst (ii) operating costs ($OpEx$) are set equal to the sum of any fixed ($FCOP$) and variable ($VCOP$) costs of production (Eq. 24).

$$CapEx = FCC + WCC \quad (23)$$

$$OpEx = FCOP + VCOP \quad (24)$$

Thus, the total cost of each process (TPC) has been calculated via Eq. 25 – assuming a plant lifetime (t_{LTP}) of 20 years and an annual discount rate (I_{dr}) of 5.5 % [10, 15].

$$TPC = CapEx + \sum_{n=1}^{t_{LTP}} \frac{OpEx}{(1+I_{dr})^n} \quad (25)$$

Within this, the FCC costs for each process have been estimated by taking the sum of any inside battery limits, outside battery limits, engineering and contingency costs – ultimately allowing any WCC costs to be calculated as 15 % of the FCC. Meanwhile, $VCOP$ costs have been calculated by assessing the raw material, waste disposal, and utility requirements of each process.

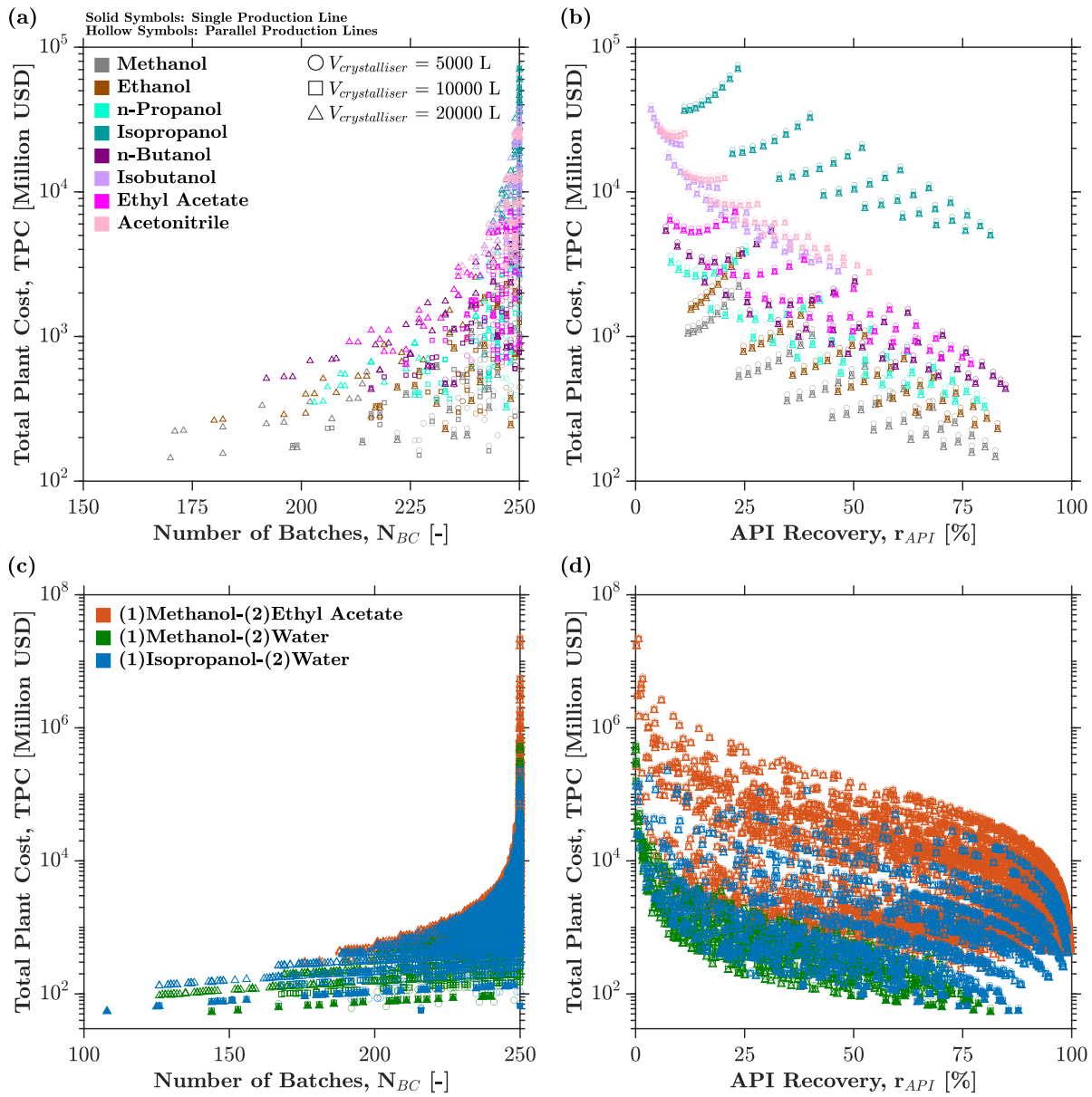

Figure 3. Impact of solvent system and crystalliser volume on the batch processing requirements (left), API recovery (right), and process costs associated with the production of pregabalin when using (a, b) pure and (c, d) mixed solvent systems to bring about its crystallisation under varying process conditions ($x_{1,0}$, $x_{1,f}$ T_0, T_f).

Any *FCOP* costs have then been evaluated by assessing any supervision and management, labour, and maintenance costs incurred alongside any costs arising from property taxes, rental payments, insurance premiums and direct salary overheads.

Considering this, an energy efficiency of 40 % has been assumed for any electrical equipment designed in his work. Meanwhile, any raw materials required by each process have been priced using: (i) average vendor prices published by market research firms (e.g., the IMARC group [16]); and (ii) national import and export reports across major markets. Whereas waste disposal costs have been calculated in line with recommendations made by the World Health Organization (1999) [12] and Jolliffe and Gerogiorgis (2017) [11].

5. DISCUSSION OF RESULTS

The modelling framework developed in Sections 2-4 has been used to map the design space associated with each crystallisation process considered herein. From this, it has been shown that for each solvent system: (i) the

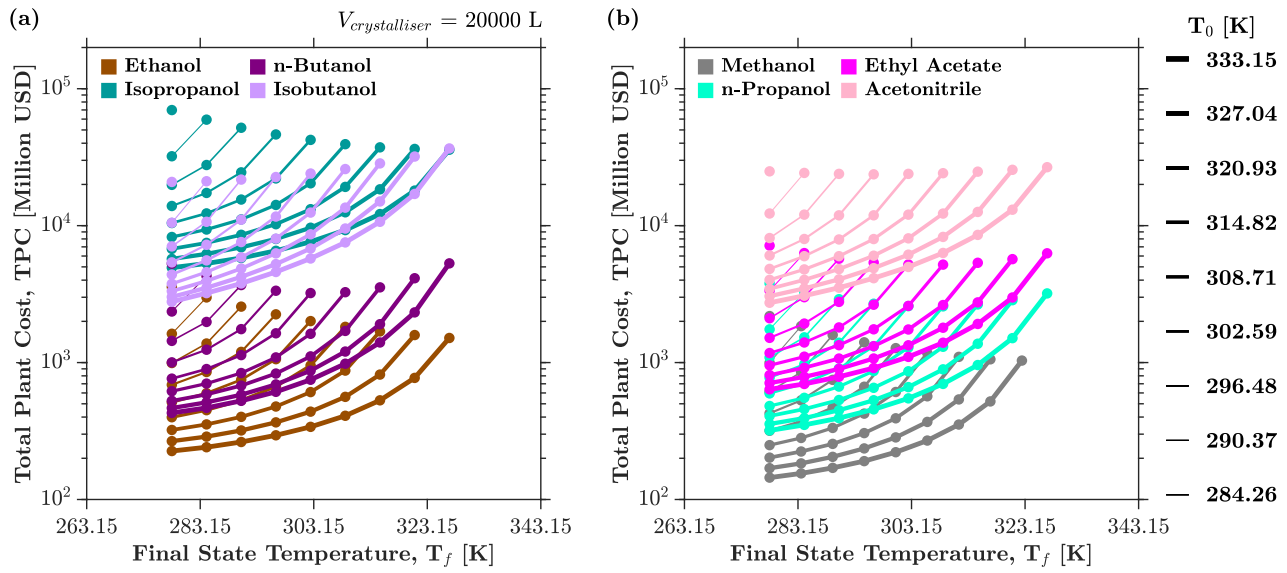

Figure 4. Impact of T_0 and T_f on the total cost of each pure solvent system.

cost of crystallisation is proportional to its expected carbon emissions, and (ii) its total costs drop when larger crystallisers are used (Fig. 2). Hence, crystalliser volume should be maximised (i.e., set to 20000 L) to simultaneously minimise process costs and environmental impact. Fig. 3 has been used to highlight this concept by demonstrating that increasing crystalliser volume: (i) reduces process costs, and (ii) simplifies manufacturing strategy (i.e., the number of parallel production lines required by a process, and the number of batches that these lines must produce to meet throughput targets). It is, therefore, clear that maximising crystalliser volume leads to cheaper, faster, and simpler pregabalin production.

Upon fixing the crystalliser volume for each solvent system at 20000 L, relationships between process temperature (T_0, T_f) and process cost can be determined for each of the pure solvent systems (Fig. 4). Meanwhile, the impact of any changes in process temperature (T_0, T_f) and the initial ($x_{1,0}$ and $x_{2,0}$) and final ($x_{1,f}, x_{2,f}$) compositions of the mixed solvent systems can be established (Figs. 5-6). In this regard, identical trends can be seen for each of the pure solvent systems whereby maximising their initial temperature whilst minimising their final temperature minimises costs (Table 1) – with methanol offering the most cost-effective process overall on account of its high API solubility (Fig. 1) and low purchase cost [16]. However, much more complicated trends exist when dealing with the mixed solvent systems – specifically because their cost depends strongly upon their initial and final solvent compositions (Fig. 5). For example, looking at the (1) methanol-(2) ethyl acetate system in Fig 5, it can be concluded that maximising its initial temperature whilst using an initial solvent composition ($x_{1,0}$) of either 0.0 or 1.0 mol mol^{-1} will yield reduced process costs regardless of the final temperature used. On the other hand, when looking at the (1) methanol-(2) water system, it can be seen that (again, regardless of the final temperature used) employing an initial solvent composition ($x_{1,0}$) of 0.30 mol mol^{-1} whilst maximising its initial temperature gives lower costs. Meanwhile, the (1) isopropanol-(2) water system benefits from maximising the initial temperature and using an initial solvent composition ($x_{1,0}$) of 0.10 mol mol^{-1}. Interestingly, however, it can be seen that, for all three systems, setting the initial and final solvent compositions equal to one another generally reduces costs. To illustrate this point, Fig. 6 has been used to examine the impact of changing the final temperature and solvent composition on each system more closely. From this, it can be seen that minimising the final temperature of each mixed solvent system minimises costs (just as seen for the pure solvent systems), whilst maintaining a constant solvent composition throughout the process also reduces costs. This is because introducing fresh antisolvent to each system raises operating costs whilst often only marginally reducing API solubility.

Considering this, optimal process conditions for each of the pure and mixed solvent systems could be identified as shown in Table 1. Hence, it could be deduced that the mixed solvent systems containing (1) methanol-(2) water and (1) isopropanol-(2) water will likely offer the lowest process costs, whilst methanol is expected to be the best performing pure solvent. However, as can be seen rom Table 1, the two mixed solvent systems greatly outperform methanol in terms of their overall cost and carbon emissions. Interestingly, however, the (1) methanol-(2) water system is expected to offer lower manufacturing costs but higher emissions than the (1) isopropanol-(2) water system. In fact, upon

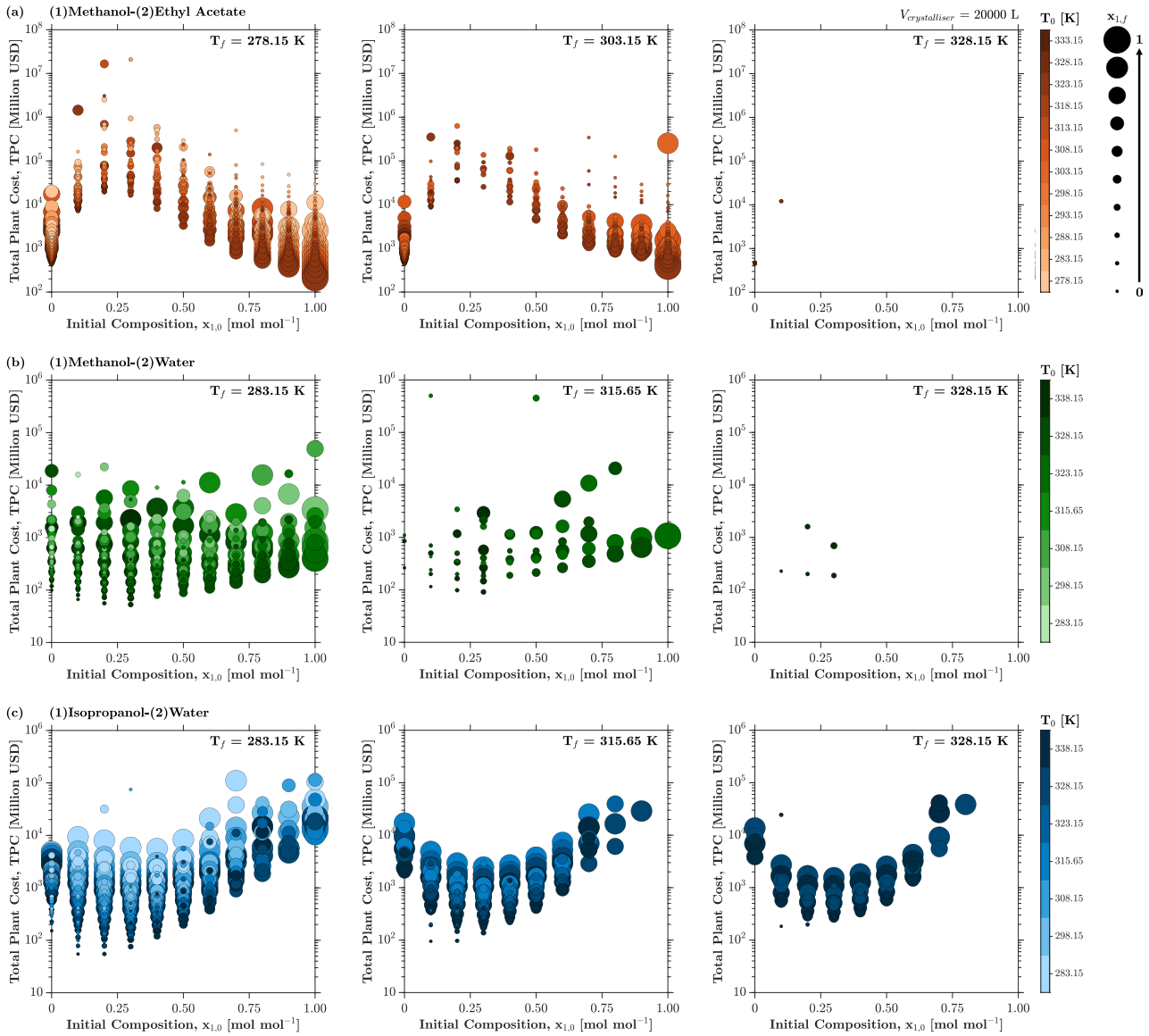

Figure 5. Impact of solvent composition ($x_{1,0}$ and $x_{1,f}$) and operating temperature (T_0 and T_f) on the total cost of each mixed solvent system.

closer inspection of the results in Table 1, it can be seen that the (1) methanol-(2) water system will only offer a saving of 3.21 % when compared with the (1) isopropanol-(2) water system, yet will emit 25.13 % more CO_2e. Thus, the (1) isopropanol-(2) water system should be selected as the best performing system.

It is important to note, however, that these results have been gathered using thermodynamic principles alone, and do not consider the crystallisation kinetics of each system as a consequence. Hence, they should only be used as a guide to rank promising systems before conducting experimental trials – thereby streamlining experimental campaigns.

6. CONCLUSIONS

This study has demonstrated that pharmaceutical crystallisation processes can be visualised in silico using thermodynamics principles alone for pure and mixed solvent systems. Further to this, it has shown how this approach can be used to identify promising process configurations (and operating conditions) when presented with a wide range of potential manufacturing routes for a new drug. Indeed, it has then used this framework to identify cost-optimal and environmentally friendly manufacturing routes for pregabalin production by carefully considering a wide range of process conditions ($x_{1,0}, x_{1,f}$ T_0, T_f) and solvent systems (i.e., 9 pure solvents, 3 mixed solvents): ranking each of these routes from best to worst based on their expected emissions and total manufacturing costs. This ultimately resulted in a mixed solvent system (i.e., (1)

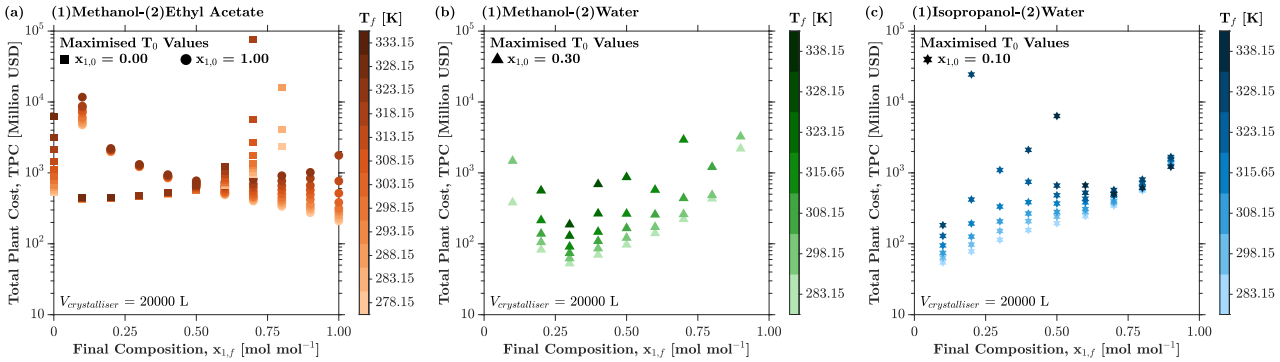

Figure 6. Impact of $x_{i,f}$ and T_f on process cost for each mixed solvent system, using maximised T_0 and optimised $x_{i,0}$.

Table 1: Cost-optimal process conditions for each crystallisation process ($V_{crystalliser}$ = 20000 L).

	T_0 [K]	T_f [K]	$x_{1,0}$ [mol/mol]	$x_{1,f}$ [mol/mol]	*PCE* [kg_{CO_2e}/kg_{API}]	*TPC* [Million USD]
(1) Methanol-(2) water	**328.15**	**283.15**	**0.30**	**0.30**	**11.60**	**52.78**
(1) Isopropanol-(2) water	**328.15**	**283.15**	**0.10**	**0.10**	**9.27**	**54.53**
Methanol	333.15	278.15	–	–	50.70	144.44
(1) Methanol-(2) ethyl acetate	318.15	278.15	1.00	1.00	58.01	210.09
Ethanol	333.15	278.15	–	–	94.89	226.02
n-Propanol	333.15	278.15	–	–	176.92	319.26
n-Butanol	333.15	278.15	–	–	167.98	429.01
Ethyl acetate	333.15	278.15	–	–	214.47	637.34
Acetonitrile	333.15	278.15	–	–	843.98	2734.47
Isobutanol	333.15	278.15	–	–	1029.57	2784.17
Isopropanol	333.15	278.15	–	–	1785.30	4935.44

isopropanol-(2) water) being selected as the most promising process available (c.f. Table 1).

More importantly, however, this work has served to demonstrate how the enhanced solubility trends often seen for solvent mixtures (Fig. 1) do not promise that antisolvent crystallisation will yield cost-optimal results. In fact, it shows that adding an antisolvent to a system could increase its process costs quicker than it decreases an API's solubility, ultimately causing the volume of solvent available for the API to dissolve into to increase faster than API recovery. As such, it is clear that new crystallisation processes should be studied in-silico (using models such as those proposed herein) prior to conducting experimental trials if one wishes to streamline their experimental campaigns by reducing their search space.

ACKNOWLEDGEMENTS

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