

# Challenges and opportunities for computer-aided molecular and process design approaches in advancing sustainable pharmaceutical manufacturing

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Pharmaceutical manufacturing gives rise to a large amount of waste per kilogram of active ingredient, a growing concern with the trend towards larger therapeutic molecules. Achieving better sustainability requires new approaches to process development. We explore the role that computer-aided molecular (and process) design (CAMPD) methods can play, highlighting the value of an end-to-end design mindset that can enable a more holistic assessment of sustainability. We discuss the challenges that must be overcome to deploy such an approach, identifying new structure-property models and the integration of CAMPD with process synthesis and computer-aided synthesis planning as possible research directions.

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## Introduction

In the pharmaceutical industry, new chemical entities (NCE) spend several years in development, during which they are tested through extensive clinical trials that run in tandem with the design and gradual scale-up of the process, as well as the formulation of the NCE into a medicine. This expensive and time-consuming activity is subject to many external pressures — minimising time-to-market and costs, meeting regulatory requirements, and maintaining very high safety

standards. Additionally, the pharmaceutical industry is under pressure to reduce drug shortages and recalls and to improve its environmental record [1]. Responding to these pressures requires taking into consideration multiple criteria (robustness to uncertainty, greenhouse gas emissions, waste production) during process development and exploring a wide range of design alternatives.

Of interest here is the growing imperative to tackle sustainability concerns [2]. The pharmaceutical industry's environmental performance lags behind that of other chemical industries as indicated by metrics such as the E factor [3], which quantifies the mass of waste generated when producing one mass unit of active pharmaceutical ingredient (API) or the process mass intensity (PMI), which quantifies the mass of all materials used to produce one mass unit of API (E factor = PMI-1). For small molecule drugs, the mainstay of pharmaceutical portfolios, the E factor is often of the order of a few hundreds [3,4]. This compares poorly to values typically less than 5 for the wider chemical industry [3]. The current evolution of therapeutics towards larger molecules, such as peptides [5] and oligonucleotides [6], exacerbates this issue. A study [7] of eight oligonucleotides revealed PMI values of 3000–7000, with peptide manufacturing also reported to be associated with large PMIs (13 000 on average during late-stage development [8]). Moreover, the high demand for some peptide- and oligonucleotide-based therapeutics results in the use of large quantities of organic solvents and potential supply chain vulnerabilities [7].

These pressures, combined with evolving legislation [9], give an impetus to adopt new approaches to improve sustainability assessment and to consider new technologies and tools during process development without compromising the ability to meet stringent technical objectives, such as critical quality attributes (CQAs). The growth in the use of computer-aided process design [1,10], which has been encouraged through the regulatory shift to Quality by Design [11], may be helpful in this context.

In this opinion paper, we discuss considerations that impact the sustainability of pharmaceutical processes. We then highlight computer-aided methodologies that connect molecular- and process-level decisions and can support the development of more sustainable processes.

We discuss the research challenges that need to be addressed to make these approaches more effective.

### Sustainability: key issues and assessment

The work of the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable has led to a more holistic and quantitative approach to sustainability. The outcomes have been published in two key surveys [12,13], focusing on synthesis and solvents. Pharmaceutical waste streams largely consist of solvents (75–80% of solvents) [12], which are a major contributor to Scope 2 greenhouse gas emissions through energy consumption and Scope 3 emissions through disposal/incineration.

One popular approach to sustainability assessment is based on green chemistry principles [14], in which substances are associated with an inherent level of harmfulness and given a classification or scores that reflect their effect on safety, health, and the environment (SH&E), and thus consider both environmental and social impacts. This is the approach adopted by the International Conference on Harmonisation [15] and in most solvent guides. A recent example is the CHEM21 selection guide [16], which includes ‘nonclassical’ solvents that are rated for their ‘greenness’, a term that usually encompasses aspects of environmental and social (safety and human health) performance. Such a score-based system is easy to use across many stages of process development, offers a clear way to communicate decisions and is easily extended to include novel solvents or new criteria. It is clear that some solvents, for example, those classified as ‘Highly Hazardous’ such as Benzene [16], should not be used. However, it is more difficult to make evidence-based decisions for solvents that have similar scores with different areas of concern.

It is common practice to equate green chemistry principles with a set of rules (e.g. favour biodegradable chemicals) to be adopted during process development. This approach may lead to poor decisions [17] as the validity of such rules depends strongly on context, for example, whether the chemicals in question can be recycled, reused, or repurposed. A limitation of focusing on the properties and scores of the materials used is that it does not allow for a quantitative assessment on the basis of the *amounts* used. For solvents, the amount used depends directly on the solubility of the solute(s) (a property which depends on the solvent and the operating conditions, e.g., temperature, and what other components are present in the mixtures). In turn, the amount of solvent used affects the amount of energy required for processing, solvent inventory risks, and the requirements for waste treatment. Better environmental and safety performance may in fact be achieved by using a small amount of a less ‘green’ solvent than a larger

quantity of a ‘green’ solvent. Water is a case in point. Whilst it is often touted as the greenest solvent, its large heat capacity and latent heat of vaporisation make its use energy-intensive. Furthermore, the cost of removing organic contaminants from what are often large quantities of water (due to the low aqueous solubility of most organics) is very high.

An instructive critical evaluation of the concept of a ‘green solvent’ and its development is given by Winterton [18], who identifies some of the challenges that make conducting a holistic assessment difficult, including a tendency to focus primarily on reaction solvents without due regard for their impact on downstream separations, the difficulty in determining appropriate weights between criteria (also noted in Ref. [19]) and the lack of knowledge related to newer solvents (e.g. on toxicology). Through the consideration of several types of solvents, the author makes a compelling case that ‘no solvent can be considered inherently or universally green’ [18], and that solvent performance must be considered in the context of its use, whether in a process or in a product.

One approach to address these shortcomings is to combine a score-based assessment with a life-cycle assessment (LCA) that takes into account the impact (e.g. cumulative energy demand) of producing and recovering or treating each kilogram of solvent [20]. Clark [17] points out that one should exercise caution when applying LCA to pharmaceutical processes (Misunderstanding no. 10) because the outcome depends on the availability of a large amount of high-quality data. Ensuring the broader applicability and adoption of LCA in pharmaceutical process development and providing more data (measured or predicted [19]) emerge as key directions in enhancing the sustainability of the chemical industry. Nevertheless, there is significant potential to make LCA an integral part of decision-making rather than an add-on [21,22].

The realisation that there is no such thing as a green solvent is relevant to many aspects of the chemistry of pharmaceutical processes, such as reactions. When assessing the sustainability of a reaction, it becomes apparent that the specific chemistry (reagents, catalysts) and the reactor design and operating conditions dictate yield and selectivity, which have a knock-on effect on downstream operations, including the recovery of unreacted raw materials and the purification and isolation of the API. Even a solvent-free reaction can lead to substantial impacts due to downstream processing. Making pharmaceutical processes more sustainable requires going beyond process chemistry and considering instead an integrated system that includes materials/molecules + process. Decision criteria must account for the impacts of raw material/solvent manufacture and

ultimate disposal, which can be quantified with tools such as cradle-to-grave LCA and alternatives assessment [23]. There is also a need to adopt more thorough approaches to the assessment of the social dimension of sustainability, going beyond the health and safety of workers to account for the impact of manufacturing on health equity, access to medicines, and the effectiveness of healthcare systems. Given the complexity of such integrated systems and the challenge of exploring a large number of manufacturing options at the molecular and process scales, model-based process systems engineering (PSE) methods can provide much-needed decision support [24]. Within pharmaceutical development, PSE approaches have so far been deployed mostly in the context of monitoring, control, and design space characterisation in response to the evolving regulatory framework [1,24,25]. There is however significant potential value in advancing and deploying such methods in the early stages of process development [1,24].

### Model-based approaches to design from molecules to process

We now turn our attention to the use of model-based approaches to improve the performance of individual units and of entire processes. Given the interdependence between process chemistry and process design, we focus on computer-aided molecular design (CAMD) [26] and computer-aided molecular and process design (CAMPD) [27] methodologies. At the molecular level, we primarily consider decisions related to solvents, which greatly impact process sustainability, but also touch on the choice of reaction route as another important aspect of process chemistry that needs to be integrated into holistic process design [28].

#### Overview of computer-aided molecular (and process) design methodologies

In CAM(P)D methodologies, the aim is to determine the optimal molecule, blend, process unit, and/or entire process, given (i) one or more objective functions, (ii) a set of design constraints, (iii) a set of design variables, and (iv) a mathematical model that relates the molecular and process design variables to the objective functions and constraints. Typically, the model consists of algebraic equations, and the variables include continuous variables to represent process quantities such as temperatures, pressures, compositions, and flow rates, as well as integer variables to represent discrete decisions such as whether a specific solvent is used, or which atom groups appear in a solvent. The CAM(P)D problem can thus be framed as a (multiobjective) mixed integer nonlinear program (MINLP).

Several strategies have been proposed to solve the CAM(P)D problem [29], as illustrated in Figure 1. In generate and test approaches [30], property prediction methods and databases are used to generate a list of candidates to

be evaluated. In continuous molecular targeting with CAMD (CoMT-CAMD) [31], the process is optimised using thermodynamic model parameters as decision variables to represent the molecular choices. A molecule is then found that gives a best match to the optimal thermodynamic parameter values [32]. In decomposition-based approaches, optimisation subproblems are solved to identify candidate molecular structures for which the process can be optimised [26,33]. Finally, the simultaneous optimisation of a solvent/solvent blend and the process [34] can be undertaken.

CAM(P)D approaches should be seen as a tool to support conceptual process design: they can be used to evaluate a large number of design options *in silico* and therefore serve to prioritise experimental and detailed studies. Follow-up experiments are required to validate model predictions and to assess properties and performance measures that were not considered during CAM(P)D due to the lack of accurate or tractable computational models.

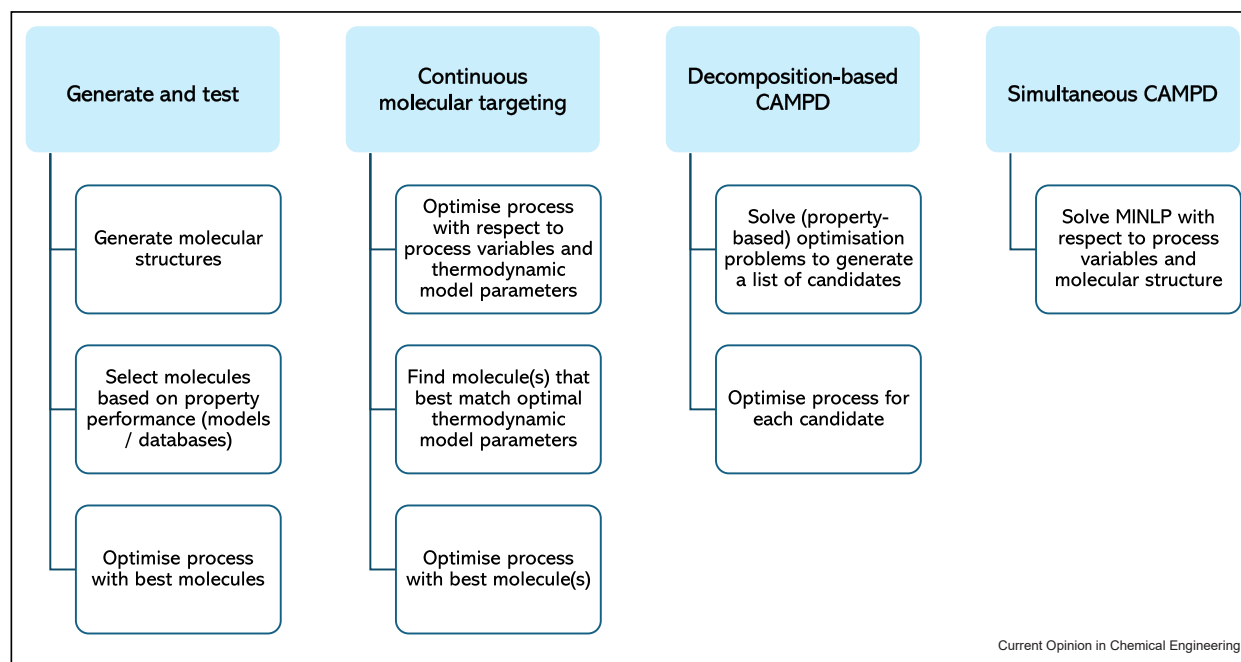
#### A unit-centric view of process development

When considering a single unit, one can use rules-of-thumb to select unit operations that are perceived to afford better environmental performance. For instance, Kekessie et al. [8] identified liquid-phase peptide synthesis (relative to solid-phase peptide synthesis) or multicolumn countercurrent solvent gradient purification (relative to single-column purification) as technologies that may lead to lower PMI. Given a model that connects decision variables, such as the operating conditions and the solvent or solvent blend, to unit-specific key performance indicators (KPIs), such as impurity rejection, and CQAs [11], sustainability assessment takes place at the level of the unit (solvent consumption, E factor), rather than through broader LCA impact categories such as climate change or ozone depletion.

As an exemplar, crystallisation processes provide interesting challenges for CAM(P)D approaches, as unit KPIs and CQAs depend strongly on the choice of solvent(s) and process conditions [35]. In early work, Karunanithi et al. [36] developed a decomposition approach to identify a solvent that maximises API solubility in an aqueous solution. The design scope has since been expanded to include additional properties, objectives, and design variables. Jonuzaj et al. [37] designed blends with up to three solvents to maximise solubility. Watson et al. [34] extended the approach to different modes of crystallisation while maximising crystal yield and minimising solvent consumption as a sustainability metric. They found significantly enhanced performance through this simultaneous design approach.

In most cases, kinetics (e.g. nucleation, growth) and product attributes (e.g. crystal morphology, particle size

Figure 1



Generic schemes for four approaches to CAMPD: Generate and test, Continuous molecular targeting (CoMT-CAMD), decomposition-based CAMPD, and simultaneous CAMPD. CAMD approaches follow similar schemes but do not include process optimisation.

distribution), which are also influenced by solvent choice, are neglected, but there have been encouraging advances in accounting for crystal shape. Karunanithi et al. [33] proposed a constraint on a solvent solubility parameter that correlates with the crystal aspect ratio. Rigorous methods have emerged to model crystal shape by computing adsorption energies at the quantum mechanical level [38,39] or via kinetic Monte-Carlo and group contribution [40], providing a pathway to include shape into the MINLP formulation.

The design of reaction solvents has also seen rapid development, with CAM(P)D approaches based on the prediction of equilibrium properties (e.g. solubility of the reactants) [30] or on the prediction of reaction rate constants [41,42]. This enables trade-offs between selectivity and yield to be understood better, eventually leading to improved performance.

#### An integrated view of process development

As the benefits of CAM(P)D methodologies for individual unit operations have become clearer, there have been efforts to apply them to multiple unit operations, recognising that all characteristics of a stream (impurities, solvents, temperature) leaving one unit impact the performance of downstream units and restrict possible designs (e.g. a low crystallisation temperature may require refrigeration during washing [35], incurring large energy costs and associated greenhouse gas emissions).

From a mathematical perspective, the solution of an integrated optimisation problem (for the entire process) is always at least as good, and often better, than the solution of a series of problems (one unit at a time). Since the integrated problem is more challenging to solve, it is important to make sure that the additional effort leads to substantial improvements.

The value of a quantitative whole-system evaluation has been illustrated by Yamaki et al. [43], who undertook the conceptual design of a reaction/extraction process for Suzuki-Miyaura couplings, with and without solvent recycling. They considered only 5 solvents and assessed performance in terms of overall cost and CO<sub>2</sub> emissions. Their results illustrated the strong interplay between solvent choice, thermodynamic properties, and the optimal process, showing that it is not always necessary to separate all solvent blends into their individual components. Furthermore, they found that combined optimisation of solvent and process resulted in reductions in CO<sub>2</sub>-equivalent emissions by a factor of up to 8 (a factor of 2–3 arising from process optimisation and a factor of 3–4 from solvent choice), with different optimal solvents for different substrates. Given the small set of solvents considered, it is remarkable that such large benefits could be derived.

Waste reduction is an especially promising direction in terms of sustainability, not only through a decrease in

solvent consumption but also through solvent recycling, which has not been widely adopted in the industry. In a series of papers (e.g. [44]), Lakerveld and co-authors deployed the CoMT framework [31] to select crystallisation solvents from a database, considering different crystalliser types (cooling, antisolvent, or evaporative) and including filtration and a flash drum for solvent recovery and re-use [44]. High-performance designs were found with antisolvent crystallisation, with 40% of the antisolvent being recycled.

The solution of a multi-unit design problem makes it possible to avoid solvent combinations that are incompatible. For instance, the integrated design of cooling and/or antisolvent crystallisation, filtration, and washing units via CAMPD [45] results in a crystallisation solvent that is miscible with the subsequent wash solvent. Taking this further, Muhieddine et al. [46] considered solvent choice across synthesis and crystallisation, focusing on the impact of solvent choice on the solubility of reactants, products, and impurities. Process variables and solvent(s) were optimised using a multicriteria approach based on SH&E metrics such as the process E factor and safety indicators associated with each solvent. Mendis et al. [47] considered a process system consisting of a reactor, extraction unit, and two crystallisers, using a metric representative of the cost of

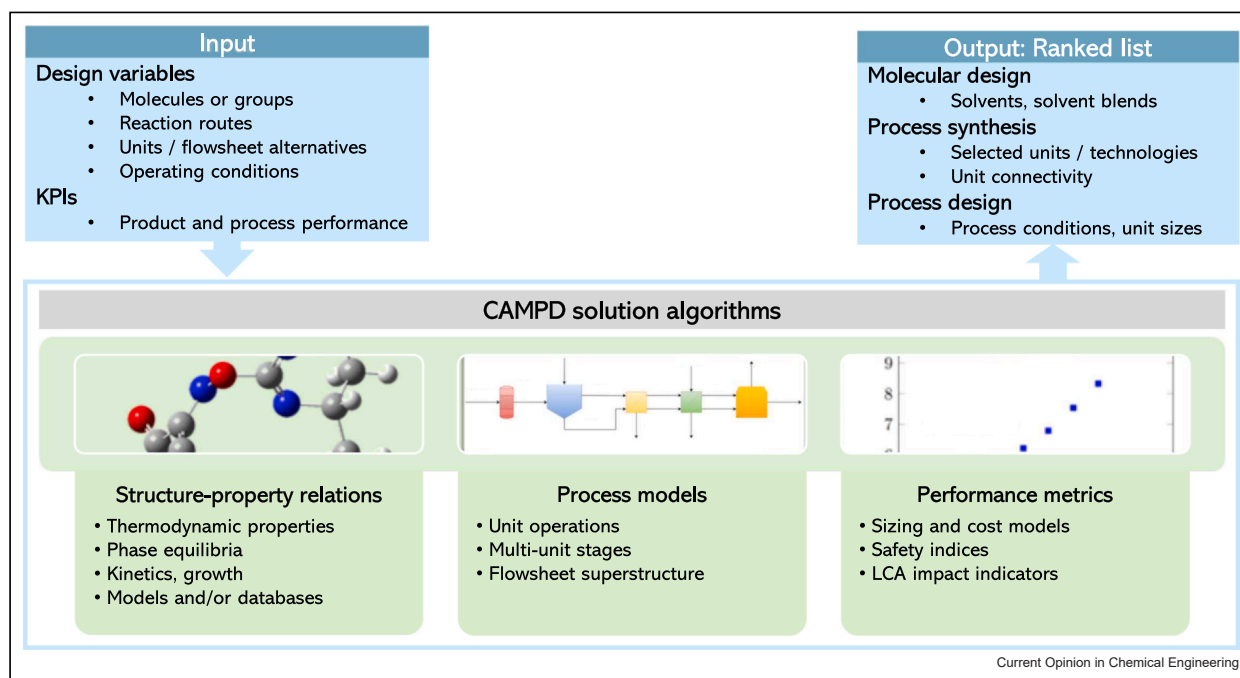
goods as the objective function. The application of this design framework to the production of dalfampridine revealed a high sensitivity of the optimal solution to the design variables, with a difference of 15% between the best objective function and the second-best (local) optimum.

## Outlook and research directions

The use of CAMPD methods during the early stages of process development to improve sustainability is a promising concept that requires further advances to support the greater adoption of existing methods in industry and to expand current capabilities. In Figure 2, we present a blueprint for a comprehensive CAMPD framework that could be integrated into the wider process development effort. As new knowledge on materials and process is acquired through experiments and computational tools, the underpinning models can be updated to refine design decisions through iterative application of CAMPD and targeted experiments. In this final section, we describe some of the advances necessary to realise this.

The availability of predictive models that combine accuracy with computational tractability is a critical component of CAMPD. Suitable models are often available for the relevant unit operations, but property prediction models need further development [19]. There has been

Figure 2



Blueprint for a comprehensive CAMPD approach to sustainable pharmaceutical process design. Images reproduced from Ref. [48].

rapid progress in the area of solubility prediction, provided that the properties of the solid state are known (e.g. [49–52]). These approaches benefit from complementary features. For instance, the SAFT-type models [50,51] are readily applicable to electrolyte systems and polymer-API-solvent mixtures. Additionally, the SAFT- $\gamma$  Mie equation [50] provides an accurate representation of both phase equilibria and caloric properties. On the other hand, the generation of new parameters (sigma profiles) for COSMO-SAC [52] is a comparatively rapid process that does not require any experimental data. Emerging machine learning models offer a promising alternative, especially when combined with physics-based models [53] to make their integration into CAMPD more straightforward.

Numerous properties other than solubility are required to successfully model a pharmaceutical process but cannot yet be calculated with sufficient accuracy or ease, as has been discussed for crystallisation [54]. These properties include transport properties, kinetics, and phase stability. Machine learning models may be useful in cases where computational cost is the main hurdle, as has been shown for the calculation of phase stability within CAMD [55] and in developing models in the absence of a mechanistic understanding of the complex systems under investigation [56].

The proposed blueprint also includes an expansion of the set of decision variables considered within an integrated CAMPD problem in two directions that we believe offer particular promise: process synthesis, which has been demonstrated in a nonpharmaceutical application, and route selection/retrosynthesis, which has been advancing rapidly as a field but where performance assessment has so far been focused mostly on the synthesis step.

Ma et al. [57] have demonstrated the benefits that accrue from considering molecular design (or selection) [37] in conjunction with process synthesis to optimise a process for the separation of naphtha into naphthenic and aromatic fractions, determining the identity of the pure solvent, the number of stages in the extraction column, and the operating conditions that minimise the total annualised cost (TAC). They found an alternative to the commonly used solvent, sulfolane, that achieves a slightly smaller TAC and much-improved sustainability performance. The integration of process synthesis and CAMPD would make it possible to determine simultaneously the best operating conditions, solvents, and process topology, for example, whether to use a solvent swap or stage telescoping, whether to recycle a solvent or not, and what separation technologies to include in the flowsheet.

Finally, computer-aided synthesis planning (CASP) has been gaining traction in the early stages of route

exploration [28], enabling the identification of novel pathways to synthesise the desired API. As discussed by Griffin et al. [28], route selection needs to be considered alongside process development. Similarly to the limitations of thinking about the ‘greenness’ of solvents, the performance of a route is not an intrinsic property. The consideration of the sustainability implications of different routes very early on, by focusing on the thermodynamic limits of the process, reveals striking differences in KPIs [48], indicating that the integration of CASP and CAMPD is a worthwhile goal.

## Data Availability

No data were used for the research described in the article.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Claire S Adjiman reports financial support was provided by Engineering and Physical Sciences Research Council and Eli Lilly and Company. Amparo Galindo reports financial support was provided by Royal Academy of Engineering.

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