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The thermodynamic pharma challenge: A cross-cutting perspective

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ABSTRACT

The development of pharmaceutical products and processes is associated with inherent challenges related to the stability, safety and purity of products for therapeutic applications. Low solubility and bioavailability of newly developed active pharmaceutical ingredients are among the biggest challenges in pharmaceutical development today, as this affects >90 % of newly developed drug molecules. Therefore, thermodynamic research could and should play a crucial role in the modelling and measurement of thermodynamic and kinetic data required for the understanding and design of safe and stable pharmaceutical products as well as their efficient and reliable production. The sixth edition of the IUT Symposium at the ECCE/ECAB 2023 meeting therefore focused on this "Thermodynamic Pharma Challenge". The aim was to initiate an open discussion between stakeholders from industry and academia to share knowledge and identify bottlenecks that need to be addressed by the thermodynamic community. This manuscript addresses the topics discussed and presented in two sessions of the symposium: the panel discussion and the contributed talks. The symposium emphasized the need for advanced thermodynamic modeling to reduce the experimental effort required to estimate the solubility, stability and dissolution behavior of APIs. This is the most important prerequisite for the development of stable formulations and for increasing the efficiency of pharmaceutical production processes.

1. Introduction

The working party on Thermodynamics and Transport Properties initiated a series of symposia, called "Industrial Use of Thermodynamics" (IUT) that aim at promoting interactions between academia and industry (de Hemptinne et al., 2017; Kontogeorgis et al., 2022; Kontogeorgis et al., 2013; Economou et al., 2014; Mathias et al., 2018). Whenever possible, these symposia are organized as part of larger events, so that partners from various working parties can contribute. A round-table discussion is an important part of such a symposium, allowing all stakeholders to present their vision, including those who may not be able to communicate as a paper because of IP issues. At each of these occasions, a short publication is issued that summarizes the main topics that were brought up. The current paper is an account of the discussion during the ECCE/ECAB 2023 meeting held in Berlin. The ECCE/ECAB meeting is the largest conference organized every two years by the European Federation of Chemical Engineers (EFCE) in collaboration with the European Society of Biochemical Engineering Sciences (ESBES). The 2023 meeting held in Berlin gathered >1000 participants in 15 parallel sessions.

Two of these sessions focused on the challenges facing the pharmaceutical industry, which is making a significant contribution to overcoming the health challenges of a growing world population. These challenges arise from the fact that active pharmaceutical ingredients (APIs) are very complex molecules, 90 % of which are very hydrophobic and therefore have very low bioavailability. Some of them exhibit a water solubility that is even lower than that of marble. Achieving the desired therapeutic effect thus requires an efficient development of formulations (such as tablets or vaccines) that enable drug delivery into the human body. Suitable formulation recipes for chemical API molecules and biopharmaceuticals are currently being identified through extensive screenings. If no suitable formulation is found, this prevents a

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drug from being used at all. Chemical engineering knowledge, and in particular thermodynamic principles, could significantly contribute to formulation design and to solve this "Pharma Challenge".

The IUT "The Pharma challenge" comprised two sessions. The first session was a round-table discussion and the second session comprised five lectures given by Fiora Artusio (Self-assembled monolayers as supports for pharmaceutical crystallization), Gabriele Sadowski (Pharmaceutical Formulations), Georgios Kontogeorgis (Biotechnology), Gianvito Vilé (Molecule manufacturing), and Dimitrios Gerogiorgis (Process Design and Optimization). The same authors also served as panelists in the first session. The sessions were moderated by Antoon ten Kate, on behalf of the organizing working parties. The present document reports essentially on the round-table discussion, but evidently there was a lot of overlap between the two sessions. The audience mainly originated from academia and about 12 % of the audience came from industry, as illustrated in Fig. 1.

2. Panel discussion

The panel discussion was based on three questions, inspired by the three working parties involved in the discussion (Crystallization, Process Design as well as Thermodynamics and Transport Properties). For each of these questions, first, the audience was invited to express their main interests in terms of keywords. This was done through Wooclap (https://www.wooclap.com/), a web-based application that creates word clouds based on the input from the audience. Below, we present both the resulting word clouds and the main thoughts that were brought up during the discussion.

2.1. *From molecules to physical state: what are the challenges?*

This first question mainly focused on the description of physical properties, and more specifically on phase equilibria. Fig. 2 shows the responses provided by the audience.

Clearly, the availability of data is most important. This is a multi-dimensional problem. (1) The molecules of interest in pharmaceutical development are big molecules which usually have multiple functional groups, (2) they may exist in a large number of possible isomers, conformers, or polymorphs, and (3) they may form hydrates, solvates, or co-crystals and thus may exist in different solid forms depending on the environmental conditions. Often, the metastable form is the one of most interest for pharmaceutical application as it has both higher solubility and higher dissolution rate than the more stable ones.

However, this in turn means that the challenge is not just the availability of data but even more important it is the reliability of data and the knowledge of all factors impacting the results. For example, a useful solubility measurement does not only require analysing the saturated liquid to determine the solubility but – equally important - it requires to analyse the solid (amorphous vs. crystalline, which polymorph, hydrate/solvate?) in equilibrium with that liquid to know the solubility of which substance has been measured. While this is meanwhile common sense in pharmaceutical and thermodynamic communities, it becomes critical when solubility data are used as input for solubility-prediction methods such as machine learning (Kalepu and Nekkanti, 2015).

Addressing additional constraints, such as the scarcity of available data due to small quantities of available substances or challenging measurement processes emphasized the necessity for models and the strategic use of design of experiments. The use of simulation tools may possibly help providing atomic level insight, whereas thermodynamic modelling offers predicted macroscopic data.

The survey findings indicate a reluctance of pharmaceutical industry to adopt thermodynamic models, attributing it to the perceived unreliability of existing models. However, numerous works already convincingly demonstrated predictive capabilities of thermodynamic modelling. Several models have been used to identify suitable solvents for API molecules, such as COSMO-RS (Klamt et al., 2002), UNIFAC (Kolář et al., 2002), CPA (Mota et al., 2011), or NHRB (Tsivintzelis et al., 2009). PC-SAFT was shown to successfully predict the physical stability of API formulations based on polymers as well as based on lipids (Brinkmann et al., 2020; Lehmkemper et al., 2018; Dohrn et al., 2020; Prudic et al., 2015). Despite these efforts, there appeared to be a reluctance to engage in collaborative efforts between industry and academia, mainly caused by Intellectual property (IP) problems. A notable challenge identified during the discussion was the difficulty in establishing an effective communication between academia and pharmaceutical industry. The use of technical jargon, such as "chemical potential" or "activity coefficient", presents a significant barrier for collaboration. However, successful examples exist, such as long-lasting collaborations of academia with companies such as AbbVie or Janssen Pharmaceutica (e.g. (Lehmkemper et al., 2018; Dohrn et al., 2020; Artusio and Pisano, 2018; F. Artusio et al., 2020)) and more examples are expected in the future.

2.2. *Product design: what properties are essential, and how to define the adequate formulation?*

Pharmaceutical industry, more than others, focuses on the product, rather than on the process. The primary goal is to always ensure patient safety and to meet regulatory standards. This question aimed at

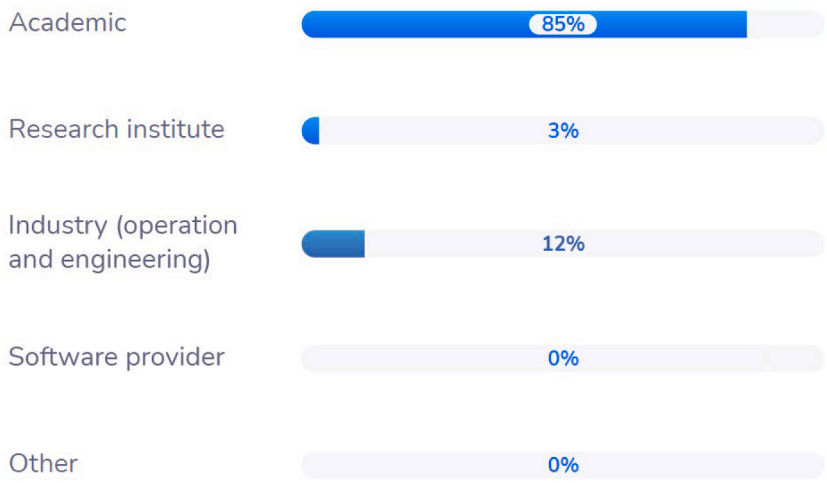

Fig. 1. Origin of the audience.

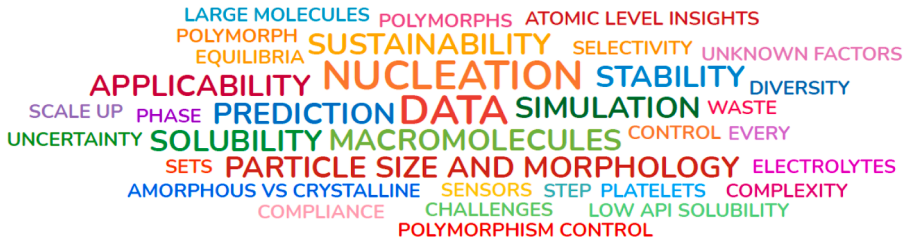

Fig. 2. Word Cloud resulting from the audience replying to the question: "From molecules to physical state: what are the challenges?" (41 respondents).

discussing this. Fig. 3 shows the input from the audience.

The properties of most importance for pharmaceutical products are – as expected- related to the solid state of the product and/or the pharmaceutical ingredient: solubility, crystallinity, melting properties, crystal size and shape, dissolution kinetics as well as product stability in general.

Patient safety places a strong emphasis on product stability over time. Since the most stable API polymorph tends to be the least soluble, there exists an inherent challenge in balancing solubility with thermodynamic product stability: the higher the solubility, the lower the thermodynamic stability and vice versa. A commonly-used strategy are amorphous solid dispersions, in which a polymer matrix is used to stabilize the metastable amorphous form of an API molecule. Although none of these formulations (tablets) currently on the market is thermodynamically stable, their high viscosity hinders crystallization and thus kinetically stabilises the amorphous form of the drug at least for a certain time period.

The impact of polymorphism was highlighted with a real-world example of an HIV treatment drug being withdrawn from the market due to the emergence of a previously unknown and significantly more stable (and almost insoluble) polymorph. The occurrence of polymorphs often necessitates a reformulation and redesign of the manufacturing process for both API and the other formulation components.

This stability encompasses not only the API but also the excipients, stabilizers, and other components in the formulation. As an example, during storage, the crystallisation of mannitol, a common excipient in freeze-dried products, can trigger water release and potential degradation reactions, thereby compromising drug stability and preservation.

An additional issue concerns the end-of-life properties of drugs. It was noted that, while much attention is given to the safety and stability of pharmaceuticals during storage and within the human body, there seems to be a lack of consideration for what happens to these products once they are excreted and enter wastewater systems.

In summary, the discussion revolved around the critical nature of stability, the challenges introduced by polymorphism, the thermodynamic and kinetic stability, and the complexities associated with crystallization kinetics. The question about disposal properties prompted reflection on the often-overlooked environmental impact of pharmaceutical products after they exit the human body.

2.3. Process design: what are the specific needs of pharma processes?

The constraints related to production process in pharmaceutical industry necessarily have an impact on the commercial success. Here again, the audience was asked to give some input through keywords as shown in Fig. 4.

The problem of scale-up has clearly been recognized as a major challenge that needs to be solved convincingly. In practice, many pharmaceutical processes are carried out in batches and "scale-up" is often replaced by a "numbering up". Although there is a trend towards continuous processes, the transition to this more modern design is difficult. Designing continuous processes for increasingly complex molecules is a major challenge. Nevertheless, the importance of continuous processes in pharmaceutical production is expected to increase, which would lead to a decrease in production costs. However, the main constraints are not technical: intellectual property protection and legal aspects make any change to existing processes - if possible at all - extremely time-consuming and expensive. The approval procedure by regulatory agencies as FDA/EMA is extremely tedious and long. Even small changes of operating conditions again require a new approval.

Pharmaceutical research currently focuses on developing a suitable dosage form and formulation for a specific drug molecule. For approval purposes, this is then produced in small batches. At that stage, pharma companies may settle for suboptimal designs for the sake of ensuring first-to-market achievements. The limited lifespan of patents was identified as a factor contributing to the relatively low efforts on process optimization. Once approved, however, the process can no longer be changed and thus, numbering up is the straightforward upscaling method. This could only be improved by simultaneous product and process development prior to the approval process. Yet, it would require close collaboration between pharmacists and process engineers from the outset and could be facilitated by increased use of process simulators (and modelling tools) in pharmaceutical companies.

3. Highlights from the presentations

The panelists were asked to summarize their contributions, which is provided below.

Fig. 3. Word Cloud resulting from the audience replies on the question: "Product Design: what properties are essential, and how to define the adequate formulation?" (43 respondents).

Fig. 4. Word Cloud resulting from the audience replies on the question: "Process design: what are the specific needs of pharma processes?" (43 respondents).

3.1. On the use of self-assembled monolayers as supports for pharmaceutical crystallization (Fiora Artusio)

In the pharmaceutical industry, crystallisation is often employed not only to isolate and purify a drug or an intermediate product, but also to support the formulation step. Crystallisation affects many of the properties of the final product, such as its flowability, biological activity, and tableting behaviour. Therefore, crystallisation is intimately related to the physical and chemical properties of the drug product and has also an impact on the management of further downstream procedures, such as filtration, drying, and milling. The design of crystal properties is therefore crucial and relies on the understanding and control of nucleation and crystal growth (Artusio et al., 2024). In this framework, heterogeneous nucleation can be exploited to guide the crystallisation pathway of molecules thanks to the specific surface properties of the heteronucleants, including morphology, charge, chemistry, or crystallinity. Based on these features, it has been possible to fine tune the crystal form, habit, and size, as well as shorten nucleation induction times or carry out crystallisation at very low supersaturation levels (Artusio and Pisano, 2018; F. Artusio et al., 2021; F. Artusio et al., 2020). Surface-solute interactions can either take place at the surface of the heteronucleant or involve the bulk of the material, as for porous structures.

In this perspective, Self-Assembled Monolayers (SAMs), exposing different chemical groups and sub-nm surface roughness, have been immobilised on glass and used as heterogeneous nucleation sites (F. Artusio et al., 2020). SAMs result from spontaneous organisational processes and couple robust surface functionalisation to extremely smooth topography. This feature enables the direct investigation of the heteronucleants' surface chemistry effects on crystallisation, apart from any topographical effects. When used in combination with batch cooling crystallisation techniques, SAMs boosted or delayed the nucleation kinetics of small API molecules, such as aspirin, depending on the chemical groups exposed on their surface (F. Artusio et al., 2021).

To better investigate the surface-API interactions, SAMs have also been employed as supports for Spin-Coating Crystallisation (SCC) of aspirin. SCC guarantees isotropic interaction between the heteronucleant and the drug, while limiting local gradients. Thanks to the confinement of aspirin crystallisation to a very thin film over the SAMs surface, a preferential growth of selected crystal faces was imposed by different SAMs exposed chemistries. The presentation reported that this result was achieved thanks to the different molecular interactions occurring at the interface between the heteronucleant and the solution (F. Artusio et al., 2021).

SAMs can also be used to investigate the effects of surface chemistry on the crystallisation of much more complex molecules, such as proteins. The interaction with SAMs is protein-specific and also depends on pH and supersaturation level of the solution. The nucleation kinetics of proteins having wide metastable zones, i.e., lysozyme, was modulated by the SAMs chemistry. When proteins having narrower metastable zones were investigated, i.e., catalase, SAMs exposing different groups were still able to modify the crystallisation pathway by promoting the appearance of previously unknown polymorphs. This effect was attributed to the SAM-specific stabilisation of pre-nucleation clusters through selective SAM-protein interactions (F. Artusio et al., 2021).

Overall, engineered surfaces can support the understanding of heterogeneous nucleation of APIs thanks to tailored interactions between functionalized surfaces and APIs.

3.2. Thermodynamics of pharmaceutical formulations (Gabriele Sadowski)

APIs usually are crystalline solids that are very little soluble in aqueous media. Application in patients therefore requires approaches to increase the water solubility and bioavailability of these APIs. This can be achieved by using so-called formulations, which usually are complex mixtures that accommodate and stabilize an amorphous/metastable API against unwanted state changes (e.g. crystallization, denaturation or aggregation) during product preparation, storage, and administration. To achieve this, formulations usually contain numerous excipients, such as polymers, lipids, sugars, amino acids, salts, or surfactants. The choice of excipients for a given target API is called formulation design. However, identifying appropriate excipients is quite challenging and today usually established by expensive and time-consuming "trial-and-error" approaches assisted by high-throughput screening techniques. In that context, thermodynamic predictions using PC-SAFT allow remarkably reducing the experimental effort for formulation design. As small API activity coefficients mean strong molecular interactions between API and excipients and thus high API solubility in the formulation, excipients leading to small API activity coefficients result in most-stable formulations. Thus, thermodynamic activity-coefficient predictions and solubility calculations using PC-SAFT (Lehmkemper et al., 2018; Dohrn et al., 2020; Prudic et al., 2014) are able to reduce and eventually to replace time-consuming, expensive and wasteful screening experiments.

The shelf life of a formulation is defined as the storage time during which formulation does not change, e.g. due to API crystallization. This shelf life is mainly influenced by the storage conditions temperature and relative humidity (RH), which determine the amount of water absorbed by the formulation (Prudic et al., 2015). The latter influences both the solubility of the (hydrophobic) active ingredient and the viscosity of the formulation unfavorably, which leads to a drastic reduction in the shelf life of the pharmaceutical product. PC-SAFT modeling of the solubility of the active ingredient and water absorption in combination with viscosity modeling of polymer-based formulations (so-called amorphous solid dispersions, ASDs) makes it possible to estimate the shelf life of ASDs (tablets), which ranges from a few hours to months or even decades (Wolbert et al., 2022; Wolbert et al., 2023; Grönniger et al., 2024).

Once administered by a patient, the formulations should dissolve in the aqueous gastrointestinal body fluid. This is, of course, the environment with the highest conceivable relative humidity - almost one. This means that what can be successfully avoided during storage now happens to the highest degree: while the ASD dissolves, it absorbs water from the aqueous medium. Depending on the relative rates of water absorption and ASD dissolution, this can lead to phase separation or API crystallization in the outer areas of the ASD tablet (which have already absorbed water) before it is fully dissolved. The resulting layers formed by the API-rich phase or even crystalline API are very hydrophobic and eventually completely shield the rest of the ASD interior, preventing its complete dissolution (Borrmann et al., 2025). This effect becomes worse the higher the API content (drug load) is and may even lead the

counterintuitive effect that the higher the API content, the lower the absolute amount of API released. For example, an ASD containing 6 mg indomethacin (IND) released 6 mg IND, while a tablet of the same size containing 42 mg IND released only 1 mg of IND before dissolution stopped completely. Water sorption, phase separation and resulting release profiles were successfully modelled using PC-SAFT combined with a Stefan-Maxwell diffusion model (F. Artusio et al., 2021).

It can therefore be stated that thermodynamic modeling with PC-SAFT is capable of (1) modeling the aforementioned effects and, more importantly, (2) in-silico determining excipients and/or conditions to avoid undesirable phenomena and promote the desired behavior and functionality of pharmaceutical formulations.

3.3. Thermodynamics, a frontier for biotech? (Georgios Kontogeorgis)

The use of thermodynamics in the pharmaceutical industries and in biotechnology in general is rather limited. This is partially understood by the very challenging systems involved, the complexity of typical phase behavior encountered (liquid-liquid and solid-liquid equilibria) and the very complex interactions involved (polarity, hydrogen bonding, electrolytes). The complexity is such that some 22 years ago (Chen and Mathias, 2002), in a manuscript authored by ASPEN presenting primary and secondary models for 13 categories of industrially relevant systems, they concluded that for pharma/biological applications there are neither primary nor secondary models to choose. And for the pharma/biological fields, the "problem areas" include data, databanks and models, i.e. pretty much everything! Even for "rather simple" systems, the challenges are significant as illustrated by the partition coefficient by Stockar and van der Wielen (von Stockar and van der Wielen, 1997).

The situation today was summarized in two perspectives papers (de Hemptinne et al., 2022; Gupta et al., 2023) pointing to the developments, but also to the need for further work to reach predictive power for complex biomolecule. In a recent industrial survey (Kontogeorgis et al., 2021), several pharma/bio companies expressed concerns related to collaborations with universities due to confidentiality/IPR issues including the time and effort required to set up legal agreements which, in some cases, deprive the companies from seeing any return on investment. However, most of the concerns from the bio/pharma industries are related to the actual capabilities and use of thermodynamics and a rather consistent picture is obtained that the use of thermodynamics in pharma and bio industries is not as mature as in the (petro) chemical industries. The properties of interest involve thermodynamics and beyond (solids description, polymorphism, crystallization, flowability, solubility in dynamic conditions…), while the systems of interest concern complex multicomponent mixtures (including water, organic solvents, dissolved solids, and ionic species). The characterization of the equilibrium properties of such systems requires a deep understanding of the interactions between the molecules, especially the hydration of the species in the presence of several phases of different natures (liquid, gaseous and solid).

Many simulators still do not have models suitable for pharmaceuticals, but many companies happily comment that software companies are paying now a lot of attention to the needs of the pharmaceutical industry and that crystallization process modeling & process optimization in process simulators start becoming more standard and is something that some companies see happening. So there is positive news. Moreover, many companies appear to be familiar with both classical (NRTL, UNIFAC) and more advanced models (SAFT, COSMO-RS) available in thermodynamics toolbox. They recognize that while model parameters are often available for solvents, this is typically not the case for complex molecules, not even for group contribution methods. They also commented that quantum calculation tools like Turbomole also enable to have more structural information especially regarding conformers. Some companies clearly stated that they expect that the BioTech/ BioPharm/ C&G Therapy sectors will start getting more involved in modeling over the next 10 years and go beyond the empirical methods used now.

Successful examples of the use of thermodynamic models for solubility prediction of pharmaceutical molecules, either with CPA (Mota et al., 2011), with PC-SAFT (Cassens et al., 2010; Ruether and Sadowski, 2009; Spyriouni et al., 2011), or with NRHB or COSMO-RD (Tsivintzelis et al., 2009). These advanced models are very promising also because they use the rather limited data available for pharmaceuticals and often use group-contribution or related predictive approaches for determining the pure- and mixture parameters necessary for the calculations. We notice that AI/ML may also offer a way forward at least for systems for which there is sufficient data. There have been applications for aqueous two-phase systems (Y. Chen et al., 2023; Y. Chen et al., 2023) and it is hoped that such methods can also be used for systems with pharmaceuticals when sufficient data become available.

3.4. The critical role of property prediction in advanced (Bio) Pharmaceutical manufacturing, design and optimization (Dimitrios Gerogiorgis)

In an era of ever-increasing pressure on global material and energy resources, Advanced Manufacturing can only remain relevant by sustainably fostering plant agility, loss prevention and process intensification. The prospect of Continuous Pharmaceutical Manufacturing (CPM) emerges as a ground-breaking technology which can invigorate the global pharmaceutical industry by sustainably fostering its agility and the affordability of healthcare for large populations.

Process simulation has already secured (and continues to provide) time and cost benefits to the pharma industry but must rely on strong connections with experimental reality, as kinetic and thermodynamic data are required for credible process simulation and optimization (particularly for multiphase systems encompassing substances/APIs recently discovered, hence never studied before). Process Systems Engineering (PSE) methodologies have already had a demonstrable impact on continuous pharma R&D (process synthesis, parameter estimation, model-based simulation and optimization, and design space visualisation) towards evaluating technical efficiency, environmental impact and economic viability of new or existing active substances (APIs); often, many PSE methods must be combined (Jolliffe and Gerogiorgis, 2016).

Continuous pharmaceutical production, however, is a grassroots plant design target (rather than a retrofit option), significantly fostered by numerous new organic synthesis routes suitable for continuous operation (Baumann et al., 2020; Kerr and Cole, 2022). The foundation of every truly novel process is the continuous synthesis chemistry, demonstrated for many APIs, from common painkillers and blockbuster anti-cancer medications, to key therapeutics against widespread devastating diseases (Diab and Gerogiorgis, 2018; Diab et al., 2021).

Nevertheless, an efficient synthesis chemistry fostering process intensification does not warrant technoeconomic profitability. Fully continuous reactions and separations require model-based investigation (hence accurate thermophysical and reaction property estimation) which saves time and cost before committing resources only to production-scale ventures with truly strong potential. A scaleable chemistry still requires unit design at-scale and reliable Process Analytical Technology (PAT), to achieve Quality by Design (QbD).

Comparative economic analyses must illustrate clear advantages in order to justify corporate investments in continuous production-scale facilities, and quantitatively pinpoint the projected gains in footprint, efficiency, energy, solvents and cost use; above all, the business case for a product must be strong enough to cover both synthesis and process R&D against incessant competition and quick (7–10 years) patent expiry. Fig. 5 illustrates a technical application of PSE methods (starting with Population Balance Modeling, PBM) for optimal design of continuous Mixed Suspension, Mixed Product Removal (MSMPR) crystallization: the number, size (volume) and operating temperature of

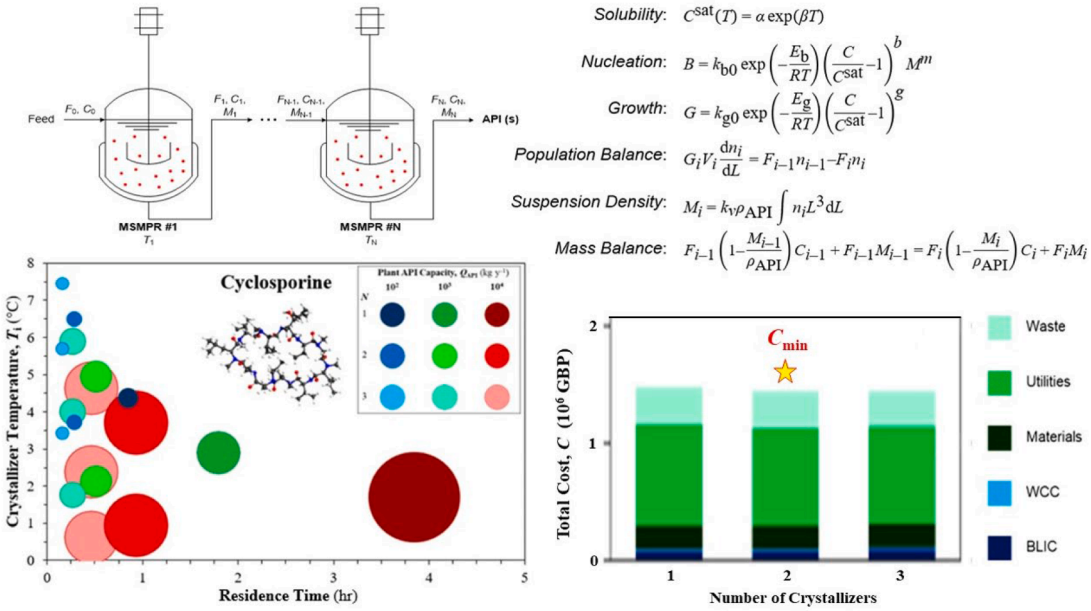

Fig. 5. Technoeconomic analysis of continuous cyclosporine crystallization in MSMPRs via PBM (Diab and Gerogiorgis, 2018).

crystallizers have been determined for different APIs whose crystallization kinetics vary (Diab and Gerogiorgis, 2018). The total annual cost can be subsequently computed, with a full range of design choices and trade-offs visualized, to facilitate business decisions.

The technical showstoppers for pharma (esp. continuous) process innovation thus emerge clearly, but two corporate ones (terminology, compartmentalisation) also merit discussion (priorities and targets between chemists and engineers differ, for a good reason, and organizational structures have evolved to follow them, possibly impeding radical leaps and risky advances). The bench-scale and production-plant views of the world may differ enormously, particularly when the former insinuates (possibly in great error) that building the latter is a really bad idea, missing that economies of scale are quite possible. Beyond this, however, the inevitable race against time, in order to see the API through and 'first to market' has its inherent deficiencies, as e.g. certain downstream decisions on formulation type (solid, liquid, spray?) and delivery form (oral/nasal administration, injectable?) may render the upstream optimal design problem iterative and possibly ignoring superior product and process candidates, due to the lack of time. This is why, in contrast to the key point of Fig. 5, a (seemingly elusive) optimal Scale-Up is often replaced by Number-Up, at the expense of lower technical and economic efficiency.

4. Concluding remarks

The IUT symposium held during the ECCE/ECAB 2023 meeting in Berlin brought together people from different origin who shared their views and visions on thermodynamic challenges in pharmaceutical development. It became clear that collaboration between different disciplines is quite essential throughout the entire product and process development chain.

Thermodynamic research focuses on a better understanding and prediction of the physico-chemical properties of API systems, such as solubility, physical stability, dissolution kinetics and bioavailability. The aim is to apply and to further develop predictive models that reduce the effort involved in formulation development by reducing the time and resources currently required for extensive experimental studies. Instead of just correlating experimental data, current thermodynamic models use molecular properties of API molecules - e.g. size, polarity, or the number of association sites - to predict their macroscopic behaviour, like solubility. One the one hand, this reduces the experimental data required as an input to a minimum and on the other hand, this allows for save and physically meaningful extrapolations in terms of system temperature or concentration.

The further development of knowledge-based thermodynamic modelling goes hand in hand with data-driven modelling based on AI (artificial intelligence) methods such as machine learning (ML). On the one hand, ML methods are already being used to improve thermodynamic models and to parameterize new substances for which no experimental data is available. On the other hand, cheap and reliable data from thermodynamic modelling will significantly expand the database used as a training set for the development of ML methods and thus enable their safe applicability.

Today, most of the pharmaceutical production processes are batch processes which moreover usually need to be developed before clinical studies, i.e. in the early stage of formulation design. Yet, the use of process-simulation techniques based on physico-chemical modelling is an important enabling tool for process development based on a limited amount of experimental data. Additionally, it allows the design of continuous processes that increase both product quality and production efficiency.

Pharmaceutical development of increasingly complex products nowadays is a cross-disciplinary activity and requires an effective communication and collaboration of experts from pharmacy, physical chemistry and engineering. Crossing the barriers between the different communities requires an ongoing communication effort, which was the main objective and an important contribution of this IUT.

CRediT authorship contribution statement

Gabriele Sadowski: Writing – original draft, Validation, Supervision, Methodology. **Georgios M. Kontogeorgis:** Writing – original draft, Validation. **Fiora Artusio:** Writing – original draft, Validation. **Dimitrios I. Gerogiorgis:** Writing – original draft, Validation. **Grazia De Angelis:** Validation, Supervision, Conceptualization. **Antoon ten Kate:** Supervision, Methodology, Conceptualization. **Jean-Charles de Hemptinne:** Writing – review & editing, Validation, Conceptualization.

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Data availability

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

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