Front. Chem. Sci. Eng. 2013, 7(1): 1–8
DOI 10.1007/s11705-013-1304-y

REVIEW ARTICLE

Problems, potentials and future of industrial crystallization

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Abstract This review discusses important research developments and arising challenges in the field of industrial crystallization with an emphasis on recent problems. The most relevant areas of research have been identified. These are the prediction of phase diagrams; the prediction of effects of impurities and additives; the design of fluid dynamics; the process control with process analytical technologies (PAT) tools; the polymorph and solvate screening; the stabilization of non-stable phases; and the product design. The potential of industrial crystallization in various areas is outlined and discussed with particular reference to the product quality, process design, and control. On this basis, possible future directions for research and development have been pointed out to highlight the importance of crystallization as an outstanding technique for separation, purification as well as for product design.

Keywords industrial crystallization, potentials and future, product design

1 Introduction

One of the important challenges in the field of industrial crystallization is to match the changing requirements across all industrial sectors by controlling the crystal morphology, size distribution and polymorphism (in terms of product quality e.g., purity, filterability, flowability and reactivity). Both, application-oriented and theoretical multi-disciplinary approaches have to be applied to solve the emerging issues that spread over fundamental aspects to commercial applications.

Great progress has been made during the last decades. Due to the better understanding of fundamental aspects, significant improvements in the industrial practice were achieved and integral approaches were enhancing the design of crystallization processes (e.g., crystal shape, product handling, and downstream processing performance). Nonetheless, further research is necessary to overcome the recent requirement-driven problems in industrial crystallization processes which can be summarized as follows: (i) prediction of separation coefficients (kinetics of crystallization); (ii) prediction of phase diagrams; (iii) prediction of effects of impurities on metastable zone, on nucleation, and on growth rate of crystals; (iv) design of fluid dynamics for each equipment and each product; (v) process control with process analytical technologies (PAT) and development of adequate measuring techniques; (vi) polymorph screening; (vii) stabilization of non-stable phases; (viii) product design (PD); and (ix) classical understandings of the mechanisms of nucleation, growth and aggregation. A few of the named nine fields which need more knowledge to improve processes and products will be discussed here.

Research efforts to solve these multifaceted problems also illustrate the manifold potentials for customized solutions in industry sectors such as: chemical, pharmaceutical and processing industries, food and nutrition and agro-chemistry. Thus, the solution for the problems can serve as "door-opener" for the development and further optimization of new materials and products that are able to combine previously unattained functional properties with economic benefits and therefore match the industries specific demands. This means in practice more stable, purer, from the economical point of view considerably lower in costs, more sustainable, and more functional products.

The review aims to highlight the basic problems of industrial crystallization from which potentials can be derived that demonstrate its future viability and sustainability.

2 Problems in the field of Industrial Crystallization

According to different industrial requirements a preferred crystalline product has high purity, desired size distribu-

Received September 16, 2012; accepted November 28, 2012

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tion, enough stability, and good shape. The latter is not only essential for the efficient implementation of required downstream processes such as filtration, drying, and milling, but also responsible for physical and chemical properties of the final product [1,2]. Furthermore, industrial processes have to meet strict economic and environmental criteria, which also need to be taken into consideration for future developments in the field of crystallization. To achieve progress in crystallization processes and products a wide range of problems need to be addressed by multidisciplinary approaches – starting from the molecular level (molecular modeling), to the crystal and, subsequently, the product design, and up to advanced measurement techniques for an efficient process control and scale-up.

In the following, scientifically important fields along with the resulting industrial challenges are briefly described.

2.1 Prediction of phase diagrams

The understanding of phase diagrams and phase equilibria is essential for the development of appropriate crystallization processes and, consequently, of a desired product design. Phase diagrams are based on the knowledge of thermodynamic properties of the material, gained in the past by experimental approaches and collected in the form of thermodynamic databases. However, the complexity of real materials complicates experimental studies for the establishment of complex phase diagrams that are, in general, time consuming and expensive [3,4].

With the developments of computation, modeling and simulation techniques and the generation of equations, methods for the modeling of thermodynamic properties and phase diagrams of multicomponent systems are gaining grounds. All available thermodynamic and phase equilibrium data are evaluated simultaneously by thermodynamic modeling (optimization) in order to obtain a set of model equations for the Gibbs energies of all phases in relation to temperature and composition [5]. These equations allow a back-calculation of all thermodynamic properties and phase diagrams and, therefore, ensure all data rendered self-consistent and consistent with thermodynamic principles. Furthermore, interpolations and extrapolations can be applied in a thermodynamically correct manner [5]. Nonetheless, the existence of reliable and consistent thermodynamic pure-component data are crucial for the existent modeling methods and can be found in databases like the Gmelin database, owned by the German Chemical Society [3].

The development of several software packages for the modeling of phase diagrams and thermodynamic properties offer valuable information that even go beyond the field of equilibrium thermodynamics. Those include in particular e.g., data for multi-scale modeling and modeling of diffusion processes in multicomponent systems. As software packages are available, e.g., Thermo-Calc, MTDA-TA, Pandat and FactStage, modeling methods, based on semi-empirical approaches can provide significant economic benefits. Time and cost consuming experiments can be reduced and fast and reliable material processing simulations can be achieved [3,4].

2.2 Prediction of effects of impurities and additives

It is well known and comprehensively described that the presence of impurities or additives can strongly affect the width of the metastable zone, nucleation, crystal growth, agglomeration, and crystal morphologies as well as crystal stability [6,7]. Trivalent metal ions such as Fe^{3+}, Cr^{3+}, and Al^{3+} show a strong impact on crystallization parameters of inorganic compounds. These include the metastable zone width and the crystal growth rate and, consequently, product quality criteria which play a crucial role in the success of industrial crystallization processes [8,9].

Nowadays, the prevention of undesired crystal morphologies is mainly achieved by additives, which are found by screening in the form of time and money consuming experiments. Due to the advanced acquisition of knowledge in the field of crystal growth coupled with increasing computational capacities, new dynamic simulation approaches are developing [10,11]. Among them, molecular modeling concepts are applied to predict morphology in the presence of impurities and additives or in the presence of solvents [11].

Despite the high accuracies of the introduced methods, reliable predictions are still time-consuming and require manual steps to be carried out by an experienced operator. It must be pointed out additionally, that the implementation of these predicting methods is a model-based approach and not a method by first principles [9].

Regardless of the described drawbacks, the recent advantages in the morphology prediction modeling in the presence of one or more additives or one solvent, in particular, the developing of routines in the established methods concerning the solid (the crystal side) of surface docking [12] or build-in [13] are reliable tools. In terms of liquid side modeling there is the approach of Winn and Docherty [14] or the break-through approach of the layer docking method of Schmidt and Ulrich [15], since it is combined with the solid side and, therefore, gives reliable morphology predictions [9]. Schmidt [15] gives a handbook on how to use this successful approach.

In addition to the effects of impurities and additives described above, the important role of additives for the stabilization of metastable polymorphs or solvates is highlighted in Sect. 2.6.

2.3 Design of fluid dynamics for each equipment and each product

Theoretical process models commonly assume a perfectly

mixed volume. But even a stirred tank represents an inhomogeneous fluid mechanical environment. Especially, around the impeller zone the relevant mean-flow and turbulence quantities can vary by orders of magnitude throughout the vessel [16,17]. This reveals the general issue of the above-mentioned assumption that, used for the modeling of crystallization processes, will lead to errors in the growth, nucleation and agglomeration rates, and consequently, in the crystal size distribution [16]. To this problem has to be added the limited validity of existing models in terms of an extrapolation to other scales of operations or other geometries. This is due to the fact that available models still are input-output models which are tuned for a single configuration [18]. In real processes, fluid dynamics and crystallization are closely interrelated and should be modeled together [19]. Thus, to obtain a rigorous process description an anisotropic flow field in the crystallizer needs to be considered, and consequently, also the population balance problem has to be simultaneously solved with the fluid dynamics Equations [20]. Various approaches to solve the corresponding simulation problem and to demonstrate the importance of the interaction of fluid dynamics and crystallization are discussed in the literature [18,17,21]. However, these problems are far from being solved. An appropriate process development and scale-up requires knowledge of the solid concentration distribution, local velocities, shear rates and energy dissipation rates [16]. Considered in total, a complex multi phenomenon and a multi-scale problem need to be addressed by means of computer-aided tools [19].

Computational fluid dynamics (CFD), a comprehensively investigated computer-based methodology, has been successfully used for the modeling of mixing and turbulence in stirred tanks, for multi-fluid modeling (MFM), and for the modeling of heat transfer using different vessel and impeller configurations [22]. CFD models allow to gain a valuable quantitative insight into mixing, turbulence, and heat transfer but cannot guarantee a successful scale-up process development, resulting from the interplay between fluid dynamics and crystallization kinetics that scale in different ways [22,23]. Therefore, to predict the crystallization behavior upon scale-up, fluid dynamic information combined with crystallization kinetic models using a compartmental modeling approach need to be applied [24]. A coupled simulation implemented in specialized software tools exploits the full benefit of CFD and allows the development of scale-up strategies of crystallizers. New dynamic and steady-state process modeling tools (e.g., gPROMS) can be used to model fluid dynamics and predict particle size distributions. Additionally, predictive CFD simulations to determine the effects of scale-up on the mixing, energy dissipation, and heat transfer were performed [22].

These outlined approaches demonstrate how numerical simulations and other software tools help to understand the interactions of fluid dynamics and crystallization kinetics and how they can be used for the design and upgrade of industrial crystallizers as a cost-effective approach to process optimization and to address arising issues of scaling up crystallizers [25,22].

2.4 Process control with process analytical technology

Since its formal introduction by the US Food and Drug Administration (FDA), PAT was increasingly being explored and adopted for crystallization processes and is currently an area of high interest, especially for the pharmaceutical industry [26–28]. PAT tools can be used for design, analysis, and control of crystallization processes to assure critical quality and performance attributes of raw materials, in-process materials and final products [27,29]. In the field of crystallization, PAT technologies are able to provide a wealth of real-time data for the understanding and control of crystallization processes, especially, by an *in situ* use. Routinely used techniques are focused beam reflectance measurements (FBRM) and optical reflection monitoring (ORM) in order to analyze the evolving crystal size distribution *in situ* (particle engineering) [30][1)], e.g., in-line spectroscopic techniques primarily attenuated total reflectance Fourier transformation infrared (ATR-FTIR) and ATR ultraviolet-visible (UV-vis) spectroscopy. The latter can be applied for solution concentration measurements [31] and to monitor polymorph and solvate conversations in real-time [28,32,33]. Furthermore, *in situ* imaging techniques for the direct observation of the appearance and growth of crystals such as PVM (particle vision monitor) were developed recently [34]. A number of in-line and online monitoring techniques were developed and are still evolving.

With a focus on the in-line analyzing, new sensor technologies based on the ultrasound technique using different frequencies (e.g., out of plane ultrasonic system (OPUS), based on ultrasonic extinction) are currently established that are able to offer real-time process information under real, dynamic conditions. After the detection of the liquid concentration by ultrasound based on only one frequency, Stelzer and Pertig [35] introduced e.g., an innovative ultrasonic probe technique to measure the mean particle size and suspension density of crystals in a saturated solution by a single ultrasound sensor at only one frequency.

Feasibility and usability were proven for industrial ammonium sulfate and urea crystals. In Fig. 1, the data of ultrasound velocity and attenuation (based on mathematical abstractions) as a function of the suspension density were combined and related to characteristic properties of

1) Peda S, Smieszek M, Stollberg C, Ay P. Interpretation of FBRM and 3D ORM SMF data via simulated nucleation and crystal growth. In: Stelzer T, Ulrich J eds. Proc. Of BIWIC 2010. Cuvillier Verlag, Goettingen, 2010, 468–475

suspensions solid phase [35].

In addition, appropriate functions considering the effects of different suspension densities are required and two suitable mathematical abstractions were shown. Even in optically non-transparent media where other optical processes fail, the presented technique provides sufficient in-line process control of the liquid and the solid state for suspension densities up to 40 wt-% [35].

The conclusion of the above stated is the importance that only the combined use of appropriate analytical technologies along with smart modeling, which is already far advanced, leads to the promised success and unveils all benefits of having real-time process analytical data [27].

2.5 Polymorph and solvate screening

Polymorphism is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice while retaining the same chemical composition [36]. Solvates in the contrary, incorporate molecules of one or more solvents. If those solvents are solid at ambient conditions, the structure is referred to as co-crystal [37]. The influence of polymorphism and solvates on the physical properties of the solid, such as crystal habit, solubility, speed of dissolution, density, hardness, optical properties (color), melting point, bio-availability and chemical reactivity is known and requires profound consideration in crystallization process design and control [38,39]. In awareness of a distinct need, all industries dealing with pure or formulated solids, particularly the pharmaceutical industry know about the importance of polymorph or solvate monitoring and control (including formation, prediction, transformation, and stability) [38,40]. Latter requires a deep understanding of the kinetics and thermodynamics of the polymorphic or solvate system and will not be further discussed here [41].

To characterize polymorphs or solvates, traditional offline analytical techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), solid state nuclear magnetic resonance (NMR) and infrared spectroscopy (IR) are commonly applied [38]. However, to uncover all possible crystalline phases in order to find an optimal solid form a large set of experiments need to be performed, which is time consuming and a waste of resources and therefore uneconomic [37,41].

New methods in polymorph and solvate screening are necessary to discover all potential crystalline phases in early stages of development including the evaluation of the solid-state properties and to find the important purpose-oriented form [41,42]. Molecular modeling approaches are still not advanced enough to be helpful. Therefore, laboratory work is still dominating.

Nowadays, high-throughput polymorph and solvate screening methods (technology to assist in parallel experimentation) are increasingly performed. Moreover, real time monitoring (*in situ*) would be advantageous due to the dynamic nature of the transformation and the instability of certain polymorphs. The retrieved kinetic data of the process allow to identify and quantify undesirable polymorphs and solvates in real time and open up the possibility to intervene during the production process (e.g., *in situ* Raman spectroscopy) [38,43].

Despite the recent advances, polymorph and solvate screening is still a sophisticated, complex, time and money consuming task and provides challenges to researchers and practitioners in the laboratory.

2.6 Stabilization of non-stable phases

The phenomenon of polymorphism and the solvates are of great importance, especially, in the pharmaceutical industry as different polymorphs or solvates can exhibit different

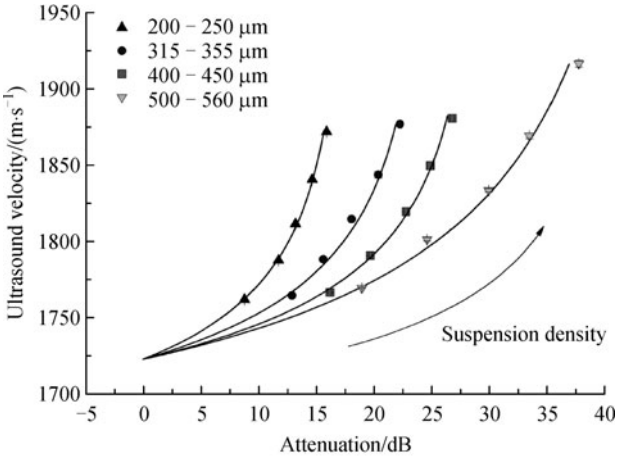

Fig. 1 Ultrasound velocity and attenuation measured as a function of suspension density and different particle sizes of urea [35]

physical and chemical properties with great influence on the bio-availability, stability, filtration, and tableting properties of the drug substance [1,44].

In general, the thermodynamically stable polymorph or solvate is used in the most commercial dosage forms. For this reason, the formation of previously unknown polymorphs or solvates during production or an uncontrolled transformation to other polymorphs or solvates is highly undesirable. However, in the case of active pharmaceutical ingredients (API) with low solubility in water, the most stable polymorph, which also shows the lowest solubility, might have an insufficient bio-availability. From that, the necessity to develop metastable polymorphs or solvates arises which offer improvements of certain properties such as a higher bio-availability [40,45].

Several methods are known to crystallize a less stable polymorph or solvate, including high pressure crystallization, spray drying, and crystallization from a melt or a quenched amorphous state. However, these methods are difficult to control in terms of avoiding the formation of more than one polymorph [45,46]. Moreover, the isolation of a metastable polymorph is difficult and challenging before it undergoes a solvent-mediated phase transformation to the more stable form. Therefore, several studies investigated the use of additives and substrates either to encourage the preferential nucleation of one polymorph or to disrupt the crystal growth of the other form. The limited success of these methods is due to the non-consideration of kinetic factors that play a dominant role during the crystallization, and the transformation process [45]. As a consequence, to exploit the superior properties of a metastable polymorph or solvate a kinetic stabilization by inhibiting the formation of a more stable polymorph or solvate is required [47].

More advanced ways to obtain desired metastable polymorphs or solvates are the use of external fields or surface templating, the selective nucleation by controlling the supersaturation and nucleation temperature, and seeding experiments with great care by ensuring the absence of the stable polymorph nuclei while the nucleation of the metastable polymorph or solvate [1].

The above mentioned shows that the crystallization and stabilization of less stable or metastable polymorphs or solvates continue to improve but are in many cases still far away from industrial use.

2.7 Product design

The properties of a crystalline product, such as filterability, flowability, drying, caking, and tableting behavior are mainly determined by the product quality, which refers to the crystal size distribution, crystal morphology, polymorphic outcome, degree of agglomeration, and purity [48,49]. The majority of the mentioned product properties is affected by nucleation, growth, and aggregation mechanism and can be pre-fixed or even generated by a controlled production process [48].

Considering the classical nucleation theory, multiple challenges arise from the two-stage theory as well as the theory of structured liquids. The classical nucleation theory that assumes the spontaneous appearance of a fully ordered nucleus has been questioned and a two-stage mechanism has been suggested. Starting with the formation of an intermediate ordered state, referred to liquid-like clusters, the second step involves the structural evolution to the regular crystalline form [50,51].

Further on, observations of macro building blocks and oriented aggregation challenge the classical growth and aggregation theories. In the special case of oriented aggregation, secondary particles that are new single crystals, twins or intergrowths are produced by the mutual attachment of primary particles in a highly oriented and irreversible manner. As a result, defects and often symmetry-defying morphologies are occurring [52,53].

Taking this into account, classical measuring techniques are no longer sufficient and show the importance of more advanced, *in situ* measurement techniques that are a exemplar presented in Sect. 2.4.

This also underlines the importance of process design for the production of solid products with desired properties. In fact, no product design is possible without process design (control) [33]. Consequently, product and process designs have to be considered together to match the high demands and standards on the desired product qualities [54,55]. This in turn leads to the essential need to possess extensive knowledge of the entire crystallization process. Along with recent changes of industrial procedures from quality-by-testing (QbT) to quality-by-design (QbD) and recent developments of process analytical technologies, shown in Sect. 2.4, approaches to design desired product properties are of great interest [56].

Beyond the state of the art, next generation of product design approaches, such as crystalline coatings and hollow crystals have been introduced recently [57,58]. These tools describe the coating by filling hollow crystals as a new and more elegant way of forming covers for pharmaceuticals. Forward thinking, the hollow needle-like crystals could be used as a container for pharmaceuticals that is able to extend the shelf life of the enclosed drug, through to the facilitation of a retarded drug release by a slow dissolution rate of the surrounding material [57]. Furthermore, a self-controlled coating process (*in situ*) was introduced by Roembach et al. [59] that allows the formation of a solid material and the coating, simultaneously.

Nonetheless, classical crystallization control approaches, focused on the objective to control the crystal size distribution (e.g., average size maximization, coefficient of variation minimization) can lead to an inefficient and conservative process design. Therefore, novel control approaches that incorporate robustness in the crystallization process control [60,61] and include the application to the control of polymorphic transformations [62] need to

be applied [56]. Nonetheless, all simulated crystallization systems need to be supported by results from experimental work which illustrates the importance of an intelligent combination of state-of-the-art instrumentation (PAT tools) and efficient optimization algorithms. This ensures a successful implementation of model-based crystallization control and, consequently, a desired product design [56].

3 Conclusions

It has been shown, that the field of industrial crystallization faces great challenges to match the growing and changing requirements of different industries. To address these challenges, application and theoretically based multi-disciplinary approaches were discussed in a problem-orientated way that potentials could have been derived and future prospects were described.

With the developments of computation, modeling, and simulation techniques, the modeling of phase diagrams and thermodynamic properties offer valuable information, which are essential for the development of appropriate crystallization processes. Together with this, reliable tools for the prediction of effects of impurities and additives were introduced and evaluated. Especially, the layer docking method of Schmidt and Ulrich [61] combined with the solid side ensures a reliable morphology prediction modeling and is trend-setting. Nonetheless, experimental data and a large amount of manual steps are still necessary for both of the above mentioned fields of research. Furthermore, the design of fluid dynamics via CFD tools was outlined, which is able to predict the crystallization behavior upon scale-up by combining fluid dynamic information with crystallization kinetics using a compartmental approach. Subsequently, new PAT tools were described in order to obtain real-time data under real, dynamic conditions for a better understanding and control of crystallization processes.

Polymorph and solvate screening and the stabilization of non-stable phases are sophisticated tasks that are still performed without strategies and profound knowledge. Although new advanced methods were developed, a large set of experiments is still necessary, which means a high complexity, and a waste of time and money.

As the majority of the product properties, especially size, size distribution, and crystal shape, are affected by nucleation, growth, and aggregation mechanism, the importance of process design for a desired product design is undeniable. Next generation approaches to prepare complex final products, such as direct product coating while crystallizing the products (e.g., filling of hollow crystals or *in situ* coating processes) are moving in the right direction.

Finally, all presented approaches that are able to face actual challenges and future requirements still need to be supported by experimental work, combined with state-of-the-art process analytical technologies and brought together in efficient model-based optimization tools with sufficient computational capacities.

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