Extended abstract

This section is based on Chapters 1 and 11 of the candidate´s PhD Thesis. The references to other Chapters of the Thesis are now complemented with highlighted information about the reference to the candidate's publication where the results in question are published [1-8]. An additional publication is included in the "Key results and future applications" section, illustrating the current research that the candidate is carrying on in the protein crystallization field [9].

Introduction and state of the art

When, in 1973, Ohara and Reid discussed the applicability and feasibility of sophisticated crystal growth models of surface diffusion growth and two-dimensional nucleation [10], they probably would not anticipate that the same theories would remain the fundamental basis of crystal growth science more than 50 years after their introduction. In fact, the means and instrumentation available nowadays regularly lead to important new findings that have not been considered in the classical models update. This is valid for both the physical premises of the crystal growth mechanisms and for the critical evaluation the growth models against experimental results. At the beginning of this study in 2001, the transfer of impurities into crystals in solution growth was the primary subject of study, as a natural sequence of previous works of Faria [11], Gonçalves [12] and Chorão [13] within the sugar system, and following the current trend in many research groups on industrial and fundamental crystallization. Nevertheless, as the work progressed, it became clear that considerable research in pure systems would have to be done before centering the attention on the impurity uptake. The alternative could be an essentially experimental work describing several pure solute/impurity systems; although interesting from a practical point of view, such a work would always have a limited application field. Presently, a great number of experimental data is published documenting the growth of crystals in the most diverse systems, by employing several growth techniques, and focusing the majority of growth variables. In so doing, the main emphasis is not anymore on the indiscriminate measurement of additional kinetic data of crystallization but instead on the development of new theoretical tools for their interpretation. This was a major conclusion from the panel discussion "Towards the Future of Industrial Crystallization" presented by Roger Davey, John Garside and Ronald Rousseau in the last day of the 16th International Symposium on Industrial Crystallization held in Dresden, Germany [14]. In a time when this thesis was nearly finished (September of 2005), it was satisfying to realize that the guidelines for forthcoming studies appointed by those recognized authors, corresponded to the main objective envisaged by us during 2001: To combine the new experimental insights and the accepted theoretical grounds on the development of new crystal growth models that are able to shorten the existing gap between theory and practice. In so doing, the ultimate goal of estimating crystal growth rates a priori would be gradually accomplished.

The objectives outlined are manifestly challenging. Yet, in a first phase, the concrete problems found in the design, operation and management of industrial crystallizers were thought to be more effectively approached through pilot scale experimental investigation. The established cooperation with the Audubon Sugar Institute at Louisiana State University would make possible to perform sugar crystallization experiments in a pilot evaporative crystallizer, thus providing the proper starting point for increasingly sophisticated studies. As suggested by Ohara and Reid, the development and verification of any crystal growth theory should be based on kinetic data documenting the influence of specific independent variables [10]. According to the same authors, the most important variables are supersaturation, temperature, crystal size, mass transfer, and impurity type and level. More recently, the growth rate history and the energetics of the crystal faces have also been found to have a considerable role during growth. Unfortunately, few experiments have been reported where all the main variables were considered. Moreover, growth rates measured at similar experimental conditions can diverge significantly, when different growth techniques are employed [15,16]. As a consequence, laboratory growth experiments under well-defined conditions are still required to evaluate the isolated influence of some of the above mentioned variables.

In this regard, the mass transfer studies during crystal growth are an illustrative case: although this subject is been considered in many works, only a small fraction of these are suitable to be used in the rational assessment of diffusion-integration models. This happens because the evaluation of the mass transfer resistances is often merely qualitative, or else, their quantification is based on doubtful simplifying hypothesis. As illustrated by the well-known series of 3 papers of Garside and Mullin dated from 1967/8 [17-19], the comprehensive modeling of the problem requires considerable amounts of growth and dissolution rate data, over a wide range of crystal-solution velocities. By this way, the relationship between the diffusional resistances during growth and dissolution can be clarified and, on the other hand, important indications can be provided on how mass transfer is affected by surface adsorption during growth. The existence of a multilayered adsorption phase at the surface of growing crystals is admitted by many authors (see for example the revision made by Tai et al. [20]), but the incorporation of this concept in the crystal growth theories has not been effective [21-23]. The adsorption step is also thought to play an important role on the growth of crystals in the presence of impurities. In this field of study, numerous authors are in accordance about the kinetic patterns obtained, even though the existing theories do not completely explain those evidences. It is considered that further investigation has to be performed on the competitive nature of surface adsorption when the crystallizing solute and the impurity are involved. The demand for new theoretical growth models results, to a great extent, from the perspectives provided by modern microscopic techniques on the molecular mechanism of crystal growth [24]. This is, therefore, an important source to be explored on the fundamental research envisaged for this thesis.

Methodology

In this work, crystal growth from solution is progressively discussed from industrial, engineering and scientific perspectives. Following this order, new experimental methods and theoretical models are presented in the first three parts of the thesis, and in the last part, illustrative examples are given where the new concepts are jointly applied to crystallization data.

Part I, named “macro scale approach”, comprises Chapters 2 and 3 and deals with the evaporative crystallization of sucrose at pilot scale. In **Chapter 2 [1]**, new industry-oriented methods are purposed and applied to sugar boiling runs. The results obtained are then used in **Chapter 3 [2]** on the estimation of the respective sucrose growth kinetics.

In Part II, “new engineering models” are introduced to describe diffusion-affected growth in pure solutions (Chapters 4 and 5) and crystal growth in the presence of impurities (Chapter 6). **Chapter 4 [4]** is purely theoretical, providing the physical and mathematical concepts of the “parallel step model”. In **Chapter 5 [3]** the validation of the model is made against experimental data taken from literature and obtained in sucrose growth experiments at laboratory scale. **Chapter 6 [5]** is concerned with the proposal and validation of the “competitive adsorption model” about the effect of impurities on the crystal growth rates.

Part III is named “crystal growth science”, since new fundamental perspectives documented in literature are discussed in the light of a new “spiral nucleation model”. In **Chapter 7 [6]** the theoretical basis of the model is introduced and the model practical interest is pointed out. In **Chapter 8 [7]**, the phenomenon of size dependent growth is studied according to the spiral nucleation model.

The three chapters of Part IV consist in “application examples and conclusions”. In **Chapter 9 [2,5]** the influence of cane sugar impurities on the sucrose growth kinetics is investigated using the kinetic data obtained in Part I and the theoretical background provided by the competitive adsorption model and the spiral nucleation model. In **Chapter 10 [8]**, a synthesis of the several approaches discussed in the thesis is made through their use on the interpretation of sucrose growth rate data. In particular, the effect of temperature and growth rate history on the crystallization kinetics is analyzed, and the importance of the growth rate measurement technique is discussed. Finally, in Chapter 11 the general conclusions and future work suggestions are referred.

Key results and future applications

The measurement of reliable crystal growth kinetics and subsequent rational interpretation were discussed according to classical and newly proposed perspectives. The crystallization of sucrose is used as a case study in laboratory and pilot scale experiments. Departing from identified limitations of the existing crystal growth theories, alternatives were proposed to characterize the influence of growth parameters such as supersaturation, temperature, hydrodynamic conditions, impurity concentration and crystal size. Developments on the molecular description of the crystal growth phenomenon provided new tools for the determination of interfacial and topological properties from growth rate data.

Practical difficulties found in industry-like environment were the starting point for a systematic study of the factors affecting crystal growth. In Part I of the thesis, new methods were proposed for characterization and management of sugar evaporative crystallizers: by the **mass balance method [1]**, the vacuum pan content of sucrose, impurities, and water was dynamically computed using typical sugar boiling data and the initial parameters of the cane syrups. This way, the evolution of the crystal content, mass of crystals, liquor purity, and liquor non-sucrose to water ratio was possible to be determined during sugar boiling runs. Using modern image processing techniques, the progress of the mean crystal size in the first phases of sugar boiling experiments was followed. The results obtained in this **image analysis method [1]** compared well with the ones calculated by mass balance. The next challenge was to process the obtained supplementary boiling data so as to estimate sucrose growth kinetics in other conditions than of conventional laboratory experiments. This was firstly done by determining equilibrium data at the particular conditions of the pilot pan experiments. The

estimation of sucrose solubility from crystallization curves [2] was accomplished by fitting the derived theoretical concentration profile to the sucrose concentration curves calculated by the mass balance method. The resulting sucrose solubility coefficients were in good agreement with published data measured at similar conditions of sugar cane boiling. Then, a new **growth rate measurement method [2]** was proposed, where the measured evolution of mass of crystals with time was used to calculate the corresponding variation of the sucrose growth rate. The used equation takes into account the variation of the crystal surface area, instead of assuming a mean surface area over the growth period. Kinetic curves were obtained by representing the sucrose growth rates as a function of the liquor supersaturation during the experiments. The methods for equilibrium and kinetic data determination proved to be robust and of direct application to large-scale sugar crystallization.

A number of different factors affected the growth rates of sucrose obtained in the first part of thesis. Thus, the isolated role of important variables such as supersaturation, crystal size, impurity concentration, hydrodynamic conditions, etc, is difficult to be inferred from those results. In the succeeding chapters, new theoretical and experimental studies focusing some of the most important crystallization variables were presented. In spite of the importance of the transport phenomena during crystal growth, significant limitations of typical diffusion-reaction models were identified when confronting the theory against experimental data. An attempt was made to fulfil this gap by means of the novel **parallel step model [4]**. In this model, the existence of interfacial adsorption is considered not only in physical terms, but also in the mathematical derivation of the growth rate equations. Adopting a methodology comparable to the derivation of the Brunauer-Emmett-Teller isotherm, it was concluded that the rate at which molecules integrate the crystal lattice corresponds to the net adsorption velocities extended to the thickness of the adsorbed multilayer. Consequently, simultaneous occurrence of solute diffusion and adsorption was assumed to occur before the integration of the adsorbed molecules at crystal surface. Different situations were analysed concerning the crystal shape, integration kinetic order and diffusional resistance, and a generalized overall growth rate equation was proposed. The **comprehensive test of the new model [3]** was carried out using crystallization data obtained under different and well-defined diffusional conditions, and available information about limiting cases of pure chemical and diffusional regimes. Mass transfer coefficients were determined from the growth rate data using the conventional two-step model and the parallel step model. In the first case, an unrealistic variation of the coefficients with the relative crystal-solution velocity was obtained when compared with the behaviour expected from standard mass transfer correlations. Conversely, the mass transfer coefficients obtained by the parallel step model were confirmed both in their order of magnitude and in the way they were influenced by the hydrodynamic conditions. Closely controlled **laboratory experiments were conceived [3]** to study the influence of agitation speed on the sucrose growth rates in a batch crystallizer. Contrarily to what happened in the pilot-scale runs, this procedure allowed accurate investigations on the kinetic influence of isolated growth variables. As predicted by the parallel step model, the presence of a thick adsorbed layer around the sucrose crystals is likely to have affected the solute molecular diffusivity in the medium. According to that, the results obtained were well described by the parallel step model.

The other engineering approach in Part II consists in a new **competitive adsorption model [5]** to describe the growth of crystals in impure solutions. A dispute between the crystallizing solute and the impurity was considered to exist for the surface coverage and for the occupation of energetically favourable places at surface steps. The impurity effect on the crystal growth rates is characterized by a Langmuirian isotherm for competitive adsorption and by the parameter β, accounting for the impurity ability to move across the surface and occupy a stable position at the active sites. Published experimental data showing different types of impurity-affected kinetics was adequately described by the competitive adsorption model. The contribution of the new model on explaining unresolved mechanistic and kinetic evidences was highlighted.

Regardless of the advancements on crystal growth characterization provided by the new engineering models, many questions can only be answered through molecular scale fundamentals of the phenomenon. In Part III of the thesis, the limitations of classical two-dimensional nucleation models and of the Burton-Cabrera-Frank theory were recalled in view of recent observations of growth features using modern microscopic techniques. An alternative theory was proposed in which new and classical concepts were combined in the so-called “**spiral nucleation model**” **[6]**. Initial growth nuclei are assumed to result from the organization of adsorbed molecules in spirals around surface dislocations. The energetic barrier for the activation of the spiral nuclei is considerably lower than the admitted in other energy-activated mechanisms. Stable nuclei evolve into bigger growth hillocks in supersaturated media through the incorporation of adsorbed units into their steps. The displacement velocity of steps in solution and vapour growth is calculated under different kinetic premises, taking into consideration the importance of surface diffusion in each process. A generalized expression was obtained relating the crystal growth rate with main variables such as supersaturation, temperature, crystal size, surface topology and interfacial properties. An application example was given, where the **supersaturation-dependence of the interfacial**

tension [6] is determined from the crystal growth kinetics of sucrose at 40 ºC. Additionally, the spiral nucleation model was applied on the estimation of the **optimum interstep distance and of critical parameters of the growing hillocks [6]** without the use of microscopic techniques. The published data in this field supports the consistency of those findings.

Finally, in Part IV of the thesis, the potential of the new fundamental end engineering models was illustrated in several application examples. The occurrence of **size-dependent growth [7]** in the crystallization of sucrose was investigated according to the new insights provided by the spiral nucleation model. Laboratory growth experiments carried out with crystals of different size confirmed that the integration rate is linearly dependent on the crystal characteristic dimension. Accordingly, an innovative growth rate definition was put forward by expressing the mass deposition rate per crystal volume units. The **volumetric growth rates [7]** demonstrated to be size independent over the considered supersaturation range. Moreover, this formalism is of great practical interest since it can be used in situations of unknown crystal number and size. Since crystal size also affects the mass transfer processes, the parallel step model was recalled for the diffusional effect quantification. The conventional growth rates measured in the sugar boiling experiments of Part I were conveniently converted into volumetric growth rates to study the isolated **influence of cane sugar impurities on the sucrose growth kinetics [2,5]**. Empirical correlations used in sugar industry satisfactorily described the growth rate decrease with the non-sucrose compounds concentration. On the other hand, besides being consistent with the experimental findings, the proposed competitive adsorption model additionally contributed for the logical understanding of the impurities action. The estimated model parameters indicate that cane sugar impurities can be greatly adsorbed at the sugar crystal surface, even though their kinetic effectiveness is low. In a concluding example, empirical, engineering and fundamental models were combined on the interpretation of the **effect of temperature** and **growth rate history [8]** on the growth kinetics. The apparent and true activation energies of sucrose were determined from the growth rate curves measured at different temperatures. A theoretical relationship between the two activation energies was derived from the parallel step model. The influence of temperature on the crystal growth rates was measured by the innovative **constant supersaturation method [8]** by allowing the crystals to grow at controlled supersaturation and decreasing temperature. Differences between the results of the isothermal and constant supersaturation methods were explained from the viewpoint of the spiral nucleation mechanism, taking into account **different crystal surface properties [8]** caused by the growth rate history in each case. The same framework was used to explain the growth rate curves measured in the batch crystallizer and in a fluidized bed crystallizer at the same temperature. Apparently divergent results were successfully described by the combined effects of crystal size, hydrodynamic conditions and growth rate history that have been proposed throughout this thesis.

More than setting the end of the thesis, the conclusions summarized above are expected to provide some of the guidelines for future works in this field. Desirably, the presented methods and theories will continue to be developed through their application to new systems and purposes.

From the literature reviews made, the new engineering models will be very welcomed in other systems than sucrose. For example, the parallel step model demonstrated to be of great applicability in the crystallization of inorganic salts from solution, and the competitive adsorption model adequately described uncharacteristic crystal growth curves in the presence of impurities. In addition, the parallel step model can be further explored in view of straightforward determinations of the diffusional resistance. It would be interesting to combine the parallel step model and the competitive adsorption model on the investigation of the impurity effect at different mass transfer resistances. A natural follow-up of the competitive adsorption model would be the study of non-equilibrium impurity adsorption during crystal growth. In this concern, the occurrence in some systems of growth rate hysteresis is a good experimental evidence of the impurity adsorption kinetics. So far, the existing theoretical models did not give a completely satisfactory justification for this fact, possibly because the competitive nature of surface adsorption has been disregard.

The fundamental views provided by the spiral nucleation model can be extended through many branches of crystal growth science. In this thesis, some application examples were given by applying the new theory to crystal growth from solution, using the pure sucrose system. In the future, the spiral nucleation model might be useful in varied fields such as molecular beam epitaxy, chemical vapor deposition, crystal growth of metals, minerals, semiconductors, superconductors, magnetics and biological substances, either in bulk or as thin films. The current quest for large protein crystals with low defect contents is believed to be a privileged application field of the new growth theories. Such crystals are of key importance in contemporary molecular biology or in drug discovery, for suitable protein structure determinations by diffraction of X-rays, electrons or neutrons. A good understanding of the factors influencing crystal growth is therefore essential for biochemical and biomedical research, and can contribute to **find alternatives to the expensive microgravity techniques of producing well grown protein crystals [9]**.

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