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An umbrella-like approach for design of crystals with specified properties

Caliane Bastos Borba Costa[a], Rubens Maciel Filho[b]

[a]*UNICAMP,Chemical Engineering School - Cidade Universitária Zeferino Vaz, CP 6066, CEP 13081-970, Campinas – SP, BRAZIL, caliane@lopca.feq.unicamp.br*
[b]*UNICAMP, Chemical Engineering School –Cidade Universitária Zeferino Vaz, CP 6066, CEP 13081-970, Campinas – SP, BRAZIL, maciel@feq.unicamp.br*

Abstract

In the product design area, the major concern is how to obtain the desired product requirements in a physically possible and economical process way. A reverse engineering based approach is proposed here for the generation of possible process alternatives applied to crystallization area, in order to obtain desired crystal features. The called umbrella-like approach integrates thermodynamics and crystallization kinetic data to compose a tool able of generating and analyzing suitable operating strategies to obtain tailor made crystal products. New process alternatives can be generated and improved alternatives of existing ones can be analyzed, providing insights to product and process design tasks. The direct approach can be then utilized in order to completely design the process.

Keywords

Crystallization, reverse engineering, process design, thermodynamics and kinetic data, product design.

1. Introduction

Crystallization is the preferred unit operation for fine chemical, photographic materials and active pharmaceutical ingredients. The crystal size distribution

(CSD) of the produced material is the major characterization factor of crystals application, but, besides that, the morphology is also important.
The present contribution focuses on crystal process design through a reverse engineering based approach, in an analogy with an umbrella: given a desired crystal property, a CAD tool is developed to generate and evaluate process alternatives able of producing crystals with the target property. The main steps in this approach include the definition of target properties, the generation, synthesis and analysis of process alternatives, ranking of possibilities and selection of the most promising alternative through a process perspective.

2. The crystallization process

Crystallization is an unit operation normally used for the purification of solid products and for the separation of substances. This unit operation represents a fundamental role in the solid extraction in chemical industries, mainly because of the product purity achieved with it.
Once one is involved in a crystallization design, the many possible alternatives the process can be conducted drives to too many routes. The way the crystallization can be conducted is determined by the solvent and solute interactions, which are decisive in the thermodynamic properties of the solution. Both phenomena that dominate crystallization processes, i.e. nucleation and growth of existing crystals, have supersaturation as driving force, which is a measurement of how far the solution is from the equilibrium state (saturation).The most common manner to generate supersaturation is by the cooling of the solution, which is used when the solubility strongly decreases with temperature. Fig. 1 depicts a general solubility curve and the operation curves for two cooling crystallization processes. Evaporative crystallization is the second most used manner and it is indicated when the solubility is a weak function of temperature. Besides those, adiabatic crystallization (system pressure decrease, vaporizing solvent and decreasing solution temperature), salting out (addition of another solvent to the system, decreasing the solute solubility) and precipitation (production of a solute, through a chemical reaction, that is insoluble in the solution) are also of significant relevance.

3. The reverse and direct approaches

In a direct approach, a crystallization process design is solved as depicted in Fig. 2. In order to achieve a desired product and process specification, one must first have some definitions of parameters and system variables, like which are the solute, the solvent, the initial process conditions and type of crystallization to be conducted. Then, through a deterministic or heuristic model, the operational conditions and / or operational path are sought, which is normally made using the optimization theory, for which deterministic or stochastic algorithms can be used (outer dotted box in Fig. 2), making automatic the generation of different conditions / path during the search.

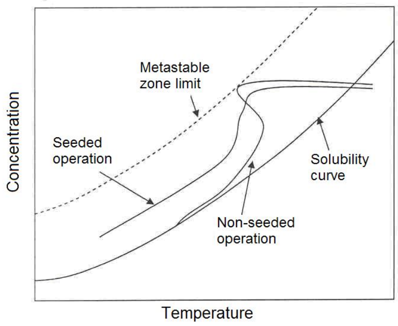

Figure 3: General solubility curve and two operation lines

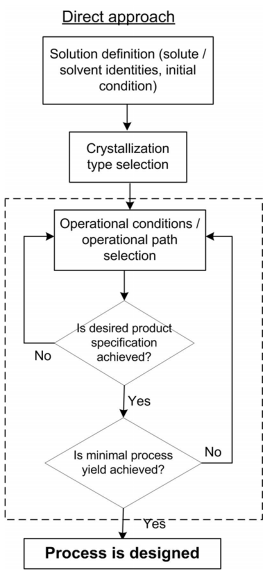

Figure 2: Direct approach in a crystallization process

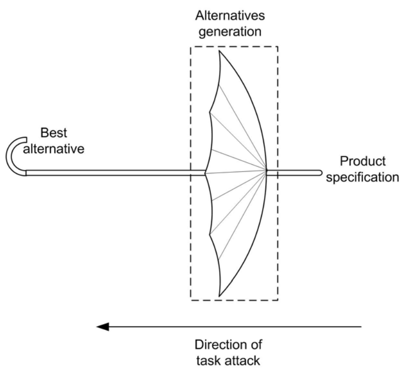

Fig. 3: Umbrella-like approach

The umbrella-like approach (Fig. 3) establishes a reverse engineering based approach, which provides a systematic way of analyzing how to attack the combined process and product design: given a desired product property (specification), the approach looks for alternatives for producing the desired property.

In Fig. 3, the product specification is well-defined, being associated with the end of the umbrella. The more the product is specified, the smaller the canopy of the umbrella, i.e. less number of possible alternatives for producing a product with the required specification(s). For example, if one just specifies that looks for crystals of substance A with medium size x, many solvents, ways of generating supersaturation and path ways during the process are enumerated as possible alternatives, as long as the medium size x of substance A can be achieved. However, if, besides specifying the solute and the required medium size, the solvent and the minimal productivity are also set, the number of possible alternatives decreases, making the convex part (the canopy) of the umbrella smaller.

Among all alternatives generated through the umbrella-like approach, it is possible to detect, through a process perspective, the most promising way (Fig. 4). This is based on the reverse engineering, starting with the target to be achieved and generating process routes to achieve the target [1, 2].

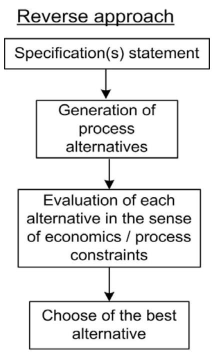

Figure 4: Reverse engineering approach in process design

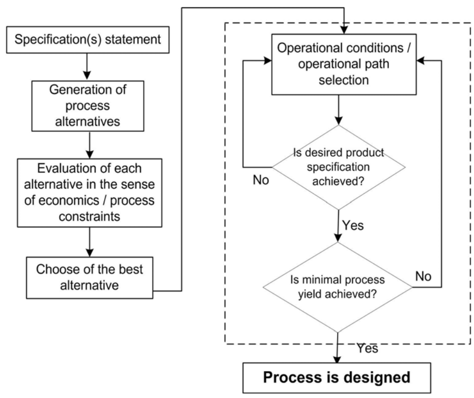

Figure 5: Concurrent crystallization design

This alternative is selected to be further detailed, using the direct approach from the optimization task on, in a concurrent engineering analysis for the combined crystallization process and product design (Fig. 5). The concurrent engineering is a conceptual way to apply the engineering philosophy in order to work interactively to conceive, approve, develop and implement product programs to meet the specified targets [3].

4. Umbrella-like approach – Problem definition and main steps

The process design must integrate thermodynamics data and crystal nucleation as well as growth kinetics in order to drive a reverse analysis of the system to reach the desired property (see Fig. 1). Information on solvents (solvation power and solubility curve), seeding effects and metastable zone limit, as well as on its width, are valuable because the dynamic equilibrium of formation and disintegration of solute quasi-liquid aggregates takes place in this region.

The proposed approach may use any number of property models (even experimental data), as long as the desired targets are matched. This significantly increases the search space for possible process alternatives for crystal production.

The steps to be followed in this approach for any crystallization process are as follows:

1. Definition of target(s) to be achieved (normally to fulfil customer demand): the more refined the specification, less is the freedom degree of further steps, because the search space is more restricted. A point of concern here is how to characterize this specification in measurable properties;
2. Evaluation of possible solutes and solvents that could meet the target(s): a pair solvent-solute has its associated thermodynamic parameters;
3. Evaluation of possible types of operation (batch, semi-batch or continuous);
4. Evaluation of possible ways to generate supersaturation (cooling, evaporative, adiabatic, salting out or reactive crystallization);
5. Evaluation of possible inlet and outlet conditions (like temperature, concentration, pressure, initial particle distribution and so on);
6. Generation, synthesis and analysis of process alternatives, combining items 2, 3, 4 and 5 and additional path actions, like fines dissolution or addition of seeding with different ages;
7. Ranking of possibilities;
8. Selection of the most promising alternative through a process perspective.

5. Theoretical example of the proposed methodology application

For the sake of brevity, due to pages limitation, a theoretical example of the umbrella-like approach is here presented. The steps defined for the approach are followed:

1. Target: crystals of substance A from the solution of A in B (available plant solution) for a pharmaceutical application which requires very small crystals (maximum size is defined).

2. The target does not allow any freedom degree at this step. Solute A and solvent B are already selected.

3. Although not strictly prohibited, continuous operation is not recommended for pharmaceutical applications, due to the purity required, the small order of production and the frequently changing recipes. So, batch and semi-batch operation are selected

4. A solution is already supposed to be available, so as reactive crystallization is discarded. The other ways of generating supersaturation are considered, as long the initial solution temperature are not so high to damage the pharmaceutical properties of A, in case it is temperature sensitive; and the second solvent to be added, in salting out alternative, is not contaminant to the pharmaceutical component.

5. The inlet and outlet conditions are dependent on the thermodynamic data of the solution of A in B and on the available plant solution conditions. Every possible condition should be enumerated.

6., 7. and 8. A process model should be available, either a deterministic or heuristic one, so that the synthesis evaluation of the possible alternatives can be made. Every alternative that leads to production of crystals in the size required is considered as possible. The best of them (in a process perspective and even economical sense) is selected.

6. Conclusions

The umbrella-like approach applies the conceptual treatment of the concurrent engineering for the design of crystals with specified properties. Since there are a lot of ways through which crystallization can be conducted, the proposed approach establishes steps to be followed in order to enumerate, analyze and select possible alternatives to obtain crystals, whose targets properties are the starting point of the methodology. Attacking the problem first as a reverse problem and then, with the most promising alternative, performing a direct process design compose the concurrent approach. Thus, new process alternatives can be generated and improved alternatives of existing ones can be analyzed, providing insights to product and process design tasks.

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