1 Crystallization as a Separation and Particle Generation Process

Crystallization is a common process in nature and every day's life. Since millions of years it has played a vital role in the formation of stalactites within caves and precious stones such as diamonds and sapphires. The knowledge of crystallization of salt from seawater can be dated back as far as 2700 BC found on a Chinese print and on an Egyptian "Papyrus Ebers" at around 1500 BC. In 800-700 BC Homer described frozen water by using the Greek term "crymos/crymyos" [Hur93]. Besides the wonderful different snowflakes, nature controls the formation of ice in a very efficient manner using additives. Fish that inhabit the polar seas are using anti-freeze proteins [Kni91], whereas other proteins can induce the formation of ice already at 5 °C [Pat97].

Performance criteria of consumer products are strongly dependent on the understanding of crystallization phenomena. The mouth feel of chocolate is mainly determined by the crystal form of the cocoa butter [Cos06]. In the making of ice cream, crystals should have a size smaller than 100 µm to control the texture [Cos06]. Furthermore, crystallization can determine the free flowing and non-caking behaviour of table salt and the brightness of colours (pigments) [Aue05].

Crystallization, however, is not always desired. It can become a sincere problem such as in the occurrence of kidney and ureteric stones [Gro06]. Lime depositing inside kettles or sediments forming in wine are further examples. Polymorphism can cause problems in intellectual property rights as the cases Ritonavir and Zantac® showed [Sed99, Dat04]. The law case of the latter had an estimated value of US$ 1,500,000,000 [Sed99]. This situation is further complicated by the report of "disappearing" polymorphs leading to an apparent loss of control [Dun95]. The manufacturing of crystals and layers can be characterised as a "multi-billion-dollar industry" [Sch00]. Charpentier [Cha07] noted that crystalline, amorphous or polymeric substances represent 60% of all products sold by the chemical industry.

However, in comparison with fluid phase processes, particulate processes are still not as developed as documented by the "Rand and Merrow Reports" [Mer00a], summarising significant differences in scale-up and start-up performances. Possible reasons might be the complex physics of particulate processes that are much harder to model and/or the non-availability of appropriate measuring instruments. This is mirrored by the "use maturity versus technological maturity" diagram shown in figure 1-1 that was proposed by Keller [Kel87] and still declared valid in 2005 [Gór05]. It compares the crystallization process to other separation methods.
Figure 1-1: Position of crystallization within the "use maturity versus technological maturity" diagram [Kel87] (taken from Seader et al. [Sea06])

From a historical point of view, the process of crystallization was in 1984 still described as an "art" [Gar84]. Concerted effort has since been made to represent crystallization within the general framework of chemical (reaction) engineering [Gar84, Kle91, Lor04, Sch05]. Although crystallization has gained increasing importance during the last decades, surprisingly little has changed in the actual design of crystallizers [Hof05, Hei06]. According to Hofmann [Hof05], 92% of the current build crystallizers are of "Forced-Circulation" type. It seems to be that industry does not ask for a more well defined larger particle size distribution that can be produced by a "Draft-Tube-Baffle" (7%) or "Oslo" (1%) crystallizer. For the production of particles in the sub-micron range, the use of micro-reactors, T- or Y-Mixers, Impinging Jet, Taylor-Couette or Oscillatory Flow Reactor as well as working with supercritical solutions might be appropriate [Hei06]. However, the developments of most of these reactors are still only at the research or pilot-plant level and do not always offer an improvement over conventional techniques. Therefore, industry is still mainly using the "old" equipment, often just simple stirred tank reactors [Hei06]. Downstream processes such as filtration and drying, size enlargement (tabletting), size reduction (grinding) up to packaging of the product can significantly alter the carefully controlled product properties produced in the crystallizer [Jon02].

During the last years a refocusing of the industry, from "commodities" to fine, specialty, pharmaceutical, food and biotechnology industries took place. Crystallization is thereby often the key step in the production of high-value added products with specific properties and functionalities. Févotte [Fév07] and Nagy [Nag07] estimated that crystallization is involved in 80 to 90% of the production processes of high-performance chemicals. All of these products must meet defined physical (size, morphology, surface properties, polymorph) and chemical (purity, composition) properties. From a conceptual point of view, independent of the
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respective industry, the desired product quality of the final crystals is influenced by the technical equipment, the kinetics and the underlying thermodynamics (chemistry). Figure 1-2 illustrates the product design that can be seen as a forward and an inverse problem (see also Wibowo et al. [Wib05]).

![Product Design Diagram](image)

**Figure 1-2: Product design as a forward and inverse problem**

The work will restrict itself to the kinetics. Kinetics are describing the time behaviour of a particle generation process. The rate constants are the key to answer the following questions:

- How long must the residence time be to get 10 nm or 1000 µm crystals?
- How must the process be operated to get a narrow or broad size distribution of a median size of 200 µm?
- Is the desired size distribution feasible at all (reverse engineering)?

Without the knowledge of the kinetics designing any crystallizer becomes speculative and difficulties arise when estimating capital and operating costs. In other word, although the process might, in principle, be possible from a thermodynamic point of view (solid-liquid equilibrium phase diagram) the kinetics can still make the process infeasible. Because of the competitive market situation, a faster development and implementation of new and more reliable crystallization processes becomes increasingly critical. The kinetic rate constants must often be determined under minimising time and resource expenditure, reducing the amount of starting material by simultaneously increasing the statistical confidence of the derived constants.

Within this work, special emphasis is placed on crystallization from solution. Important trends in this field have been reviewed on a regular basis [Gar85, Ulr94, Ulr03a, Kra03a, Ulr04]. The main points can be summarised as:

- Still, although much progress has been made, the development of sensors that measure supersaturation and particle size distributions (in-line or in-situ, fast)
- Working on and combining of all length and time scales
- Finding and predicting polymorphs
- Crystallization of substances originating from bioprocesses, for example proteins
- Modelling of multiphase flow, particle-particle interactions
The work will focus on the first bullet point and its application towards the determination of crystallization kinetics although the second bullet point will be partly touched on. Many advances have been made in the field of in-situ measurement techniques that allow the actual recording of product properties in "real time". In particular, the pharmaceutical industry is forced by the Food and Drug Administration to implement "Process Analytical Technologies (PAT)", whereas other "commodity" industries are already advanced in applying it [Dün07]. This strategy has led to a shift from quality-by-testing towards quality-by-design. However, the use of these in-situ measurement techniques often pose new challenges in evaluating the large amount of recorded data, especially if quantitative information must be obtained.