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Development of Crystallization Processes for Pharmaceutical Applications

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ABSTRACT

Health care is a critical issue in our society. Development of new drugs is a complex and challenging work that requires the participation of researchers in both industry and academia. The preferred route of administration of most drugs is in oral dosage forms with the active ingredient as a crystalline solid. The production of crystalline active pharmaceutical ingredients (API) by crystallization is therefore crucial in drug development. Understanding of the key process parameters and its effect on the characteristics of the end product is an essential part of the process development. A number of technologies are currently available to support the research work of crystallization process development at laboratory scale.

This article will review technologies that may be used in the development of crystallization processes for pharmaceutical applications. A methodology for planning, design and running robust crystallization experiments at a laboratory scale is introduced. This methodology allows control of the key crystal properties, which determine some of the relevant characteristics of the new drug, such as pharmacokinetics and bioavailability. The article emphasizes the importance of research work at the lab to support the development of new pharmaceutical products.

Keywords: Process development, Crystallization, Pharmaceutical products.

1. INTRODUCTION

Pressure to shorten the time to market in the pharmaceutical industry is demanding innovative ways to accelerate the process to develop new drugs. Developing a pharmaceutical product usually involves a number of stages including drug discovery, design of dosage form and development of the process to produce the drug. Typically, process is developed at various scale levels: lab-scale, pilot plant scale, and manufacturing scale. Pharmaceutical manufacturing includes different unit operations such as reaction systems, crystallization, filtration, drying and milling. Crystallization is a critical operation, which need to be well understood in order to obtain the desired specifications of the final drug. This paper is focused on the development of crystallization processes at a laboratory scale.

The end goal is to outline a methodology which intend to be a systematic guide for the planning, designing and executing lab-scale experiments to develop crystallization processes.

2. TECHNOLOGIES FOR CRYSTALLIZATION PROCESS DEVELOPMENT AT LAB SCALE

There are a number of analytical technologies to measure critical process parameters and product attributes of crystals. The use of those technologies may contribute to accelerate development of crystallization processes in the pharmaceutical industry, and helps to generate valuable information to support decisions during the development of new drugs. In this section, some of the most utilized technologies are reviewed and particular applications in crystallization studies are discussed. For this review, analytical technologies are grouped as Spectral, Diffraction, Reflective and Thermal methods.

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SPECTRAL METHODS: INFRARED SPECTROSCOPY

Infrared (IR) Spectroscopy is the absorption measurement of different IR frequencies by a sample placed in the path of an IR beam. At temperatures above absolute zero, all the atoms in molecules are in continuous vibration with respect to each other. When the frequency of a specific vibration is equal to the frequency of the IR radiation directed on the molecule, the molecule absorbs the radiation.

IR Spectroscopy is used for quantitative determination of compounds in mixtures. It is a nondestructive method. The basis for quantitative analysis of absorption spectrometry is the Bouguer–Beer–Lambert law, commonly called Beer's law. This law basically states that the intensities of absorption bands are linearly proportional to the concentration of each component in a homogeneous mixture or solution.

Two of the principal techniques based on IR Spectroscopy that are utilized in crystallization studies are Fourier Transform Infrared Spectroscopy and Raman Spectroscopy. A Fourier Transform Infrared system (FTIR) consists of three components: radiation source, interferometer, and detector. The interferometer produces interference signals, which contain infrared spectral information generated after passing through a sample. A mathematical operation known as Fourier transformation converts the interferogram to the final IR spectrum, which is generally a spectrum with frequency (wavenumber) as the x-axis and absorption intensity as the y-axis.

When light is scattered from a molecule a fraction of the photons are inelastically scattered, producing a characteristic spectrum. This phenomenon is known as Raman Scattering. Raman Spectra is useful for identification of compounds by matching spectrum of unknown compound with reference spectrum (fingerprint).

Major applications of IR Spectroscopy includes liquid phase concentration measurement, polymorph profile monitoring and turbidity measurements. ATR-FTIR Spectroscopy has been used to monitor the liquid phase concentration profile of L-glutamic acid in water and used this information to estimate the nucleation and growth rate kinetic parameters (Schöll et al., 2006). Also, it has been used for in-situ concentration measurement during antisolvent crystallization of paracetamol from acetone-water. An automated method for calibration of IR spectra to concentration has been developed (Zhou et al., 2006)

In-situ ATR-FTIR Spectroscopy has been used to measure the transient supersaturation profile or α-glycine in aqueous solution and compared the results with gravimetric method to confirm the validity of the measurements (Doki et al., 2004). Solubility curve of paracetamol in water has been obtained using ATR-FTIR Spectroscopy (Fujiwara et al., 2002). Besides, they used the FTIR to measure on line the solution concentration of paracetamol and used this information to operate a concentration-controlled batch crystallization.

Raman Spectroscopy has been used to monitor the profile of α and β polymorphs of L-glutamic acid in water during solvent mediated polymorphic transformation. Measurement of composition was based on the relative area of the characteristic peaks of both polymorphs (Schöll et al., 2006).

Concentration of an Active Pharmaceutical Ingredient (API) has been measured during batch crystallization by using FTIR Spectroscopy and controlled the antisolvent addition based on the measured concentration (Nonoyama et al., 2006).

IR based turbidity probes has been used to measure solubility of glycine and mannitol in water, paracetamol in 2-propanol, and adipic acid in ethanol (Yi et al., 2005). They showed that results were in good agreement with data reported in the literature.

DIFFRACTION METHODS: X-RAY POWDER DIFFRACTION AND SINGLE CRYSTAL DIFFRACTION.

The diffraction pattern generated when X-rays pass through the 3-D arrangement of atoms in a crystalline structure is used to identify and characterize unknown crystalline material. Mixtures of crystalline materials can also be analyzed and relative peak heights of multiple materials may be used to obtain estimates of relative

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composition. All the X-ray diffraction techniques are based on the Bragg's law, which describe that diffraction of a monochromatic X-ray is incident on the surface of lattice points with separation d at angle θ, according to the following relationship: nλ=2d sinθ , where λ is the wavelength of the X-ray and n is an integer.

In Single Crystal Diffraction, a crystal sample is placed in the X-ray beam, and the three dimensional structure of the molecule is determined. In Powder X-ray diffraction, samples of many crystals with random orientations are analyzed and the scattered intensity is measured as a function of the outgoing angle.

Quantification of the solution mediated polymorphic transformation rate of anhydrous L-phenylalanine in aqueous solution has been done using powder X-ray diffraction technique (Mohan et al., 2001). This analytical method was used to assess the effect of additives in the transformation behavior of the anhydrate form into monohydrate.

Single crystal X-ray diffraction technique has been used to determine the structure of three polymorphs of an API and to quantify the effect of impurities in the polymorphic transformation rate. Results are compared with good agreement with data obtained from concurrently molecular modeling studies (Mukuta et al., 2005).

FOCUSED BEAM REFLECTANCE MEASUREMENT (FBRM) METHODS.

The Focused Beam Reflectance Measurement (FBRM) provides an on-line, in-situ information of crystal size and crystal count number by measuring the chord length of the particles.

The converged laser beam is projected through the sapphire window of the probe into particle suspension, and it is scanned at a high speed. Because of the high scanning speed, the movement of particles does not have any effect on the measurement. As particles pass by the window surface, the beam will intersect the edge of a particle and the particle then will begin to backscatter laser light. The backscatter continues until the beam has reached the opposite edge of the particle.

Thus, the chord length of the particle, a straight line between any two points on the edge of a particle, is measured from the time period of backscatter, and accordingly the number of backscatter (corresponding to the particle count number) per unit time is collected for particles coming on the window surface. The chord length of the particle is transferred into a chord length distribution histogram. Thus, the CLD provides online particle count and particle dimension information.

On-line information of crystal in the form of a chord length distribution (CLD) has been obtained using focused beam reflectance measurement (FBRM) (Worlitschek and Mazzotti, 2004). A method using a three-dimensional geometrical CLD model and an inverse technique based on projections onto convex sets (POCS) was introduced to calculate PSDs from CLD raw data. These concepts were applied to the batch cooling crystallization of paracetamol in ethanol.

In situ chord length distributions of crystals obtained from laser backscattering has been used to obtain characteristics of the crystal size, as well as to determine the metastable limit, and used this information to operate a concentration-controlled batch crystallization in a paracetamol-water system (Fujiwara et al., 2002).

Information obtained in-situ from FBRM particle counter has also been used to determine the temperature profile required to generate the metastable α polymorph of glycine (Doki et al., 2004).

Studies of the crystallization of L-glutamic acid in water have been conducted using FBRM to measure the CLD profile and obtain valuable information about nucleation events and evolution of the particle size (Schöll et al., 2006).

Examples of process developments have been reported to obtain well-defined, large crystals of an API with a narrow particle size distribution, by controlling the acid addition method (Kim et al., 2005). FBRM technology was used for insitu monitoring of the particle size distribution.

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TERMAL METHODS: DIFFERENTIAL SCANNING CALORIMETRY (DSC).

Differential scanning calorimetry (DSC) is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. Both the sample and reference are maintained at the same temperature throughout the experiment. Generally, the temperature program for a DSC analysis is designed such that the sample holder temperature increases linearly as a function of time. The reference sample should have a well-defined heat capacity over the range of temperatures to be scanned. The basic principle underlying this technique is that, when the sample undergoes a physical transformation such as phase transitions, a difference between the heat flow to the sample and the heat flow to the reference is measured. This difference could be positive or negative, depending whether the process is exothermic or endothermic. For instance, as a solid sample melts to a liquid it will require more heat flowing to the sample to increase its temperature at the same rate as the reference. This is due to the absorption of heat by the sample as it undergoes the endothermic phase transition from solid to liquid. Likewise, as the sample undergoes exothermic processes, such as crystallization, less heat is required to raise the sample temperature. By observing the difference in heat flow between the sample and reference, differential scanning calorimeters are able to measure the amount of heat absorbed or released during such transitions.

The result of a DSC experiment is a heating or cooling curve. This curve can be used to calculate enthalpies of transitions. This is done by integrating the peak corresponding to a given transition.

A methodology has been reported to measure the solubility in microsamples employing a differential scanning calorimeter (DSC) for several aqueous and nonaqueous systems: (RS)-mandelic acid, (S)-mandelic acid, adipic acid, diphenhydramine HCl, α-glycine, and terephthalic acid in water, (RS)-mandelic acid and β-succinic acid in ethanol and methanol, and adipic acid in ethanol. Results showed that the solubility data of most compounds studied using this technique are within 5% of solubility data obtained from the literature (Mohan et al., 2002).

Mohan and Myerson developed a method to obtain growth kinetics from desupersaturation curve of adipic acid in ethanol in seeded isothermal growth experiments performed in a differential scanning calorimeter (DSC). This technique was found to be very useful when small amounts of sample are available or data are needed at high temperatures and pressures (Mohan et al., 2000).

Another example of solubility determination has been reported (Park et al., 2003). The solubility of both stable and metastable polymorphs of carbamazepine (forms I and III), glycine (α and γ forms), and mefenamic acid (forms I and II) was measured using differential scanning calorimeter (DSC). The three systems under investigation were found to be enantiotropic. Solubility was determined using heat flow derivative curves, where solubility is given by the peak of a heat flow curve.

3. METHODOLOGY FOR PROCESS DEVELOPMENT

A systematic methodology is proposed for gathering and evaluating the information required to develop a robust crystallization process. The methodology is organized in seven steps, covering the planning, screening, optimizing and verifying stages of lab-scale experiments for crystallization process development. An overview of the methodology is shown in Figure 1.
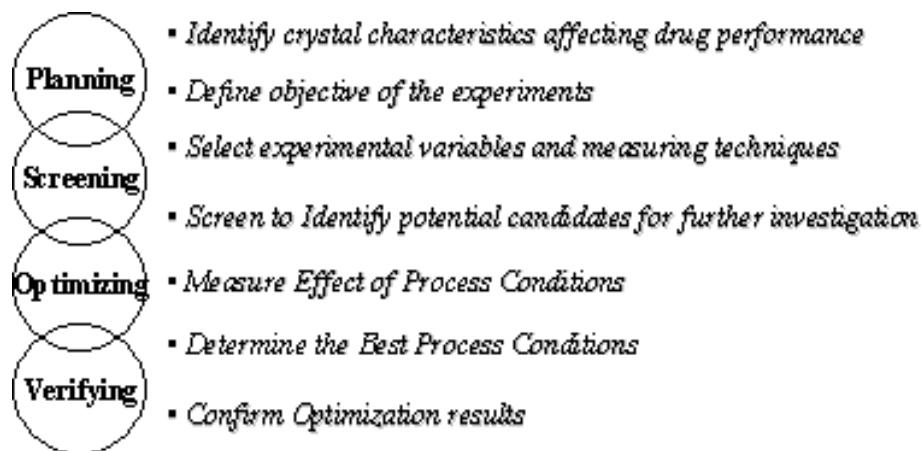
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Figure 1: Methodology for Crystallization Process Development

PLANNING STAGE

Planning involves clearly defining the objectives of the experiments and the environment in which the experiments will be carried out. In the early stage of planning, effort is concentrated on identifying the physical properties of the crystals that have a relevant impact on the properties and performance of the final drug. Crystal size, morphology, polymorphism and crystal size distribution are some of the crystal properties associated with the final performance of the pharmaceutical product. For instance, in some cases small crystals are desirable because or their rapid dissolution and consequent bioavailability. Also, narrow particle size distributions are usually preferred to avoid manufacturing problems in downstream operations like filtration and drying. The purity of the crystals may also affect the stability of the drug.

Objective of the experiments shall be defined in terms of the critical characteristics of the crystals associated with the drug performance. Examples of objective statements may be:

a) Develop a process to crystallize Compound X with a crystal average size of 10 μm

b) Develop a process to consistently crystallize the α-Polymorph of Compound X

c) Develop a process to crystallize Compound X with 98% of the particles in the range of 20 to 90 μm

SCREENING STAGE

Screening involves the execution of initial small scale tests to identify potential candidates for further investigation. High Throughput methods are sometimes employed for initial screening. High Throughput screens allow to effectively conduct a large number of simultaneous experiments at small scale in a workstation. Some of the typical screening tests carried out in development of crystallization process includes solvent screening and polymorph screening.

In the solvent screening, the most promising candidates are then evaluated by carrying out additional experiments, for instance, construction of solubility and metastable zone width curves, as well as experiments to obtain information on the kinetic parameters of nucleation and growth rate parameters. Figure 2 presents a schematic solubility curve to compare the behavior of different solvents, as well as a Growth rate curve utilized for

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estimation of kinetic parameters. Information from the Solubility Screens is useful to select candidate solvents for cooling crystallization processes, or candidates for antisolvent crystallization alternatives
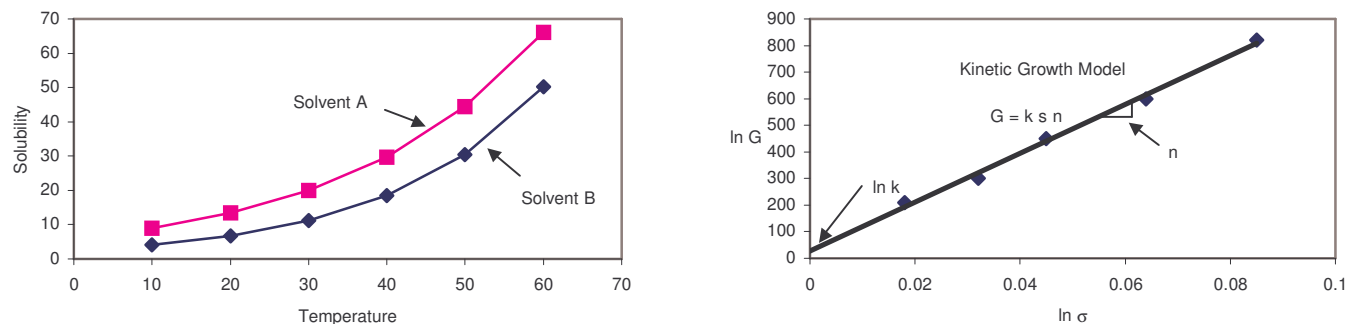
Figure 2: Schematic of two basic crystallization experiments: Measure of Solubility curve for various solvents and estimation of kinetic parameters from linearized curve of Growth Rate

OPTIMIZATION STAGE

Optimization involves determining the best operating conditions that enable meeting the experimental objectives. Examples of optimization experiments include

a) Characterization of the effect of seed size distribution on the solvent mediated polymorphic transformation

b) Characterization of the effect of cooling profile to obtain an optimal cooling rate

c) Characterization of the effect of antisolvent profile to optimize the addition rate.

The discovery and characterization of polymorphs are important in the pharmaceutical field. The sudden appearance of a more stable polymorph that was not discovered at early stage of development can cause loss of time and resources. Solution based polymorphic transformation studies are conducted to characterize the rate of transformation from metastable to stable forms. In Figure 3, a schematic result of experiments to evaluate the effect of seed size on Polymorphic Transformation rate is presented. Seed with different Particle size distribution are characterized and their influence in the transformation rate is quantified. Results are utilized to define the seeding protocol of the process.
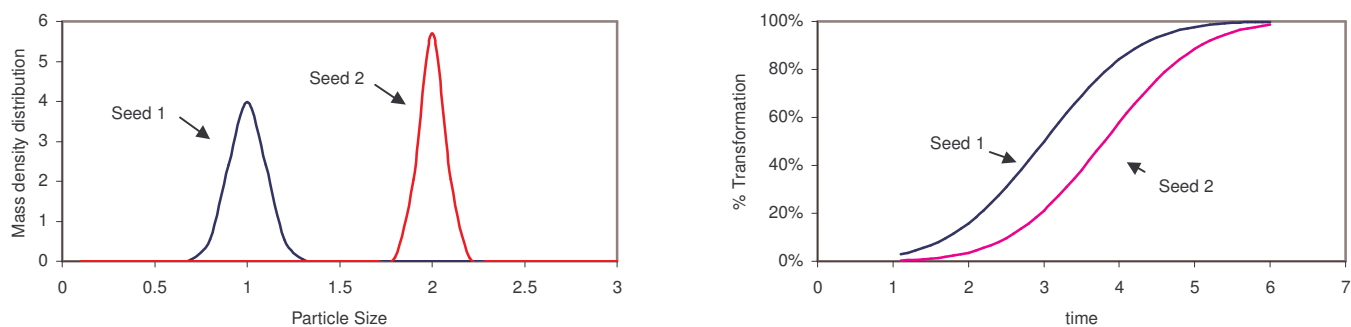
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Figure 3: Schematic Curves of the Effect of Seed Size on the Rate of Polymorphic Transformation

Figure 4 shows a typical result of experiments to assess the effect of cooling rate on the Crystal Size Distribution (CSD). In the optimized cooling profile, the temperature is decreased slowly at the beginning of the process, and faster at the end. This profile leads to a controlled supersaturation profile that avoid excessive nucleation, leading to a shift of the population toward larger particle sizes.
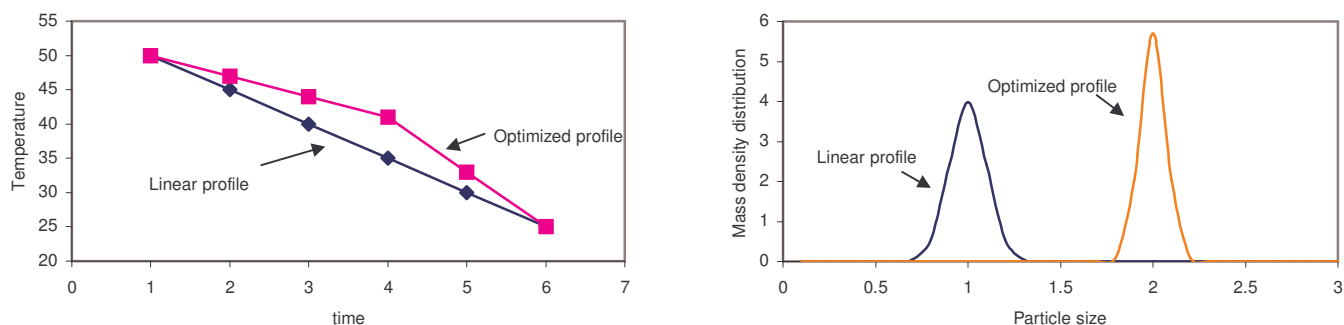

Figure 4: Schematic Curves of the Effect of Cooling Profile on the Particle Size Distribution

Figure 5 shows a typical result of experiments to assess the effect of antisolvent addition rate on the Crystal Size Distribution (CSD). In the optimized antisolvent profile, the crystal size distribution is controlled by maintaining the supersaturation at a constant level. At the beginning of the process, the solubility curve is steep and the antisolvent is added very slowly to avoid an excessive increase in supersaturation. In a later stage, the solubility curve is flatter and thus, antisolvent can be added more rapidly. Using the optimized profile, narrower size distributions of the crystals can be obtained.
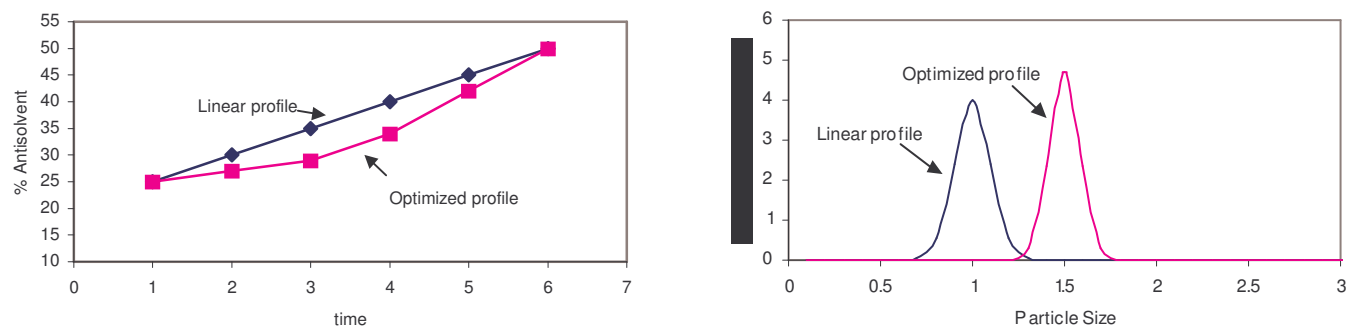
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Figure 5: Schematic Curves of the Effect of Antisolvent Addition on the Particle Size Distribution

VERIFICATION STAGE

Once the effect of individual process variables of process conditions has been evaluated, additional experiments shall be conducted to confirm that the "best process conditions" produce the desired result in the crystal properties. At this stage, accomplishment of the initial objectives of the experiments is evaluated and further scale-up experiments can be foreseen. Process is documented with all the relevant information obtained at the lab-scale to support further steps of development.

4. CONCLUSION

This paper reviewed some of the state of the art analytical technologies currently available to support the development of crystallization processes. A methodology for developing robust crystallization processes was outlined. This methodology is intended for planning, designing and conducting crystallization experiments in a systematic and organized way. The methodology is structured in seven steps, covering the planning, screening, optimizing and verifying stages of lab-scale experiments for crystallization process development. Application of the methodology leads to gather key information for a better understanding of the key process parameters and its effect on the characteristics of the end product, which help to shorten the time required to new process development in the pharmaceutical field.

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