API Crystallisation

WHITE PAPER

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The ability to deliver a drug to a patient in a safe, efficacious and cost-effective manner most commonly depends on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state. In this context, crystallisation is of critical importance in pharmaceutical industry as it defines physical and powder properties of crystalline APIs. Detailed knowledge of the various aspects of crystallisation process, and in particular, an understanding of the relationships between crystallisation, solid-state form and properties is required to deliver the desired therapeutic effect and to avoid undesirable effects.

Crystallisation

The vast majority of small molecule (<500 Dalton) APIs are formulated as solid dosage forms due to their convenience and excellent patient compliance, with most marketed products containing APIs and/or excipients in the crystalline state. Bioavailability of the dosage form is strongly dependent on physical properties of the actual API to be formulated (crystalline form, morphology, particle size distribution). In addition, the processability (filtration, drying, milling, granulation, tableting) is determined by the physical properties of the material.

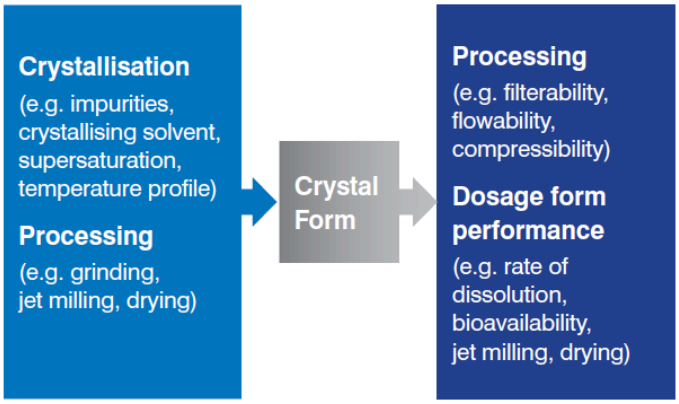

Fig 1: Representation of the relationship between operating conditions & dosage form performance.

Crystallisation from solution is the mainstay in the production of APIs and is used as a separation and purification procedure. Even minor changes in crystallisation conditions can significantly alter the crystal and powder properties, including particle size, shape & surface characteristics. These effects have been recognized as the major batch-to-batch and source variation problems leading to inconsistency of the final tablet properties[1]. In addition, the particle size distribution will tend towards becoming monosized when the solid remains in contact with its own saturated solution as larger crystals tend to undergo Ostwald ripening at the expense of smaller ones[2]. Allowing Ostwald ripening on an industrial scale is time-consuming.

Industrially produced crystals are typically polycrystals composed of a great number of small crystals whose lattices show numerous imperfections. The nature and frequency of the crystal defects may change as a function of mechanical (e.g. grinding or milling) or thermal stress applied to the material. Milling, for example, can result in the formation of a large number of vacancies and dislocations[3]. These defects are an important source lot-to-lot variations giving rise to processing problems and poor and inconsistent product performance.

Poor primary crystallisation techniques lead, inter alia, to agglomeration and solvent inclusion in the final crystalline API. They can also trigger the conversion of one polymorph into another in storage. Any or all of these changes can drastically alter the purity of a batch, and, *in extremis*, results in a total write-off of expensive product.

In addition, downstream milling remains an undesirable unit operation due to its poor energy efficiency where only 0.1–2% of energy supplied to a mill affects particle size distribution reduction and the remainder emanates as heat[4]. This alters the surface energy of crystalline APIs which, in turn, can induce amorphisation or polymorphic change and affect API pharmacokinetics[5].

Therapeutic implications

Two areas of drug delivery, inhaled medicines and long-acting injectables (LAIs), are particularly impacted by particle size.

1. For inhaled medications, particle size impacts the region of the lung which aerosols target as well as the mechanism of action in the respiratory system. Delivery patterns vary with differing dimensions in the respiratory system with the result that the majority of particles do not reach the intended respiratory region. As a result, there is a need for monodispersed particles to be able to more efficiently target specific respiratory regions. Furthermore, a

[1] Shekunov et al 2000, "Crystallisation processes in pharmaceutical technology and drug delivery design", *J Cryst Growth 211:122–136.*
[2] Ostwald 1897, "Studien über die Bildung und Umwandlung fester Körper", *Zeitschrift für Physicalische Chemie 22:289–330.*
[3] Fabbiani et al 2006, "High-pressure studies of pharmaceutical compounds and energetic materials". *Chem Soc Rev 35:932–942.*
[4] S. Naik et al 2015, "Quantifying dry milling in pharmaceutical processing: a review on experimental and modeling approaches" *J. Pharm. Sci., 2015, 104, 2401–2413.*
[5] M. Descamps et al 2016, "Perspectives on the amorphisation/milling relationship in pharmaceutical materials", *Adv. Drug Delivery Rev., 100, 51–66.*

monodispersed and precise control of particle size in the respiratory range will allow for personalized therapy and effectively treat patients across a diverse demographic range.

2. Particle size for LAIs impacts the dissolution profile where larger particles typically result in longer release profiles which is in direct conflict with the need for smaller particles to facilitate suspension syringeability. For many diseases, there exists a need to improve patient compliance and convenience by providing single dose LAIs.

Manufacturing considerations

Supersaturation is the driving force for crystallisation processes and influences crystal size distribution. This is achieved by reducing the solubility of the product in solution through choosing one of two common approaches.

Batch cooled crystallisation. Supersaturation is generated in this approach by decreasing the temperature in the solution. The rate in which the temperature is decreased will influence the level of supersaturation and can be used as a control variable to achieve the desired solid-state properties. Crystal seeding is frequently employed to initiate a crystal growth process.

As previously discussed, this 'top down' approach subsequently involves mechanical reduction of larger particles by the technologies available including; jet milling, pearl mill, and high-pressure homogenization. These downstream processing, activities result in operational challenges including, electrostatic charge generation, dusting, caking as well as crucially, a polymorphic transformation. In the case of inhalables one result of grinding / milling is an increase in Van der Waals forces thereby making the particles stick together as clumps and adversely affecting their flowability.

Today this traditional mantra of "grow it big and then mill it small" no longer suffices. Property control strategies focus on delivering the final particle size or specific surface area specifications through a controlled, well-defined crystallisation process[6].

Antisolvent crystallisation. In this type of system, the API is crystallized from a primary solvent by the addition of a second solvent (antisolvent) in which the API is relatively insoluble[7]. In antisolvent crystallisation the primary solvent activity also changes significantly, hence this approach can have more profound effect on the crystal morphology or polymorphic form then in the case of the cooling crystallisation. A major advantage of this method includes a lower operating temperature; particularly important for heat sensitive products.

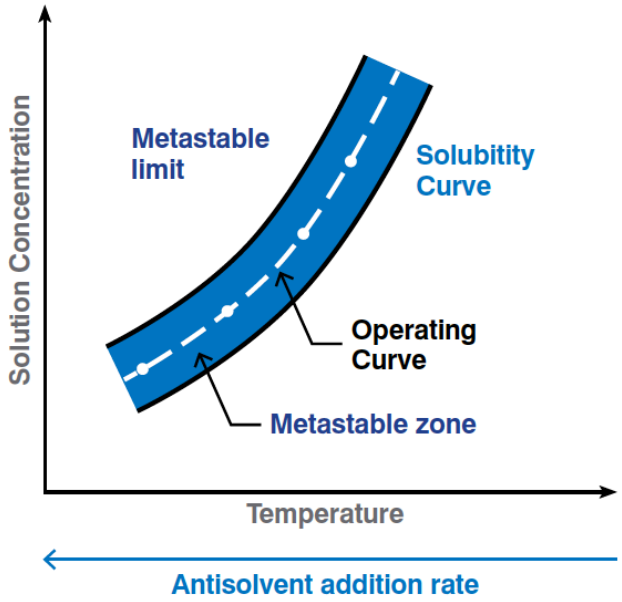

Fig 2: Schematic comparison of cooling vs. anti-solvent crystallisation.

Unfortunately, many industrial antisolvent crystallisation operations are far from optimal. One problem of anti-solvent crystallisation methods is the tendency for organic compounds to oil out or agglomerate as fine particles into amorphous undefined structures. One possible cause of oiling out is that drops of the product solution are surrounded by the anti-solvent, in which the solubility is very low, and this low solubility creates localized regions with very high super saturation ratios. Before mixing to the molecular level is achieved, the localized high super saturation forces the product out of solution without allowing sufficient time for ordering of molecules to enable crystal development. The resulting oily particles have a tendency to clump together before the occluded solvent migrates throughout the solution. As the mixture is aged, the oiled-out particles may transform into amorphous solids or become crystalline. Solids developed in this manner will likely have poor lattice structure.

The Micropore difference

Membrane crystallisation is a relatively new technique based on the use of a porous material as a semi-permeable barrier between two phases. The membrane can be used to create supersaturation by solvent evaporation, antisolvent or reactant addition, and mixing with a colder solvent[8]. The first membrane crystallisation process dates back to 1917[9] but recently, membranes have been used to crystallize proteins and macromolecules. The presence of a membrane adds a supplementary resistance to mass transfer, but it also offers additional control over nucleation kinetics.

[6] Burcham et al 2013, "Industrial Crystallisation of Pharmaceuticals: Capability Requirements to Support an Outsourcing Paradigm", *Pharmaceutical Outsourcing September 2013.*
[7] Ed. Jansens et al 2006, "13th International Workshop on Industrial Crystallisation", *IOS Press: 17*
[8] Chabanon et al 2016. "Membranes & crystallisation processes: State of the art and prospects". *J. Member. Sci., 509, 57–67.*
[9] Kober 1995, "Pervaporation, perstillation & percrystallisation", *J. Member. Sci., 100, 61–64.*

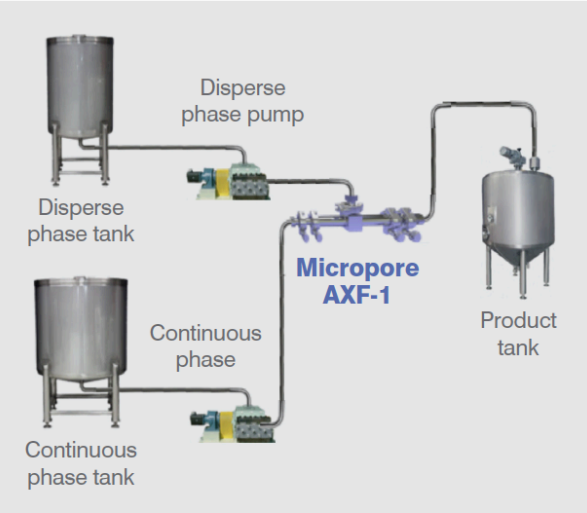

Fig 3: Schematic of Micropore crystallisation plant.

A study using piroxicam[10] compared crystals obtained by conventional antisolvent addition with those from polymorphic transformation. Crystals of monohydrate could not be obtained by cooling crystallisation with in-situ transformation, whereas the membrane technique did. The membrane allowed a narrow crystal size distribution to be obtained without significant agglomeration. This technique also produced crystals in a faster and more efficient way compared to polymorphic transformation. Micropore Technologies' robust continuous membrane technology serves a variety of pharmaceutical applications. As a gentle, precise process it can eliminate many of the issues faced by both batch-cooled and anti-solvent approaches to crystallisation. This offering is scalable to tonnes per hour.

We're ready to help you with your API crystallisation challenges.

[10] Simone et al 2018, "Preventing Crystal Agglomeration of Pharmaceutical Crystals Using Temperature Cycling and a Novel Membrane Crystallisation Procedure for Seed Crystal Generation", *Pharmaceutics 2018, 10, 17*