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Crystallization processes in pharmaceutical technology and drug delivery design

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Abstract

Crystallization is a major technological process for particle formation in pharmaceutical industry and, in addition, plays an important role in defining the stability and drug release properties of the final dosage forms. Industrial and regulatory aspects of crystallization are briefly reviewed with reference to solid-state properties of pharmaceuticals. Crystallization, incorporating wider definition to include precipitation and solid-state transitions, is considered in terms of preparation of materials for direct compression, formation of amorphous, solvated and polymorphic forms, chiral separation of drugs, production of materials for inhalation drug delivery and injections. Finally, recent developments in supercritical fluid particle technology is considered in relationship to the areas discussed.

Keywords: Particle technology; Crystallization and precipitation; Pharmaceuticals; Solid drugs and excipients; Supercritical carbon dioxide

1. Introduction

Solution crystallization is widely used for manufacturing bioactive drug substances and formulation excipients during final and intermediate stages of purification and separation. This process defines drug chemical purity and physical properties: particle habit and size, crystal structure and degree of crystal imperfection. Consequently, crystalline variations are responsible for a wide range of pharmaceutical formulation problems, such as bio-inequivalence, as well as chemical and physical instability of the solid drugs in their final dosage forms. The crystallization process requires considerable time and energy resources and defines such economical issues as the efficiency of solvent recycling, separation of waste (impurities) and consumption of raw materials [1]. Over 90% of all pharmaceutical products, such as tablets, aerosols, capsules, suspensions and suppositories contain drug in particulate, generally crystalline, form [2]. Although the influence of the crystallization process on the properties of dosage forms and products is well documented, particle formation and crystallization have often been regarded as a "low-tech" area of chemical production. Advances of chemical synthesis have achieved control over drug identity and purity, but control over the physical form and crystallinity remains poor.

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Chemically equivalent materials are commonly found to perform or behave unpredictably and impair product development or manufacture. For example, one-fifth of all plant handling particulate material fails to attain more than 20% efficiency [2]. These problems rapidly become recognized on scientific and technical levels and, because pharmaceutics is a part of health care system, have a pronounced commercial and social importance. The purpose of this mini review is to indicate the variety of research directions and industrial crystallization problems associated with engineering of solid-state properties of drug substances, stability of drug products and consistency of crystallization process. Crystal growth mechanisms, with reference to pharmaceutical systems, have been discussed in reviews [3,4].

2. Regulatory aspect

Table 1 summarizes the most important solid-state and drug delivery characteristics affected by crystallization. Pre-formulation and formulation drug development stages are associated with manufacturing control, characterization and optimization of the solids. Pre-formulation concerns "rational, science-based requirements for drug substances and excipients" [5] which include physicochemical stability, consistency and solid state-properties (Table 1). This stage begins immediately after the synthesis and initial toxicity screening of a new drug. Formulation research is more related to the drug products (e.g. final composition of drug and functional excipient substances in the dosage form) and focused on stability and

Table 1
Solid-state properties defined by crystallization process and their relationship with specific characteristics of drug substances and drug products

Solid-state properties	Effect on drug substance and/or drug product
Structural	
Crystallinity (existence of amorphous and semi-crystalline forms)	Physical and chemical stability
Polymorphs	%RH profile (hygroscopicity)
Solvates (hydrates)	Solubility profile and dissolution rate
Salts	All aspects of processing
Crystal defects	
Dimensional	
Particle size distribution	Processing behaviour: bulk density, agglomeration, flow/rheology, compaction
Particle morphology	Particle permeability (i.e. particle adsorption)
Particle surface structure	Bioavailability (drug absorption)
	Consistency and uniformity of the dosage form
Chemical	
Organic and inorganic impurities, residual solvent and decomposition products	Toxicity
Chiral forms and chiral separation	Chemical, physical and enantiomeric stability
Sterility (microbial limits)	
Mechanical	
Brittle/ductile transitions, fracture stress, indentation hardness, stress/strain relaxation, yield pressure, Young's modulus	Milling and tableting behaviour
Electrical	
Electrostatic charge distribution	Agglomeration and flow properties

drug release properties to be carried out through Phases I–III (i.e. different degrees of clinical evaluation) [6]. This development work, combined with results of clinical tests, culminates in a New drug application (NDA) submitted to a government regulatory body such as US Food and Drug Administration (FDA) [6,7]. The newness of a drug product may arise not only from a new bioactive chemical form, but also from a different solid-state form (e.g. polymorphic, amorphous or chiral), combination with other solids (excipients, carriers, coating), different delivery method or even a different proportion of the drug in this combination. New drugs and any associated manufacturing and formulation aspects, including crystallization methods for a particular solid-state form, are typically protected by patents. These patents guarantee the future financial security of the company-sponsor and become very sensitive issues as, for example, occurred during the case concerning the different polymorphic forms of the popular ulcer drug Zantac [8]. Therefore, screening of all different solid state forms and the development of corresponding crystallization techniques should ideally be carried out as early as possible.

The drug substance section of an NDA must contain specifications related to purity, solubility, crystal properties, morphology, particle size and surface area. Both drug substance and drug product sections of NDA require detailed investigation into the influence of structure on stability, in order to avoid negative recrystallization phenomena, and also into the relationship between structure and drug release rate. An NDA also requires complete proof of structure on all crystalline drug candidates, preferably from single-crystal structural data. Often, a growth technique will have to be developed to produce single crystals, which may prove a challenging task for large molecular substances or substances with low solubility. If production of single crystals is difficult, X-ray powder diffraction will have to be used to assure crystal and solid-state phase identity. Additional requirements are imposed on chiral drugs, which may possess different toxicological and pharmacological effects depending on their enantiomeric form. These requirements consist of identification of enantiomeric composition and (optical) purity, resolution (if the drug is used in a single enantiomeric form) and the confirmation of enantiomeric stability in formulation.

The potential impact of changing crystal properties during late-stage drug development, in terms of both cost and product delay has led to specific guidelines on the control of physicochemical properties according to the NDA requirements and further inspections. These guidelines have been developed as a result of collaboration between regulators, industry and academia [9–11] and presented in the form of algorithms. The four types of solid-state phases identified according the FDA charts are polymorphs, solvates (e.g. hydrates), desolvated solvates (pseudopolymorphs) and amorphous compounds. A combined flow chart is presented in Fig. 1. The crystallization process must be controllable with respect to the solid form produced. Once the properties of these solid forms are identified using appropriate analytical techniques and these properties are different, control and specification procedures should be defined to ensure consistency and stability of the product. Extended international guidelines have been formulated as collaboration has grown between different regulatory organizations through the International Conference on Harmonization (ICH). The standards of potency, purity and other physicochemical properties and the standard analytical methods for most commonly used drugs and drug products are given in pharmaceutical compendia such as the United State Pharmacopoeia (USP) and British Pharmacopoeia (BP). The above regulations, combined with internationally accepted manufacturing rules covering current good manufacturing practices (cGMP) [12] make the crystallization process among the most important industrial and regulatory recognized issues in pharmaceutical development.

3. Crystallization process and design of solid dosage forms

3.1. Crystal properties and direct compression

Tablets are still by far the most widely used, simple and convenient solid dosage form. A number

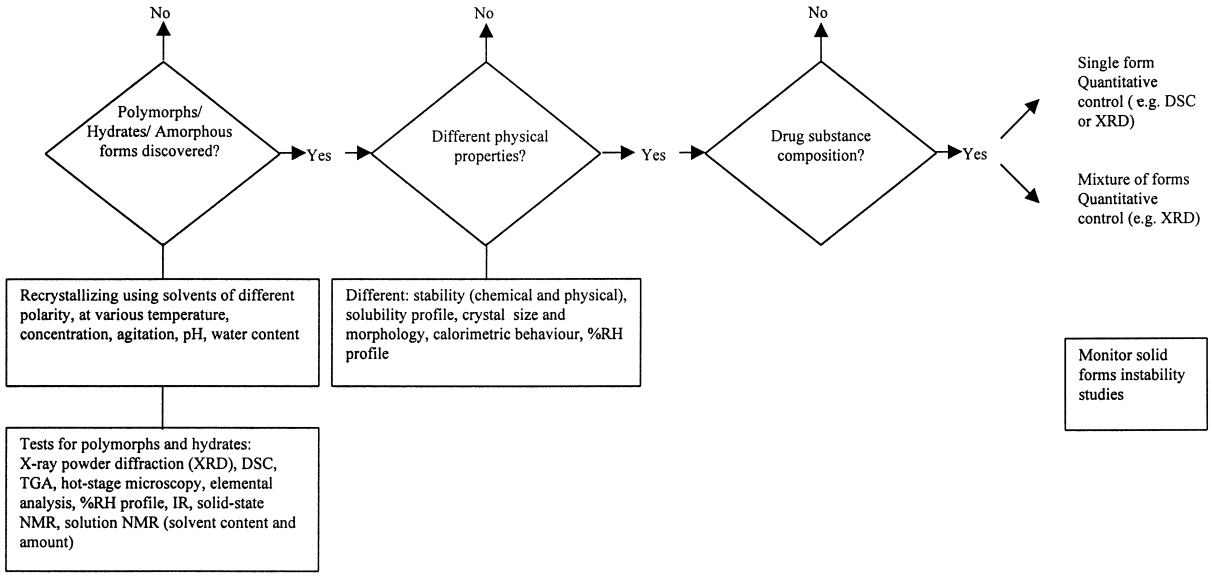

Fig. 1. Algorithm for identification of solid forms (following the FDA guidelines).

of different solids, mostly crystalline excipients such as bulking and binding agents, lubricants, plasticizers as well as other ingredients may be included in the formulation. The success of any direct-tabletting procedure and resulting mechanical properties of tablets are strongly affected by the quality of the crystals used in this process. The manufacture of tablets by directs compression offers advantages over conventional wet granulation procedures in reducing the number of manufacturing steps (typically from six down to two) and the elimination of any undesirable exposure to water or solvent and elevated temperature [13,14]. Direct compression requires good powder flow properties, uniform mixing between the drug and excipients and the ability to consolidate and bond under pressure and maintain interparticle bonds on ejection from the tablet machine. Relevant processing and mechanical parameters are shown in Table 1. The carrier capacity of excipients for drug in tablets is typically limited to 25%. However, since about two-thirds of the currently marketed tablets contain less than 100 mg of drug [13], the mechanical properties and compressibility of the excipient will be the controlling factor. Because of increased potency of the modern drugs, such low dose tablets will dominate in the future. In the remaining one-third of tablet formulations, the mechanical characteristics of the drug substance will be important.

Considerable research efforts have been made to optimize crystals for compression. For example, particles with elongated morphology and enhanced compression behaviour were obtained by changing the solvent polarity during crystallization of nitrofurantoin and ibuprofen [15,16] or pH and supersaturation of octotiamine [17]. The tableting behaviour of acetaminophen, known by its poor compression ability, can be improved by crystallizing particles of platy morphology with lower hardness and greater plasticity then those of prismatic form [18], changing thermodynamic crystal properties [19,20], or crystallizing the recently reported orthorhombic polymorph [21]. Studies into modification of crystal structure and crystal shape by specific additives has shown that an incorporated additive increases the crystal free energy and entropy, reduces the enthalpy of fusion and increases the dissolution rate. For example, low levels of n-alkanoic acid in adipic acid crystals lead to an increase in lattice strain, reducing the energy required for plastic deformation which resulted in improved tabletting performance [22,23].

Crystallization of acetaminophen has been studied with the structurally related impurity, p-acetoxyacetanilide (PAA) [24,25] and work showed the importance of additives in modifying the crystal habit and the intrinsic dissolution rate. Lactose, perhaps the widest used excipient, exhibits mechanical properties of which are directly related to the crystallization process [26,27]. Relatively slow crystallization produces single crystals of α-lactose monohydrate, whilst rapid crystallization results in aggregates of anhydrous α- and β-lactose microcrystals. On compression, the aggregates undergo intensive fragmentation, leading to higher tablet crushing strength as compared with α-lactose tablets. Amorphous lactose can be obtained using a spray-drying technique with its superior bonding ability attributed to the plastic flow on compression.

It should be emphasized, however, that even minor changes in crystallization conditions, for example, supersaturation, temperature, impurity or cooling rate can produce significant changes in the crystal and powder properties, notably particle size, shape, purity and defect structure [22–25,28] followed by less pronounced but significant variations in thermodynamic and mechanical properties. These effects have been recognized as the major batch-to-batch and source variation problems leading to inconsistency of the final tablet properties. Clearly, the radical solution of these problems is to design more advanced crystallization methods in order to achieve full control of required characteristics. Spherical agglomeration [29,30] and spherulitic crystallization [31] techniques allow production of particles (polycrystalline aggregates of characteristic size 100–200 μm) with improved flow characteristics and compressibility. Modification of both the crystal structure and crystallization process can be achieved by the formation of series of salts based on the same parent active drug [32,33]. About 95% of all pharmaceutical substances are ionizable and such salts as hydrochloride (anion), potassium or sodium (cation) are commonly used in pharmaceutical formulation especially when intrinsic solubility, crystallinity or mechanical properties of the parent drug are inadequate.

The complexity and variety of crystallization problems attributed to pharmaceutical processes involving mechanical treatment such as milling and compression warrant studies of more fundamental aspects of particle formation and crystal growth in this area. For example, surface kinetics and crystal defects, surface energetics, influence of additives and solvent–surface bonding have been investigated using laser interferometric technique for acetaminophen crystals [18,25,34]. Theoretical models have been developed to obtain ad hoc the crystal morphology [35,36], polymorphic form [37] and mechanical properties [38] of organic molecular solids. However, further work is needed to study the relationships between crystallization conditions and the formation of defects, to predict the crystal properties on the basis of molecular and crystallographic structure and to understand in detail the mechanism of nucleation and agglomeration processes.

3.2. Amorphous and partly crystalline substances

Different crystallization processes, spray drying and lyophilization, and post-crystallization treatment, such as heating, milling, granulation, compaction and polymer coating, leads to various degree of disorder in the form of crystal defects and amorphous regions [13,39]. Production of highly disordered materials is very compound-specific. Relatively large molecules and molecules with a certain degree of rotational flexibility tend to form a disordered state even at mild crystallization conditions. The quantification of crystallinity is critically important in considering both the controlled modification of pharmaceutical powders and the resulting solid-state stability. According to the USP, crystallinity is determined by the fraction of completely crystalline material in the mixture (two-state model). More physically realistic, the one-state model incorporates the concept of a gradual decrease of crystallinity with no sharp distinction between the completely crystalline (100% crystallinity) and amorphous (0% crystallinity) states [40]. The degree of crystallinity is frequently characterized using X-ray powder diffraction (XRD), differential calorimetry (DSC) or water sorption (%RH) techniques (Fig. 1). An alternative approach involves the measurement of changes in entropy, ΔS, between processed and reference

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