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Crystalline solids

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Abstract

Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling during the various stages of drug development. Crystalline solids can exist in the form of polymorphs, solvates or hydrates. Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport characteristics of the drug. Hence it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development. The current focus of research in the solid-state area is to understand the origins of polymorphism at the molecular level, and to predict and prepare the most stable polymorph of a drug. The recent advances in computational tools allow the prediction of possible polymorphs of the drug from its molecular structure. Sensitive analytical methods are being developed to understand the nature of polymorphism and to characterize the various crystalline forms of a drug in its dosage form. The aim of this review is to emphasize the recent advances made in the area of prediction and characterization of polymorphs and solvates, to address the current challenges faced by pharmaceutical scientists and to anticipate future developments.

Keywords: Crystallinity; Polymorphs; Hydrates; Solvates; Formulation; Drug substance; Phase transformation; Characterization

Contents

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1. Introduction

Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. When applied to solids, the adjective, *crystalline,* implies an ideal crystal in which the structural units, termed *unit cells,* are repeated regularly and indefinitely in three dimensions in space. The unit cell has a definite orientation and shape defined by the translational vectors, a, b, and c, and hence has a definite volume, V, that contains the atoms and molecules necessary for generating the crystal. Each crystal can be classified as a member of one of seven possible crystal systems or crystal classes that are defined by the relationships between the individual dimensions, a, b, and c, of the unit cell and between the individual angles, α, β, and γ of the unit cell [1,2]. The structure of a given crystal may be assigned to one of the seven crystal systems, to one of the 14 Bravais lattices, and to one of the 230 space groups [1]. All the 230 possible space groups, their symmetries, and the symmetries of their diffraction patterns are compiled in the International Tables for Crystallography [3].

The common crystalline forms found for a given drug substance are polymorphs and solvates. Crystalline polymorphs have the same chemical composition but different internal crystal structures and, therefore, possess different physico–chemical properties. The different crystal structures in polymorphs arise when the drug substance crystallizes in different crystal packing arrangements and/or different conformations. The occurrence of polymorphism is quite common among organic molecules, and a large number of polymorphic drug compounds have been noted and catalogued [4–7].

Solvates, also known as pseudopolymorphs, are crystalline solid adducts containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug. If the incorporated solvent is water, a solvate is termed a hydrate. Adducts frequently crystallize more easily because two molecules often can pack together with less difficulty than single molecules. While no definite explanations can be given, possible reasons include adduct symmetry, adduct-induced conformation changes, and the ability to form hydrogen bonds through the solvent molecules [2,8,9]. Desolvated solvates are produced when a solvate is desolvated and the crystal retains the structure of the solvate [10]. Desolvated solvates are less ordered than their crystalline counterparts and are difficult to characterize, because analytical studies indicate that they are unsolvated materials (or anhydrous crystal forms) when, in fact, they have the structure of the solvated crystal form from which they were derived [11].

Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color [12]. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products [13], while differences in solubility may have implications on the absorption of the active drug from its dosage form [14], by affecting the dissolution rate and possibly the mass transport of the molecules. These concerns have led to an increased regulatory

interest in understanding the solid-state properties and behavior of drug substances. For approval of a new drug, the drug substance guideline of the US Food and Drug Administration (FDA) states that "appropriate" analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of product development [11]. It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics [15].

Various pharmaceutical processes during drug development significantly influence the final crystalline form of the drug in the dosage form. The various effects of pharmaceutical processing on drug polymorphs, solvates and phase transitions have been described in detail by Brittain and Fiese [16] and will be discussed in later chapters. Briefly, processes such as lyophilization and spray drying may lead to the formation of the amorphous form of drug, which tends to be less stable and more hygroscopic than the crystalline product. Also, processing stresses, such as drying, grinding, milling, wet granulation, oven drying and compaction, are reported to accelerate the phase transitions in pharmaceutical solids. The degree of polymorphic conversion will depend on the relative stability of the phases in question, and on the type and degree of mechanical processing applied. Keeping these factors in mind, it is desirable and usual to choose the most stable polymorphic form of the drug in the beginning and to control the crystal form and the distributions in size and shape of the drug crystals during the entire process of development. The presence of a metastable form during processing or in the final dosage form often leads to instability of drug release as a result of phase transformation [17].

Crystallization plays a critical role in controlling the crystalline form and the distribution in size and shape of the drug. The significance of crystallization mechanisms and kinetics in directing crystallization pathways of pharmaceutical solids and the factors affecting the formation of crystals have been reviewed in detail by various researchers [12,18,19]. A crystalline phase is created as a consequence of molecular aggregation processes in solution that lead to the formation of nuclei, which achieve a certain size during the nucleation phase to enable growth into macroscopic crystals to take place during the growth phase. The factors affecting the rate and mechanisms by which crystals are formed are: solubility, supersaturation, rate at which supersaturation and desupersaturation occur, diffusivity, temperature, and the reactivity of surfaces towards nucleation. The various forces responsible for holding the organic crystalline solids together, such as nonbonded interactions and hydrogen bonding, have been discussed in detail by Byrn et al. [2] and Etter [20].

Various analytical methods are being currently used to characterize the crystalline form of the drug during the various steps of processing and development. These methods have been reviewed recently in detail by many authors [7,10,21–25]. The single most valuable piece of information about the crystalline solid, including the existence of polymorphs and solvates, is the molecular and crystalline structure, which is determined by single-crystal X-ray diffractometry [2]. Powder X-ray diffractometry provides a "fingerprint" of the solid phase and may sometimes be used to determine crystal structure. Once the existence of polymorphism (or solvate formation) is definitely established by single-crystal and powder X-ray diffractometry, spectral methods, such as Fourier transform infrared absorption (FTIR) spectroscopy, Fourier transform Raman scattering (FT Raman) spectroscopy, solid-state nuclear magnetic resonance (SSNMR) spectroscopy, ultraviolet and visible (UV–Vis) and/or fluorescence spectroscopy [23] may be employed for further characterization. Of special significance are thermal methods, such as differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and optical microscopy using a hot stage [24]. These methods are almost always employed for further characterization. Modulated (temperature) differential scanning calorimetry (MDSC) in combination with DSC and optical microscopy are able to identify the glass

transition of amorphous forms with much greater clarity and allow unique insights into the glass transitional and polymorphic behavior of drug substances [26].

Because solid-state NMR spectroscopy can be used to study crystalline solids, as well as pharmaceutical dosage forms, this powerful method is finding increasing application in deducing the nature of polymorphic variations [27], such as variations in hydrogen bonding network and molecular conformations among polymorphs [28,29] and for the determination of molecular conformations and mobility of drugs in mixtures and dosage forms [2]. Solid-state ^{13}C-NMR in conjunction with the techniques, known as high power proton decoupling, cross polarization (CP), and magic-angle spinning (MAS) offers information not obtained readily by other techniques. Recently, two-dimensional ^{13}C-solid-state NMR spectroscopy has been used to study the three conformational polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile [30]. Use of two-dimensional NMR and total suppression of spinning side bands (TOSS) pulse sequences allowed the separation of isotropic and anisotropic chemical shifts for the three forms. This is a very powerful method for analyzing differences in the chemical environment and is finding increased application in the study of conformational polymorphism.

With advances in analytical methods, the current focus of research in the solid-state area is to understand polymorphism and pseudopolymorphism at the molecular level. Knowledge of the crystal packing arrangements and the various intermolecular forces involved in the different packing arrangements will help in the prediction and preparation of the most stable polymorphs of a given compound well in advance, to avoid surprises during product development. A current emphasis is on the development of software to predict crystal structures of polymorphs from molecular structures. A thorough understanding of the physicochemical properties of polymorphs and solvates (hydrates) is of primary importance to the selection of a suitable crystalline form and development of a successful pharmaceutical product. Bray et al. [31] have shown that, by thorough characterization of four different crystalline forms of L-738,167, a fibrinogen receptor antagonist by various analytical techniques, it was possible to determine the suitability of one or two forms for the development of pharmaceutical oral dosage forms.

The present review aims to emphasize the recent advances made in the area of prediction and characterization of polymorphs and solvates, attempts to address the current challenges and problems faced by pharmaceutical scientists and intends to anticipate future development. This review does not attempt to provide solutions to the problems but attempts to review comprehensively the advances made in recent years to help address these problems.

2. Recent advances in the identification, prediction and characterization of polymorphs

2.1. Types of polymorphism

Based on differences in the thermodynamic properties, polymorphs are classified as either enantiotropes or monotropes, depending upon whether one form can transform reversibly to another or not. In an enantiotropic system, a reversible transition between polymorphs is possible at a definite transition temperature below the melting point. In a monotropic system, no reversible transition is observed between the polymorphs below the melting point. Four useful rules have been developed by Burger and Ramburger [32,33] to determine qualitatively the enantiotropic or monotropic nature of the relationship between polymorphs. These rules are the heat of transition rule, heat of fusion rule, infrared rule and density rule.

If, by use of the above rules, it is established that the polymorphs of a particular drug are enantiotropic or monotropic, then the next goal is to define the thermodynamically stable (or metastable) domain of each crystalline phase of a substance as a function of temperature. The plot of the Gibbs free energy difference, ΔG, against the absolute temperature, T, gives the most complete and quantitative information on the stability relationship of polymorphs [22], with the most stable polymorph having the lowest Gibbs free energy. The ΔG between the polymorphs may be obtained using several techniques operating at

different temperatures, such as solubility [34] and intrinsic dissolution rate. Yu [35] has derived thermodynamic equations to calculate ΔG between two polymorphs and its temperature slope from the melting data. This method is essentially an extension of the heat of fusion rule, which is based on statistical mechanics. Extrapolating ΔG to zero gives an estimate of the transition temperature, from which the existence of monotropy or enantiotropy is inferred. The integration of different types of data provides the ΔG vs. T curve over a wide temperature range and allows the consistency between techniques to be checked [22]. Another approach to establish the order of stability among various polymorphs has been studied using pressure versus temperature plots, e.g., for sulfanilamide and piracetam [36]. This approach is based upon Ostwald's principle of least vapor pressure, according to which the stable polymorph exhibits the lowest vapor pressure. The accuracy of this approach to establish the stability hierarchy among the polymorphs has been shown to be very much dependent on the accuracy of the experimental data.

In recent years, the main focus of research has been the characterization of polymorphs arising from structural differences in the crystal lattice. It has been established for some time that organic molecules are capable of forming different crystal lattices through two different mechanisms. One of the mechanisms is termed *packing polymorphism*, and represents instances where conformationally relatively rigid molecules can be assembled into different three-dimensional structures through the invocation of different intermolecular mechanisms. The other mechanism is termed *conformational polymorphism* and arises when a nonconformationally rigid molecule can be folded into different arrangements, which subsequently can be packed into alternative crystal structures. The distinction between *packing polymorphism* and *conformational polymorphism* is somewhat artificial because different packing arrangements impose different conformations on the molecules, however slight, and different conformations will inevitably pack differently. The structural aspects associated with polymorphs have been reviewed recently [2], as have the analogous features of solvate and hydrate systems [9]. In the next section, the results of some more recent investigations are discussed.

2.2. Packing polymorphism

An investigation into the structures and charge densities of two polymorphs of *p*-nitrophenol has been performed with the aim of deducing the different modes of inter-molecular hydrogen bonding that lead to the formation of the two structures shown in Fig. 1a and b [37]. A detailed analysis of the charge density of the two forms indicates charge migration from the benzene ring region to the nitro and hydroxyl groups that accompanies the transformation of one form into the other. In addition, polarization of the oxygen lone-pair electrons was found to be substantially larger in the crystal forms than in the free molecule, resulting in considerably larger dipole moments in the solid state.

During the study of a new crystal form (form I) of

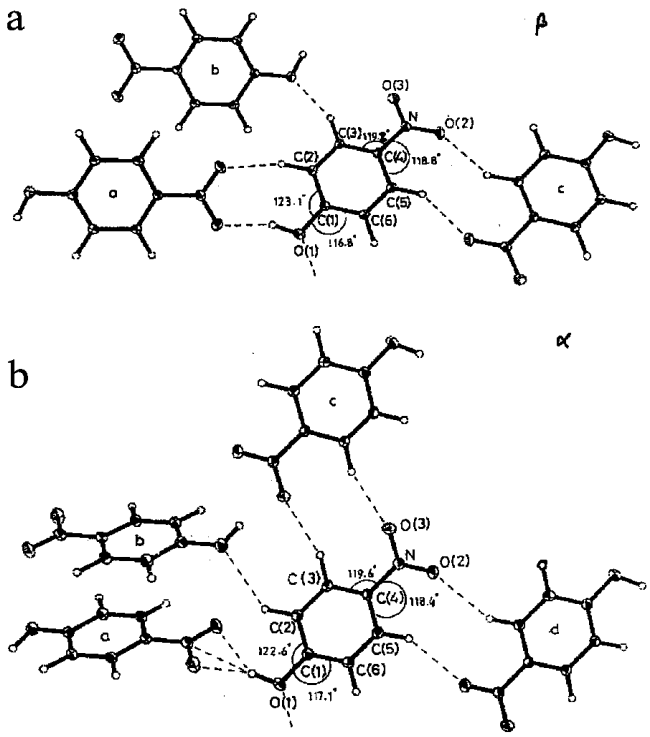

Fig. 1. Molecular packing diagrams of the (a) β polymorph of *p*-nitrophenol, (b) α polymorph of *p*-nitrophenol, showing 50% probability displacement ellipsoids ([37], reproduced with the permission of the American Chemical Society).

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