Introduction

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, containing at least one molecule, has a definite orientation and shape defined by the translational vectors, a, b, and c. The unit cell therefore has a definite volume, V, that contains the atoms and molecules necessary for generating the crystal.1 Amorphous solids lack the long-range order present in crystals.1

Each crystal can be classified as a member of one of seven possible crystals 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.2,3 The structure of the 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.4 All the 230 possible space groups, their individual symmetries, and the symmetries of their diffractions patterns are compiled in the International Tables for Crystallography.5

Certain space groups occur more frequently than others. According to the Cambridge Structural Database,6, 7 about 76% of all organic and organometallic compounds crystallize in only 5 space groups, P 2₁/c, P 2₁2₁2₁, P 1, P 2₁, and C 2/c, and about 90% of all organic and organometallic crystal structures are covered by the 17 most common space groups.6

The present review does not consider pharmaceutical co-crystals, which are solid phases that contain two or more components, such as a drug and an excipient. The preparation and study of co-crystals add appreciable complexity to the topic, which could justify an additional review.

Abstract

The majority of drug products are solid dosage forms, most of which contain the drug substance in the crystalline state. This review considers the forces responsible for crystal packing, the various types of pharmaceutical crystals, and the methods used to determine the structure of pharmaceutical crystals. These topics provide background for the main thrust, which focuses on the importance of studying the structure of pharmaceutical crystals with particular stress on phase changes of crystal forms of drugs during pharmaceutical processing and implications of different solid forms of drugs on its mechanical properties. The present review does not consider pharmaceutical co-crystals, which could be the subject of another review.

Key words: Mechanical properties, Hydrates/solvates, Amorphous, Clathrates, Crystal-structure, Processing, Polymorphism, Physicochemical properties, X-ray powder diffractometry, Solid state

Relationship between the Structure and Properties of Pharmaceutical Crystals†

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Forces responsible for crystal packing

While the intramolecular interactions bond the atoms in a molecule, the intermolecular forces minimize the energy of the molecules in the crystal and are primarily responsible for the formation of organic crystals. A crystal structure therefore corresponds to a free energy minimum that is not necessarily the lowest (so called, global) minimum. The intermolecular forces may be either attractive or repulsive. The attractive interactions consist of three types: non-bonded (sometimes termed non-covalent interactions) such as van der Waals forces (which depend on dipole moments, polarizability, and electronic distribution of the molecules) and hydrogen bonds (which require donor and acceptor functional groups), ionic interactions, and electrostatic interactions. The major attractive interactions in most pharmaceutical crystals are hydrogen bonds and van der Waals interactions. However, in ionic crystals, electrostatic interactions can significantly affect the overall crystal packing energy.

Non-bonded interactions are relatively weak and are generally treated as isotropic, although a more realistic interpretation may require the inclusion of anisotropcity in the treatment. Hydrogen bonds, the energies of which are in the range of 1-10 kcal/mol, are anisotropic and directional. The magnitude of the sum of the forces acting on a molecule, and the energies involved in the interactions of individual atoms of a molecule with atoms of the surrounding molecules, may be estimated from the sublimation energy of the molecular crystal. For most molecular crystals, the sublimation enthalpy is within the range, 10-25 kcal/mol.

The arrangement of molecules in a crystal determines its physical properties and, in some cases, its chemical properties. The physicochemical properties of the solid drug can affect its performance. Thus, an understanding of the crystalline state leads to an understanding of the drug properties, which is crucial for preformulation and formulation in the pharmaceutical industry.

Types of pharmaceutical crystals

The molecules in an organic pharmaceutical crystal may be chiral or achiral. Some pharmaceuticals are salts. Based on its internal structure, a pharmaceutical crystal may be a molecular adduct (hydrate or solvate), or may be one of a group of polymorphs, as shown in Table 1 and explained below.

Polymorphism, in general, denotes the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Conformationally rigid molecules exhibit orientational, or packing, polymorphism. Conformational polymorphism arises when a flexible molecule adopts different conformations in different crystal structures.

Polymorphs can be classified as enantiotropes or monotropes, depending on whether or not one form can transform reversibly to another. Enantiotropes are members of a pair of polymorphs whose mutual transition temperature is less than the melting point of either polymorph. Each enantiotrope has its own temperature range of stability. Monotropes are members of a pair of polymorphs that have no mutual transition temperature. One monotrope is always more stable than the other polymorph under all conditions in which the solid state can exist.

A crystal is termed a molecular adduct when its lat-

| Table 1 | Classification of pharmaceutical crystals. Modified from reference 16 |

Pharmaceutical crystal (containing chiral, achiral or salt form of the compound)

- Single entity, exhibiting polymorphism
  - Orientational polymorphism
  - Conformational polymorphism
- Molecular adduct (hydrates and solvates)
tice consists of more than one chemical component, and includes solvates and hydrates. A solvate is a solid phase containing solid molecules in addition to molecules of the major component in the crystal lattice. When the solvent is water, the solid phase is termed a hydrate. Molecular adducts can be stoichiometric or nonstoichiometric in nature. Clathrates are special types of molecular adducts that consist of two distinct components, a relatively rigid host and a quite mobile guest. Within clathrates, the guest molecules lie trapped in closed, three dimensional cavities or cages formed by the crystalline structure of the host. The term clathration is used instead of solvation when there is no specific interaction between the solvent and solute. Approximately one third of active pharmaceutical substances are capable of forming crystalline hydrates. Solvates and hydrates generally demonstrate different solubilities and consequently different intrinsic dissolution rates (dissolution rates per unit surface area) than their unsolvated counterparts. Moreover, the stability profiles of hydrates and solvates at various temperatures and at different vapor pressures of water or organic solvents differ from those of the unsolvated crystal form. These differences can influence formulation, processing, and stability under various storage conditions of the drug compound, as well as in the pharmaceutical product.

Polymorphism and the formation of molecular adducts are also common among pharmaceutical salts, leading to unique molecular environments and physicochemical properties that differ from those of their respective free acid or base. Polymorphism in a chiral drug can be exhibited by individual enantiomers (for example, carvoxamine and nitrendipine) as well as by racemates (for example, mandelic acid) and can be expressed by the interconversion between different types of racemates, as shown by nicotine derivatives and sodium ibuprofen.

**Determination of the structure of pharmaceutical crystals**

Methods for determining the structure of pharmaceutical crystals fall into three broad categories: (1) methods utilizing single crystals, (2) methods utilizing powder X-ray diffraction patterns, and (3) methods that determine crystal structure from molecular structure alone, i.e., ab initio methods. Each of these methods may be further subclassified, as in Table 2. The salient features of the three methods are outlined below.

**Table 2** Classification of methods used to determine structures of pharmaceutical crystals
Once the integrated intensities are known, an individual reflection directly from the PXRD data is to extract the integrated Bragg intensities of approach for crystal structure solution from PXRD methods and direct-space approaches. The traditional patterns. Methods utilizing powder X-ray diffraction (PXRD) \initio methods can be used. \n
Twinned polarized light microscopy, these crystals are usually composed of microcrystalline aggregates. Twin crystals have different growth sectors that are related by symmetry to one another. The sectors have different orientations that can be related to one another through applications of twinning laws to relate the orientation matrices of the different growth sectors. However, solving twinning structures by single crystal diffraction is not always a straightforward task.\n
Crystal structure determination using single crystal diffraction is the most reliable technique. However, when suitable single crystals are not available, techniques utilizing powder X-ray diffractometry and ab initio methods can be used.\n
Methods utilizing powder X-ray diffraction (PXRD) patterns \n
Methods in this category include traditional methods and direct-space approaches. The traditional approach for crystal structure solution from PXRD data is to extract the integrated Bragg intensities of individual reflections directly from the PXRD pattern. Once the integrated intensities are known, an electron-density map (assuming X-ray radiation) is constructed using the same techniques that have been developed for single-crystal diffraction data. To extract the integrated intensities, various modification techniques of the Pawley or Lebail methods are commonly used. Variants of this basic idea have been applied successfully to organic systems with up to 31 non-H atoms. Although traditional techniques for structure solution from PXRD data have been applied successfully in several cases, these techniques have certain intrinsic limitations and organic molecular crystals represent a particularly challenging case. Peak overlap can create major difficulties in extracting intensities from PXRD patterns, which limits the complexity of structures that can be solved by traditional methods. \n
Direct-space approaches postulate structural models in direct-space, independently of PXRD data. The suitability of these models is assessed by direct comparison of the PXRD patterns calculated from these models with the experimental PXRD patterns. Most direct-space approaches are stochastic in nature, and so it is recommended that calculation of the structure solution be repeated several times from different random starting populations. Possible methods that can be used to locate the global minimum within direct-space structure solution include Monte Carlo simulated annealing, genetic algorithm techniques, and techniques employing a systematic search approach using a grid-based search with lattice energy calculations. Besides determination of crystal structures from PXRD, simulated annealing can also be used for improved predictions in ab initio crystal structure determination. In general, this approach can be used in conjunction with other techniques for improved predictions. Direct-space approaches were utilized to determine crystal structures of a series of organic compounds. However, in this case, unit cell parameters and space groups were obtained from published work, and only the steps of unit cell refinement and structure solution were performed. Moreover, not all the compounds tested were pharmaceutical crystals. The reader is directed to appropriate references for underlying theory and mathematical treatment on powder-indexing, pattern decomposition and unit cell refinement using the Pawley method, the Monte Carlo method, the Monte Carlo importance sampling technique, simulated annealing, and structure refinement using the Rietveld method.

Because the PXRD pattern is collected from a sample of crystallites of random orientation, structure
solution by this method circumvents the problem of crystal quality and twinning through the nature of this experimental approach.\textsuperscript{63} Hence, it is also not necessary to apply the twin laws by the powder method.

Crystal structure determination from PXRD patterns can, however, be complicated. For powder diffraction patterns, the reflections from different crystal planes are averaged over directions and projected onto a single variable, the diffraction angle (2θ). This averaging makes the reconstruction of the underlying crystal structure much more difficult than for single-crystal diffraction patterns.\textsuperscript{43} Space group determination on powders is more ambiguous than with single crystal diffraction, because of limitations of the regions in the pattern where systematic absences are free from peaks due to other reflections. Also, poor-quality PXRD patterns preclude their successful indexing. Furthermore, preferred orientation affects the relative intensities of given peaks and hinders the correct solution of the pattern.\textsuperscript{64}

Determining crystal structures from PXRD data is an important and emerging discipline. There is still considerable potential for the continued development and improvement of the methodologies in this field.\textsuperscript{43} Also, during crystal structure determination by PXRD patterns, other analytical techniques, such as vibrational spectroscopy and solid-state nuclear magnetic resonance spectroscopy, can provide additional structural information complementary to that obtained by PXRD patterns, as in the case of N-(p-tolyl)-dodecylsulfonamide\textsuperscript{65} and acetohexamide form B.\textsuperscript{96}

\textit{Ab initio} crystal structure determination

In more challenging cases, where suitable experimental data are not available, crystal structure determination can be guided by lattice energy calculations instead of powder pattern comparisons, to generate initial models for subsequent Rietveld refinement. Success using this technique is limited\textsuperscript{67} and such \textit{ab initio} prediction of crystal structures still remains an admirable long-term goal\textsuperscript{68} because of the complexity of the task.\textsuperscript{69} Such methods are still plagued by difficulties, including the location of global energy minima, force field accuracy, description of the electrostatic interactions, and inclusion of the entropy term that contributes to the free energy. The ability to determine the crystal structure from the molecular structure of a compound is the ultimate goal of computational crystallography.

\textbf{Importance of studying the structure of pharmaceutical crystals}

An organic molecule, which may be chiral or achiral or a pharmaceutical salt, can, in the crystalline state, exist as polymorphs and/or molecular adducts. Differences in crystal packing forces (i.e., intermolecular forces) lead to differences in long-range periodicity of the molecules. This difference in long-range periodicity in turn leads to differences in energy, and hence, differences in physical reactivity, between the various crystalline forms of the organic molecule. For conformationally flexible molecules, intramolecular forces may also contribute to such differences. The various solid forms of a drug substance can also differ in their chemical reactivity.\textsuperscript{70} Hence, the physical (and also chemical) properties of the organic pharmaceutical crystal will depend on its solid form. Table 3 shows the differences in physical properties that can be shown by the different crystalline forms of an organic molecule.

These differences in physical properties arising from differences in structure of the various crystal forms of an organic pharmaceutical compound has implications in candidate-selection for drug development, processing, formulation, and performance of drug products, regulatory aspects, and intellectual property issues. Differences in solubility and dissolution rate of the various crystal forms can affect drug performance, especially that of BCS Class II drugs.\textsuperscript{71} Existence of different solid forms of a drug can also lead to phase transformations during its processing and formulation (e.g., milling, granulation, drying, compaction),\textsuperscript{72, 73} as observed in theophylline,\textsuperscript{74} chlorpropamide,\textsuperscript{75} carbamazepine,\textsuperscript{76} phenobarbital,\textsuperscript{77} lactose,\textsuperscript{78} chlorpromazine hydrochloride,\textsuperscript{79} uricosuric agent FR76505,\textsuperscript{80} cefixime trihydrate,\textsuperscript{81} and pentamidine isethionate.\textsuperscript{82} These phase changes can affect the stability of the product and, in some cases, even the bioavailability of the drug.\textsuperscript{83} An understanding of the relationship between the solid state properties and crystal structures of the likely phases may be utilized for optimizing operational and formulation strategies and for designing suitable stability protocols to avoid later problems.\textsuperscript{17, 84} Additionally, each of the several pharmaceutical excipients utilized in drug formulations can also exist in different solid forms, and the solid nature of the excipients may also influence the final physical form of the tablet,\textsuperscript{14, 70} such as tendency to stick,\textsuperscript{85} or polymorphic conversion of the active ingredient.\textsuperscript{86} Among chiral drugs, it is known that the pharmacological, toxicological, phar-
macodynamic, and pharmacokinetic properties differ markedly between its opposite enantiomers and racemates. The molecular environments in each of these solids are unique and impart different physicochemical properties to the crystals. Among pharmaceutical salts, which can also exist in different crystal forms, the presence of ions influences the physicochemical properties of the crystals, including solubility, dissolution rate, stability, and hygroscopicity.

The structure of a crystal also affects its mechanical properties, thereby affecting its processability. Thus, theophylline monohydrate, because of the greater number of intermolecular hydrogen bonds in its crystal structure, possesses higher mechanical strength and is also less brittle than anhydrous theophylline. The presence of water molecules in the crystal structure of the monohydrate of 4-hydroxybenzoic acid facilitates its plastic deformation as compared with its anhydrate. The term slip refers to the translational motion of lattice planes relative to each other. Such planes are termed slip planes and a family of slip planes, together with the slip direction, is termed a slip system. Knowledge of crystal structure and slip systems can be utilized to model the tableting and compaction behavior of molecular crystals such as the anhydrate and dihydrate forms of L-lysine hydrochloride and polymorphs I and II of sulf...

Table 3: Physical properties that differ among the various crystalline forms of a drug substance

| Physical Properties | Properties |
|--------------------|------------|
| 1. Packing properties | a. Molar volume and density |
|                    | b. Refractive index |
|                    | c. Conductivity, electrical and thermal |
|                    | d. Hygroscopicity |
| 2. Thermodynamic properties | a. Melting and sublimation temperatures |
|                    | b. Internal energy (i.e. structural energy) |
|                    | c. Enthalpy (i.e. heat content) |
|                    | d. Heat capacity |
|                    | e. Entropy |
|                    | f. Free energy and chemical potential |
|                    | g. Thermodynamic activity |
|                    | h. Vapor pressure |
|                    | i. Solubility |
| 3. Spectroscopic properties | a. Electronic transitions (i.e. ultraviolet-visible absorption spectra) |
|                    | b. Vibrational transitions (i.e. infrared absorption spectra and Raman spectra) |
|                    | c. Rotational transitions (i.e. far infrared or microwave absorption spectra) |
|                    | d. Nuclear spin transitions (i.e. nuclear magnetic resonance spectra) |
| 4. Kinetic properties | a. Dissolution rate |
|                    | b. Rates of solid state reactions |
|                    | c. Stability |
| 5. Surface properties | a. Surface free energy |
|                    | b. Interfacial tensions |
|                    | c. Habit (i.e. shape) |
| 6. Mechanical properties | a. Hardness |
|                    | b. Tensile strength |
|                    | c. Compactibility, tableting |
|                    | d. Handling, flow, and blending |
merazine. The Young’s modulus of aspirin has been determined from its crystal structure and the mechanical properties of aspirin, sulphonilazole, carbamazepine, and polymorphs of primidone (forms A and B) can be predicted by applying lattice dynamics to the atom-atom potential model while also taking into account the crystal morphology. Even though it is possible to predict the mechanical properties of a compound from its crystal structure, crystal engineering of pharmaceuticals has not yet resulted in the design of crystals with desired mechanical properties. By developing a molecular basis for the origins and magnitude of mechanical properties, the required controlled modification might be achieved by analysis of the structural and constituent molecular information. The knowledge thus gained might be utilized to design crystals with desired mechanical properties.

Differences in the physical and mechanical properties of the various crystal forms of a drug substance also affect scale up and transfer from laboratory quantities and procedures through pilot plant and full production as equipment changes, variations in heating/cooling rates, variations in stirring procedures, and seeding, can all influence the result of a crystallization procedure and the solid form obtained.

Characterization and understanding of the crystal properties is also important for quality control and regulatory purposes. Information about the various crystal forms of a drug substance is required by the United States Food and Drug Administration (USFDA) in a New Drug Application and a set of decision trees has been provided to assist in the presentation of data for different crystal forms of a drug substance to the USFDA. Guidelines have also been set up the International Committee of Harmonization to address the existence of different crystal forms of a drug substance. Furthermore, the different crystal forms of a drug and processes for preparing them are patentable. Among the frequently cited uses for patenting different crystal forms are improved formulation, handling and stability, reduced hygroscopicity, and improved solubility and bioavailability.

Conclusions

Most marketed pharmaceuticals consist of molecular crystals. Selection of the most suitable crystalline form of a drug in the initial stages of drug development is crucial to save time and cost associated with the drug development process, and, in recent years, much research has focused on achieving this goal. Isolation and thorough characterization of the maximum number of solid forms of a drug substance reduce the possibility of surprises resulting from inadvertent phase changes during processing or from crystallization of previously unknown forms.

For a given crystalline drug substance, the intermolecular and intramolecular interactions in its lattice, manifested by the molecular arrangement, packing and conformation, determine its observed physicochemical properties, including mechanical properties, which may in turn impact even the pharmaceutical properties of the drug product. To better understand, control, and possibly predict, these properties of pharmaceutical crystals, a thorough understanding of the underlying crystal and molecular structures of the maximum number of solid forms of a drug substance is desirable. While single crystal X-ray diffraction unambiguously establishes the crystal and molecular structure, the continuous development of sophisticated computational tools for the ultimate prediction of crystal and molecular structures provides valuable alternatives when single crystal diffraction is not successful.

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Author’s short biography

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David J.W. Grant is a graduate of Oxford University, UK: B.A. in Chemistry in 1960; D.Phil. in Physical Chemistry in 1963; M.A. (Keble College, 1963); and D.Sc. for recognized published research on the physical chemistry of pharmaceutical systems (October 1990). He has held academic appointments at the University of Nottingham, UK, and University of Toronto, Canada. In 1988, he was appointed to the William and Mildred Peters Chair in Pharmaceutics, University of Minnesota. Since July 1998, he has served as Director of the Drug Delivery Center in the University. Since January 1994, David Grant has served as Associate Editor of the Journal of Pharmaceutical Sciences. He is also a member of the Editorial Advisory Board of the journals Pharmaceutical Development and Technology, Kona Powder and Particle and The AAPS Journal. David Grant teaches the physical chemistry of pharmaceuticals in which he is co-author of an undergraduate text. In 1978 and 1980 he worked on the intermolecular interactions of drugs in solution at the University of Kansas in the laboratory of the late Dr. Takeru Higuchi, with whom he is the co-author of a book entitled, Solubility Behavior of Organic Compounds. Since 1978 David Grant has been studying the crystal engineering of drugs and the properties of the solid state, particularly the thermodynamics, solvation, polymorphism, crystallization, compaction, solubility, and dissolution of drugs. He is also studying the effects of doping, hydration, hydrogen bonding, and chirality in the solid state. David Grant’s recent work has focused on the structure and properties of hydrates and the molecular basis of polymorph crystallization and screening. He is the author or co-author of over 200 peer-reviewed scientific articles and reviews and serves as a consultant for numerous companies that manufacture fine chemicals and pharmaceuticals. David Grant is a Fellow of AAAS, AAPS, IUPAC and the Royal Society of Chemistry (Chartered Scientist, UK). He was awarded the PhRMA Foundation Pharmaceuticals Award in Excellence in 1999, the European Society of Applied Physical Chemistry Award in 2004, the AAPS Dale E. Wurster Award in Pharmaceutics in 2004, and the Mettler-Toledo Award in thermal analysis from the North American Thermal Analysis Society in 2005. Memberships also include ACA, ACS, AIChE, and the Rho Chi Honor Society.