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Recent progress of structural study of polymorphic pharmaceutical drugs☆

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ABSTRACT

This review considers advances in the understanding of active pharmaceutical ingredient polymorphism since around 2010 mainly from a structural view point, with a focus on twelve model drugs. New polymorphs of most of these drugs have been identified despite that the polymorphism of these old drugs has been extensively studied so far. In addition to the conventional modifications of preparative solvents, temperatures, and pressure, more strategic structure-based methods have successfully yielded new polymorphs. The development of analytical techniques, including X-ray analyses, spectroscopy, and microscopy has facilitated the identification of unknown crystal structures and also the discovery of new polymorphs. Computational simulations have played an important role in explaining and predicting the stability order of polymorphs. Furthermore, these make significant contributions to the design of new polymorphs by considering structure and energy. The new technologies and insights discussed in this review will contribute to the control of polymorphic forms, both during manufacture and in the drug formulation.

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1. Introduction

The structure of an active pharmaceutical ingredient (API) is evaluated from the early stage of development by the pharmaceutical industry because the molecular state of the API alone, or in each formulation, affects important physicochemical properties such as stability and solubility. For example, when an API is to be formulated as a solid dosage

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form, its crystal form and physicochemical properties must be characterized in order to select the optimum structure and morphology of the compound. Recently, methods have been developed to study the crystal structures of APIs complexed with other formulation components.

"Polymorph" or "polymorphism" is an established term used to describe materials with structural differences; however, the definition of this term can differ between researchers and research fields. The most well-known definition, provided by McCrone in 1965, states that "A polymorph is a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecule of that compound in the solid state" [1]. Definitions of polymorphs provided by many other researchers relate to the categorization of the chemical structures and composition of materials [2–6].

When the term polymorph is used for compounds with the same chemical structure, it can refer to differences in crystal structure, such as packing polymorphs and conformational polymorphs [7]. A packing polymorph shows a different crystal packing of a compound with the same conformation, whereas a conformational polymorph shows the same crystal packing, but with a different conformation. Enantiomeric and tautomeric polymorphs or polymorphisms have different chemical structures and this definition is not appropriate when referring to polymorphs with the same chemical structure. On the other hand, a polymorph of a free drug, the salt, the solvate, or the cocrystal is an appropriate description of the difference in the crystal structure of each composition, because it takes the compositional difference into account for the comparison. "Solvatomorph" or "solvatomorphism" are sometimes used in the case of the solvate. "Pseudopolymorph" or "pseudomorphism" are sometimes also used in this context, although these are not appropriate because the nomenclature can lead to a misunderstanding of polymorphs [5,6]. When the polymorph term is used in accordance with the wider definition provided by the U.S. Food and Drug Administration, which related to different solid crystal forms of the same substance, both solvates and amorphous forms are regarded as polymorphs [8]. This definition of polymorph encompasses structural differences, independent of the chemical structure and composition. Although it can be apparent that compounds show structural differences, it can be difficult to identify these precisely. In this review, we use the term polymorph to refer to compounds with the same chemical structure and composition. Generally, polymorphs are numbered in order of their discovery, although the terms used can differ depending on the material (a, b, c; α, β, γ; I, II, III; or 1, 2, 3). In this review, we term these as form I, form II, and form III.

The number of crystal forms of an API is determined by its chemical structure. Why is crystal form screening of APIs important in the pharmaceutical industry? One reason is that each polymorphic form has unique physical properties. These exert a major influence on the stability, solubility, and dissolution rate of the raw material. Ritonavir polymorph is a well-known example [9]. The disappearing form I and appearing form II has a large solubility difference, resulting in temporally withdrawal of this drug from the market. Second reason is that, on the production process, these differences affect not only the processing but also the bioavailability of the API from the formulation. Third reason is the regulation issue. There are a lot of contestations of a polymorph patent between the inventor and the generic companies. Finding an unidentified and inventive polymorph (e.g. with easy to manufacture and similar effectiveness as original drug) may allow the generic company to produce its product without infringing on the inventor's patent.

Because each polymorph has their own phase based on the thermodynamic property, understanding of the thermodynamic characteristics of each polymorph is required to control the quality of the drug and of the formulation. To differentiate between monotropic and enantiotropic polymorphs, some rules have been devised such as heat of fusion and heat of transition rules; these are evaluated by thermal analysis. Assuming the monotropic and enantiotropic relationships between $G_{\text{form I}}$ and $G_{\text{form II}}$ described above, the heat of fusion rule means that the enthalpy of fusion of form I ($\Delta H_{\text{form I}}$) is higher than $\Delta H_{\text{form II}}$ in a monotropic system, whereas $\Delta H_{\text{form I}}$ is lower than $\Delta H_{\text{form II}}$ in an enantiotropic system. The heat of transition from the metastable form II to the stable form I is exothermic in monotropic systems, whereas the heat of transition from stable form II to metastable form I is endothermic above the transition temperature in enantiotropic systems. However, the heat of transition from the stable form I to the metastable form II is exothermic in a monotropic system if the transition occurs below the transition temperature. Phase transition is irreversible in a monotropic system and reversible in an enantiotropic system. With respect to solubility, the polymorphic phase with the higher G shows the greatest solubility. When an API has a large number of polymorphs, the system has to be evaluated using an energy-temperature phase diagram because the monotropic and enantiotropic relationships are different for each pair of polymorphic phases. The thermodynamic properties of polymorphs have been described and discussed by many researchers and a more detailed description is available in the recent book chapter by Harry G. Brittain [10].

Polymorphs of APIs can be produced by standard pharmaceutical processes, such as crystallization, milling, and heating. Solution cooling, solvent evaporation, antisolvent addition, and spray-drying are well-known bottom-up methods for API crystallization. For the purpose of high-throughput polymorph screening, solvent evaporation in a multiple well plate provides an efficient methodology [11,12]. Recently, crystallization using a supercritical fluid has been applied for polymorph screening and for preparation of a metastable crystal form [13,14]. The conditions and process parameters employed affect the crystalline form that is produced. Milling is one of the pharmaceutical processes that is classified as a top-down method; this can reduce the size of a drug powder and also can be used to prepare a different crystal form or the amorphous form [15,16]. Milling in solid state changes crystalline form, and new crystalline form is sometimes produced along with the amorphous phase. Heating affects polymorph formation through melting and subsequent recrystallization or through solid phase transformation.

The physical properties of each polymorph, including density and thermal and electrical conductivity, can be measured by the apparatus such as gas pycnometer and conductivity sensor. Structural characterization of each polymorph and phase transformations during processing are evaluated using various analytical techniques. Morphological observation of crystal forms and the crystal habit has been performed using microscopic techniques, such as optical microscopy, scanning electron microscopy (SEM), and transmission electron microscopy (TEM). Atomic force microscopy (AFM) can be used to evaluate differences in the crystalline surface [17,18]. Hot-stage microscopy (HSM) provides an effective tool to investigate heat-induced polymorphic phase transformation. Thermal analyses such as thermogravimetry (TG), differential thermal analysis, and differential scanning calorimetry (DSC) have been used to evaluate the thermal behavior of polymorphs. In the case of solvates, TG measurement provides information relating to stoichiometry, as well as to the structural changes caused by heat-induced desolvation. Crystal structure information can be confirmed by single-crystal X-ray crystallography or powder X-ray diffraction (PXRD) when the API cannot be obtained as a single crystal. Recently, PXRD using synchrotron radiation has made it possible to evaluate the crystal structure [19,20]. Vibrational spectroscopies such as infra-red (IR) and Raman spectroscopies have been used to assign functional groups, as well as to identify differences in the vibrational mode of chemical bonds caused by structural differences [21,22]. In addition to the middle frequency range, near-IR (NIR), far-IR (FIR), or terahertz spectroscopies have been used to evaluate polymorph differences in vibrational modes [23,24]. The application of chemometric data interpretation allows these vibrational spectroscopies to be used for the mapping of each component in the formulation [25,26]. Solid state nuclear magnetic resonance (NMR) spectroscopy has been used to differentiate the magnetic state and mobility of nuclei in each polymorph, which influence the