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Commentary

Scientific Considerations of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications

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Purpose. This commentary is intended to provide a scientific perspective on pharmaceutical solid polymorphism in Abbreviated New Drug Applications (ANDAs).
Methods. This report proposes recommendations for monitoring and controlling drug substance polymorphs and describes scientific considerations of pharmaceutical solid polymorphism in the determination of drug substance sameness.
Results. It presents three decision trees for solid oral dosage forms or liquids containing undissolved drug substances to provide a process for evaluating when and how polymorphs of drug substances are monitored and controlled in ANDA submissions.
Conclusions. It is scientifically concluded that differences in polymorphic composition of drug substances in generic drug products and reference-listed drugs are not directly relevant in the determination of drug substance sameness in ANDAs.

KEY WORDS: polymorphism; polymorph; Abbreviated New Drug Application (ANDA); drug substance; drug product; pharmaceutical solid.

INTRODUCTION

Many pharmaceutical solids can exist in different physical forms. Polymorphism is often characterized as the ability of a drug substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (1). Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or nonstoichiometric amounts of a solvent (2). If the incorporated solvent is water, the solvates are also commonly known as hydrates. Polymorphism in this commentary is defined, as in the International Conference on Harmonization (ICH) Guideline Q6A (3), to include polymorphs, solvates, and amorphous forms, as shown in Fig. 1 (4).

Pharmaceutical polymorphic solids of the same chemical compound differ in internal solid-state structure and, therefore, possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial, and mechanical properties (1). These properties can have a direct impact on drug substance processability, drug product manufacturability, and drug product quality/performance, including stability, dissolution, and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences, which may result in product development delay and commercial production disruption, as in the case of ritonavir (5). As a result, in recent years pharmaceutical solid polymorphism has received much scrutiny throughout various stages of drug development, manufacturing, and regulation (3,6–9).

Several regulatory documents and literature reports (3,6,8) address issues relevant to the regulation of polymorphism. Although many of the concepts and principles outlined in these documents are applicable to Abbreviated New Drug Applications (ANDAs), certain additional considerations may be given to ANDAs. When FDA receives an ANDA, a monograph defining certain key attributes of the drug substance and drug product is frequently available in the United States Pharmacopeia (USP). Sometimes literature information on pharmaceutical solid polymorphism may also be available. These public standards and literature data play a significant role in the ANDA regulatory review process. This commentary is intended to provide a scientific perspective on pharmaceutical solid polymorphism in the context of ANDAs. It highlights major considerations for monitoring and controlling drug substance polymorphs and describes a framework for scientific decisions regarding drug substance "sameness."

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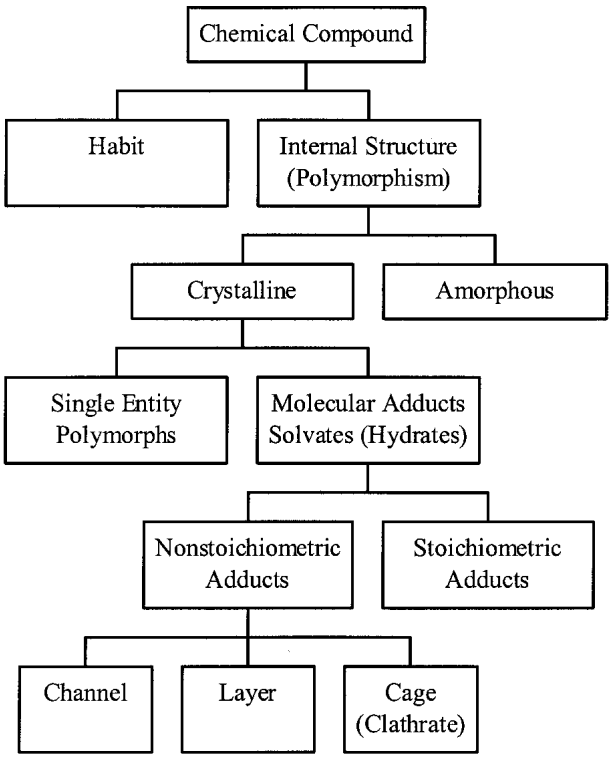

Fig. 1. Schematic of pharmaceutical solid habit and polymorphism of a chemical compound [After Haleblian, J. Pharm. Sci. 64:1269–1288 (1975)]

CHARACTERIZATION OF POLYMORPHS

Full characterization of a drug substance is important in order to develop a drug product successfully (7). Of all the methods available for the physical characterization of solid materials, it is generally agreed that crystallography, microscopy, thermal analysis, spectroscopy [IR, Raman, and nuclear magnetic resonance (NMR)], and solubility/intrinsic dissolution studies are the most useful methods for characterization of polymorphs and solvates (10).

Single crystal X-ray diffraction studies lead to the structural elucidation of small molecules within a crystal lattice and provide the single most valuable piece of information on the polymorphic solid. In fact, the definitive criterion for the existence of polymorphism is demonstration of a nonequivalent crystal structure. However, a limiting requirement of this technique is the necessity of obtaining appropriate single crystals for analysis. X-ray powder diffraction is another powerful technique suited for distinguishing solid phases with different internal crystalline structures. However, unlike single crystal X-ray diffraction, X-ray powder diffraction does not require single crystals and is also an effective tool for the routine analysis of powdered samples. In some instances, X-ray powder diffraction has been used in the determination of the unit cell parameters and space group as well as in molecular structure determination (11). X-ray powder diffraction may also be used for the determination of degree of crystallinity, quantitative analysis of polymorphic solids, and kinetic determination of solid-state reactions (2,12).

Once the existence of polymorphism is established, other methods such as solid-state spectroscopy, microscopy, and thermal analysis may be used for further characterization. Microscopy (light and electron) characterizes polymorphs through the optical and morphologic properties of the crystal. Microscopy is especially useful when only a limited amount of the drug substance is available. A full microscopic examination can reveal possible differences in crystal habit or structural class. Hot-stage microscopy is a useful tool for discovering polymorphs and determining their stability relationship, as illustrated through a study of a fluoroquinolone (13).

Thermal analysis, such as differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), distinguishes polymorphs on the basis of the phase transitions they undergo during heating and can be used to obtain additional information regarding these phase transitions including melting, desolvation, crystallization, and glass transition. These thermal methodologies can also be used to determine the relative stability among polymorphs and to differentiate enantiotropic and monotropic systems. For an enantiotropic system, the relative stability of a pair of solid forms inverts at some transition temperature beneath the melting point, whereas in a monotropic system, a single form is always more stable beneath the melting point (1).

Solid-state spectroscopy (IR, Raman, and NMR) has become an integral part of the physical characterization of pharmaceutical solids (14). Both IR and Raman spectroscopy measure the fundamental molecular vibrational modes and provide a fingerprint of the pharmaceutical solid (7). Both of these techniques complement one another in that IR spectroscopy measures vibrational modes that change in dipole moment, whereas Raman spectroscopy measures vibrational modes that change in polarizability. Solid-state NMR is a powerful technique used to measure the magnetic environment around a nucleus. Solid-state NMR can be used not only to differentiate between solid-state forms in the bulk drug substance and in the drug product but also to probe the molecular structure of each solid-state form. The NMR technique is finding increasing utility in deducing the nature of these solid-state polymorphic variations, such as variations in hydrogen bonding, molecular conformation, and molecular mobility (15).

PROPERTIES OF POLYMORPHS

Solubility and Dissolution

Solubility and dissolution information is important in ANDAs. The solid-state characteristics of drugs are known to potentially exert a significant influence on the solubilization of drugs. Polymorphs of a drug substance can have different apparent aqueous solubility and dissolution rates. When such differences are sufficiently large, bioavailability may be altered, and it may be difficult to formulate a bioequivalent drug product using a different polymorph.

Solubility at a defined temperature and pressure is the saturation concentration of the dissolved drug in equilibrium with the solid drug. Aqueous solubility of a drug is traditionally determined using the equilibrium solubility method and involves suspending an excess amount of a solid drug in a selected aqueous medium. The equilibrium solubility method may not be suitable to determine the solubility of a metastable form because the metastable form may convert to the stable form during the experiment.

When the solubility of metastable forms of a drug substance cannot be determined by an equilibrium method, the intrinsic dissolution method may be useful to deduce the relative solubilities of metastable forms (16). Use of the intrinsic dissolution method assumes that the intrinsic dissolution rate is proportional to the solubility, the proportionality constant being the transport rate constant, which is constant under the same hydrodynamic conditions in a transport-controlled dissolution process. It should be noted, however, that polymorphic conversion is still possible during the measurement of intrinsic dissolution rate (17).

Polymorphic differences and transformations that result in different apparent solubilities and dissolution rates are frequently detected by dissolution testing. This testing provides a suitable means to identify and control the quality of a product from both bioavailability and (physical) stability perspectives. When solubilities and dissolution rates of the relevant polymorphic forms are sufficiently high, and oral absorption is not controlled via dissolution, regulatory concerns with respect to bioavailability are minimal. The Biopharmaceutics Classification (18,19) criteria of high solubility and rapid dissolution should also be considered in regulatory decisions.

Stability and Manufacturability

Polymorphs of a pharmaceutical solid may have different physical and solid-state chemical (reactivity) properties. The most stable polymorphic form of a drug substance is often used in a formulation because it has the lowest potential for conversion from one polymorphic form to another. On the other hand, metastable (a form other than the most stable form) and even amorphous forms may be chosen to enhance the bioavailability of the drug product (20). Gibbs free energy, thermodynamic activity, and solubility provide the definitive measures of relative polymorphic stability under defined conditions of temperature and pressure (21).

Solid-state reactions that occur in the bulk drug substance and in the drug product formulation include solid-state phase transformations, dehydration/desolvation processes, and chemical reactions (22). One polymorph may convert to another during manufacturing and storage, particularly when a metastable form is used. Because an amorphous form is thermodynamically less stable than any crystalline form, inadvertent crystallization from an amorphous drug substance may occur. As a consequence of their higher mobility and ability to interact with moisture, amorphous drug substances are also more likely to undergo solid-state reactions.

A range of manufacturing processes can influence the polymorphic form of the drug substance in the dosage form. Processing-induced transformations of polymorphs are known but are often difficult to predict (23). Different effects of pharmaceutical processes on drug polymorphs, solvates, and phase conversions have been described in the literature (24). Processes such as lyophilization and spray-drying may result in the formation of an amorphous form. Process stresses such as drying, grinding, milling, wet granulation, and compaction, can accelerate the phase conversion of polymorphic solids. The extent of polymorphic conversion depends on the relative stability of the polymorphs, on the kinetic barriers for phase conversions, and on the type and degree of mechanical forces. Based on the potential for polymorphic conversion, the most stable polymorphic form is often selected and controlled during the entire manufacturing process. Nevertheless, phase conversions that may occur should generally not be of serious concern, provided they occur consistently and are reproducible as a part of a validated manufacturing process.

PHARMACEUTICAL SOLID POLYMORPHISM AND THE ISSUE OF "SAMENESS"

An ANDA must contain sufficient information to show that the drug substance is the "same" as that of the reference listed drug (RLD); otherwise, FDA will refuse to approve the ANDA. "Sameness" between the drug substance in the generic drug product and the RLD is established by demonstrating the same chemical structure, as appropriate. Because a drug substance that exists in different polymorphic forms or crystal habits has the same chemical structure, it has been concluded that polymorphism is not directly relevant in the determination of drug substance "sameness" (Fig. 1).

Moreover, differences in solubility of polymorphs of a drug substance may not necessarily lead to bioinequivalent products. Apart from dissolution, the rate and extent of oral drug absorption is also dependent on permeability, metabolic stability, and other physiologic factors (18,19). For example, in the case of ranitidine, whose absorption is limited by its intestinal permeability, both polymorphic forms I and II are bioequivalent. On the other hand, in the case of carbamazepine, whose absorption is limited by its dissolution, polymorphic forms I and III and the dihydrate are not bioequivalent (25). Because an ANDA applicant is required to demonstrate that the proposed product is bioequivalent to the RLD, it logically follows that pharmaceutical solid polymorphism has no relevance to the determination of drug substance "sameness."

Furthermore, drug product performance and stability are dependent not only on the solid-state characteristics of the active ingredient but also on the drug product formulation and on the process used to manufacture the drug product. Therefore, if the applicant demonstrates that the proposed drug product meets the standards for identity, is bioequivalent to the RLD, and exhibits sufficient stability, the drug substance in a proposed generic drug product need not have the same physical form (particle size, shape, or polymorph form) as the drug substance in the RLD.

Over the years FDA has approved many generic drug products based on a drug substance with a different physical form from that of the respective RLD (e.g., warfarin sodium, famotidine, and ranitidine). Also, many ANDAs have been approved in which the drug substance differed from that of the corresponding reference listed drug with respect to solvation or hydration state (e.g., terazosin hydrochloride, ampicillin, and cefadroxil).

Nonetheless, because polymorphs exhibit certain differences in physical properties (e.g., powder flow, compactability, apparent solubility, and dissolution rate) and solid-state chemistry (reactivity), they may affect drug product stability and bioavailability. Therefore, it is essential that, during drug product development and regulatory review, close attention be paid to pharmaceutical solid polymorphism. This scrutiny is essential to ensure that polymorphic differences (when present) are addressed via design and control of the formulation and manufacturing process to achieve physical and

chemical stability of the product over the intended shelf life and ensure bioavailability/bioequivalence.

CONSIDERATIONS OF POLYMORPHISM IN ANDAS

Decision Trees 1–3 in Figs. 2(a), 2(b), and 2(c) provide a suggested process for evaluating when and how polymorphs of drug substances are monitored and controlled in an ANDA submission. These decision trees were developed based on the ICH Guideline Q6A decision trees on polymorphism and adopt the concepts from the Biopharmaceutics Classification System. In general, polymorphic monitoring of drug substances for solutions is not necessary unless precipitation occurs and results in liquids containing undissolved drug substances.

Decision Tree 1 considers whether there is a need to set polymorphic acceptance criteria for drug substances and drug products. These decisions focus on polymorphs that could

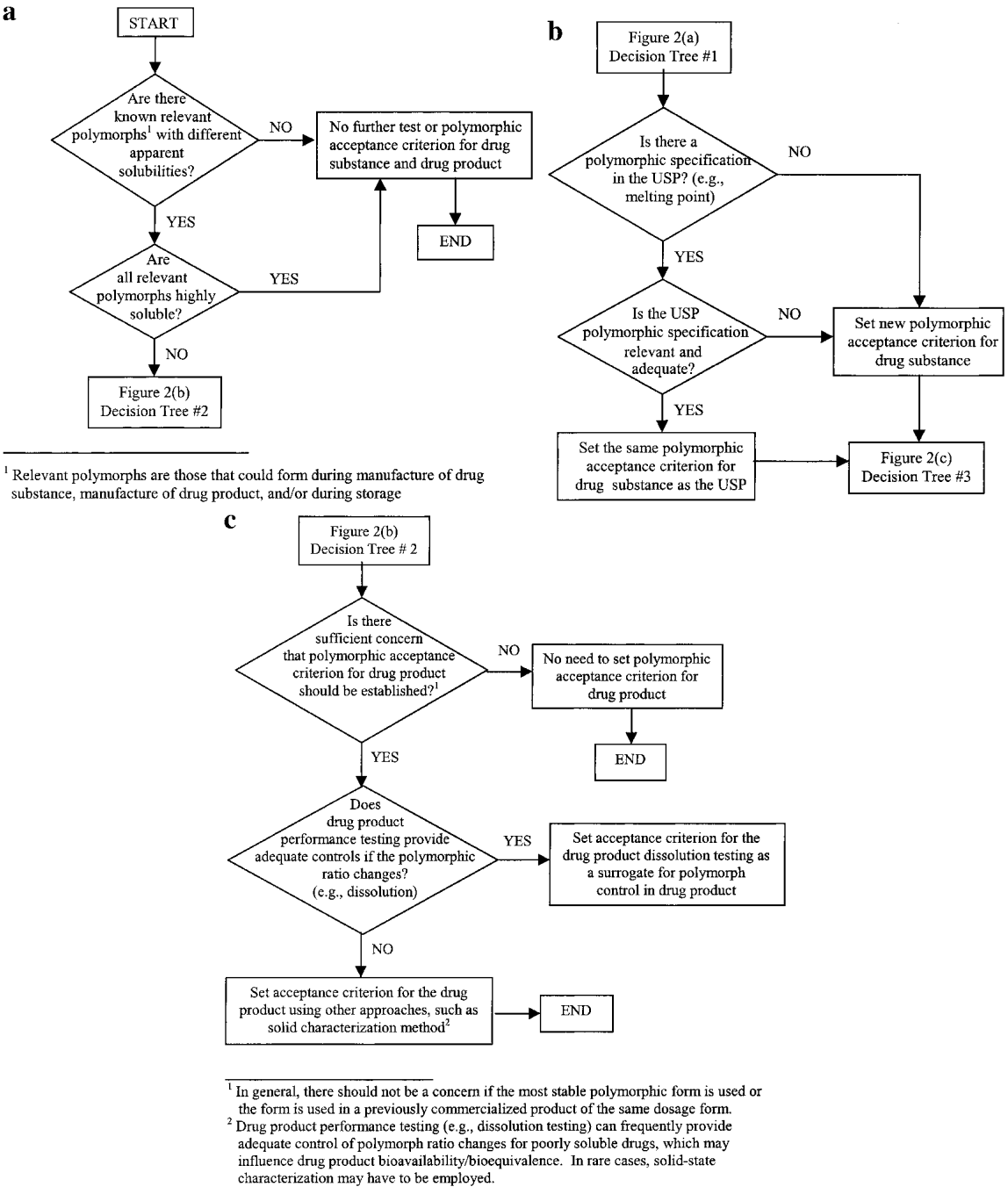

Fig. 2. (a) Decision Tree 1. Investigating the need to set acceptance criteria for polymorphs in drug substances and drug products in ANDAs for solid dosage forms or liquids containing undissolved drug substance. (b) Decision Tree 2. Investigating how to set acceptance criteria for polymorphs in drug substances in ANDAs for solid dosage forms or liquids containing undissolved drug substance. (c) Decision Tree 3. Investigating the need to set acceptance criteria for polymorphs in drug products in ANDAs for solid dosage forms or liquids containing undissolved drug substance.

form during manufacture of the drug substance or drug product or on storage. For example, a solvate containing a solvent that is not used in the manufacturing process would not be considered a "relevant" polymorph in the context of Decision Tree 1. If only a single relevant polymorph exists, all relevant polymorphs have no different apparent solubilities, or all relevant polymorphs are highly soluble, it is expected that polymorphism is unlikely to have a significant effect on bioavailability. It is recommended that adequate knowledge of drug substance polymorphs be available by the time an ANDA is filed. Adequate information on drug substance polymorphism may come from the scientific literature, patents, compendia, other references, and, in some cases, polymorph screening.

Decision Tree 2 discusses how to set a polymorph specification for a drug substance, given the fact that at least one polymorph is known to have low solubility based on the BCS. If the ANDA has the same polymorphic specification as defined in the USP, and the USP specification is adequate, no further polymorphic test or acceptance criteria for the drug substance beyond the existing USP methodology would be necessary. Otherwise, the ANDA applicant should establish a new polymorphic acceptance criterion for the drug substance.

Decision Tree 3 gives an approach if a polymorph specification for a drug product is sought. It is generally not necessary to have a polymorph specification for a drug product if the most stable polymorphic form is used or if the form is used in a previously commercialized product. However, because the manufacturing process can potentially impact polymorphism of a drug substance, caution must be taken if the form in the previously commercialized product is amorphous or is a hydrate. Furthermore, drug product performance testing (e.g., dissolution testing) can frequently provide adequate control of polymorph ratio changes for poorly soluble drugs, which may influence drug product bioavailability/bioequivalence. In rare cases, solid-state characterization may have to be used.

SUMMARY

This commentary proposes recommendations for monitoring and controlling drug substance polymorphs and discusses scientific considerations of pharmaceutical solid polymorphism in the determination of drug substance "sameness." Decision trees for solid oral dosage forms or liquids containing undissolved drug substances are developed based on the ICH Guideline Q6A decision trees on polymorphism and on the solubility classification concept from the Biopharmaceutics Classification System. These are presented as tools for determining if there is a scientific need to establish polymorphic acceptance criteria for drug substances and drug products and, if appropriate, for assisting in the establishment of such acceptance criteria. It is scientifically concluded that differences in polymorphic composition of drug substances in generic drug products and reference listed drugs are not directly relevant in the determination of drug substance "sameness" in ANDAs. FDA has approved generic drug products with different polymorphic form, and no safety or efficacy issues have ensued.

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