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Pharmaceutical solvates, hydrates and amorphous forms: A special emphasis on cocrystals☆

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ABSTRACT

Active pharmaceutical ingredients (APIs) may exist in various solid forms, which can lead to differences in the intermolecular interactions, affecting the internal energy and enthalpy, and the degree of disorder, affecting the entropy. Differences in solid forms often lead to differences in thermodynamic parameters and physicochemical properties for example solubility, dissolution rate, stability and mechanical properties of APIs and excipients. Hence, solid forms of APIs play a vital role in drug discovery and development in the context of optimization of bioavailability, filing intellectual property rights and developing suitable manufacturing methods. In this review, the fundamental characteristics and trends observed for pharmaceutical hydrates, solvates and amorphous forms are presented, with special emphasis, due to their relative abundance, on pharmaceutical hydrates with single and two-component (i.e. cocrystal) host molecules.

Contents

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1. Introduction

Pharmaceutical solids are classified as thermodynamically stable crystalline and unstable amorphous forms. A crystalline solid can be characterized by the presence of three-dimensional long-range order. However, amorphous solids are characterized by the presence of random atomic structure and a short range order of molecules. These molecules are randomly oriented in different directions and show different conformational states. The lack of three-dimensional long-range order is commonly manifested as a diffuse X-ray diffraction pattern and lack of melting endotherm [1]. A mesophase material (e.g. liquid crystals) is described as having intermediate symmetry, while the amorphous state shows no symmetry (Fig. 1) [2,3]. Such differences in the range of molecular or atomic order and packing properties can lead to differences in pharmaceutically relevant physicochemical properties such as flow, compression properties, hardness, density, solubility and bioavailability [1]. Some studies caution that what appears to be an amorphous solid may not be a completely amorphous phase, but can comprise some structurally ordered components (Fig. 1), insufficient to signify crystallinity by routine analysis techniques [4,5].

The behavior of amorphous materials can be elucidated by changes in thermodynamic parameters (free volume, enthalpy and entropy) with a variation in temperature. Amorphous solids are further characterized by the absence of distinctive melting points. When the molar volume or heat content of an amorphous sample is plotted against the temperature, these variables vary smoothly until it comes to the region known as glass transition temperature (T_g), where they change sharply. The T_g can be defined as the temperature at which a material is converted from an equilibrium super-cooled state to a non-equilibrium glassy state during cooling or vice versa during heating, and is manifested as a step change in heat flow due to an abrupt change in heat capacity during the heating. A glass transition is a thermodynamic event that is associated with structural relaxation of the amorphous material which, in turn, depends on heating rate [6]. The physicochemical properties of the amorphous materials vary in the glassy compared to the supercooled state [7]. Amorphous solids in the glassy state have rheological properties of solids, but have a high molecular mobility [8].

The solubilisation of crystalline solids comprises of three processes: solvation, cavitation and disruption of crystal packing. The disruption of the crystal lattice by a solvent requires energy input during the dissolution process. Amorphous systems do not require the breakage of the crystal lattice and hence they have a solubility advantage compared to the equivalent crystal solid forms [9]. An important characteristic of amorphous forms is that they are thermodynamically unstable, and tend to crystallize with time, which is generally associated with an increase in density, higher density being a characteristic feature of the crystalline form [8].

Crystalline systems may exist in various polymorphic forms, containing the same elemental composition and characterized by differences in unit cell structure arising from packing or conformational disparities. Mitscherlich (in 1822 and 1823) was the first to use the term polymorphism in crystallography, even though this term has been used in a variety of disciplines [10]. Active pharmaceutical ingredients (APIs) and excipients may contain solvent(s) in the crystal structure. The term hydrate is used for crystal structures that contain water molecule(s) in the crystal lattice. Solvated organic compounds contain a solvent of crystallization other than water. Pfeiffer et al. [11] suggested a classification system based on the crystallographic characteristics of solvated and desolvated crystalline compounds. For the hydrated and solvated APIs, cephalexin hydrate and hydrocortisone *tert*-butylacetate ethanolate, the crystal structures remain intact after desolvation and the powder diffraction patterns are similar. Such systems were identified as pseudopolymorphic forms, whereas solvated or hydrated APIs (deoxyadenosine hydrate, cytosine hydrate, and 5-nitouracil hydrate) that transform into a new crystal structure after desolvation were classified as polymorphic solvates. Thus, polymorphic solvates will have different X-ray powder diffraction patterns due to the difference in crystal structure [11,12]. Recently the term "pseudopolymorphism" has become more commonly used for all crystal structures with differences in elemental composition due to the presence of solvent molecules in the crystal structure. The term "solvatomorphism" has also been used repeatedly in books and publications instead of "pseudopolymorphism" [13]. Both polymorphic and amorphous forms are considered as a special type of polymorphism according to FDA guidelines [14].

In this manuscript we review the fundamental characteristics and trends observed for pharmaceutical hydrates, solvates and amorphous forms, placing special emphasis on pharmaceutical hydrates comprising both single and two-components (i.e. cocrystals). We briefly discuss basic concepts related to pharmaceutical solvates, hydrates and related amorphous forms. We consider factors influencing amorphisation of crystalline and cocrystalline forms and present advances in tools for characterization of different solid states. In describing these various solid state forms our objective is to make particular reference throughout to cocrystals (or equivalent coamorphous forms).

2. Pharmaceutical hydrates and solvates

Different polymorphic or pseudopolymorphic forms often show differences in physicochemical properties, for example, hygroscopicity, solubility, surface chemistry, stability, and processability. For example, stable and metastable carbamazepine can transform to the dihydrate form when exposed to water vapor at 37 °C [15]. The dihydrate of carbamazepine can also be generated by cooling crystallization from a saturated ethanol solution [16]. The stable anhydrous form I of carbamazepine showed a marked improvement in dose-dependent bioavailability (both C_{max} and AUC) compared to the dihydrate form [17]. Different physical properties can have a significant effect on dosage form design and the selection of manufacturing routes. The appropriate