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Review

Crystalline Multicomponent Solids: An Alternative for Addressing the Hygroscopicity Issue in Pharmaceutical Materials

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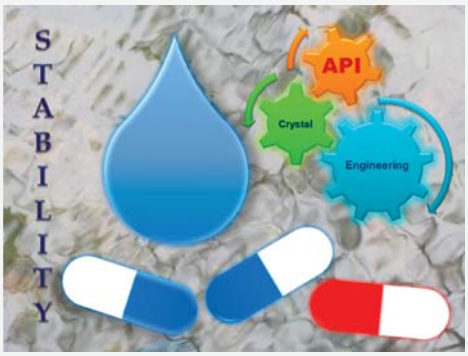
ABSTRACT: The ambient humidity varies with seasons and geographical altitude across the regions. A change in relative humidity during processing, storage, and transportation can cause instability to the active pharmaceutical ingredient (API) solid form, which may sometimes lead to the formation of hydrates, decomposition, and dissociation (or disproportionation) of the drug product. A thorough understanding of the interaction of crystalline solid with atmospheric water is necessary to understand this phenomenon and to develop a potential solution to this problem. In this review, we discuss various aspects of this phenomenon along with some examples from the literature wherein the physical stability enhancement of an API is addressed through the multicomponent solid form (salts, cocrystals, and eutectics) development. The review also presents an overview of computational approaches employed to predict the hydration behavior of an API, their susceptibility to form hydrates, and studies on the crystal structure prediction of hydrates. Additionally, a few representative studies highlighting the moisture-induced phase transformations to polymorphs, hydrates, and cocrystal formation and their dissociation are discussed.



INTRODUCTION

The physical stability of solids is assessed based on its susceptibility to absorb atmospheric water or moisture. A solid is called hygroscopic if it absorbs, retains, or releases water or can become deliquescent. Water intake by a hygroscopic active pharmaceutical ingredient (API) solid form can happen anytime during processing (crystallization, lyophilization,[1] wet granulation, compaction, and spray drying), storage, and transport. Hygroscopic behavior can lead to alteration in various physicochemical properties of solids such as crystallinity, stability (physical and chemical), solubility, dissolution behavior, bioavailability, wettability, powder flow property, powder compactibility, and hardness.[2−6] Moisture uptake by solids can lead to the formation of clumps, crusts, and layers, which can cause problems during materials processing. The interaction of solids with atmospheric water can also induce an anhydrate−hydrate type phase transformation, and it can also facilitate interaction between drug and excipients, which may sometime trigger the formation of new multicomponent phases.[7−11] The undesirable transformation of an anhydrous form to a hydrate alters the crystal packing that induces change in the stability, solubility, and bioavailability of the drug.[12−15] Thus, an early assessment of the possibility of hydration and/or the hygroscopic behavior of the API solid form is an essential step in the pharmaceutical industry. Hygroscopicity of crystalline solids (crystalline salts, cocrystals, polymorphs) is mainly governed by adsorption, whereas that of amorphous solids (amorphous drug, coamorphous solids/salts) is by an absorption process. The formation of an unwanted, stable hydrate of API with poor physicochemical attributes may require immediate crystal engineering intervention to develop new solid forms such as cocrystals or salts as alternatives. Hygroscopic behavior can also reduce the effectiveness of solid dosage forms. For example, the solid particles used in aerosols or dry powder inhalers intended for pulmonary administration are generally exposed to high temperatures and humid environments inside the lungs. Such extreme conditions can cause hygroscopic growth (an increase in the particle size) on exposure to high relative humidity, which in turn affects their deposition and distribution inside the lungs.[16] The hygroscopicity property of excipients has also been exploited to obtain a better aerosol delivery efficiency through an excipient enhanced growth (EEG) strategy.[17] The EEG strategy uses smaller sub-micrometer size particles for delivery to minimize loss due to the deposition of particles in the mouth-throat region. It uses a hygroscopic excipient in the aerosol particles, which exhibit hygroscopic growth in the humid environment in

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