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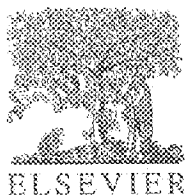
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Pharmaceutical hydrates

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Abstract

A hydrate is a solid adduct containing both the parent compound (e.g., the anhydrate of a drug or excipient) and water. This review discusses only the crystalline stoichiometric hydrates in which the environment of the water molecules exhibits various defined patterns, and emphasizes pharmaceutical hydrates and their behavior. The presence of the water molecules influences the intermolecular interactions (affecting the internal energy and enthalpy) and the crystalline disorder (entropy), and hence influences the free energy, thermodynamic activity, solubility, dissolution rate, stability, and bioavailability. In addition, many solid-state properties are altered, including mechanical behavior, such as tableting, grinding, and product performance. The physicochemical characterization of hydrates is included in a flow chart of questions to be answered as part of a "decision tree" during the process of product development. Pharmaceutical hydrates may be characterized by a variety of complementary physicochemical methods most of which are well-known. This review details the characterization of hydrates by solid-state nuclear magnetic resonance spectroscopy, Raman spectroscopy, and isothermal microcalorimetry, and considers a variety of pharmaceutical examples.

Keywords: Bioavailability; Dehydration; Drug; Hydrate; Pseudo-polymorphism; Stability

1. Introduction

Pharmaceutical solids may come in contact with water during processing steps, such as crystallization, lyophilization, wet granulation, aqueous film-coating or

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spray-drying. Moreover, they may be exposed to water during storage in an atmosphere containing water vapor or in a dosage form consisting of materials that contain water and are capable of transferring it to other ingredients. Water may be adsorbed onto the solid surface and/or may be absorbed in the bulk solid structure. The former is dependent on the specific surface area while the latter is independent of the specific surface area of the solid [1].

With some crystalline solids, solvent in the surrounding medium may become incorporated into the crystal lattice of the compound in stoichiometric proportions. These molecular adducts are termed solvates. Hydrates are formed when water is the solvent of crystallization. In hydrates water occupies definite positions in the crystal lattice, usually by forming hydrogen bond(s) and/or coordinate covalent bond(s) with the anhydrate drug molecules. This article discusses only the crystalline stoichiometric hydrates in pharmaceutical solids.

Incorporation of the solvent molecules into the crystal lattice produces a new unit cell different from that of the anhydrate and, consequently, the physical properties of the solvate may differ from those of the anhydrate. This effect is analogous to polymorphism, a term which indicates the existence of at least two different crystal structures of the same chemical substance, although solvates are strictly molecular adducts. To distinguish solvates from polymorphs, the term pseudopolymorphs has been applied to solvates [2]. Like many other chemical compounds, however, certain solvates may themselves exhibit polymorphism, as in the case of fluprednisolone monohydrate [3], succinyl sulfathiazole monohydrate [4], and nedocromil sodium monohydrate [5]. It is important to emphasize that the two crystal forms must have the same stoichiometry in order to be termed polymorphs.

2. Nature of the water molecule environment in hydrates

The water molecule H_2O behaves as if it consists of a tetrahedral distribution of two positive and two negative regions of charge. On each negatively charged region, the water molecule interacts with its neighbors via a coordinate covalent (dative) bond or by accepting a hydrogen bond. On each positively charged region the water molecule interacts with its neighbors via a donated hydrogen bond. Thus, the neighbors of a water molecule in a hydrate include electron acceptor groups (or proton donors), such as M^{n+} , $R-OH$, R_1R_2NH , and electron donor groups (or proton acceptors), such as $R-COO^-$, $R-O^-$, Cl^- . The neighbors of a water molecule may include other water molecules suitably oriented for hydrogen bond formation. The water molecule may also participate in the various types of van der Waals' interaction (dipole-dipole, dipole-induced dipole and dispersion forces).

Some of the numerous possible environments of a water molecule in a hydrate are presented in Fig. 1. Wells [6] has proposed a classification of water molecules in hydrates based on the number of nearest H_2O neighbors. Fig. 1 shows that a water molecule in a hydrate may have (a) four, (b) three, (c) two, (d) one or (e) zero water molecules as nearest neighbors. When several types of water molecule occur in the same crystal structure, finite or infinite hydrogen-bonded water

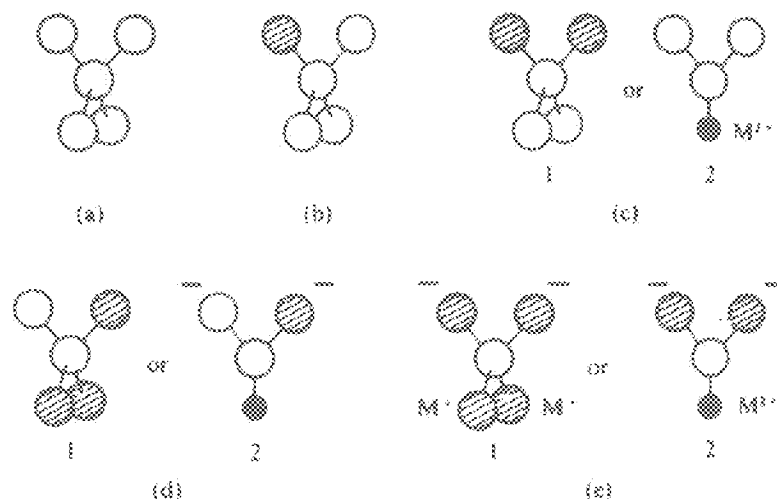


Fig. 1. Environment of water molecules in hydrates. The non-shaded larger circles represent water molecules, the smaller shaded circles represent multivalent metal ions, and the larger shaded circles represent univalent metal ions or any electron accepting (or proton donating) groups or electron donating (or proton accepting) groups other than water. (Reproduced from Ref. [6] with the permission of the copyright owner, Clarendon Press, Oxford, UK.)

networks may be formed [7]. Thus, water molecules in Fig. 1(a) and (b) will yield all possible types up to and including three-dimensional water networks; Fig. 1(c) occurs in rings or chains of water molecules (*n*mers, $3 \leq n \leq \text{infinity}$); Fig. 1(d) occurs in pairs (dimers) of water molecules, while Fig. 1(e) represents a single (monomer) water molecule (associated with metal ions in the case of salt hydrates).

3. Reasons for the differences in the physical properties of hydrates

Incorporation of the water molecule(s) in the crystal lattice of the anhydrate or a lower hydrate changes the dimensions, shape, symmetry and capacity (number of molecules, *z*) of the unit cell. As a result, the anhydrate and each hydrate of a given chemical compound exhibit different physical properties as described below [8].

A change in the volume of the unit cell upon hydration corresponds to a change in the molar volume and hence to a change in the density of the substance. Incorporation of water molecules into the crystal lattice of the anhydrate or of the lower hydrate alters the following behavior of the crystals: (a) the interaction of the electron vibrations with light quanta changing the refractive index; (b) the interactions of the molecular motions with heat quanta changing the thermal conductivity; (c) the movement of the electrons in an electric field changing the electrical conductivity. Formation of additional bonds between the host molecules and the water molecules and changes in the bonding between the host molecules themselves alter the cooperativity of the molecules in the crystal lattice and hence alter the melting point.

Fig. 2 summarizes the effect of hydration of a drug on its physical properties [5]. Incorporation of the water molecule(s) into the crystal lattice of the anhydrate or of a lower hydrate changes the intermolecular interactions within the solid and

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