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GENETIC ENGINEERING TO HYDROGELS

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Hydrates

Introduction

During the development of a new drug, from the synthetic process to dosage form design, the interaction of water with the solid form is of great concern since it affects bulk properties and chemical stability. A major consideration in preformulation studies is to define the ability of the drug powder to take up water and to characterize the state of this water, because this information is relevant in developing strategies for the process and storage of dosage forms.

It is important to know the mechanism of water uptake, where the water is located, and the nature of the water molecule environment. The water vapor–solid interaction may result in surface adsorption (physisorption or chemisorption) or incorporation into the bulk (interstitial voids or part of the crystal lattice). This article describes the latter, that is, solids that form solvates and in the case of water, hydrates. The water molecule in these crystals is frequently involved in hydrogen bonds and contributes to the coherence of the crystal structure.

Most of the work in the pharmaceutical literature involving hydrates has focused on their characterization [1–4], vapor–solid interactions [5], and hydration–dehydration kinetics in the solid state [6]. Some work [7–9] has addressed the consequences of the hydrate choice on the thermodynamic properties of the solid and on pharmaceutical properties such as dissolution and bioavailability. To date, little emphasis has been placed on liquid–solid interactions and the phase changes that may result during crystallization.

It is essential to define the transformations between solid phases in the development of a dosage form, since the presence of a metastable phase during processing or in the final product could result in a system that is in continuous evolution and instability in drug release. Erratic bioavailability of theophylline [10] and carbamazepine [11] from solid dosage forms has been reported to be the result of a phase change caused by the formation of a hydrate during dissolution. Crystallization in tablets that have been in contact with water has been observed for caffeine [12], theophylline [13], carbamazepine [14], lactose [15], and mannitol [16].

In the case of a solid that exists in various hydrated forms, possible transformations associated with exposure to water are of interest in both the liquid and the vapor states, for instance, during solubility measurements, wet granulation processes, dissolution studies, and accelerated stability tests.

Questions that may need to be answered are:

- Does the solid exist as a hydrate? How is the water incorporated?
- What is the range of relative humidities and temperatures in which the desired hydrate is thermodynamically stable?

- How will the hydrated or anhydrous solid form be prepared? By crystallization from liquid solution or by vapor sorption–desorption?
- Is a metastable solid phase desired? How do interactions at the solid–vapor and solid–liquid interfaces affect the transformation rate?

In this article, the thermodynamic, crystallographic, and kinetic aspects of phase transformations associated with hydrates are discussed, as well as the methods used for their characterization.

Hydrogen Bonding Mechanism in Hydrates

The ability of water to form hydrogen bonds and hydrogen-bonding networks gives it a unique behavior with respect to colligative properties such as boiling and melting points. Similarly, hydrogen bonding between water molecules and drug molecules in the solid state dictates its role in the structure of all classes of crystalline hydrates. Water is, of course, hydrogen bonded whenever physically possible. This may take the form of hydrogen bonding to other water molecules, functional groups on other molecules, or anions. Hydrogen bonding to other water molecules is common both in the crystal lattice and in interstitial cavities or channels. Hydrogen bonding to other moieties and anions in crystalline hydrates is primarily within the lattice. In addition, the lone-pair electrons on the water oxygen may be associated with metallic cations present in many salts. This interaction is largely electrostatic in nature for the metal cations common to pharmaceutics (Na, Ca, K, Mg). These metals lack the ability (*d*-orbitals of proper energy) to form coordinate covalent or coordination bonds that some transition metals may form with oxygen. It is often stated that Mg has a coordination number of 4. However, this is a result of packing (or geometric) restrictions, arising when fitting water molecules around the cation in response to the electrostatic attraction. Since these "bonds" are electrostatic, they are not properly described quantum mechanically by a molecular orbital, but rather by classical electrostatics [18]. These bonds are often stronger than hydrogen bonds with less directional dependence. A typical water hydrogen bond is on the order of 19 kJ/mol (4.5 kcal/mol), whereas a sodium–oxygen lone-pair electrostatic interaction can be four to five times stronger [18]. These bonds also exert their influence through hydrogen bonds in the form of cooperative effects. The specific characteristics of the hydrogen bond are discussed here in the formalism of Falk and Knop [17].

The ubiquitous hydrogen bonding of water is largely a result of the fact that it is both a hydrogen-bond donor and acceptor. It may participate in as many as four hydrogen bonds, one from each hydrogen and one for each lone pair on the oxygen. Classification schemes based solely on the type of coordination of the water oxygen have been proposed [17]. As each bond is formed, it makes the other sites more attractive as partners for additional bonds. Hydrogen-bond acceptors must be electronegative and include oxygen from other water molecules, oxygen and nitrogen from other functional groups, and chlorine. Hydrogen-bond donors include protons on nitrogen, oxygen, and sulfur, usually found on water, alcohols, amines, etc.

Free water (vapor) has an OH bond length of 0.0957 nm (0.957 Å) and an HOH angle of 104.52°. As soon as the molecule starts interacting with other molecules through hydrogen bonds, coordination, or other electrostatic bonds, the molecule is distorted from its free conformation. The OH bond length usually increases up to 0.01 nm for an exceptionally strong hydrogen bond, but is more typically on the order of 0.001 to 0.002 nm for organic hydrates with hydrogen bond lengths of 0.27 to 0.29 nm (O—O distance). Depending on the hybridization of the water oxygen as sp^2 (trigonal coordination) or sp^3 (tetrahedral), the HOH angle is more typically 109.5 and 120°, respectively.

The limits of length of a hydrogen bond are bound on the lower end by the van der Waals radii of the two atoms, and on the upper end arbitrarily by the length of the weakest hydrogen bond observed. This can be seen more quantitatively by expressing the hydrogen bond distances shown in Fig. 1 in terms of the van der Waal radii, as in Eq. (1).

$$R(H\text{--}Y) < r(H) + r(Y) - 0.02 \text{ nm} \tag{1}$$

Since r(H) = 0.12 nm, R(H--Y) < r(Y) − 0.1 nm where 0.02 nm is the combined experimental and statistical uncertainty. The compounds studies by Falk and Knop [17] were inorganic and small organic hydrates. Of the 129 compounds studied, only one failed this criterion. Hydrogen bond lengths are often given as the distance between O and Y (e.g., oxygen–oxygen or oxygen–chlorine). This is because in x-ray diffraction studies it is often difficult or impossible to accurately locate the hydrogen atoms due to their inherently low scattering and their relatively high mobility. (Because of the large cross-sections, hydrogens are often located by neutron diffraction studies.) Under these circumstances, crystallographers report

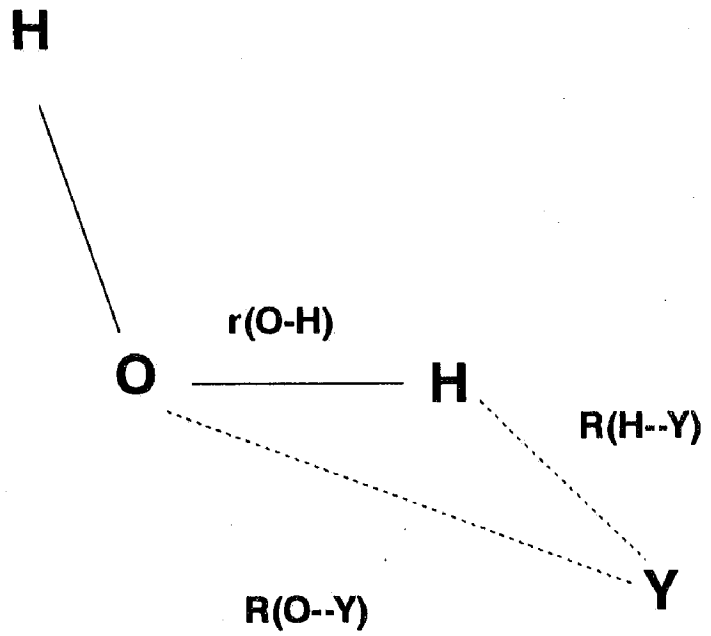

FIG. 1. Formalism used in the discussion of hydrogen-bond strength and length [17].

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