

Water Clusters in Amorphous Pharmaceuticals

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ABSTRACT: Amorphous materials, although lacking the long-range translational and rotational order of crystalline and liquid crystalline materials, possess certain local (short-range) structure. This paper reviews the distribution of one particular component present in all amorphous pharmaceuticals, that is, water. Based on the current understanding of the structure of water, water molecules can exist in either unclustered form or as aggregates (clusters) of different sizes and geometries. Water clusters are reported in a range of amorphous systems including carbohydrates and their aqueous solutions, synthetic polymers, and proteins. Evidence of water clustering is obtained by various methods that include neutron and X-ray scattering, molecular dynamics simulation, water sorption isotherm, concentration dependence of the calorimetric T_g , dielectric relaxation, and nuclear magnetic resonance. A review of the published data suggests that clustering depends on water concentration, with unclustered water molecules existing at low water contents, whereas clusters form at intermediate water contents. The transition from water clusters to unclustered water molecules can be expected to change water dependence of pharmaceutical properties, such as rates of degradation. We conclude that a mechanistic understanding of the impact of water on the stability of amorphous pharmaceuticals would require systematic studies of water distribution and clustering, while such investigations are lacking. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 103:2663–2672, 2014

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INTRODUCTION

Amorphous solid (glassy) states are ubiquitous in both natural (e.g., dehydrated drought- and frost-resistant organisms) and man-made or processed (e.g., freeze-dried pharmaceutical and biopharmaceutical) systems.^{1–9} In practically all the cases, such amorphous systems contain a certain amount of water, which can range from less than 1% (w/w) (as in freeze-dried materials) to 30% (w/w) or more, as with maximally freeze-concentrated solutions of sugars and proteins. Because of the ubiquity of amorphous states in pharmaceutical materials, and the fact that the presence of water has a major impact on their stability, there are numerous studies of various aspects of water relationships in amorphous solids. Major efforts have been devoted to the investigation of the impact of water on the molecular mobility, including the relationship between the glass transition temperature and water content^{10–12} and the interaction between water vapor and amorphous solids.^{13–16} More recently, the subject of the structure of amorphous solids has also attracted the attention of the pharmaceutical science community.^{17–20} In particular, the heterogeneous nature of amorphous solids, which are proposed to consist of domains with local (short-range) order resembling local arrangements in the crystal lattice, has been emphasized.¹⁸ The lack of translational and rotational coordination of molecules belonging to different domains results in the loss of the long-range order. The origin of this domain-structure concept is probably related to the Adam–

Gibbs theory²¹ of cooperatively rearranging clusters, with heterogeneity length scale corresponding to the cluster size.

In the reviews on the structure of amorphous pharmaceutical solids, however, water distribution has not been considered in any detail, and the intention of the present paper is to highlight this gap. In particular, one could raise several relevant questions, such as: (1) Are water molecules distributed homogeneously, or do they form clusters in certain conditions?; (2) What are conditions for cluster formation, that is, type of system, water content, and temperature?; (iii) What are the properties of these clusters, for example, size; Are they similar to three-dimensional droplets of a minor “phase” or two-dimensional chains of water molecules?; (iv) What is the impact of water clusters on the properties and performance of amorphous pharmaceutical materials? For example, it would be natural to expect that water impact on stability (both physical and chemical) could depend on the clustering patterns.

The paper starts with a brief overview of water distribution in solutions. This appears to be a necessary starting point as we consider the wealth of studies on water clustering and distribution in amorphous liquid systems. In addition, solution chemistry approaches were extended to describe particular features of amorphous pharmaceutical solids.^{22,23} After a consideration of the distribution of water in mixed solvent systems in section *Water Clusters in Solutions*, two important types of pharmaceutical glass-forming constituent materials, that is, polyhydroxycompounds (PHCs) and polymers, will be discussed in some detail in sections *Water Distribution in Concentrated Solutions of Sugars and Sugar Alcohols and Their Glasses* and *Water in Polymers*. The potential pharmaceutical relevance of water clustering will be highlighted in section *Significance for Pharmaceutical Science*, which will also emphasize the scarcity

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of direct studies of water clustering in pharmaceutical systems. We will conclude that water molecules can exist in unclustered form or as aggregates (clusters) of different sizes and geometry, both in solutions and amorphous solids. Clustering depends on water concentration, with unclustered water molecules existing at lower water contents, whereas clusters form at intermediate water contents. It is proposed that studies on water clustering would greatly facilitate the development of a quantitative understanding in such practically important areas as the relationships between water content and chemical degradation in freeze-dried and other amorphous pharmaceuticals, the stabilization of amorphous materials by annealing, and the cryopreservation of proteins and biopharmaceuticals.

WATER CLUSTERS IN SOLUTIONS

In contrast to other solid materials such as crystals and crystalline mesophases, amorphous solids do not possess long-range translational and rotational order. However, all condensed phases, including both amorphous solids (glasses) and amorphous liquids, have short-range structure (local ordering). Because of the structural similarity, and also considering the fact that many pharmaceutical glasses, such as freeze-dried powders, are produced from aqueous solutions, a brief consideration of the distribution of water molecules in the liquid state would be a logical starting point. In addition, there is emerging evidence that important features of chemical processes in glasses resemble those in solutions.²⁴

Various liquid systems exhibit clustering of solvent and/or solute molecules that results in inhomogeneity on the nm-length-scale.^{25–29} In particular, the concept of water clusters is central to the subject of the structure of water and aqueous solutions. In a seminal paper, Frank and Wen proposed that water consisted of flickering clusters of various size and shapes, with half-lives of 10^{-11} – 10^{-12} s.³⁰ The Frank–Wen model, with the addition of unclustered water proposed by Nemethy and Sheraga,³¹ is represented in Figure 1. More recently, a two-

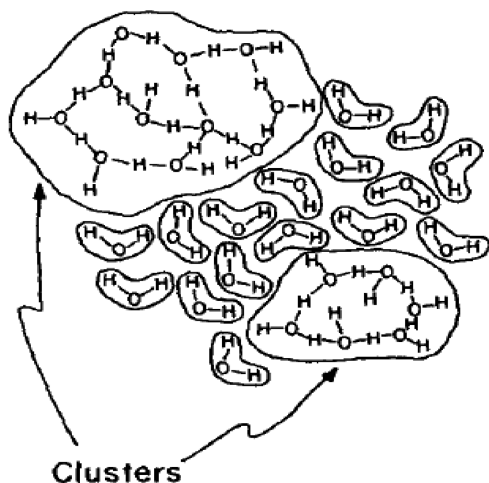


Figure 1. Schematic representation of the model of liquid water, showing hydrogen-bonded clusters and unclustered water molecules. The molecules in the interior of the clusters are tetracoordinated, but not drawn as such in this two-dimensional diagram. The representation is based on the Frank–Wen model of liquid water. The Figure is reproduced from Ref. 31 with permission of the AIP Publishing LLC.

fluid model of water and aqueous solutions has been suggested on the basis of quantum electrodynamic considerations,²⁵ in which coherent domains (or a coherent phase, CD) coexist with a noncoherent phase (NCP). In this model, CD molecules can be considered as equivalent to water clusters, whereas the NCP would represent unclustered water molecules.

It is commonly accepted that an understanding of local structure is essential in studies of various chemical and physical processes. In such fundamental processes, as proton transfer in water, for example, three-coordinated water molecules provide the most favorable configuration for proton transfer.³² Furthermore, a study of microscopic structure and clustering in water–alcohol mixtures was used to understand solvent effects in various physicochemical processes, such as fluorescence quantum yield for 10-hexylacridineorange, the fluorescence lifetime of acridine, the fluorescence pattern of pyrene, and the rate constant for the hydrolysis of t-BuCl.³³ In another example, the structure of water clusters, in particular, the formation of six-member rings with long-lasting hydrogen bonds (lifetime >2 ns), was shown to be essential to the nucleation of ice in supercooled water.³⁴ In addition, the size of the clusters associated with crystallization was observed to be 150–300 molecules, although the relatively small size of the system studied consisting of 512 water molecules might not be sufficient to make a solid conclusion about the size effects.

Even in highly miscible organic solvent–water mixtures, water and cosolvent molecules are not necessarily distributed homogeneously, as taken into account by various thermodynamics models of binary liquid solutions such as Wilson’s model, NRTL model, and UNIQUAC model. These models account for microheterogeneity; they assume that the local composition around a molecule of compound “1” is different from the local composition around a molecule of compound “2,” the local compositions being driven by the 1–1, 2–2, and 1–2 interaction energies.³⁵ In a systematic investigation of thermodynamic properties of water–alcohol systems,^{36,37} three composition regions have been identified in each of which the mixing behavior is qualitatively different from the other regions.³⁸ Region III, the low-water (water-poor) content region, is the most relevant from the perspectives of this paper. In this region, water behavior has been shown to depend on the molecular weight and chain length of the alcohol present. For smaller alcohol molecules, water molecules interact with the OH-groups of clustered alcohol molecules predominantly as single molecules. The water–water interaction is enthalpically unfavorable and entropically favorable for lower molecular weight alcohols. However, water–water interactions become more enthalpically favorable as water content increases. For larger alcohol molecules, water molecules form clusters around the alcoholic OH-groups even in the low-water region, water being more structured in these clusters than in bulk water.

A comprehensive investigation of water clusters in binary alcohol–water mixtures (methanol, ethanol, 1-propanol, and glycerol) at different temperatures has been performed by wide-angle neutron scattering.^{39–41} For example, water clustering was observed at a methanol concentration of 0.27–0.7 mol fraction, with the percolation threshold between 0.54 and 0.7 mol fraction of methanol.⁴⁰ It should be stressed again that formation of water clusters depends on water concentration, as shown in a neutron scattering study of water–glycerol solutions.⁴¹ At a lower water concentration of approximately 5 wt %, water exists as monomers with water molecules distributed

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