# The State of Water and Its Impact on Pharmaceutical Systems: Lipid-Based Drug Delivery Systems and Amorphous Solids

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## Abbreviations

| | |
|---|---|
| DOPC | 1,2-Dioleoyl-*sn*-glycero-3-phosphocholine |
| IMC | Indomethacin |
| MD | Molecular dynamics |
| PVAc | Polyvinylacetate |
| PVP | Polyvinylpyrrolidone |
| RH | Relative humidity |

## 1 Introduction

Physicochemical properties relevant to aqueous pharmaceutical formulations such as drug solubility and stability have clearly been a focal point of research for many decades. As a result, pharmaceutical scientists have access to a large body of knowledge that provides a framework for understanding the properties of drugs in aqueous solution, such as the kinetics and mechanisms of their degradation, solubility as influenced by ionizable substituents and various solution equilibria, etc. However, most drug products are manufactured, stored, and most frequently administered as solid formulations (e.g., tablets, capsules, suppositories, polymer implants, transdermal patches) rather than as aqueous solutions or suspensions. For these nonaqueous systems, the state of current understanding of the equilibria and kinetics that govern performance is less advanced. Recently, interest in various nonaqueous delivery systems has been increasing because, as drug potency has

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received greater emphasis during the selection of new drug candidates, the lead compounds emerging from these selection processes tend to be more lipophilic and less water soluble. Consequently, a variety of amorphous or lipid-based delivery systems such as self-emulsifying or self-microemulsifying lipid dispersions often administered in soft gelatin capsule form for oral delivery are now being considered for commercialization. Similarly, various types of colloidal or nanoparticle formulations (e.g., nanosuspensions, solid-lipid nanoparticles, liposomes, micelles, polymeric micelles) in which the drug is suspended as a nano-sized particle or incorporated into a lipid particle have become increasingly attractive as possible vehicles for enhancing the bioavailability of orally administered drugs having poor water solubility, controlling drug release, enabling intravenous injection of nearly insoluble compounds, reducing side effects after intravenous administration, and in some cases providing enhanced permeability and retention in tumor tissue for the treatment of cancer.

In all of the aforementioned solid formulations, lipid dispersions, and nanoparticle or colloidal systems, the drug molecules may reside largely in a nonaqueous environment. Nevertheless, water is ever present in such environments and may have an impact on the formulation properties that is disproportionate in terms of the wt% of water present. Removing all water from a product and preventing atmospheric moisture from diffusing into a product are virtually impossible. The small size of a water molecule enhances its diffusivity through packaging materials and the drug formulation matrix, while the low molecular weight of water means that even trace quantities of water may represent a significant molar percentage in relation to the active pharmaceutical ingredient.

After administration of one of the above solid or lipid-based drug delivery systems to a patient, the uptake of water into the formulation matrix and its interactions with various components of the formulation remain of interest but for quite different reasons. In such cases, water is no longer a contaminant to be avoided. Rather, it becomes essential in facilitating dispersion of the delivery system and ultimately governs the kinetics of drug release and overall bioavailability. Many lipid dispersions and amorphous solid dispersions have recently been designed with the intent of producing supersaturated aqueous solutions of the drug after their administration in order to promote oral bioavailability. For these systems, understanding how to optimize performance extends beyond knowledge of their equilibrium properties and will ultimately require a deeper understanding of the dynamics of water uptake and the effect of water on other processes that influence delivery system performance.

Our laboratory has been employing both experiments and molecular dynamics (MD) computer simulations to address a number of questions relating to the state of water and its impact on the performance of lipid-based delivery systems and amorphous solid matrices useful for pharmaceutical formulations (Anderson and Marra 1999; Cao et al. 2004; Xiang and Anderson 2004, 2005, 2013; Rane and Anderson 2008a, b; Anderson et al. 2010). Some of these questions relate to the state of water in lipid-based formulations and amorphous solids. For example: (1) What factors govern the extent and rate of $H_2O$ uptake?; (2) Where are water molecules

located and how is the water organized?; (3) Do sorbed water molecules alter the local structure of the matrix?; and (4) Does the presence of water alter the solvent characteristics of the amorphous or lipid matrix, possibly leading to either enhanced solubility or perhaps unwanted phase transformations?

For a number of years, we have also had interest in various properties of lipid bilayer membranes, such as the influence of lipid composition and permeant structure on permeant binding to bilayer membranes (Xiang and Anderson 1994a, 1999; Xiang et al. 2006; Tejwani et al. 2010, 2011) and membrane transport (Xiang et al. 1992; Xiang and Anderson 1993, 1994b, c, 1995a, b, 1997, 1998a, b, 2002, 2006; Mayer 2001; Mayer and Anderson 2002; Mayer et al. 2003) and the design of liposomal drug delivery systems with optimal loading and release characteristics (Joguparthi and Anderson 2008a, b; Joguparthi et al. 2008a, b; Modi et al. 2012). Particularly relevant to the present discussion are these questions: (1) Where does water reside in lipid bilayers?; (2) How does the presence of water in the lipid bilayer influence drug binding and permeability? These questions will be addressed in this review through a combination of experiments and molecular dynamics computer simulations, which can shed light on the molecular phenomena underlying the experimental observations.

## 2 Molecular Dynamics Simulations

Molecular dynamics simulations as performed in this laboratory involve the construction of an ensemble of the molecules of interest within a supercomputer. The complete atomic detail of the molecules comprising the system of interest is represented. Typically, the ensemble includes molecules of a polymer excipient, lipid, or membrane matrix along with a small number of solute (drug) molecules and perhaps several water molecules. For each atom in the ensemble, Newton's equations of motion are integrated over time to obtain information on position, velocity, and acceleration of each atom subject to certain constraints reflecting the forces acting on each atom as obtained from a potential function ($U$), as shown below:

$$U = \sum_{\text{bonds}} \frac{k_{ij}^{b}}{2}\left(r_{ij} - r_{ij}^{\text{eq}}\right)^2 + \sum_{\text{angles}} \frac{k_{ijk}^{\theta}}{2}\left(\theta_{ijk} - \theta_{ijk}^{\text{eq}}\right)^2 + \sum_{\text{dihedrals}} k^{d}[1 + \cos\left(n(\phi - \phi^{\text{eq}})\right)] + \sum_{i<j}\left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}\right]$$

The terms in the above equation refer to contributions due to covalent bond energies, bond angles, dihedrals, and intermolecular van der Waals and electrostatic interactions. Numerous references available can provide further details on the potential function or molecular dynamics simulations in general (see, for example, Allen 2004 and Tieleman et al. 1997).

## 3 Water Uptake, Distribution, and Effects on Drug Solubility in Lipid Vehicles Composed of Triglycerides and Monoglycerides

In several recent publications, we have addressed drug solubility, water uptake, and the state of water in various mono-, di-, or triglycerides or their mixtures that have been popular formulation components for use in lipid-based drug delivery systems (Anderson and Marra 1999; Cao et al. 2004; Rane et al. 2008; Rane and Anderson 2008a, b; Anderson et al. 2010). Typical lipid-based delivery vehicles contain triglycerides of varying chain length combined with surfactants/emulsifiers such as long-chain carboxylic acids, mono- and diglycerides, phospholipids, or pegylated versions of these compounds. Water-soluble organic solvents such as polyethylene glycol or glycerol may also be included. Shown in Fig. 1 are the structures of a medium-chain triglyceride (tricaprylin) and two medium-chain monoglycerides (monocaprylin and monocaprin) often used in lipid-based formulations. These lipids were employed in experimental studies in our laboratory, aimed at understanding the specific intermolecular interactions that govern water uptake into these lipid solvents. As shown by the phase diagram in Fig. 1, Friberg and Mandell (1970) demonstrated that mixtures containing monocaprylin and tricaprylin form microemulsions upon dilution with water. Similar behavior would be expected in the stomach after administration of a pre-concentrate to

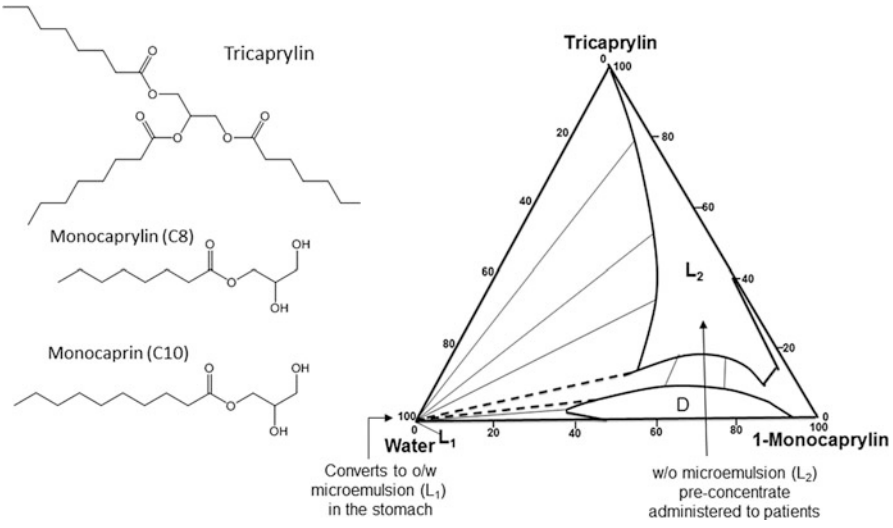



**Fig. 1** Molecular structures of tricaprylin, monocaprylin, and monocaprin used as model lipids for studies of water uptake and solubility. The phase diagram for systems containing varying percentages of tricaprylin, monocaprylin, and water from Friberg and Mandell (1970) illustrates the microemulsion formation that occurs when mixtures of tricaprylin and monocaprylin contain small percentages of water. *Right panel* reprinted with kind permission from Springer Science + Business Media: J Am Oil Chem Soc, Phase equilibria and their influence on the properties of emulsions, 47 (5), 1970, 149–152, Friberg S, Mandell L, figure number 2

patients. Thus, the dynamics of water uptake into these solvent mixtures leading to the formation of stable microemulsion particles and the thermodynamics associated with their stability and solvent characteristics are important features underlying their use in enhancing oral drug bioavailability.

Given the diversity and complexity of such lipid mixtures, simple quantitative principles that govern water uptake, its organization, its effects on organization of the lipids, and its effects on the solubility of drugs in lipid formulations would be desirable to elucidate. We have been interested, in particular, in the important role of hydrogen bonding, both in determining water uptake and its organization in lipid mixtures. Figure 2 (left panel) illustrates the water uptake as a function of monoglyceride concentration in triglyceride/monoglyceride mixtures at 37 °C and 100 % relative humidity, either in the presence of an added solute (benzamide) at its saturation solubility or in the absence of solute. Triglycerides consisting of tricaprylin and monoglycerides consisting of either monocaprylin (C8) or monocaprin (C10) were employed. Water content increased approximately linearly with the relative humidity (Rane et al. 2008) and, as evidenced by the profiles, was similar at the same molar concentration of either monoglyceride, indicating that the most important variable is the molar concentration of hydroxyl groups in the lipid mixture. The effects of monoglyceride concentration and water uptake on the solubility of benzamide are shown in the right panel of Fig. 2. An increase in the concentration of monoglyceride in the lipid mixture resulted in corresponding increases in benzamide solubility. As benzamide is an amide-containing solute, this enhanced solubility is likely due to the formation of hydrogen bonds between the amide carbonyl and hydroxyl groups in the lipid mixtures. As shown by the

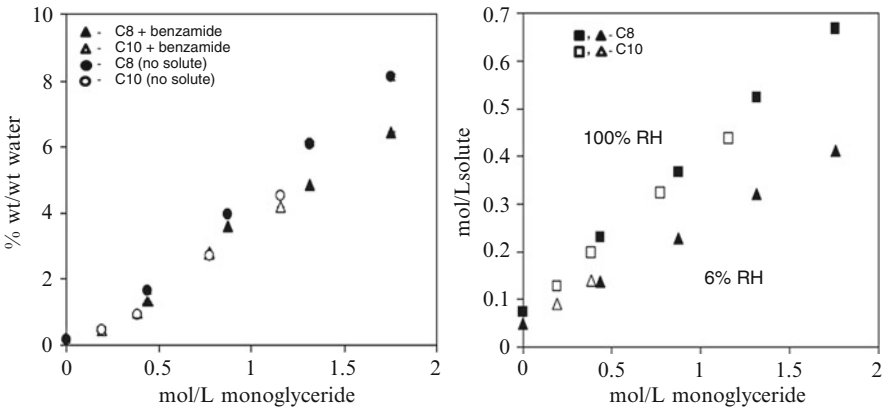



**Fig. 2** *Left panel*: Water uptake as a function of monoglyceride concentration at 37 °C in monocaprylin (C8)/tricaprylin or monocaprin (C10)/tricaprylin mixtures in the absence of solute or saturated with benzamide. *Right panel*: Benzamide solubility as a function of monoglyceride concentration in monocaprylin (C8)/tricaprylin or monocaprin (C10)/tricaprylin mixtures at 100 % or 6 % relative humidity. Reprinted with kind permission from Springer Science + Business Media: Pharm Res, Quantitative Solubility Relationships and the Effect of Water Uptake in Triglyceride/Monoglyceride Microemulsions, 25 (5), 2007, 1158–1174, Rane SS, Cao Y, Anderson BD, figure numbers 1B (*left panel*) and slight modification of figure 2A (*right panel*)

higher benzamide solubility in these lipid mixtures at a high relative humidity (RH) of 100 % compared to relatively dry conditions (6 % RH), water uptake also enhances the solubility of benzamide. Surprisingly, however, the presence of benzamide at saturation concentrations did not appear to influence water uptake. As shown by the left panel in Fig. 2, water uptake was either the same or perhaps slightly lower in lipid mixtures saturated with benzamide.

Molecular dynamics computer simulations may provide valuable insights into molecular interactions in lipid mixtures. We conducted MD simulations in a lipid mixture containing 60 % tricaprylin and 40 % monocaprylin that was saturated with water, a system that coincides with one of the compositions examined in experimental studies. These simulations employed 111 molecules of monocaprylin, 77 molecules of tricaprylin, and 219 molecules of TIP3P water with a single molecule of benzamide solute (Rane and Anderson 2008b).

A snapshot of the distribution of water molecules taken from one of these simulations is shown in Fig. 3. Most striking is the fact that the water molecules are not uniformly distributed in the lipid mixture. Rather, most of the water molecules reside in interconnecting clusters wherein they are hydrogen bonded to each other. Individual water molecules within each cluster were tracked over time, which revealed that individual water molecules within each cluster were highly mobile, but excursions of individual molecules between clusters were much less frequent.

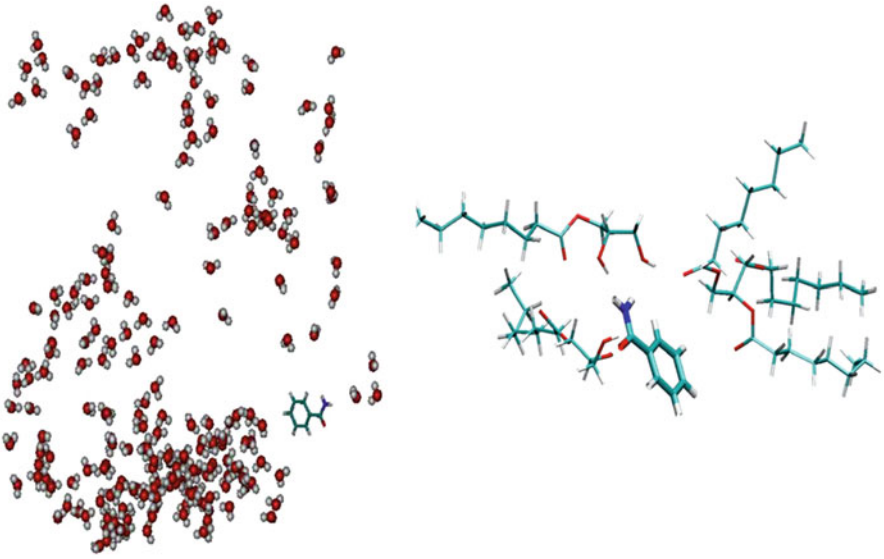


**Fig. 3** *Left panel*: Snapshot from a molecular dynamics simulation showing the distribution of water molecules in a water saturated 60 % tricaprylin/40 % monocaprylin lipid mixture at 37 °C. Water molecules are rarely found to be hydrogen bonded to the single molecule of benzamide. *Right panel*: Monocaprylin chains hydrogen bonded to benzamide

Gradually, individual water clusters would shrink or expand as others contracted. Radial distribution functions indicated that the lipid environment surrounding individual water clusters was enriched in hydroxyl and carbonyl groups and somewhat depleted in alkyl chain atoms, indicative of hydrogen bonding between polar functional groups in the lipid chains and water molecules within the cluster.

The significant influence of water content on the solubility of benzamide (Fig. 2) suggests that it may be important to carefully control the water content in lipid formulations to ensure the desired drug solubility. For benzamide, the solubility enhancement that was found experimentally at high relative humidity would be consistent with the expectation that water molecules would enhance benzamide's solubility through hydrogen bonding, but the MD simulation snapshot shown in Fig. 3 indicated that benzamide was generally far removed from any water clusters. During the entire dynamic simulation (30 ns) monomers of water would only occasionally localize in the vicinity of the benzamide molecule, forming a hydrogen bond with the benzamide carbonyl. The amide nitrogen typically formed hydrogen bonds with adjacent lipid oxygen atoms. There was at most one water molecule interacting with benzamide at any given time. Thus, the enhancement in the solubility of benzamide with increasing water content may not simply reflect an increase in benzamide-water hydrogen bonding.

## 4 Water Uptake and Its Implications in an Amorphous Glass (PVP)

Unlike moisture uptake in crystals, where stepwise changes in water content occur with increasing relative humidity due to formation of stoichiometric hydrates, water uptake in amorphous solids increases in a continuous fashion with relative humidity, though the increases are not typically linear. Studies of moisture uptake in polyvinylpyrrolidone (PVP), polyvinylacetate (PVAc), and their copolymers (Taylor et al. 2001) demonstrated an important role of the functional group composition of the polymer in determining water affinity. PVP exhibits substantially greater water affinity than PVAc, presumably due to the greater hydrogen-bond accepting ability of the amide carbonyl in PVP. The water uptake obtained in PVP/PVAc copolymers was close to that predicted assuming additivity of the functional group contributions from the individual PVP and PVAc chains, as expected if hydrogen bond formation were the dominant factor governing water uptake.

Molecular interactions such as hydrogen bonding may be significantly affected, however, by the degree of metastability of a given amorphous glass. Dawson et al. (2009) recently found substantial differences in the water uptake profiles for an ordinary indomethacin (IMC) glass prepared by cooling, an annealed glass, and a more stable glass prepared by vapor deposition, with the more stable glass exhibiting a fivefold lower moisture uptake than an ordinary glass. Dramatic differences in the rates of water uptake were also noted. The authors speculated

that water sorption into indomethacin is driven by hydrogen bonding and that in stable IMC glasses, more hydrogen bonds are formed between IMC molecules themselves, leaving fewer hydrogen-bonding sites available for water molecules. This competition would account for the reduced water uptake in more stable IMC glasses. Physical aging of trehalose for 120 h at 373 K resulted in a decrease in equilibrium moisture uptake from 1.4 to 0.8 % at 10 % relative humidity (Surana et al. 2004), again suggesting that water uptake in amorphous solids depends not only on the functional groups present in the amorphous material but also on their availability for interaction with water.

We have recently conducted an MD simulation of an amorphous indomethacin glass to investigate various structural and dynamic properties, including the interactions of water with IMC. The assembly consisted of 105 indomethacin molecules and 12 water molecules, corresponding to a water content of 0.6 % w/w (Xiang and Anderson 2012). At this relatively low water content, >90 % of the water molecules at any given time formed 1–3 hydrogen bonds with indomethacin with probabilities of $0.36 \pm 0.13$, $0.28 \pm 0.07$, and $0.29 \pm 0.10$, respectively. Figure 4 (left panel) is a snapshot of the distribution of water molecules in IMC indicating that, even at 0.6 % w/w water content, some water dimers co-exist with monomers. The right panel in Fig. 4 shows the probability distribution for either the IMC carboxylic acid group or water to donate a hydrogen to various atoms. Water molecules acting as hydrogen donors have a similar tendency to form hydrogen bonds with the IMC benzoyl C = O ($39 \pm 8$ %) and the carboxylic acid C = O ($37 \pm 12$ %) with a smaller percentage forming hydrogen bonds at the $OCH_3$ group ($12 \pm 6$ %) or with other water molecules ($12 \pm 9$ %).

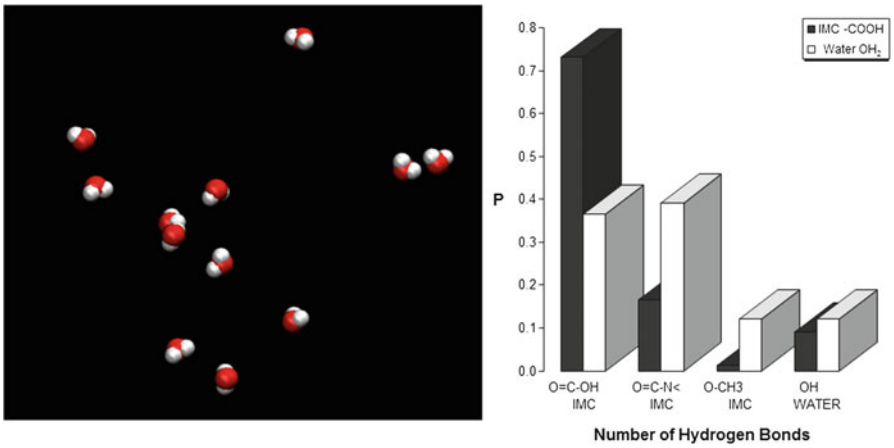



**Fig. 4** *Left panel*: A representative snapshot showing the water distribution in an amorphous IMC glass at 298 K. *Right panel*: Probability distributions for different HB acceptor sites to form hydrogen bonds with either the IMC –COOH (*black*) or the water H–O groups (*white*) in the simulated IMC glass at 298 K

Several investigators have examined the state of water in amorphous PVP, with the following general conclusions. Lebedeva et al. (1999) determined from FTIR spectra of sorbed water in PVP at lower water contents that water molecules were predominantly hydrogen bonded to PVP carbonyl oxygen atoms. At higher water concentrations, experimental data suggest that water self-associates in PVP. For example, Taylor et al. concluded from peak shifts in the Raman spectra for the PVP carbonyl and water at various relative humidities that some water molecules were hydrogen bonded directly to the polymer, while additional water molecules were hydrogen bonded to each other (Taylor et al. 2001).

Our group has also conducted molecular dynamics simulations to explore the distribution and plasticization effects of water, along with other phenomena in PVP polymer assemblies containing six PVP chains (each having 40 monomers) with 8–167 water molecules, corresponding to approximately 0.5 % and 10 % w/w water, respectively (Xiang and Anderson 2004, 2005). Consistent with the experimental evidence, we found that at higher water content, water self-associates to form hydrogen-bonded strands or clusters, similar to the pattern previously observed in lipid mixtures. As shown in Fig. 5, this tendency for water to

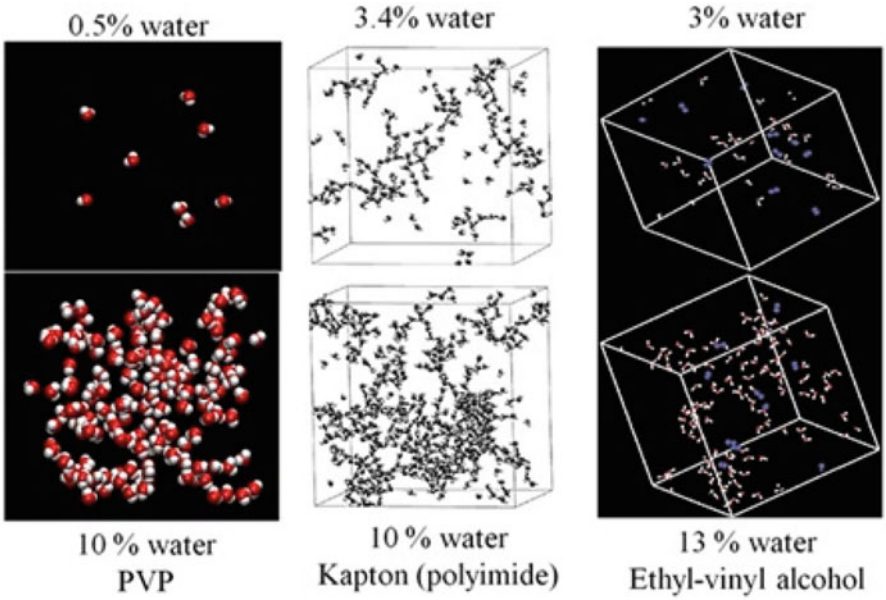



**Fig. 5** Water clustering with increasing water content as demonstrated in molecular dynamics simulations in various polymers. *Left panel* reprinted with kind permission from Springer Science + Business Media: Pharm Res, Distribution and Effect of Water Content on Molecular Mobility in Poly(vinylpyrrolidone) Glasses: A Molecular Dynamics Simulation, 22 (8), 2005, 1205–1214, Xiang T-X, Anderson BD, figure number 4. *Middle panel* reprinted with kind permission from American Chemical Society: Macromolecules, Molecular Dynamics Simulation Study of Water in Amorphous Kapton, 41 (9), 2008, 3349–3362, Marque G, Neyertz S, Verdu J, Prunier V and Brown D, figure number 16. *Right panel* reprinted with kind permission from Elsevier: Polymer, Effect of absorbed water on oxygen transport in EVOH matrices: A molecular dynamics study, 45 (10), 2004, 3555–3564, Kucukpinar E, Doruker P, figure number 5

self-associate at higher concentrations in amorphous polymers has been reported in several simulation studies (Xiang and Anderson 2005; Marque et al. 2008; Kucukpinar and Doruker 2004). The implications of these observations and their effects on water affinity, rates of water uptake, and the solubility of active pharmaceutical ingredients in amorphous solids are under investigation, but not fully understood.

## 5 Water Distribution, Mobility, and Effects on Transbilayer Diffusion of Permeants in Lipid Bilayers

Numerous experimental (Xiang et al. 1992; Xiang and Anderson 1993, 1994b, c, 1995a, b, 1997, 1998a, b; Mayer 2001; Mayer and Anderson 2002; Mayer et al. 2003) and computational (Xiang and Anderson 2002, 2006) studies in our laboratories and others have established that the barrier domain for small drug-like molecular permeability across lipid bilayer membranes is the hydrocarbon-like acyl chain interior. This region is nearly devoid of water, as illustrated by the results of a recent MD simulation in 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC) bilayers, where the center of the bilayer is indicated at 0.0 Å (Fig. 6, left panel). Given that most drug molecules have one or more polar functional groups, the dislocation

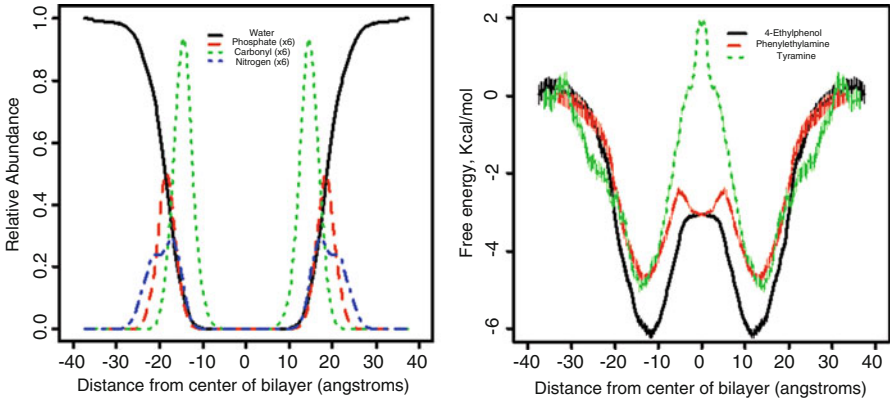
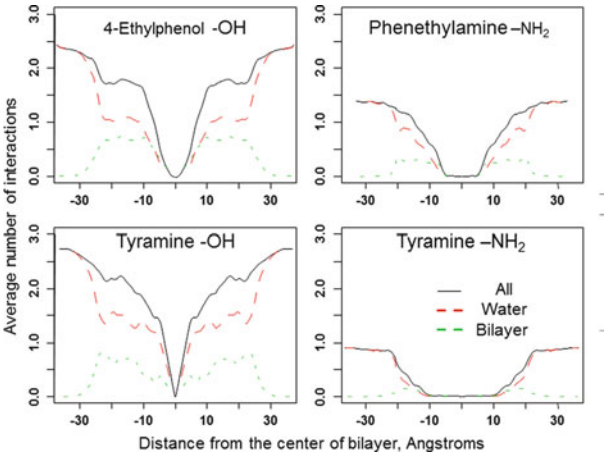



**Fig. 6** *Left panel*: Position-dependent distributions of various atoms, molecules, or functional groups in a DOPC bilayer as determined in MD simulations. The distribution for water molecules was reduced by sixfold in relation to other atoms and functional groups shown. *Right panel*: Free energies of transfer of various solutes from water to various locations within the DOPC bilayer. Reprinted with kind permission from American Chemical Society: Mol Pharmaceutics, An Atomic and Molecular View of the Depth Dependence of the Free Energies of Solute Transfer from Water into Lipid Bilayers, 8 (6), 2011, 2204–2215, Tejwani RW, Davis ME, Anderson BD, and Stouch TR, figure 2




| | $R_1$ | $R_2$ |
|---|---|---|
| Phenethylamine | $NH_2$ | H |
| 4-Ethylphenol | H | OH |
| Tyramine | $NH_2$ | OH |

**Fig. 7** Average number of hydrogen bond interactions formed by phenethylamine, 4-ethylphenol, and tyramine versus their location in a DOPC lipid bilayer. The location indicated is that of the phenyl carbon attached to the ethyl chain (the actual location of the hydrogen bond may within 2–5 Å of this position). *Left panel* reprinted with kind permission from American Chemical Society: Mol Pharmaceutics, An Atomic and Molecular View of the Depth Dependence of the Free Energies of Solute Transfer from Water into Lipid Bilayers, 8 (6), 2011, 2204–2215, Tejwani RW, Davis ME, Anderson BD, and Stouch TR, modified from figure 4 (*upper panels*)

of drug molecules from the interfacial region of the bilayer where the polar groups are hydrogen bonded to water or phospholipid head groups into the hydrocarbon interior is energetically highly unfavorable.

We recently explored the membrane partitioning and permeabilities of a set of structurally related permeants, as shown in Fig. 7 (i.e., phenethylamine, 4-ethylphenol, and tyramine), in an effort to couple experimental results to results from MD simulations (Tejwani et al. 2010, 2011). In particular, the effects of the hydroxyl and amine substituents, either alone or when both were present on the same molecule (as in tyramine) on the free energy profiles within DOPC bilayers, were examined, as shown in the right panel of Fig. 6. Two prominent features were noted in the free energy profiles. The water/bilayer interface was the preferred binding region for all solutes, while the highest free energy region (least favorable for partitioning) was the center of the bilayer. The barrier domain region in the hydrocarbon chain interior was found to be highly selective to the number of polar residues on the permeant, while the preferred binding region at the interface was relatively insensitive to such differences in chemical structure.

These differences in chemical selectivity between the interfacial region and the hydrocarbon interior reflect the abilities of permeants to adopt orientations that favor hydrogen bonding with water or polar head groups in the interfacial region, while in the hydrocarbon chain interior all hydrogen bonds are lost, unless the molecule is sufficiently large to span a significant fraction of the bilayer thickness. This is shown by the number of hydrogen bond interactions that each of the three

solutes formed at various locations within the bilayer, as illustrated in Fig. 7. As the permeants move away from the bilayer interface, a substantial fraction of the hydrogen bonds are formed with water molecules that have partially penetrated the bilayer.

In some snapshots from the MD simulations, we were able to observe that removal of a solute from the interface was facilitated by hydrogen bonding to water molecules, which were in turn linked to either another water molecule closer to the interface or one of the polar atoms in the phospholipid head group. Water wires involving multiple hydrogen-bonded water molecule chains accompanied by head-group migration appear to be particularly important in facilitating anion and cation transport across bilayers (Xiang and Anderson 2006; Tepper and Voth 2006; MacCallum et al. 2008), since the free energy penalty for removing water of solvation from a charged residue is extremely large.

## 6 Conclusions

Because of its small size, enhanced mobility, and hydrogen-bonding capacity, water may have profound effects on local molecular organization in both lipid vehicles and amorphous solids frequently utilized as pharmaceutical formulations. The presence of moisture may determine both the physical stability and chemical stability of these systems by altering either the system thermodynamics, molecular dynamics, or both. Water-induced reorganization of local structure in lipid bilayer membranes may be essential for the transport of highly polar permeants such as anions and cations. Molecular dynamics simulations coupled with experiments on similar systems are providing valuable molecular insights into these important phenomena.

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