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International Journal of Pharmaceutics 354 (2008) 248–254
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Note

Physicochemical properties of water and its effect on drug delivery A commentary

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Received 23 July 2007; received in revised form 27 August 2007; accepted 30 August 2007
Available online 4 September 2007

Abstract

The structure and properties of water are integral to the existence and evolution of life on any number of levels. Consistent with this overarching statement, the unique physiochemical properties of water affect the pharmacological actions and delivery of drugs to the body whether they are administered orally, topically or by injection. This last topic is explored in the current review. While water is a group VIA hydride, it is distinct from other members of the class based on density, dielectric constant, surface tension as well as melting and boiling point. These differences are attributed to the ability of water to hydrogen bond to itself and other substrates resulting in the formation of strongly cohesive systems which molecularly resemble highly dynamic polymeric networks. As a consequence of these properties, hydrophobic compounds tend to aggregate in solution sometimes at the nanoscale. The practical consequence of this aggregation may be observed as spurious results associated with receptor-based high throughput screening assays as well as anomalies in phase-solubility analysis encountered in the study of hydrophobic materials with cyclodextrins. Other insights provided by a knowledge of the structure of water include the actions of excipients. Thus, materials that contribute to the hydrogen-bonding aqueous network (i.e., kosmotropes) will tend to salt more non-polar materials out of solution while material that destabilize the network structures (i.e., chaotropes) will tend to preferentially bind to solutes, reducing unfavorable interactions with water, resulting in solubilization. At membranes, the unique properties of water can affect drug absorption based on resistance in the unstirred water layer (UWL) which resides directly adjacent to the barrier. Depending on the nature of the membrane and the drug, the UWL can effectively reduce drug uptake and penetration. Furthermore, excipients that affect water structure can either contribute to or detract from the ability of a compound to pass the UWL and consequently the membrane. The increasing realization that water influences the actions and interactions drugs and excipients opens a variety of new avenues with regard to the rationale design of useful dosage forms.

Keywords: Hydrogen-bonding; Water clusters; Solubility; Permeability; Unstirred water layer; Aggregate

Experimental and computational approaches used to evaluate "drugability" of new chemical entities (NCE), such as the biopharmaceutic classification system (BCS) and Lipinski's rule of 5 (Amidon et al., 1995; Lipinski et al., 2001; Kerns and Di, 2004), suggest that two of the most important physicochemical properties required for drug delivery are aqueous solubility and ability of the dissolved drug molecules to permeate biological membranes. These properties will not only affect the rate and extent of drug absorption but also impact overall drug disposition, including routes of drug elimination and the effects of efflux and absorptive transporters on oral uptake (Wu and Benet, 2005). Both aqueous solubility and permeability through biomembranes are affected by the unique physicochemical properties of liquid water, which is not surprising since about 60% of our bodies are made up of water. Although the unusual structural characteristics of water are known to effect drug delivery and biological activity, they are seldom taken into account during drug development (Plumridge and Waigh, 2002; Homans, 2007). The structure of liquid water and its interaction with solutes and membrane surfaces is a very active area of research that will, without doubt, affect our future research endeavors within drug delivery and development (Chaplin, 2006). Here an attempt is made to use recent data on the structure and physicochemical properties of water to explain several phenomena

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doi:10.1016/j.ijpharm.2007.08.049

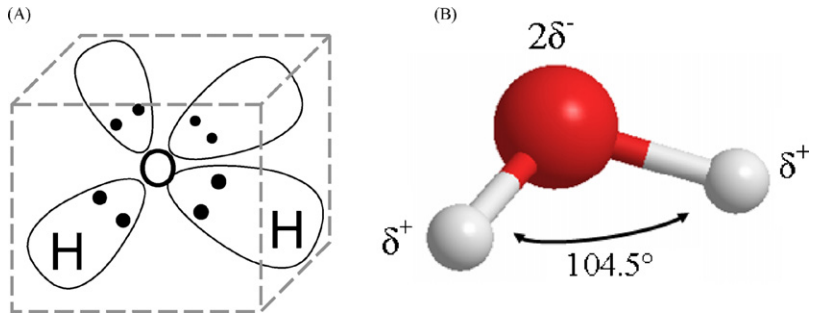

Fig. 1. (A) The tetrahedral structure of a single water molecule with the oxygen atom in the center and the two hydrogen atoms in two corners of the tetrahedron. (B) Ball and stick model of a water molecule.

that are frequently observed during drug action and development.

The structure of isolated water molecules is well-known. The oxygen atom has six valence electrons and each hydrogen atom has one, such that the two hydrogen atoms form covalent bonds with the oxygen leaving two lone pairs of electrons on the oxygen (Fig. 1). The length of the O–H bond is 1 Å and the angle between the bonds is 104.5°, or very close to the angle between the vertices of a regular tetrahedron (109°). Although the structure appears trivial, the physicochemical properties of water are far from simple (Chaplin, 1999; Schmid, 2001; Michot et al., 2002; Griffith and Scheraga, 2004). Based on electronegativity, the electrostatic surface of water is associated with a dipole with a partially negative oxygen atom and partially positive hydrogen atoms. (Fig. 1). The polarity of each water molecule results in an attraction between it and other water molecules, resulting in formation of a hydrogen bond. Hydrogen bonds are relatively strong (~5–40 kJ/mol) compared to van der Waals interactions (~1–10 kJ/mol) but much weaker than covalent bonds (~200–1000 kJ/mol). Intermolecular hydrogen-bonding of water leads to enhanced molecular cohesion. Studies have shown that at room temperature, 80% of water molecules make one strong hydrogen bond and, by symmetry, accept one hydrogen bond for a total of two hydrogen bonds per water molecule (Wernet et al., 2004). These discoveries have altered the conventional view of liquid water from being a tetrahedrally coordinated random network to being a structural organization that strongly favors hydrogen-bonded water chains or large rings embedded in a weakly hydrogen-bonded disordered network. These structures are continually forming, breaking apart and re-forming on the femtosecond (10^{-15} of a second) timescale (Michot et al., 2002; Cabane and Vuilleumier, 2005; Eaves et al., 2005; Head-Gordon and Johnson, 2006). The hydrogen bond connections in thread-like water structures are constantly being broken and reformed, pulsating at 170×10^{-15} s (Fernández-Serra and Artacho, 2006). Due to this molecular cohesion, water behaves like macromolecules ($(H_2O)_n$) rather than the independent dihydrogen oxide (H_2O) units. It has been estimated that if water did not possess this extensive cohesion such that it behaved more like other group VI6 hydrides, then its boiling point (BP) would be about −90 °C or almost 200 °C lower than the actual value (Table 1). The electronegativity of the heavier VI6 elements, i.e., sulfur, selenium and tellurium, is much lower than that of oxygen, and close to that of hydrogen. Thus, their hydrides are unable to form hydrogen bonds (Pauling, 1967) and consequently both their melting point (MP) and BP are much lower than that of water (Table 1). Hydrogen bonds also affect other physicochemical properties of liquid water, such as its dielectric constant (ε 78.5 at 25 °C), density (1.000 g/ml at 3.98 °C), surface tension and heat of vaporization (40.65 kJ/mol), making them all higher than expected (O'Neil et al., 2001; Cabane and Vuilleumier, 2005). In addition, the dielectric properties of organic solvents, for example glycerol (ε 42.5 at 25 °C), ethanol (ε 24.3 at 25 °C), isopropanol (ε 18.3 at 25 °C) and diethyl ether (ε 4.3 at 20 °C), are much lower than that of water. Movement of protons (H^+) through water is about 6.5-times faster than expected if they moved by hydrodynamic diffusion of the smallest protonated water cluster (H_3O^+). This suggests that protons are transferred via "water wires" where the addition of a proton to one end of the wire (hydrogen-bonded water chain) results in the cascade flipping of a hydrogen-bond down the chain releasing a different but identical proton at the

Table 1
The electronegativity of hydrogen and the group VIA elements, and the molecular weight (MW), melting points (MP) and boiling points (BP) of their hydrides[a]

	Symbol	Electro-negativity	Group VIA hydrides	MW (Dalton)	MP (°C)	BP (°C)
Oxygen	O	3.5	H_2O	18	0	100
Sulfur	S	2.5	H_2S	34	-85	-60
Selenium	Se	2.4	H_2Se	81	-66	-41
Tellurium	Te	2.1	H_2Te	130	-49	-2
Hydrogen	H	2.1	H_2	2	-259	-253

[a] Values from the Merck Index, 13th ed., 2001, Merck & Co., Whitehouse Station, and Atkins, P., de Paula, J., 2006. Physical Chemistry for the Life Sciences, Oxford University Press, Oxford.

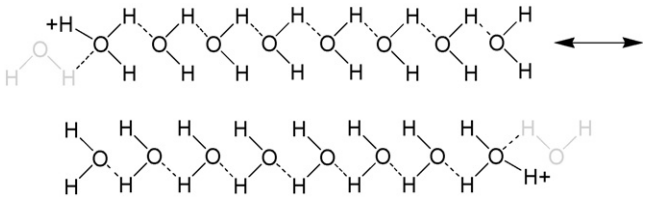

Fig. 2. Highly schematic drawing of a proton being transferred in a "water wire". Based on Cukierman (2006).

other end of the wire (Fig. 2). This is referred to as the Grotthuss mechanism (Cukierman, 2006). Likewise, hydroxide ions (OH^-) move about 3.3-times faster than expected if the ions moved through water by hydrodynamic diffusion. Water can appear homogeneous when observed at micrometer scale but nonhomogeneous on a nanometer scale. In that sense, homogeneity is a function of size or scale.

Any hydrophilic or hydrophobic, unionized or ionized cosolvents, solutes and solid surfaces will affect the structure of water. For example, ethanol–water binary mixtures appear homogeneous but shows phase separation at the nanoscale level (Wakisaka and Matsuura, 2006). Structure-breaking solutes (chaotropes) destroy the hydrogen-bonded water network in a manner which is similar to the effect of increased temperature while structure-forming solutes (kosmotropes) increase the structural complexity. Sugars, such as fructose, glucose and sucrose, behave as chaotropes at low concentrations, while at higher concentrations they act as kosmotropes (Giangiacomo, 2006). Water-soluble polymers, such as cellulose derivatives and polyethylene glycols, form hydrogen bonds with water that are stronger than water-water bonds, i.e., a positive hydration, characterized by low exchange rates of the water molecules around the polymers. This results in increased water networking and viscosity even at very low excipient concentrations (McBrierty et al., 1999; Branca et al., 2002). Hydration of low molecular weight solutes, wherein water molecules bind to solute molecules, is also well-known, as are the strong interactions between water and ionized molecular moieties. Positively-charged ions attract the negatively-charged end of the water molecules (the oxygen) and negatively-charged ions attract the positively-charged side (the hydrogens). The ordered structure within the primary hydration shell creates, through hydrogen-bonding, a somewhat less ordered region further away from the ion. In some cases the ions can share electrons with nearby water molecules, i.e., covalent-like bonds are formed between the ions and the surrounding water molecules (Näslund et al., 2003). These and other observations show that on the nanoscale, and sometimes even on microscale level, aqueous solutions should be regarded as a heterogeneous systems that are composed of regions of different structures and physicochemical properties.

The conventional approach of describing the process of solute solubilization by water is to divide the process into three stages: (a) removal of a single solute molecule from its solid or liquid stage, (b) formation of a cavity in the water structure just large enough to accept the solute molecule and (c) movement of the solute molecule into the cavity and simultaneous bond forming between the solute and the surrounding water molecules (Florence and Attwood, 2006; Sinko, 2006). Bonds are broken (i.e., energy is absorbed) during the first two stages but formed in the last stage (i.e., energy is released). This simplified description of solubilization can be used to explain, at least qualitatively, the correlation among aqueous solubility and melting and boiling points, ionization, proton donating and proton accepting groups, and molecular size. Aqueous drug solubility has been estimated from easily obtainable properties, such as the melting point, the octanol–water partition coefficient, the hydrogen-bonding capacity of the molecule and its non-polar surface area (Yalkowsky, 1999; Bergström et al., 2002; Bergström et al., 2004; Votano et al., 2004; Bergström, 2005; Delaney, 2005; Johnson and Zheng, 2006; Loftsson and Hreinsdóttir, 2006). In general, such computational methods for solubility estimation are limited in their accuracy and do not replace experimental determinations. The experimental solubility is usually determined by the equilibrium method, which employs a saturated solution of the compound at some given pH and temperature, obtained by stirring an excess of the compound in the aqueous medium for a prolonged period until equilibrium between solid and dissolved drug molecules is achieved. The equilibrium time ranges from a few minutes to a few days up to several weeks or months for slowly dissolving compounds. Automated and miniaturized versions of this method have been developed (Bergström et al., 2002; Glomme et al., 2005). However, the equilibrium solubility method is time consuming and usually requires large sample making it of limited applicability for high throughput screening for new drug candidates. Instead kinetic solubility is determined wherein dimethyl sulfoxide solution of the compound is gradually added to an aqueous media and the solubility determined as the concentration at which a precipitate is formed as detected by light scattering or particle counting. The advantages of the kinetic method are that it is relatively rapid, requires only small sample and it is easily automated (Dehring et al., 2004). The disadvantages of this method are the presence of dimethyl sulfoxide in the final medium (frequently 0.5–5%, v/v) and potential formation of supersaturated solutions. The obtained kinetic solubilities are often higher than measured equilibrium solubilities but neither the equilibrium method nor the kinetic method gives an accurate account of the dissolved molecules at the nanoscale level.

One consequence of the molecular cohesion of water is that solutes that have limited solubility in water tend to associate into molecular aggregates of two or more solute molecules (Yaminsky and Vogler, 2001). Interactions associated with the formation and longevity of these aggregates of hydrophobic materials are mainly associated with the strong self-association of water through hydrogen-bonding. The diameter of these drug aggregates in aqueous solutions is frequently only a few nanometers and, thus, it can be difficult to detect them directly but indirect evidence is frequently available. For example, false positive and negative results during high throughput screening of bioactive compounds are frequently associated with molecular aggregation (Dalvit et al., 2006). The screening technique is frequently based on interaction (i.e., substrate–ligand binding) of individual test molecule with the receptor but when most of the molecules aggregate into dimers, trimers and/or higher

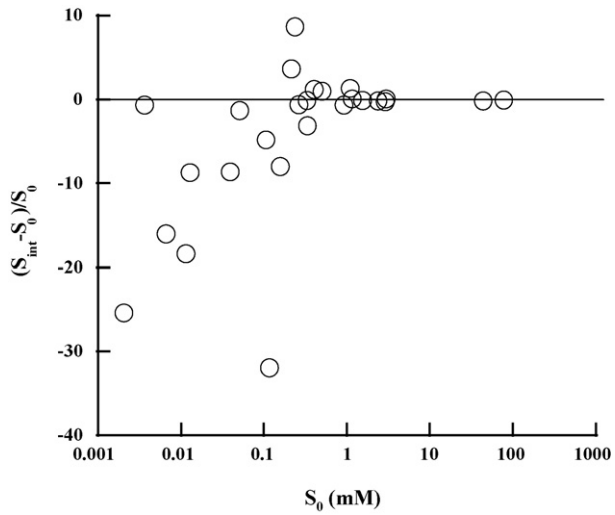

Fig. 3. Plot of the determined intrinsic molar solubility (S_0) vs. the relative deviation of the intercept (S_{int}) obtained from phase-solubility studies from the determined value at ambient temperature. Twenty-six different drugs, molecular weight ranging from 178 to 1202 with mean of 348 Da, melting point ranging from 19 to 293 with mean of 182 °C. From Loftsson et al. (2005).

order molecular aggregates, then a false negative result might be expected. Similarly, erroneous results are sometimes obtained during formation of water-soluble cyclodextrin complexes of drug molecules that have limited solubility in water, especially if their solubility is less than about 250 μg/ml (or about 0.3 mM) (Loftsson et al., 2005). When linear phase-solubility diagrams (i.e., drug solubility vs. cyclodextrin concentration plots) are obtained it is assumed that the *Y*-intercept (S_{int}) is equal to the intrinsic solubility (S_0) (Higuchi and Connors, 1965). However, when S_0 is less than about 250 μg/ml the *Y*-intercept is, in general, much smaller than S_0 (Fig. 3) indicating that the availability of single free drug molecules (i.e., not in drug aggregates) is much lower than would be expected based on the observed S_0. Furthermore, since in general only single drug molecule is for the most part able to enter the cyclodextrin cavity, and not the drug aggregates, the linear phase-solubility diagram is shifted away from the *Y*-axis.

The rate and mechanism by which crystallization takes place are determined by a number of thermodynamic, kinetic and molecular recognition phenomenon (Miller et al., 2007). A solid phase will crystallize out of solution if the chemical potential of the solid phase is less than that of the dissolved phase. In order for crystallization to proceed, supersaturation must occur as this is the driving force for nucleation and crystal growth. The rate of nucleation is generally expressed by the following equation:

$$J = N_0 \nu \exp\left(\frac{-16\pi \upsilon^2 \gamma_{12}^3}{3(k_B T)^3 (\ln(c/s))^2}\right) \quad (1)$$

where J is the number of nuclei formed per unit time per unit volume, N_0 is the number of molecules of the crystallizing phase per unit volume, ν is the frequency of transport through the nucleus–liquid interface, υ is the molecular volume of the crystallizing solute, γ is the interfacial energy per unit area, k_B is the Boltmann constant, T is temperature and c/s is the extent of supersaturation. As described by Miller et al., 2007, solubility, interfacial tension and viscosity are the solvent-related features most likely to affect nucleation. From this point of view, cohesion of water molecules (i.e., water cluster formation) relative to other solvents will delay nuclei formation and slow crystal growth, and excipients that promote the cohesion are likely to stabilize supersaturated solutions (Brewster and Loftsson, 2007). By analogy, cohesion of water molecules will hamper drug dissolution through formation of somewhat viscous unstirred water layer (UWL) at the solid/liquid interphase. Also, hydration of dissolved solubilizing agents, such as cyclodextrins, can hamper their solubilizing ability. Thus, methods that decrease the thickness of the UWL or decrease the hydration of solubilizing excipients, such as heating and sonication of the dissolution media, will increase the dissolution rate and solubilization (Loftsson et al., 2005; Loftsson and Hreinsdóttir, 2006).

Kosmotropes, such as sucrose, betaine, maltose, sodium sulfate and sodium chloride, are more polar than water and act to enhance its structure due to their ability to form hydrogen bonds. Kosmotropes interact preferably with the water molecules rather than non-polar solutes resulting in stronger repulsion between water and the non-polar solute (Al-Maaieh and Flanagan, 2002; Moelbert et al., 2004; Magazù et al., 2007). The intermolecular separation between solute molecules are consequently reduced minimizing the total exposed surface resulting in an enhancement of hydrophobic aggregation and consequently a decrease in aqueous solubility (i.e., salting-out effect). Chaotropes, such as urea, sodium perchlorate and sodium thiocyanate, are less polar than water and consequently their presence in solution leads to an energetically unfavorable disruption of water structure. Chaotropes are therefore excluded from bulk water, resulting in an effect known as "preferential binding" to the solute molecules and particles (Timasheff, 2002; Moelbert et al., 2004). Consequently fewer water molecules will be in contact with the surface of the non-polar solute increasing its aqueous solubility (i.e., salting-in effect). In this way common pharmaceutical excipients can affect water structure and cluster formations leading to either increase or decrease the aqueous drug solubility but may also have no effect.

The core structure of biological membranes is the lipid bilayer, composed of about 4 nm thick double layer of phospholipids, with occasional intertwined proteins, some of which function as channel formers. The hydrophobic tails of the two phospholipids layers face one another while their hydrophilic phosphate moieties face the aqueous medium on either side of the membrane (Fig. 4). Water molecules are bound to phospholipids, proteins and other membrane constituents resulting in a water layer thickness of about 1 nm (or about three water molecules thick) on each side of the membrane (Disalvo et al., 2004). In general, water structures at membrane surfaces are strongly affected by the ability of the surface to form hydrogen bonds with water (Gun'ko et al., 2005). Virtually no water adsorbs to graphitized carbon, a hydrophobic surface. The self-association of water molecules is much stronger than interactions of water molecules with the hydrophobic surface,

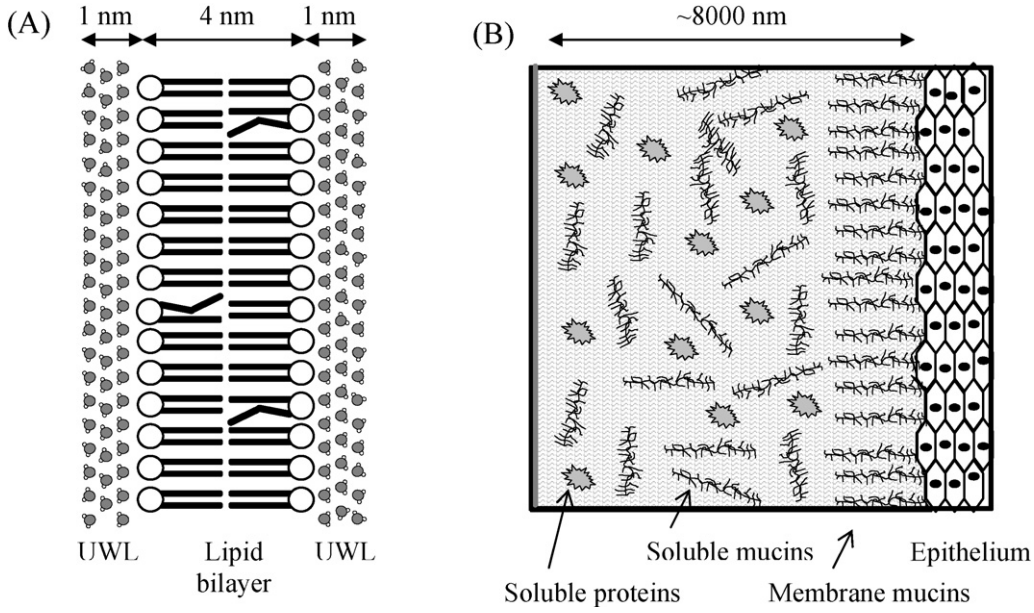

Fig. 4. Schematic drawings of (A) a simple lipid bilayer with two unstirred water layers (UWL) on either side of the membrane and (B) the aqueous tear film on the eye surface.

a phenomenon analogous to the hydrophobic effect observed when non-polar solutes are dissolved in water (Vogler, 1998; Yaminsky and Vogler, 2001; Michot et al., 2002; Chandler, 2005). On the other hand, water in contact with hydrophilic surfaces, e.g., some silica-based materials, forms a water film where hydrogen-bonding in the network of water molecules are partly substituted by bonds between the water molecules and the surface (Vogler, 1998). These interactions result in a reduction of the mobility of water molecules directly adsorbed on the surface by more than one order of magnitude. These water layers are usually only a couple of water molecules thick (Michot et al., 2002). Water molecules are bound to the skin surface as well as within the outermost layer of the skin, the stratum corneum, but the resulting UWL is relatively thin and permeable (Wertz, 2004). Mucosal epithelium (mucosa) contain mucosal cells that secretes mucus, a gel-like fluid containing mainly water (~95%) and mucin (Bansil and Turner, 2006). Mucins are large glycoproteins with MW ranging from 0.5 to 20 MDa. Some are membrane-bound but others are not. Mucin forms hydrogen bonds with surrounding water molecules enhancing cluster formation and, consequently, decreased water mobility. This leads to up to 10^5-fold enhancement in the thickness of the UWL in, for example, the gastrointestinal tract, the respiratory tract, the ocular-rhino-otolaryngeal tracts and the reproductive tract (Lennernäs, 1998). The tear film on the eye surface is about 8 μm thick (Fig. 4) but the thickness of the gastrointestinal mucus layer can be about 100 μm. Under unstirred *in vitro* condition the thickness of the UWL can be much grater, even in absence of mucus (Karlsson and Artursson, 1991; Youdim et al., 2003; Avdeef et al., 2004; Brewster et al., 2007). However, the observed thickness of the UWL depends also on the physicochemical properties of the permeating drug molecules, including their ability to form ionic and hydrogen bonds with mucin, and thus fixed UWL thickness for all drugs does not exist (Pohl et al., 1998). The UWL owns its existence to the cohesion properties of water, i.e., its ability to form both hydrogen bonds with not only other water molecules but also hydrocarbons, proteins, glycoproteins (such as mucin), ions and other membrane structures. UWLs, such as mucus layers, are significant barrier to drug absorption for lipophilic drugs (Behrens et al., 2001).

Passive drug permeation through multilayer barriers, such as through the UWL and lipophilic epithelium, is described as series of additive resistances analogous to electric circuits (Higuchi, 1960; Flynn et al., 1972; Flynn and Yalkowsky, 1972). Assuming independent and additive resistances of the individual layers, the total resistance (R_T) of a simple membrane (Fig. 4) can be defined as:

$$J = P_T C_V = R_T^{-1} C_V = (R_D + R_M + R_R)^{-1} C_V = \left(\frac{1}{P_D} + \frac{1}{P_M} + \frac{1}{P_R}\right)^{-1} C_V \quad (2)$$

where J is the flux of the drug through the membrane, P_T is the overall permeability coefficient, C_V is the drug concentration in the vehicle (i.e., donor phase), R_D, R_M and R_R, and P_D, P_M and P_R are the resistances and permeability coefficients in the UWL at the donor side, within the membrane and in the UWL at the receptor side, respectively (Loftsson et al., 2007). If R_R is assumed to be negligible due to relatively rapid removal of drug molecules from the receptor side of the membrane, Eq. (3) is obtained:

$$J = \left(\frac{P_D P_M}{P_D + P_M}\right) C_V \quad (3)$$

The relationship between the permeation coefficient (P) and the diffusion coefficient (D) is given by Eq. (4):

$$P = \frac{DK}{h} \quad (4)$$

where h is the thickness (h_D, h_M or h_R) and K is the partition coefficient between the aqueous phase and the membrane. For P_D and P_R the value of K is unity. Finally D can be estimated from the Stokes–Einstein equation:

$$D \approx \frac{RT}{6\pi\eta r N} \quad (5)$$

where R is the molar gas constant, T is the absolute temperature, η is the apparent viscosity within the UWL or the lipophilic membrane, r is the radius of the permeating drug molecule and N is Avogadro's number. Thus, the diffusion constant within the UWL (D_D) will decrease with increasing viscosity of the layer as well as with increasing molecular weight of the drug. For example, small lipophilic drug molecules frequently possess a large permeability coefficient through the lipophilic membrane (i.e., large P_M value) and, thus, may be able to permeate lipophilic membrane much faster that they can be transported through the UWL. Under such conditions, diffusion through the UWL becomes the rate-limiting step in the absorption process. Presence of mucin in the mucus layer not only increases the thickness (h) of this UWL but also its viscosity (η) both of which will increase its resistance (R_D) and consequent decrease in permeability (P_D) (Eqs. (4) and (5)). Other surface structures, such as villi and microvilli, can also increase h and η of the UWL. Studies have shown that drug diffusion through mucus is up to 100-times slower than through pure water (Khanvilkar et al., 2001). In the preceding discussion it has been assumed that drug permeated through both the UWL and the membrane is via passive diffusion. It is, however, well-known that although permeation through the UWL is always passive, uptake can be either passive and active through the biomembrane. No matter how the drug is transported through the membrane, the drug molecules will always have to permeate the UWL to reach the membrane surface. Thus, Eqs. (2) and (3) can also be applied to describe the effects of the UWL on active transport of drugs through biomembranes.

The serial nature of resistances to drug flux through UWL and membranes (Eq. (2)) have been used to show how excipients can affect drug bioavailability. For example, it has been demonstrated that kosmotropes (structure enforcers), such as sorbitol and fructose, enhance drug permeability through lipophilic membranes but chaotropes (structure breakers), such as urea, decrease the permeability (Falk, 1988). It has also been recognized that hydrophilic cyclodextrins can only enhance drug delivery when R_D is approximately equal or greater than R_M and although cyclodextrins can act as chaotropes, their main effect is to increase the concentration gradient of drug over the UWL leading to more rapid drug delivery to the membrane surface (Mayer et al., 2005; Brewster et al., 2007; Loftsson et al., 2007). Hydrophilic cyclodextrins do not enhance drug delivery through membranes if the lipophilic membrane barrier is the limiting component. When aqueous vehicles, such as hydrogels and o/w creams, are applied to membranes, the UWL is extended into the vehicle and under such conditions cyclodextrins can increase drug delivery from the vehicle through the membrane.

Here, we have briefly reviewed recently generated data on the structure and physicochemical properties of water and used this information to explain how hydrogen-bonded water clusters and networks affect drug solubility and drug delivery through biological membranes. However, water molecules also interact with proteins within the body influencing their structures and functions (Raschke, 2006). Water molecules are located in protein cavities and they may play a role in receptor identification. Formation of water clusters and protein hydration may also be essential for both enzyme stability and activity (Castillo et al., 2006; Oliveira et al., 2006; Chen et al., 2007). Water and its physicochemical properties play an essential role in the pharmacokinetics and pharmacodynamics of drugs.

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