Cosolvency of Dimethyl Isosorbide for Steroid Solubility

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Dimethyl isosorbide (DMI), which is currently under investigation for its potential use as a pharmaceutical vehicle and drug permeation enhancer, is a water-miscible liquid with relatively low viscosity. The solubilization behavior of DMI as a cosolvent for nonpolar drugs was characterized via dielectric constant measurements of binary solvent systems containing DMI and either water, propylene glycol (PG), or polyethylene glycol (PEG). Evidence from the dielectric constant profiles and NMR studies suggest that DMI undergoes complexation with water and PG, but not with PEG, through hydrogen bonding interactions. The solvent complexation exhibited a major effect on the solubilities of prednisone, dexamethasone, and prednisolone in the mixed solvent systems. Maximum solubility of each drug was found to occur near a DMI/water or DMI/PG concentration ratio of 1:2. In the DMI–PEG mixed system, while there is no apparent interaction between DMI and PEG molecules, the solubility of prednisone was found to increase with decreasing dielectric constant.

KEY WORDS: dimethyl isosorbide; steroids; prednisone; prednisolone dexamethasone; propylene glycol; polyethylene glycol; cosolvency; solubilization.

INTRODUCTION

Dimethyl isosorbide (DMI) is a water-miscible liquid with a low viscosity, currently being investigated for its potential use as a pharmaceutical vehicle (1–3), cosolvent (4–8), and absorption enhancer in novel drug delivery (9–11). Further, the addition of DMI significantly increases the solubility of water-insoluble drugs (12) while not adversely affecting drug stability (1).

The dielectric constant has long been used as an important parameter for interpreting solubility data of both electrolytes and nonelectrolytes. In general, in a given mixed-solvent system, the solubility of an electrolyte increases with increasing dielectric constant of the solvent system (13). For nonelectrolytes, while it is generally true that the solute is more soluble in a relatively low dielectric environment, it is often found that the maximum solubility occurs in a mixed system rather than in the pure solvent of lower dielectric constant. Such a phenomenon has been described as a "dielectric requirement" for maximum solubility of a specific drug (14), but little is known as to why such requirements exist.

The dielectric constant is only one of many factors that affect drug solubility. A nonelectrolyte may be more soluble in a solvent having a higher dielectric constant than in a solvent of a lower dielectric constant for a variety of reasons including intermolecular interactions, interfacial tension, and partition coefficient (4). In a mixed-solvent system, interactions between hetero solvent molecules may occur and result in the formation of a complexed solvent system. Such complexed solvents may act more favorably in solubilizing certain drugs because of altered molecular size or perturbated molecular shape caused by the cosolvent molecules and of altered interfacial tension as well as solute–solvent–cosolvent interactions (5,15–17).

Recent studies (4–6) indicated that the solubility of some poorly soluble drugs in binary cosolvent–water systems can be approximated using a log-linear equation where the ratio of drug solubility in the mixed system to that in water is proportional to the volume fraction of the cosolvent. Further, the proportionality constant is related to a number of indices of cosolvent polarity including dielectric constant, solubility parameter, and interfacial tension. While this equation serves to indicate the total polarity of a given system, it is not clear whether intermolecular interactions between a specific solvent pair may play an important role in the solubilization behavior of a mixed solvent system. To obtain insight into the solubilization characteristics of DMI and its possible interaction with other solvent molecules, the solubility profiles of prednisone, dexamethasone, and prednisolone in mixed systems containing DMI and either water, propylene glycol (PG), and polyethylene glycol 400 (PEG) were determined. Characterization of the mixed solvent systems were made via dielectric constant measurement as a function of the mole fraction of dimethyl isosorbide.

EXPERIMENTAL

Materials. Dimethyl isosorbide (ICI America, Inc., Wilmington, DE), propylene glycol, polyethylene glycol 400 (Ruger Chemical Co., Inc., Irvington, NJ), prednisone, dexamethasone, and prednisolone (Sigma Chemical Co., St. Louis, MO) were used as received. All other chemicals were reagent grade.

Methods. Solubilities of prednisone, dexamethasone, and prednisolone were determined in triplicate at 25 ± 0.5°C. Screw-capped glass vials containing suspensions of drugs in appropriate solvents were mounted on a rotating apparatus in a bath for 24 hr. Periodical sampling was carried out to ensure equilibrium solubilization. Analysis of each drug solution was made using a double-beam UV spectrophotometer (Cary 118 C, Varian Associates, Palo Alto, CA). Dielectric constants were measured using a chemical oscillometer (Model 5, E. H. Sargent and Co., Chicago, IL). For NMR studies of DMI interaction with methanol, samples containing 1.45 *M* methanol and varying concentrations of DMI were prepared in $CDCl_3$. The NMR spectra and chemical shift measurements were obtained using a high-resolution NMR spectrometer (R-600 Hitachi Perkin Elmer, Norwalk, CT) with an error of ±1 Hz.

RESULTS AND DISCUSSION

The high solubilization affinity of DMI toward nonpolar

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drugs when compared to other solvents may be attributed to its low dielectric constant. The changes of dielectric constant in the binary systems containing DMI are shown in Fig. 1. Ideally, the dielectric constant of a mixed solvent system is the weighted mean of the individual solvents, assuming that there is little or no interaction between the solvent molecules. Thus, the plot of the dielectric constant versus the composition of the solvent (%, w/w or v/v) should yield a straight line, as seen in the DMI–PEG binary system (plot A in Fig. 1). However, in the DMI–PG and DMI–water systems (plots B and C in Fig. 1), the dielectric constant profiles show a breaking point at 51% of DMI for the DMI–PG system and at 81% of DMI for the DMI–water system. When the concentration of DMI exceeds these breaking points, the changes in dielectric constant becomes smaller as indicated by the reduced slope of the plots. At the breaking point, the molar concentration ratio of DMI to PG and to water is 1:2. These results suggest that DMI may interact with water or PG, but not with PEG to form a complexed solvent system. Since DMI has two cyclic ether oxygens similar to those of dioxane, complexation of DMI with water or PG through hydrogen bonding to form a 1:2 complex is suggested (15). In case of the DMI–water system, a much shallower inflection point occurs at 42% of DMI, which may indicate the formation of still another higher ratio, but a weaker complex.

Figure 1 further demonstrates the differences in dielectric constant changes between complexed and noncomplexed solvent systems. At a relatively high concentration of DMI, where all PG or water molecules are complexed to the DMI molecules, the change of dielectric constant is small because the system is essentially a mixture of DMI and DMI–complex. At low concentrations of DMI, i.e., below the breaking point, the system is a mixture of DMI–PG complex and PG or DMI–water complex and water. In such cases the dielectric constant is a weighted mean of the mixed solvents, and a greater slope should be expected because PG or water has a much higher dielectric constant than the complexed solvent. The results, however, do not indicate an intermolecular interaction between DMI and PEG, presumably because of the relatively larger molecule of PEG and of its high viscosity.

To demonstrate the ability of DMI to act as a hydrogen acceptor, the interaction of DMI with methanol was studied using an NMR technique. Figure 2A shows the chemical shifts of the hydroxyl and methyl protons of methanol as a function of concentration in the absence of DMI. The hydroxyl proton, which may be involved in self-association exhibits a concentration dependent chemical shift. Figure 2B shows the effect of DMI on the chemical shift of the hydroxyl proton of methanol, held at a constant concentration of 1.45 M. The results show a nonlinear change of the chemical shift as a function of the molar ratios of DMI/methanol, thus indicating the hydrogen bonding interaction between methanol and dimethyl isosorbide.

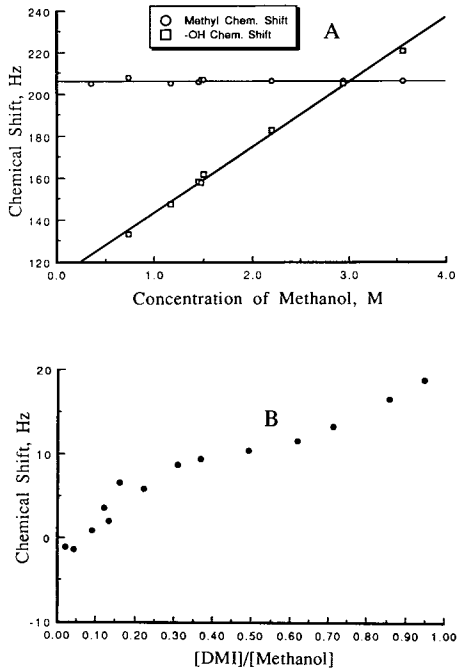

Fig. 2. (A) Chemical shift of methanol NMR signals as a function of methanol concentration in $CDCl_3$. (B) Plot of chemical shift change of the hydroxyl proton of methanol as a function of the concentration ratio of DMI/methanol.

Figures 3, 4, and 5 show the relationship between drug solubility (prednisone, dexamethasone, and prednisolone) and the dielectric constant of the mixed-solvent systems. In the DMI–PG system (Fig. 3), it is seen that the maximum solubilities of the steroids occur at about the breaking point. At a DMI concentration below the breaking point, the solubility decreases with increasing dielectric constant of the system. The change in drug solubility above the breaking point does not follow the general principle of dielectric constant as an index of solvent polarity. This result suggests that the DMI–PG complex confers a higher solubility to the steroids than pure DMI. It is quite possible that the complexed solvent molecule has a greater hydrophobicity than pure sol-

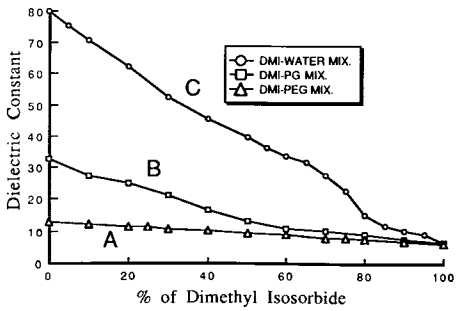

Fig. 1. Dielectric constant profiles of the binary systems.

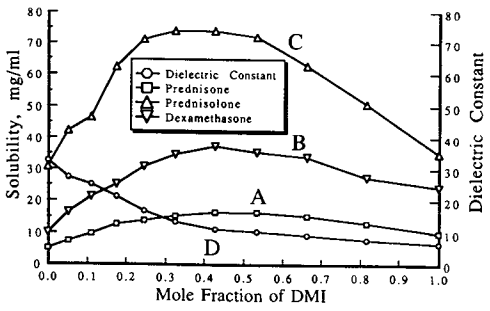

Fig. 3. Solubility profiles of steroids in the DMI–PG system. The dielectric constant curve is also given.

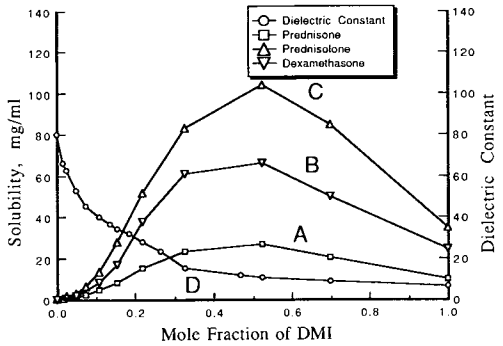

Fig. 4. Solubility profiles of steroids in the DMI–water system. The dielectric constant curve is also given.

vent for the dissolution of the nonpolar steroids used in this study.

The solubility profiles of the steroids measured in the DMI–water system are shown in Fig. 4. Maximum solubility for each drug occurred at DMI concentrations slightly above the dielectric constant breaking point. These results are similar to those obtained in the DMI–PG system. Figure 5 shows the solubility of prednisone (plot A) and dielectric constant profile (plot B) obtained in the DMI–PEG system. It can be seen that in the absence of an apparent specific interaction between the mixed solvent molecules, the solubility decreases with increasing dielectric constant.

Several studies have shown that the dielectric constant is not a good predictor of nonelectrolyte solubility in cosolvent systems, and other polarity indices such as surface and interfacial tension are more accurate in the prediction of drug solubility (4,5,18). These phenomena may in part be attributed to the complexation between hetero solvent molecules in the binary system, since the complexed solvent is likely to exhibit a higher degree of solvation of the nonpolar drug and greatly reduced solvent–solvent interactions between like molecules. Indeed, our results show that maximum solubility of the steroids occurs in the concentration region with a high degree of complexation of the binary solvents. However, the solubility maxima could result from a selective solvation, characterized by unique interactions between all three components, which in turn depends on the

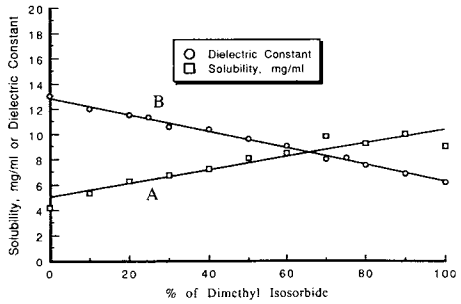

Fig. 5. Solubility and dielectric constant curves of prednisone in the DMI–PEG binary system.

physical properties of the whole system. The dielectric constant may be considered a solubility indicator when complexation of the solvent molecules is negligible as was seen in the DMI–PEG system. The solubilization characteristics of DMI is manifested by its ability to interact with proton donating solvents through hydrogen bonding. In comparing the DMI–water and DMI–PG systems, the results show that in the region of complexation, the water-containing system gives consistently higher drug solubility than the DMI–PG solvent mixture. This may be attributed to the fact that water is a stronger proton donor than propylene glycol.

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