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Effect of Hydroxypropyl β-Cyclodextrin on Drug Solubility in Water-Propylene Glycol Mixtures

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ABSTRACT

Combined effects of cosolvency and inclusion complexation on drug solubility were studied using a model hydrophobic compound (carbamazepine) and a model hydrophilic compound (Compound S). Propylene glycol (PG) was used as the nonaqueous solvent, and deionized water was employed for the aqueous systems. Hydroxypropyl β-cyclodextrin (HPβCD) was chosen as the complexing agent and studied at concentrations up to 28% (w/v). Complex formation constants (K_c) and solubility enhancement ratios were determined for the respective compounds in various water/PG vehicles. The data suggested that the inclusion of the compounds was most favorable when water alone was used as the vehicle. However, the combined approach of cosolvency and complexation resulted in a significant increase in the total apparent solubility of carbamazepine (the hydrophobic compound). The same was not observed with Compound S (the hydrophilic model), since PG weakened the interactions between the molecule and HPβCD, and thus, no synergistic or additive effects were observed with the combined approach of complexation and cosolvency.

Key Words: Complexation; Solubility; Cyclodextrins; Carbamazepine; Cosolvency; Inclusion compounds; Propylene glycol.

INTRODUCTION

The use of cosolvency with propylene glycol or complexation with cyclodextrin to improve solubility in aqueous media, dissolution rate, chemical stability, and bioavailability of various drugs has been extensively investigated in recent years.[1–6] In this study, we investigated the combined effects of cosolvency and complexation on drug solubility using two model compounds, i.e., carbamazepine (hydrophobic model) and Compound S (hydrophilic model). The intent of this work was to determine whether the combined

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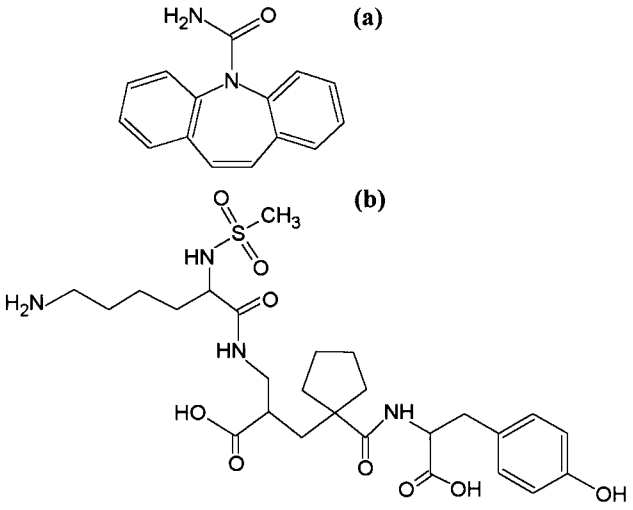

Figure 1. Chemical structures of carbamazepine (a) and Compound S (b).

approach would enhance the solubility of these compounds in an effort to provide new pharmaceutical formulations of these specific molecules.

MATERIALS

The antiepileptic drug carbamazepine (5H-dibenz-[b,f]azepine-5-carboxamide) (Fig. 1a), MW 236.27, was provided by Orgamol (Lyon, France) and used as received. Compound S (Fig. 1b), MW 584.68, a potential antihypertensive agent, was used as received. Hydroxypropyl β-cyclodextrin (HPβCD), with an average molecular weight of ~1400 and a molar substitution of 0.58–0.73, was obtained from Wacker Biochem Corporation (Adrian, MI). Propylene glycol (PG) was obtained from Dow Chemical Company (Midland, MI). Acetonitrile and water were reagent grade, purchased from Burdick and Jackson (Muskegon, MI). Ammonium acetate and methanol were reagent grade, purchased from J.T. Kaber (Philipsburg, NJ).

METHODS

Solubility Determination

An excess of carbamazepine or Compound S (~1 gram) was added to 20-mL glass scintillation vials (Kimble Glass Inc., Vineland, NJ) containing 10 mL of one of the following media: water, water/PG (w/w, 6:4 ratio), water/PG (w/w, 3:7 ratio), and PG with 0%, 16%, and 28% w/v HPβCD. The sample vials were then rotated using an end-over-end mechanical rotator at 50 rpm at room temperature for 48 hours to reach equilibrium solubility. The samples were filtered through a 0.45-μm filter (Acrodisc CR PTFE membrane filter, Gelman Sciences, Ann Arbor, MI). After discarding the first milliliter of the filtrates to eliminate any membrane adsorptive effect, the filtrates were collected for high-performance liquid chromatography (HPLC) of carbamazepine or liquid chromatography-mass spectrometry (LC-MS) analysis of Compound S. Solubility enhancement ratios were calculated by dividing the sample solubility by the compound's intrinsic solubility in water.

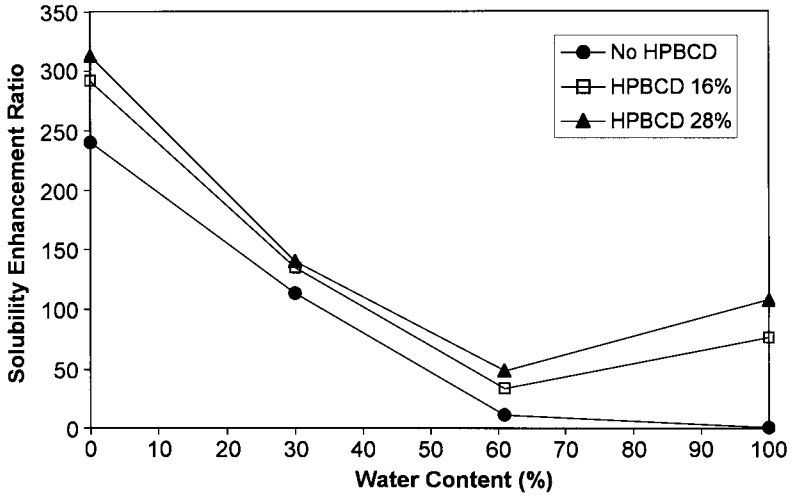

Figure 2. Effect of hydroxypropyl-β-cyclodextrin on aqueous and organic solubility enhancement ratio of carbamazepine.

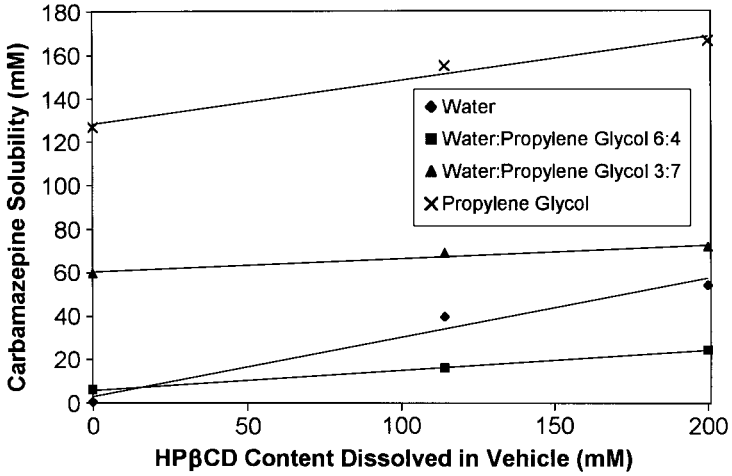

Figure 3. Molar solubility of carbamazepine as a function of HPβCD content.

HPLC and LC-MS Analyses

Filtrates from solubility studies were appropriately diluted in mobile phase and injected into the HPLC or LC-MS for analysis. Carbamazepine was analyzed on a Waters HPLC system (Milford, MA) equipped with Hypersil ODS analytical column (2.1 × 200 mm, 5 μm, Agilent Technologies, Palo Alto, CA) along with a Supelco Pelliguard LC-18 (2 × 4.6 cm, Supelco, Bellefonte, PA) guard column. The mobile phase was composed of 58% deionized water, 37% methanol, and 5% acetonitrile. The flow rate was controlled at 0.4 mL/min and the effluent was detected at 220 nm.

Compound S samples were analyzed using an LC-MS system. The LC-MS system consisted of a Waters 2690 Alliance Separation Module and a Micromass Quattro LC. A Phenomenex Luna column, C-18(2) (150 × 2.0 mm, 5 μm Phenomenex, Torrance, CA) was used with a gradient elution from 5% acetonitrile to 42% acetonitrile in 5 mM ammonium acetate for 8 minutes, then 42% acetonitrile for 2 additional minutes. Subsequently, the column was re-equilibrated at the initial conditions for 5 minutes. The flow rate was controlled at 0.25 mL/min.

RESULTS AND DISCUSSION

The solubility enhancement ratio of carbamazepine as a function of water content of the vehicle and HPβCD concentration is shown in Fig. 2. Carbamazepine is a hydrophobic drug, which is practically

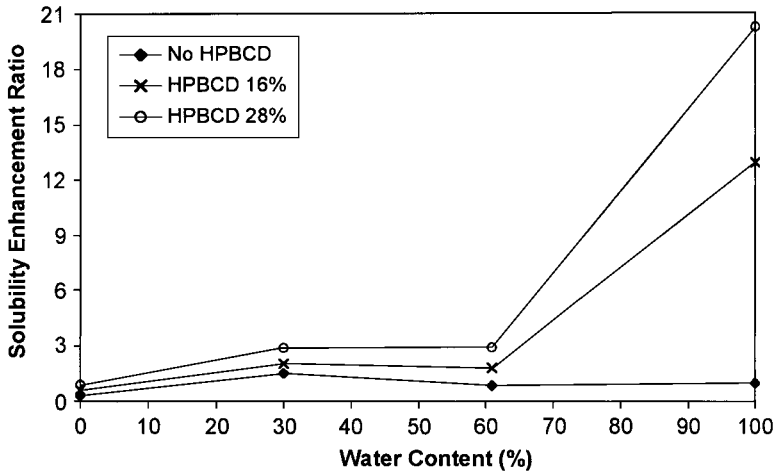

Figure 4. Effect of hydroxypropyl-β-cyclodextrin on aqueous and organic solubility enhancement ratio of Compound S.

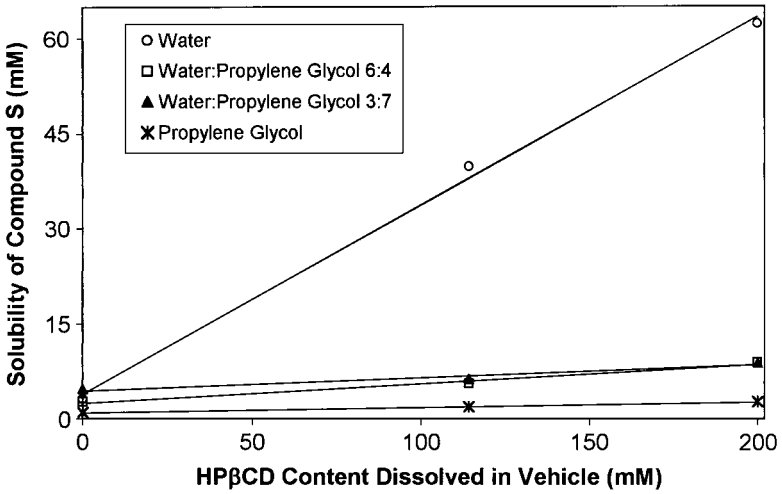

Figure 5. Molar solubility of Compound S as a function of HPβCD content.

insoluble in water with an aqueous solubility of 120 μg/mL. An increase of propylene glycol content (i.e., a decrease in water content) in the vehicles produced an exponential increase in the solubility of the drug. In 100% propylene glycol, there was a 240-fold enhancement of the solubility of carbamazepine, as compared to its solubility in water. An increase in the concentration of HPβCD produced a linear increase in the solubility of carbamazepine for all the solvent systems tested in the present study (Fig. 3). Additionally, the solubility increase afforded by the addition of HPβCD was far more significant for the purely aqueous system.

The effect of HPβCD and water content on solubility enhancement ratio of Compound S is shown in Fig. 4. Compound S is a hydrophilic compound containing one weakly acidic phenolic group, two more strongly acidic carboxylic acid groups, and one strong basic primary amine group with an aqueous solubility of 1800 μg/mL. An increase in propylene glycol content in the vehicles did not change the solubility of Compound S to a significant degree. Similar to carbamazepine, an increase in the concentration of HPβCD produced a linear increase in the solubility of Compound S for all solvent systems tested in the present study (Fig. 5). Furthermore, the solubility increase provided by the addition of

Table 1. Complex formation constants and solubility enhancement ratios for carbamazepine and Compound S in water/propylene glycol systems containing hydroxypropyl β-cyclodextrin.

Guest molecule	Vehicle system	Complex formation constant (M^{-1})[a]	Solubility enhancement ratio[b]
Carbamazepine	Water	725.3	104.3
Carbamazepine	Water/PG (6:4)	17.0	4.1
Carbamazepine	Water/PG (3:7)	1.1	1.2
Carbamazepine	PG	2.0	11.3
Compound S	Water	137.4	20.2
Compound S	Water/PG (6:4)	12.2	3.4
Compound S	Water/PG (3:7)	4.5	1.9
Compound S	PG	9.3	2.9

[a]Complex formation constants (K_c) were estimated via the solubility technique.[9] In this technique, the total apparent solubility of the substrate is measured as a function of total ligand concentration. Complex formation constants were calculated from the slope (β) of the solubility curves (Figs. 3 and 5) and the drug solubility in the pure vehicle (S_0) using the following equation: $K_c = \beta \cdot (S_0 \cdot (1-\beta))^{-1}$.

[b]Solubility enhancement ratio is the ratio between the compound solubility in the vehicle containing 28% HPβCD and the compound solubility in the pure vehicle.

HPβCD was far more significant for the system using water alone as the vehicle.

The inclusion of a guest molecule within the cyclodextrin cavity is dependent on: 1) structural factors such as the size and shape of the guest molecule as well as the dimensions of the cyclodextrin cavity, 2) the ability of the guest molecule to displace the solvent from the cavity, 3) the extent of the interactions between the hydrophobic functionalities of the guest molecule and the apolar cavity of the cyclodextrin; and 4) the extent of interactions between the hydrophilic moieties of the guest molecule and the polar exterior of cyclodextrin as well as the solvent. Table 1 summarizes the complex formation constants and solubility enhancement ratios for all the systems tested. Complex formation constants for carbamazepine derived from this study agree with other such findings in the literature.[7,8] There was a positive trend observed between complex formation constants and solubility enhancement ratios (the ratio between the drug's solubility in the system containing 28% HPβCD and the drug's solubility in the pure vehicle). The pure PG systems seemed to show a deviation from this trend. Although the applicability of a 100% pure PG system in a pharmaceutical formulation is limited, there was an interesting deviation from the trend in such solvent systems that suggest the presence of a synergy between nonaqueous solubility and inclusion complexation. This observation may warrant further investigation utilizing more solvent systems containing greater than 70% (w/w) PG.

The trend observed for both compounds tested was consistent with the inclusion of the compounds in HPβCD, having been the most favorable when using water as the vehicle. The addition of propylene glycol to the solvent system resulted in a marked decrease in the complex formation constants, which indicated the relatively weak interactions between the guest molecule and HPβCD in the cosolvent systems. However, the total apparent solubility of the drug is the sum of the free drug solubility and drug-HPβCD complex solubility, as opposed to that in water. A 317-fold overall solubility enhancement (Fig. 2) over the solubility in water was obtained for carbamazepine by using a combined approach of nonaqueous vehicle and complexation with 28% HPβCD. The combined approach did not result in any significant solubility enhancement for the hydrophilic compound in this study. This may be attributed to the effect of the nonaqueous solvent (PG) on the strength of the interactions between Compound S and HPβCD. Cosolvency weakened the interactions between the guest molecule and HPβCD, resembling the effect of a nonsolvent on the molecule's solubility.

CONCLUSIONS

Water is the most commonly used solvent in which complexation reactions are performed. Experience with other solvents is quite limited. The results from this study suggest that the inclusion of the compounds in HPβCD would be most favorable when using water as the medium. By using a combined approach of a nonaqueous vehicle with the addition of HPβCD, the total apparent solubility for carbamazepine can be significantly enhanced relative to water. However, for the hydrophilic compound the combined approach did not have an additive or synergistic effect on the molecule's solubility.

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