Synergistic Effect of PEG-400 and Cyclodextrin to Enhance Solubility of Progesterone

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INTRODUCTION

The addition of cosolvent to a formulation is a commonly used method for improving the solubility of a drug. Polyethylene glycol (PEG)-400 is one of the most widely used cosolvents for improving the aqueous solubility of hydrophobic drugs. Cyclodextrins (CDs) also have been used to improve solubility and stability of drug compounds.[1] Higher molecular weight PEGs have been used in conjunction with various CDs in solid dispersion systems.[2] Harada[3] reported that PEGs form complexes with α-CD and γ-CD, but not with β-CD. In the current study, therefore, β-CD was chosen to investigate the synergistic effects of CD and PEG-400 on the solubility of a model hydrophobic drug.

In CD aqueous solutions, the addition of propylene glycol or ethanol has been reported to reduce the solubility of testosterone and ibuprofen.[4] Hydroxypropyl methylcellulose (HPMC) was observed to increase the solubilization effect of CDs. The amount of CD needed in the solid dosage form was significantly lower in the presence of HPMC.[5] Enhancement of solubilization of ETH-615 and midazolam was reported in the presence of water-soluble polymers.[6,7] Zung[8] hypothesized that a series of alcohols have a synergistic effect on the cosolvency and complexation of pyrene. Zung also suggested that the cosolvents could act as a space-regulating molecule to assist the drug to fit inside the CD cavity.

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In this study, progesterone, a neutral hydrophobic compound, was selected as a model compound. The goal of the project was to test the hypothesis that PEG-400 and CD may have a synergistic effect on the solubility of progesterone. Captisol® (hepta sulfobutyl ether) and Trappsol® HPB (hydroxypropyl beta CD) were used as 2 different types of CDs. Captisol possesses a negative charge, whereas Trappsol HPB is uncharged. The effect of polysorbate 80 on the synergism of PEG-CD in solubilization of the model compound also was examined.

MATERIALS AND METHODS

Materials

Progesterone, micronized powder, USP was purchased from Gerdina, CA. Captisol and Trappsol HPB were purchased from Cydex, Inc, Kansas City, KS, and CTD, Inc, High Spring, FL, respectively. PEG-400 and polysorbate 80 were obtained from Sigma and Spectrum, respectively. All other chemicals used were of analytical grade and were used as is.

Methods

Solubility Experiments

In the solubility experiments, progesterone was suspended in various solvents, namely: water, polysorbate 80, PEG-400, and 3% and 6% aqueous solutions of Captisol and Trappsol HPB. The samples were shaken at 25°C ± 2°C for 24 hours and filtered through a 0.45-μm syringe filter. The drug concentration in the filtered solution was determined using high performance liquid chromatography (HPLC) after appropriate dilution with methanol. The cosolvent systems of PEG-400/water and PEG-400/water/polysorbate 80 were prepared by weight. The percentage of PEG-400 in the PEG-400/water cosolvent system was varied from 0.2% to 90%. The solubilization capacity of cosolvent systems

Table 1. Solubility of Progesterone in Selected Vehicles at 25ºC ± 2°C

Vehicles	Solubility of Progesterone (mg/mL)[*]
PEG-400	15.3 ± 0.03
Polysorbate 80	11.9 ± 2.31
3% Captisol® aqueous solution	1.6 ± 0.05
3% Trappsol® HPB aqueous solution	1.1 ± 0.02
6% Captisol®aqueous solution	5.0 ± 0.08
6% Trappsol® HPB aqueous solution	1.3 ± 0.05
Water	0.007

[*]Expressed as mean ± SD (n = 3)

was investigated in a similar fashion as mentioned in this section. In another set of solubility experiments, the solubility of progesterone was determined in a 50% PEG-400/water system containing 3% Captisol or 3% Trappsol HPB in the presence of polysorbate 80.

Chromatographic Analysis

A simple chromatographic system was developed in-house to examine progesterone in the solubility samples. The mobile phase consisted of acetonitrile and 0.5% acetic acid solution (50:50, vol/vol). A 10-cm C18 column with a particle diameter of 5 µm was used. The flow rate was 1.2 mL/min and the wavelength of detection was 254 nm. The observed retention time for progesterone in this system was 5.9 minutes.

RESULTS AND DISCUSSION

Table 1 lists the solubility values of progesterone in selected vehicles. Progesterone has very poor water solubility (0.007 mg/mL) at 25°C ± 2°C. The solubility values of progesterone in PEG-400 and polysorbate 80 were observed to be approximately 15.3 mg/mL and 11.9 mg/mL, respectively. In solutions containing 3% Captisol or 3% Trappsol HPB, the solubility values were approximately 1.6 mg/mL and 1.1 mg/mL, respectively. The solubility increased in both systems with further addition of the CDs, although not to the same degree in each. It became obvious that PEG-400, polysorbate 80 and CDs help solubilization of progesterone.

The solubility of progesterone in PEG-400 decreased significantly with a small addition of water—from approximately 15.3 mg/mL in 100% PEG-400 to 1.45

mg/mL in 90% PEG-400 system. The solubility in a 50% PEG-400/water system was found to be only 0.2 mg/mL, showing a nonlinear decline. **Table 2** lists the theoretical and observed solubility values of progesterone in the PEG-400/water systems containing 3% Trappsol HPB or 3% Captisol at 25°C ± 2°C. The data for the system containing 3% Trappsol HPB are depicted in **Figure 1**. The theoretical solubility for PEG-400/water/3% CD systems were calculated by the addition of solubilities in PEG-400/water systems and those observed in 3% CD solutions. In solutions containing Trappsol HPB, at lower PEG-400 concentrations (less than 50%), the observed solubility was significantly greater than the expected solubility. For example, the theoretical value in 5% PEG-400/water system containing 3% Trappsol HPB was 1.11 mg/mL. The observed solubility of progesterone in the same system was 2.18 mg/mL, indicating approximately a 96% increase compared to the theoretical value. In general, the improvement in solubility due to synergism was observed in samples containing 5% to 50% PEG-400 and 3% Trappsol HPB. In systems containing PEG-400 concentrations greater than 60%, the synergistic effect decreased, yielding observed solubilities close to the theoretical values. Overall, PEG-400 and Trappsol HPB showed a synergistic effect in improving progesterone solubility in water. In the case of systems containing Captisol, no synergism was observed (**Table 2**) in improving the solubility of progesterone. The observed solubility was less than the theoretical solubility.

Polysorbate 80 often is used in the PEG-400/water system as a surfactant. Different percentages of poly

Table 2. Solubility of Progesterone in PEG-400/Water Systems with 3% Trappsol ® HPB or 3% Captisol ® at 25°C ± 2 °C

% of PEG-400 in PEG-400/Wwater System	Solubility of Progesterone (mg/mL)			
	Theoretical Value (with 3% Trappsol® HPB)[*]	Observed Value with 3% Trappsol® HPB (% increase[+])	Theoretical Value (with 3% Captisol®)[*]	Observed Value (with 3% Captisol®)
90	2.55	2.79 (9.4)	3.05	1.45
70	1.90	2.09 (10.0)	2.40	1.06
50	1.30	1.77 (36.1)	1.80	1.10
30	1.15	1.91 (66.1)	1.65	1.11
10	1.11	2.09 (88.3)	1.61	1.21
5	1.11	2.18 (96.4)	1.61	ND
1	1.11	1.61 (45.0)	1.61	1.18

[*]The theoretical solubility is the solubility of progesterone in a PEG-400/water system without CD plus the solubility of progesterone in 3% CD aqueous solution.
[+]% increase = (Observed solubility - theoretical solubility)*100/theoretical solubility
Values in italics indicate that the observed values were greater than theoretical values.
ND = not determined
n=1 only few data points were listed in the table Figure 1 has all the points

sorbate 80 (0%-12%) were added to a 50% PEG-400/water system containing 3% Trappsol HPB or 3% Captisol. The solubility of progesterone in a 50% PEG-400/water system without polysorbate 80 was observed to be 0.19 mg/mL. By adding polysorbate 80, the solubility increased sequentially to 1.03 mg/mL with 12% polysorbate 80. The observed solubility in a system containing Trappsol HPB were greater than the theoretical solubility for a system containing up to 6% polysorbate 80. The increase in solubility was 37% and 12% for samples containing 0% and 6% polysorbate 80 in the PEG-400/water system. Higher amounts of polysorbate 80 nullified the synergistic effect of PEG-400 and Trappsol HPB. In the case of Captisol, no synergistic effect was observed to improve the solubility.

In early 1990s, it was believed that cosolvents reduced the solubilization capacity of CDs. The solubility of testosterone with hydroxypropyl-β-CD was reported to be lower in the presence of 80% ethanol.[9] However, in recent years, polymers have been reported to improve the solubilization capacity of CDs. A synergism between CDs and water-soluble polymers in solubilizing naproxen was observed.[10] A mathematical model was developed to describe the combined effect of cosolvency and complexation on fluasterone solubilization.[11]

The most fundamental model for solubilization of a solute in a solvent involves liberation of a solute molecule, creation of a hole in the solvent, and accommodation of the solute molecule in the solvent cavity.[12] Work must be done to overcome the intermolecular forces of attraction in dissolving a solute. Four types of interactions, namely solute-solvent, ion-dipole, dipole-dipole, and hydrogen bonding-hydrophobic, have been reported. In addition, if the system involves a polymer, the conformation of polymer chains also plays a role in solute-solvent interactions.

For a reaction (in this case, the solubilization of a solute in a solvent), free energy (ΔF) is defined as $\Delta F = \Delta H - T\Delta S$, where terms H and S are enthalpy and entropy, respectively. For a spontaneous reaction to occur, the associated ΔF must decrease or ΔF has to be negative. The dissolution of a solute involves the breaking of solid-state bonds in the solute, which is normally an endothermic process. The incorporation of the liberated solute molecules in the solvent cage is normally an exothermic process. One has to consider such enthalpic and entropic contributions in understanding the mechanism of solubilization.

Water as a solvent has some unique properties: a high level of hydrogen bonding, a sizable dielectric constant (80 at 20°C), and large surface tension (71 dynes/cm). The structure of PEG-400 is $H-(O-CH_2-CH_2)_n-OH$, where n is approximately 8 to 9. This peculiar structure makes PEG miscible with water through hydrogen bonding. The hydrophobic hydrocarbon region helps to
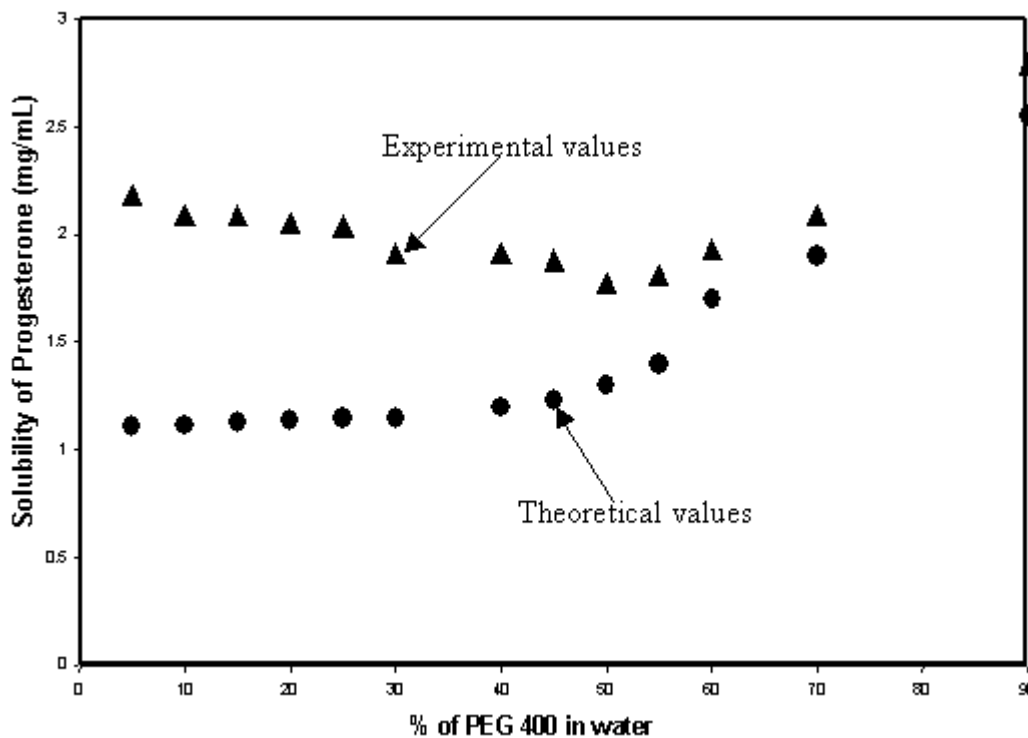
Figure 1. Effect of 3% Trappsol ® HPB on the solubility of progesterone in PEG-400/water systems.

break the hydrogen bonding between water molecules, thus reducing overall intermolecular interactions.[13] In other words, PEG may assist to reduce the dipole moment of water and allow hydrophobic compounds to fit in.

The solubilization of solute molecules because of the inclusion complex in CD has been demonstrated in numerous cases. Although a variety of other factors, such as Van der Waals, hydrogen bonding, and hydrophobic forces, play important roles in forming a stable complex, it mainly depends on the CD cavity and the accessibility of the drug molecule to the CD cavity. The type, length, and degree of substitution also affect the solubilization effect of CD. In the case of Captisol, the negative charge on the molecule also helps ion pairing with the cationic molecules.

In the current study, the system examined is very complex with 4 components: progesterone, water, PEG-400, and CD. In the quaternary system in this study, the ΔF value must be more negative than the ΔF values of the PEG-400/water/progesterone or CD/water/progesterone systems. It is possible that ΔH might have a negative value and the entropic term

must be positive ($\Delta S > 0$). The entropic term may indicate spontaneity or ease of preparation. Faucci and Mura[10] studied synergism between CD and water-soluble polymers on naproxen solubility. They reported that water-soluble polymers increased the complexation efficacy of CDs toward naproxen. No previous sonication or heating treatments of the drug/CD/polymer suspensions was necessary to obtain this favorable effect. The synergistic effect of CD and PEG-400 in the current study could be attributed to additional breaking of hydrogen bonds in water's structure and a decrease in the dipole moment. At PEG-400 concentrations of 50% and higher, the synergistic effect diminished. It must be because of a shift from a predominantly aqueous environment to a PEG-based environment. In that case, water would be acting as a cosolvent instead of the main solvent. As a result, the polymer conformation and the effect of CD on the polymer conformation would affect the solubility of the model drug.

An evaluation may indicate that the negative charge on Captisol may have a role to play in this lack of synergism. The ionic charge of Captisol must have introduced some kind of orderliness in the solvent structure,

resulting in the lack of synergism. The addition of polysorbate 80 made the system more complex and hampered the synergistic effects at higher concentrations. Polysorbate 80 is a strong surfactant, which reduces the surface tension of water. The micelle formation of polysorbate 80 may be contributing to reduce the synergistic effect. Such a micelle formation could be taking away water molecules, which are needed for the solubilization. The exact role of polysorbate 80 in such a complex system is unclear at this time.

CONCLUSION

PEG-400, polysorbate 80, and 2 CDs (Trappsol HPB and Captisol) were used in an attempt to improve the aqueous solubility of a model hydrophobic drug, progesterone. The aqueous solubility of progesterone improved significantly from 0.007 mg/mL by the addition of PEG-400, CDs, and polysorbate 80. In systems containing various amounts of PEG-400 and 3% Trappsol HPB in water (% wt/wt), the theoretical solubility was calculated by adding the solubilities in the individual systems. The observed solubility values were up to 96% higher than the theoretical values. The effect of synergism was significant in 5% to 50% PEG-400/water systems containing Trappsol HPB. Systems containing Captisol did not show such synergistic effects. In general, the addition of polysorbate 80 to the PEG-400/water systems containing CDs affected synergism negatively.

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