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The Solubility–Permeability Interplay When Using Cosolvents for Solubilization: Revising the Way We Use Solubility-Enabling Formulations

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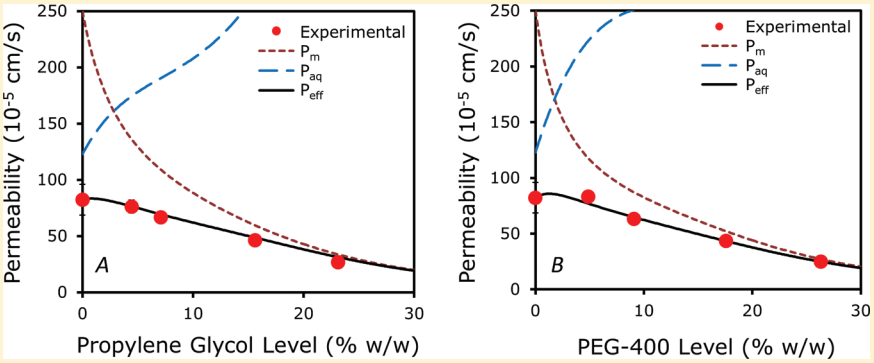

ABSTRACT: We have recently reported the interplay between apparent aqueous solubility and intestinal membrane permeability, showing the trade-off between the two when using cyclodextrin- and surfactant-based systems as solubility-enabling formulations. In these cases, the decreased permeability could be attributed directly to decreased free fraction of drug due to the complexation/micellization inherent in these solubilization methods. The purpose of this study was to investigate the direct solubility–permeability interplay, using formulations in which complexation is not the mechanism for increased solubilization. The apparent aqueous solubility (S_{aq}) and rat intestinal permeability (P_{eff}) of the lipophilic drug progesterone were measured in systems containing various levels of the cosolvents propylene glycol and PEG-400, since this solubilization method does not involve decreased free fraction. Thermodynamic activity was maintained equivalent in all permeability studies (75% equilibrium solubility). Both cosolvents increased progesterone S_{aq} in nonlinear fashion. Decreased P_{eff} with increased S_{aq} was observed, despite the constant thermodynamic activity, and the nonrelevance of free fraction. A mass-transport analysis was developed to describe this interplay. The model considers the effects of solubilization on the membrane permeability (P_m) and the unstirred water layer (UWL) permeability (P_{aq}), to predict the overall P_{eff} dependence on S_{aq}. The analysis revealed that (1) the effective UWL thickness quickly decreases with $\uparrow S_{aq}$, such that P_{aq} markedly increases with $\uparrow S_{aq}$; (2) the apparent membrane/aqueous partitioning decreases with $\uparrow S_{aq}$, thereby reducing the thermodynamic driving force for permeability such that $\downarrow P_m$ with $\uparrow S_{aq}$; (3) since $\uparrow P_{aq}$ and $\downarrow P_m$ with $\uparrow S_{aq}$, the UWL is shorted out and P_{eff} becomes membrane control with $\uparrow S_{aq}$. The model enabled excellent quantitative prediction of P_{eff} as a function of S_{aq}. This work demonstrates that a direct trade-off exists between the apparent solubility and permeability, which must be taken into account when developing solubility-enabling formulations to strike the optimal solubility–permeability balance, in order to maximize the overall oral absorption.

KEYWORDS: *low-solubility drugs, solubility–permeability trade-off, drug transport analysis, intestinal permeation, oral drug absorption*

INTRODUCTION

The rate and extent of drug absorption from the gastrointestinal (GI) tract are very complex and affected by many factors, including physicochemical, physiological and factors related to the dosage form. Despite this complexity, the work of Amidon et al.[1] revealed that the fundamental events controlling oral drug absorption are the permeability of the drug through the GI membrane and the solubility/dissolution of the drug dose in the GI milieu. These key parameters are characterized in the Biopharmaceutics Classification System (BCS), one of the most significant available tools to facilitate oral drug product development.[2−5]

Modern drug discovery techniques (e.g., advances in high throughput screening methods, the introduction of combinatorial chemistry) have resulted in increased number of drug

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candidates that exhibit low water solubility. By some estimates, more than 40% of new drug candidates are lipophilic and have poor aqueous solubility.[2,6−9] These low water solubility compounds often suffer from limited oral bioavailability. A great challenge facing the pharmaceutical scientist is to formulate these molecules into orally administered dosage forms with sufficient bioavailability.[10−18]

A wide variety of solubility enabling formulation approaches have been developed and are routinely used to tackle the problem of inadequate aqueous solubility, e.g. the use of surface active agents, lipid-based formulations, cyclodextrins, cosolvents, amorphous solid dispersions, and other techniques. While significant increased apparent solubility may certainly be achieved by these solubility-enabling formulations, the effect on the overall fraction dose absorbed is rather erratic; outcomes of increased, unchanged, or decreased absorption following the use of solubility-enabling formulations have been reported in the literature.[19−25] Although the intestinal permeability is, alongside the aqueous solubility, a key parameter that governs oral absorption, the impact of solubility-enabling formulations on the intestinal membrane permeability of a lipophilic drug is often overlooked and poorly understood. Hence, we have investigated the interplay between the apparent solubility and permeability while using solubility-enabling formulations.

We have previously showed that a trade-off exists between apparent solubility increase and permeability decrease when using a cyclodextrin-based formulation for the solubilization of lipophilic drugs.[26] We have recently further expanded the research, showing a similar phenomenon when using surfactant-based formulations.[27] These results were in corroboration with previously published papers signifying that complexation/micellization-based solubilization techniques may lead to lower absorption;[19−24,28] the complexation which gives rise to the significant apparent solubility enhancement also results in decreased free fraction of drug, which may significantly decrease the amount of drug available for intestinal membrane permeation.[29−33] While this trade-off between the apparent solubility and intestinal permeability is now well established and understood for complexation-based solubilization techniques, the focus of the current research was whether this solubility−permeability trade-off is unique to complexation-based solubilization methods or it is a general phenomenon attributable to the nature of increased apparent solubility per se, regardless of the solubilization method being used.

Cosolvent systems are frequently used to formulate drugs with low aqueous solubility.[34−36] Solubilization by cosolvent does not involve complexation with the drug, and therefore the issue of free fraction is not relevant for these systems. Hence, such a system allows us to investigate the direct solubility−permeability interplay. We have employed the single-pass rat jejunal perfusion as the permeability experimental model, since it has been proven to simulate well the real in vivo situation, including the unstirred water layer (UWL) and the intestinal membrane permeability. Given their widespread use in pharmaceutical formulations, propylene glycol and PEG-400 were chosen as the model cosolvent systems in this research. The model drug used in this work is the highly lipophilic, low-solubility, BCS class II drug progesterone, which is not known to be a substrate for transporters. Thermodynamic activity was maintained equivalent in all permeability studies (75% equilibrium solubility) to eliminate potential bias. A mass transport analysis was developed and employed to describe the direct solubility−permeability interplay. Overall, this work reveals that a direct solubility−permeability trade-off exists when using solubility-enabling formulations, which must not be overlooked. It is not enough to increase the apparent solubility of the lipophilic drug; rather, it is necessary to strike the optimal solubility−permeability balance in order to maximize the overall fraction of dose absorbed resulted by the formulation.

THEORY: QUASI-EQUILIBRIUM ANALYSIS OF THE EFFECT OF INCREASED SOLUBILITY ON MEMBRANE PERMEABILITY

The intrinsic membrane permeability of the drug ($P_{m(o)}$) in the absence of solubilizer (i.e., cosolvent) can be written as[37]

$$P_{m(o)} = \frac{D_{m(o)}K_{m(o)}}{h_{m(o)}} \quad (1)$$

where $D_{m(o)}$ is the membrane diffusion coefficient of the drug in the absence of solubilizer, $K_{m(o)}$ is the membrane/aqueous partition coefficient of drug in the absence of solubilizer, and $h_{m(o)}$ is the membrane thickness in the absence of solubilizer.

Likewise, the apparent membrane permeability of the drug in the presence of solubilizer (P_m) can be written as

$$P_m = \frac{D_m K_m}{h_m} \quad (2)$$

where D_m is the apparent membrane diffusion coefficient of the drug in the presence of solubilizer and K_m is the apparent membrane/aqueous partition coefficient of the drug in the presence of solubilizer.

Assuming that the presence of solubilizer does not affect the membrane diffusivity or thickness such that $D_{m(o)} = D_m$ and $h_{m(o)} = h_m$, eqs 1 and 2 can be combined to give

$$P_m = \frac{P_{m(o)}K_m}{K_{m(o)}} \quad (3)$$

$K_{m(o)}$ and K_m can be expressed as[38]

$$K_{m(o)} = \frac{S_{m(o)}}{S_{aq(o)}} \quad (4)$$

$$K_m = \frac{S_m}{S_{aq}} \quad (5)$$

where $S_{m(o)}$ is the membrane solubility of the drug, $S_{aq(o)}$ is the intrinsic aqueous solubility of the drug in the absence of solubilizer, S_m is the apparent membrane solubility of the drug in the presence of solubilizer, and S_{aq} is the apparent aqueous solubility of the drug in the presence of solubilizer.

Assuming that the presence of solubilizer does not affect the drug solubility in the membrane such that $S_{m(o)} = S_m$, eqs 3, 4, and 5 can be combined to give

$$P_m = \frac{P_{m(o)}S_{aq(o)}}{S_{aq}} \quad (6)$$

The intrinsic permeability of the drug through the unstirred aqueous boundary layer ($P_{aq(o)}$) in the absence of solubilizer can be written as[26,27,29,39]

$$P_{aq(o)} = \frac{D_{aq(o)}}{h_{aq(o)}} \quad (7)$$

where $D_{aq(o)}$ is the diffusion coefficient of the drug through the unstirred aqueous boundary layer in the absence of solubilizer and $h_{aq(o)}$ is the unstirred aqueous boundary layer thickness experienced by the drug in the absence of solubilizer. It is important to note that, in this model, the unstirred aqueous boundary layer is defined as the distance from the intestinal membrane surface to the point at which drug concentration in the aqueous milieu becomes constant and equal to bulk.

Likewise, the apparent unstirred aqueous boundary layer permeability of the drug in the presence of solubilizer (P_{aq}) can be written as

$$P_{aq} = \frac{D_{aq}}{h_{aq}} \tag{8}$$

where D_{aq} is the apparent diffusion coefficient of the drug through the unstirred aqueous boundary layer in the presence of solubilizer and h_{aq} is the apparent unstirred aqueous boundary layer thickness in the presence of solubilizer.

Equations 7 and 8 can be combined to give

$$P_{aq} = \frac{P_{aq(o)}D_{aq}h_{aq(o)}}{D_{aq(o)}h_{aq}} \tag{9}$$

Assuming the aqueous boundary layer thickness is inversely proportional to the drug solubility in the aqueous lumen (i.e., $h_{aq(o)}/h_{aq} = S_{aq}/S_{aq(o)}$), eq 9 can be rewritten to express the P_{aq} dependence on drug aqueous solubility:

$$P_{aq} = \frac{P_{aq(o)}D_{aq}S_{aq}}{D_{aq(o)}S_{aq(o)}} \tag{10}$$

Taking into account the membrane permeability as well as the unstirred aqueous boundary layer permeability on either side of the membrane, $P_{aq(1)}$ and $P_{aq(2)}$, the overall effective permeability (P_{eff}) of the drug can be written as[26,27,29]

$$P_{eff} = \frac{1}{\frac{1}{P_{aq(1)}} + \frac{1}{P_m} + \frac{1}{P_{aq(2)}}} \tag{11}$$

For simplicity, $P_{aq(2)}$ is assumed to have a negligible effect, such that $P_{aq(1)} = P_{aq}$, and eq 11 can be rewritten as[29]

$$P_{eff} = \frac{1}{\frac{1}{P_{aq}} + \frac{1}{P_m}} \tag{12}$$

Thus, the overall P_{eff} dependence on drug solubility and cosolvent concentration may be predicted via eq 12 wherein the P_m and P_{aq} dependence on C_S are predicted using eqs 6 and 10 with knowledge of $S_{aq(o)}$, S_{aq}, $P_{m(o)}$, $P_{aq(o)}$, $D_{aq(o)}$, and D_{aq}.

Moreover, the drug concentration at the interface between the UWL and membrane ($C_{aqMembraneSurface}$) as a function of drug solubility and cosolvent concentration can be calculated according to the following equation:[26,27,29]

$$\frac{C_{aqMembraneSurface}}{C_{aqBulk}} = \frac{P_{eff}}{P_m} \tag{13}$$

MATERIALS AND METHODS

Materials. Progesterone, propylene glycol (PG), polyethylene glycol 400 (PEG-400), phenol red, 2-(*N*-morpholino)-ethanesulfonic (MES) acid, and trifluoroacetic acid (TFA) were purchased from Sigma Chemical Co. (St. Louis, MO). KCl and NaCl were obtained from Fisher Scientific Inc. (Pittsburgh, PA). Acetonitrile and water (Merck KGaA, Darmstadt, Germany) were UPLC grade. All other chemicals were of analytical reagent grade.

Solubility Determinations. Progesterone apparent solubility at increasing concentrations (0−30% by weight) of PG and PEG-400 in 10 mM MES buffer, pH 6.5 were measured at 37 °C in triplicate, according to previously published reports.[26,40] Cosolvent solutions were added to glass vials containing excess amounts of progesterone. The vials were tightly closed and placed in a shaking water bath at 37 °C and 100 rpm. Establishment of equilibrium was assured by comparison of samples after 24 and 48 h. Before sampling, the vials were centrifuged at 10,000 rpm for 10 min. Supernatant was carefully withdrawn from each test tube and immediately assayed for drug content by UPLC.

Viscosity Determinations. The viscosity of the propylene glycol and PEG-400 cosolvent solutions at the concentrations used for the dissolution experiments were measured on a TA AR2000 controlled stress rheometer (TA Instruments, New Castle, DE), equipped with Rheology Advantage Analysis Software (Version. 4.1, TA Instruments). The experiments were carried out in the controlled stress mode, double gap Peltier cylinder system, at 37 °C. Viscosity standards for low and high viscosity ranges were used to calibrate the instrument before running the PG and PEG-400 samples. All measurements were repeated 10 times.

Rotating Disk Dissolution Experiments. Effective diffusion coefficients (D_{eff}) of progesterone at increasing concentrations (0−30% by weight) of PG and PEG-400 were measured using the rotating disk dissolution method. Progesterone powder was compressed into a 0.8 cm diameter die using a Carver hydraulic press at 170 MPa compression force and dwell time of 2.5 min. Cosolvent solutions in 10 mM MES buffer, pH 6.5 were prepared the day of the dissolution runs. The rotating disk dissolution experiments were carried out on a USP Apparatus II in 500 mL of cosolvent solution maintained at 37 °C. The dissolution tests were run for 90 min at 100 rpm with 500 μL samples taken every ten minutes and replaced by fresh medium. The samples were then centrifuged at 10,000 rpm for 10 min to separate any solid particles, and progesterone concentration was then determined by UPLC. The effective diffusion coefficient at each cosolvent concentration was calculated using the Levich equation:[41]

$$D_{eff} = \left(\left(\frac{J}{v^{-1/6}w^{1/2}S_{aq}}\right)/0.62\right)^{3/2} \tag{14}$$

where J is the dissolution rate, w is the rotation speed, and v is the kinematic viscosity at a given cosolvent concentration.

Rat Jejunal Perfusion. All animal experiments were conducted using protocols approved by the Ben-Gurion University of the Negev Animal Use and Care Committee (Protocol IL-60-11-2010). Animals were housed and handled according to the Ben-Gurion University of the Negev Unit for Laboratory Animal Medicine Guidelines. Male albino Wistar rats (Harlan, Israel) weighing 250−280 g were used for all perfusion studies. Prior to each experiment, the rats were fasted overnight (12 h) with free access to water. Animals were randomly assigned to the different experimental groups.

The procedure for the in situ single-pass intestinal perfusion followed previously published reports.[42−44] Briefly, rats were

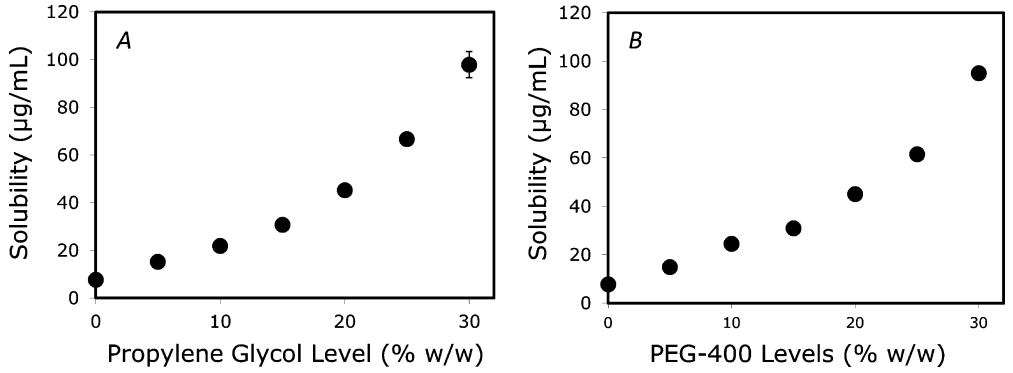

Figure 1. Apparent solubility (S_{aq}, μg/mL) of progesterone as a function of increasing propylene glycol (A, left panel) and PEG-400 (B, right panel) concentration in MES buffer pH 6.5 at 37 °C.

anesthetized with an intramuscular injection of 1 mL/kg of ketamine−xylazine solution (9%:1%, respectively) and placed on a heated surface maintained at 37 °C (Harvard Apparatus Inc., Holliston, MA). The abdomen was opened by a midline incision of 3−4 cm. A proximal jejunal segment (3 ± 1 cm average distance of the inlet from the ligament of Treitz) of approximately 10 cm was carefully exposed and cannulated on two ends with Norprene tubing (Cole-Parmer Instruments, Vernon Hills, IL). Care was taken to avoid disturbance of the circulatory system, and the exposed segment was kept moist with 37 °C normal saline solution. Stability study for progesterone in buffer that has been perfused through rat intestine confirmed the lack of luminal drug degradation. The perfusate buffer consisted of 10 mM MES buffer, pH 6.5, 135 mM NaCl, 5 mM KCl, and 0.1 mg/mL phenol red. Phenol red was added to the perfusion buffer as a nonabsorbable marker for measuring water flux. Perfusate solutions of progesterone were prepared at cosolvent concentrations of 0%, 5%, 10%, 20%, and 30% by weight. The progesterone concentration was made up at 75% the maximum apparent solubility in each cosolvent solution in order to keep thermodynamic activity constant across all perfusate solutions. All perfusate solutions were incubated in a 37 °C water bath to maintain temperature and were pumped through the intestinal segment (Masterflex L/S, Cole-Parmer Instruments, Vernon Hills, IL). The isolated segment was first rinsed with blank perfusion buffer at a flow rate of 0.5 mL/min in order to clean out any residual debris. At the start of the study, the test solutions were perfused through the intestinal segment at a flow rate of 0.2 mL/min. The perfusion buffer was first perfused for 1 h, in order to ensure steady state conditions (as also assessed by the inlet over outlet concentration ratio of phenol red which approaches 1 at steady state). After reaching steady state, samples were taken in 10 min intervals for one hour (10, 20, 30, 40, 50, and 60 min). All samples, including perfusion samples at different time points, original drug solution, and inlet solution taken at the exit of the syringe, were immediately assayed by UPLC. All investigated perfusion solutions were assessed for drug absorbance onto the tubing, to rule out misleading loss of drug. Following the termination of the experiment, the length of each perfused jejunal segment was accurately measured.

The net water flux in the single-pass rat jejunal perfusion studies, resulting from water absorption in the intestinal segment, was determined by measurement of phenol red, a nonabsorbed, nonmetabolized marker. The measured C_{out}/C_{in} ratio was corrected for water transport according to the following equation:

$$\frac{C'_{out}}{C'_{in}} = \frac{C_{out}}{C_{in}} \times \frac{C_{in\text{-phenolred}}}{C_{out\text{-phenolred}}} \quad (15)$$

where C_{out} is the concentration of progesterone in the outlet sample, C_{in} is the concentration of progesterone in the inlet sample, $C_{in\text{-phenolred}}$ is the concentration of phenol red in the inlet sample, and $C_{out\text{-phenolred}}$ is the concentration of phenol red in the outlet sample. The effective permeability (P_{eff}) through the rat gut wall in the single-pass intestinal perfusion studies was determined assuming the "plug flow" model expressed in the following equation:[45,46]

$$P_{eff} = \frac{-Q \ln(C'_{out}/C'_{in})}{2\pi RL} \quad (16)$$

where Q is the perfusion buffer flow rate, C'_{out}/C'_{in} is the ratio of the outlet concentration and the inlet or starting concentration of the tested drug that has been adjusted for water transport via eq 15, R is the radius of the intestinal segment (set to 0.2 cm), and L is the length of the intestinal segment.

Ultra Performance Liquid Chromatography (UPLC). UPLC experiments were performed on a Waters (Milford, MA) Acquity UPLC H-Class system equipped with photodiode array detector and Empower software. Progesterone was assayed using a Waters (Milford, MA) Acquity UPLC BEH C_{18} 1.7 μm 2.1 × 100 mm column. The detection wavelength was 242 nm. The mobile phase consisted of 30:70 (v:v) 0.1% TFA in water:0.1% TFA in acetonitrile and was pumped at a flow rate of 0.5 mL/min. Injection volumes for all UPLC analyses ranged from 5 to 100 μL.

Determination of Cosolvent Concentrations in Perfusate Solutions. Propylene glycol concentrations in rat intestinal pefusates were determined by gas chromatography (GC). Experiments were performed on an Agilent Technologies (Palo Alto, CA) 6890N GC equipped with flame ionization detector, and Atlas software (Version 8.20.2.7047) from Thermo Electron Corporation (Waltham, MA) was used for data collection. PG was assayed using an Agilent (Palo Alto, CA) DB 624 column with dimensions of 75 m × 0.53 mm. The inlet and detector temperatures were 200 and 250 °C, respectively. The H_2 flow at the detector was 4.0 mL/min. Helium was used as the carrier gas at a flow rate of 5.0 mL/min, and the makeup gas flow rate was 29 mL/min. Injection volume was 2 μL, with a 5:1 split ratio. The temperature program ran

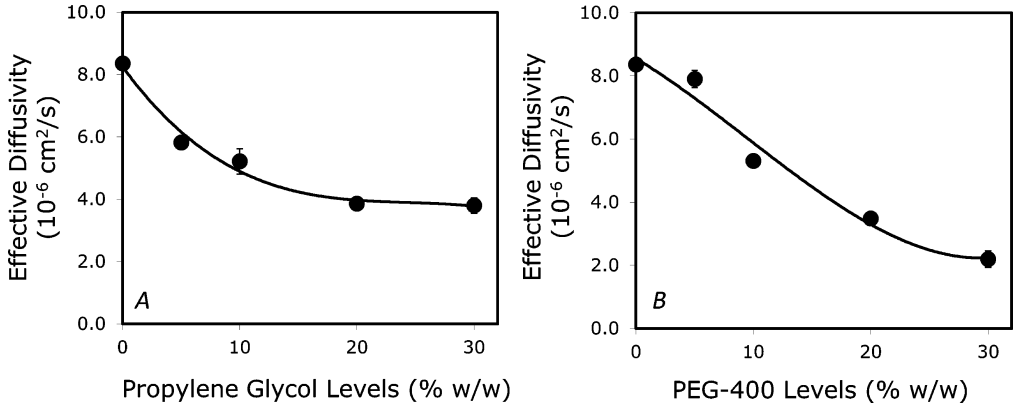

Figure 2. Effective diffusivity (D_{eff}, cm^2/s), of progesterone as a function of increasing propylene glycol (A, left panel) and PEG-400 (B, right panel) concentration in MES buffer pH 6.5 at 37 °C, determined using the rotating disk method.

Table 1. The Effect of Propylene Glycol and PEG-400 Content (% w/w) on the Viscosity (Pa s) of the Solution at 37 °C[a]

	0[b]	5[b]	10[b]	20[b]	30[b]
propylene glycol	$7.8 \times 10^{-4} \pm 2.0 \times 10^{-5}$	$1.0 \times 10^{-3} \pm 2.9 \times 10^{-5}$	$1.1 \times 10^{-3} \pm 3.4 \times 10^{-5}$	$1.5 \times 10^{-3} \pm 3.2 \times 10^{-5}$	$1.8 \times 10^{-3} \pm 3.3 \times 10^{-5}$
PEG-400		$1.1 \times 10^{-3} \pm 3.9 \times 10^{-5}$	$1.3 \times 10^{-3} \pm 1.9 \times 10^{-5}$	$1.8 \times 10^{-3} \pm 2.6 \times 10^{-5}$	$2.6 \times 10^{-3} \pm 3.0 \times 10^{-5}$

[a]Data presented as mean ± SD; $n = 10$. [b]Cosolvent level (% w/w).

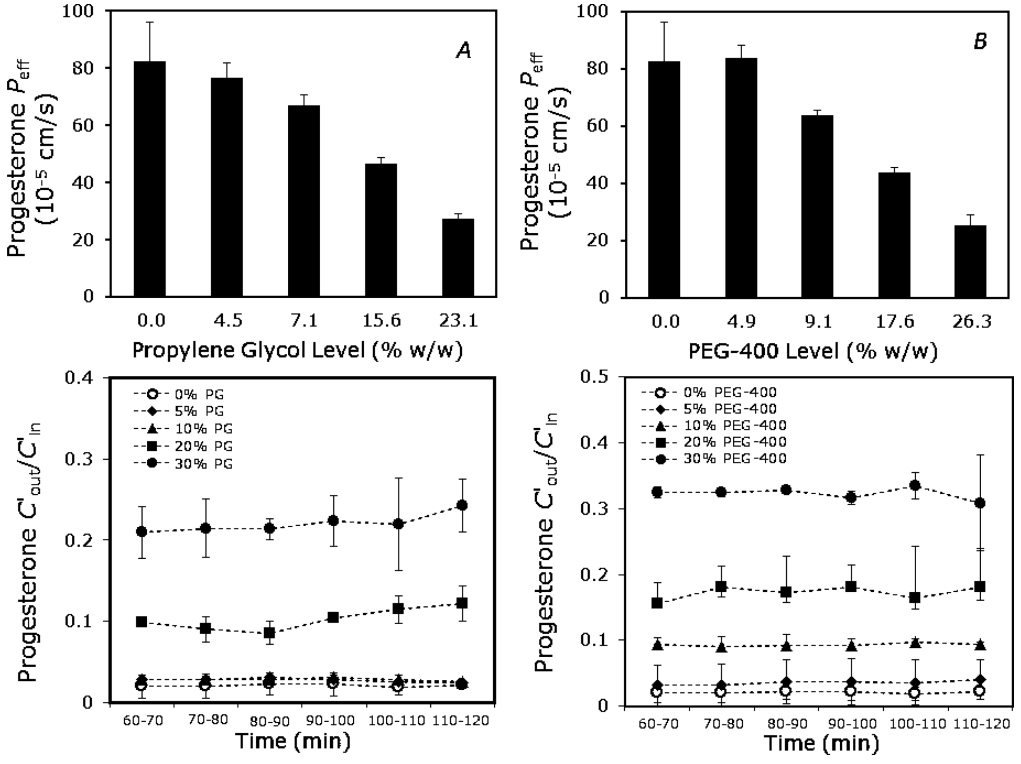

Figure 3. Effective permeability (P_{eff}, cm/s; upper panels) and outlet/inlet concentration ratio (C'_{out}/C'_{in}; lower panels) of progesterone as a function of increasing propylene glycol (A, left panels) and PEG-400 (B, right panels) concentration, determined using the single-pass rat jejunal perfusion model.

from an initial oven temperature of 40 °C. After a 5 min hold, the temperature was ramped to 175 °C over 10 min, and then the temperature was ramped to 250 °C over 25 min. The final temperature was held 14.36 min.

PEG-400 concentrations in rat intestinal perfusate were determined by aqueous normal phase chromatography with evaporative light scattering detection. A detailed report of the method was recently published.[47]

Statistical Analysis. All in vitro experiments were performed in triplicate (unless stated otherwise), and all animal experiments were $n = 4$. Values are expressed as the mean ± standard deviation (SD). To determine statistically significant differences among the experimental groups, the nonparametric Kruskal–Wallis test was used for multiple comparisons, and the two-tailed nonparametric Mann–Whitney *U*-test for two-group comparison where appropriate. A p value of less than 0.05 was termed significant.

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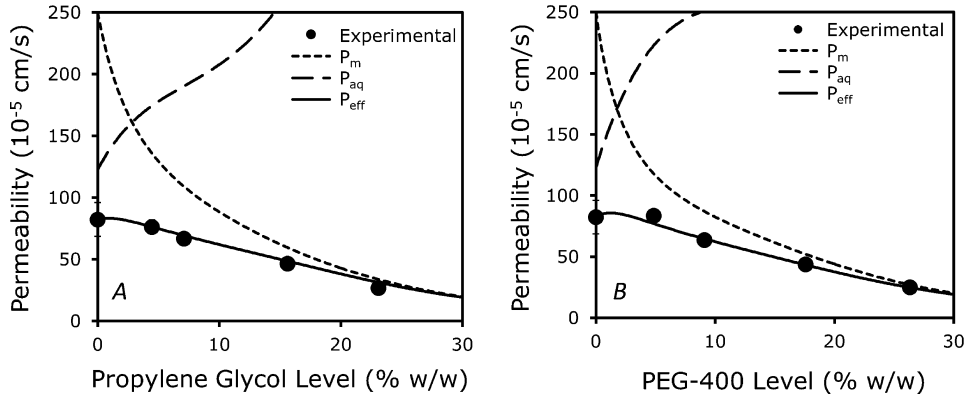

Figure 4. Permeability of progesterone as a function of propylene glycol (A, left panel) and PEG-400 (B, right panel) concentration in the rat jejunal perfusion model. The theoretical lines were calculated via eq 6 (P_m), eq 10 (P_{aq}), and eq 12 (P_{eff}).

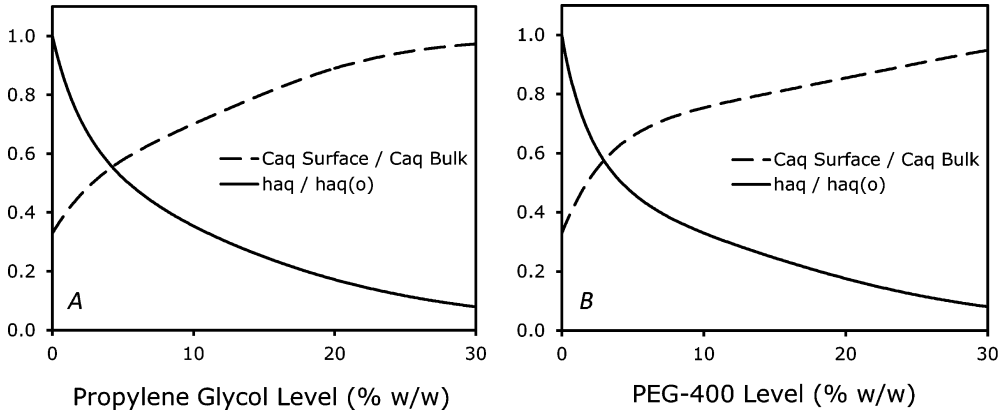

Figure 5. Theoretical membrane surface to bulk concentration ratio ($C_{aqSurface}/C_{aqBulk}$) and apparent (in presence of cosolvent) to intrinsic (in absence of cosolvent) aqueous boundary layer thickness ratio ($h_{aq}/h_{aq(o)}$) of progesterone as a function of propylene glycol (A, left panel) and PEG-400 (B, right panel) concentration in the rat jejunal perfusion model, calculated according to eqs 9 and 13.

RESULTS

Effect of PG and PEG-400 on Progesterone Solubility. Progesterone apparent solubility as a function of PG and PEG-400 concentration is presented in Figure 1. Over an order of magnitude increase in the apparent solubility of progesterone was observed in both systems, from approximately 8 μg/mL in the absence of cosolvent to nearly 100 μg/mL at 30% cosolvent.

Effect of PG and PEG-400 on Progesterone Diffusivity. Diffusion coefficients of progesterone as a function of PG and PEG-400 concentration were measured using the rotating disk method. In both systems, decreased progesterone diffusivity was observed with increasing cosolvent concentrations (Figure 2). Solution viscosity increased with increasing cosolvent concentration in both systems (Table 1), indicating that the decrease in apparent diffusivity of progesterone could be primarily attributed to the increase in solution viscosity at the higher cosolvent concentrations.

Effect of PG and PEG-400 on Progesterone Rat Jejunal Permeability. Progesterone permeability (P_{eff}) in the presence of increasing PG and PEG-400 concentration was evaluated in the rat jejunal perfusion method (Figure 3). Some of the cosolvent was lost to absorption from each perfusion solution; on average, about 25% and 11% of the starting cosolvent concentration was absorbed for PG and PEG-400, respectively. The actual cosolvent concentrations measured after perfusion (corrected for loss to absorption) are presented in Figure 3. In the absence of cosolvent, progesterone showed high permeability (82.4×10^{-5} cm/s) across rat jejunum; the P_{eff} value for metoprolol, a FDA approved marker for the low/high permeability class boundary, is typically 20-fold lower.[45,48] The P_{eff} of progesterone decreased with increasing PG and PEG-400 at cosolvent concentrations above approximately 5%. In both systems, progesterone P_{eff} decreased over 3-fold at the maximum cosolvent concentration investigated.

Figure 4 compares the predicted P_{eff} of progesterone as a function of PG and PEG-400 concentration to the experimentally observed P_{eff} values. The predicted lines for P_m, P_{aq}, and P_{eff} were calculated via eqs 6, 10, and 12, respectively. The experimental parameters used in the calculations were the solubilities and effective diffusion coefficients of progesterone as a function of cosolvent concentration in the PG and PEG-400 systems (Figures 2 and 3). The experimental value for progesterone rat jejunal $P_{m(o)}$ of 250×10^{-5} cm/s used in the calculations was previously estimated by determining the P_{eff} of progesterone at increasing perfusion flow rates.[49] The value of $P_{aq(o)}$ used in the predictions was calculated according to eq 12 from the experimental values of $P_{m(o)}$ and the P_{eff} of progesterone determined in the absence of cosolvent (82.4×10^{-5} cm/s). Excellent agreement was obtained between the experimental and predicted progesterone P_{eff} values as a function of cosolvent concentration in both the PG and PEG-400 systems (Figure 4).

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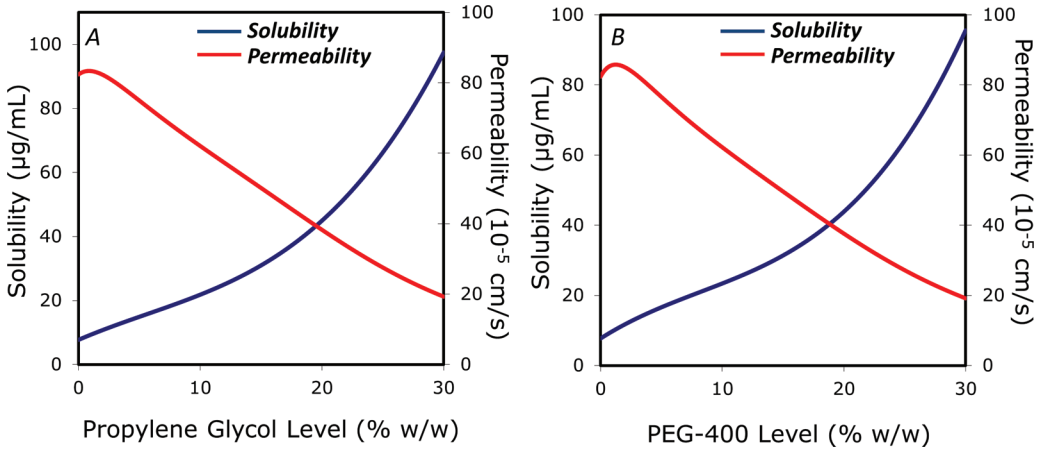

Figure 6. The effects of increasing propylene glycol (A, left panel) and PEG-400 (B, right panel) concentration on progesterone apparent aqueous solubility and intestinal permeability based on the theoretical quasi-equilibrium transport model developed in this work.

Figure 5 shows the theoretical membrane surface to bulk concentration ratio ($C_{aqSurface}/C_{aqBulk}$) and apparent (in presence of cosolvent) to intrinsic (in absence of cosolvent) aqueous boundary layer thickness ratio ($h_{aq}/h_{aq(o)}$) of progesterone as a function of PG and PEG-400 concentration in the rat jejunal perfusion model. The predicted curves were calculated according to eqs 9 and 13. $C_{aqSurface}/C_{aqBulk}$ increases to approach 1 and $h_{aq}/h_{aq(o)}$ decreases to approach 0 with increasing cosolvent concentration in both systems.

Figure 6 illustrates the effects of PG and PEG-400 on progesterone apparent aqueous solubility and intestinal permeability based on the theoretical quasi-equilibrium transport analysis developed in this work. This figure visibly illustrates the opposing effects a solubility-enabling formulation may have on the apparent solubility and intestinal permeability.

DISCUSSION

In this report, we describe the trade-off between the apparent solubility increase and intestinal membrane permeability decrease that occurs when solubility-enabling formulations are employed to increase the oral absorption of poorly soluble drugs. We show that this solubility−permeability interplay is a universal phenomenon that occurs whenever the apparent solubility of the drug is increased via formulation and even applies when using approaches in which complexation/micellization is not the mechanism for increased solubilization and the issue of free fraction is irrelevant. The mathematical model developed in this work revealed that the root for this solubility−permeability trade-off goes back to the definition of permeability; since intestinal permeability is equal to the diffusion coefficient of the drug through the membrane times the membrane/aqueous partition coefficient of the drug divided by the membrane thickness, increasing the apparent solubility of the drug in the aqueous medium via formulation will decrease the membrane/aqueous partition coefficient of the drug, directly leading to decreased apparent intestinal permeability. These opposing effects on apparent solubility and permeability must be taken into account in order to fully understand the impact on the overall fraction of drug absorbed when solubility-enabling formulations are employed to enhance the oral exposure of a poorly soluble drug. We offer a quantitative model that may be used to understand this solubility−permeability interplay, and predict a priori the trade-off that occurs between apparent solubility increase and intestinal permeability decrease when using pharmaceutical solubilizers in formulations.

The cosolvents PG and PEG-400 enabled an order of magnitude increase in the apparent solubility of progesterone in both systems, from approximately 8 μg/mL in the absence of cosolvent to nearly 100 μg/mL at 30% cosolvent. This type of apparent solubility enhancement demonstrates the widespread utility of cosolvents for enabling the oral exposure of poorly soluble drugs. However, the impact of these types of solubility enhancements on intestinal membrane permeability is often overlooked, underappreciated and poorly understood. In this work, for instance, progesterone permeability across rat jejunal segments was significantly altered as a result of drug solubilization by PG and PEG-400. As shown in Figure 3, the progesterone P_{eff} across the rat jejunum stayed relatively steady at very low cosolvent concentrations (<5%), but then decreased with increasing cosolvent concentration. This results because, at very low cosolvent concentrations, the overall P_{eff} is limited by the UWL. This is in corroboration with previous reports that have shown progesterone permeability to be limited by the aqueous boundary layer in the rat intestinal perfusion model.[26,27,29,49] Progesterone P_{eff} decreased with increasing cosolvent concentrations >5%, with over 3-fold decrease in P_{eff} at the maximum cosolvent concentration in both systems. Figure 4 contains the experimental vs predicted P_{eff} as a function of PG and PEG-400 concentration in the rat intestinal perfusion model. The predicted P_{eff} was calculated via eq 12, using the predicted values of P_m (eq 6) and P_{aq} (eq 10) as a function of apparent solubility and cosolvent concentration. Excellent agreement was obtained between the experimental and predicted progesterone P_{eff} values in both cosolvent systems at all concentrations tested.

The effective diffusivity of progesterone decreased with increasing cosolvent concentration in both the PG and the PEG-400 systems (Figure 2). This can be primarily attributed to the increase in solution viscosity in the cosolvent systems as compared to pure aqueous (Table 1). A more marked decrease in effective diffusivity was observed for progesterone in PEG-400 as compared to PG over the concentration ranges studied, due to the higher viscosity for PEG-400 vs PG. The decrease in progesterone effective diffusivity with increasing cosolvent concentration contributes to a decrease in the aqueous boundary layer permeability as expressed in eqs 8−10. However, since the effective thickness of the boundary layer

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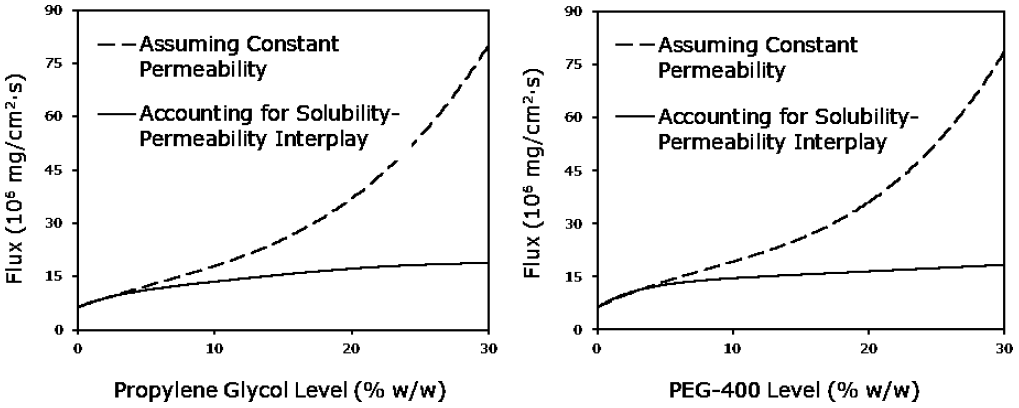

Figure 7. The effects of increasing propylene glycol (left panel) and PEG-400 (right panel) concentration on progesterone flux (mg/cm^2 s) based on the theoretical quasi-equilibrium transport model developed in this work.

decreases with increasing apparent solubility of progesterone, the decreased diffusivity is offset by the shrinking h_{aq} with increasing solubilization of progesterone, which leads to a marked increase in P_{aq} with increasing PG and PEG-400 concentrations (Figure 5). At the same time, P_m rapidly decreases with increasing cosolvent concentration. This is because the apparent membrane/aqueous lumen partition coefficient decreases with increasing drug solubility (eqs 5 and 6), thereby reducing the thermodynamic driving force for membrane permeation. Since P_{aq} increases and P_m decreases with increasing apparent solubility and cosolvent concentration, the UWL is effectively eliminated and the overall P_{eff} tends toward membrane control with increasing cosolvent concentration.

As shown in Figure 5, the progesterone concentration at the membrane surface gradually increases and becomes equal to bulk as solubility and cosolvent concentration increases, such that $h_{aq}/h_{aq(o)}$ decreases and approaches 0 with increasing PG and PEG-400 concentration. In this way, solubilization of progesterone by cosolvent effectively shorts out the UWL by facilitating the transport of drug to the membrane surface such that $C_{aqMembraneSurface} \approx C_{aqBulk}$ with increasing cosolvent concentration, and permeation across the intestinal membrane becomes rate limiting.[26,27,29,49]

Figure 7 illustrates the impact of the solubility−permeability interplay on the overall flux of progesterone as a function of cosolvent concentration. When the solubility−permeability interplay is not accounted for, i.e. P_{eff} is assumed to be constant and equal to P_{eff} in the absence of cosolvent (82.4×10^{-5} cm/s), the overall flux increases continuously and exponentially with increasing cosolvent concentration and progesterone solubility. However, when the solubility−permeability is appropriately accounted for, it is apparent that the most significant increases in flux occur between 0 and 5% cosolvent concentration. It follows that luminal concentrations of cosolvent beyond 5% may not have a significant impact on overall absorption and may perhaps have diminishing returns, especially considering the potentially toxic effects that may be induced at higher concentrations of cosolvent. It should be noted that progesterone was administered as a solution in the rat intestinal perfusion model presented in this work. Thus, the potential positive effect of increasing dissolution rate with increasing cosolvent concentration is not a consideration; this aspect will be addressed as part of future work in this area.

In applying the model presented here, it should be emphasized that the effective thickness of the boundary layer is defined as the distance from the intestinal membrane surface to the point at which drug concentration in the aqueous milieu becomes constant and equal to bulk. It is important to differentiate this thickness from that of the hydrodynamic boundary layer thickness, which is the distance from the intestinal membrane surface to the point at which the fluid hydrodynamics (i.e., mixing) become constant and equal to bulk. The hydrodynamic boundary layer thickness is fixed under set hydrodynamic conditions (as in this study) whereas the concentration boundary layer thickness may change depending on the length of the concentration gradient. Indeed, when $C_{aqMembraneSurface} \approx C_{aqBulk}$ there is no longer a concentration gradient, and hence there is no effective UWL thickness. It follows then that as the drug solubility is increased in the GI lumen, the distance from the membrane surface to the point at which $C_{aqMembraneSurface} \approx C_{aqBulk}$ decreases and becomes less dependent on the hydrodynamic conditions. In this way, the effective boundary layer thickness depends on the drug solubility and h_{aq} is essentially shrinking with increasing apparent solubility in the GI lumen. This also explains why the UWL often limits the overall permeability of poorly soluble drugs (e.g., progesterone) whereas drugs with high solubility are not susceptible to this effect.

It should be noted that the interplay between solubility increase and permeability decrease highlighted here is most applicable to drugs with low aqueous solubility and high membrane permeability, i.e. BCS class II drugs. Indeed, cosolvents may actually increase the apparent intestinal membrane permeability of drugs with poor intrinsic intestinal membrane permeability (e.g., BCS class III, IV). This may occur through the inhibition of efflux transporters and/or the disruption of membrane integrity to increase paracellular transport (e.g., tight junction opening). However, it is expected that the solubility−permeability interplay should apply for lipophilic drugs with high permeability via the trancellular route, as was the case here for progesterone.

■ CONCLUSIONS

This work demonstrates that, when using solubility-enabling formulations to increase the oral absorption of lipophilic drugs, a trade-off exists between solubility increase and permeability decrease that must be taken into account to strike the optimal solubility−permeability balance.[50,51] The model presented in this work offers the formulation scientist a method for a priori prediction of this interplay, in order to maximize the overall

oral absorption of a lipophilic drug from a solubility-enabling formulation. The insights revealed in this work enable a more efficient and intelligent use of solubility-enabling formulations in drug product development.

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