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Research paper

Accounting for the solubility–permeability interplay in oral formulation development for poor water solubility drugs: The effect of PEG-400 on carbamazepine absorption

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ABSTRACT

The purpose of this paper was to study the solubility–permeability interplay in formulation development for oral administration of poor aqueous solubility drugs. The apparent solubility of the lipophilic drug carbamazepine was measured in systems containing various levels of the co-solvent PEG-400. The corresponding permeability was then measured in the PAMPA assay and in the rat jejunal perfusion model. Thermodynamic activity was maintained equivalent in all permeability studies (50% saturation). PEG-400 increased carbamazepine solubility in a concentration-dependent fashion. Decreased carbamazepine intestinal permeability with increased apparent solubility was observed in both PAMPA and rat perfusion models. Additionally, we have shown that the intestinal absorption of carbamazepine is membrane-controlled, with essentially no effective barrier function of the unstirred water layer. A mass transport analysis was employed to describe the solubility–permeability interplay. It was shown that the increased solubility in the aqueous GI milieu reduced the apparent membrane/aqueous partitioning, thereby reducing the driving force for membrane permeability. The model enabled excellent quantitative prediction of the effective permeability as a function of the solubility. In conclusion, a direct tradeoff between solubility increase and permeability decrease has been shown, which has to be accounted for when developing oral formulation for lipophilic drugs.

1. Introduction

As was developed by Amidon et al. [1], the solubility of the drug dose in the aqueous intestinal milieu and its permeability through the intestinal membrane are the two key parameters governing the absorption following oral administration [2–4]. However, the interrelationship between these two key parameters themselves is still overlooked and largely unknown.

Low aqueous solubility is a common characteristic in today's biopharmaceutics, and according to some estimates, over 40% of new chemical entities exhibit poor solubility [5,6]. This obstacle to efficient oral delivery is most commonly tackled by formulation development, for example, amorphous solid dispersions, cyclodextrins, surfactants, co-solvents, and lipid-based formulations. While these formulations can certainly increase the apparent aqueous solubility of the co-administered lipophilic drug, their effect on the apparent permeability, the most important parameter (together with the solubility) dictating oral absorption, is rarely considered. This solubility–permeability interplay is the focus of this research.

We have recently described a tradeoff between the apparent solubility increase and permeability decrease when using cyclodextrins as pharmaceutical solubilizers [7]. For formulations based on surface active agents, similar phenomenon was shown both by us [8,9] and by others [10–13]. In all of these cases, the solubility increase occurred due to micellization/complexation, which reduces the free fraction of the drug. Decreased free fraction is directly translated to lower concentration gradient and hence thermodynamic driving force for membrane permeation. Therefore, in all of these cases, the decreased permeability with increased apparent solubility could be attributed to free fraction considerations, and not necessarily to direct interrelationship between the solubility and the permeability.

The purpose of this study was to investigate the direct solubility–permeability interplay. We have isolated the increased solubility from the free fraction by using the commonly used co-solvent PEG-400, which increases the solubility of lipophilic drugs, without affecting the free fraction. The low-solubility BCS class II antiepileptic drug carbamazepine was used as the model compound.

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The solubility of carbamazepine was investigated in systems containing various levels of PEG-400, and the corresponding permeability was then measured in PAMPA and in the rat jejunal perfusion models. A quasi-equilibrium mass transport analysis was employed to describe the solubility–permeability interplay. Overall, this work reveals that a direct solubility–permeability tradeoff exists when using solubility-enabling formulations, which must not be overlooked.

2. Material and methods

2.1. Materials

Carbamazepine, polyethylene glycol 400 (PEG-400), phenol red, MES buffer 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.

2.2. Methods

2.2.1. Solubility determinations

Carbamazepine apparent solubility at increasing concentrations (0–30% w/w) of PEG-400 in 10 mM MES buffer, pH 6.5 was measured at room temperature (25 °C) and at 37 °C in triplicates, as previously published [7,14]. PEG-400 solutions were added to glass vials containing excess amounts of carbamazepine. The vials were tightly closed and placed in a shaking water bath at 25 °C or 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 and immediately assayed for drug content by UPLC.

2.2.2. Diffusivity determinations

Effective diffusion coefficients (D_{eff}) of carbamazepine at increasing levels (0–30% w/w) of PEG-400 were measured using the rotating disk dissolution method, as previously reported [8,15]. Carbamazepine 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. Co-solvent solutions in 10 mM MES buffer, pH 6.5, were prepared the day of the dissolution runs. Rotating disk dissolution experiments were carried out on a USP Apparatus II in 500 mL of co-solvent solution maintained at 37 °C. The dissolution tests were run for 45 min at 100 rpm with 500 μL samples taken every 5 min and replaced by fresh medium. The samples were then centrifuged at 10,000 rpm for 10 min, and carbamazepine concentration was then determined by UPLC. D_{eff} at each co-solvent concentration was calculated using the Levich equation [16]:

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

where J is the dissolution rate, w is the rotation speed, and υ is the kinematic viscosity at a given co-solvent concentration. Viscosity of the PEG-400 solutions was measured on a TA AR2000 Controlled Stress Rheometer (TA Instruments, New Castle, DE), equipped with Rheology Advantage Analysis Software (Version. 4.1, TA Instruments).

2.2.3. PAMPA permeability method

PAMPA studies were carried out using a method described previously [7,17]. Briefly, solutions of carbamazepine were prepared with PEG-400 10 mM MES buffer pH 6.5 solutions. To maintain equivalent thermodynamic activity in all groups, carbamazepine concentrations were chosen according to the room temperature solubility studies, to achieve 50% saturation in all experimental groups. PAMPA experiments were carried out in Millipore (Danvers, MA) 96-well MultiScreen-Permeability filter plates with 0.3 cm^2 polycarbonate filter support (0.45 mm). The filter supports in each well were first impregnated with 15 μL of a 5% solution (v/v) of hexadecane in hexane [18]. The wells were then allowed to dry for 1 h to ensure complete evaporation of the hexane. The donor wells were then loaded with 0.2 mL of the carbamazepine PEG-400 solution, and each receiver well was loaded with 0.3 mL of blank MES buffer. Four wells were loaded at each PEG-400 level to enable collection at different time points. Each experiment was repeated three times ($n = 3$). The donor plate was then placed upon the 96-well receiver plate, and the resulting PAMPA sandwich was incubated at room temperature (25 °C). Receiver plate wells were then collected every 30 min over 2 h, and the carbamazepine concentration in each well was determined by UPLC. Permeability coefficient (P_{app}) was calculated from the linear plot of drug accumulated in the receiver side versus time, according to the equation:

$$P_{app} = \frac{dQ/dt}{A \cdot C_0}$$

where dQ/dt is the steady-state appearance rate of the drug on the receiver side, C_0 the initial concentration of the drug in the donor side, and A the membrane surface area (0.048 cm^2). Linear regression was carried out to obtain the steady-state appearance rate of carbamazepine on the receiver side.

2.2.4. Rat jejunal perfusions

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 Wistar rats (Harlan, Israel) weighing 250–280 g were used for all 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 single-pass *in situ* jejunal perfusions followed previous reports [19–21]. Briefly, rats were anesthetized (1 mL/kg ketamine–xylazine 9%:1%) and placed on a 37 °C surface (Harvard Apparatus Inc., Holliston, MA). A proximal jejunal segment of approximately 10 cm was carefully exposed and cannulated on two ends with silicone tubing (Watson-Marlow Ltd., Wilmington, MA). Care was taken to avoid disturbance of the circulatory system, and the exposed segment was kept moist with 37 °C normal saline solution. The perfusate buffer consisted of 10 mM MES buffer, pH 6.5, 135 mM NaCl, 5 mM KCl, and 20 μg/mL phenol red. Perfusate solutions of carbamazepine were prepared at co-solvent concentrations of 0%, 5%, 10%, 20%, and 30% w/w. The carbamazepine concentration was made up at 50% the maximum apparent solubility at 37 °C in each co-solvent solution in order to keep thermodynamic activity constant across all perfusate solutions. All perfusate solutions were incubated in a 37 °C water bath and were pumped through the intestinal segment (Watson-Marlow 205S, Wilmington, MA). 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. The test solutions were then 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. After reaching steady state, samples were taken in 10 min intervals for 1 h. All samples were immediately assayed for drug content by UPLC. Following the termination of the exper-