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Rapid communication

Predicting the solubility–permeability interplay when using cyclodextrins in solubility-enabling formulations: Model validation

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ABSTRACT

Although the extraordinary solubility advantage afforded by cyclodextrins has led to their widespread use as pharmaceutical solubilizers, several reports have emerged that cyclodextrins may also reduce the apparent permeability of the drug. With the purpose to investigate this solubility–permeability interplay, we have recently developed a mathematical mass transport model that quantitatively explains the impact of molecular complexation on the intestinal permeability. This model enabled excellent quantitative prediction of progesterone P_{eff} as a function of HPβCD concentrations in several experimental methods. The purpose of the present study was to challenge the predictive capabilities of this mathematical model, assessing whether the model allows the prediction of literature permeability data, as a model validation method. The mass-transport model was applied to carbamazepine and hydrocortisone, and the predicted permeability (P_{eff}, P_m and P_{aq}) vs. HPβCD concentration were plotted. Excellent agreement was obtained between literature experimental permeability and the predicted P_{eff} values for both compounds at all of the HPβCD concentrations tested. The presented validated model that considers the opposing effects of the formulation on the solubility and the permeability, can lead to a more efficient and intelligent use of molecular complexation strategies; the formulator will be able to a priori strike the optimal solubility–permeability balance to maximize and facilitate the overall oral drug absorption.

Over the last 20 years, cyclodextrins have become a very popular and useful drug delivery option for increasing the aqueous solubility and oral absorption of hydrophobic drugs (Brewster and Loftsson, 2007; Davis and Brewster, 2004; Loftsson and Brewster, 1996; Loftsson and Duchêne, 2007; Rajewski and Stella, 1996). Although the extraordinary solubility advantage afforded by the use of cyclodextrins has led to their widespread use, several reports have emerged that cyclodextrins may also reduce the apparent permeability of the drug (Carrier et al., 2007; Loftsson et al., 2005, 2007). Intuitively, this effect may be qualitatively explained by the decrease in the free fraction of the drug available for membrane permeation; it is easy to grasp that when the drug is bound to the cyclodextrin complex, it cannot be absorbed. This tradeoff between the apparent solubility increase and permeability decrease can lead to paradoxical effects on the overall fraction of drug absorbed and the in vivo performance of the formulation (Dahan and Miller, 2012; Loftsson et al., 2004; Rao and Stella, 2003).

With the purpose to investigate this solubility–permeability interplay, we have recently developed a mathematical mass transport model that quantitatively explains the impact of molecular complexation on the intestinal membrane permeability when using cyclodextrins as pharmaceutical solubilizers (Scheme 1). The model considers the effects of cyclodextrins on the membrane permeability (P_m) as well as the unstirred water layer (UWL) permeability (P_{aq}), to predict the overall effective permeability (P_{eff}) dependence on cyclodextrin concentration (C_{CD}). Complete derivation of the equations may be found in our previous publication (Dahan et al., 2010b). The analysis revealed three key points: (1) UWL permeability markedly increases with increasing C_{CD} since the effective UWL thickness quickly decreases with increasing C_{CD}; (2) membrane permeability decreases with increasing C_{CD}, as a result of the decrease in the free fraction of drug; and (3) since P_{aq} increases and P_m decreases with increasing C_{CD}, the UWL is effectively eliminated and the overall P_{eff} tends toward membrane control, that is, $P_{eff} \approx P_m$ above a critical C_{CD}. This transport model enabled excellent quantitative prediction of progesterone P_{eff} as a function of 2-hydroxypropyl-β-cyclodextrin (HPβCD) concentrations in PAMPA (parallel artificial membrane permeability assay) experiments, Caco-2 transepithelial studies, and in situ rat jejunal-perfusion model (Dahan et al., 2010b). We have later broadened the scope of this model

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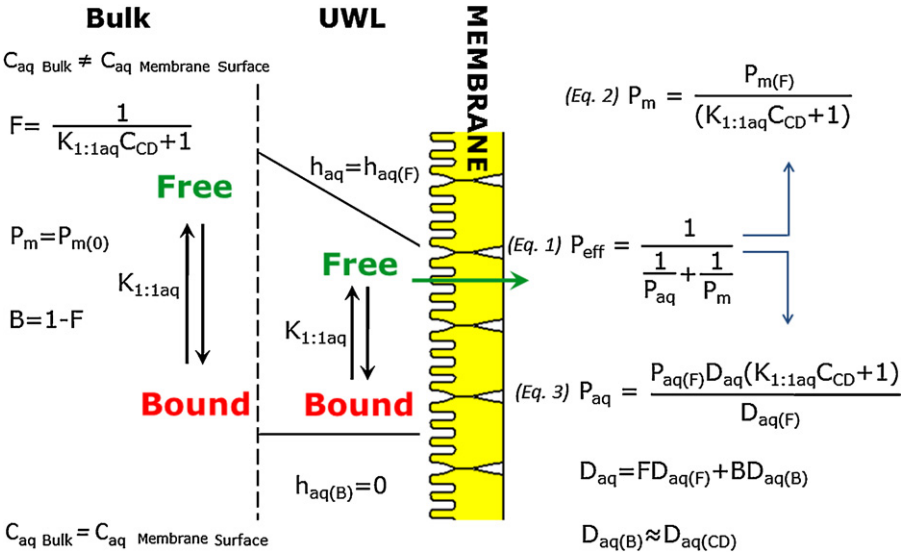

Scheme 1. Schamatic illustration of the quasi-equilibrium transport model describing the effect of cyclodextrins on the drug transport through the unstirred water layer and the intestinal membrane, developed by Dahan et al. (2010b).

to include other types of solubility-enabling formulations as well (Beig et al., 2012; Miller et al., 2011, 2012).

Brewster et al. (2007) in a publication in this journal presented the permeability of model drugs through a PAMPA membrane in the presence of different concentrations of HPβCD (0, 1, 5 and 10%). The investigated drugs were griseofulvin, carbamazepine and hydrocortisone, representing varying degrees of interaction with HPβCD, lipophilicity and aqueous solubility values. The purpose of the present study was to challenge the predictive capabilities of the mathematical model using these valuable data; applying the equations in Scheme 1 (Dahan et al., 2010b) to the initial parameters from Brewster et al. (2007), and assessing whether or not the mass-transport model will allow to predict the actual permeability data published by Brewster et al. (2007) may provide an excellent model validation method. A validated model that will consider the opposing effects of the formulation on the solubility and the permeability, to predict the overall effective intestinal absorption, will lead to a more efficient and intelligent (rather than empirical) use of molecular complexation strategies; the formulator will be able to a priori strike the optimal solubility–permeability balance to maximize and facilitate the overall oral drug absorption.

The initial parameters that are needed for the application of the quasi-equilibrium model are the association constant with the cyclodextrin ($K_{1:1aq}$), the true membrane permeability ($P_{m(F)}$), the permeability through the UWL ($P_{aq(F)}$), and the diffusion coefficients of the free drug ($D_{aq(F)}$) and the drug–cyclodextrin complex ($D_{aq(B)}$). The values for $K_{1:1aq}$ were calculated from the solubility data reported by Brewster et al., and were found to be 461.1 and 606.2 M^{-1} for carbamazepine and hydrocortisone, respectively (Brewster et al., 2007); since griseofulvin was found to exhibit very low $K_{1:1aq}$ value, indicating a negligible interaction with HPβCD, that led to significantly different permeability profile (Brewster et al., 2007), this drug was not included in the analyses of this study. The effective permeability (P_{eff}) of the drugs reported by Brewster et al. (2007) was similar at UWL lengths of 25 and

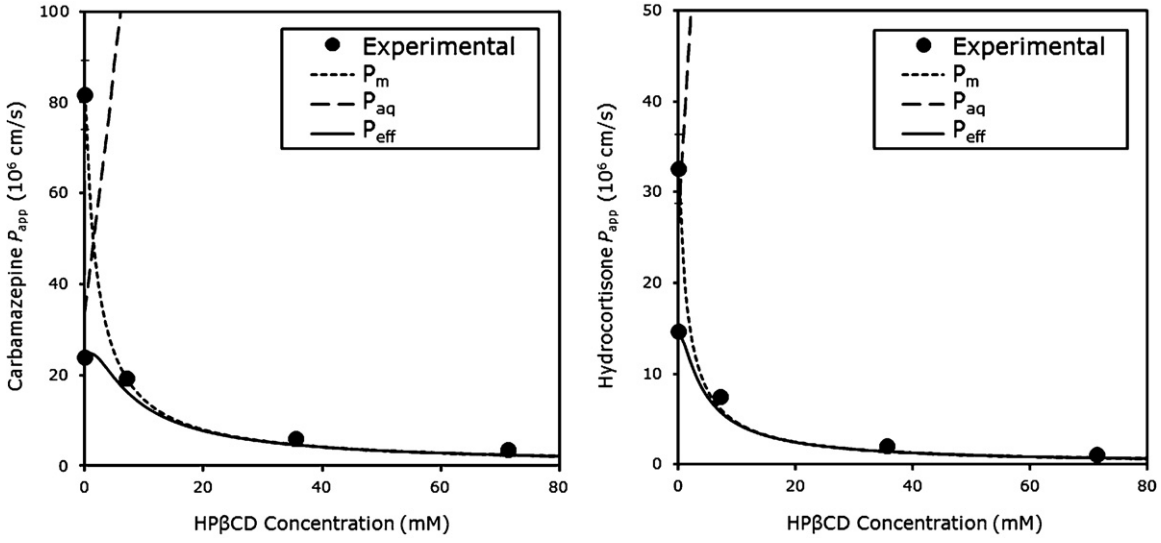

Fig. 1. The apparent permeability of carbamazepine (left panel) and hydrocortisone (right panel) as a function of HPβCD concentration in the PAMPA model. The theoretical lines were calculated according to the model presented in Scheme 1 via Eq. (1) (P_{eff}), Eq. (2) (P_m) and Eq. (3) (P_{aq}). Experimental data points were taken from Brewster et al. (2007).

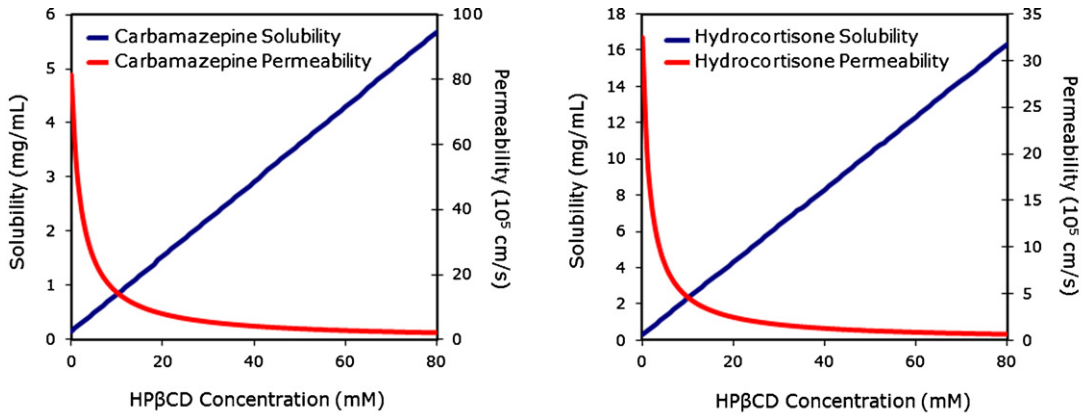

Fig. 2. The opposing effects of HPβCD on carbamazepine (left panel) and hydrocortisone (right panel) solubility (blue line) and permeability (red line) based on the theoretical quasi-equilibrium transport analysis validated in this study. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

40 μm, indicating that the overall transport was under membrane control in these conditions, i.e. $P_{eff} \approx P_m$. Therefore, P_{eff} values at UWL length of 25 μm were taken as the P_m for both compounds (81.5×10^{-6} and 32.5×10^{-6} cm/s for carbamazepine and hydrocortisone, respectively). Likewise, the P_{eff} values at UWL length of >100 μm were presumed to represent the P_{aq} for both compounds (23.7×10^{-6} and 14.6×10^{-6} cm/s for carbamazepine and hydrocortisone, respectively). The values for the diffusion coefficient of the free drugs ($D_{aq(F)}$) were previously published to be 7.6×10^{-6} cm^2/s for carbamazepine (Crison et al., 1996), and 7.05×10^{-6} cm^2/s for hydrocortisone (Seki et al., 2003). Since the molecular size of the cyclodextrin is much larger than that of the free drugs, $D_{aq(B)}$ may be assumed to be approximately equal to the aqueous diffusion coefficient of free cyclodextrin, $D_{aq(CD)}$, and was taken as 3.2×10^{-6} cm^2/s (Ribeiro et al., 2007).

Fig. 1 compares the theoretical permeability of carbamazepine and hydrocortisone as a function of HPβCD predicted by the mathematical model, to the experimentally observed values reported by Brewster et al. (2007). The theoretical lines were calculated according to the model presented in Scheme 1 via Eq. (1) (P_{eff}), Eq. (2) (P_m) and Eq. (3) (P_{aq}). It can be seen that excellent agreement was achieved between the experimental and predicted P_{eff} values for both compounds at all of the HPβCD concentrations tested. In our previous report of this solubility–permeability interplay we have validated the model using the highly lipophilic drug progesterone (Dahan et al., 2010b). Here, we add carbamazepine and hydrocortisone that exhibit significantly lower Log *P* and intrinsic permeability values than progesterone, and hence validate that our mass-transport model of the solubility–permeability tradeoff is accurate and trustworthy over a wide range of lipophilicity and permeability values.

It is also evident from Fig. 1 that very quickly, i.e. in the presence of small levels of HPβCD, the curves for P_m and P_{eff} are superposing; this phenomenon indicates that for both carbamazepine and hydrocortisone, the overall permeability is under membrane-control in the presence of lower than 1% HPβCD, and that the UWL is no longer effective as a barrier for absorption under these conditions. It can be seen that P_{aq} and P_m rapidly increases and decreases, respectively, and in fact, significant difference between P_m and P_{eff} was obtained only in the absence of HPβCD. The results suggest that for both drugs, the theoretical membrane surface to bulk concentration ratio approaches one in the presence of very small HPβCD levels. Hence, the analyses presented here reveal that the solubility–permeability tradeoff exists and follows the presented model whether the UWL is an effective barrier for absorption as in the previous publication with progesterone (Dahan et al., 2010b), or not, as in the current report with carbamazepine and hydrocortisone.

Fig. 2 illustrates the effect of HPβCD on carbamazepine and hydrocortisone apparent solubility and PAMPA permeability based on the theoretical quasi-equilibrium transport analysis validated in this work. This figure visibly illustrates the opposing effects a cyclodextrin-based formulation may have on the apparent solubility and intestinal permeability.

While solubility-enabling formulations can certainly increase the apparent aqueous solubility of the co-administered lipophilic drug, it is quite rare to consider their effect on the apparent permeability, the most important parameter (together with the solubility) dictating oral absorption (Amidon et al., 1995; Dahan et al., 2009, 2010a; Lennernas, 1998). The findings presented in this paper show that when using cyclodextrins as pharmaceutical solubilizers, on the same time that we increase the apparent solubility, we decrease the intestinal permeability, in a way that eventually might limit the in vivo performance of the formulation. Hence, this solubility–permeability tradeoff cannot be overlooked and should be accounted for when developing a solubility-enabling formulation. Moreover, we offer a validated mathematical model to predict the interplay, and to make the formulation development a more intelligent and less empiric process. This phenomenon also explains how come many formulations significantly increase the solubility but fail to improve overall absorption.

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