The solubility-absorption trade-off in using solubilizers: mechanistic PK simulations of progesterone with explicit cyclodextrin

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Introduction

Cyclodextrins improve solubility of poorly soluble lipophilic drugs due to 1:1 complexation in their nonpolar interior cavity. However, this decreases the fraction of free dissolved drug in gut lumen and, as expected, reduces the concentration gradient for absorption across the apical membrane. This solubility-absorption trade-off was taken into account by a set of models developed by Dahan et al [1] and demonstrated on the 2-hydroxypropyl-beta-cyclodextrin: progesterone system. [1,2] With the 1:1 complexation equilibrium established, these implicit models calculate the boost in solubility and reduction in absorption as linear and reciprocal functions, respectively, of the cyclodextrin concentration. Sun, et al, interpreted the latter as the analytical cyclodextrin dose concentration (i.e., dose / dose volume) and fixed its value. [2] Consequently, effective solubility and permeability were fixed input parameters, as well, since the simulation system used in [2] did not track cyclodextrin evolution through the gastrointestinal (GI) tract.

Methods

1. Cyclodextrins as solubilizers

Cyclodextrins solubilize lipophilic drugs by binding drug molecules 1:1 into their central cavity. [3] The binding is reversible and can be described by a simple stability constant: [3]

$$K_{asoc} = \frac{[Cy \cdot D]}{[D_{free}][Cy_{free}]}$$

where Cy_{free} = free cyclodextrin, D_{free} = free dissolved drug, CyD = complex. We assume that:

1. The complexation equilibrium is attained instantaneously and thus maintained in the GI tract at all times. [4]
2. Cyclodextrin itself is in dissolved state at all times, does not form aggregates, is not absorbed, degraded, or affected by the GI tract in any way other than transit.

2. Dahan model of cyclodextrin effect [1]

Dahan, et al, have recognized that although cyclodextrins do prevent precipitation of poorly soluble lipophilic drugs, the formation of cyclodextrin-drug complex results in lowering lumen concentration of the free drug and, consequently, lower permeability gradient through the intestinal wall. They modeled this solubility-absorption tradeoff by modifying the input values of drug's solubility, S_{aq}:

$$S_{aq} = S_{aq,free}\left(1 + K_{asoc}C_{Cy}\right)$$

and effective permeability, P_{eff}:

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

$$P_m = \frac{P_{m,free}}{1 + K_{asoc}C_{Cy}} \qquad P_{aq} = \frac{P_{aq,free}D_{aq}}{D_{aq,free}}\left(1 + K_{asoc}C_{Cy}\right)$$

In the above all quantities with subscript "free" pertain to drug properties in the absence of cyclodextrin. P_m = membrane permeability, P_{aq} = permeability across the unstirred water layer, D_{aq} = apparent diffusion coefficient in water. The meaning of C_{Cy}, the "concentration of cyclodextrin", was not clearly defined in [1], though. It was assumed it represents the analytical (i.e., total) concentration of cyclodextrin when dosed as a solution.

3. The ACAT Model [5]

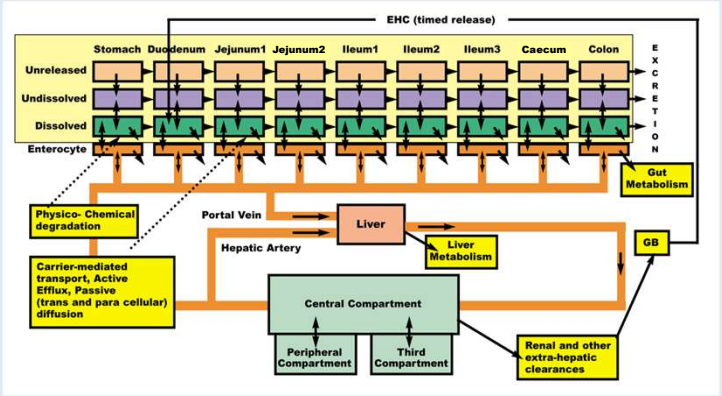

Figure 1. The ACAT model is composed of 9 intestinal compartments: stomach (St), duodenum (D), jejunum 1 (J1), jejunum 2 (J2), ileum 1 (I1), ileum 2 (I2), ileum 3 (I3), caecum (C), and ascending colon (AC). In our simulations we used only two systemic compartments: peripheral (P) and central compartment (CC).

In contrast to implicit and "static" Dahan's approach, we have included explicit cyclodextrin along with a drug as amounts tracked by the system of differential equations implemented in the ACAT model in GastroPlus® software. The extra equations added to ACAT included transit of total amount of cyclodextrin as well as the equilibrium relationship with a drug expressed by the K_{asoc} above. Free drug solubility and permeability were used as inputs.

4. Modeling progesterone in GastroPlus [5]

Following Dahan's example, progesterone was chosen as a test system for both approaches. Most of the physico-chemical and biopharmaceutical properties of the free drug were taken from literature [6-8], either directly or by fitting against the observed plasma concentration profiles. The observed data were obtained from oral doses of solid micronized progesterone [6,7] and from IV infusion. [8] This set of parameters included experimental aqueous solubility $S_{aq,free}$ = 0.00881 mg/mL. Missing parameters were predicted with ADMET Predictor software, among them human jejunal permeability $P_{eff,free}$ = 10.61*10^{-4} cm/s. [9]

The stability constant for the progesterone-cyclodextrin (HPβCD) was taken from [1] (K_{asoc} = 14,324 M^{-1}). The unstirred layer permeability was taken from [2], $P_{aq,free}$ = 5.36*10^{-4} cm/s. Assuming equimolar dosing of the progesterone-cyclodextrin complex as a solution in 250 mL of water, the following table 1 shows solubilities and permeabilities calculated by the Dahan method:

Progesterone dose [mg]	20	100	200	300
Cyclodextrin dose [mg]	89	441	882	1323
Solubility, S_{aq} [mg/mL]	0.04	0.17	0.33	0.48
Permeability, P_{eff} [cm/s *10^4]	2.91	1.93	1.5	1.27

Results

Formulation	Dose [mg]	Solubilizer	Method	%Fb	Cmax [ng/mL]	Tmax [h]	AUC(0-∞) [ng*h/mL]
Micronized, capsule	20	None	N/A	4.07	2.49 [2.48]	1 [1]	7.7 [6.0]
Supersaturated solution	20	None	N/A	4.07	2.75	0.92	7.7
Solution	20	1:1 HPβCD	Dahan	4.23	1.66	1.24	8
Solution	20	1:1 HPβCD	Explicit	4.08	2.01	1.16	7.7
Micronized, capsule	100	None	N/A	4.05	9.09 [6.22]	1.28 [2]	34.9 [53.6]
Supersaturated solution	100	None	N/A	4.05	9.33	1.2	34.8
Solution	100	1:1 HPβCD	Dahan	4.33	5.81	1.44	37.3
Solution	100	1:1 HPβCD	Explicit	4.06	6.43	1.52	35
Micronized, capsule	200	None	N/A	4.04	16.15 [13.63]	1.44 [2]	69.6 [101.9]
Supersaturated solution	200	None	N/A	4.03	16.59	1.44	69.5
Solution	200	1:1 HPβCD	Dahan	4.4	10.13	1.6	75.9
Solution	200	1:1 HPβCD	Explicit	4.05	10.86	1.84	69.7
Micronized, capsule	300	None	N/A	4.04	22.36 [31.41]	1.68 [2]	104.4 [188.5]
Supersaturated solution	300	None	N/A	4.03	23.05	1.68	104.1
Solution	300	1:1 HPβCD	Dahan	4.44	13.93	1.76	115.2
Solution	300	1:1 HPβCD	Explicit	4.02	14.72	2.08	103.8

Table 2. GastroPlus simulation results for different dosage forms of progesterone, with and without cyclodextrin solubilizer. Micronized capsule results have been verified against observed in vivo data (numbers in square brackets), while all other results are extrapolations. All the hypothetical supersaturated solution dosage forms rapidly precipitate (size of precipitate particles matches micronized powders) and redissolve with the progress of transit and absorption – these have been simulated for comparison. Cyclodextrin formulations have been simulated with both Dahan approximation and explicit method described in this work.

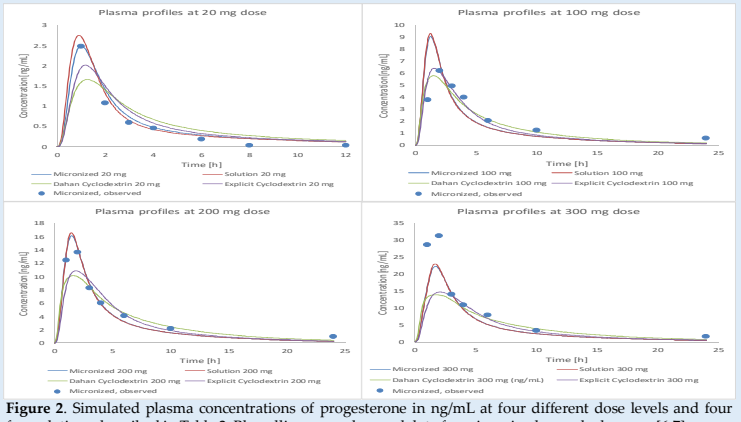

Figure 2. Simulated plasma concentrations of progesterone in ng/mL at four different dose levels and four formulations described in Table 2. Blue ellipses are observed data for micronized capsule dosages. [6,7]

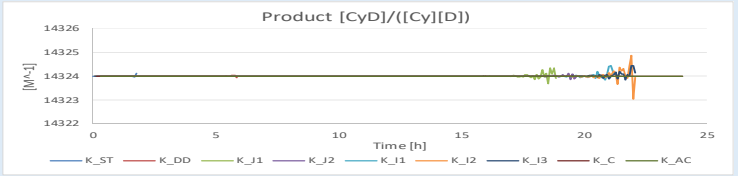

Figure 3. The product of respective concentrations that make up the K_{asoc} expression in each of the 9 ACAT compartments marked in Figure 1 at 300 mg dose. The product stays constant and equal to K_{asoc}, as expected, until concentrations reach numerical limit of the computer's CPU resulting in noise.

Conclusions

- As expected, the solubility-absorption interplay does slow intestinal permeation of progesterone in the presence of cyclodextrin.
- Explicit cyclodextrin simulations result in bioavailability and AUC similar to those of micronized and solution formulations, although lower C_{max} is reached at delayed t_{max}.
- Dahan approximation overestimates bioavailability and underestimates C_{max}.

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