PBPK Modelling of Formulation-Dependent Food Effects for Itraconazole Oral Solution: Mechanistic Insights into the Negative Food Effect Using Dynamic Dissolution-Permeation Data

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Cyclodextrins (CDs) are widely used to enhance the solubility of poorly soluble drugs. However, interactions of CDs with intestinal surfactants may alter *in vivo* performance. *Sporanox®* oral solution, where itraconazole (ITZ) is complexed with 2-hydroxypropyl-β-cyclodextrin (HP-β-CD), exhibits a negative food effect, unlike the CD-free capsule. Experimental evidence suggests bile salts displace ITZ from HP-β-CD, leading to supersaturation, precipitation, and reduced fed-state absorption.

Background and Objective

Oral delivery remains the preferred route for many drugs. However, poor aqueous solubility may limit the absorption of many new chemical entities. CDs are widely used excipients that enhance the apparent solubility of lipophilic drugs through reversible inclusion complexation.[1] Despite increasing apparent solubility, only the unbound dissolved drug is assumed to drive intestinal permeation rate. Interactions of CDs with endogenous surfactants may alter free fractions of drug in solution. Sporanox® oral solution contains ITZ complexed with HP-β-CD to solubilise the drug. Clinically, this formulation exhibits a negative food effect, whereas the CD-free capsule shows a positive food effect. *In vitro* studies suggest that bile salts compete with ITZ for HP-β-CD binding, displacing the drug and generating transient supersaturation followed by precipitation. Here, we develop a mechanistic PBPK framework to quantitatively explore bile salt–mediated displacement and its potential impact on supersaturation, precipitation, and thence overall oral drug absorption rate and extent.

Methods

The SIVA 5 toolkit and a stepwise approach were used to estimate binding constants for the ITZ–HP-β-CD system for non-micellar, fasted and fed conditions.

$$S_{Tot} = S_o + S_i + S(BSPL)_{neut} + S(BSPL)_{ion} + S_{bound,excip}$$

$$S_{bound,excip} = S_0 * \left(K_{1:1} * [CD]_{free} + K_{1:1} * K_{1:2} * [CD]^2_{free}\right) + S_i * \left(K_{i1:1} * [CD]_{free} + K_{i1:1} * K_{i1:2} * [CD]^2_{free}\right)$$

Itraconazole (Monoprotic Base)			
pKa	4.28	HP-β-CD Molecular weight	1541.5 (g/mol)
logP	4.47	Solubility Factor (SF1)	1298.3 (Estimated using SIVA 5)
Intrinsic solubility (S_o)	1E-06 (mg/ml)	logKm:w (Neutral)	6.25 (Estimated using SIVA 5)
Molecular weight	705.6 (g/mol)	logKm:w (Ion)	5.25 (Estimated using SIVA 5)

In Vitro Solubility Modelling

ITZ–HP-β-CD binding constants were estimated from solubility data in non-micellar media across a range of pH, with neutral and ionised binding constants fitted at pH 7 and 2 respectively and verified at pH 4. [3]

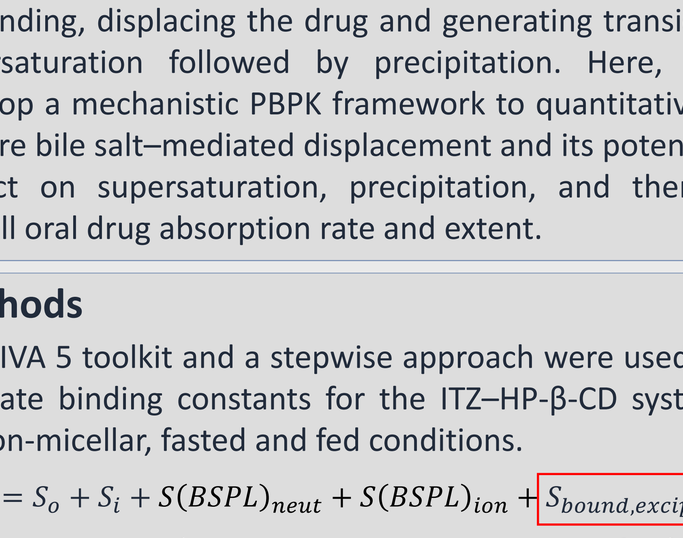

Figure 1: Excipient binding model - estimation of binding constants using SIVA.

Binding Constant Stoichiometry (API:Excipient) in non-micellar medium			
Neutral		Ion	
K1:1	7175	K1:1	9334.1
K1:2	4901	K1:2	20.64

Solubility experiments (Cuoco et al.,2022) at pH 6.5, where ITZ is largely unionised, were used to verify non-micellar binding constants and estimate neutral binding constants under 1× and 5× FaSSIF conditions.

➢ **1xFaSSIF (fasted state): (Fig. 3B)**

Excipient neutral binding constants estimated from 1×FaSSIF solubility data.

Binding Constant Stoichiometry (API:Excipient) in FaSSIF Medium	
Neutral	
K1:1	1295.8
K1:2	9756.7

➢ **5xFaSSIF (fed state): (Fig. 3C)**

Excipient neutral binding constants estimated from 5×FaSSIF solubility data.

Binding Constant Stoichiometry (API:Excipient) in 5x-FaSSIF Medium	
Neutral	
K1:1	1266.8
K1:2	6039.8

Precipitation Parameter Optimization

Supersaturation and precipitation were characterised from dissolution-permeation data (0×, 1×, 5× FaSSIF). [1] Critical Supersaturation Ratio (*CSR)* was calculated from maximum dissolved concentration ratio, and Precipitation Rate Constant (*PRC)* was fitted in the PBPK model to clinical plasma profiles.

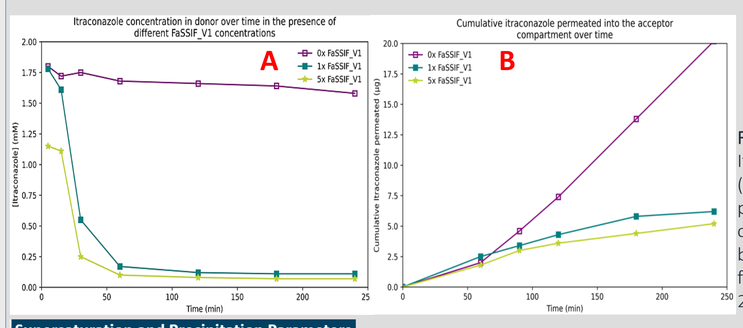

Figure 2: Itraconazole donor (A), permeation (B) profiles at different concentration of bile salts (adapted from Cuoco et al., 2023).

Supersaturation and Precipitation Parameters			
Fasted		Fed	
CSR	14.87	CSR	18.81
PRC	0.01	PRC	0.9

Results

PBPK simulations capture the negative food effect via bile salt–driven displacement of ITZ from HP-β-CD. This induces supersaturation and precipitation, reducing free drug availability and permeability.

	Fasted			Fed		
	Observed	Predicted	P/O	Observed	Predicted	P/O
AUC (ng/mL.h)	4519.9	4436.6	0.98	3161.7	5542.2	1.75
Tmax (h)	2.2	3.1	1.42	4.8	4.3	0.9
Cmax (ng/mL)	545.7	418.6	0.77	306.9	375.3	1.22

Discussion

The itraconazole solution PBPK model was developed and verified to capture its PK under fasted and fed conditions (Fig. 5). The model predicted Cmax within 80-125% and AUC of 98% (fasted) and 175% (fed), supporting the hypothesis of bile salt driven displacement of ITZ from HP-β-CD as the cause of fed state precipitation and reduced absorption. Per Fig. 4, CD reduces free itraconazole and permeability (Peff) via complexation, while bile salts competitively displace ITZ, inducing supersaturation and precipitation. Dynamic bile salt-CD interactions may ultimately govern free drug concentration and thence apparent permeability.

References

[1] Cuoco et al., 2022. When Interactions Between Bile Salts and Cyclodextrin Cause a Negative Food Effect: Dynamic Dissolution/Permeation Studies with Itraconazole (Sporanox) and Biomimetic Media. *J. of Pharm Sci,* 112, 1372-1378.
[2] Barone et. al., 1998. Food Interaction and Steady-State Pharmacokinetics of Itraconazole Oral Solution in Healthy Volunteers, *J. Pharmacotherapy,* 18, No. 2
[3] Peeters et. al. 2002. Characterization of the Interaction of 2-Hydroxypropyl-bcyclodextrin With Itraconazole at pH 2, 4, and 7, *J. Pharm Sci*, 91, No. 6

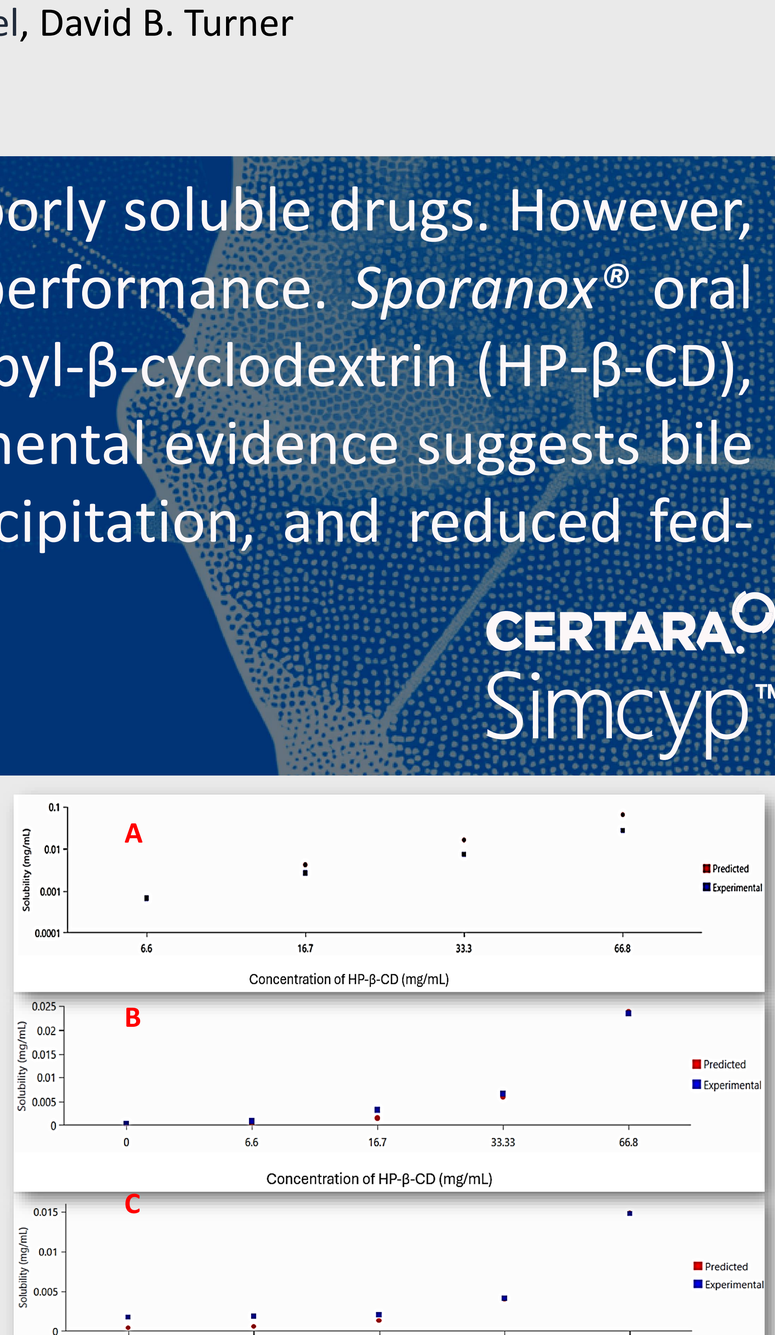

Figure 3: Solubility modelling of Itraconazole at various concentrations of CD, in non-micellar medium (A), in 1xFaSSIF (B), in 5x-FaSSIF (C). Experimental data is taken from [2].

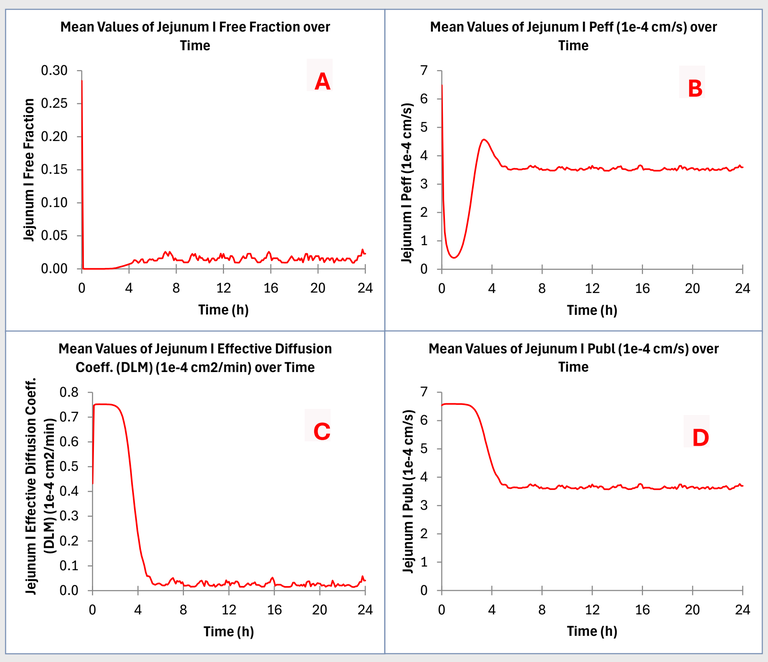

Figure 4 : Dynamic impact of [CD](t) on solution free fraction (A), Effective Permeability (Peff) (B), Effective Diffusion Coefficient (C), Permeability of Unstirred mucus/water Boundary Layer (Publ) (D).

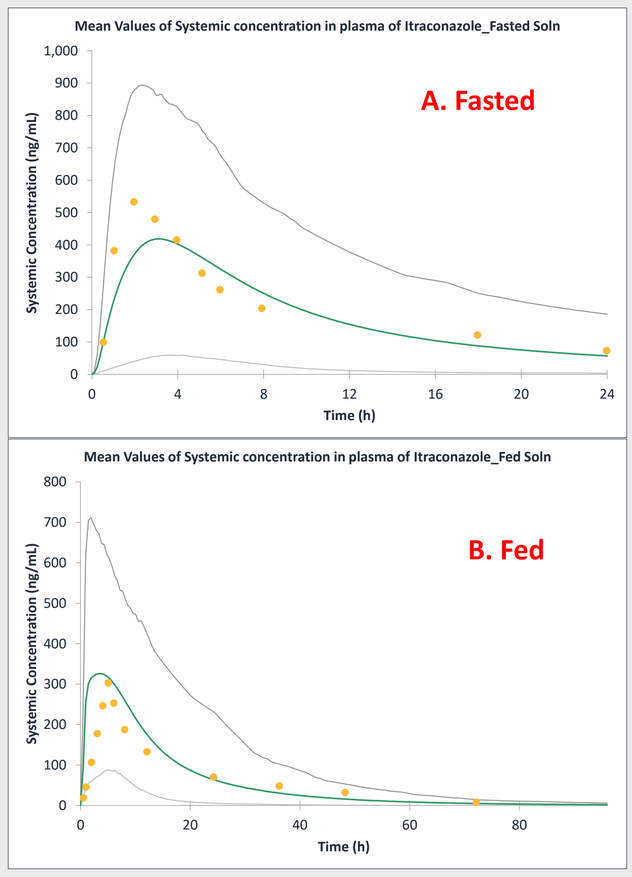

Figure 5: Systemic concentration profiles for fasted (A), and fed (B), conditions. The PBPK model simulated 10 virtual trials of 30 healthy volunteers, matching the trial design of [2].