DISSOLUTION STUDIES TO PREDICT PERFORMANCE IN THE GI TRACT

Jennifer Dressman

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Setting up dissolution studies to predict performance in the GI tract

WHAT INFLUENCE DO **ACID REDUCING AGENTS** HAVE ON RATE AND EXTENT OF DRUG RELEASE?

DO ALL **AMORPHOUS SOLID DISPERSIONS** HAVE THE SAME FOOD EFFECT?

WHAT HAPPENS TO DRUG RELEASE IN AN **OVERDOSE** SITUATION?

INFLUENCE OF **ACID REDUCING AGENTS (ARA)** ON RATE AND EXTENT OF RELEASE?

- **Step 1: literature survey** on changes in upper GI physiology following ingestion of ARAs
- **Key findings:**
- High impact of PPIs and H2R antagonists on gastric pH and composition of gastric fluids.
- PPIs cause some decrease in gastric volume and pepsin concentration, and may slow gastric emptying of solids.
- Effects on viscosity and surface tension appear minor.

Impact of Acid-Reducing Agents on Gastrointestinal Physiology and Design of Biorelevant Dissolution Tests to Reflect These Changes

Domagoj Segregur [1], Talia Flanagan [2, 3], James Mann [2], Andrea Moir [2], Eva M. Karlsson [4], Matthias Hoch [5], David Carlile [5], Sakina Sayah-Jeanne [6], Jennifer Dressman [1, *]

Journal of Pharmaceutical Sciences 108 (2019) 3461-3477

INFLUENCE OF **ACID REDUCING AGENTS (ARA)** ON RATE AND EXTENT OF RELEASE?

- **Step 2: propose media to reflect the observed changes**
- **Key aspects:**
- As H2-receptor antagonists and PPIs differ in potency and dosing, a bracketing approach was proposed to cover the range of possible physiological responses

=> pH 4 and pH 6 media were composed at low buffer capacity

Table 4
The Composition of Media Recommended for Simulating Fasted State Gastric Fluid Under PPI/H_2RA Co-administration

Component/Parameter	Acetate pH 4 Medium	Maleate pH 6 Medium
Pepsin (mg/mL)	0.1	–
Sodium taurocholate (mM)	0.08	0.08
Phosphatidylcholine (mM)	0.02	0.02
Sodium chloride (mM)	-	22.7
Maleic acid (mM)	-	2.31
Sodium acetate (mM)	33.3	-
+ NaOH (1 M) (mL)	-	qs. (~3.5)
+ HCl (1 M) (mL)	qs. (~25)	-
pH	4	6
Buffer capacity (mEq/pH/L)	7.5	1
Osmolality (mOsmol/kg)	91	50
Surface tension (mN/m)	64.49	67.21

Minus sign indicates the absence of component.

INFLUENCE OF **ACID REDUCING AGENTS (ARA)** ON RATE AND EXTENT OF RELEASE?

- **Step 3: compare dissolution results in ARA media with clinical profiles**
- **Work flow:**
- For dipyridamole and an AZ development compound (both weak bases) and potassium raltegravir (salt of a weak acid), the ARA media dissolution profiles were combined with PBPK modeling to predict the *in vivo* performance.
- The work flow for the AZ compound is shown in the diagram

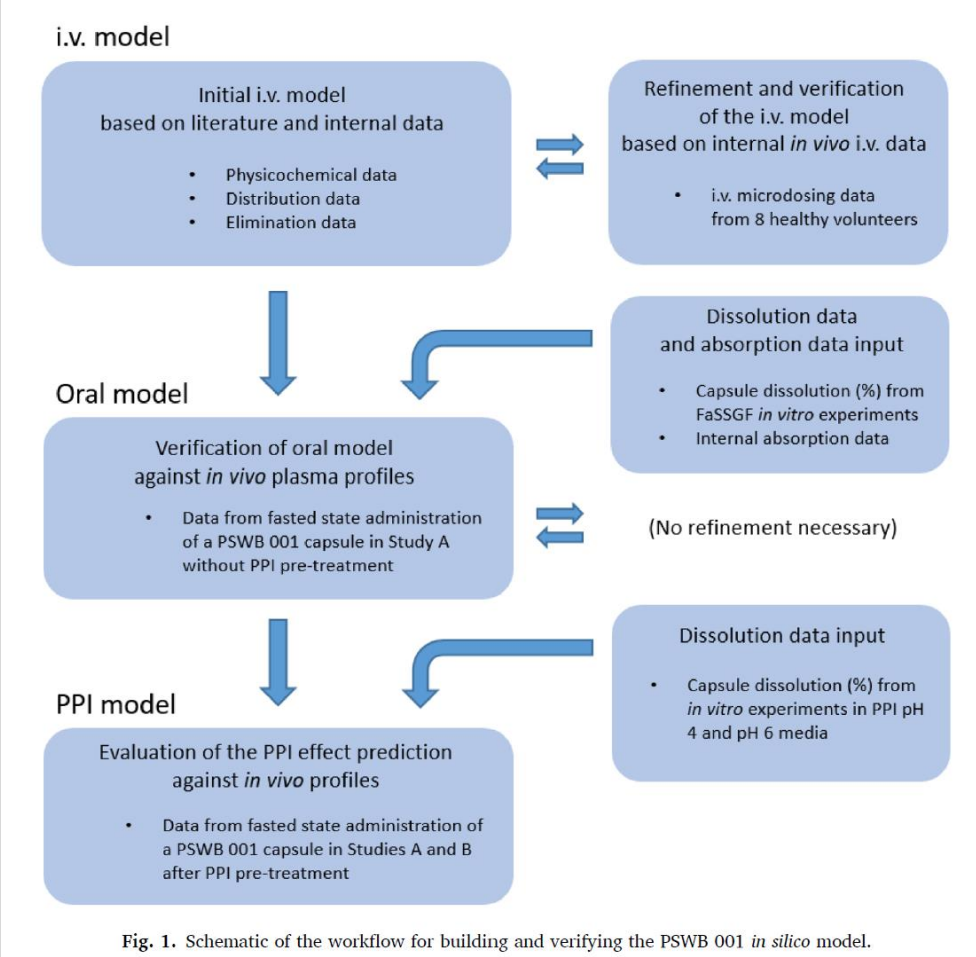


Fig. 1. Schematic of the workflow for building and verifying the PSWB 001 *in silico* model.

INFLUENCE OF **ACID REDUCING AGENTS (ARA)** ON RATE AND EXTENT OF RELEASE- WEAK BASE

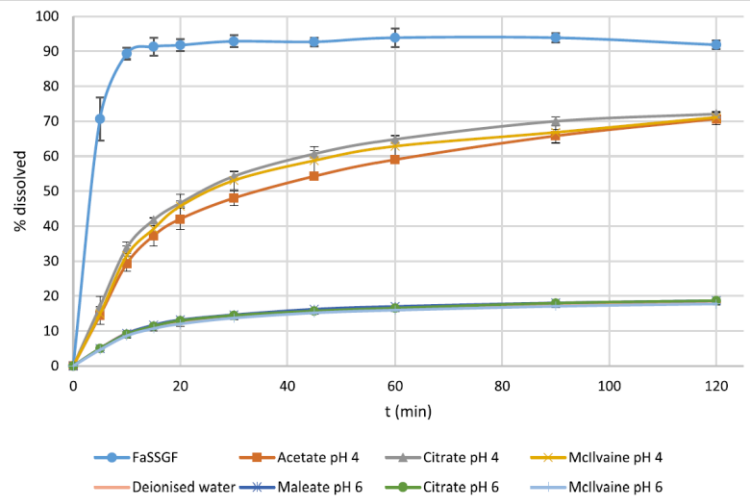
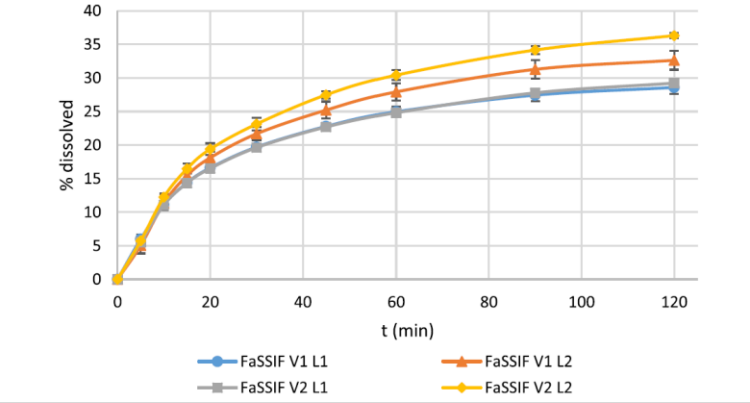
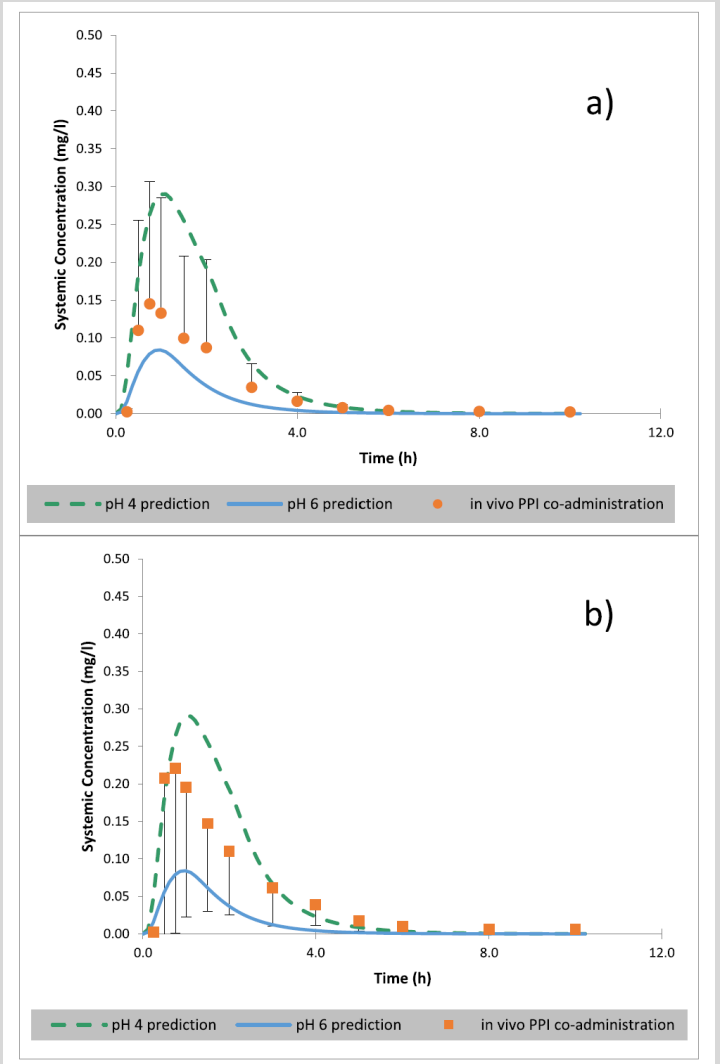


Fig. 2. Dissolution of PSWB 001 capsule in 250 ml of FaSSGF, PPI pH 4 and pH 6 media and in deionised water.



<= Dissolution testing of AZ product in FaSSGF, ARA media and FaSSIF

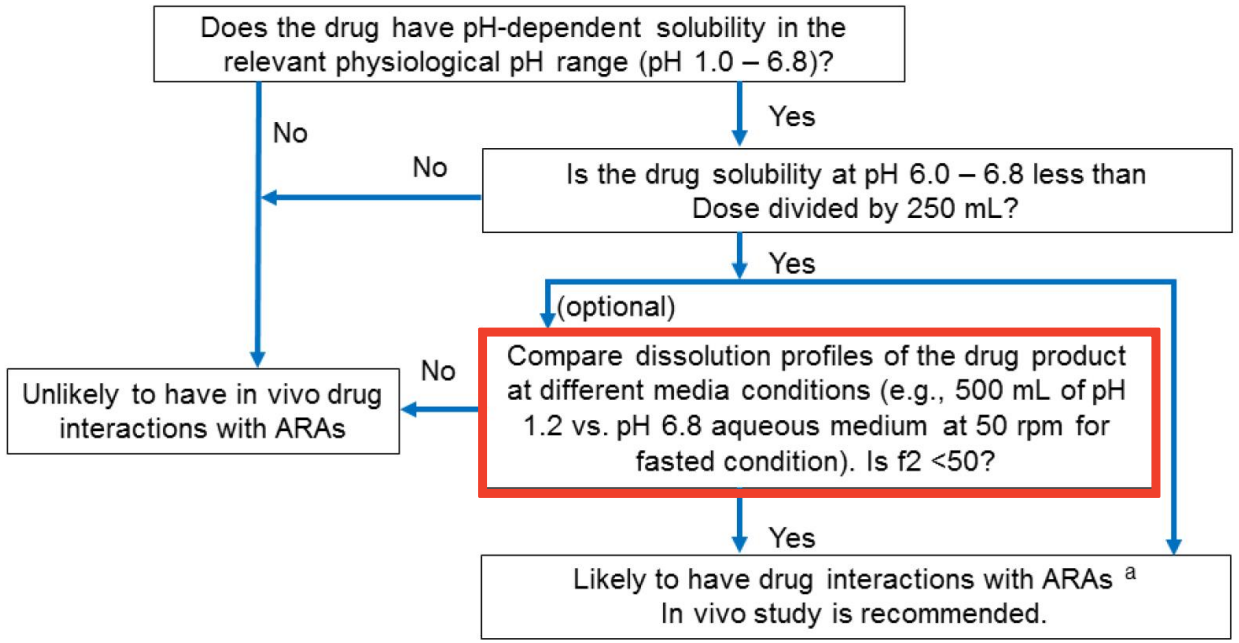
=> Comparison of dissolution/PBPK predictions with results in two AZ clinical studies



INFLUENCE OF **ACID REDUCING AGENTS (ARA)** ON RATE AND EXTENT OF RELEASE

KEY MESSAGE: FOR H2R-ANTAGONISTS AND PPI THE HIGH PH IS DUE TO A LACK OF ACID OUTPUT, NOT THE ADDITION OF BUFFER => USE OF STANDARD USP BUFFERS AT PH 4.5 OR 6.8 IS MISLEADING!!

Figure 1. A Framework to Assess Clinical DDI Risk With ARAs for Immediate-Release Products of Weak-Base Drugs



Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications Guidance for Industry

https://www.fda.gov/media/166156/download

12.06.2023

Do all **amorphous solid dispersions (ASD)** have the same food effect?

- By making an amorphous solid dispersion (ASD), one hopes to minimize the food effect – but are all ASD equal in this regard?

- **Case example – ITRACONAZOLE solid dispersions (Sporanox and Tolsura)**
  - **Sporanox (100mg) consists of itraconazole fixed on pellets in an ASD with HPMC**
  - **Tolsura (65mg) consists of a powdered ASD of itraconazole with HMPCAS**

Do all **amorphous solid dispersions (ASD)** have the same food effect?

Approach: compare the two ASDs in biorelevant media representing the fed state (FedGAS and FeSSIF-V2)

Results I. FedGAS

The Sempera (= Sporanox) pellets released best in late FedGAS, where the pH is lower (follows ITRA pH trends in solubility)

The Tolsura powder only released well in early FedGAS, where the pH is high (follows HPMCAS pH trends in solubility)

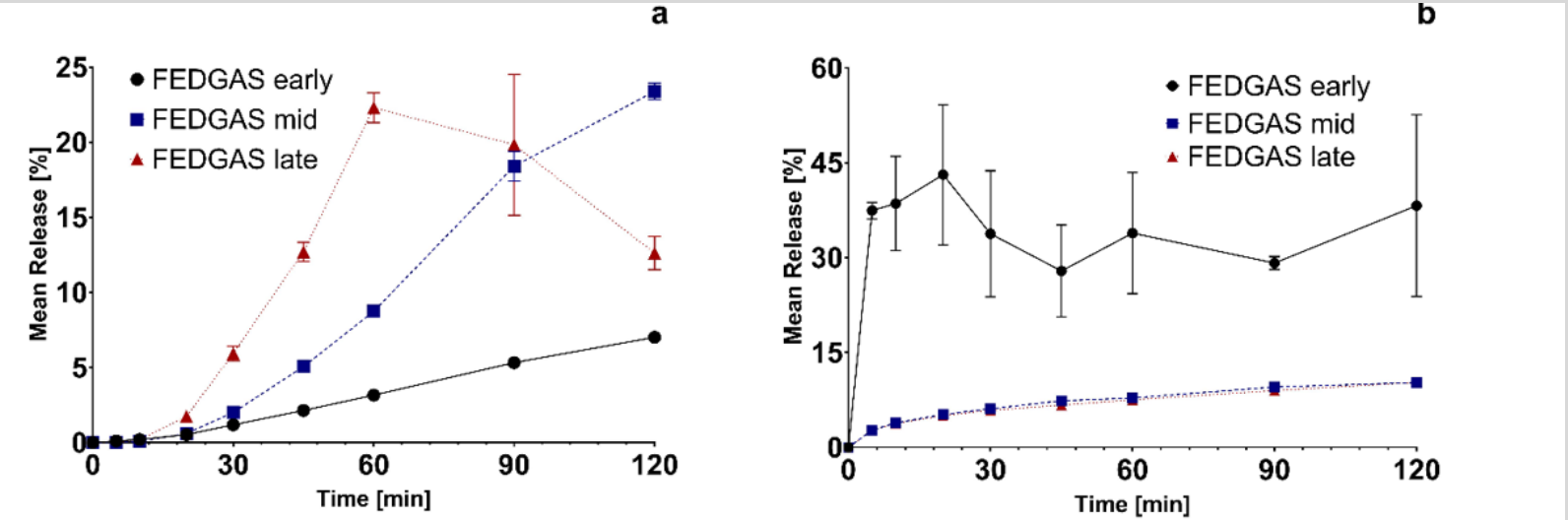
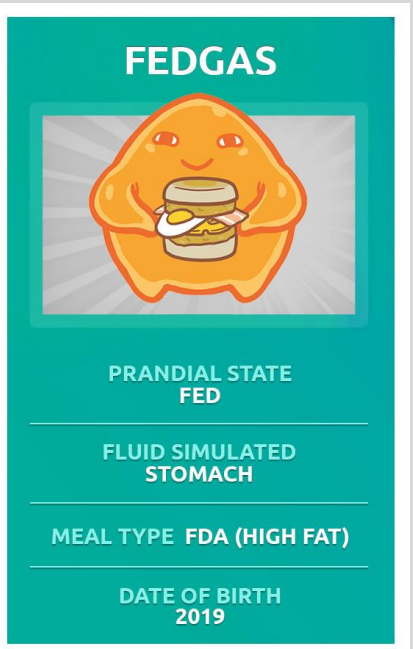


Figure 1: Mean release [%] of ITRA from (**a**) Sempera 100 mg pellets and (**b**) Tolsura 65 mg powder in FEDGAS with a paddle speed of 75 rpm.



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Results II. FeSSIF-V2

The release from Tolsura powder was clearly higher than from Sempera (=Sporanox) pellets in FeSSIF-V2

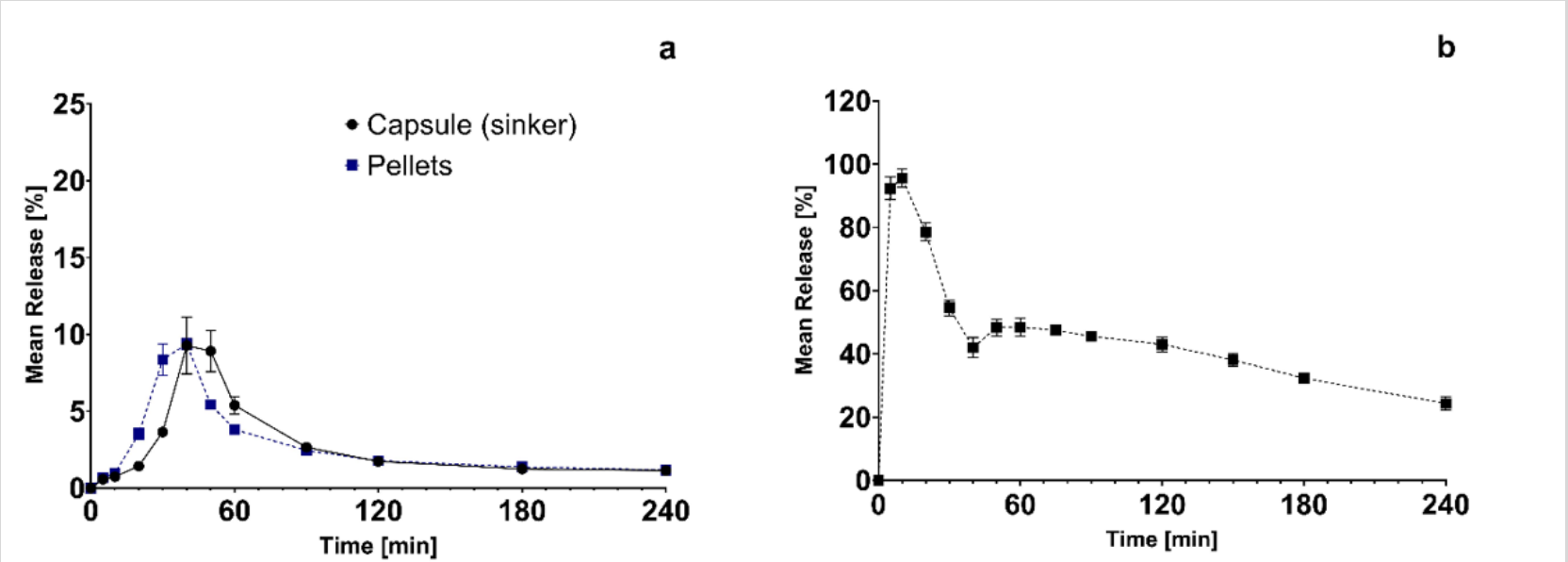
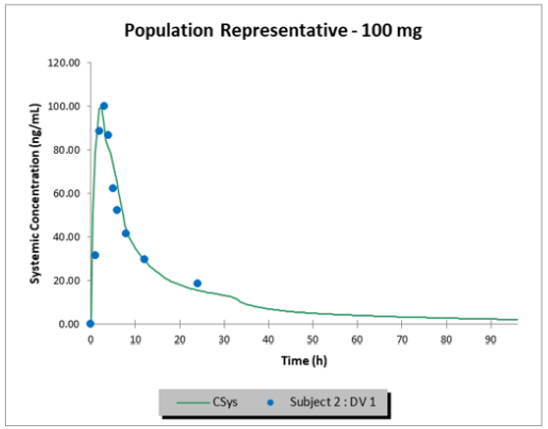


Figure 2: Mean release [%]of ITRA from (**a**) Sempera 100 mg capsules (sinker) (black dots) or pellets (blue squared) and from (**b**) Tolsura 65 mg powder in FeSSIF-V2 with a paddle speed of 75 rpm.

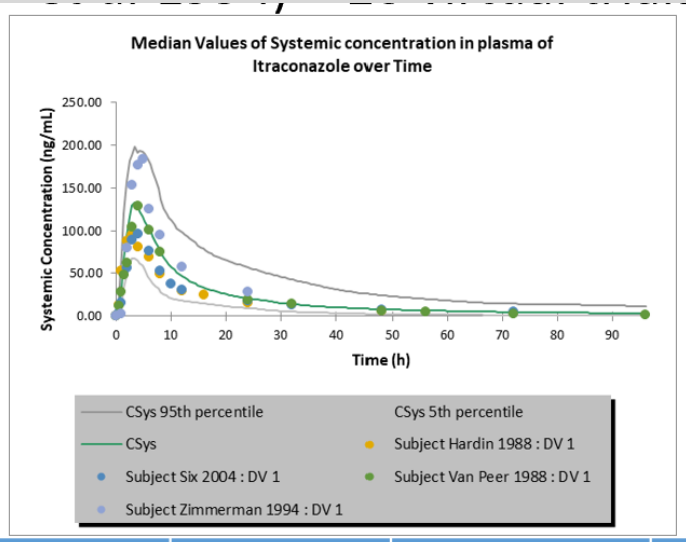
Do all **amorphous solid dispersions (ASD)** have the same food effect?

PBPK and clinical results – Sporanox fasted vs. fed



Parameter	SIM	OBS	Ratio
AUC	1460	1620	0.90
C_{max}	100	110	0.91

Zimmerman et al, 1994. *Eur J Clin Pharmacol* 46:147-150.

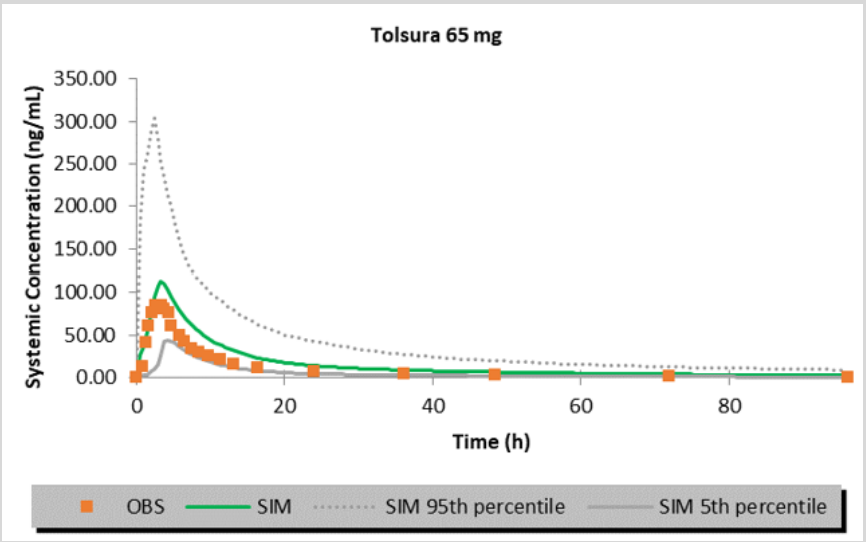


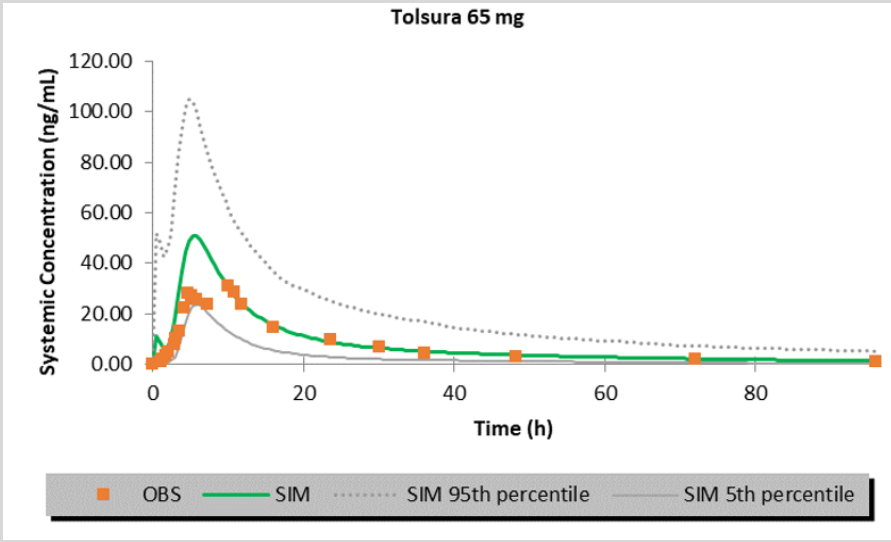
Parameter	SIM	OBS	Ratio
AUC	1896	1320 - 2290	0.83 – 1.43
C_{max}	132	110 - 184	0.72 – 1.20

Hardin et al, 1988. *Antimicrob Agents Chemother* 32(9):1310-1313.
Peer et al, 1989. *Eur J Clin Pharmacol* 36:423-426.
Zimmerman et al, 1994. *Eur J Clin Pharmacol* 46:147-150.
Six et al, 2006. *Eur J Clin Pharmacol* 24:179-186.

Do all **amorphous solid dispersions (ASD)** have the same food effect?

PBPK and clinical results – Tolsura fasted vs. fed





Whereas Sporanox has a *positive* food effect, Tolsura has a negative *food effect.*

***This could be explained by input to PBPK from dissolution in* biorelevant media, including FedGAS for the fed state gastric conditions**

12.06.2023

WHAT HAPPENS TO DRUG RELEASE IN AN **OVERDOSE** SITUATION?

- Overdose of drug products is a much-reported problem in the USA and abroad.
- Up till now, dissolution methods for studying how overdose will change release in the GI tract and thus the absorption profile of the drug have not been developed.
- **Approach:**

  1) Test release from 1, 10, 20 and 50 units of a drug product in the **USP 3 apparatus** to better understand what happens to the rate and extent of release in overdose situations

  2) Study the **effect of formulation** on the rate and extent of release

  Test drug: **Acetaminophen**

  Test formulations: IR tablets, hard capsules and soft gelating capsules, ER tablets

WHAT HAPPENS TO DRUG RELEASE IN AN **OVERDOSE** SITUATION?

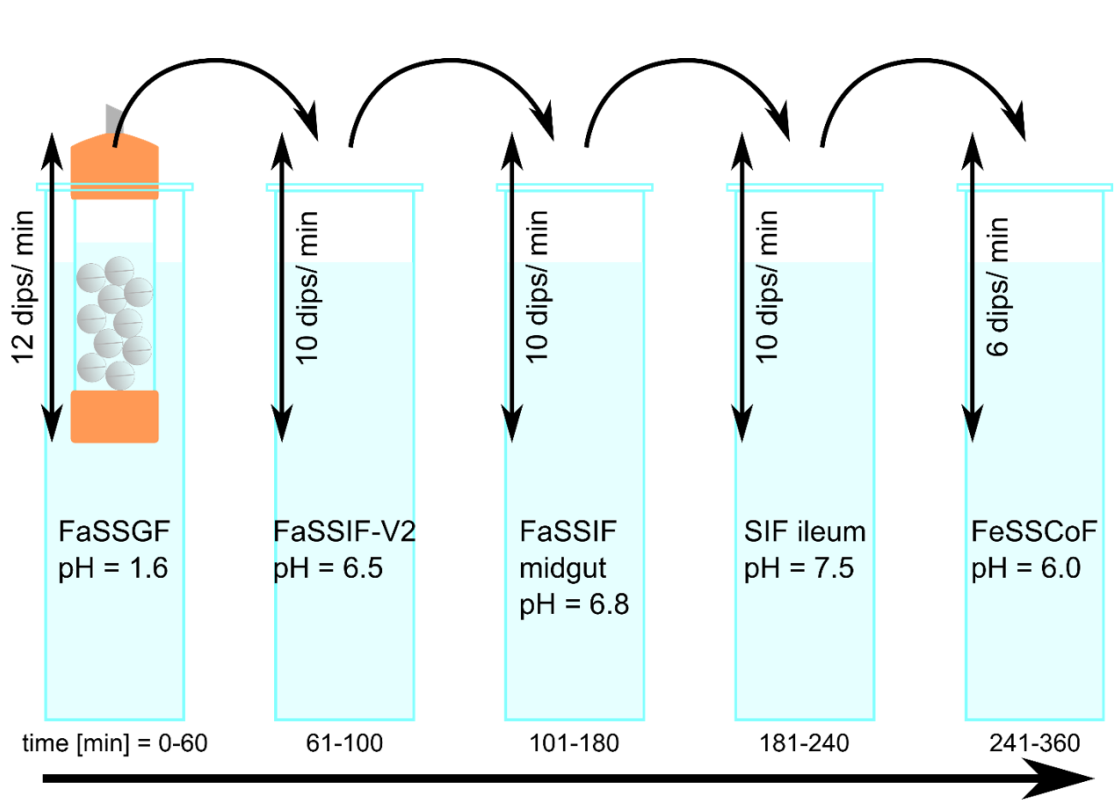
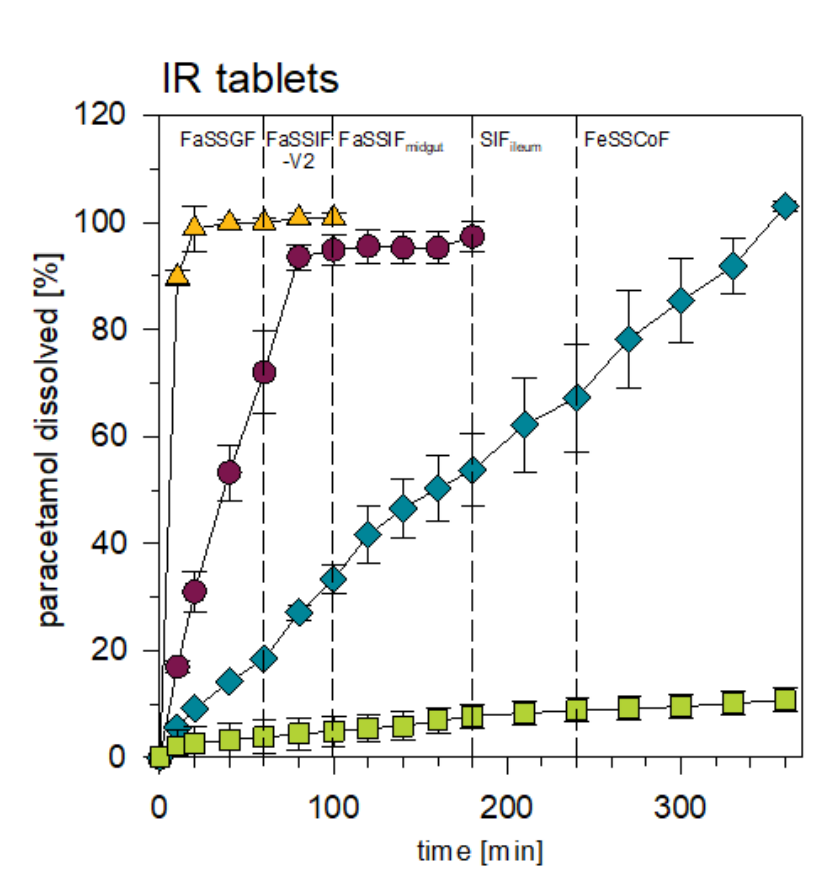


Figure 1. USP 3 dissolution testing set-up

- Set-up in the USP 3 to mimic passage of the Acetaminophen dosage forms through the GI tract

WHAT HAPPENS TO DRUG RELEASE IN AN **OVERDOSE** SITUATION?



- With one tablet, release from the IR tablet is fast and complete
- At ten or 20 tablets, the release is still complete but slower
- At fifty tablets, very little release occurs, due to clumping of the tablets and associated restriction of flow between the inner and outer vessels.
- Clumping into a „bezoar“ formation has also been observed clinically in overdose cases.

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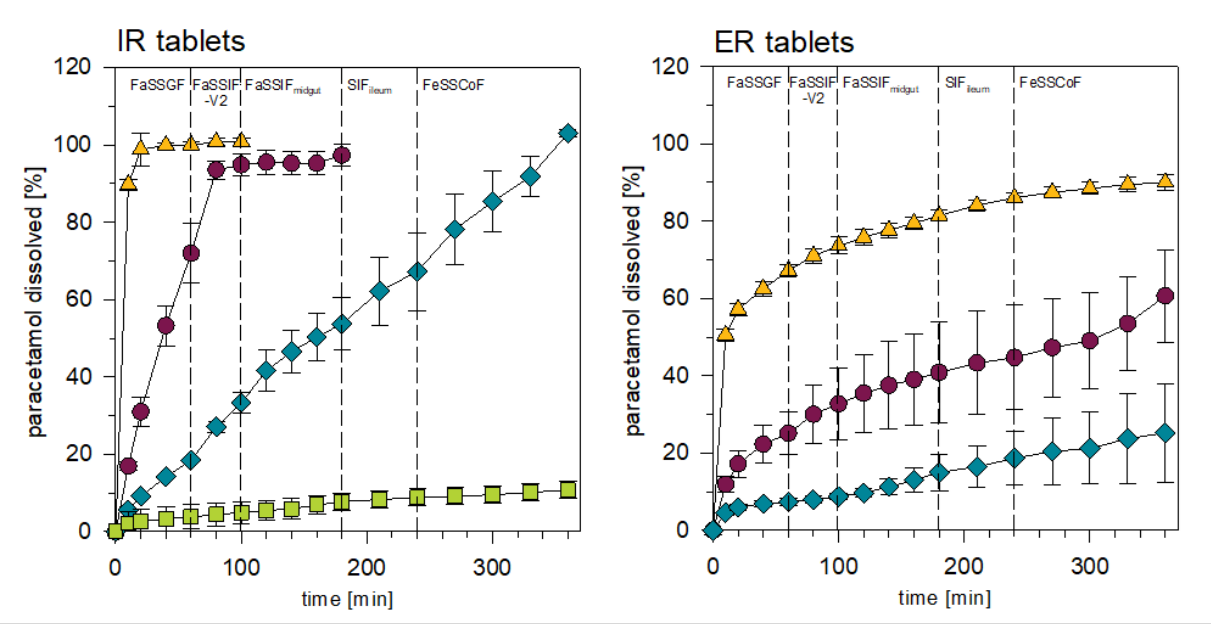

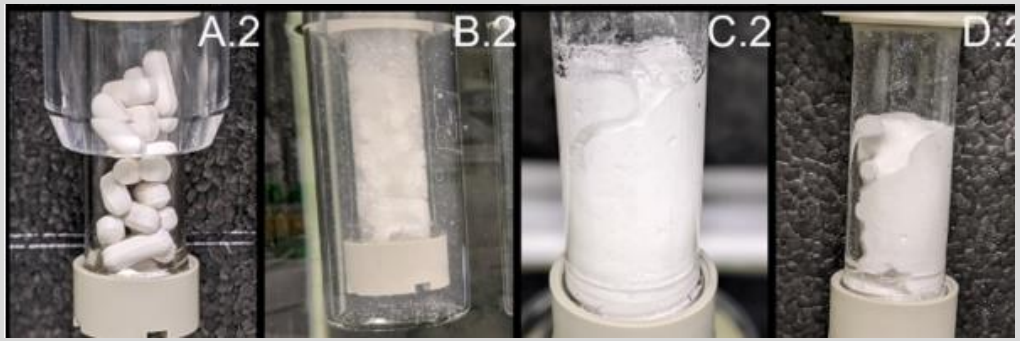

- For the ER tablets, the extent of release decreased markedly with dose: at 20 tablets, only 20% of the dose was released over 6 hours
- Here too, clumping was seen at higher doses

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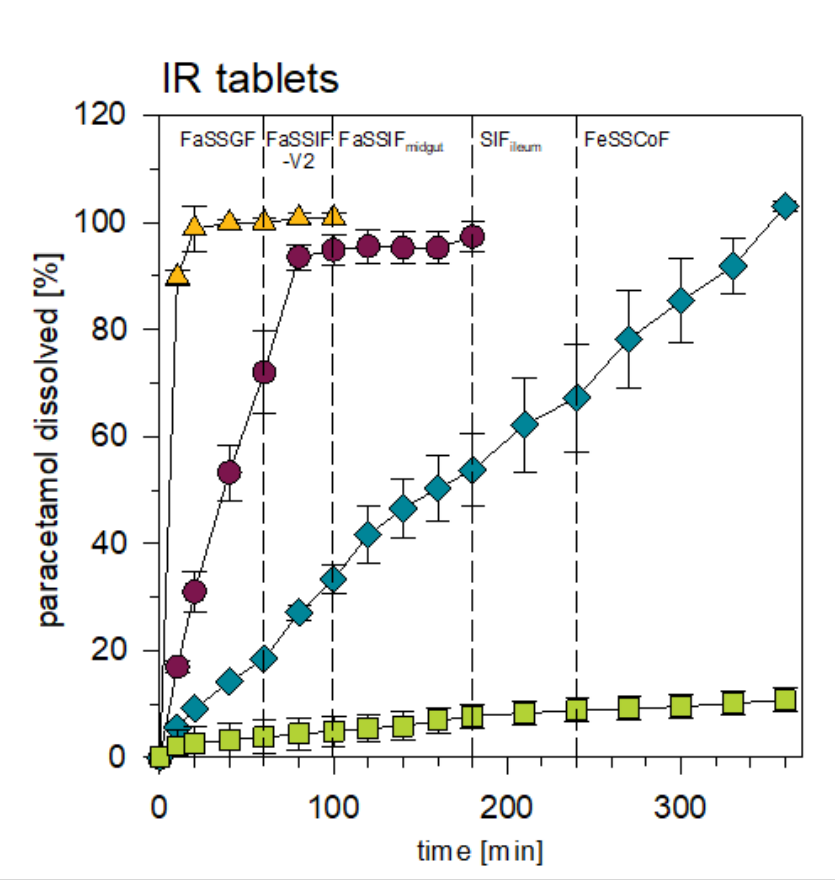

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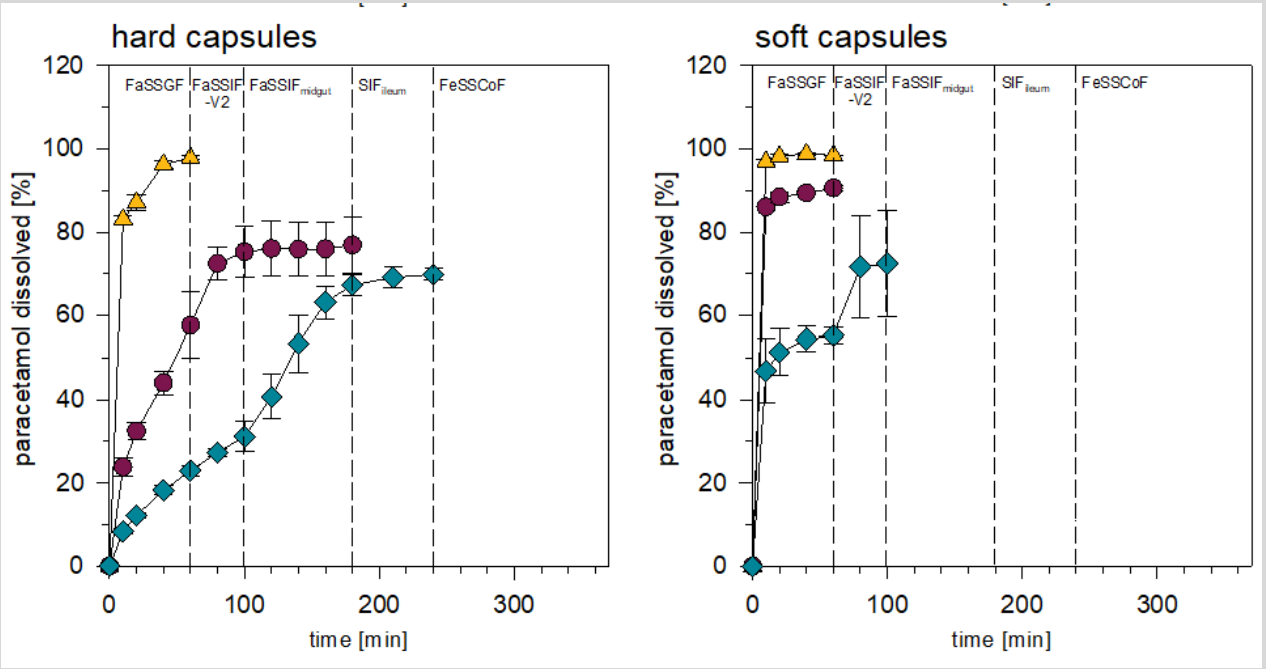
WHAT HAPPENS TO DRUG RELEASE IN AN **OVERDOSE** SITUATION?

- A similar trend was seen with the capsules, with slower and lower release observed with increasing dose (1 => 20 dosage units)



WHAT HAPPENS TO DRUG RELEASE IN AN **OVERDOSE** SITUATION?

- In summary, the overdose method was able
  - to show that at higher doses, release of acetaminophen is slower and, for some dosage forms, incomplete.
  - to distinguish the behaviour of different types of dosage form in an overdose situation
  - To reproduce „bezoar“ formation, which has been reported in cases where large numbers of dosage forms had been ingested

The method may be applicable to other products in addition to acetaminophen and provide insight as to the onset and duration of toxic levels of drugs in overdose situations.

Setting up dissolution studies to predict performance in the GI tract

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Niklas Rudolph

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Greetings from…..

…….and many thanks for your attention!