National and Kapodistrian
University of Athens

Rationale for using biorelevant media in dissolution testing

Christos Reppas

Disso-Europe 2016
Advances and Applications in Dissolution Science
20 October 2016
Bucharest, Romania

Last 5 years:
50-60% of novel approvals in the US* are administered orally
(injectables follow)

*Blood, gene therapy, tissues products, and vaccines are excluded

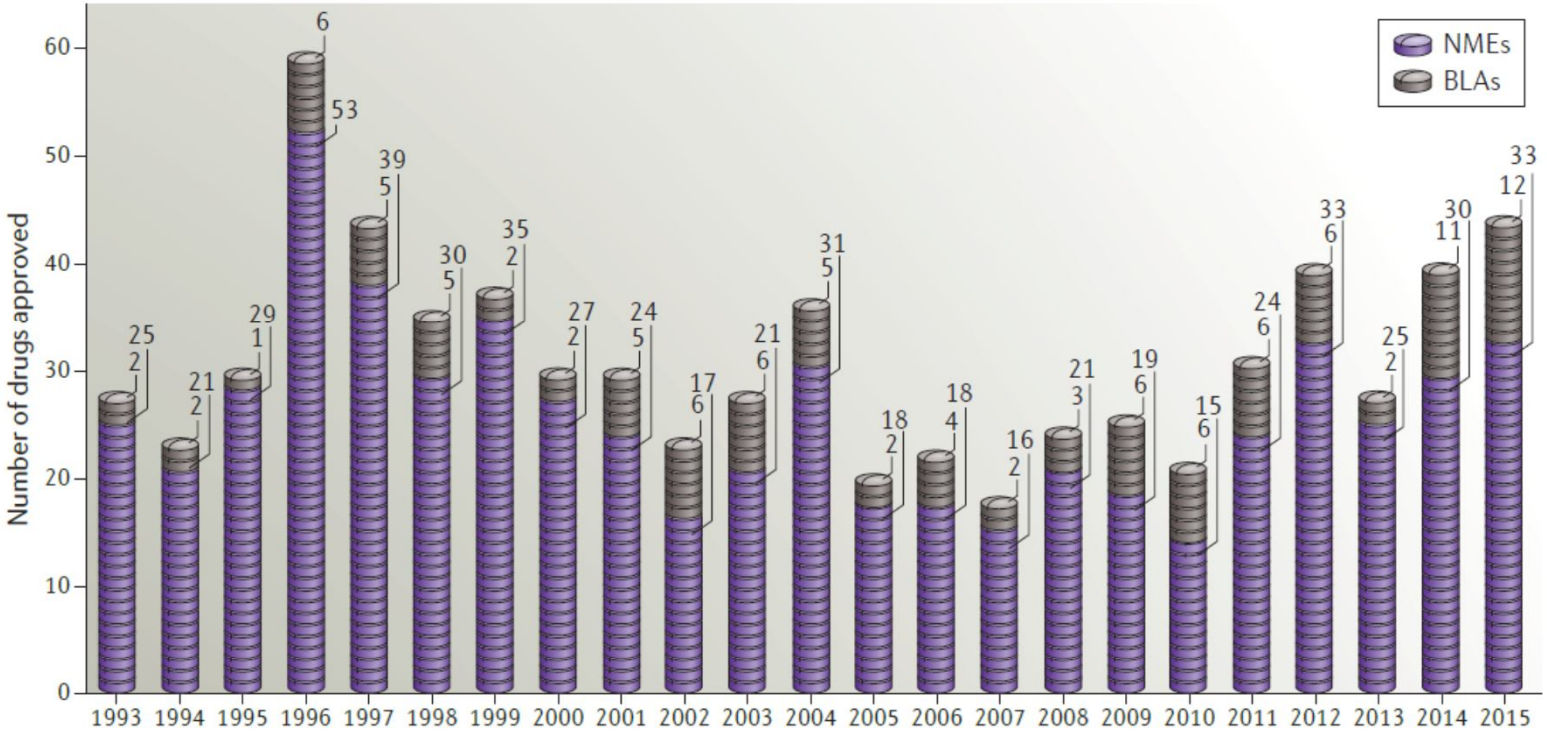


Figure 1 | **Novel approvals since 1993.** New molecular entities (NMEs) and Biologics License Applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER) since 1993. Approvals by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count. Data are from Drugs@FDA and the FDA.

Oral administration is highly desired for various reasons
(e.g. adherence/persistence to therapy, costs)

Since newer APIs are bigger, have more stability issues, and/or are more lipophilic, efficacious and safe oral administration requires appropriate chemical and/or formulation interventions more than in previous years

Increased interest for understanding the performance of
oral drug products prior to going to the clinic

Preclinical evaluation of oral drug product performance

animal studies (indirectly/directly)

Ethical concerns
High costs
Technical issues
Model restrictions

in vitro studies (directly)

An *in vitro* test that mimics the intraluminal performance of an orally administered drug product and/or the active pharmaceutical ingredient (API) is termed *biorelevant* or *physiologically relevant*

Reppas et al. Pharm. Res. 2014

Biorelevant oral drug product performance testing coupled with PBPK modeling are key components of the “patient-centric drug development” process

Selen et al.
The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance.
J Pharm Sci. 2014

Table 1. Some Examples of Drug Products with Drug Delivery Characteristics Relevant for the Discussed Scenarios

Drug Delivery Scenario	Drug Product [References]
Rapid onset (Scenario 1)	Ibuprofen capsules oral [33,34], triptans [35,36], fentanyl citrate sublingual tablet [37]
Multiphasic delivery (Scenario 2)	Methylphenidate tablets, oral [38], Zolpidem CR [39,40], Treximet [41]
Targeted time-window or chronotherapeutic (Scenario 3)	Fluoroucil (5-FU) infusion [42], Verapamil [43]
Targeted prolonged exposure (Scenario 4)	Metoprolol Tartrate [44,45], Nitropatch [46] Oxybutynin OROS Once-a-day formulation [47]

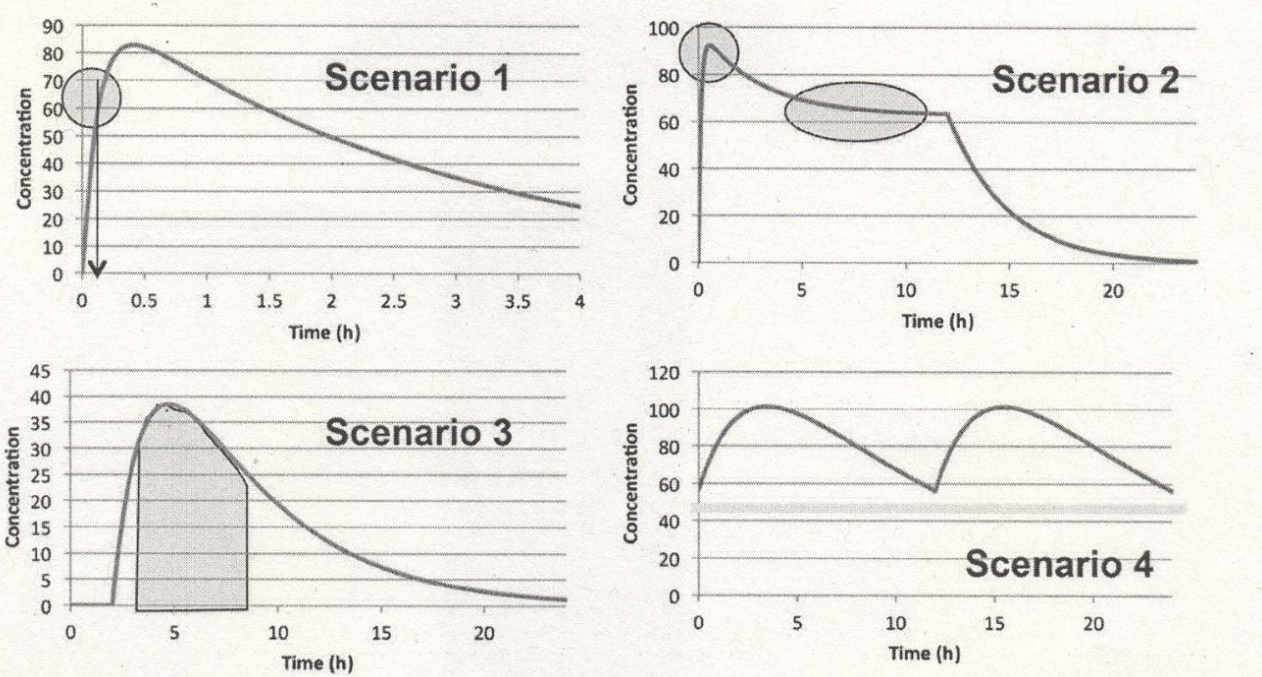


Figure 2. Four drug delivery scenarios depicted as drug concentration–time profiles.

Biorelevant oral drug product performance testing requires consideration of the required level of simulation of the luminal environment

Starting point

The closer the test conditions to the luminal environment, the better the chances of predicting product performance

The level of simulation of luminal environment required for obtaining information on the drug product performance varies with

- the API structure
- the type of dosage form, and
- the type of requested information

Levels of simulation of luminal composition

+ dietary proteins, enzymes (not digestion products), viscosity effects

Level III

+ bile components, dietary lipids, lipid digestion products, osmolality

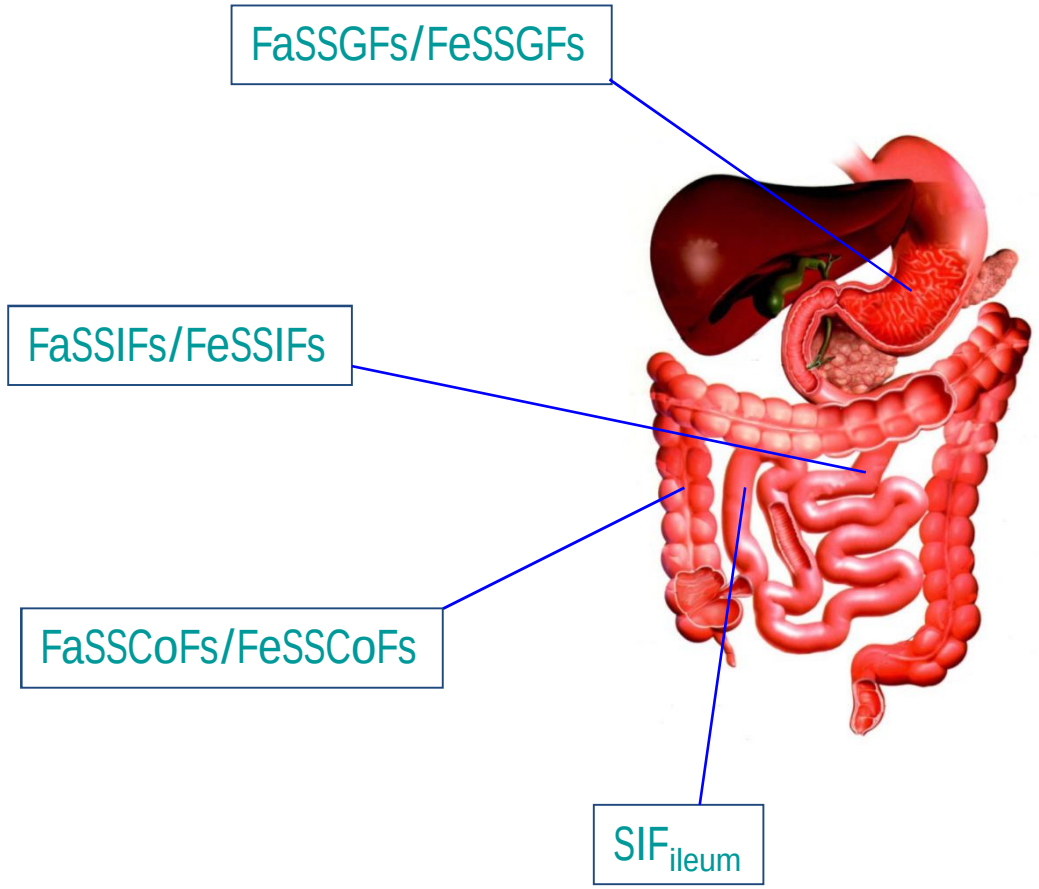
Level II

+ buffer capacity

Level I

pH

Level 0



Markopoulos, Andreas et al. EJPB 93: 173-182(2015)

Level 0 simulation of luminal composition

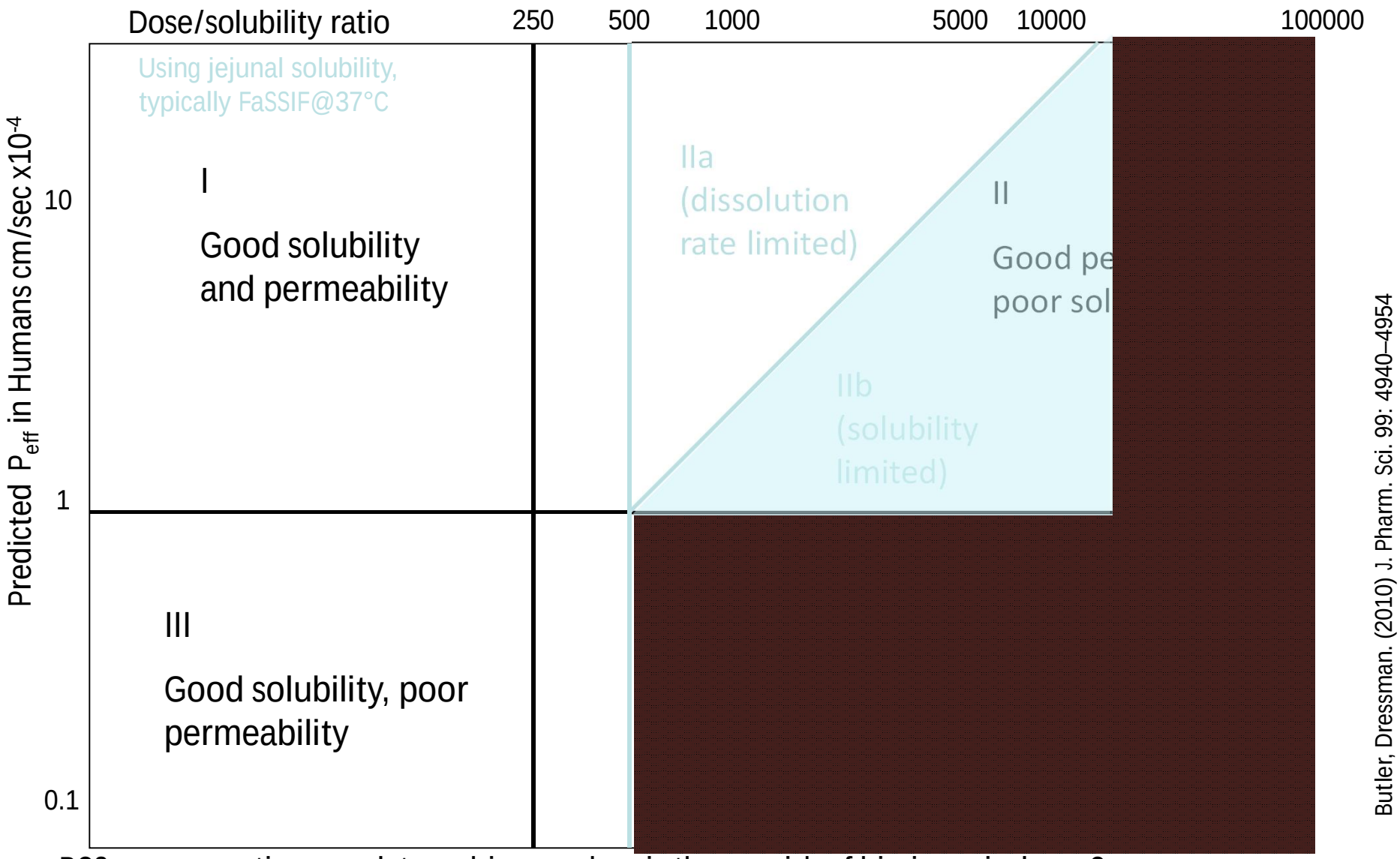
- Only luminal pH is simulated / no consideration of dosing conditions

- Distilled water or any buffer system with a pH value within the usual GI pH range could be used (e.g. compendial tests without enzymes)

- Adequate for DCS Class I and III APIs / IR tablets without pH related food effects and certain ER products not affected by buffer capacity, e.g. osmotic pump

pH

Level 0



BCS – conservative, regulatory driven - when is there a risk of bio-inequivalence?

DCS – developability classification system - what is most likely to happen?

Blue shaded area : saturation/supersaturation in GI tract likely, especially in fasted state

Courtesy James Butler, GSK

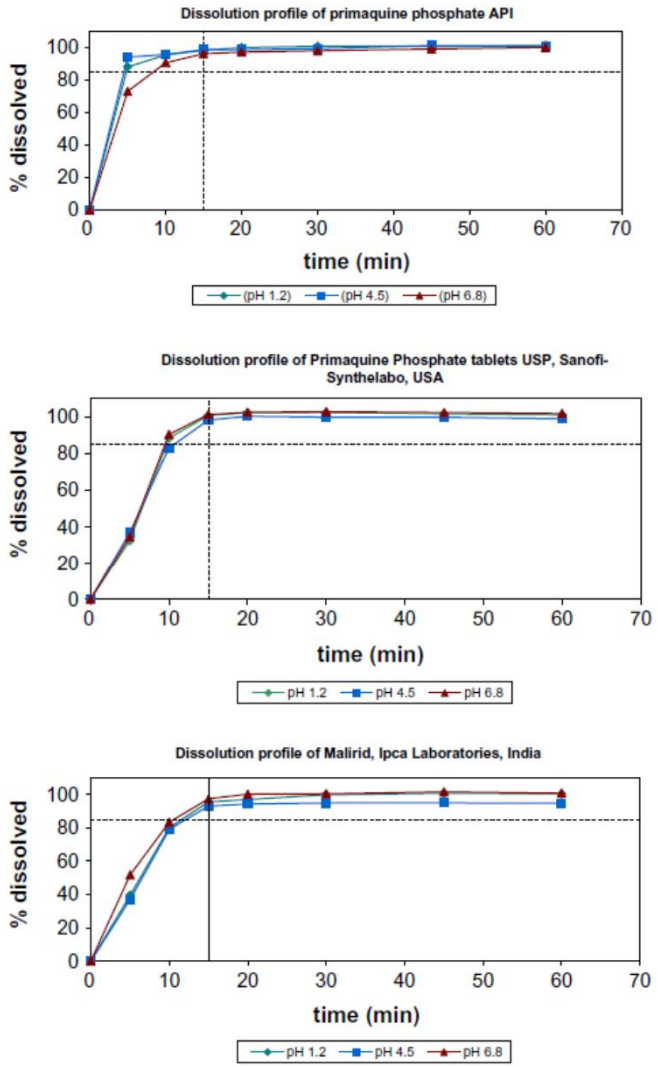


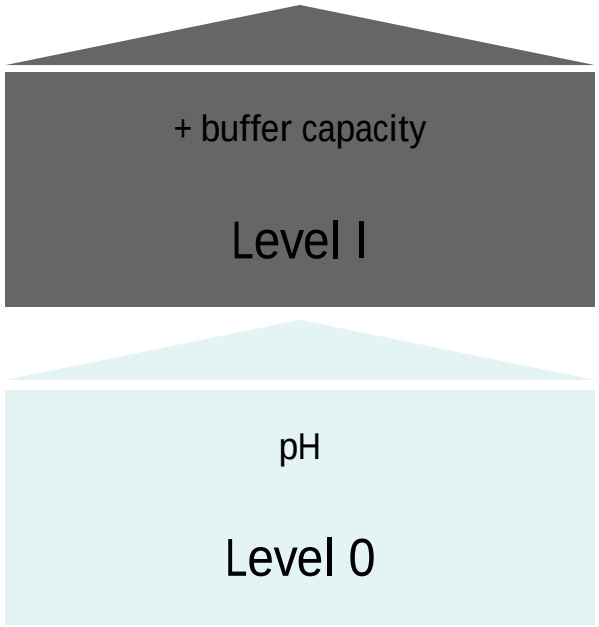
Fig. 3. Dissolution profiles of primaquine phosphate and pure API using Level 0 biorelevant media at various pH values. Graphs were extracted from Nair et al. [69] after receiving approval from John Wiley and Sons.

Level 0 biorelevant media are adequate for IR products of primaquine phosphate (dibasic API, pka 3.2 and 10.4), a DCS Class I API.

More than 85% dissolved within 15 minutes

Level I simulation of luminal composition

- Distinction between fasted and fed state conditions / simulation of buffer capacity
- Adequate for DCS Class I and III APIs / potential pH related food effects
- Adequate for DCS Class I and III APIs housed in ER products (when release is affected by luminal pH and buffer capacity)



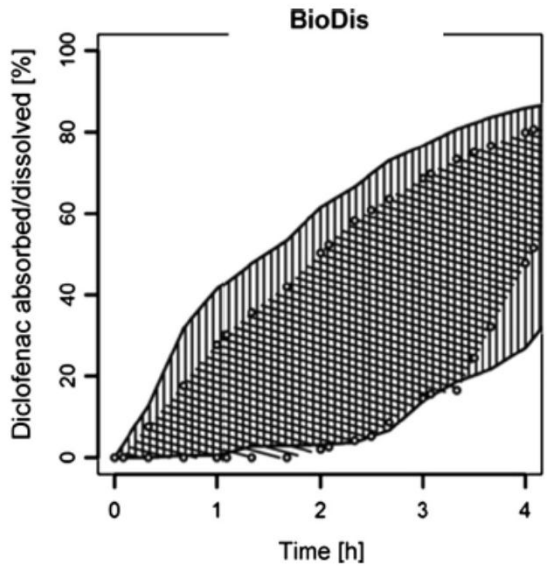


Fig. 4. Prediction of the *in-vivo* absorption (vertical lines) using Level I media in the BioDis (USP apparatus III) with a mathematical gastric emptying approach (diagonal lines) for diclofenac sodium pellets. Graph was extracted from Klein et al. [73].

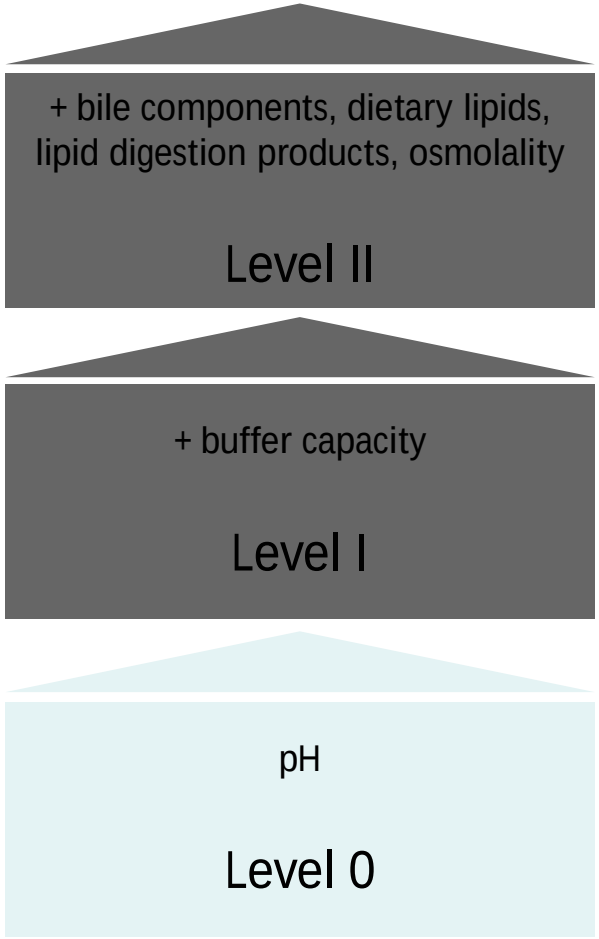
Level I biorelevant media are adequate
for ER pellets of diclofenac sodium.
Diclofenac is a weak acid (pka 4.0) with poor
Solubility under acidic conditions.
Absorption is rapid and complete,
i.e. a DCS Class I API.

Release in Level I biorelevant media adequately
predicted the absorption process.

Levels II simulation of luminal composition

- Buffer capacity, osmolality and, depending on the location and dosing conditions, the presence of bile components, dietary lipids and relevant digestion products are simulated

- Adequate for DCS II and IV APIs



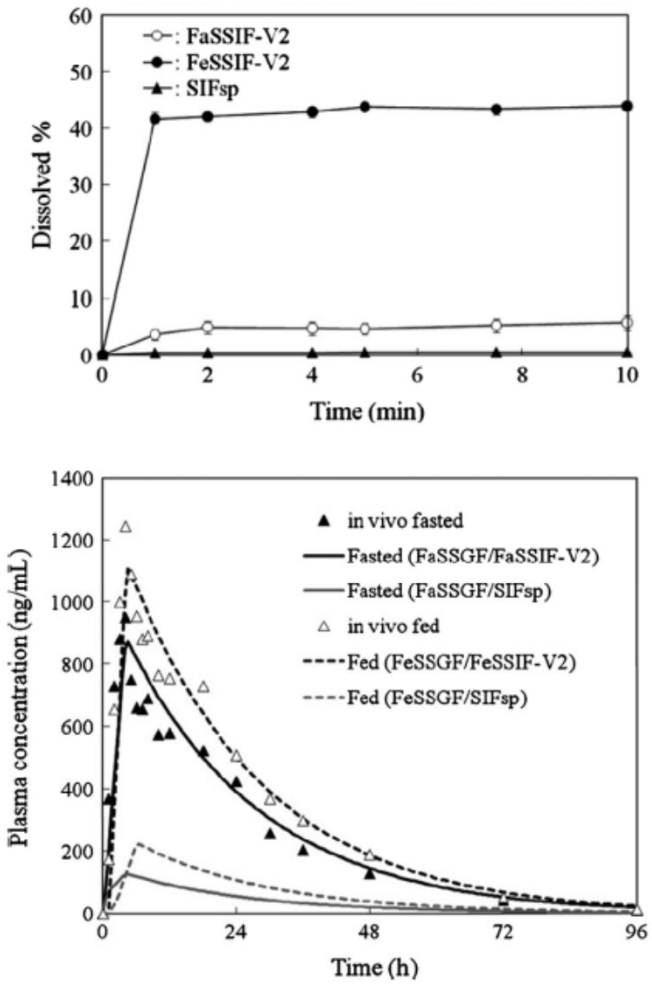


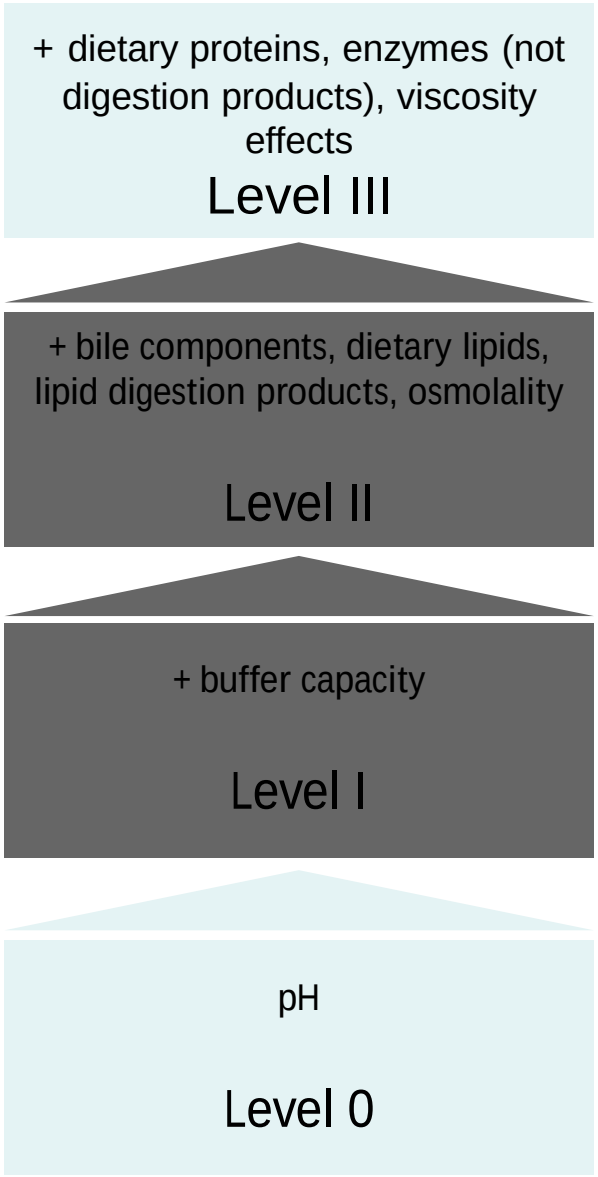
Fig. 5. Dissolution of nanosized aprepitant in the USP apparatus II at 50 rpm with the small intestinal level 0 and Level II biorelevant media (upper plot) and plasma profile simulations of nanosized aprepitant under both prandial states using Level 0 and Level II simulated intestinal media (lower plot). Please note that Level III simulated gastric media were used in these experiments. Graphs were extracted from Shono et al. [74].

Level II biorelevant media are needed for predicting the absorption of aprepitant
(a DCS Class II/IV API).

Dissolution data couples with PBPK modelling
led to adequate prediction of the average plasma profile

Levels III simulation of luminal composition

- Buffer capacity, osmolality and, depending on the location and dosing conditions, the presence of bile components, dietary lipids and relevant digestion products and, also, viscosity and digestion are simulated
- Certain lipid-based formulations (LFCS Type I, II and IIIa)
- Evaluation of luminal stability characteristics
- Certain modified release formulations (perhaps in conjunction with consideration of luminal shear stresses)



Level III biorelevant media should be used only when specific questions need to be answered, and, perhaps, should not be linked to a specific DCS Class.

In the example below, Level II media were modified by adding pancreatin and calcium ions, in order to enable simulation of digestion and were useful for screening four lipid based formulations of danazol (DCS II API), as an alternative to pH-stat models.

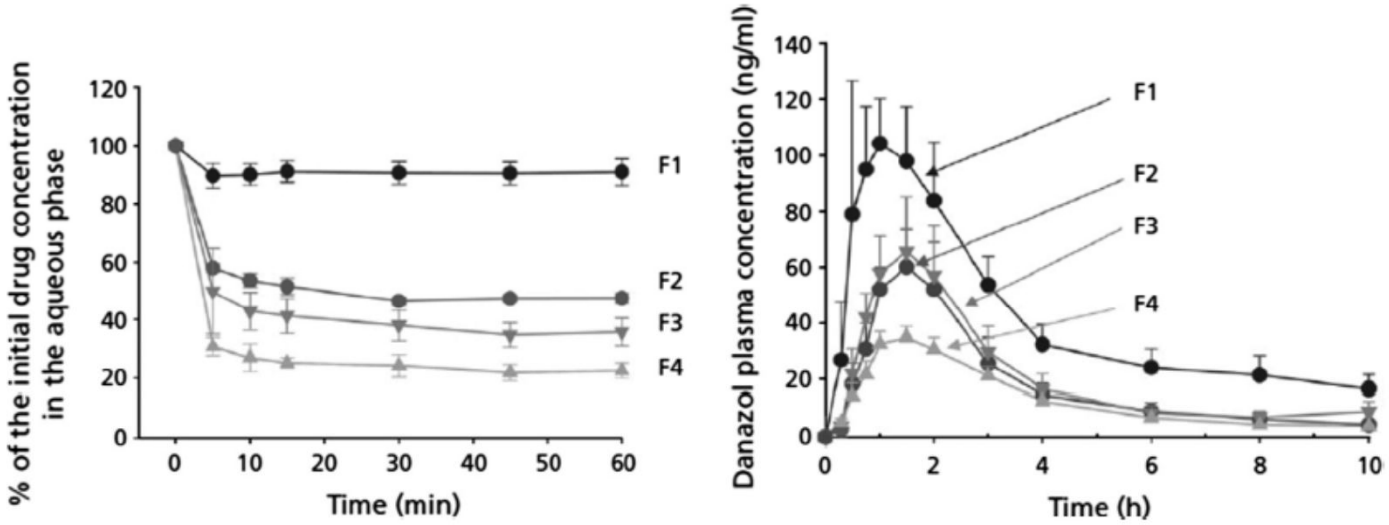
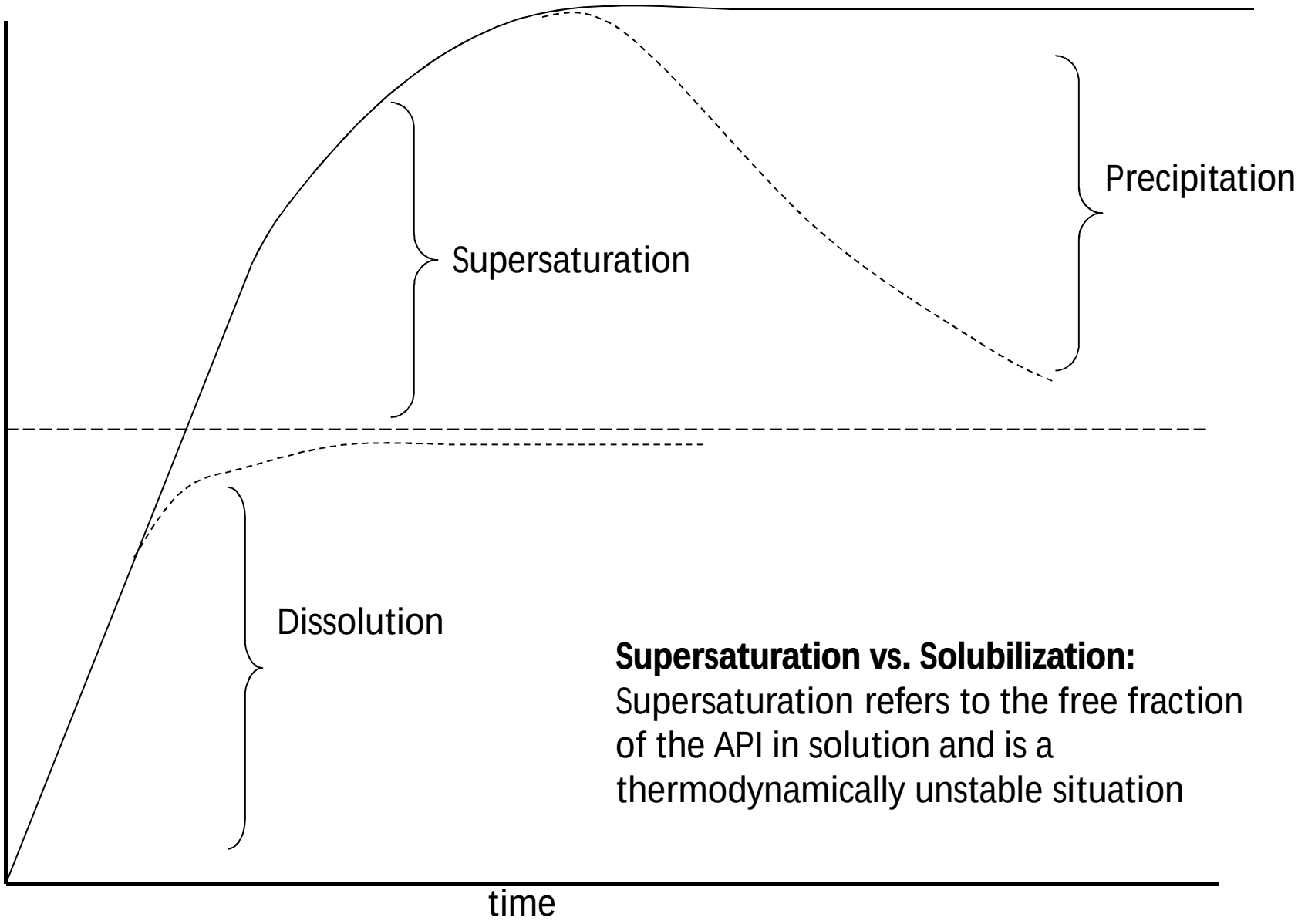


Fig. 6. The results of four lipid formulations of danazol composed with various ratios of lipid (50:50 soybean oil and maisine 35-1), Cremophor EL® and ethanol using the Level III biorelevant media in a simplified *in-vitro* lipolysis model and their corresponding plasma profiles in beagle dogs. The graphs were extracted from Kilic et al. [42].

Usefulness of biorelevant media for the evaluation of enabling drug products



Supersaturation vs. Solubilization:
Supersaturation refers to the free fraction of the API in solution and is a thermodynamically unstable situation

Usefulness of biorelevant media for the evaluation of enabling drug products

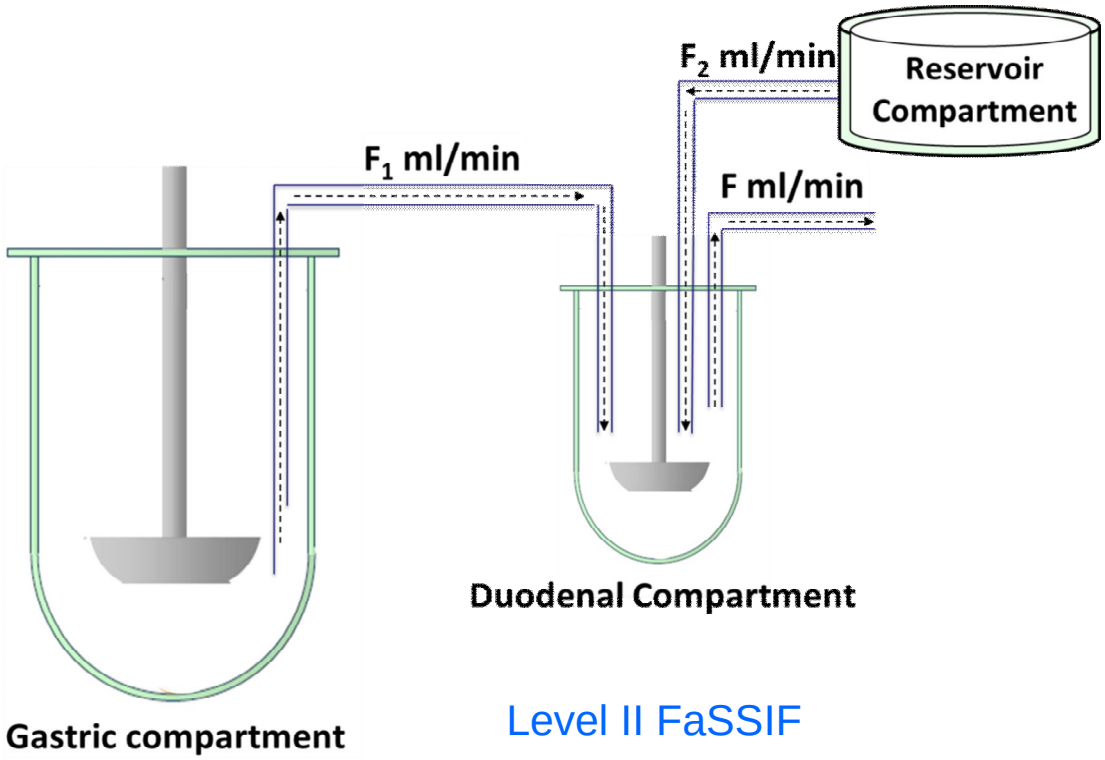
- Lipid based formulations
- Complexes with cyclodextrins
- (Nanosized drug particles)
- Solid dispersions

Table 1 Examples of FDA-approved medicines that use solid dispersion technologies.

Product name	API	Polymer[a]	Maximum API dose per tablet or capsule (mg)[b]	API T_m (°C)[c]	Solid dispersion preparation method[e]	Year of approval[b]
Cesamet	Nabilone	PVP	1	160	—	1985
Sporanox	Itraconazole	HPMC	100	166	Spray drying on sugar beads	1992
Prograf	Tacrolimos	HPMC	5	128	Spray drying	1994
Kaletra	Lopinavir/ritonavir	PVP/VA	200/50	125/122	Melt extrusion	2005
Intelence	Etravirine	HPMC	200	265[d]	Spray drying	2008
Zotress	Everolimus	HPMC	0.75	115	Spray drying	2010
Novir	Ritonavir	PVP/VA	100	122	Melt extrusion	2010
Onmel	Itraconazole	HPMC	200	166	Melt extrusion	2010
Incivek	Telaprevir	HPMCAS	375	246	Spray drying	2011
Zelboraf	Vemurafenib	HPMCAS	240	272	Co-precipitation	2011
Kalydeco	Ivacaftor	HPMCAS	150	291	Spray drying	2012

[a]Best guess based on the inactive ingredient list, patents and other literature information.
[b]Information based on the drug product labels from the FDA website.
[c]From Merck index or otherwise specified.
[d]Decomposition temperature.
[e]From Brough and Williams[2].

Usefulness of biorelevant media for the evaluation of enabling drug products

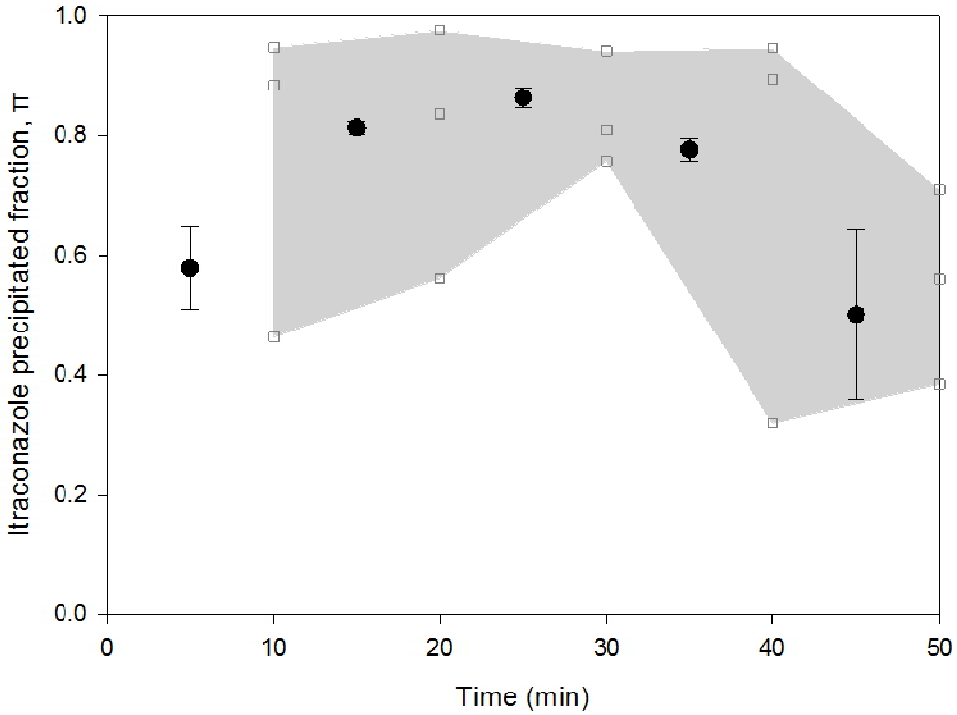


Level II FaSSIF

Level III FaSSGF

Kourentas et al. Eur J Pharm Sci. 82:106-14 (2016)

Sporanox® cyclodextrin solution



Black dots

Mean±SD (n=3) values for the precipitated fraction, π, in the duodenal compartment *vs*. time after initiation of the BioGIT experiment with Sporanox® solution

Grey area with squares indicating the individual values

Precipitated fractions in the contents of the upper small intestine, after oral administration of the Sporanox solution to healthy adults (Brouwers et al. 2015)

Kourentas et al. Int. J. Pharmaceut. in press

When is supersaturation likely to occur in vivo?

- Enabling drug products
- Salts, particularly of poorly soluble weak acids
  - In the stomach
- Poorly soluble weak bases
  - Mainly in the intestine, mainly when dosed fasted

Salt case example: L-870,810

Petrakis et al. JPP 2015
Markopoulos et al. JPS 2015

Free acid properties:

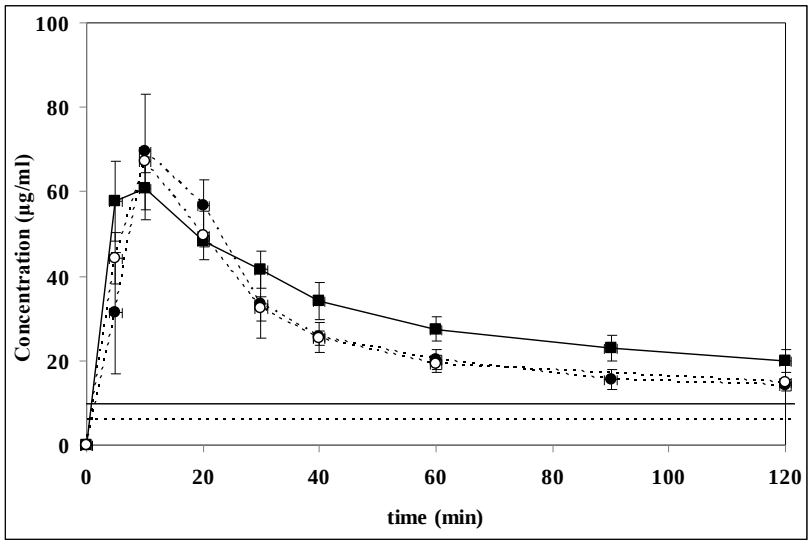
pka: 7.3
Dose: 400 mg
logP: 2.1

(DCS Class II API)

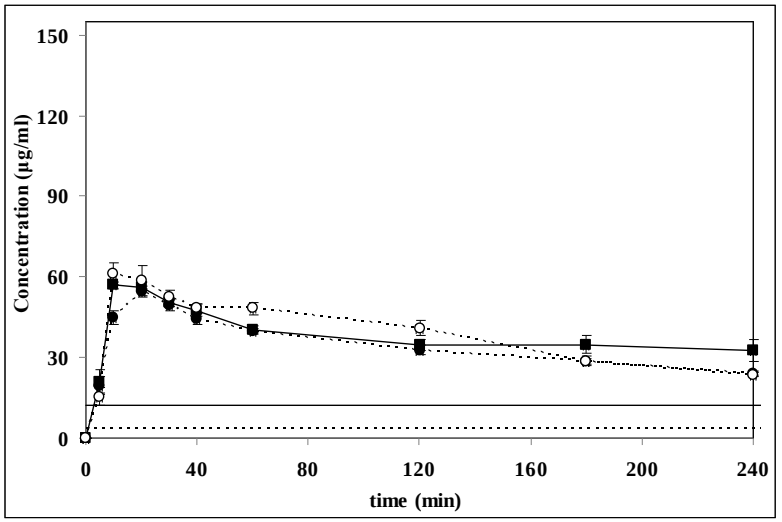
Available as sodium salt

Salt case example: L-870,810

In vitro dissolution data (mini-paddle, 250 ml volume, 75 rpm)



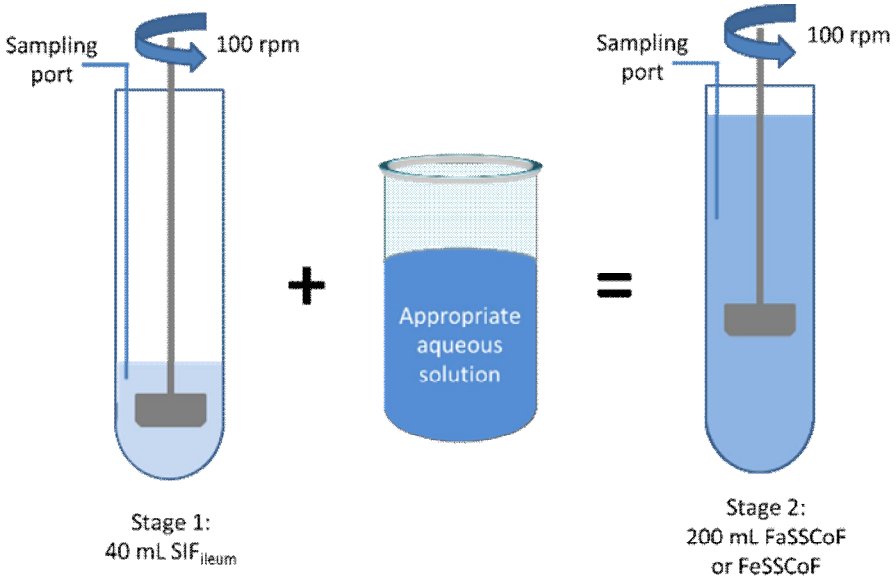
Mean ± SD (n = 3) concentration (µg/ml) during the dissolution of 800 mg NaA granules (400 mg dose) in Level 0 FaSSGF (○), Level I FaSSGF-V2 (●), and in Level II FaSSGF-V2 (■). Horizontal lines indicate previously measured solubility of HA in Level I FaSSGF-V2 (dashed) and in Level II FaSSGF-V2 (continuous).



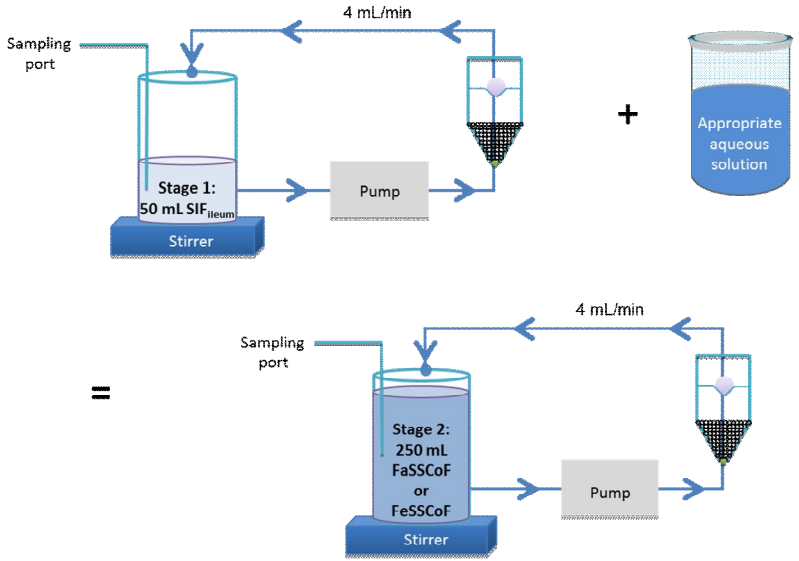
Mean ± SD (n = 3) concentration (µg/ml) during the dissolution of 800mg NaA granules (400 mg dose) in Level 0 FaSSIF-V2 (○), Level I FaSSIF-V2 (●), and in Level II FaSSIF-V2 (■). Horizontal lines indicate previously measured solubility of HA in Level I FaSSIF-V2 (dashed), and in Level II FaSSIF-V2 (continuous).

Two-stage single-compartment models to predict drug release / dissolution in the lower intestine (terminal ileum / ascending colon)

Mini-paddle setup



Flow – Through setup (closed loop)



Ratio of volumes in Stage 1 and Stage 2 is 1:5

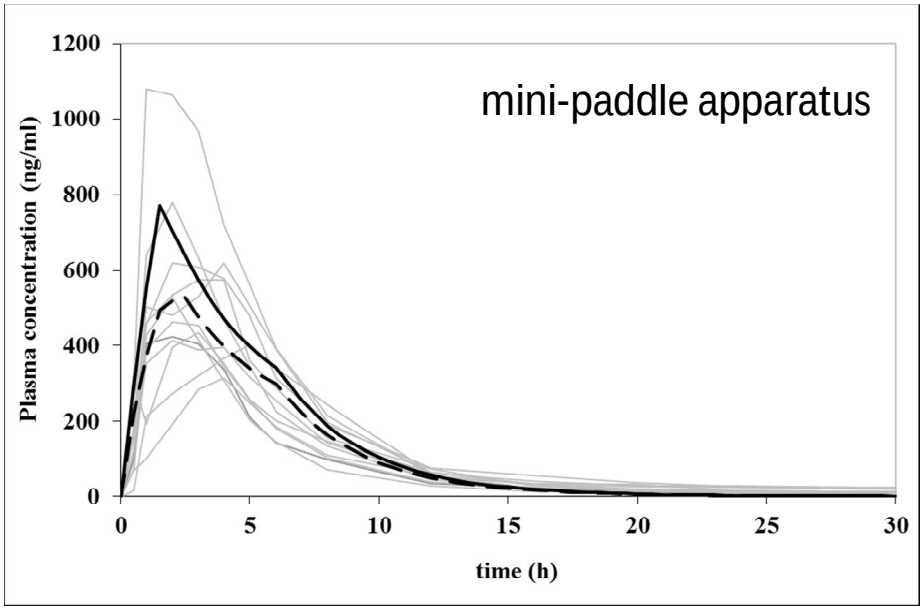
Markopoulos et al. JPS 2015

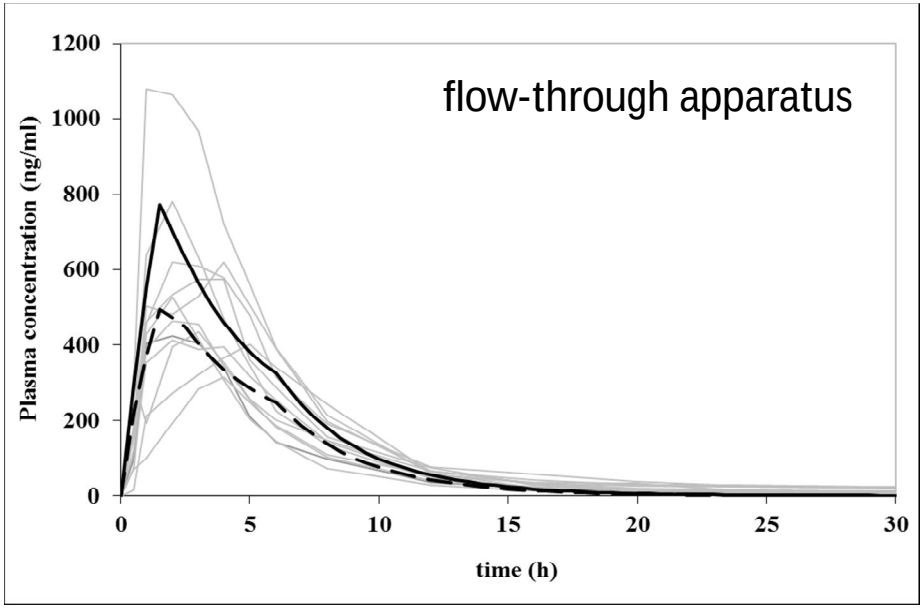
SIF_{ileum}, FaSSCoF, and FeSSCoF compositions

Level I simulation
Simulation of luminal pH and buffer capacity

Level II simulation
Simulation of luminal pH, buffer capacity, and
bile acid content, osmolality/carbohydrate digestion product, and
lipids (non-pancreatic origin)

Markopoulos, Andreas et al. EJPB (2015)





Continuous grey lines

Individual plasma concentrations vs. time data after single dose administration of 800 mg L-870,810 granules (400 mg dose) to healthy fasted adults ()

Continuous bold lines

Simulated concentrations vs. time constructed by using in vitro data in Level II media

Dashed bold lines

Simulated concentrations vs. time constructed by using in vitro data in Level I media

Level I media for DCS II salts of weak acids?

Markopoulos et al. JPS 2015