HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: Rationale, Challenges, Opportunities

Christos Reppas

Workshop on Drug Dissolution in Oral Drug Absorption
University of Maryland School of Pharmacy
23 May 2023

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: **Rationale**

After administration of *enabling drug products* or *conventional products of lipophilic weak bases*, drug concentrations in the micellar phase of contents of upper small intestine can be crucial for the overall luminal product performance

Drug concentrations in the micellar phase of contents of upper small intestine are highly sensitive to
- the “total drug” arrival and elimination (intestinal transit and epithelial transport) rates, and
- the physical state of the drug that enters the upper small intestine from the stomach

For enabling drug products or lipophilic weak bases, the usefulness of in vitro (or in silico) methodologies which do not take into account the above considerations is limited and data cannot be generalized.

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: **Challenges**

1. Definition and understanding the system

The system

Healthy adults – disintegrating dose units

Operating conditions ("fasted state" – "fed state" / "modified fasted state conditions")

Difficulties in understanding the system

Intrinsic variability of the system (number of individuals *vs.* ethical issues *vs.* costs)

Limitations of the applied experimental methodology (Direct sampling / imaging)

Knowledge gaps in understanding the system

- Drug presence in the micellar phase of contents at midgut / distal intestine
- Impact of gastric environment in the "fed state" on the disintegration of the dose unit
- The *drug* gastrointestinal transfer process in the "fed state"

Wagner et al. Use of Physiologically Based Pharmacokinetic Modeling for Predicting Drug-Food Interactions: Recommendations for Improving Predictive Performance of Low Confidence Food Effect Models. AAPS J. 2021 23(4):85

- No data after the recently proposed "low fat meal"

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: **Challenges**

2. Required level of simulation of the system

Level II or Level III biorelevant media, and

Simulation of the “total drug” arrival and elimination (intestinal transit and epithelial transport) rates

3. Reliability of *in vitro* data

Concentrations in vitro *vs.* Concentrations in the lumen

In vitro precipitation rate constant *vs.* ?

Supersaturation ratio based on in vitro data *vs.* ?

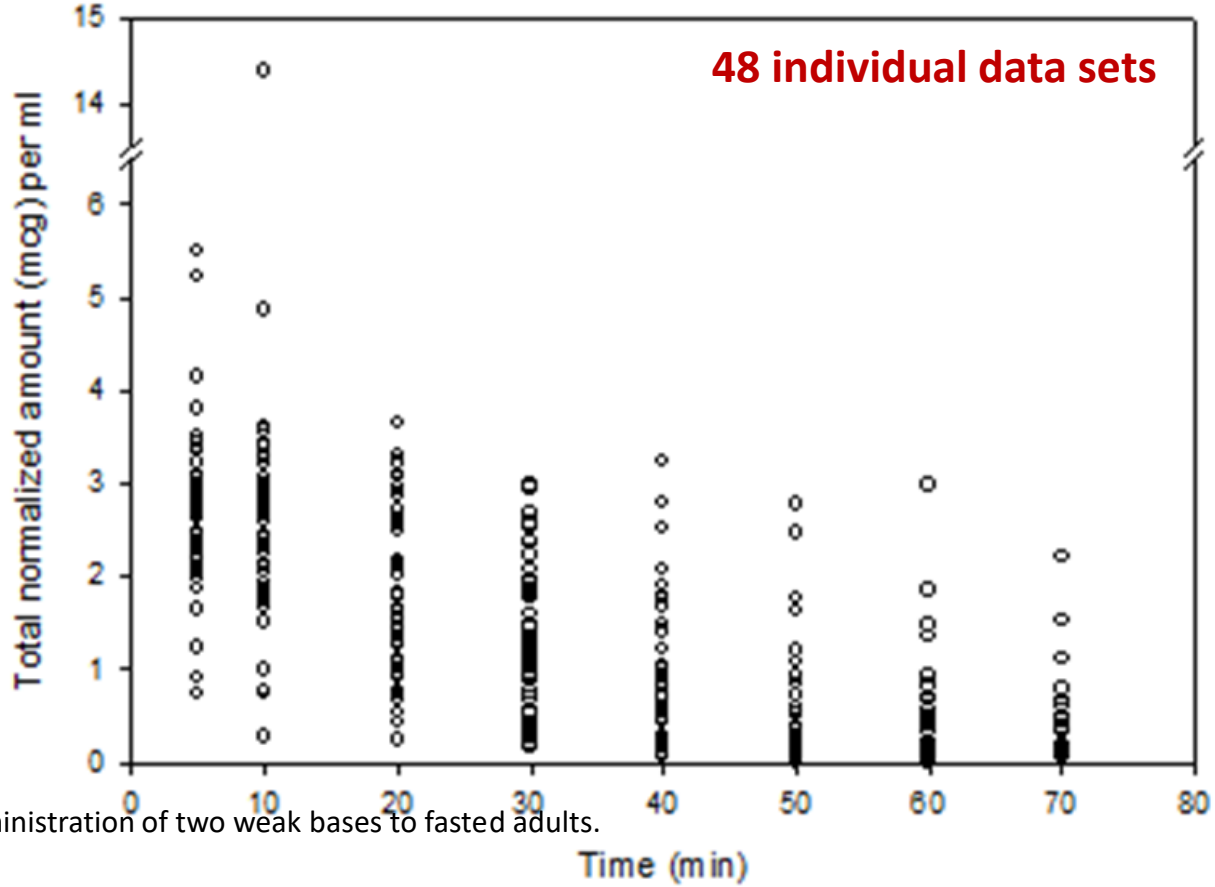
Precipitation time based on in vitro data *vs.* ?

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: **Characterization of the system in the "fasted state"**

Dipyridamole | Two single doses: 30 mg and 90 mg
Ketoconazole | Two single doses: 100 mg and 300 mg

Each dose was administered to 12 healthy adults

Dose normalized total drug amount per volume of intestinal contents *vs.* time post-dosing

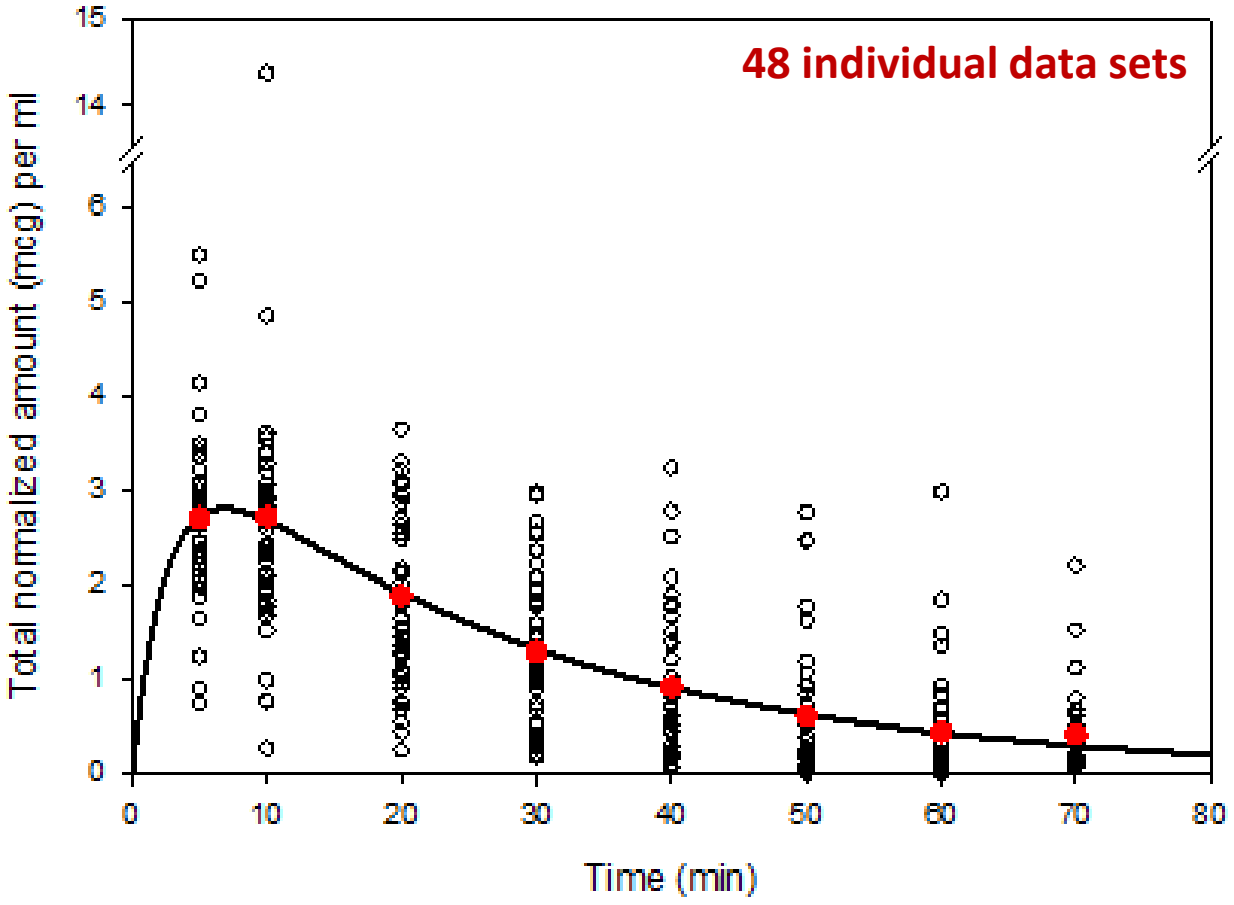


Psachoulias D, Vertzoni M, Goumas K, Kalioras V, Beato S, Butler J, Reppas C.
Precipitation in and supersaturation of contents of the upper small intestine after administration of two weak bases to fasted adults.
Pharm Res. 2011 28(12):3145-58.

Psachoulias D, Vertzoni M, Butler J, Busby D, Symillides M, Dressman J, Reppas C.
An in vitro methodology for forecasting luminal concentrations and precipitation of highly permeable lipophilic weak bases in the fasted upper small intestine.
Pharm Res. 2012 29(12):3486-98.

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: **Characterization of the system in the "fasted state"**

$$y = Dose \frac{1}{V_I} \frac{k_G}{k_G - k_I} (e^{-k_I t} - e^{-k_G t})$$



orbito
Innovative Tools for Oral Biopharmaceutics

In vitro evaluation of drug presence in the micellar phase of contents of upper small intestine: **Characterization of the system in the "fasted state"**

	Ketoconazole and Dipyridamole n=336, R=0.670, p<0.0001
k_G (min^{-1})	0.0371 (0.0041)
k_I (min^{-1})	0.372 (0.094)
$1/V_I$ (ml^{-1})	0.036 (0.010)

→ **Half life of gastric emptying ≈ 18 min**

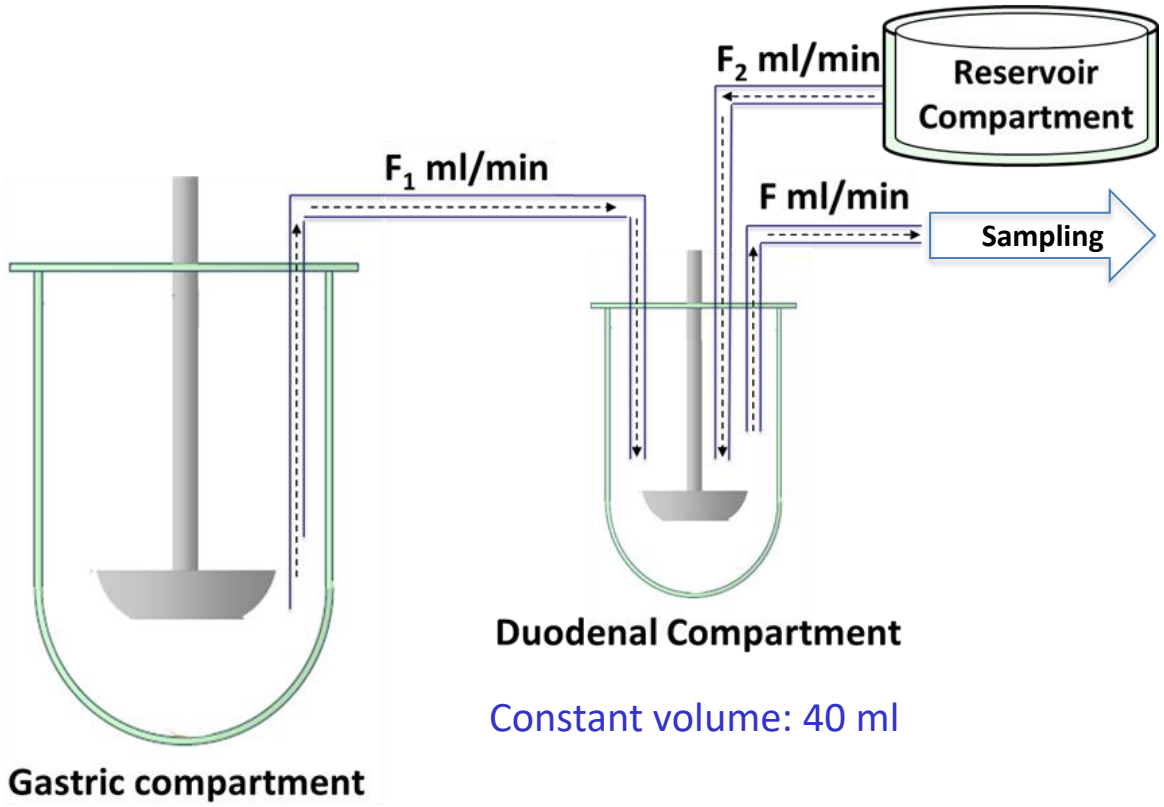
→ Half life of duodenal emptying ≈ 1.9 min

→ **Volume of duodenal contents ≈ 28 ml**

Kourentas A, Vertzoni M, Stavrinoudakis N, Symillidis A, Brouwers J, Augustijns P, Reppas C, Symillides M.
An in vitro biorelevant gastrointestinal transfer (BioGIT) system for forecasting concentrations in the fasted upper small intestine: Design, implementation, and evaluation.
Eur J Pharm Sci. 2016 82:106-14

In vitro evaluation of drug presence in the micellar phase of contents of the upper small intestine: Operating conditions of the BioGIT system

37 °C 75 rpm GE $t_{1/2}$: 15 min



Initial volume: 250 ml

Constant volume: 40 ml

$$F_1 + F_2 = F$$

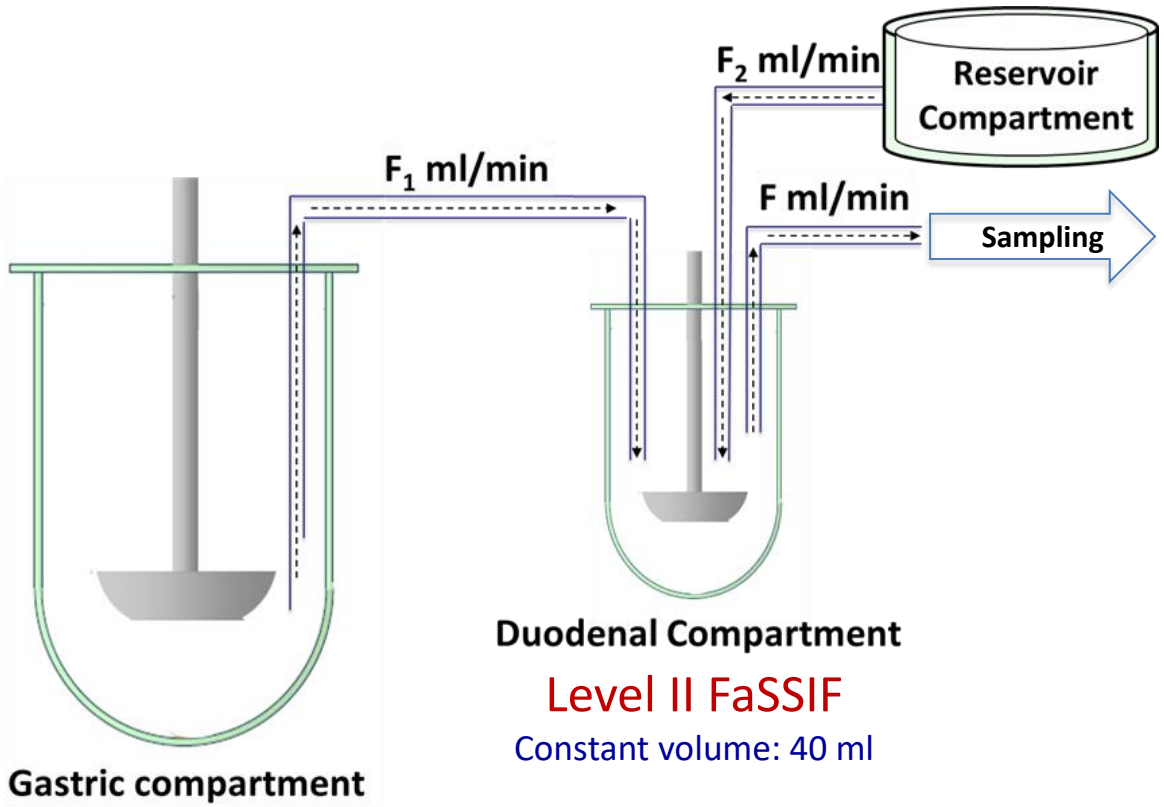
$$\frac{A_I}{V_I} = Dose\frac{1}{V_I}\frac{k_G}{k_G - F/V_I}(e^{-(F/V_I)t} - e^{-k_G t})$$

For practical reasons, incoming flow rates are changing every 10 min so that sampling is possible at midpoint

Time Interval (min)	F_1 (ml/min)	F_2 (ml/min)	F (ml/min)
0-10	9.3	2.3	11.6
10-20	5.9	5.7	
20-30	3.7	7.9	
30-40	2.3	9.3	
40-50	1.4	10.2	
50-60	0.9	10.7	

In vitro evaluation of drug presence in the micellar phase of contents of the upper small intestine: Operating conditions of the BioGIT system

37 °C | 75 rpm | GE $t_{1/2}$: 15 min



Level III FaSSGF

Initial volume: 250 ml

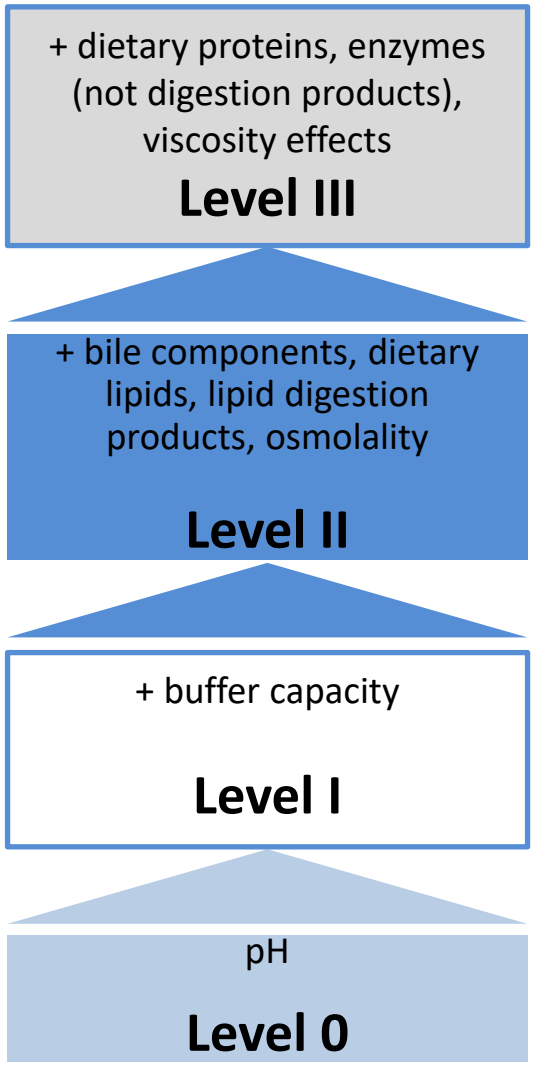
Level II FaSSIF

Constant volume: 40 ml

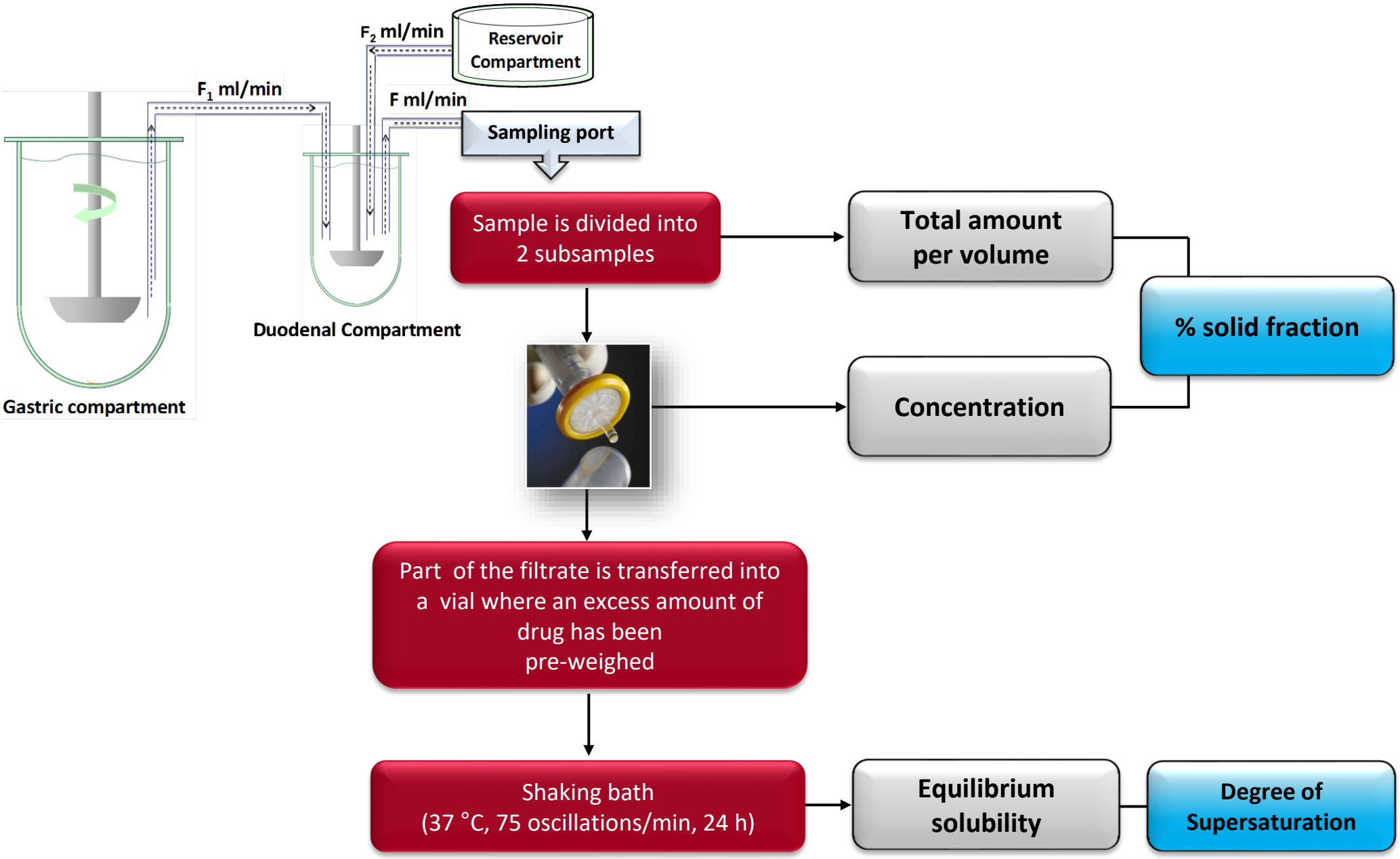
A series of phosphate buffer solutions containing sodium chloride, bile salt and lecithin are pumped from the reservoir compartment into the duodenal compartment

Composition of simulated duodenal contents (pH, buffer capacity, osmolality, bile salt and lecithin concentration) remains unaltered during the experiment

Levels of simulation of luminal contents characteristics



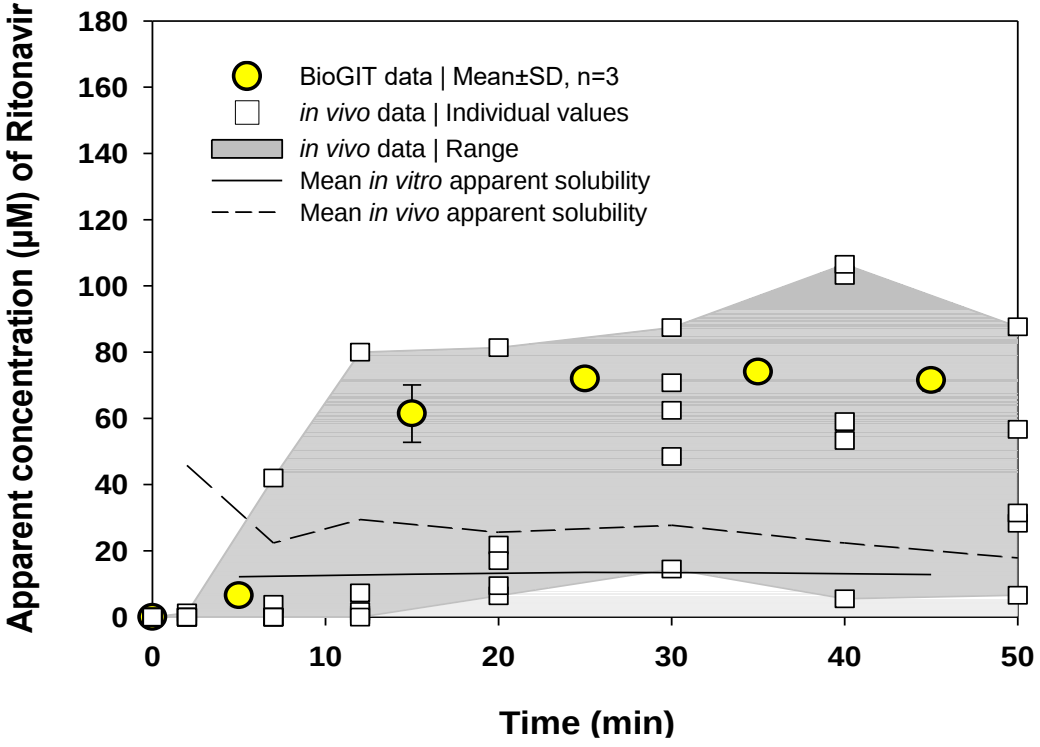
Markopoulos C, Andreas CJ, Vertzoni M, Dressman J, Reppas C.
In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media.
Eur J Pharm Biopharm. 2015 93:173-82.



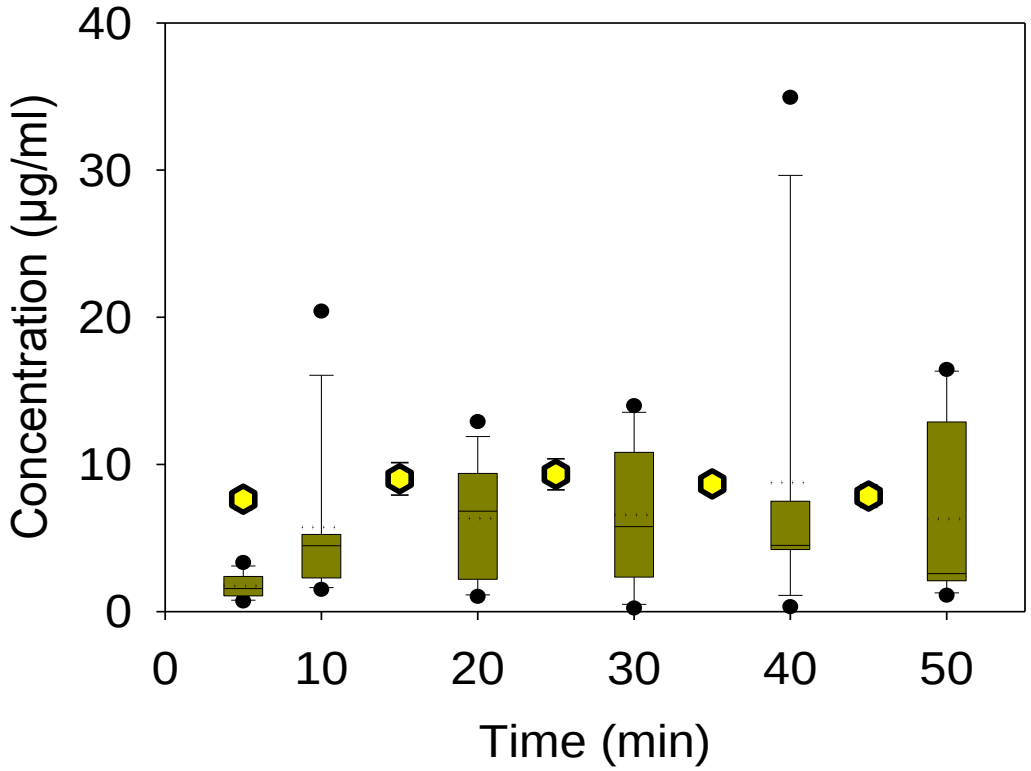
Wilson CG, Aarons L, Augustijns P, Brouwers J, Darwich AS, De Waal T, Garbacz G, Hansmann S, Hoc D, Ivanova A, Koziolek M, Reppas C, Schick P, Vertzoni M, García-Horsman JA. Integration of advanced methods and models to study drug absorption and related processes: An UNGAP perspective. Eur J Pharm Sci. 2022 172:106100.

Micellar drug concentrations in the duodenal compartment of the BioGIT system are in line with micellar drug concentrations in the upper small intestine

Ritonavir | ASD | Norvir® tablets (100 mg)



Albendazole | Suspension



Kourentas et al. Int. J. Pharm. 515:352-358 (2016) – Posaconazole and Itraconazole

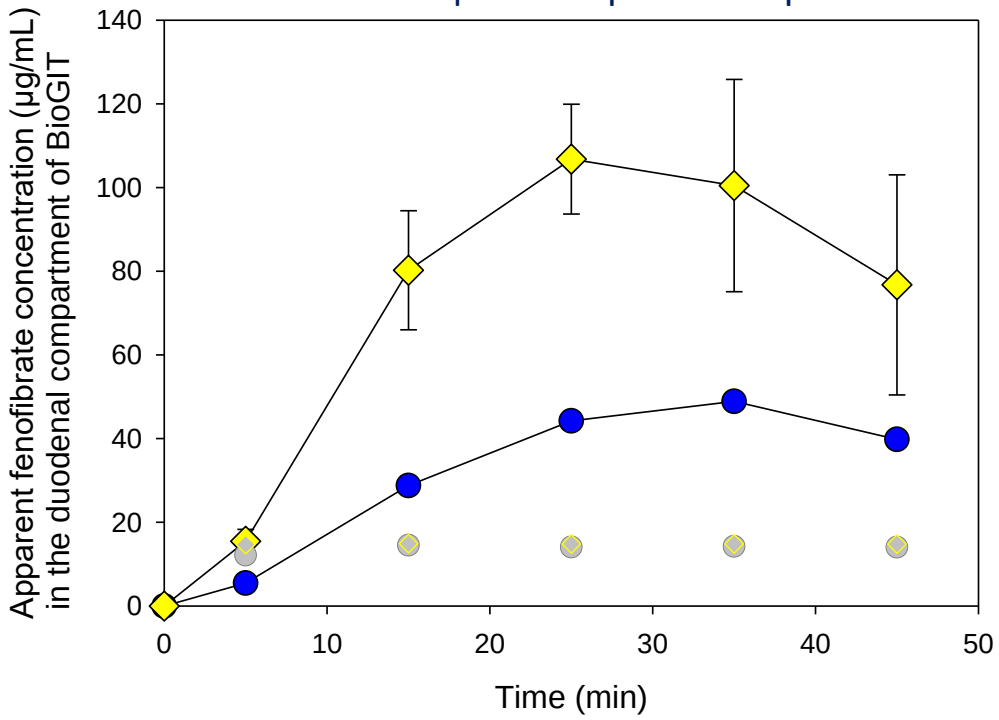
Van Den Abeele et al. Eur J Pharm Sci. 2020 Aug 1;151:105377 – Ritonavir ASD

Kourentas et al. J. Pharm. Sci. 105:2896-2903 (2016) – Albendazole

Hens et al. Eur. J. Pharm. Sci. 15:63:233-42 (2014) – Paromomycin

The BioGIT system for evaluating the impact of dose on early exposure, after oral administration of *disintegrating solid dose units of enabling drug products to fasted adults with a glass of water*

Fenofibrate|solid dispersion capsules



160 mg/tab

◆ Mean(SD) concentrations in the contents of the duodenal compartment

◆ Mean equilibrium solubility values in the contents of the duodenal compartment

54 mg/tab

● Mean(SD) concentrations in the contents of the duodenal compartment

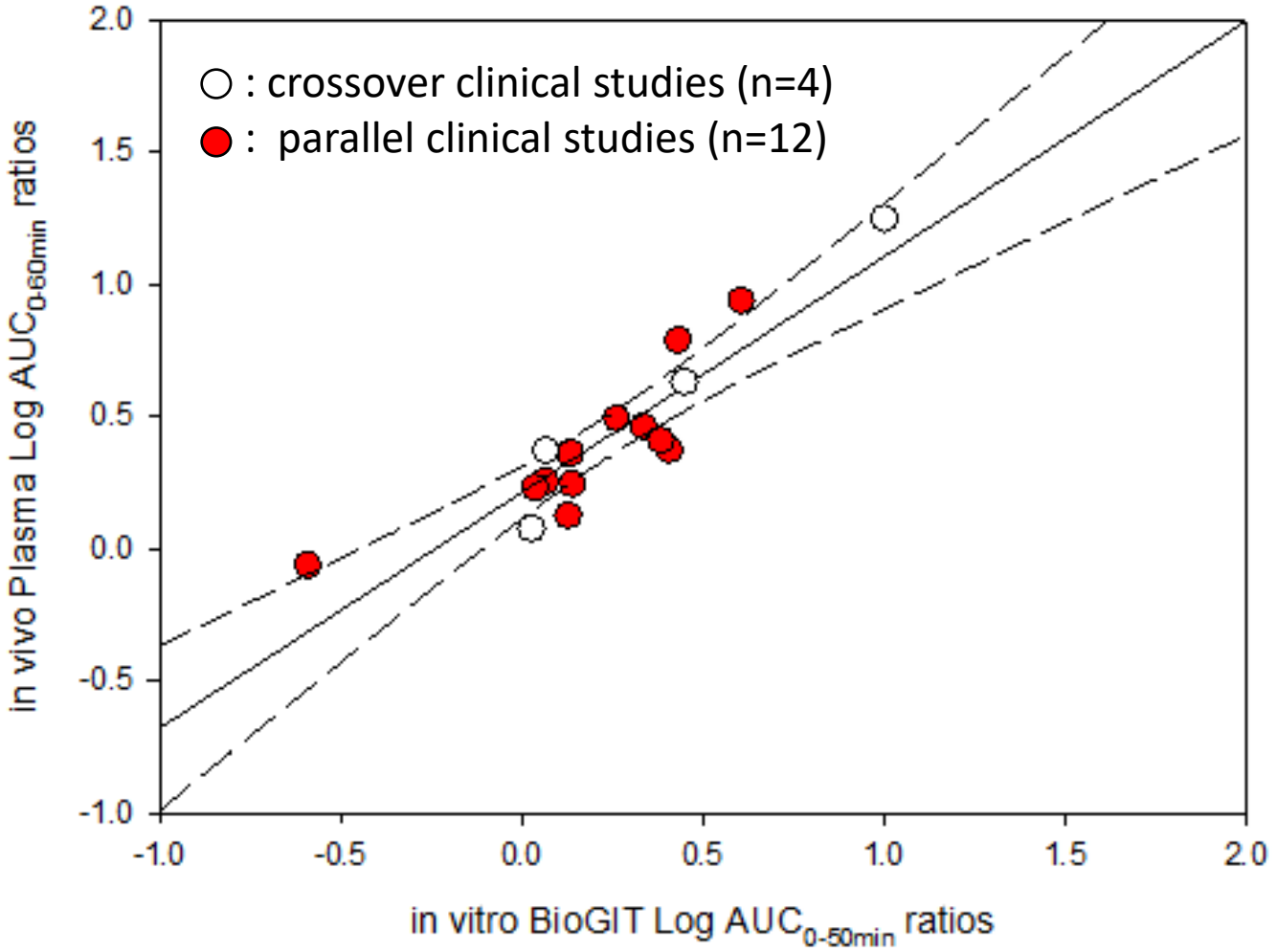
● Mean equilibrium solubility values in the contents of the duodenal compartment

✓ Contents of the duodenal compartment are supersaturated with fenofibrate

AUC (ng/ml)×min	54 mg/tab	160 mg/tab	$\frac{AUC_{1h}^{160mg}}{AUC_{1h}^{54mg}}$
$AUC_{\text{plasma data}}^{0\text{-}60min}$	1.31(0.62)	3.1(2.0)	2.4
$AUC_{\text{BioGIT data}}^{0\text{-}50min}$	21.9(3.5)	56.2(8.1)	2.6

The BioGIT system for evaluating the impact of dose and/or formulation on early exposure, after oral administration of *disintegrating solid dose units to fasted adults with a glass of water*

n=16
Slope = 0.89 (0.11)
Intercept = 0.211 (0.046)
R = 0.90



Kostantini C, Spilioti E, Bevernage J, Ceulemans J, Hansmann S, Hellemans K, Jede C, Kourentas A, Reggane M, Shah L, Wagner C, Reppas C, Vertzoni M.
Usefulness of the BioGIT system in screening for differences in early exposure in the fasted state on an a priori basis.
Int J Pharm. 2023 634:122670.

Could facilitate formulation and dose selection, and could support regulatory decisions

Screening for differences in early exposure in the fasted state with *in vitro* methodologies can be challenging: Experience with the BioGIT system

Slight elevation of the pH in the gastric compartment of BioGIT system may be needed when nanocrystals of weak bases are under investigation

BioGIT data may be inconclusive or misleading in the evaluation of differences in early exposure

- when the product(s) under investigation are *not disintegrating*
- when dealing with ingested *aqueous drug solutions*
- when the *volume of co-administered water* is not controlled in the clinical study

Kostantini C, Spilioti E, Bevernage J, Ceulemans J, Hansmann S, Hellemans K, Jede C, Kourentas A, Reggane M, Shah L, Wagner C, Vertzoni M, Reppas C. Screening for Differences in Early Exposure in the Fasted State with in Vitro Methodologies can be Challenging: Experience with the BioGIT System. J Pharm Sci. 2023 12:S0022-3549(23)00101-6.

In vitro evaluation of drug presence in the micellar phase of contents of the upper small intestine: Characterization of the system in the “fed state”

PEARRL

InPharma

www.inpharma-network.eu

Understand key characteristics of gastric contents that control disintegration of dose units

Dietrich S., Bakolia A., Chorianopoulou C., Ceulemans J., Vertzoni M., Reppas C.
Proposing in vitro testing conditions for the evaluation of intragastric disintegration of solid dose units in the fed state
EUFEPS Annual Meeting, May 31 – June 2, 2023, Lisbon, Portugal

Characterize the *drug* GI transfer process after disintegration in stomach

Abstract submitted to AAPS Pharm Sci 360, AAPS annual meeting, Orlando, USA 2023

Evaluate drug presence in the micellar vs. colloidal (non-droplet) phase

Thank you

HELLENIC REPUBLIC

National and Kapodistrian University of Athens

EST. 1837