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Advantages and Impact of Biorelevant Dissolution Media

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Linking the lab to the patient

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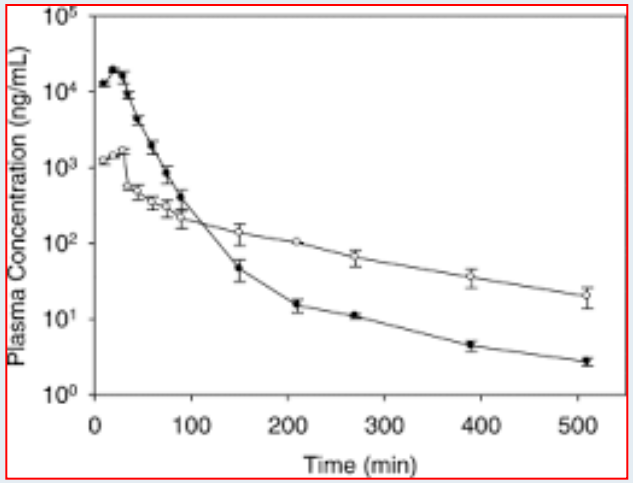
Picture of rat

Picture of dog

Picture of girl at computer

Picture of patient



„Dissolution Plus PBPK“ Approach

in vitro

QC tests

Biorelevant tests in **fasted state**

Biorelevant tests in **fed state**

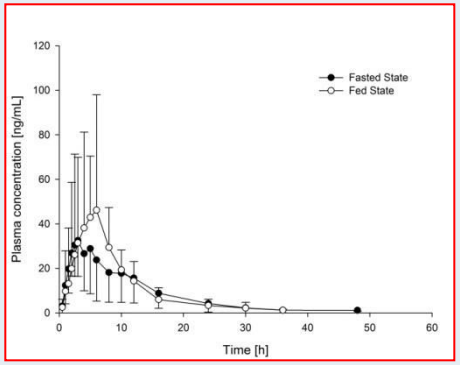
in silico

Deconvolution

PBPK modeling

IVIVC

in vivo



Picture of girl at computer

Picture of dog

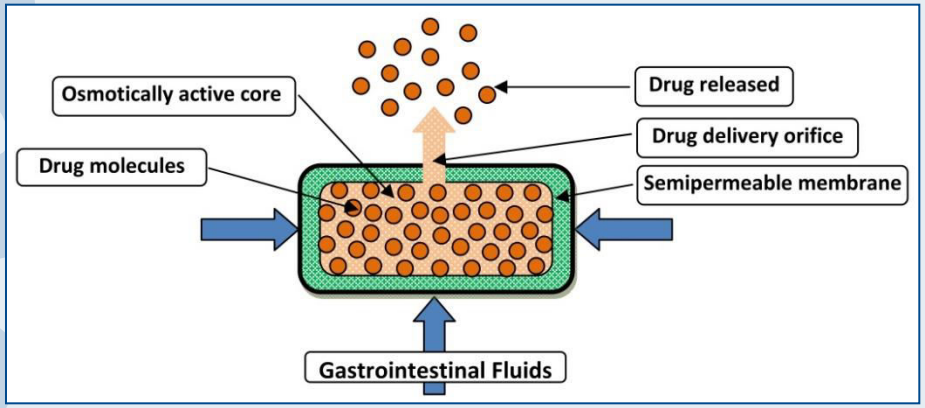
The aim is to
→ reduce the number of PK studies and
→ accelerate formulation development

QC or Biorelevant dissolution tests?

For some formulations, there is little dependency on GI physiology……..

e.g. Immediate release dosage forms containing highly soluble drugs

e.g. simple osmotic pumps.



For such formulations, media such as water, dilute HCl or phosphate buffer should be sufficient and a simple apparatus (Paddle or Basket) can be used

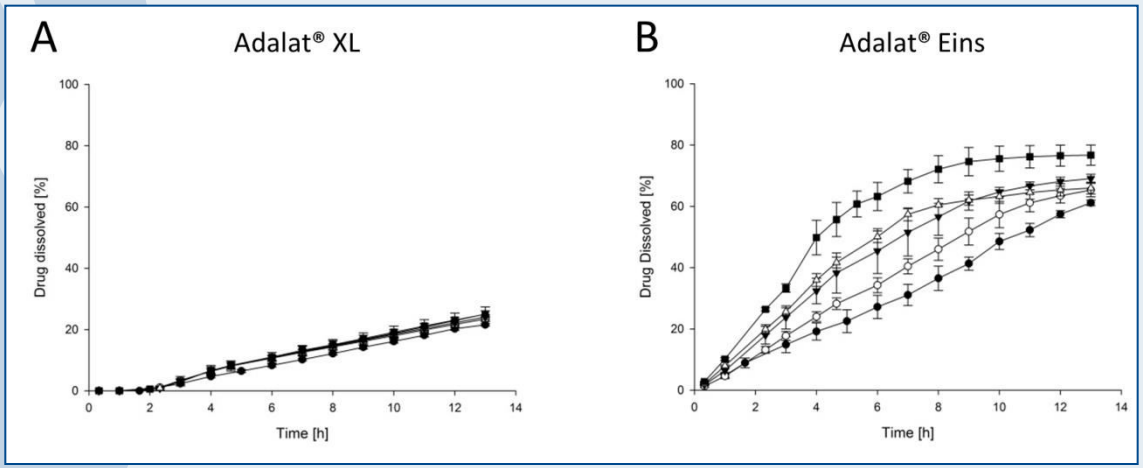
QC or Biorelevant Dissolution Tests?

.....while for other formulations, release may be highly dependent on GI physiology

e.g. Immediate release dosage forms containing poorly soluble drugs

e.g. enteric coated pellets

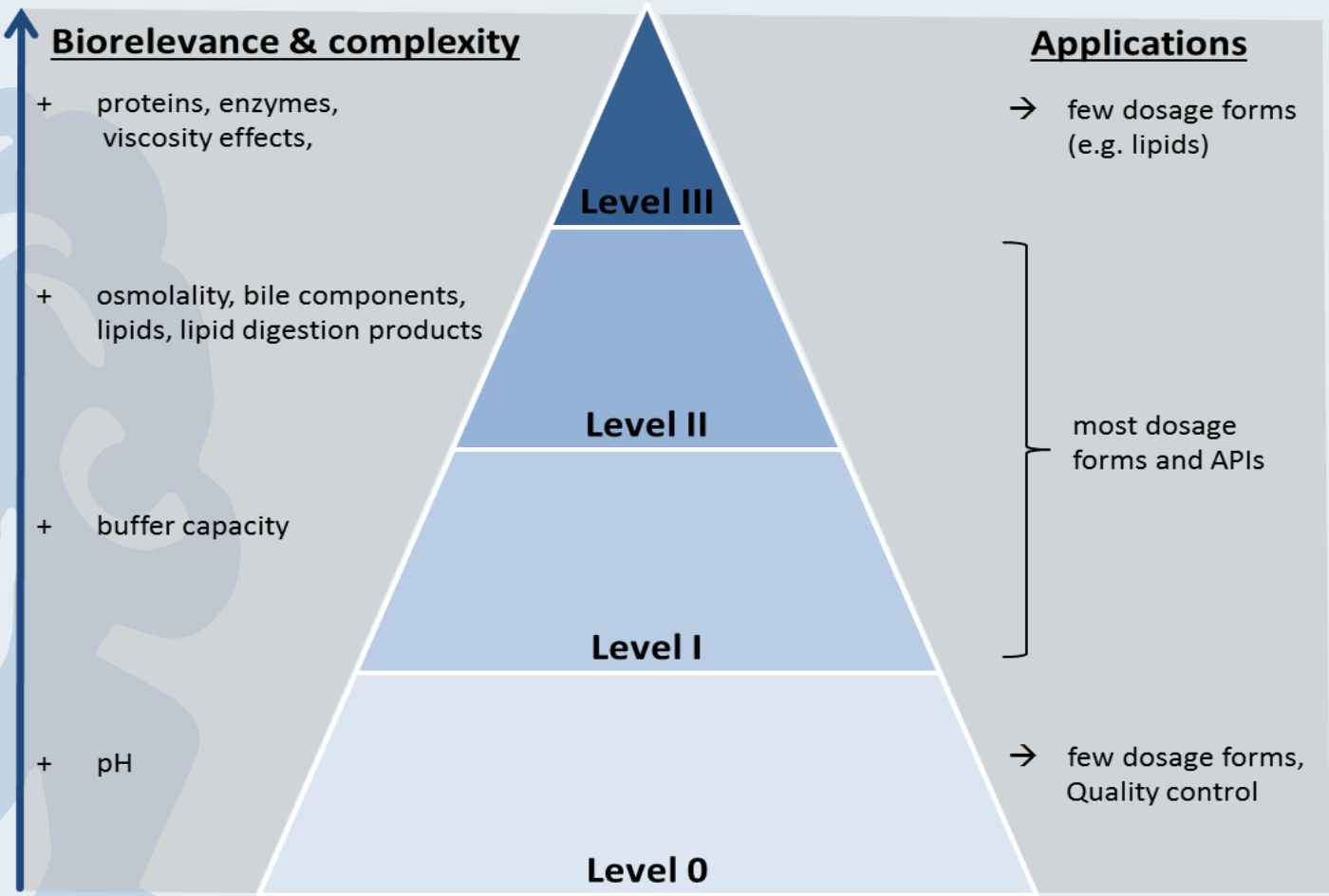
e.g. matrix tablets for modified release



osmotic pump **matrix tablet**

For such formulations, aspects of GI physiology that are key to release should be accounted for and an apparatus that facilitates media change should be used

The Dissolution Media Pyramid



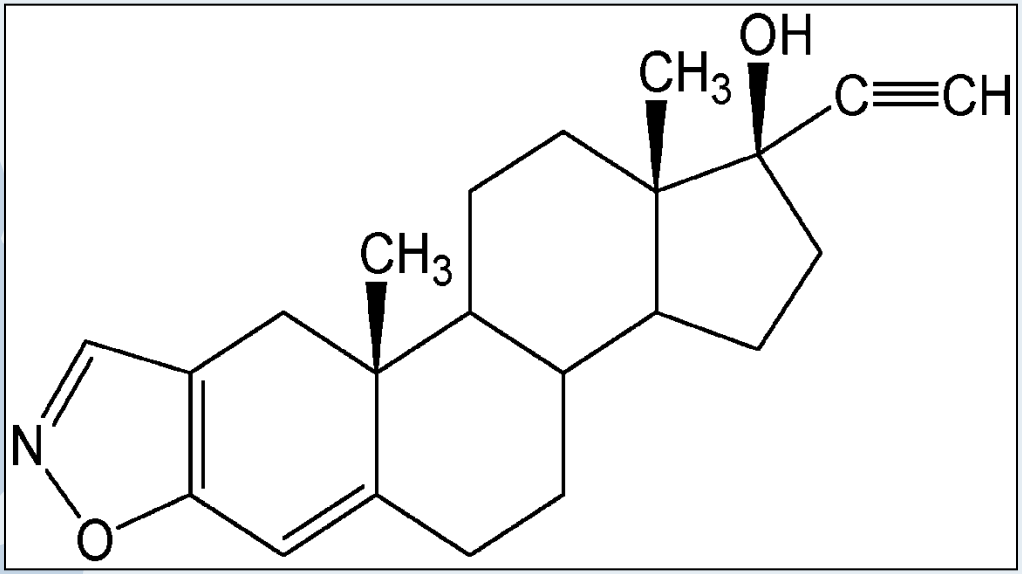
Markopoulos, Andreas et al. In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: Choosing the appropriate test media
Eur. J. Pharm. Biopharm. **93**: 173-182 (2015)

Linking the Lab to the Patient with Dissolution + PBPK

some case examples

Case example 1: Relationship between dissolution and PK of Danazol (a poorly soluble but highly permeable drug)

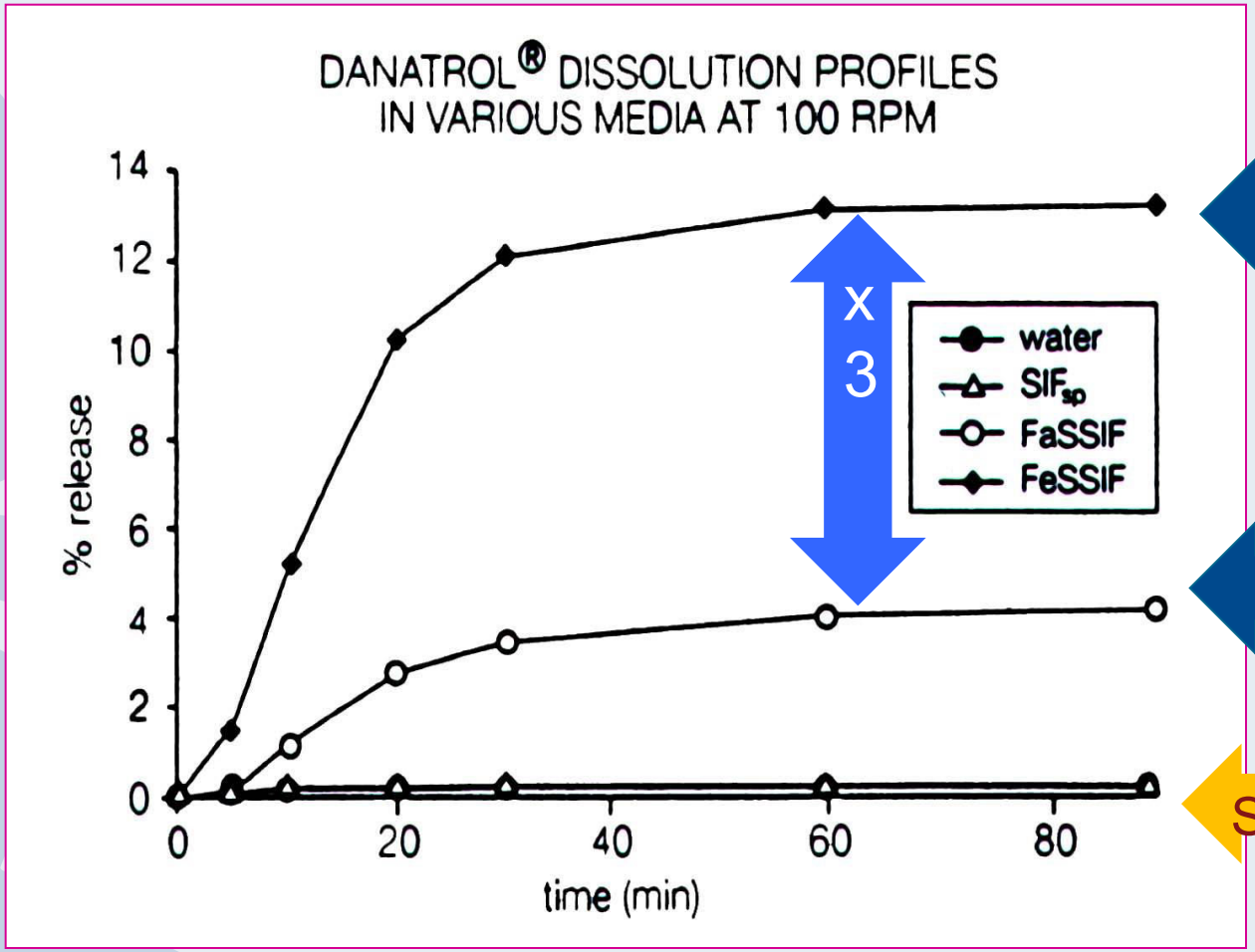
Case example: danazol



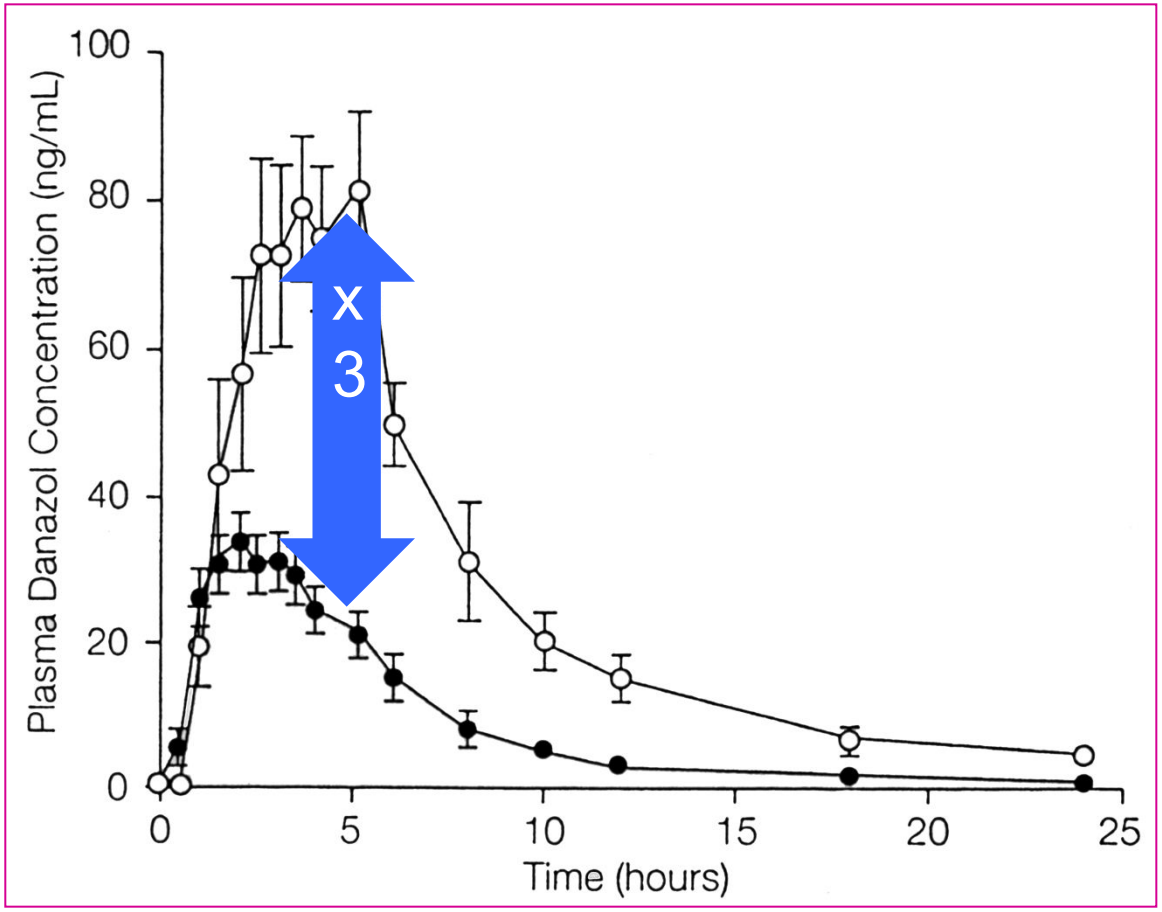
Aqueous solubility: 1µg/ml
Dose: 200 mg
pKa: neutral
log P: 4.53

D:S 200 liters H_2O
20 liters FaSSIF
6 liters FeSSIF

Danatrol dissolution profiles in various media at 100 rpm



Danazol's food effect reflects its dissolution characteristics



Plasma profiles of danazol after administration in the fasted (●) and fed (○) state *(from Charman et al.)*

Linking the Lab to the Patient with Dissolution + PBPK

case example 2

Case example 2: predicting the *in vivo* behaviour of poorly soluble bases

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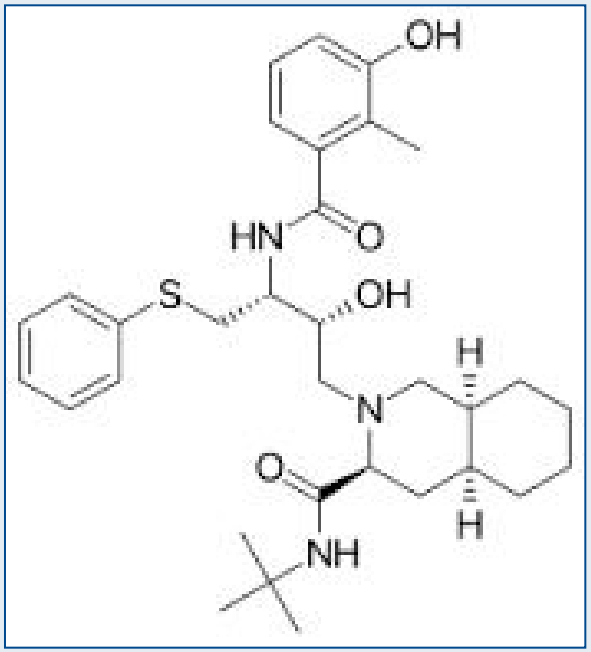
Poorly soluble bases may dissolve well in the stomach but then precipitate in the small intestine, leading to poor bioavailability.

e.g. Nelfinavir mesylate

Y. Shono et al. EJPB 79: 349-356 (2011)



Case example 2: Nelfinavir mesylate

BCS Class 2 (low solubility and high permeability)

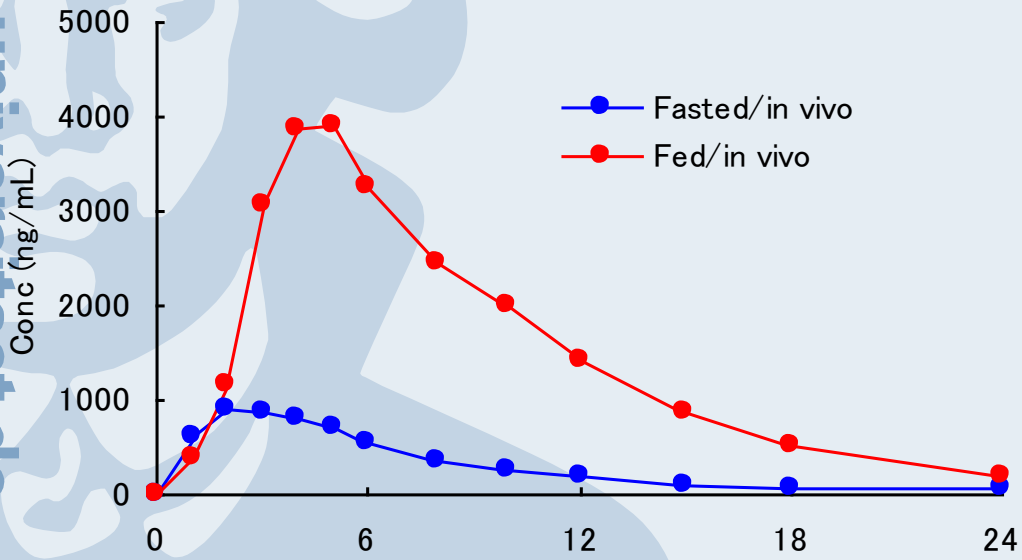
pK_a : 6 and 11 (highly pH dependent solubility)

Cs : 2.16mg/mL in SGF_{sp} (pH1.2)
: 0.003 mg/mL in SIF_{sp} (pH 6.8)

Log *P* : 4.0

P_{app} : 3.4×10^{-6} cm/sec (Caco-2)

Mean plasma plofiles of nelfinavir 1250mg
(250mg tablet x 5)



4.9-fold increase in AUC

4.4-fold increase in C_{max}

Recommended to be taken with food

Dissolution of nelfinavir mesylate 250mg tablets in 250mL of biorelevant media

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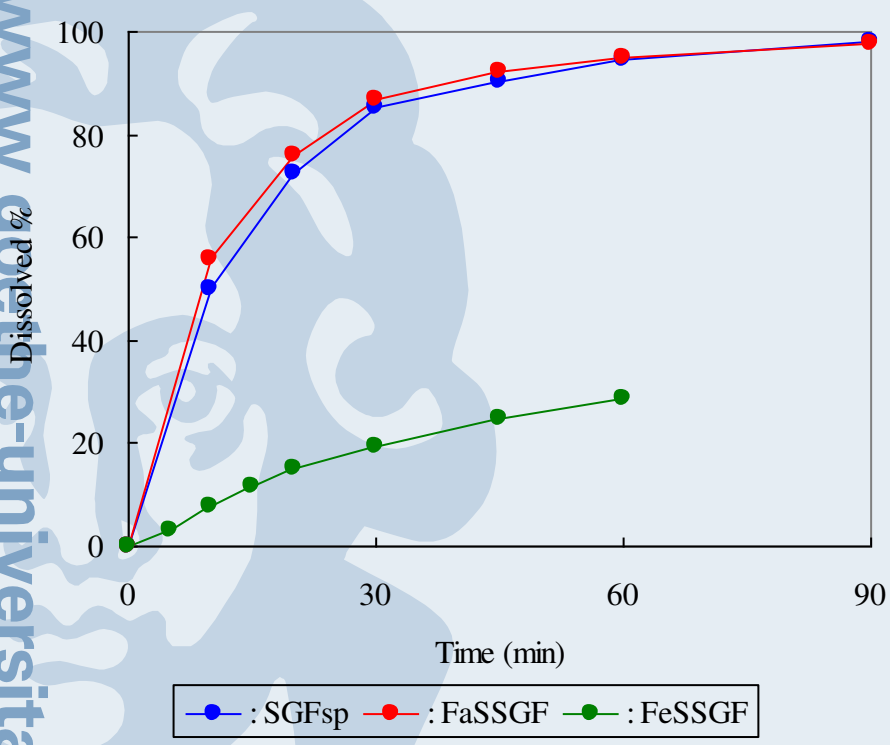
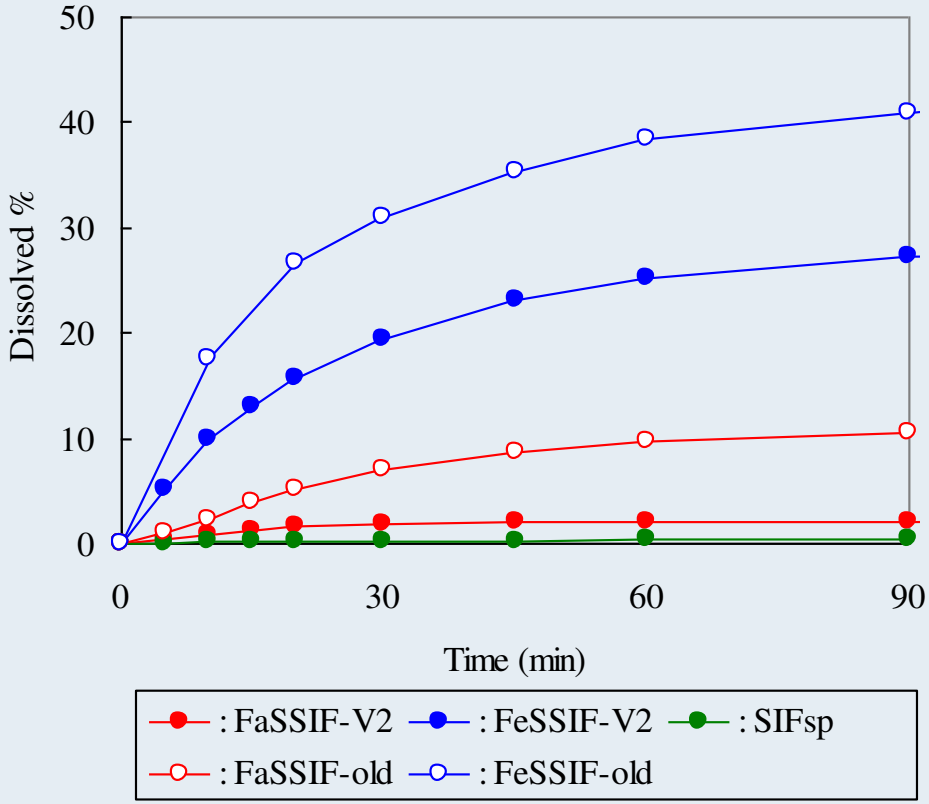
Gastric media



Dissolution profiles of nelfinavir mesylate in gastric biorelevant media

Small intestinal media



Dissolution profiles of nelfinavir mesylate in intestinal biorelevant media

For nelfinavir mesylate, the solubility gap in the fasted state suggests precipitation could occur

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Drug precipitation is likely to occur in the fasted state due to the solubility gap between the stomach and the small intestine.

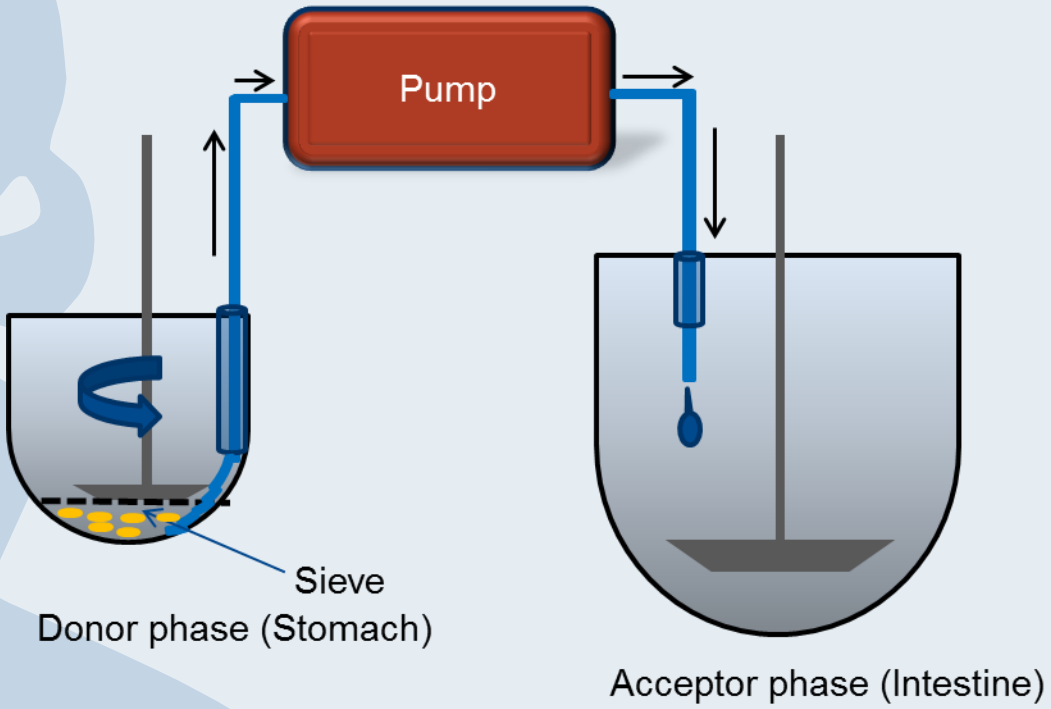
From the dissolution results alone, it is difficult to weigh the contributions from events in the stomach to the bioavailability.

PBPK modeling was invoked to predict food effects for nelfinavir mesylate, using crystal growth theory to describe the precipitation

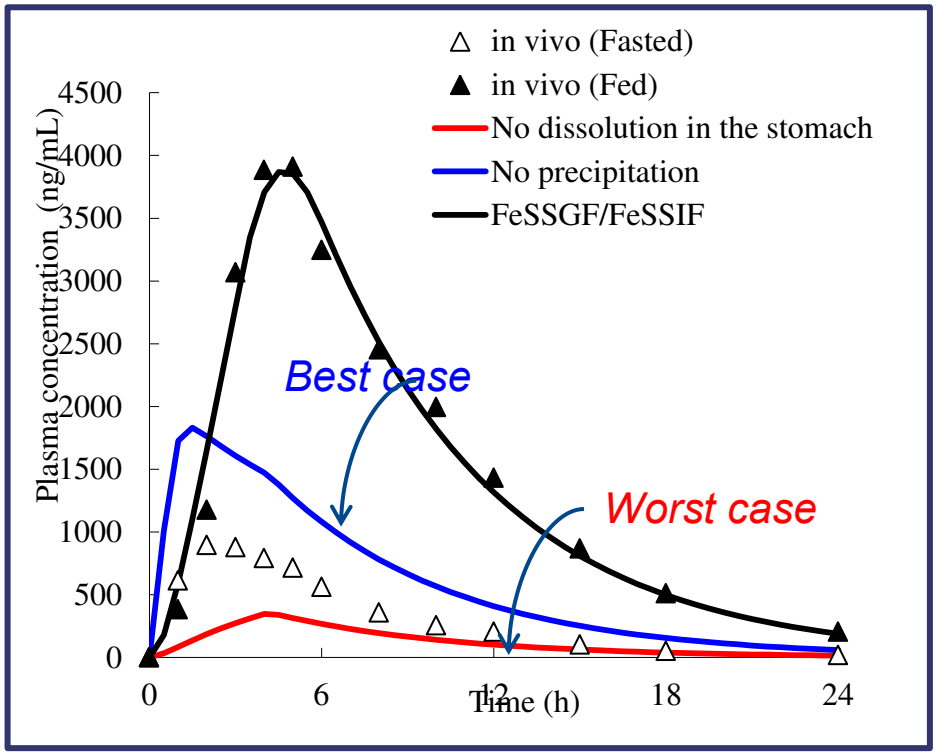
Shono et al. Eur. J. Pharm. Biopharm. 79: 349-356 (2011)

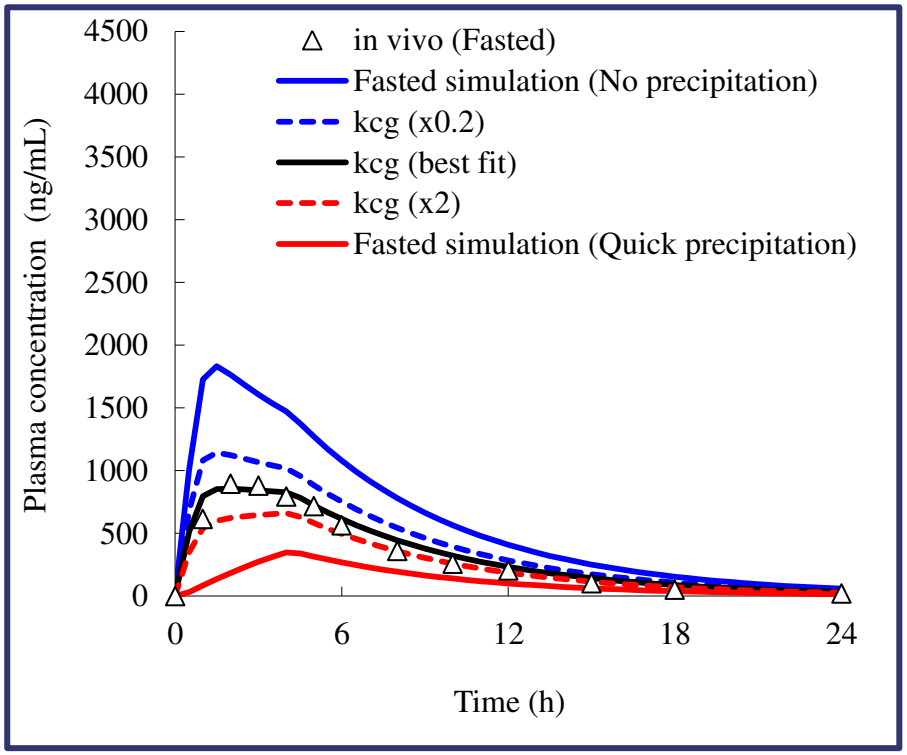
Alternative: Transfer Model approach

In the lab, the Transfer Model can be used to detect precipitation of weak bases upon entry into the small intestine



Contribution of Dissolution in the Stomach and Effects of Precipitation on the Absorption of Nelfinavir Mesylate





Results with the model indicated that invoking drug precipitation in the small intestine is necessary to describe the *in vivo* performance of nelfinavir mesylate in the fasted state.

In the fed state, the dissolution is higher under intestinal than under gastric conditions: no precipitation is expected.

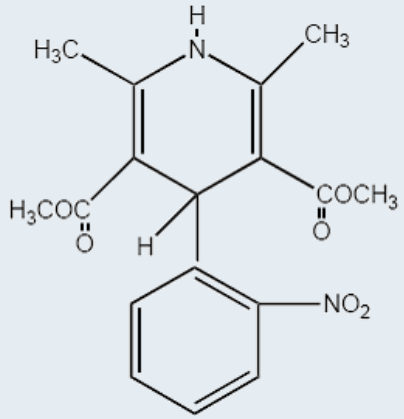
Linking the Lab to the Patient with Dissolution + PBPK

case example 3

Nifedipine– API and formulations

API

- indication: hypertension
- BCS class II
- pKa = neutral
- logP = 2.2
- light-sensitive
- Half life: 2-4h



Formulations

- Adalat XL *(extended release)*
- Adalat Eins *(extended release)*

Picture of Adalat XL

Picture of Adalat Eins

Andreas et al., 2016

Nifedipine– research question

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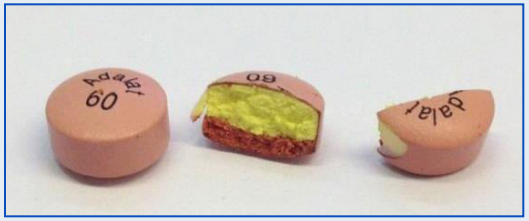
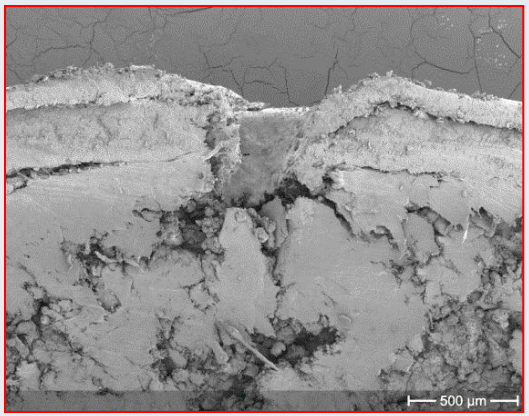
Can the dosage-form dependent food effect be predicted using *in vitro* tests?

Nifedipine – Adalat XL



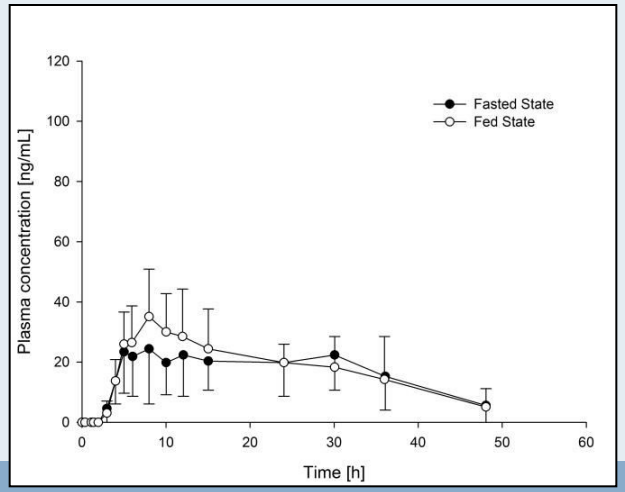


Release characteristics:

- osmotic pump
- approx. 2 hour lag time
- zero-order release rate

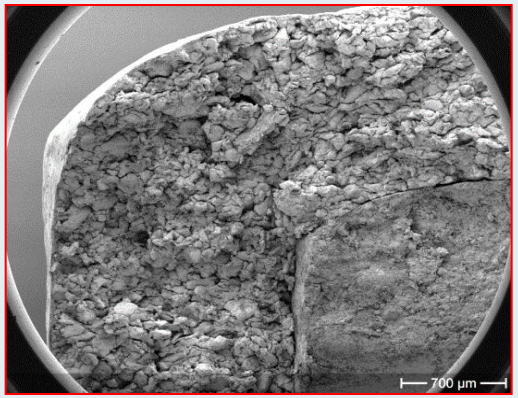
In vivo data :

- **Cmax** Fed-to-Fasted ratio: **1.21**
- **AUC** Fed-to-Fasted ratio: **1.03**



Andreas et al., 2016

Nifedipine – Adalat Eins

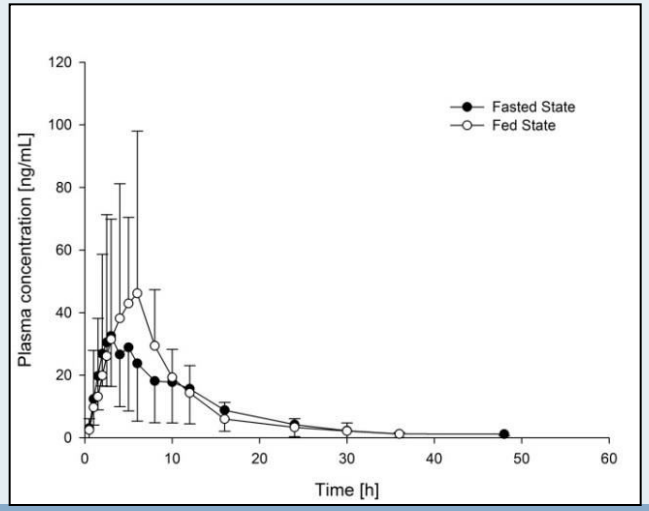


Release characteristics:

- coat core formulation
- slowly eroding coat, fast disintegrating core
- no lag time

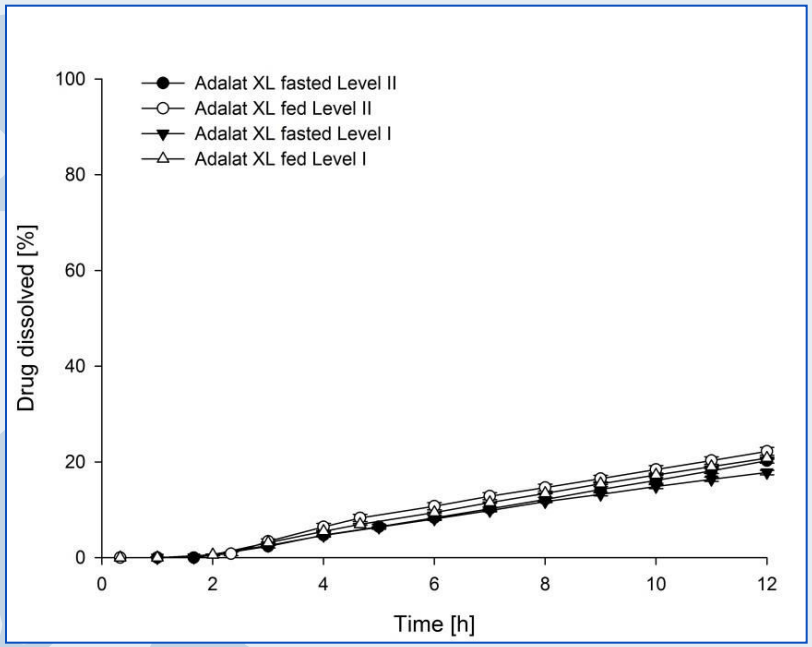
In vivo data :

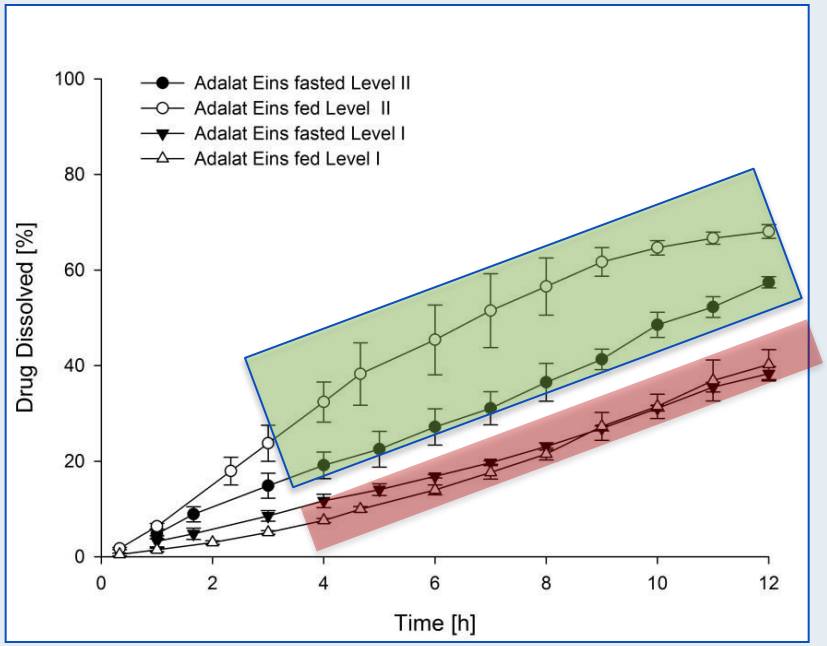
- **Cmax** Fed-to-Fasted ratio: **2.24**
- **AUC** Fed-to-Fasted ratio: **1.20**



Andreas et al., 2016

Nifedipine – Biorelevant dissolution results





Adalat XL

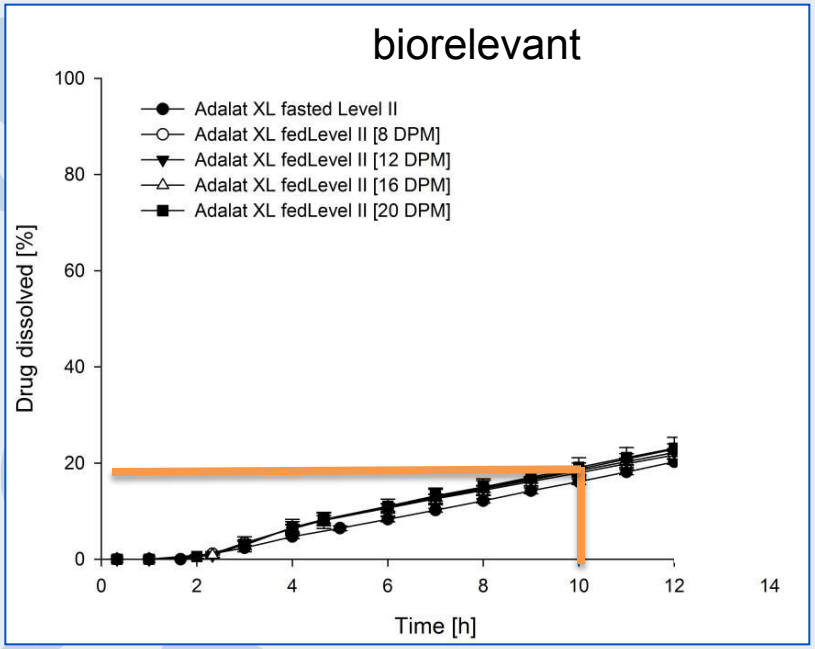
- no indication of food effect with either Level 1 or 2 media

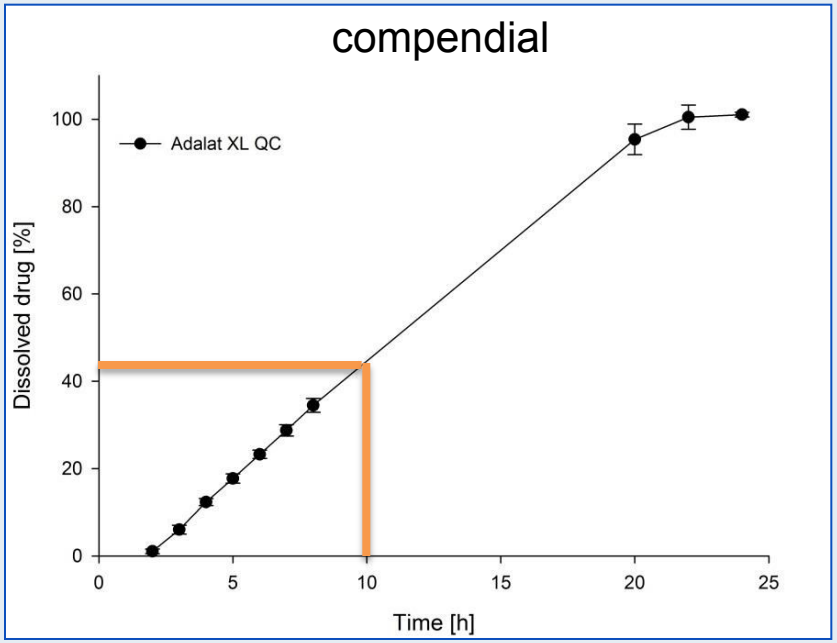
Adalat Eins

- no indication of food effect using Level 1 media
- bile salt/lipid containing media (Level 2) were necessary to predict the food effect

Andreas et al., 2016

Nifedipine – Biorelevant vs. compendial dissolution results



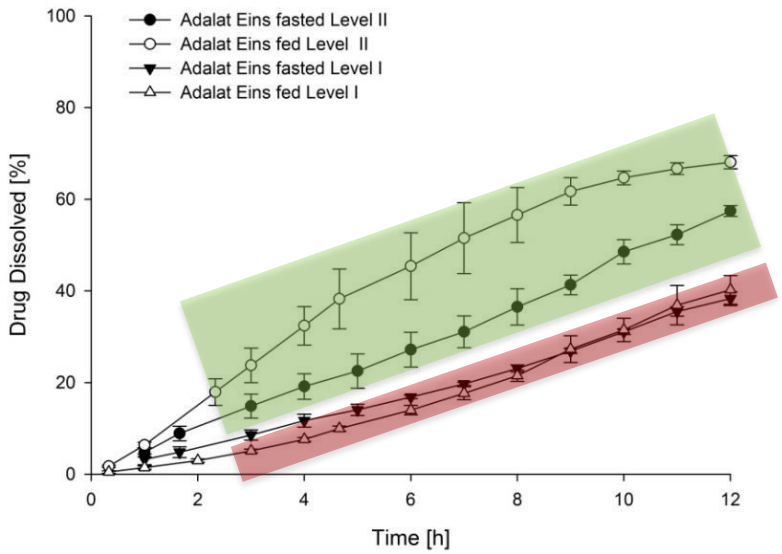


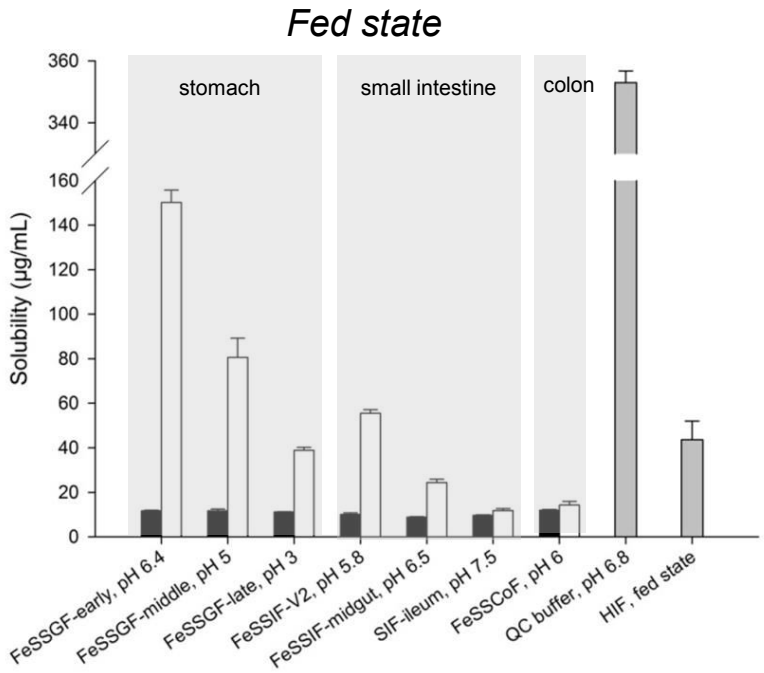
Adalat XL (osmotic pump)

- different dissolution rates in biorelevant vs. compendial (1% SDS) dissolution methods
- no impact of hydrodynamics on dissolution rate
- significantly higher dissolution rate in compendial media

Andreas et al., 2016

Nifedipine – Solubility profile

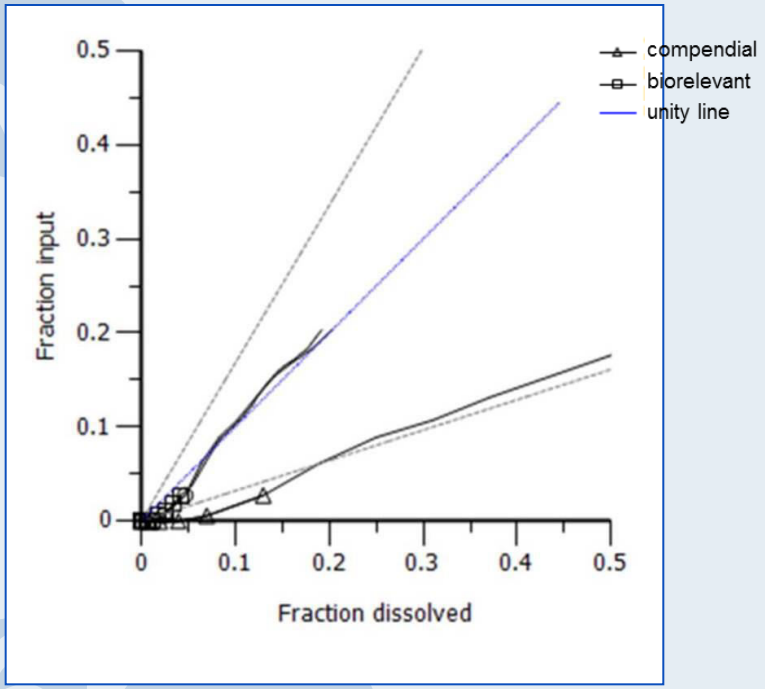


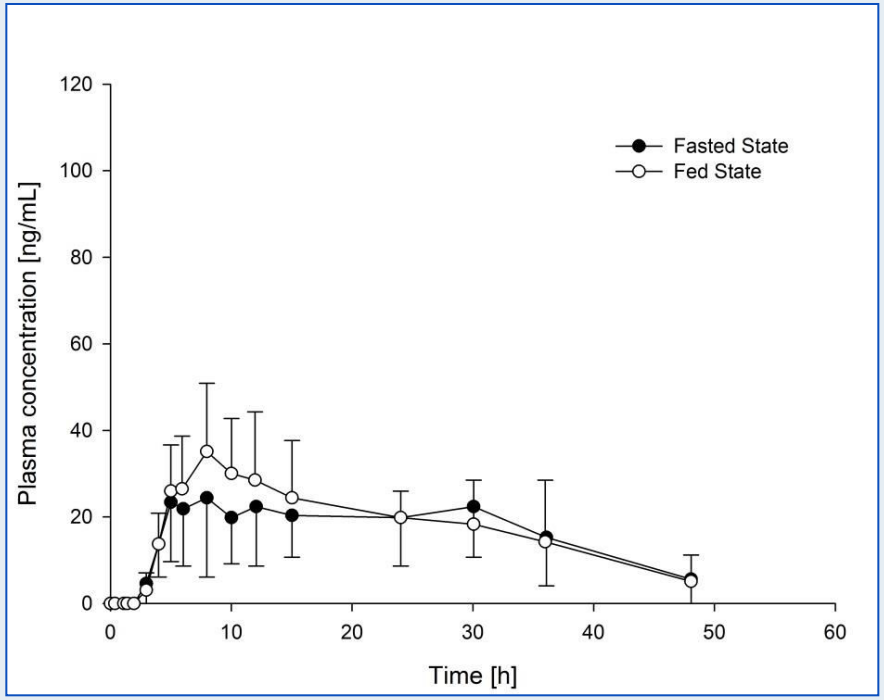


- pH-independent solubility profile
- bile-salt/lipid mediated solubility enhancement
- excessive solubilization in compendial media
- biorelevant media show much closer solubility values to intestinal aspirates (HIF)

Andreas et al., 2016

Nifedipine – Adalat XL - IVIVC





- IVIVC indicated that dissolution rates were more physiological using the biorelevant setup
  - compendial setup: release rate = dissolution rate
  - biorelevant setup: release rate ≠ dissolution rate

Andreas et al., 2016

Nifedipine - summary

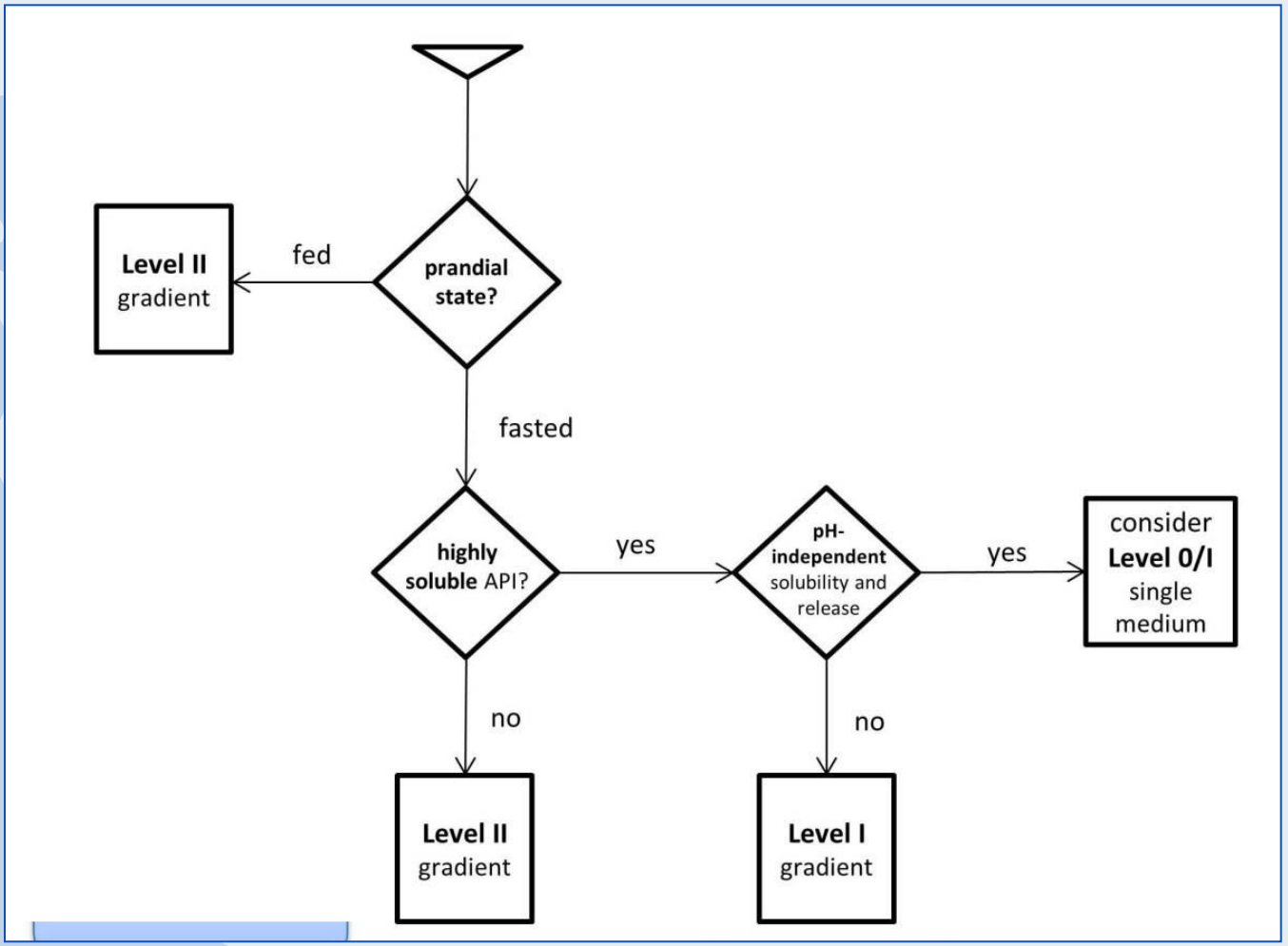
Food effects

- most likely caused by better solubilization of the API in the fed state
- Adalat XL (osmotic pump):
  - Effect is limited due to the 2 hour lag time and slow release from the osmotic pump combined with slow dissolution rate of the suspension
- Adalat Eins (matrix-type):
  - Positive food effect due to solubility enhancement of the API in the fed state

Accuracy of generated *in vitro* data

- biorelevant dissolution method:
  - successful identification of dosage-form dependent food effect
  - complex composition (Level 2) media necessary
  - *in vitro* input resulted in more physiological IVIVC
- compendial dissolution method:
  - 1% SDS overestimated the dissolution rate
  - indication of food effects not possible with QC media

Decision tree for most appropriate media selection for predictive tests (MR Dosage Forms)

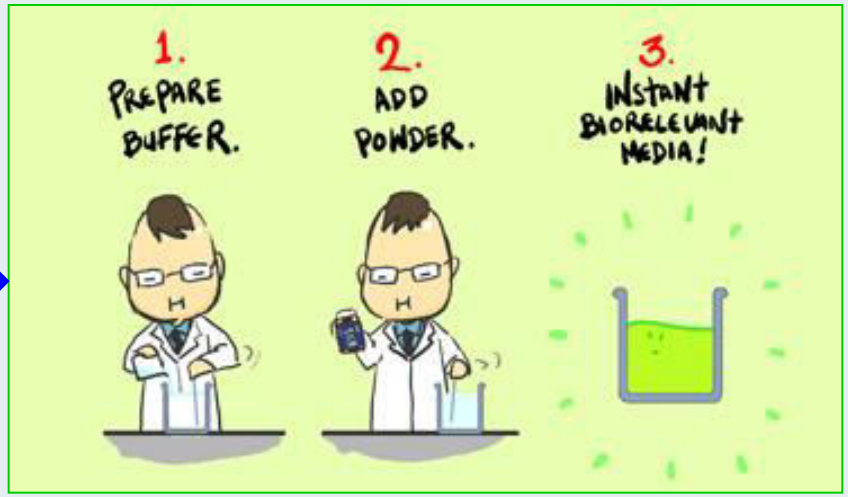


Biorelevant dissolution media

Using „instant“ powders to make the biorelevant media:

„Study of a Standardized Taurocholate–Lecithin Powder for Preparing the Biorelevant Media FeSSIF and FaSSIF“

Dissolution Technologies



source: www.biorelevant.com

What are the benefits of combining Biorelevant dissolution with PBPK?

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- Better understanding of exactly which factors really affect the PK profile
- Fewer (no?) animal experiments in the pharmaceutical development phase of R&D of new drugs
- Easily able to predict PK profile in patients with non-standard GI physiology (pediatric, geriatric, PPI users etc.) => reduce the number of clinical studies necessary
- Predict food effects on the PK profile => recommend dosing
- Predict whether a SUPAC change will be BE with the predecessor formulation (predict outcome of bridging studies)

Let's all work together to provide optimal therapy for the patient!

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Picture of elephants kissing

Thank you for your attention!

Acknowledgements:

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