Analysis and comparison of dissolution time profiles based on a first-principles disintegration-dissolution model.

A contribution to model-informed drug development

Stefan Horkovics-Kovats
Mail: stefan.horkovics-kovats@shk.sk
Tel.: +43 699 19570309

BioBridges September 20-21, 2023, Prague

Content

- Introduction
- Mathematical models of dissolution
- DDM and its application (Augmentin XR tablet)
- Comparison of dissolution profiles based on DDM

Dissolution profile analysis

Quality assurance

Development tool

Basis for in vitro – in vivo correlations

IMP identification for BE studies

First mathematical models

Noyes-Whitney 1897

$$\frac{dc}{dt} = -k(c_s - c)$$

Brunner-Tolloczko 1900

$$\frac{dc}{dt} = -kA(c_s - c)$$

Consider solid and dissolved API. The given equations lead to an exponential function, the real measured profiles of FDFs deviate significantly from this function.

Dissolution of an individual particle

Dissolution occurs on the particle surface.

$$\frac{dm}{dt} = -v_1 S + v_2 S \frac{M}{V}$$

$$\frac{dM}{dt} = v_1 S - v_2 S \frac{M}{V}$$

Surface expressed by mass of the particle surface.

$$\frac{dm}{dt} = -\alpha m^{2/3}\left(1 - \frac{M}{c_s V}\right)$$

$$\frac{dM}{dt} = \alpha m^{2/3}\left(1 - \frac{M}{c_s V}\right)$$

The dissolution profile must be described by a system of differential equations, 2004.

Dissolution of particles released from FDF

Particle

$$\frac{\partial m(\xi,t)}{\partial t} = -\alpha m^{2/3}(\xi,t)\left[1 - \frac{M(t)}{c_s V}\right]$$

Dissolved drug

$$\frac{dM(t)}{dt} = -N_0 \int_0^t \frac{\partial m(\xi,t)}{\partial t} \nu(\xi)\, d\xi$$

Dissolved drug with degradation in medium

$$\frac{dM(t)}{dt} - k_{deg} M(t) = -N_0 \int_0^t \frac{\partial m(\xi,t)}{\partial t} \nu(\xi) d\xi$$

This leads to Volterra integral equations, 2015

$\nu(\xi)$ FDF – Disintegration function

FDF disintegration-dissolution model

The above system of equations represents a first-principles-based mechanistic disintegration-dissolution model (DDM).

Dissolution White Paper. Zaborenko N. et al., AAPS-Journal (**2019**), 10.1208/s12248-019-0297-y

Disintegration-dissolution model

Analysis of profiles

- Based on nonlinear, fixed-effect optimization (SADAPT)
- Assessment of dissolution relevant properties of FDF and API

Prediction of profiles

- Profile predictions for given FDF and API characteristics
- Can consider changed conditions of dissolution (pH-dependent solubility, degradation, Volume, etc.)

Applicability of DDM analysis

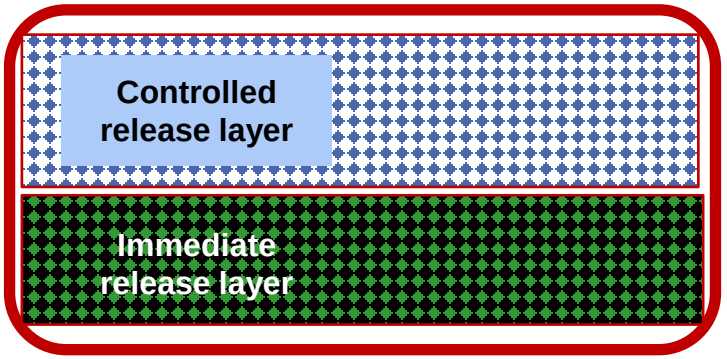
Augmentin XR bilayer tablet as example

- Immediate release layer (Amoxicillin & Clavulanic Acid)
- Extended-release layer (Amoxicillin only)

Applicability of DDM analysis

Weitschies et al. European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 641–648

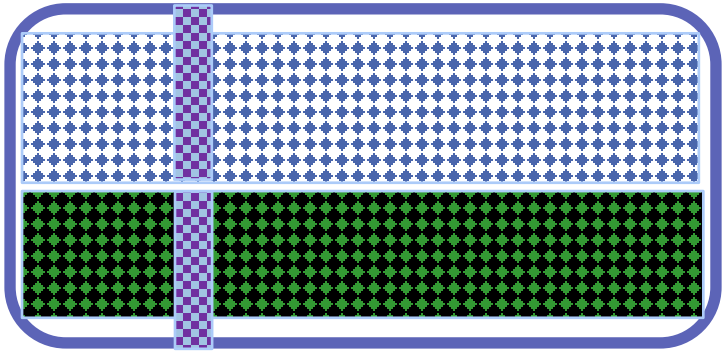
Augmentin XR used in Bioavailability studies



Amoxicillin

Amoxicillin + Clavulanic acid

Augmentin XR used in Disintegration measurements

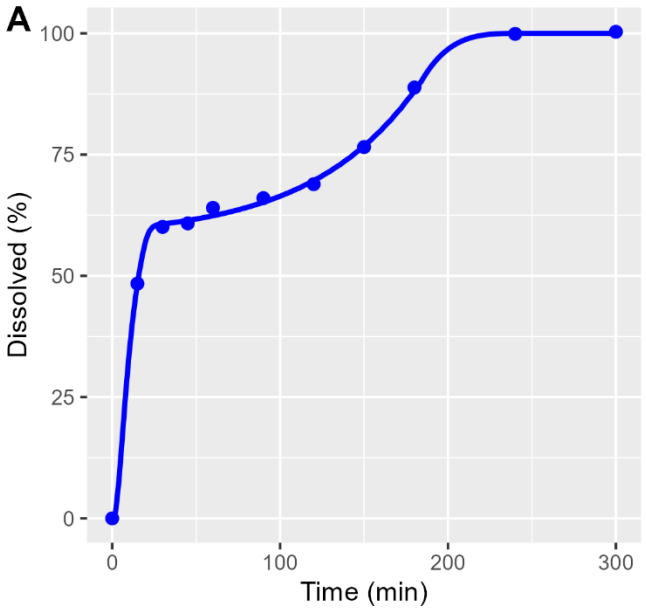


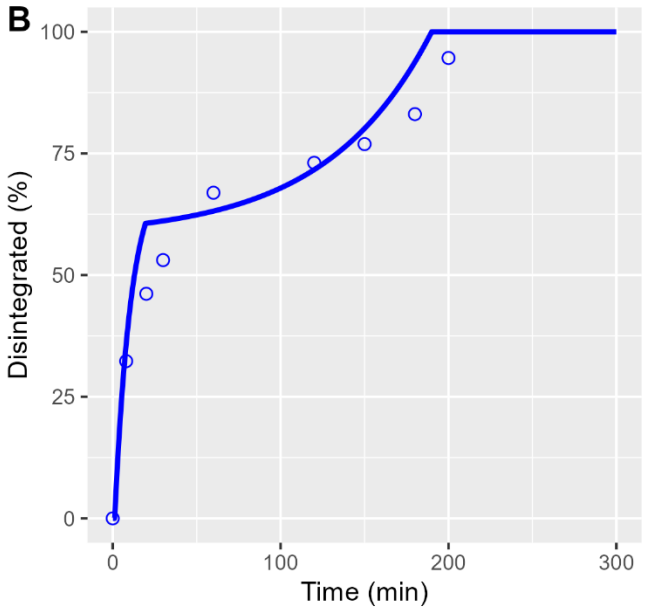
Amoxicillin + iron oxide + microcrystalline cellulose

Amoxicillin + Clavulanic acid + iron oxide + microcrystalline cellulose

Disintegration measured by **decay of magnetic moment** form magnetized iron oxide

Applicability of DDM analysis





Dissolution	Augmentin XR
Tau1 (min)	9.87
Tau2 (min)	45
R1	0.602

Disintegration	Augmentin XR
LAG1 (min)	1.16
Disint1 (min)	19.5
Lag2 (min)	9.25
Disint2 (min)	190
Dic1	1.88
Dic2	-2.88

Influence of food intake and gastric emptying

Weitschies et al. European Journal of Pharmaceutics and Biopharmaceutics 70 (2008) 641–648

Study	AUC Amox (µg*min/mL)	Ratio to FDA	AUC CA (µg*min/mL)	Ratio to FDA	Gastric Emptying (min)	Ratio to Fasting
Fasting	1854	0.71	191	1.52	62	1
Beginning of meal	2452	0.94	189	1.50	222	3.6
FDA breakfast	2605	1	126	1	300	4.8

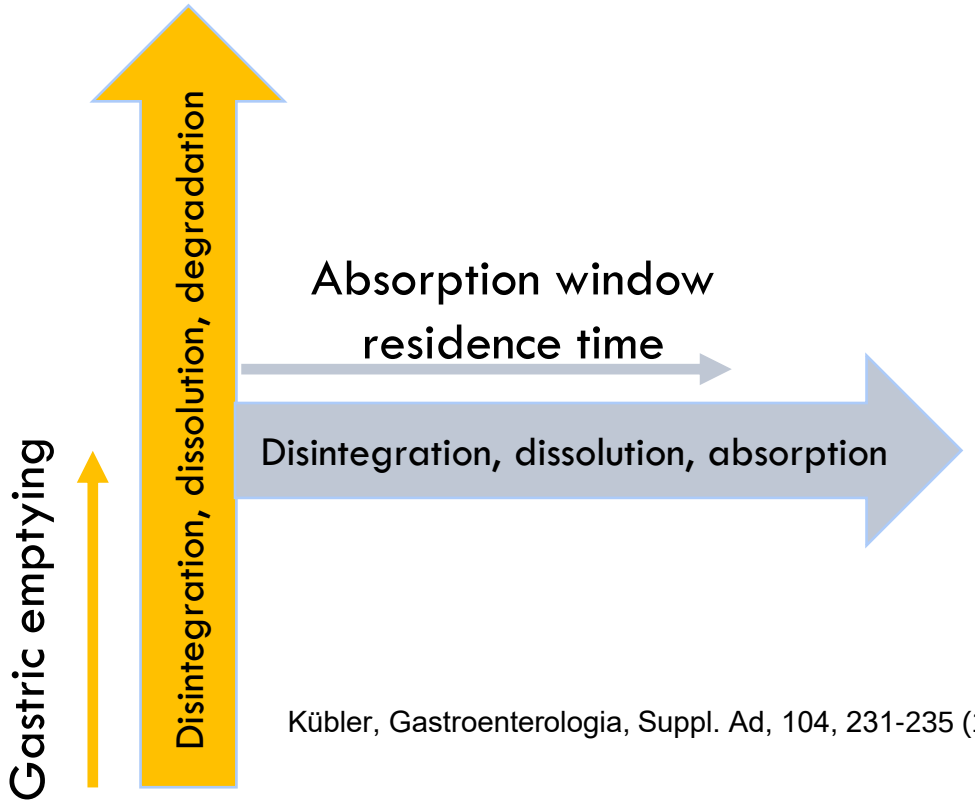
Aim: to connect the dissolution profiles with the bioavailability data.

Amoxicillin – almost stable in the GI tract, absorption limited through an absorption window.

Clavulanic acid – shows strong pH-dependent degradation

What impacts the drug bioavailability?

The available amount of dissolved drug is evaluated.



Stomach

- Variable pH conditions
- Possible pH-dependent degradation and/or solubility of API.

Absorption window

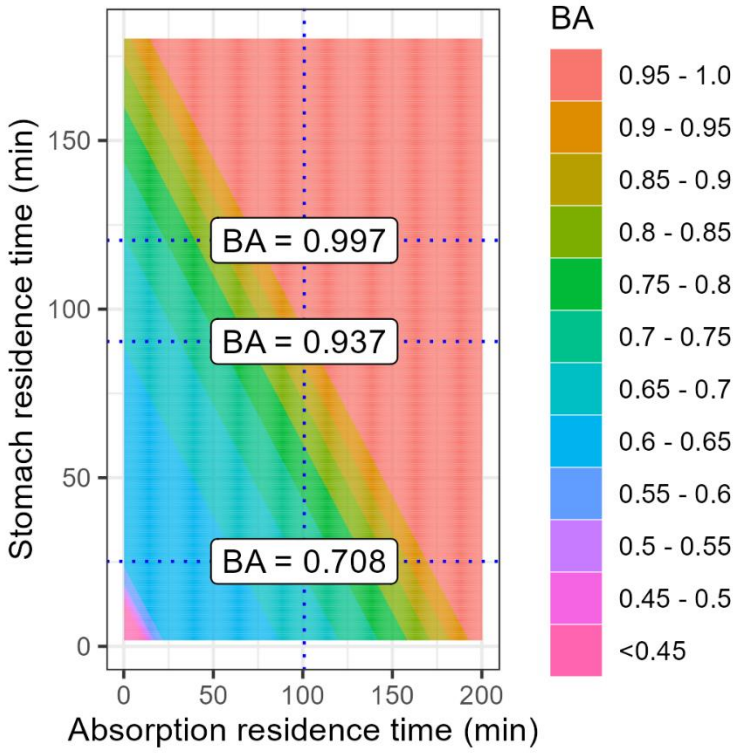
- limits the bioavailability
- Sudden change in pH condition with possible impact on stability, and solubility of API

Kübler, Gastroenterologia, Suppl. Ad, 104, 231-235 (1965)

Mapping the influence of gastric emptying- and absorption residence time

Model calibration

Availability of Amoxicillin as function of gastric emptying and absorption window



The ratios of GE times correspond to the BE results.

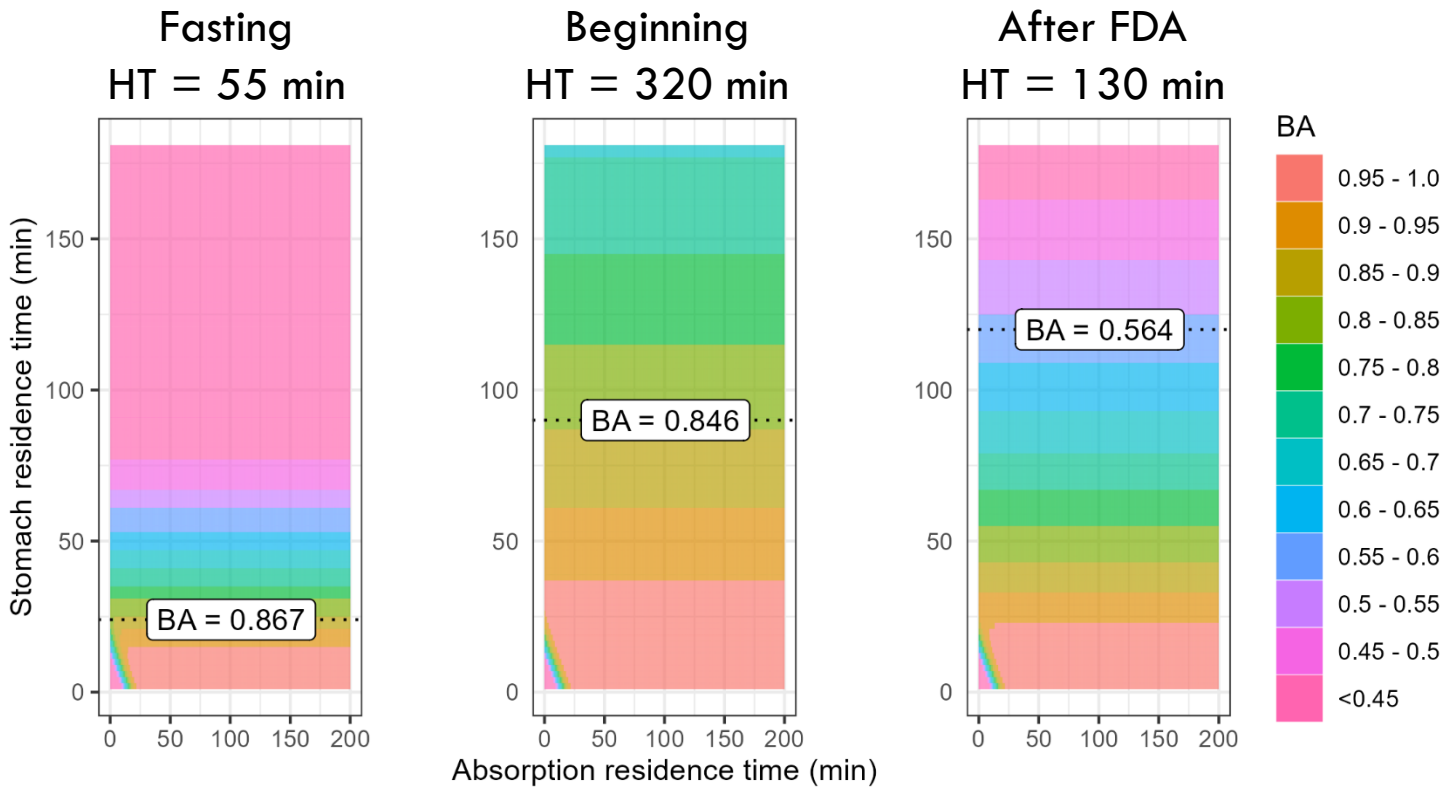
Gastric emptying

- Fasting = 25.1 min
- Beginning of meal = 90.4 min
- After FDA breakfast = 120.5 min

Absorption residence time

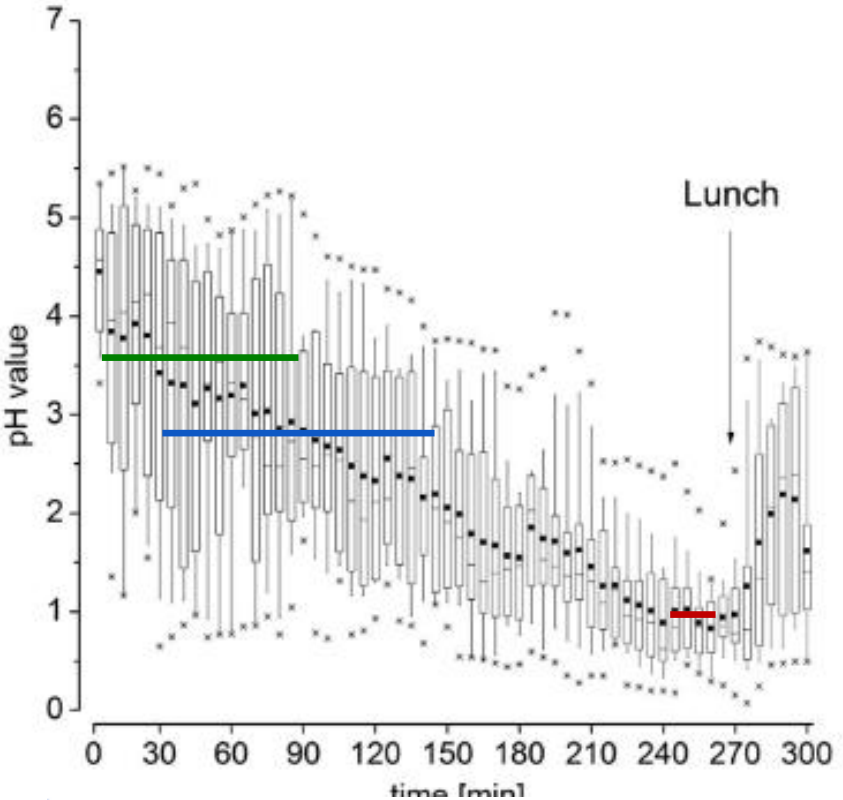
- Common = 97.3 min

Model calibration



Gastric emptying times and absorption window residence time set by amoxicillin data

Availability of Clavulanic acid released from XR bilayer tablet in dependence of food intake.



Journal of Controlled Release, (2015), 71-78, 220

Fig. 3. Gastric pH values for the initial 5 h time frame after TMC administration. Each box represents a 5 min interval. Box: 50%, whisker: 10–90%, square: mean, asterisks: max/min; n = 16. The three subjects, for whom post-calibration could not be performed, were excluded from this statistical analysis.

Journal of Controlled Release 2015 71-78

The assessed halftimes of degradation:

for **fasting** = **55** min,

after meal = 320 min

FDF high-fat breakfast = 130 min

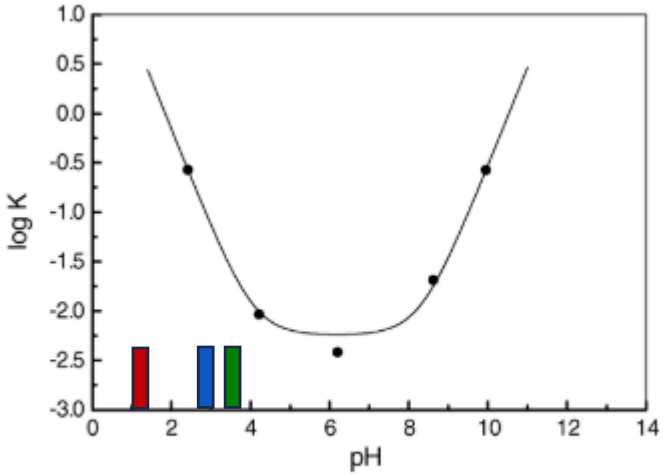


Fig. 1. Effect of pH on the first-order rate constants for the clavulanic acid hydrolysis at 20 °C and $\mu = 0.5$ [5].

Biochemical Engeneering Journal 2005 (23), 31-36

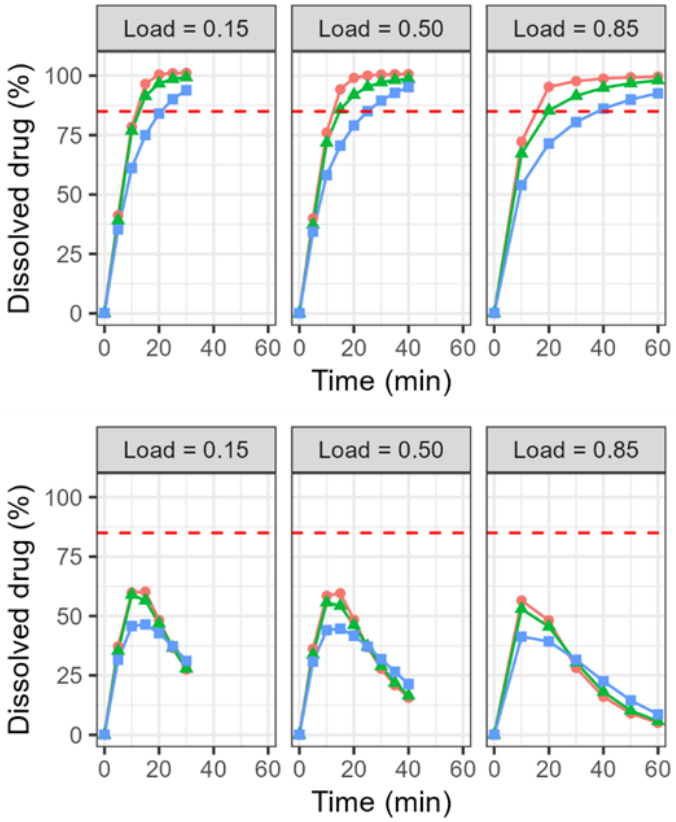
Comparison of dissolution profiles

Predicted profiles of 3 different compositions in three strengths

Composition	τ_1 [mn]	τ_2 [min]	R_1	σ_1 [min]	σ_2 [min]	DISINT [min]	TLAG [min]	L=0.15 [mg]	L=0.50 [mg]	L=0.85 [mg]
1	2.0	10.0	0.80	1.93	3.97	15.0	1.5	0.15	0.50	0.85
2	4.0	20.0	0.50	1.99	1.97	10.0	1.0	0.15	0.50	0.85
3	8.0	40.0	0.30	3.03	1.53	5.0	0.5	0.15	0.50	0.85

Comparison of FDF dissolution using DDM

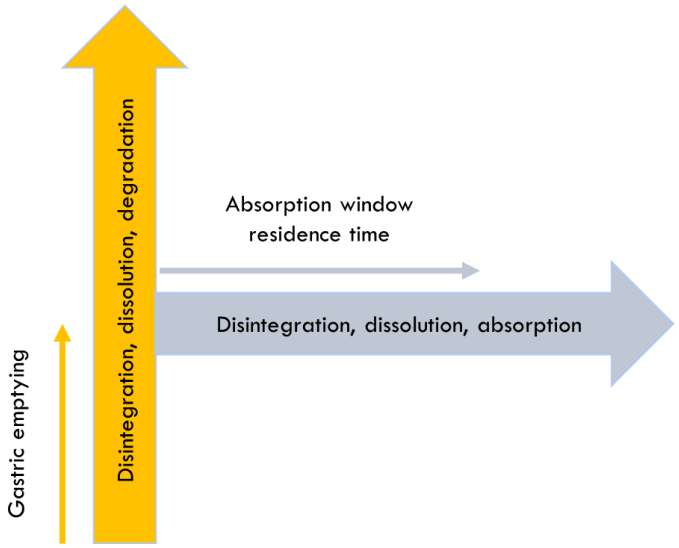
The predicted profiles for increasing drug load for stable API

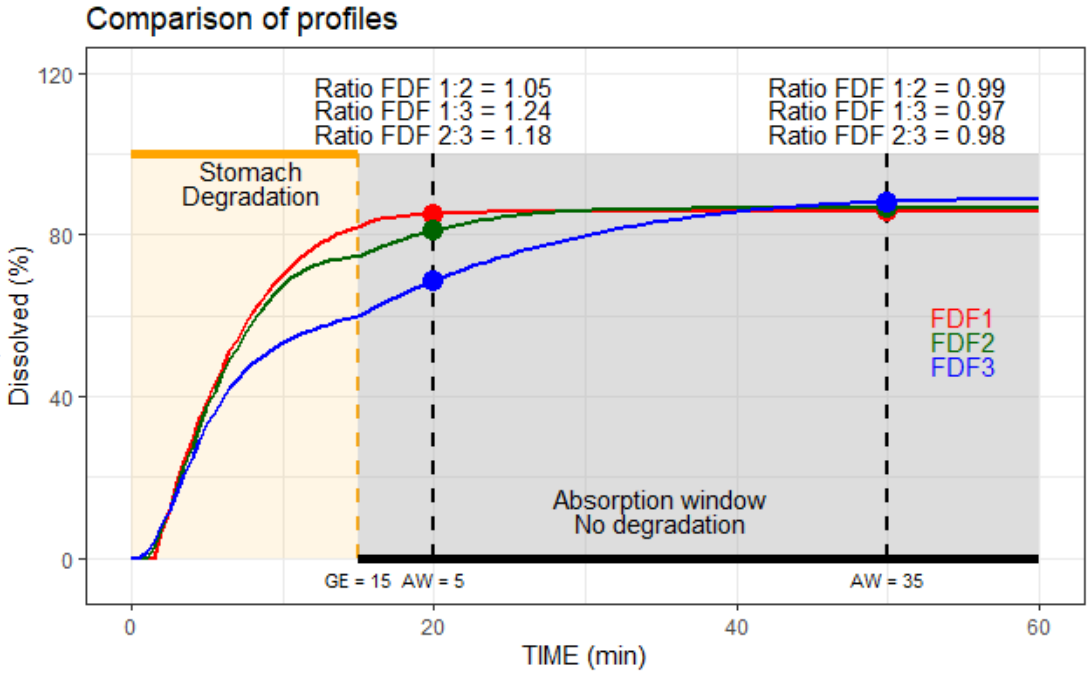


The predicted profiles for increasing drug load with chemical instability of the API, Kdeg = 0.06 min^(-1)

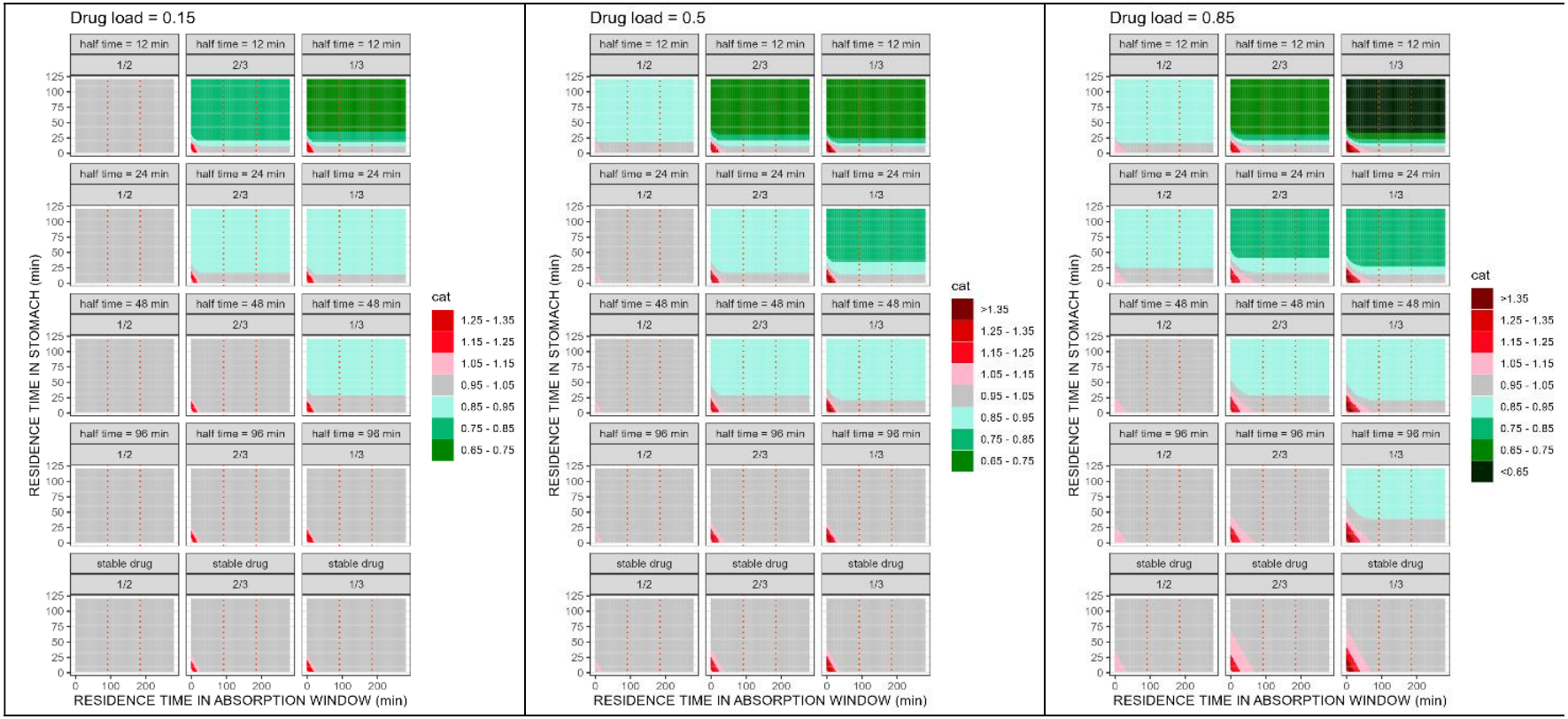
Comparison of dissolution time profiles

The concept of comparing dissolution profiles is based on the ratio in the gastric emptying and absorption residence time-space.



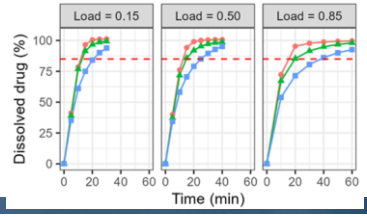


Comparison of dissolution time profiles

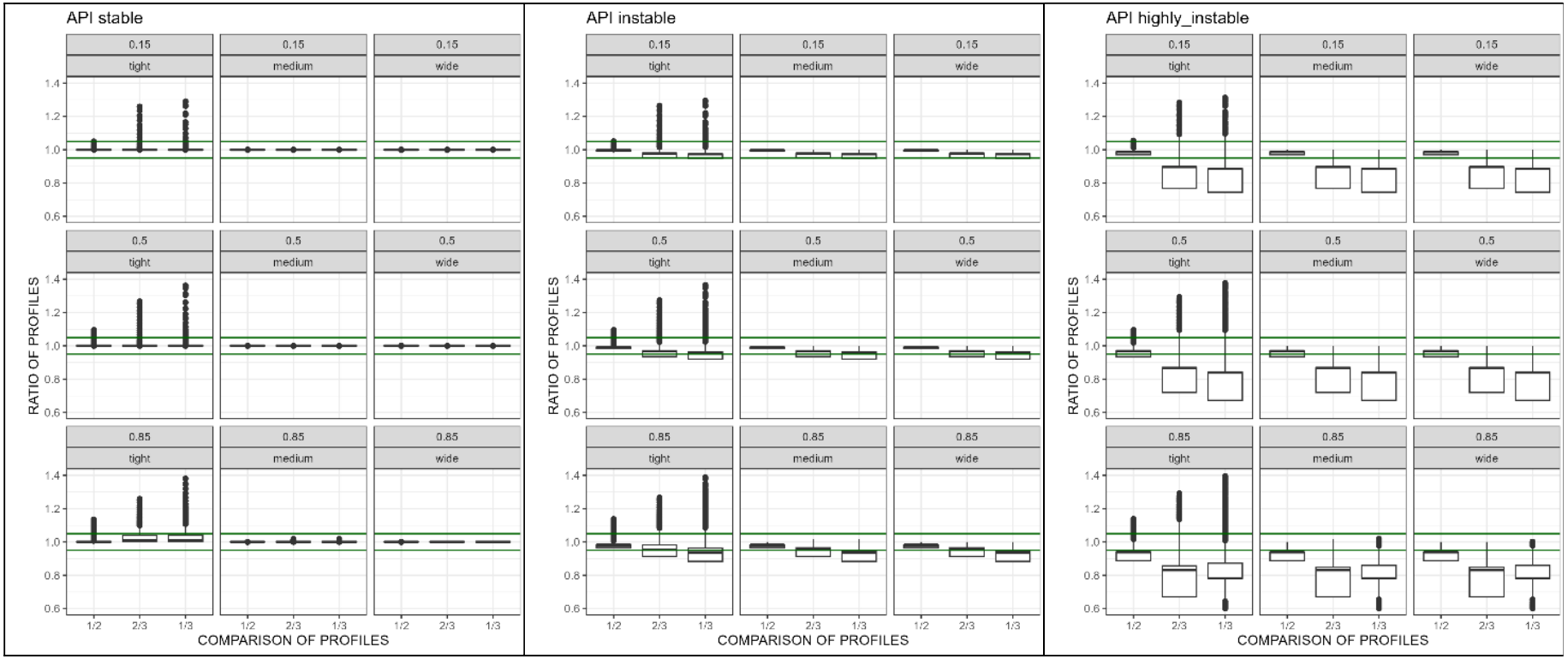


As the drug load increases, the differences in the dissolution profiles are more pronounced.

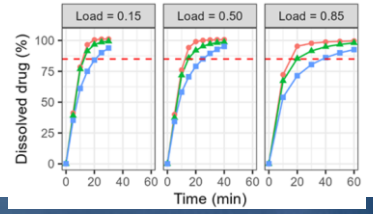
For nonlinear absorption additional dose effects are expected.



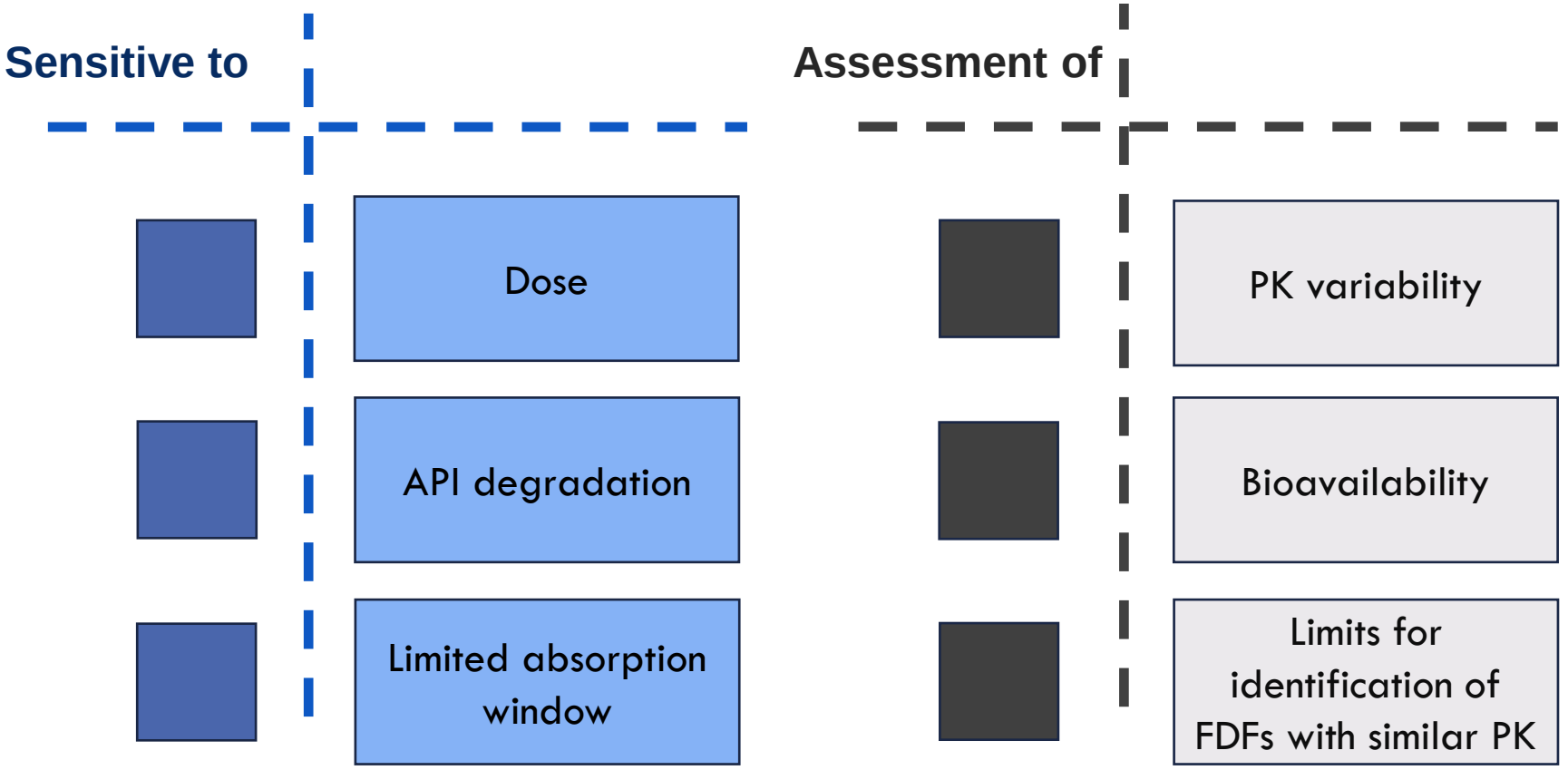
Comparison of dissolution time profiles



Impact of API chemical instability and width of the absorption window on the available API amount in the absorption window.



Summary of dissolution profile comparison.



My vision: DDM in pharmaceutical research

- estimates dissolution-relevant properties of FDF & API
- links FDF/API properties with GI physiology
- represents a new level of in vitro – in vivo correlation's

Relevant publications

1. Noyes A., Whitney W.: The rate of solution of solid substances in their own solutions. J Am Chem Soc, 19(12), 930-934, 1897
2. Brunner L., Tolloczko S.: Über die Auflösungsgeschwindigkeit fester Körper, Z. Phys Chem, 35, 283-290, 1900
3. Kübler W, Quantitative Blutspiegeluntersuchungen über die Kinetik der Dünndarmresorption. Gastroenterologia, Suppl. ad, 104, 231-235, 1965
4. Horkovics-Kovats S.: Characterization of an active pharmaceutical ingredient by its dissolution properties: Amoxicillin trihydrate as a model drug. Chemotherapy, 50(5), 234-244, 2004
5. Bersanetti. P. et al.: Kinetic studies on clavulanic acid degradation. Biochemical Engineering Journal, 23(1), 31-36, 2005
6. Weitschies W. et al.: Bioavailability of amoxicillin and clavulanic acid from extended-release tablets depends on intragastric tablet deposition and gastric emptying. Eur J Pharmaceut Biopharmaceut, 70(2), 641-648, 2008
7. Horkovics-Kovats S.: Disintegration rate and properties of active pharmaceutical ingredient particles as determined from the dissolution time profile of a pharmaceutical formulation: An inverse problem. J Pharm Sci, 103, 456-464, 2014
8. Horkovics-Kovats S. et al.: Population data analysis of dissolution time profiles: Assessment of physicochemical properties of the drug, drug particles and the pharmaceutical formulation. Eur J Pharm Sci, 78, 245-254, 2015
9. Koziolek M. et al.: Intragastric pH and pressure profiles after intake of the high-caloric, high-fat meal as used for food effect studies. J Controlled Release 220, 71-78, 2015
10. Horkovics-Kovats S.: Dissolution and coarsening of polydisperse, polymorph drug particles liberated from a disintegrating finished dosage form: Theoretical considerations. Eur J Pharm Sci, 91, 265-277, 2016
11. Zaborenko N., et al.: First-Principles and Empirical Approaches to Predicting In Vitro Dissolution for Pharmaceutical Formulation and Process Development and for Product Release Testing, The AAPS J, 2019, 21:32, DOI: 10.1208/s12248-019-0297-y