Role of Biopredictive Dissolution and Oral PBPK to Evaluate the Impact of Food on Drug Absorption

Jozef Al-Gousous

Oct-12th-2023

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

JG|U

EFFECT OF FOOD-INDUCED VISCOSITY ON DRUG RELEASE

- Higher viscosity retards water penetration into tablet.
- According to Washburn equation

$$\frac{dL}{dt} = \sqrt{\frac{\gamma r_{pore} \cos\theta}{8\eta t}}$$

This retards disintegration and accordingly dissolution

- Disintegration and accordingly dissolution can become 1-2 orders of magnitude slower
- USP type I and II dissolution apparatuses not suitable because of strong coning under viscous conditions (elimination of eddies).

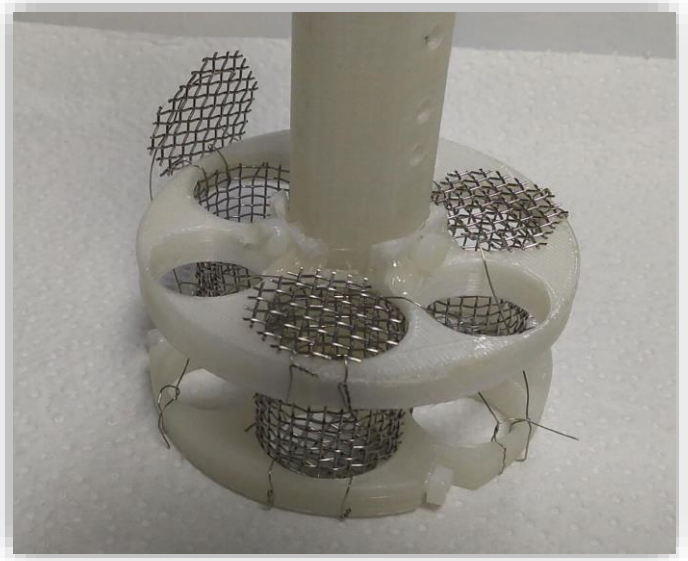
3D DISSOLUTION

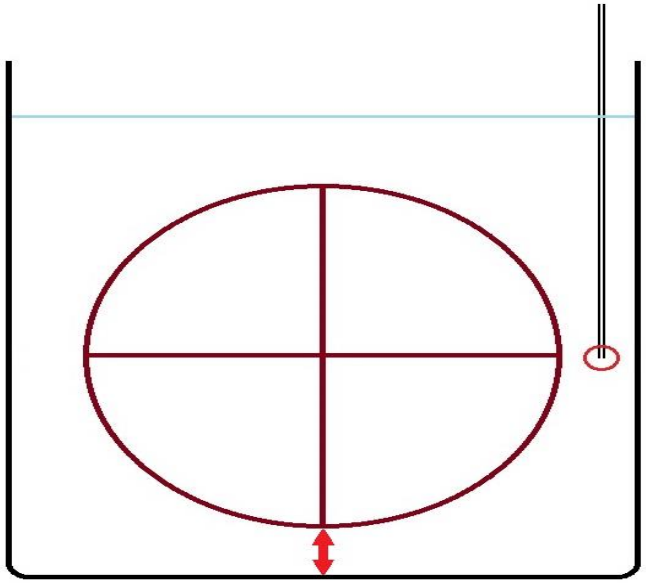
Novel disintegration tester (CNC-operated) as previously introduced now operated as

Novel Dissolution Tester

with improved basket design

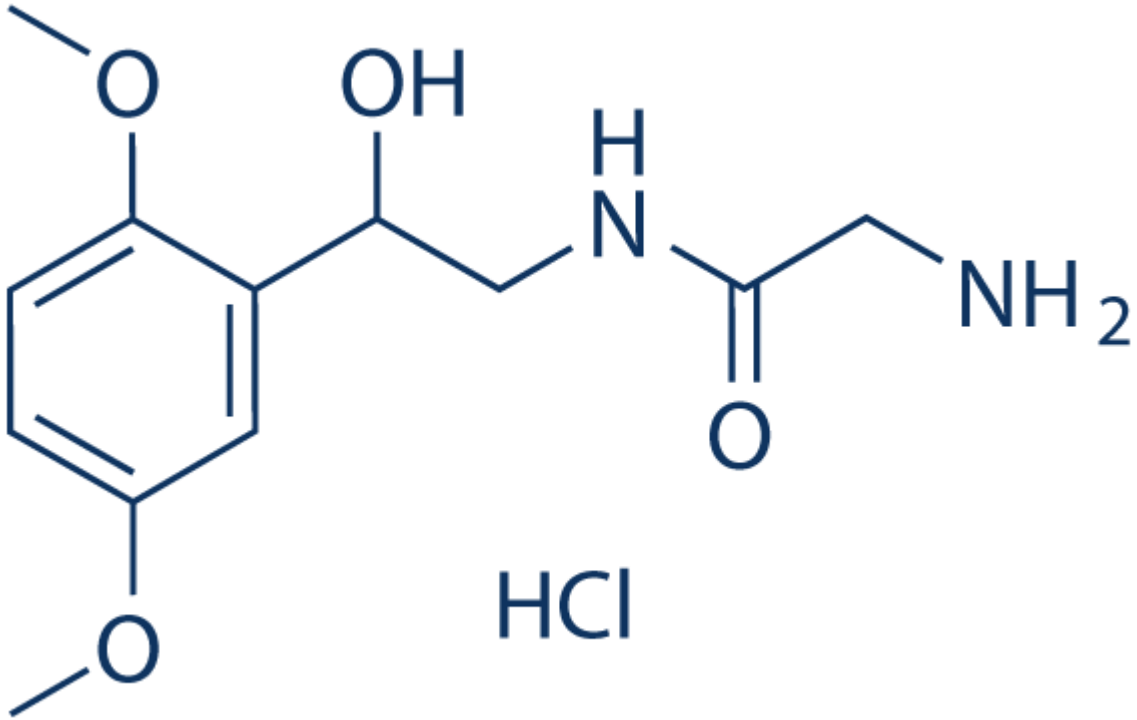
Pooled dissolution of 3 samples
Volume 1500 ml
The effect of coning formation is greatly reduced thanks to beneficial new basket design





CASE STUDY: MIDODRINE HCL

- A prodrug used for orthostatic hypotension
- Publically available PK data from ANDA for two IR tablet products



MIDODRINE P.O. SOLUTION REFERENCE

Taken from
”Arzneimittelforschung, 1987“

Aus der Universität Regensburg, Lehrstuhl für Pharmakologie[1], Regensburg, und der Biomedizinischen Forschungsgesellschaft mbH, Linz (Österreich)

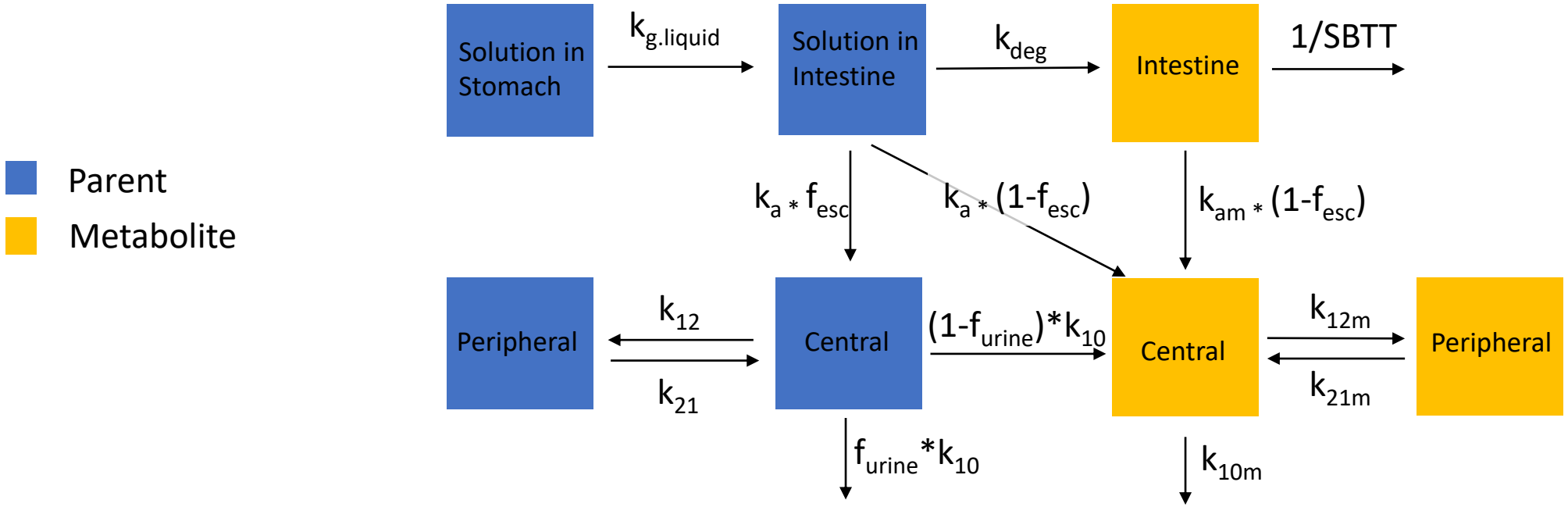
Untersuchungen zur Bioverfügbarkeit von Midodrin und α-2,5-Dimethoxyphenyl-β-aminoethanol-hydrochlorid

Von H. Grobecker[1], F. Kees[1], M. Linden[1], E. Schrader[1] und S. Welte[2]

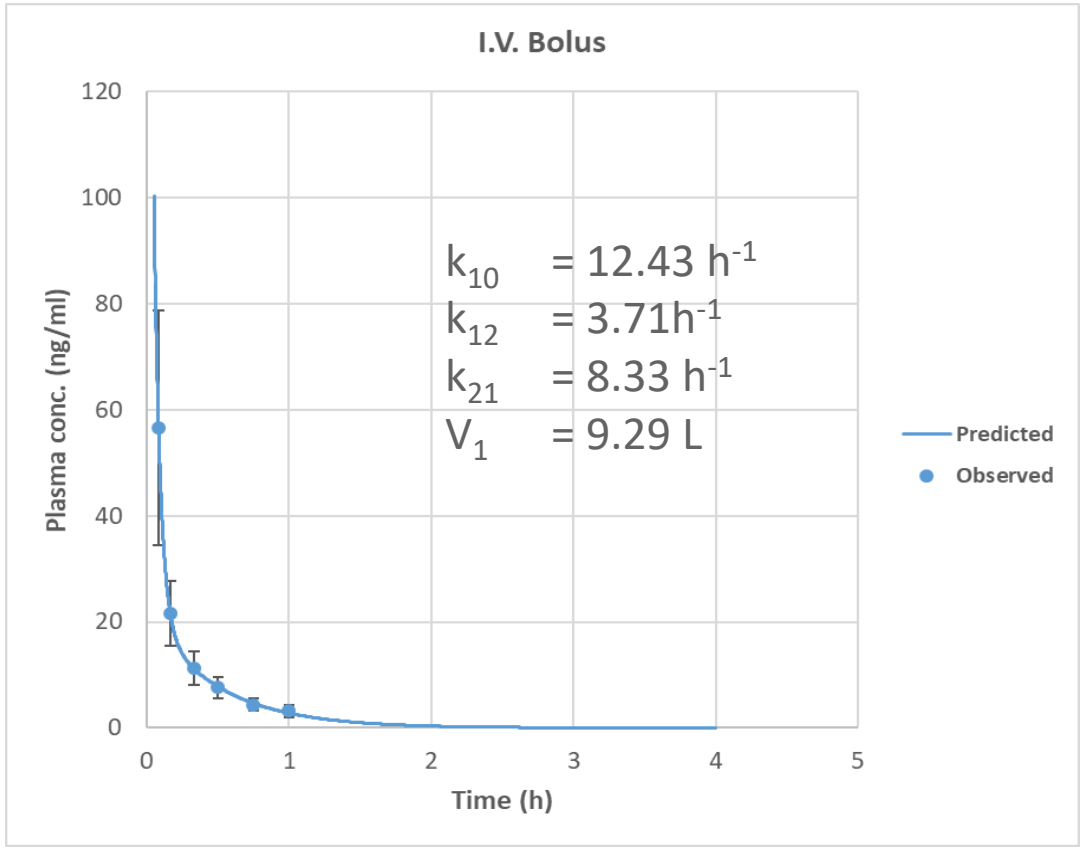
Zusammenfassung: *Die Pharmakokinetik von Midodrin (α - 2,5 - Dimethoxyphenyl - β - glycinamidoethanol - hydrochlorid, ST 1085) und seines aktiven Hauptmetaboliten ST 1059 (α-2,5-Dimethoxyphenyl-β-aminoethanol-hydrochlorid) wurde an 12 gesunden, freiwilligen, männlichen Probanden untersucht. 2,5 mg Midodrin-HCl wurden im randomisierten cross-over-Versuch intravenös, als Trinklösung und als Tablette (Gutron®) verabreicht. Die bis zu 24 h nach der Applikation gesammelten Plasma- und Urinproben wurden mit Hilfe von Hochdruckflüssigkeitschromatographie und fluorimetrischem Detektor analysiert. Die mittleren Maximalkonzentrationen von Midodrin betrugen 20–30 min nach oraler Applikation ca. 10 ng/ml, für ST 1059 nach 1 h ca. 5 ng/ml. Für Midodrin wurde eine terminale Plasmahalbwertzeit von etwa 0,5 h, für ST 1059 eine Plasmahalbwertszeit von 3 h berechnet. Die Fläche unter der Plasmaspiegel-Zeit-Kurve (AUC) betrug im Mittel für ST 1059 nach Applikation von 2,5 mg Midodrin i.v. 28,7 ng × h/ml und als Trinklösung oder als Tablette 25,7 bzw. 25,6 ng × h/ml. Für die Berechnungen der Bioverfügbarkeit waren jeweils die AUC von ST 1059 aus den Daten von 10 Probanden auswertbar. Auf Grund der geringen Fallzahl wurde ein Äquivalenzintervall von 0,75–1,25 angenommen. Unter diesen Voraussetzungen sind alle drei galenischen Formulierungen als äquivalent zu bezeichnen.*

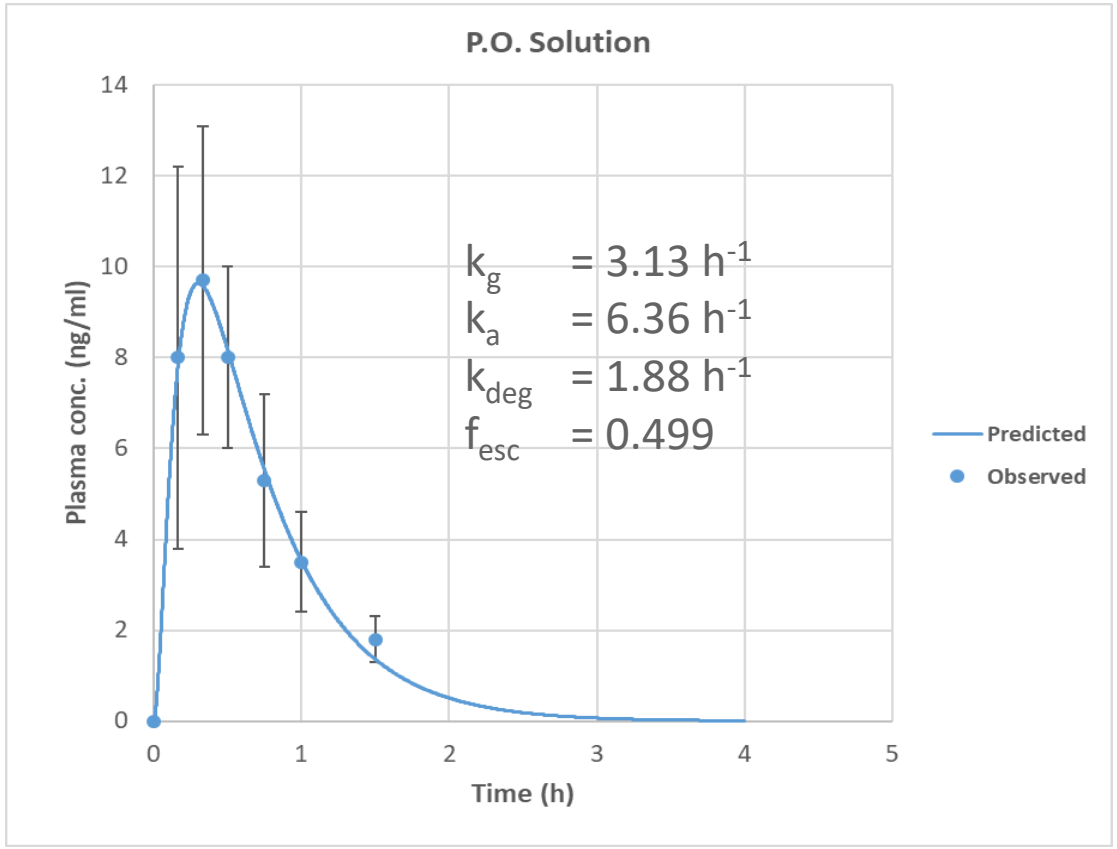
Summary: *Studies on the Bioavailability of Midodrine and α-2,5-Dimethoxyphenyl-β-aminoethanol Hydrochloride*
The pharmacokinetics of midodrine (α-2,5-dimethoxyphenyl-β-glycinamidoethanol hydrochloride, ST 1085) and its main metabolite ST 1059 (α-2,5-dimethoxyphenyl-β-aminoethanol hydrochloride) have been investigated in 12 male healthy volunteers. 2.5 mg midodrine hydrochloride were applied intravenously, as drinking solution or as tablet (Gutron®) according to a randomized cross-over design. Plasma and urine samples collected up to 24 h after application were analyzed by high-performance liquid chromatography with fluorescence detection. The mean maximum concentration in plasma for midodrine was ca. 10 ng/ml 20–30 min after oral administration, for ST 1059 ca. 5 ng/ml after 1 h. Midodrine was eliminated with a terminal half-life of 0.5 h. The half-life of ST 1059 was determined to be 3 h. The mean area under the plasma-level vs. time curve (AUC) of ST 1059 after administration of 2.5 mg midodrine i.v. was 28.7 ng × h/ml, and as drinking solution or as tablet 25.7 and 25.6 ng × h/ml, respectively. The data of 10 volunteers could be used for the calculations of the bioavailability of ST 1059 by the AUC. Assuming an interval of equivalence of 0.75–1.25 because of the relatively small number of volunteers, the three galenical formulations are considered to be equivalent.

MYLAN: FASTED



ADJUSTED MODEL FOR MIDODRINE PK



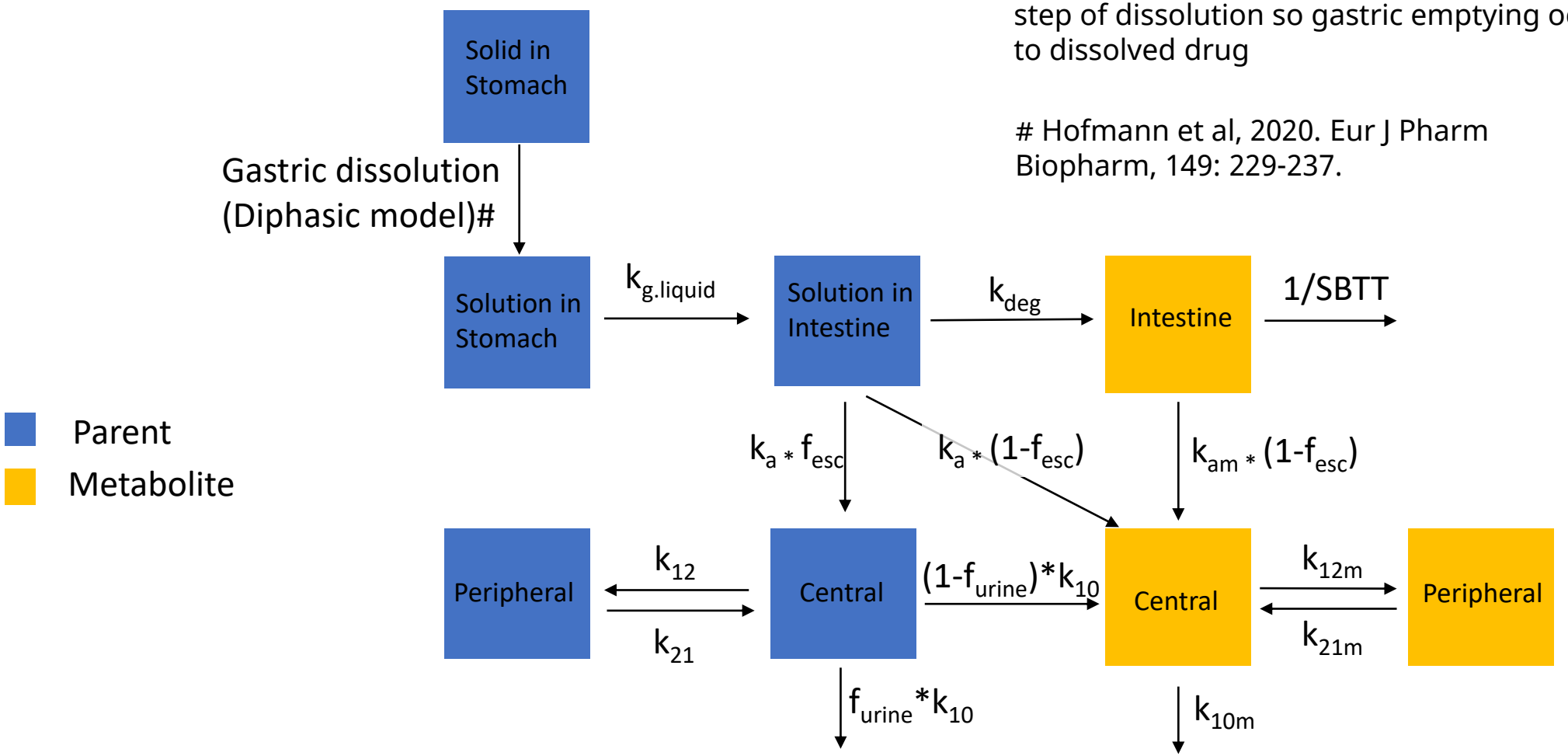


Only minor changes from before

TABLETS IN FED STATE MODEL

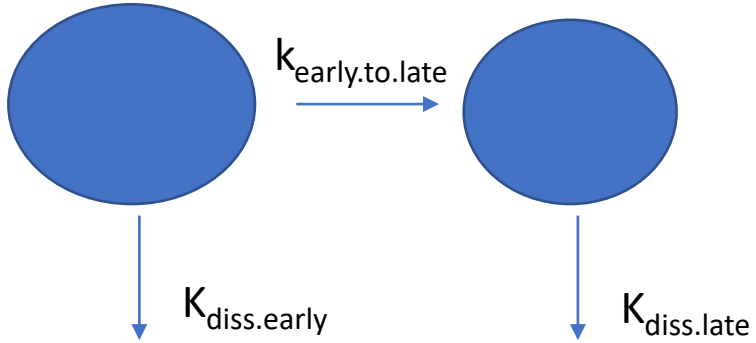
*Disintegration assumed to be rate determining step of dissolution so gastric emptying occurs only to dissolved drug

Hofmann et al, 2020. Eur J Pharm Biopharm, 149: 229-237.

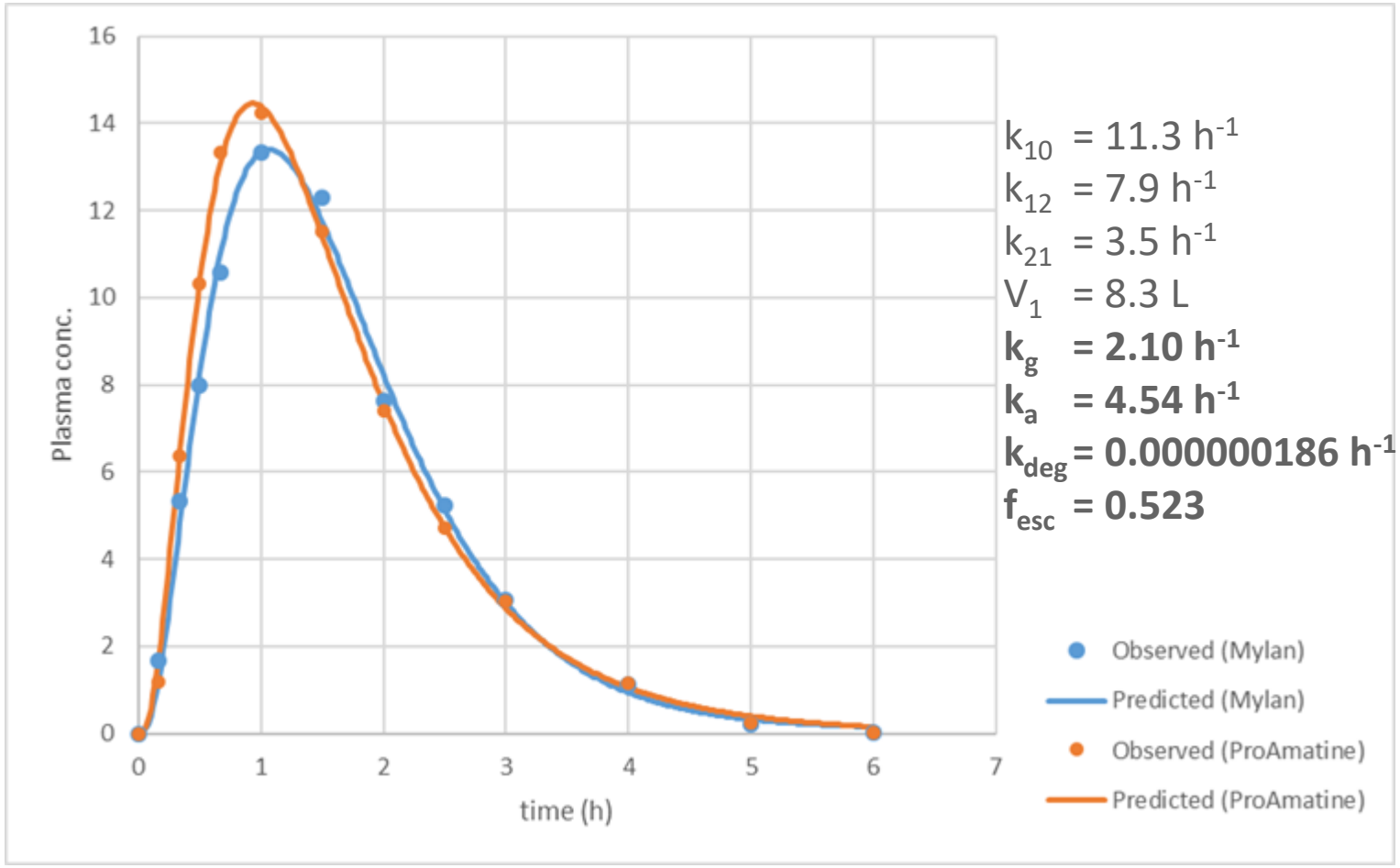


DIPHASIC DISSOLUTION

- Drug dissolution from formulation is supposed to undergo two phases: An early and a late; each with a first-order rate constant in addition to first order transfer between the phases.
- Affords great flexibility dealing with shifting dissolution conditions as well as changes resulting from e.g. disintegration and shrinking particle size without time invariance problems.



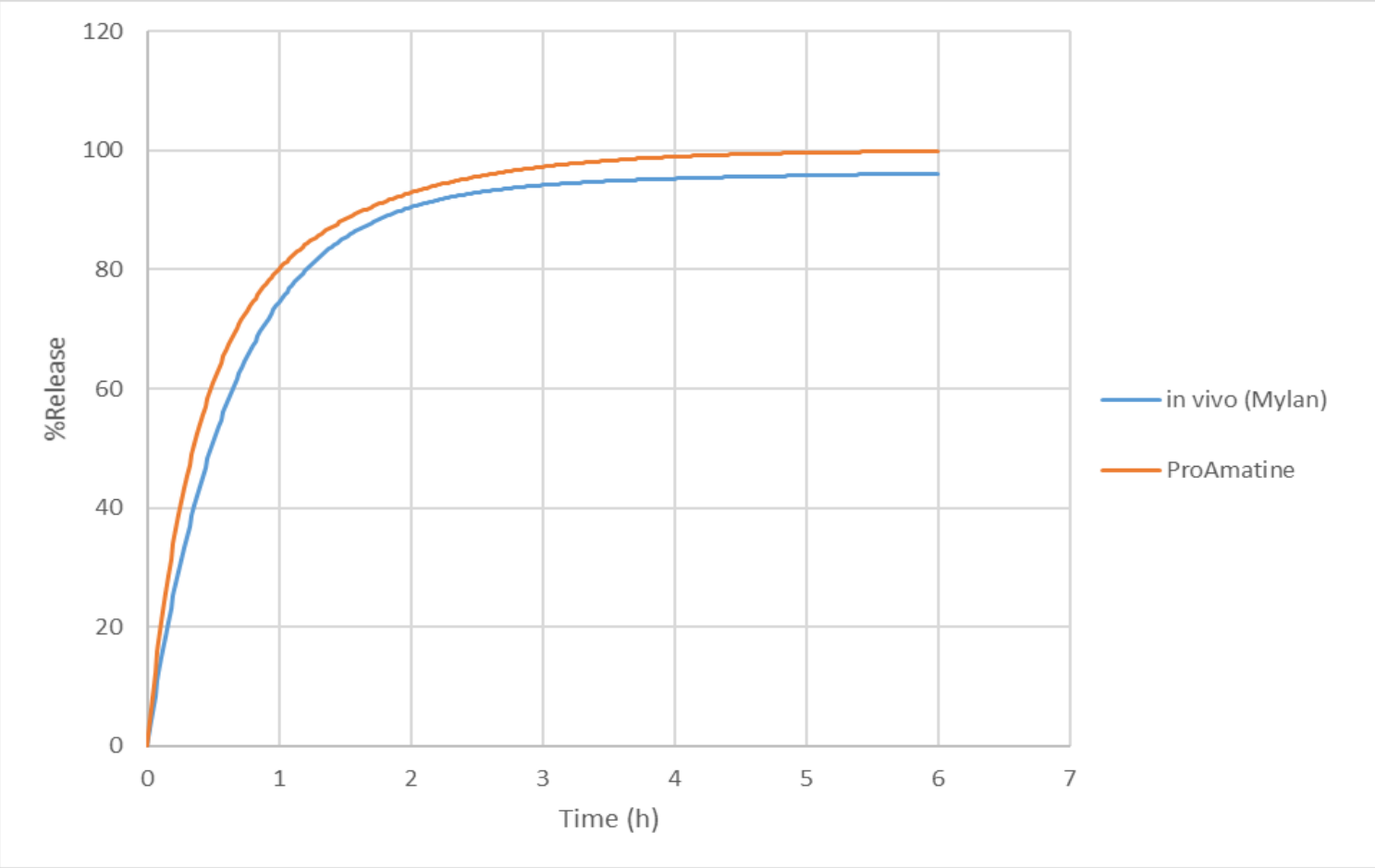
MYLAN: FED



- Food inhibits luminal hydrolysis (but little impact on gut wall or hepatic metabolism) leading to an increase in AUC.
- Probably due to competition from food peptides.
- Potential minor decrease in permeability due to this competition.
- Gastric emptying is slower but not much slower indicating the existence of the magenstrasse.

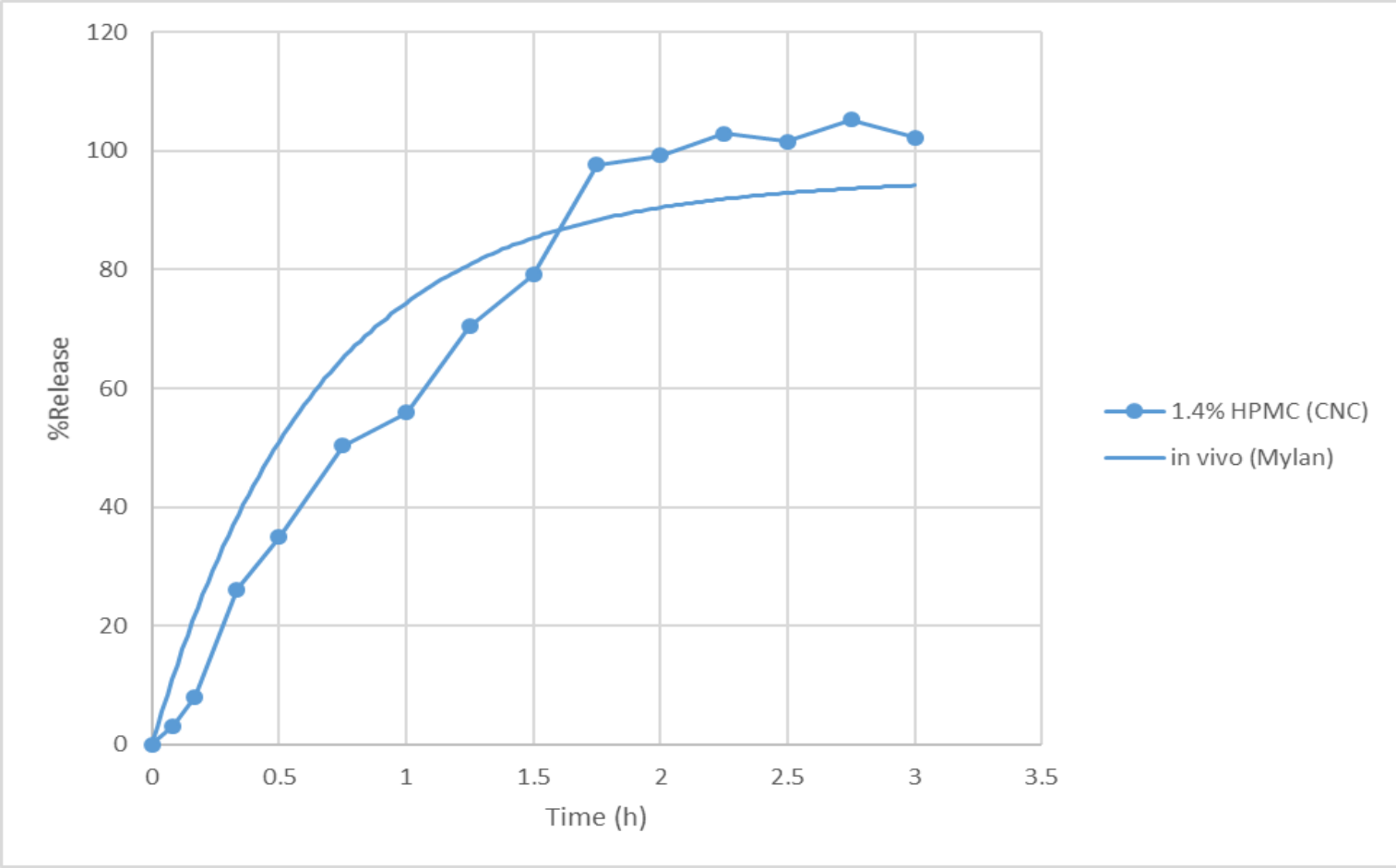
Bold means fitted; V1 was changed due to the lower body mass

IN VIVO DISSOLUTION



- However the water in this magenstrasse seems to partially mix with the food components leading to increased viscosity and slowed down dissolution.
- But not as much as complete meal homogenization would indicate.
- ProAmatine releases faster despite lack of superdisintegrant (the effect of which is discernible in vitro) → Mechanical crushing forces are important

MYLAN: IN VIVO VS IN VITRO



- Water apparently mixes with the chyme resulting in viscosity increase within the magenstrasse but not as fully as meal blending would indicate.
- Slow final portion probably caused by fraction entrapped in the most viscous regions of the meal

IN VITRO IN VIVO COMPARISON

Testing 2 different Midodrine-HCl products Dissolution profiles in CNC 3D setup:

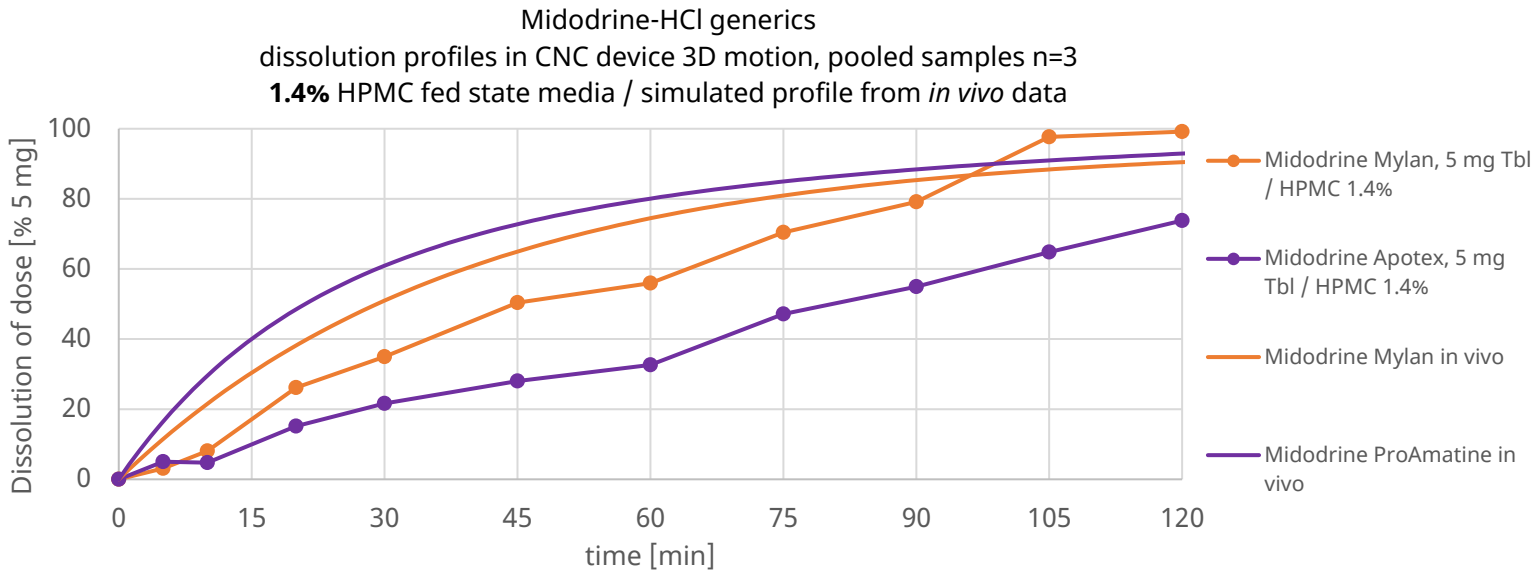
- 1.4% HPMC media discriminates between samples *in vitro*
- Less so in 1.0% HPMC media

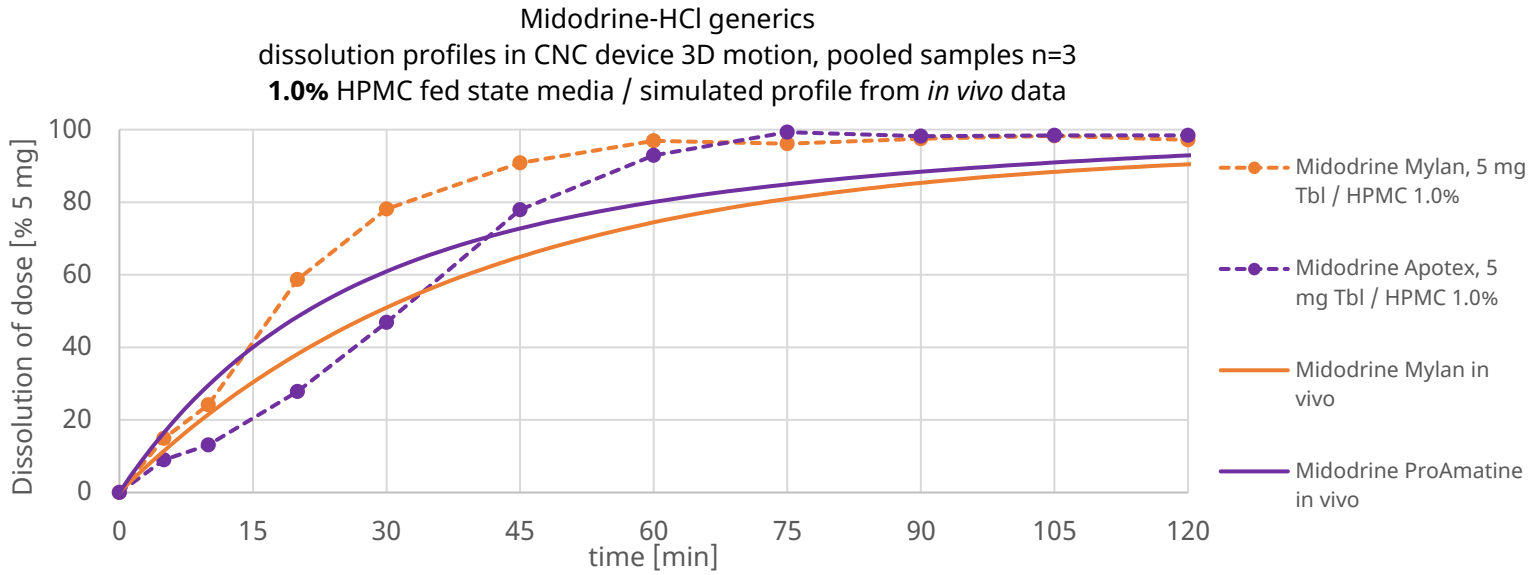
In vivo: deconvoluted profiles from *in vivo* plasma profiles

ProAmatine: same qualitative composition as Apotex

Observation: even altered viscosity doesn't fully convey the *in vivo* performance

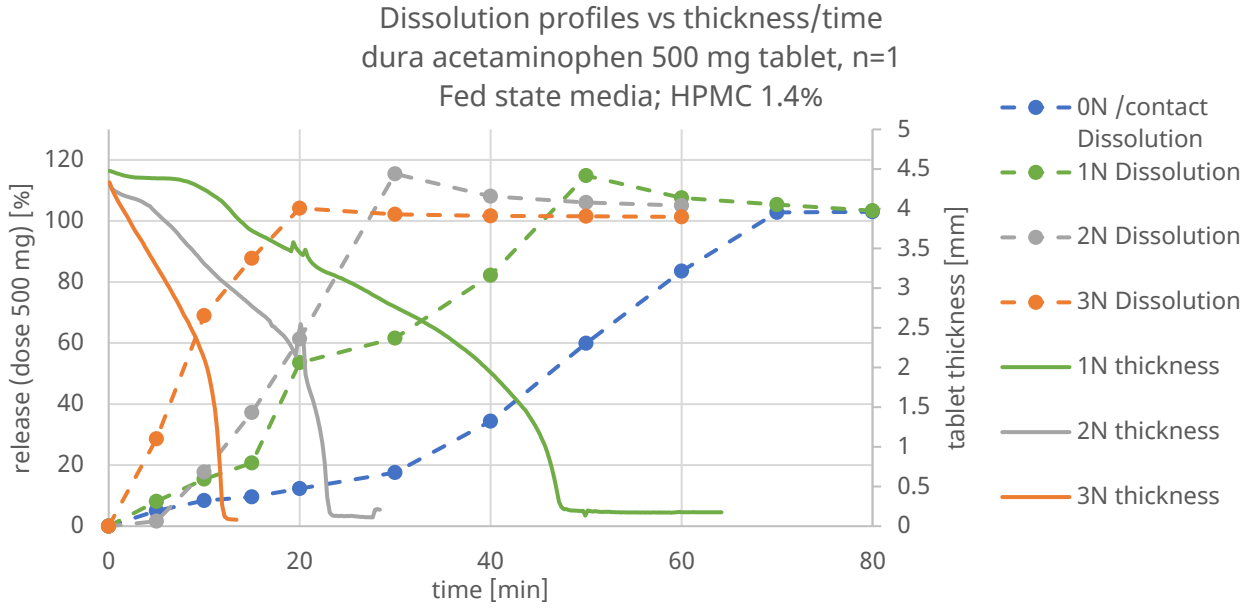
Hence, this indicates the formulation is susceptible to other factors, like **mechanical stress**

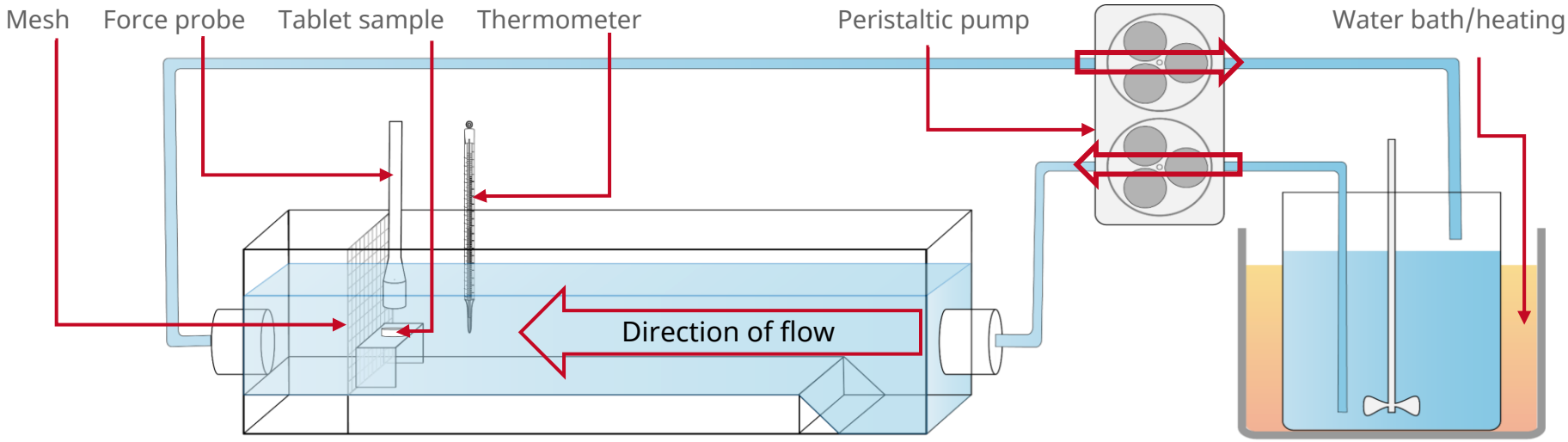




FED STATE DISSOLUTION & DISINTEGRATION TESTING INVOLVING MECHANICAL STRESS

- Development of a novel Fed State Flow Through Cell
- Probe connected to load cell exerts controlled force unto sample
- Varying flow rate, force intensity/patterns, viscosity
- Allows simultaneous disintegration and dissolution monitoring





CONCLUSION

- The fluid within the magenstrasse is viscous, but not as viscous as a completely homogenized meal
- Complete dissolution within the magenstrasse is often not likely
- The need to incorporate viscosity into dissolution testers creates challenges.
- Mechanical forces probably play an important role under viscous conditions.

ACKNOWLEDGMENTS

- Prof Peter Langguth
- Dr Thomas Nawroth
- Valentin Stahl
- Farooq Umer
- US FDA

Thank you.

Questions & Discussion

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

JG|U