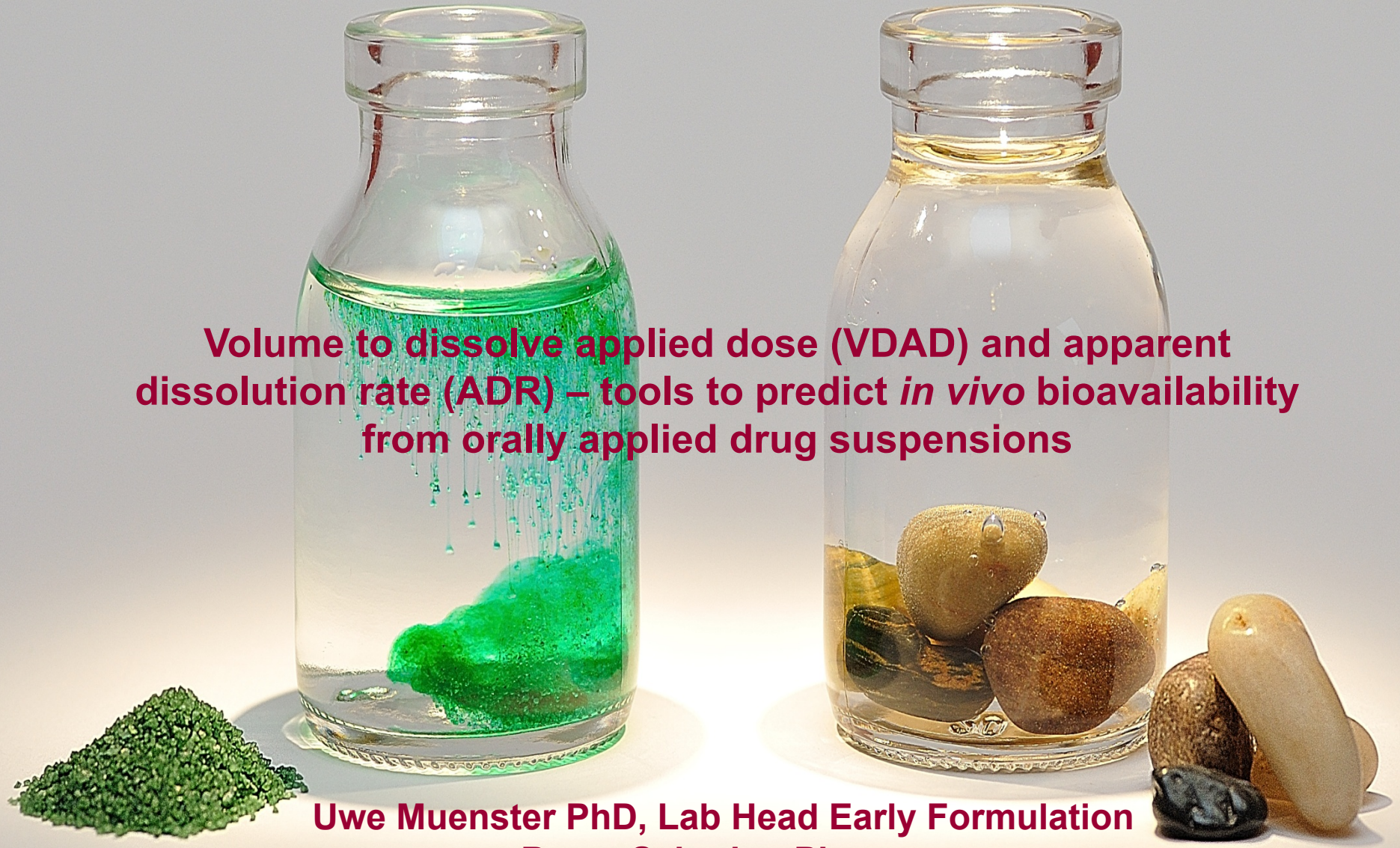
Volume to dissolve applied dose (VDAD) and apparent dissolution rate (ADR) – tools to predict *in vivo* bioavailability from orally applied drug suspensions



Uwe Muenster PhD, Lab Head Early Formulation
Bayer Schering Pharma

- Introduction
- Methods and Materials
- Results
- Summary

Bayer HealthCare
Bayer Schering Pharma

Stomach

pH: fasted, 1-3; fed, up to 7
(Dressman JB et al., Adv Drug Del Rev 59; 2007)

Half-life gastric emptying: ~ 20-40 min. (water)
(Lin HC et al. Digestive Diseases and Sciences 6; 2005)

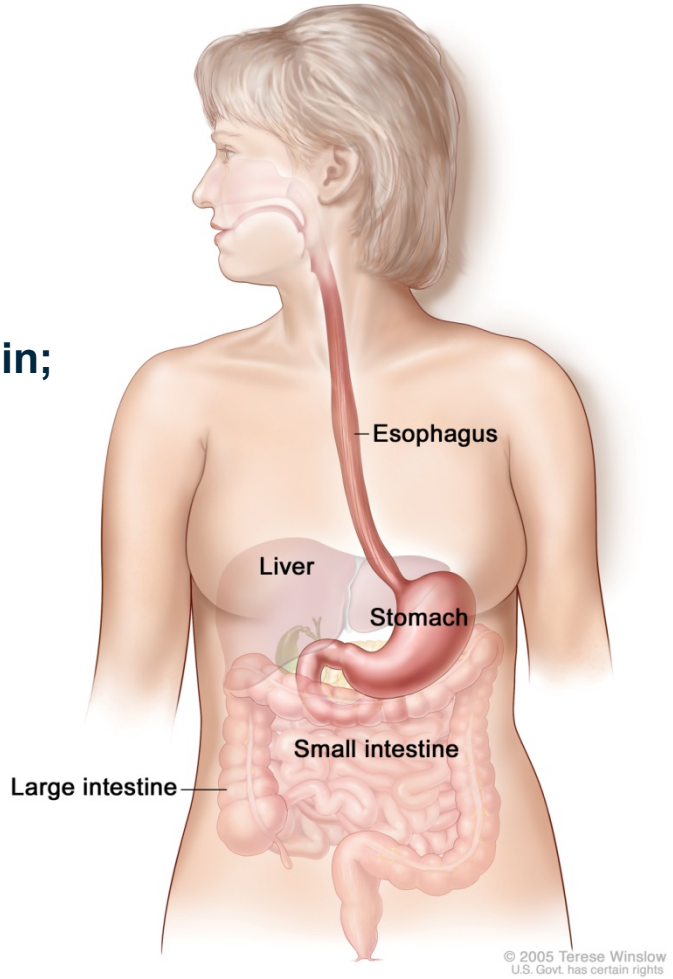
Liquid Volume: fasted, 25ml, secretion 1-2ml/min; fed, secretion 10-50ml/min
(Kong F et al., JFS 73; 2008)

Small Intestine

pH: fasted, 6 - 7.5, fed, 5 - 7.5
(Dressman JB et al., Adv Drug Del Rev 59; 2007)

Transit Time: ~ 2 - 4 hours
(Maurer AH et al. Seminars in Nuclear Medicine 4; 1995)

Liquid Volume: fasted, ~ 90 - 165 ml
Fed, up to ~ 400 ml
(Sutton SC, AAPS 11; 2009, Marciani L et al., Gastroenterology 138; 2010)



→ Orally applied compounds have to face varying conditions

Bayer HealthCare
Bayer Schering Pharma

Stomach

pH: fasted, 1-3; fed, up to 7
(Dressman JB et al., Adv Drug Del Rev 59; 2007)

Half-life gastric emptying: ~ 20-40 min. (water)
(Lin HC et al. Digestive Diseases and Sciences 6; 2005)

Liquid Volume: fasted, 25ml, secretion 1-2ml/min; fed, secretion 10-50ml/min
(Kong F et al., JFS 73; 2008)

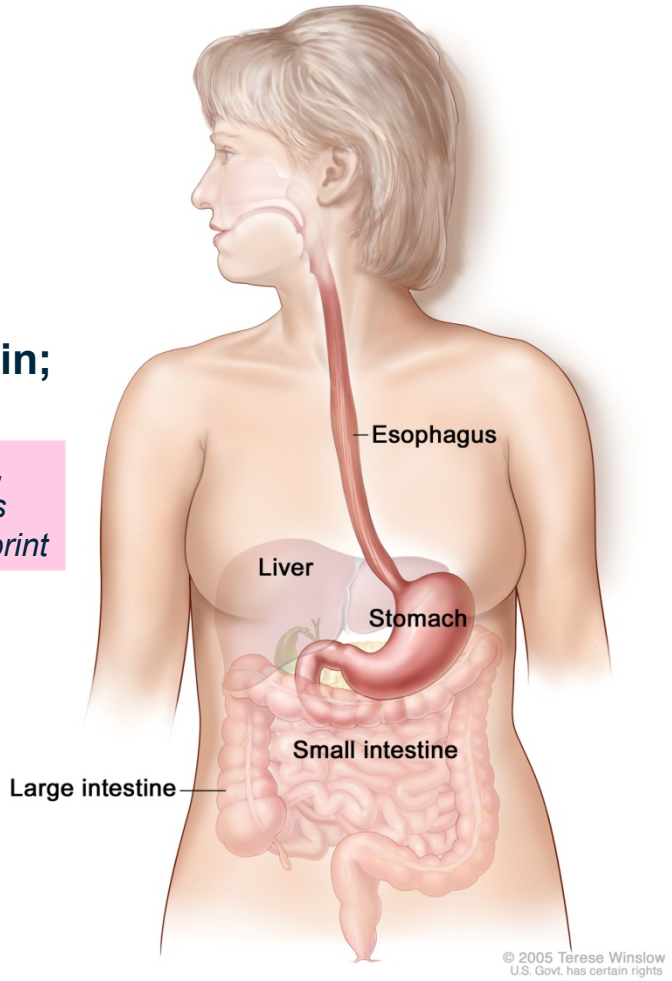
Review: Mudie DM et al., Molecular Pharmaceutics Sep 2010; ePub ahead of print

Small Intestine

pH: fasted, 6 - 7.5, fed, 5 - 7.5
(Dressman JB et al., Adv Drug Del Rev 59; 2007)

Transit Time: ~ 2 - 4 hours
(Maurer AH et al. Seminars in Nuclear Medicine 4; 1995)

Liquid Volume: fasted, ~ 90 - 165 ml
Fed, up to ~ 400 ml
(Sutton SC, AAPS 11; 2009, Marciani L et al., Gastroenterology 138; 2010)



→ Orally applied compounds have to face varying conditions

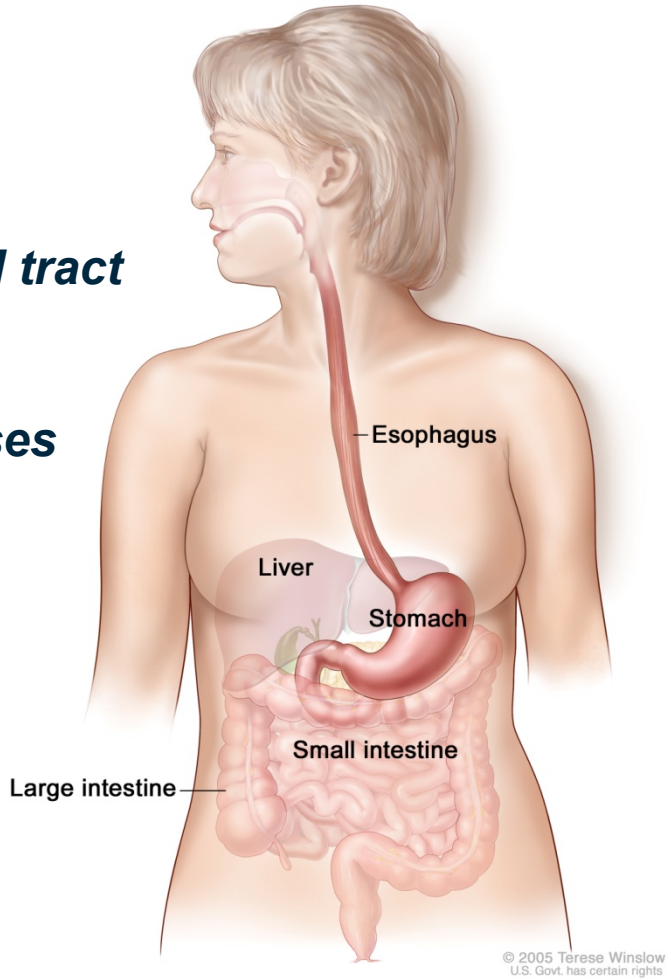
Various scenarios possible

→ *Compound not dissolving throughout entire GI tract*

→ *Compound dissolves in stomach, precipitates in intestine (crystalline?amorphous?), e.g. bases*

→ *Compound not dissolving in stomach, but dissolves in intestine; e.g. acids*

→ *Compound soluble throughout entire GI tract*

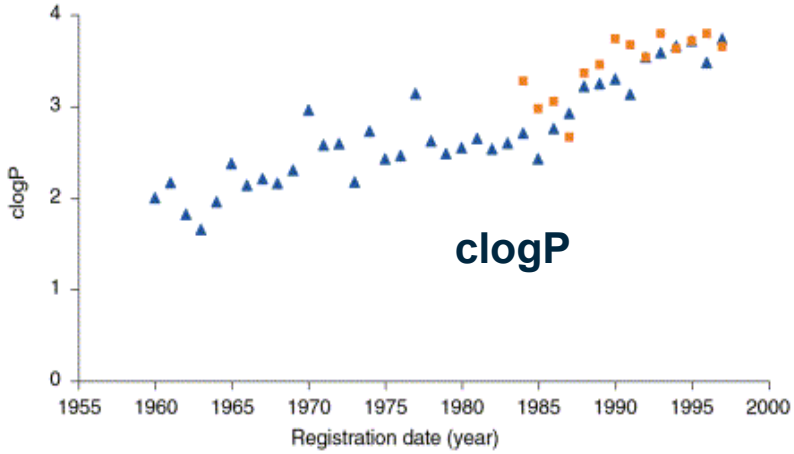


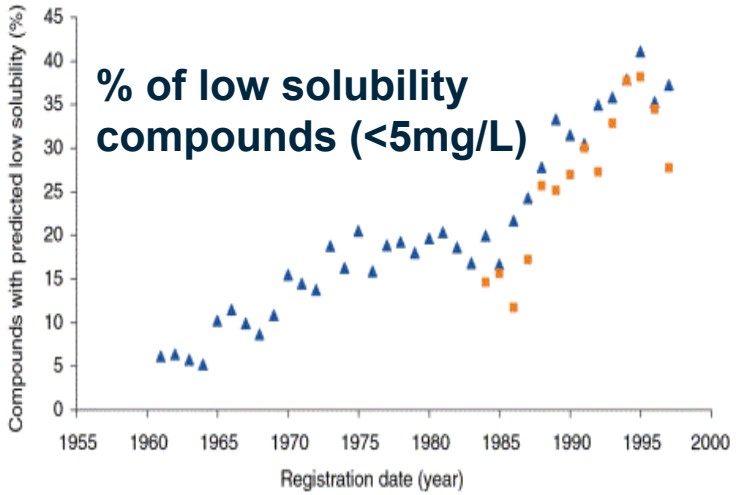
→ Varying conditions may influence dissolution, thus bioavailability

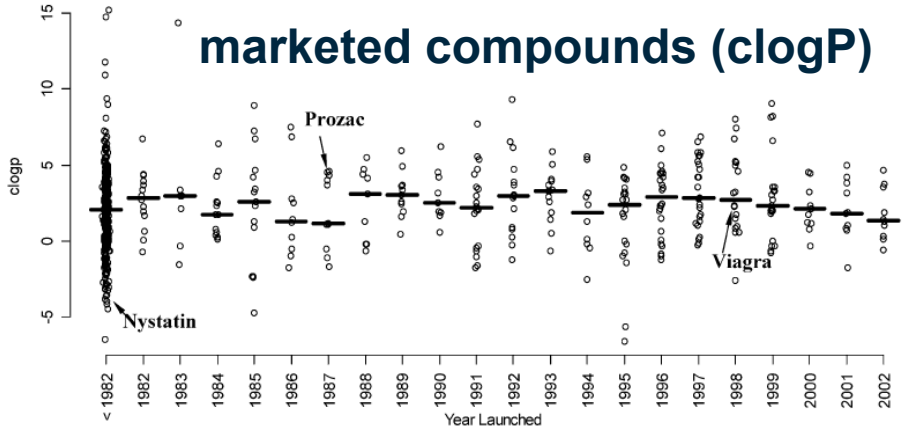
PhysChem selection pressure

Bayer HealthCare
Bayer Schering Pharma

Pfizer compound file *(Gribbon P et al., DDT 10; 2005)*





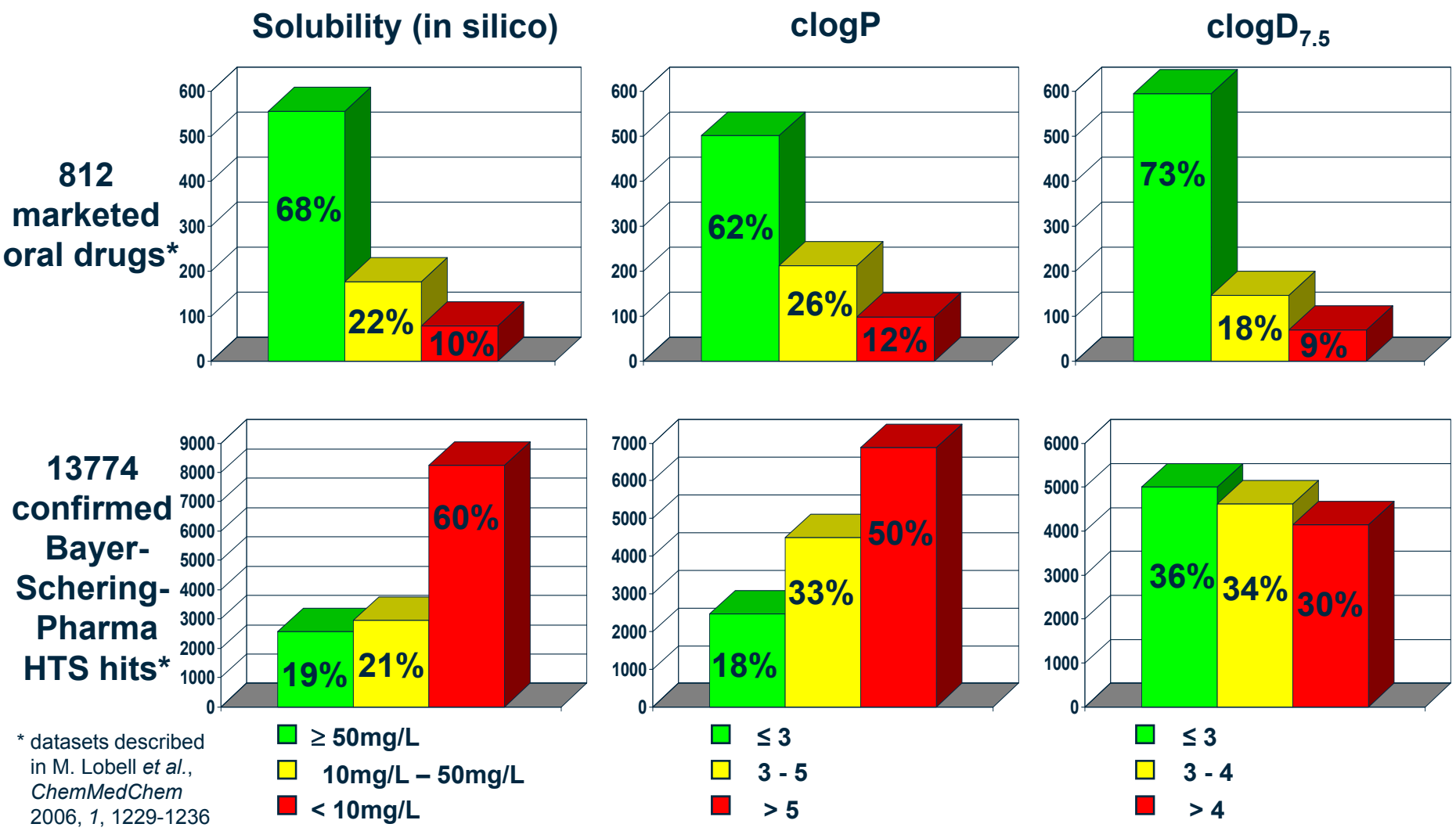


(Vieth M et al., J Med Chem 47; 2004)

→ PhysChem selection pressure increased with time

PhysChem selection pressure

Bayer HealthCare
Bayer Schering Pharma



* datasets described in M. Lobell *et al.*, *ChemMedChem* 2006, *1*, 1229-1236

→ Confirmed HTS hits at BSP show lower solubility, higher clogP, and higher clogD$_{7.5}$ when compared to oral market drugs (< Dec. 2004)

Reasons

HTS Assays performed from DMSO stock solutions

→ *concentration in assay is reflected by kinetic solubility*

Broadening of chemical space

→ *supported by launch of combinatorial chemistry*

→ *increased ligand-receptor affinity often achieved by addition of lipophilic residues*

→ *occasionally IP status*

Indication (e.g. Cancer)

→ Various matters of modern drug discovery contribute to an increase of low-solubility compounds

Problems

Difficulties in reaching sufficient multiples of exposure during animal toxicology testing

Poor absorption in humans

- → *lack of efficacy*
- → *increased risk of absorption variability (often supported by increased food effect)*
- → *increased risk of side effects with compounds of low safety window*
- → *increased cost for development of drug product (e.g. solubilization technologies)*
- → *increased cost due to respective clinical trials*

→ Solubility related absorption limitation may lead to an unacceptable risk for the patient
→ Attrition risk increased due to increased cost and decreased probability of success

Typical project team conversation

PK scientist: The oral bioavailability of solid compound in rat is really low…

Chemist: Oh no, that sucks!

PK scientist: Indeed, maybe formulation development can save the compound?

Chemist: Yeah, that sounds like a really great idea!

Form.Scient.: No way, make the compound more soluble!

Chemist (a bit displeased since he already spent 3 years on lead optimization):

´So then, how soluble do you want it?´

→ How soluble must a compound be at a given dose to ensure complete *in vivo* dissolution?

Hypothesis

Bayer HealthCare
Bayer Schering Pharma

Correlation of *thermodynamic solubility or dissolution* with oral *relative bioavailability (BA suspension vs. BA solution)* reveals thermodynamic solubility and *in vitro* dissolution data that indicate sufficient in vivo dissolution.

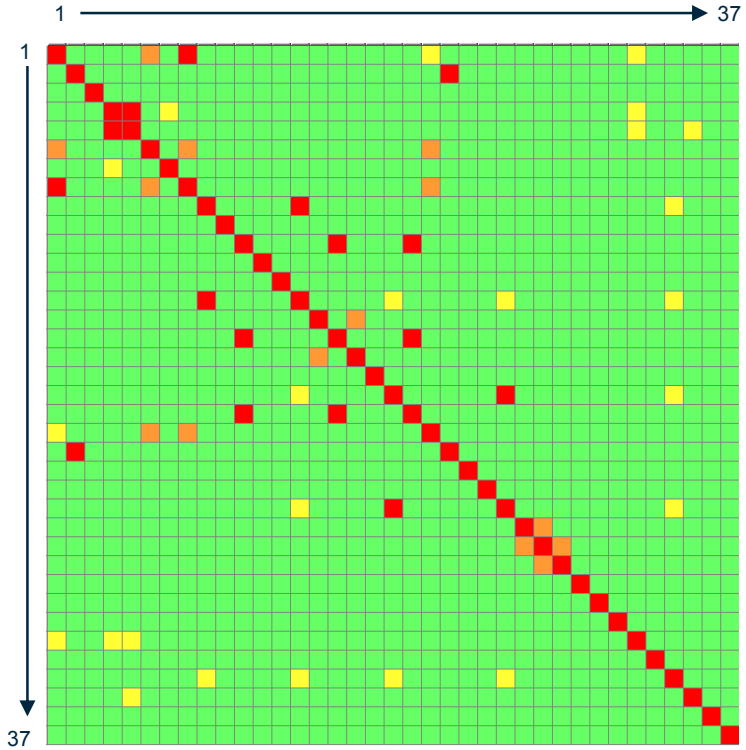
- Introduction
- Methods and Materials
- Results
- Summary

Compound Inclusion Criteria

Heatmap for the structural similarity calculated as pair-wise-Tanimoto coefficient

- **> 0.9**
- **> 0.8**
- **> 0.7**
- **< 0.7**

< 0.85 considered dissimilar



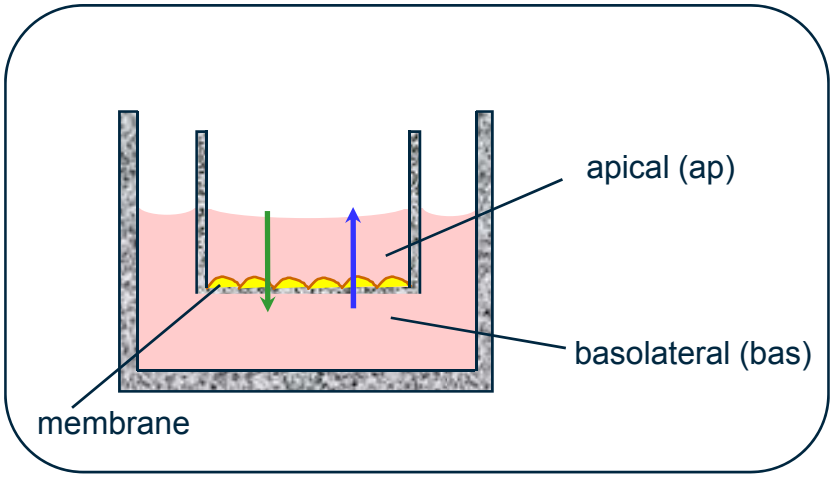
- **37 structurally diverse compounds**
- **molecular weight: 289 to 676 g/mol**
- **clogP values (BioByte™): -0.49 to 6.93**
- **topological polar surface areas (TPSA): 49.3 to 162 Å²**
- **calculated pKa values for strongest acid: -2.23 to no deprotonation**
- **calculated pKa values for strongest base: 12.4 to no protonation**

→ Structurally diverse compound set was used for studies

Caco-2 transport assay

Validated using 20 market compounds (fraction dose absorbed in humans (F_{abs}) known)

Permeability BCS classification	Fraction dose absorbed human [%]	Papp values in Caco-2 assay [nm/s]
High	≥ 90	≥ 70
Moderate	50-90	10-70
Low	< 50	< 10



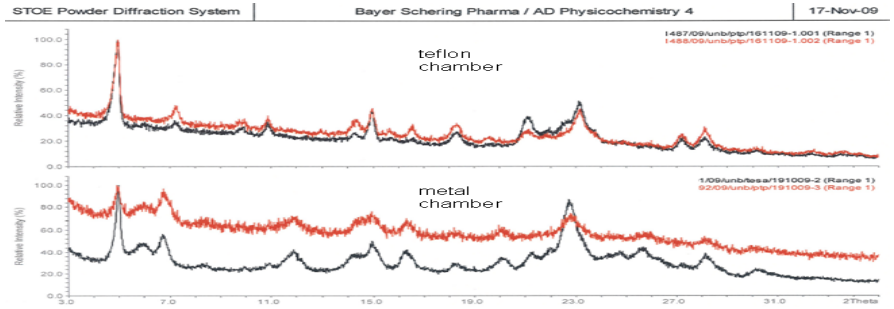
$$P_{app} = \frac{V\ (receiver) * conc.\ (receiver\ @\ 2h)}{conc.\ (donor\ @\ 0h) * surface\ area * time}$$

Efflux Ratio: P_{app} bas/ P_{app} ap

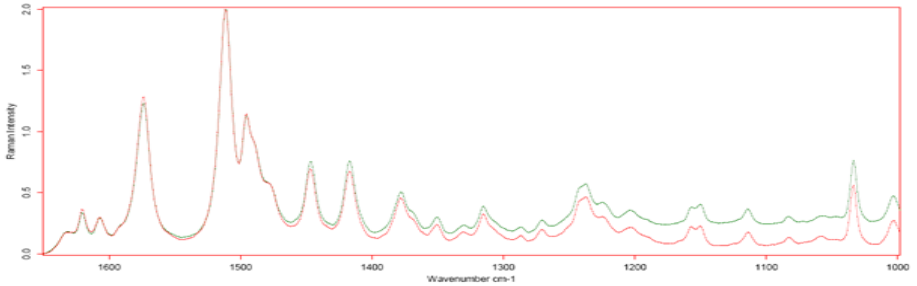
→ Compounds exhibit Papp values > 10nm/s, indicating moderate to high permeability
→ Compounds exhibit absolute bioavailabilities (solution, p.o. rat) of > 20%

Bayer HealthCare
Bayer Schering Pharma

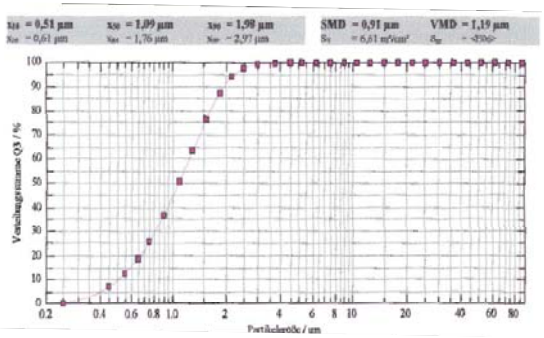
Micronization (Air Jet Mill)



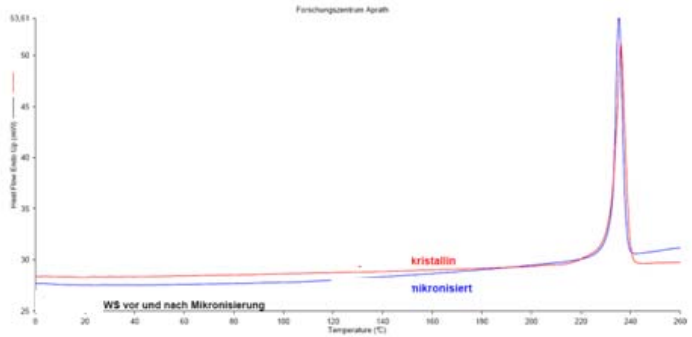
XRPD



FT-Raman Spec.



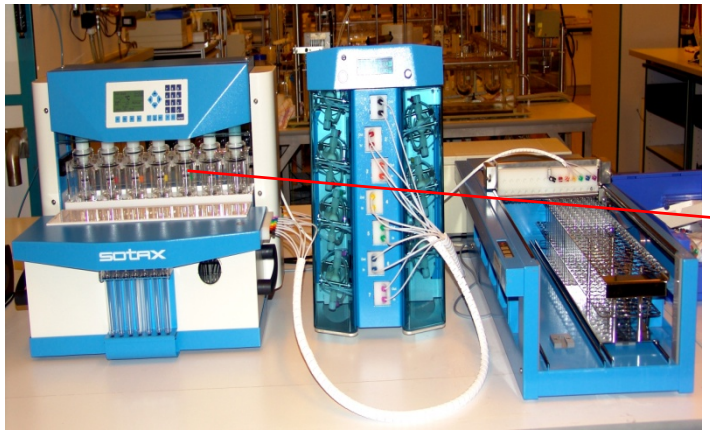
Particle Size
Ø x10, 0.7 µm
Ø x50, 2.1 µm; Ø x90, 5.2 µm



DSC

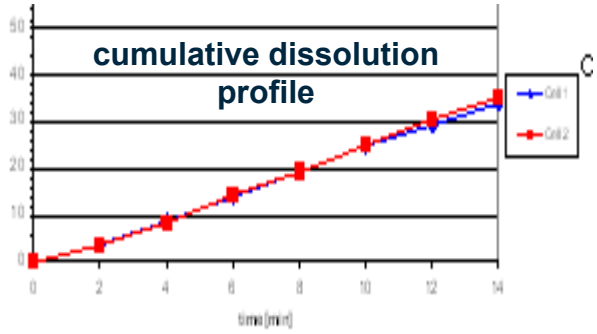
→ Particle size in the single digit micrometer range
→ Micronization had no significant influence on solid state characteristics

Apparent Dissolution Rate



Mini-Flow-Thru Cell (USP apparatus IV)

- 1 mg micronized API per cell
- Flow Rate 2 ml / min
- pH 1, 4.5, 6.8
- 2 minute fractions collected over 14 minutes
- HPLC Analytics

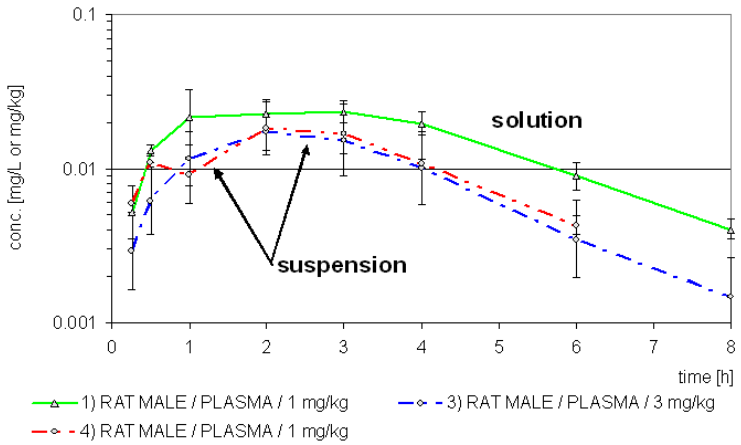


→ Apparent dissolution rate was determined using the Mini-Flow-Thru Cell
→ Thermodynamic Solubility was determined using the Shake Flask Method

Relative Bioavailability

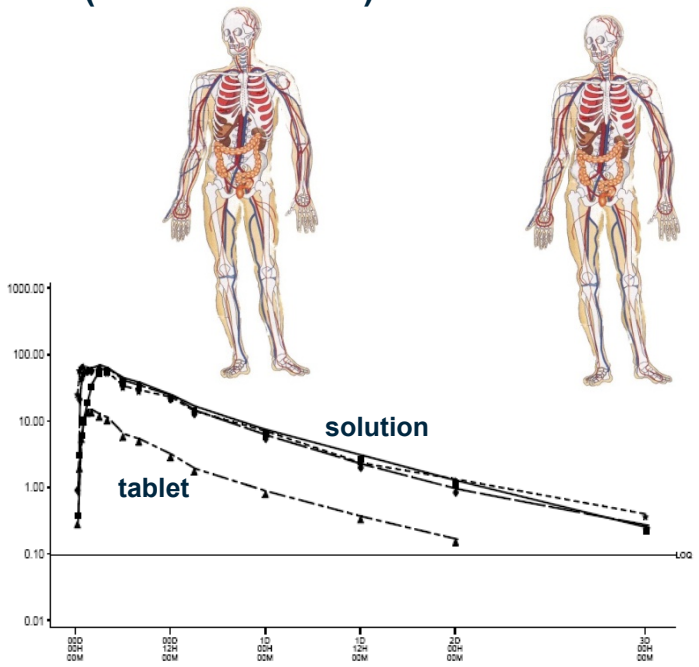
Micronized API suspension

API solution (e.g. PEG/EtOH/H2O)



Immediate release tablet (micronized API)

API solution (e.g. PEG 400)

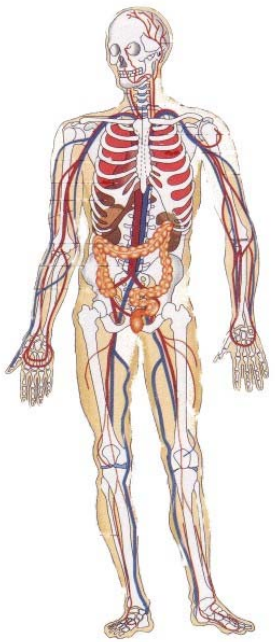


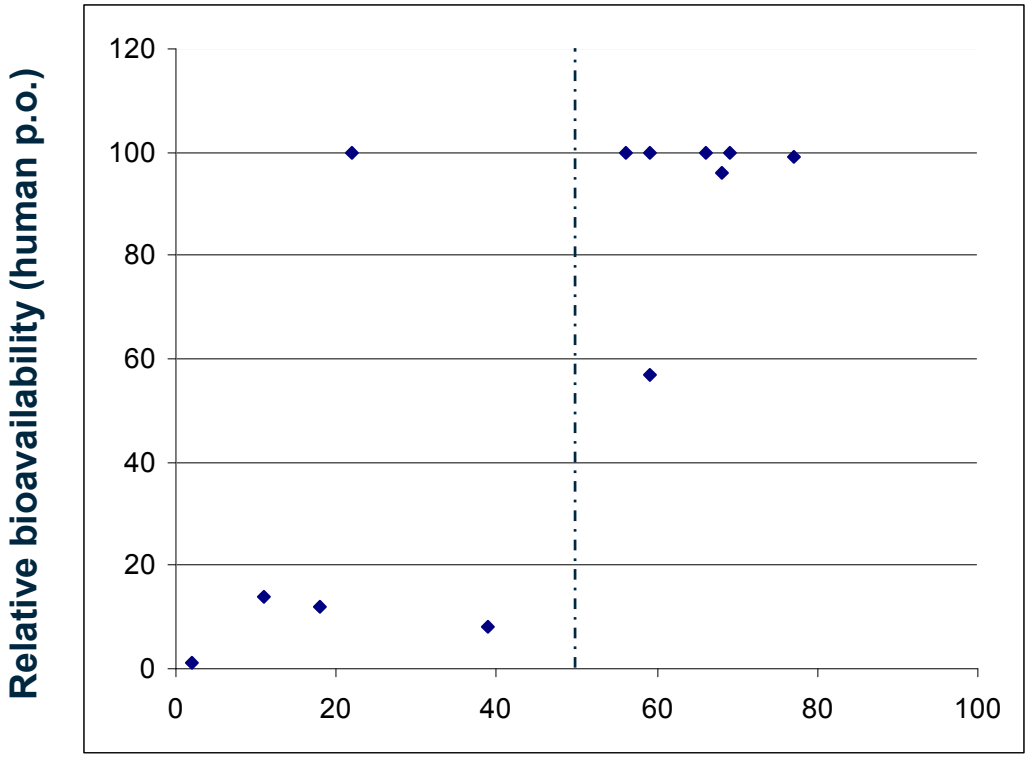
$$\frac{AUC_{norm}(suspension/tablet)}{AUC_{norm}(solution)} = \text{relative bioavailability}$$

→ **Relative bioavailability is postulated to represent *in vivo* dissolution**

- Introduction
- Methods and Materials
- Results
- Summary

Relative bioavailability rat vs. human (p.o.)



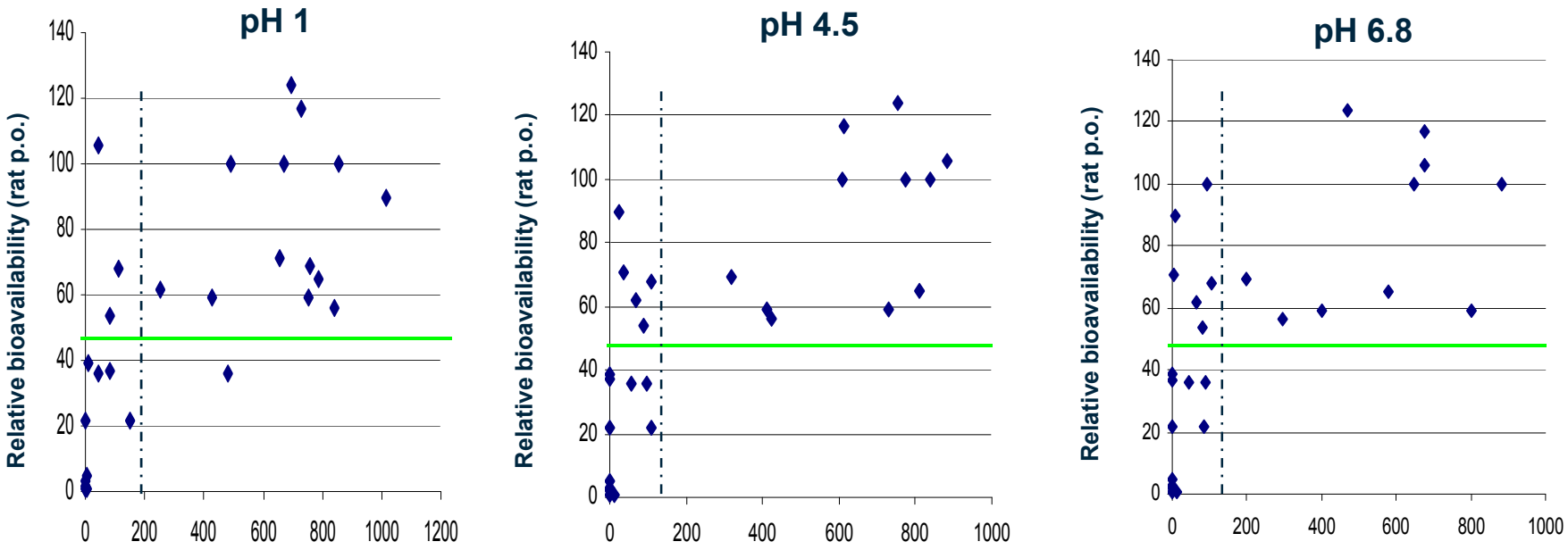


~ 50% relative bioavailability in rat is considered uncritical with respect to in vivo dissolution in human

In vitro dissolution vs. relative bioavailability (rat p.o.)

Bayer HealthCare
Bayer Schering Pharma

Rel. BA > 50% considered uncritical



Amount API [µg] dissolved after 14 minutes, flow rate 2ml/min, 37°C

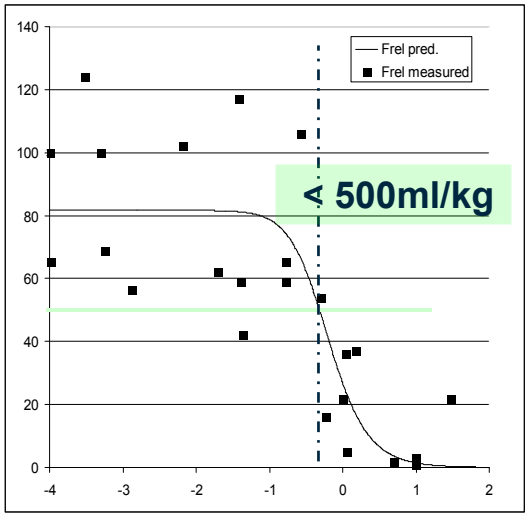
→ Relative bioavailability (rat p.o.) increases with increasing in vitro dissolution
→ Relative bioavailability (rat p.o.) > 50% is reached with ~ 150 – 200 µg API dissolved

Log Volume to dissolve applied dose vs. rel. BA (rat p.o.)

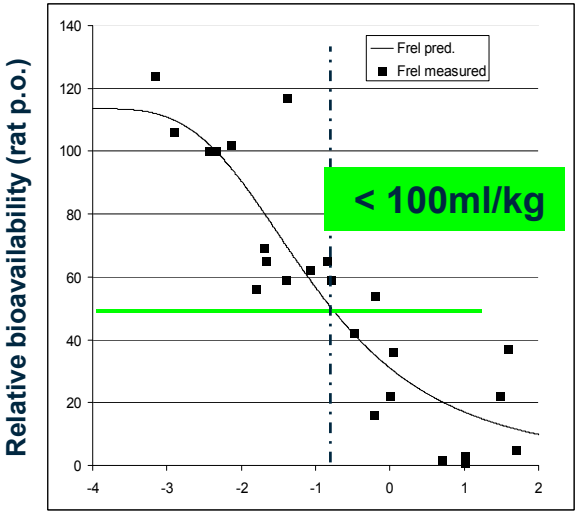
Bayer HealthCare
Bayer Schering Pharma

Rel. BA > 50% considered uncritical

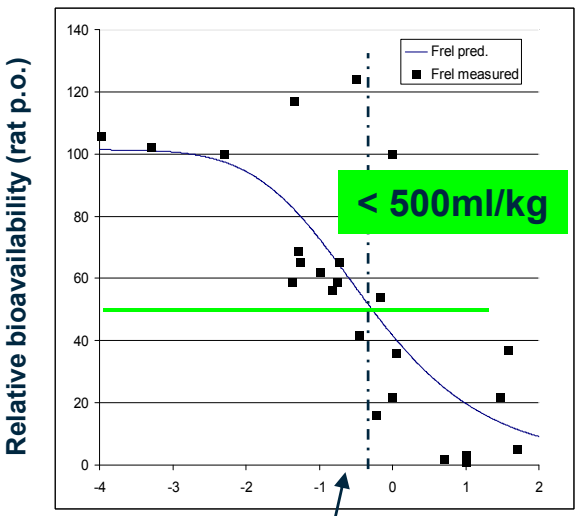
pH 1



pH 4.5



pH 7



Log (Volume to dissolve applied dose [L/kg]) @ 25°C

→ Relative bioavailability (rat p.o.) > 50% is reached with ´volumes to dissolve the applied dose´ of < 100 ml/kg (pH 4.5) and < 500 ml/kg (pH 7)
→ Correlation @ pH 1 is of limited predictive value: gastric pH in rat is 3.8 - 5

Example: dose 10mg/kg; solubility @ pH 7: 40 mg/L

$$\text{Lg VDAD} = \lg \frac{\text{dose}}{\text{solubility}} = \lg \frac{10\ \text{mg/kg}}{40\ \text{mg/L}} = \lg 0.25\ \text{L/kg} = -0.60 = \sim \underline{60\%\ \text{rel. BA}}$$

Current Solubility Evaluation

Bayer HealthCare
Bayer Schering Pharma

Example: dose 10mg/kg; solubility @ pH 7: 40 mg/L

´When the dose/solubility ratio is > 1000 ml, even in the presence of favorouble psysiological factors (pH, bile salts), the solubility is likely to cause problems with bioavailability.´
(Dressman JB et al., Clin Pharmacokinet 47; 2008)

Dose/solubility ratio: 17.5L

´Compounds with aqueous solubilities of < 100mg/L often present dissolution limitations to absorption.´
(Hörter D et al., Adv Drug Del Rev 46; 2001)

Solubility of 40 mg/L

A solubility of 10 - 100 mg/L received a medium risk (´0´, on a ´+, 0, -´ scale) in the Aventis PhysChem Score card
(Balbach S et al., Journal of Pharmaceutics 275; 2004)

+ (low risk)

→ Current estimates of critical solubility values that would dictate absorption limitation appear to be rather conservative

Data in view of BCS classification

Bayer HealthCare
Bayer Schering Pharma

Biopharmaceutics Classification System (BCS):
´A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5´

Class 1: High Solubility – High Permeability
Class 2: Low Solubility – High Permeability
Class 3: High Solubility – Low Permeability
Class 4: Low Solubility – Low Permeability

Compound	Thermodynamic Solubility [mg/L] @ 25°C							
	pH 1	pH 4.5	pH 7	Daily dose [mg]	Volume to dissolve daily dose at worst case pH [L]	P_{app} A-B Caco-2	Prelim. BCS classification	Rel. BA
1	>10000	4466	9.4	210	22.3	22	4	124
2	26	24	22	70	3.18	55	4	117
3	1.1	250.6	2547	21	19.1	429	2	106
4	> 10000	215	< 1	70	> 70	42	4	100

→ Complete in vivo dissolution despite ´class 2/4´ according to BCS classification
→ BSC classification might be too strict

- Introduction
- Methods and Materials
- Results
- Summary

Summary

- In vivo dissolution was described by means of relative bioavailability (solution vs. suspension, p.o.)
- A diverse set of 37 compounds with Papp > 10 nm/s and > 20% F (rat) was used to perform in vitro/in vivo correlation of dissolution
- A relative bioavailability in rat (p.o.) of 50% was assumed to be rather uncritical with respect to in vivo dissolution in humans
- Apparent dissolution rates of ~ 150-200 µg/14 minutes (under respective assay conditions) result in relative bioavailability > 50% (rat p.o.)
- Volumes to dissolve applied dose of ~100 ml/kg (pH 4.5) – 500 ml/kg (pH 7) result in relative bioavailability > 50% (rat p.o.)
- Data provide guidance for medicinal chemists during the lead optimization phase

Thanks to all my dear colleagues!

Bayer HealthCare
Bayer Schering Pharma

Pharmaceutical Development

T. Backensfeld, A. Ohm
C. Pelzetter, S. Burkert
C. Prümper, J. Freundlieb
A. Hornig, J. Borczuch
G. Winter

Research Pharmacokinetics

J. Keldenich, K. Lustig
J. Schumacher, K. Engel
S. Greschat, K.H. Schlemmer
M.J. Gnoth

Chemical Development

H. Mueller, T. Kuhlmann
A. Grunenberg

Clinical Pharmacokinetics

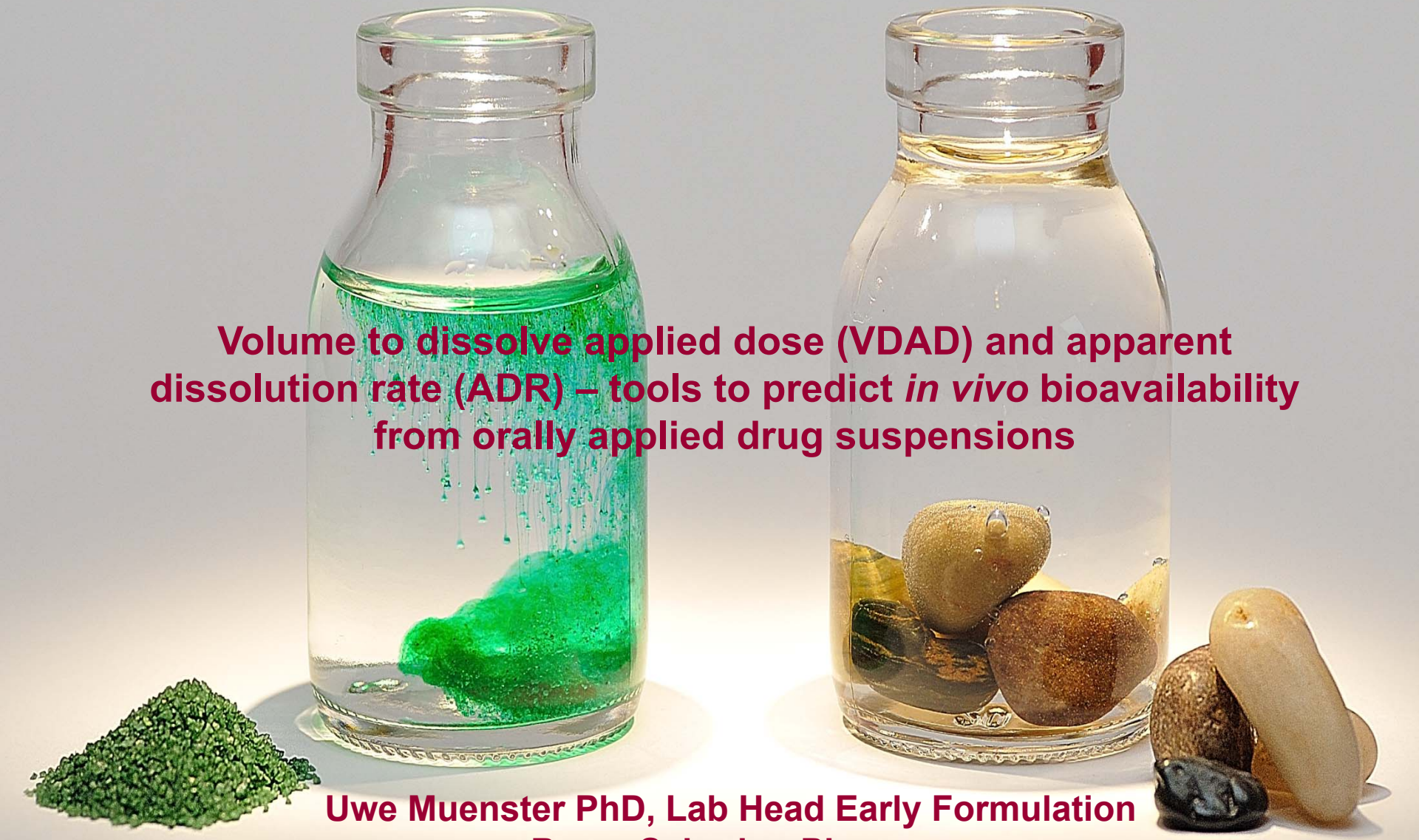
G. Ahr, W. Mück

Computational Chemistry

A. H. Göller, M. Lobell

Thanks for your kind attention!

Bayer HealthCare
Bayer Schering Pharma



Volume to dissolve applied dose (VDAD) and apparent dissolution rate (ADR) – tools to predict *in vivo* bioavailability from orally applied drug suspensions

Uwe Muenster PhD, Lab Head Early Formulation
Bayer Schering Pharma