Early *in silico* & *in-vitro* prediction of oral drug absorption and implication on formulation development

Prof. Dr. Martin Kuentz
University of Applied Sciences Northwestern Switzerland
Institute of Pharma Technology,
Gründenstr. 40, CH-4132 Muttenz
martin.kuentz@fhnw.ch

Outline

I. Biopharmaceutical classification tools for early development

II. Physiologically-based PK models (PBPK)

III. Towards model improvement in the fields of drug precipitation and lipid drug delivery

Focus on early development phase

Ref. Rang & Vasella 2006

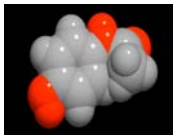
I. Biopharmaceutical classification tools for early development

- **Scope in pharmaceutical profiling & early development**
  - Anticipate drug absorption hurdles
  - Identify viable formulation principles
  - Allocate resources for development of a formulation

anticipate issues "along the road"

Anticipate drug absorption hurdles

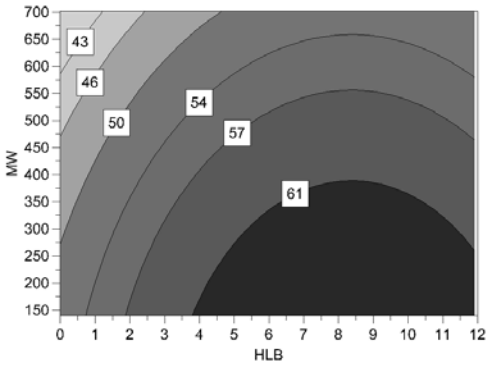
- **A first impression of a new drug candidate can be obtained from the "rule of five" (Lipinski)**
  - Not more than 5 H-bond donors
  - Not more than 10 H-bond acceptors
  - MW less than 500
  - cLogP less than 5
- **We can further inspect the polar surface area (PSA)**
  - Is calculated from the sum of all polar groups
  - Not more than 1.4 nm^2



- **Number of rotatable bonds was considered (Veber et al 2002)**

More recent work

- **Partial least square (PLS) models can be made with respect to the fraction absorbed or even oral bioavailability**
- **It is interesting to concentrate on the chemical space of poorly soluble drugs → importance of further parameters identified for oral BA e.g. solubility parameter and HLB**

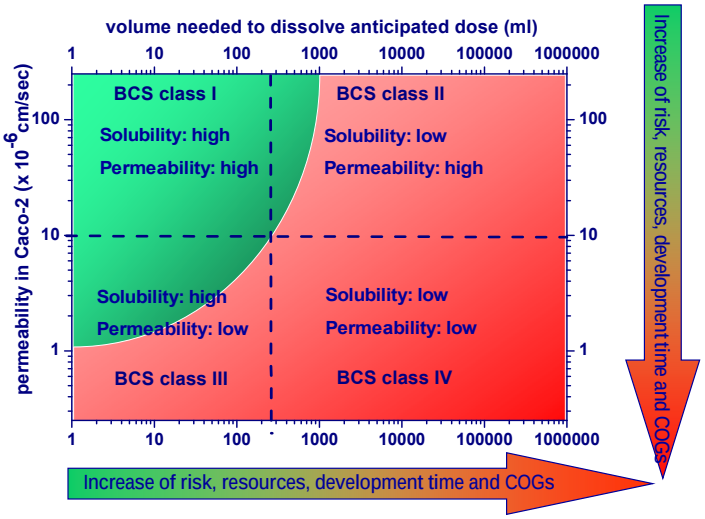


Ref. Kuentz & Arnold PDT, 2009

Limits of any molecular property-based rule

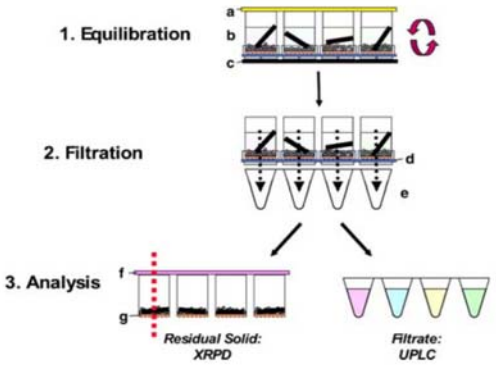
- The predictively of such models (Q^2) is often quite limited
- We should keep in mind that the primary use of molecular property rules is the selection of a drug candidate
- Alternatively, the Biopharmaceutical Classification System (BCS) is often used in an early phase as formulation risk tool (even though this is not the original use of BCS)

Slightly adapted BCS



Getting data of solubility and permeability from parallel testing

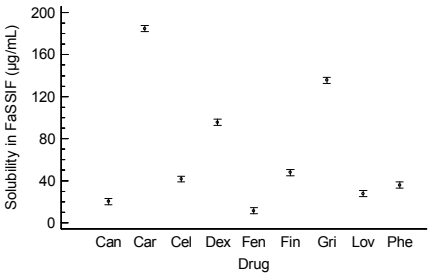
- **Permeability data from PAMPA (Kansy et al., 1998) or Caco2 assay in 96 well format (Alsenz and Haenel, 2003)**
- **Interesting new solubility assay (control of residual solid):**

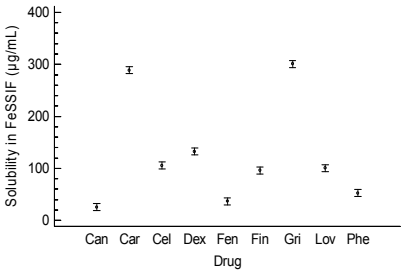


Ref. Wyttenbach et al., Pharm. Res. 2007

Solubility should be tested in biorelevant media

Ref. Schwebel et al., 2011



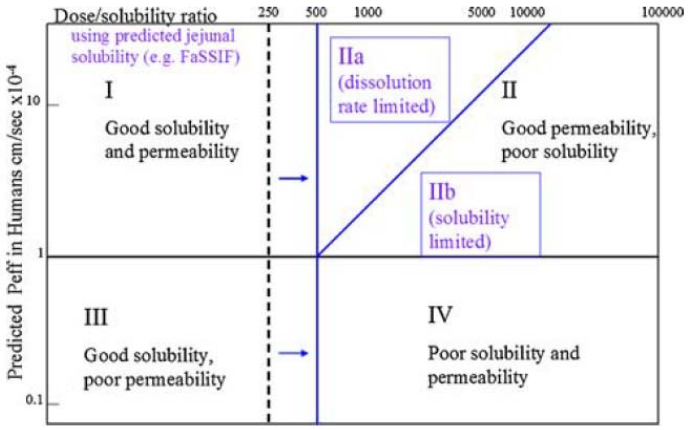


$$S_{Fa} \cong S_{W\,6.5} + \kappa_{Fa} \cdot Cs_{Fa}$$

$$S_{Fe} \cong S_{W\,5.0} + \kappa_{Fe} \cdot 5Cs_{Fa}$$

- **The apparent solubilizing capacity κ is characteristic for the drug and the type of mixed micelles. FaSSIF and FeSSIF exhibited different values of κ**

Developability Classification System (DCS)



Ref. Butler & Dressman, JPS 2010

Differentiation of class II

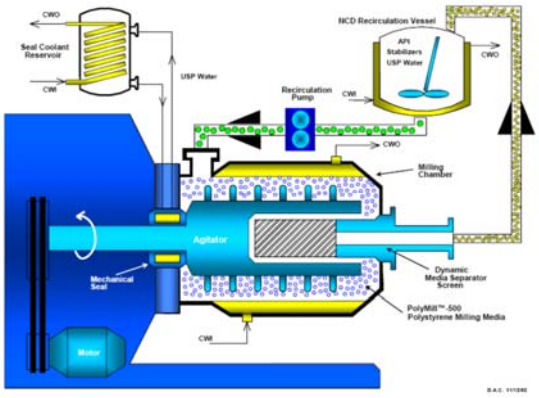
- **Differentiation in class II is meaningful because some standard formulations might cope with "dissolution limited absorption". Examples:**
  - High-shear granulation with hydrophilic excipients
  - Granulation with dissolved surfactant in the added liquid (high-shear or fluid bed)

In case of IIb, we need “enhanced formulation principles”

Ref. Nano spray dryer B90, Buchi, Switzerland

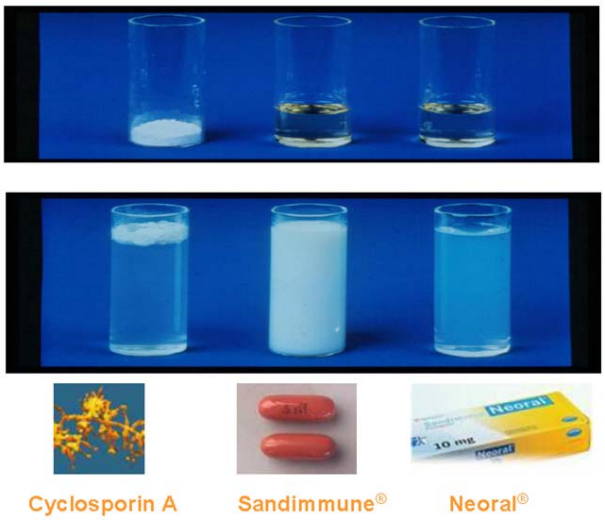
- **Solid dispersions or amorphous drug formulations can be obtained from hot melt extrusion or spray drying**

Alternative formulation principle is based on drug nano suspensions



- **Nano suspension can be obtained from wet- milling (“top-down”) and further processing might take place in a fluid bed or high-shear mixer**

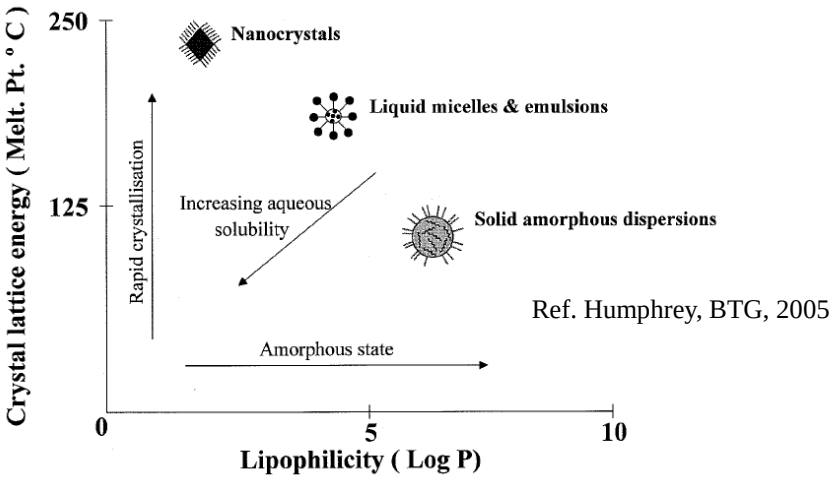
Example of a lipid-based drug delivery system to cope with a class IIb drug



Cyclosporin A Sandimmune® Neoral®

Ref. Novartis

Which "enhanced formulation principle" should be selected based on physical API properties

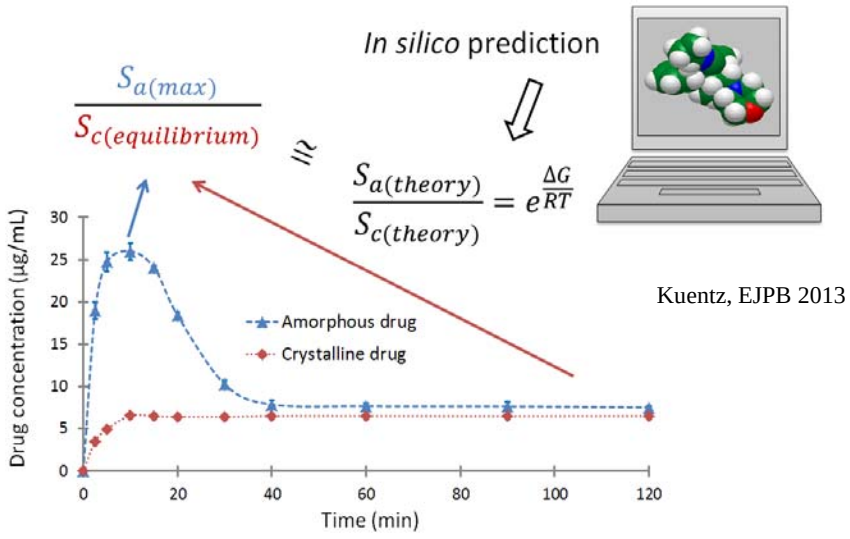


Ref. Humphrey, BTG, 2005

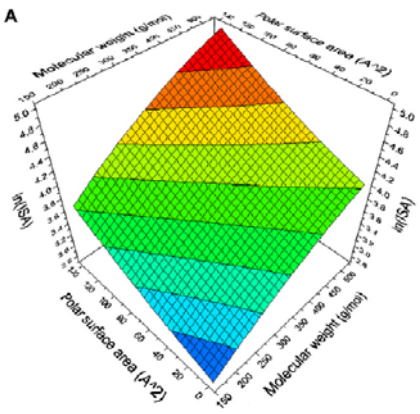
Are there molecular properties rules for selecting formulation principles?

- **We learned about property-based rules for the selection of drug candidates**
- **However, some candidates may be rescued by proper formulation technology**
- **Can we early on roughly estimate the potential of a formulation principle for a new compound based on molecular property rules?**

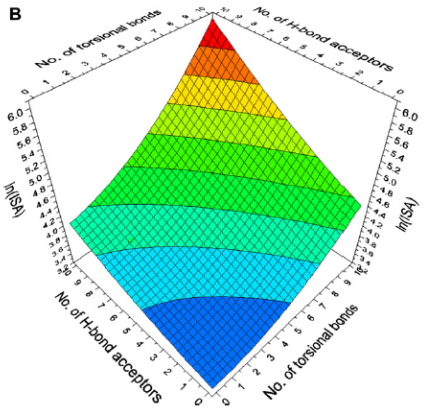
A recent work focused here on the solubility gain from amorphous formulations



Kuentz, EJPB 2013



Natural log. of the *in silico* amorphous solubility advantage, ln(ISA)

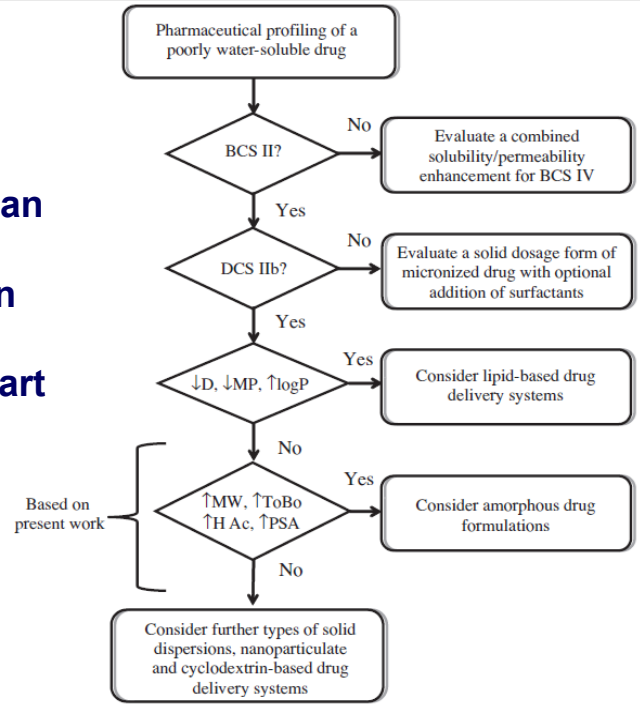


No. of H- Bonds and torsional bonds as continuous variables for modeling purpose

Martin Kuentz

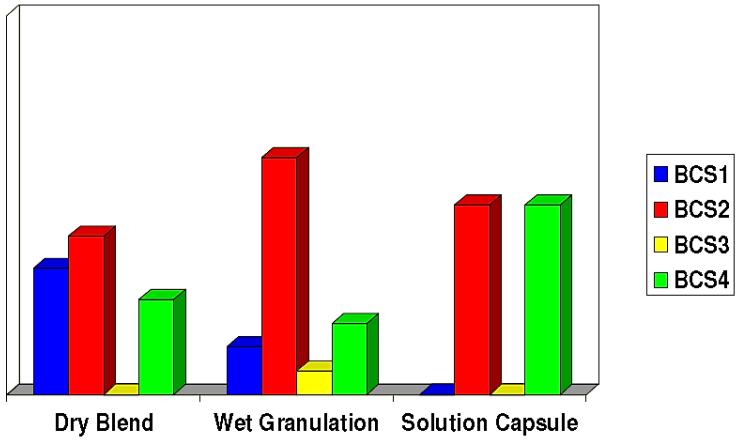
n|w University of Applied Science School of Life Sciences

Proposal of an early formulation principle selection chart



Martin Kuentz

Which formulation techniques are typically selected for Ph.1 clinical studies?



Ref. S.Ku, AAPS 2010

Conclusion of the first part

- **Molecular property are primarily intended to select drug candidates**
- **New is to anticipate the best formulation principle for a given drug**
- **The proposed formulation selection flow-chart makes use of the "Developability Classification System (DCS)"**
- **More guidance requires better tools such as Physiologically-Based Pharmacokinetic (PBPK) modeling**

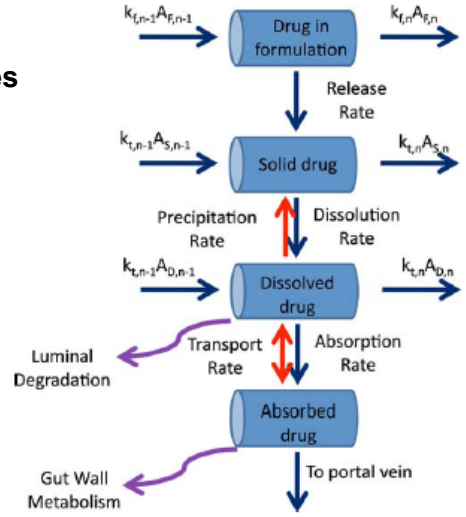
II) Physiologically-based PK models (PBPK)

- **Simple equilibrium concepts such as BCS or DCS are limited in their biological relevance**
- **Physiologically-based pharmacokinetic models are mechanistic models of drug absorption**
- **Large set of diff. equations used to model the amount of drug that is released, solubilized and absorbed in the different segments of the GI- tract**

Identification of drug absorption hurdles

- **Different software packages are available, e.g.,**
  - GastroPlus™
  - PK-SIM®
  - SimCyp®

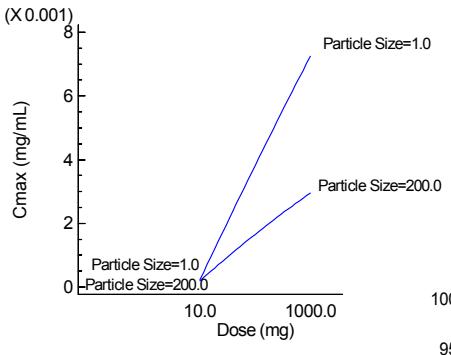
→ Identify drug absorption hurdles

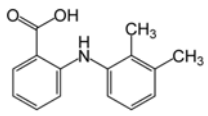


Ref. Jamei et al., 2009

Example: mefenamic acid as model drug

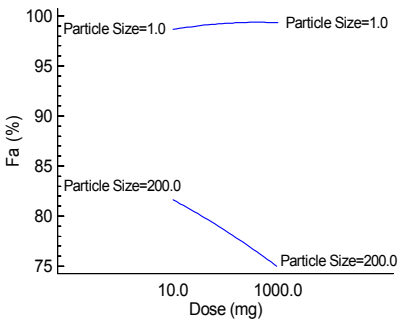
- **Phys. chem. and PK parameters are best determined from experiments (e.g. solubility values from experiments in simulated intestinal fluid)**
- **Model should be first compared with *in vivo* data (animal experiments in early development) → only then a prediction should be dared**
- **More important than absolute values is the sensitivity of the prediction to changes in the input parameters**
- **We used the plug-flow and dispersion model (PK- SIM)**





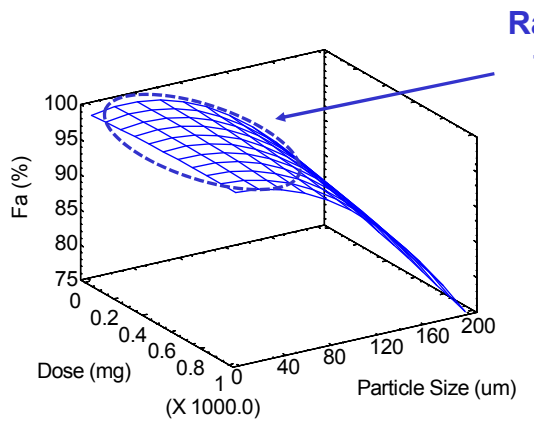
Look for interactions within relevant factor ranges

Effect of particle size depends on the dose



Kuentz, AAPSJ 2008

Response surface of the fraction absorbed



Key strengths of PBPK drug absorption prediction in early development

- **Strengths:**
  - PBPK models indicate how critical the absorption step is
  - Sensitivity of responses to changes of input parameters can be studied (parameter sensitivity analysis) → study parameters such as dose, particle size, solubility or permeability can guide formulation development

- **Weaknesses:**
  - 1) Incertitude of input parameters (especially in early development)
  - 2) Lack of model adequacy concerning some mechanistic processes. Two examples are a) drug supersaturation/precipitation and b) the fate of lipid formulations

III) Towards model improvement in the fields of drug precipitation and lipid drug delivery

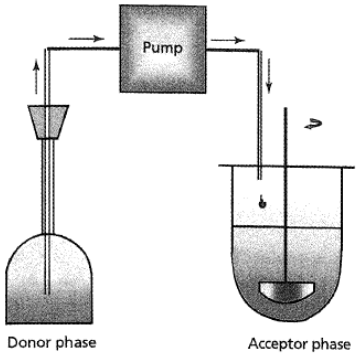
- **A solution that keeps a drug dissolved or a simple solid formulation can nowadays be modeled adequately**
- **However, some aspects are still topics of active research**
  - a) Supersaturation and drug precipitation
  - b) Fate of lipid-based formulations
  - (Role of transporters and how they are influenced by excipients)

A) Supersaturation and drug precipitation

- **Can also occur with pure APIs (no excipients), i.e. a weak base can precipitate in the intestine**
- **Drug supersaturation is an important mechanism for "enhanced formulations":**
  - Solid dispersions and amorphous drug formulations
  - Nano suspensions
  - Lipid-based formulations

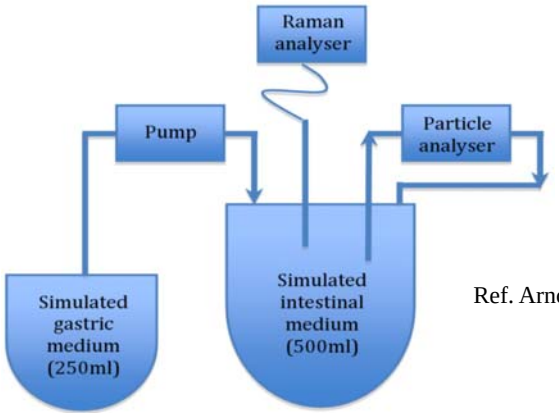
Let's consider supersaturation of the weak base dipyridamole (without excipients)

- **Classical in vitro transfer test was published by Kostewicz et al, J Pharm Pharmacol. 2004**



A new “instrumented” transfer test

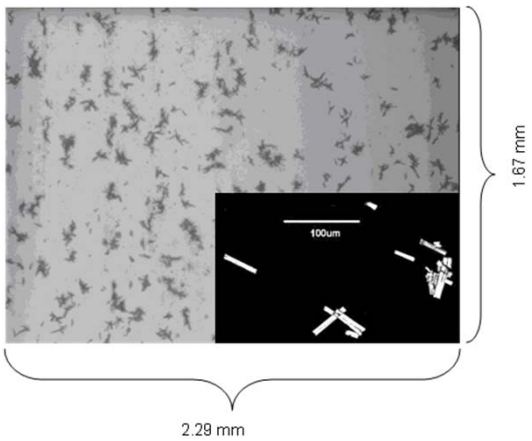
- **We employed dynamic image analysis, Raman spectroscopy and modeling to better understand drug precipitation**



Ref. Arnold et al., JPP 2011

Particle analysis by dynamic image analysis

Installation of a dynamic image analysis with software for particle size and shape analysis



Dipyridamole transfer into FeSSIF V2: t = 3 hours

Significant particle agglomeration was observed (here dipyridamole without lipid)

Supersaturation

⇩

Drug nucleation

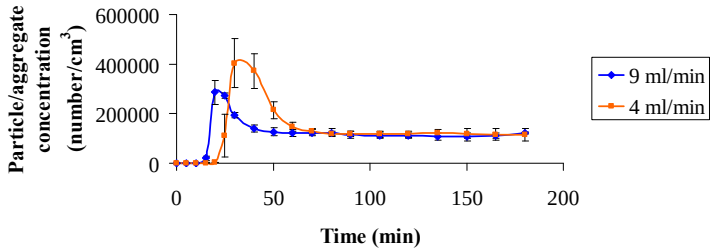
⇩

Particle growth

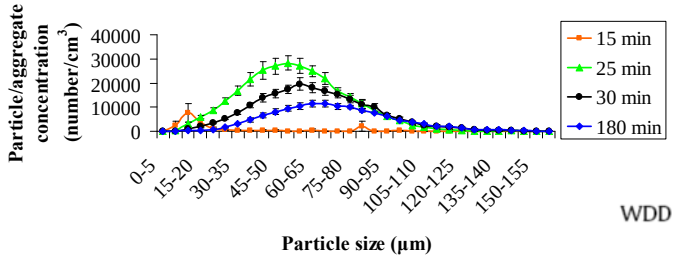
⇩

Particle aggregation

Particle/aggregate concentration of dipyridamole as a function of time

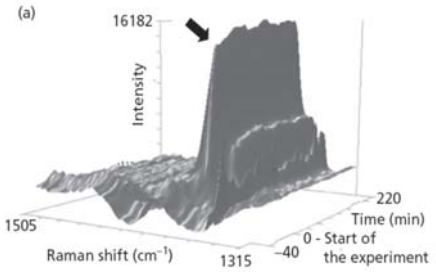


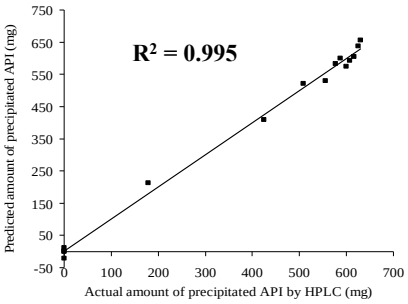
Particle size distribution at flow rate 9 ml/min



$$WDD = 2\sqrt{\frac{A}{\pi}}$$

Some results from Raman spectroscopy





- **We used the entire spectrum for PLS analysis (504–2922 cm^{-1}) It was possible to differentiate the precipitated from dissolved drug (in-line monitoring)**
- **Currently, it is a hot topic to better understand drug nucleation and precipitation in bio-relevant media**

A mass transfer model for drug nucleation and growth

I. From the beginning to the start of nucleation: $[0, t_{nu}]$

II. From the start of nucleation to the end of the medium transfer: $[t_{nu}, t_{tr}]$

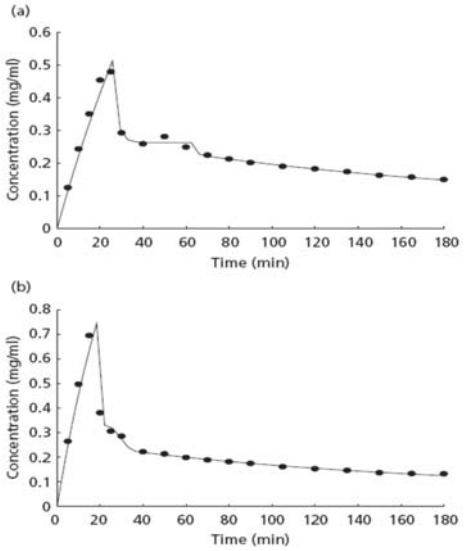
III. From the end of the medium transfer to the start of particle growth: $[t_{tr}, t_{gr}]$

IV. From the beginning of particle growth to infinity: $[t_{gr}, \infty]$

Interval I $[0, t_{nu}]$:	Interval II $[t_{nu}, t_{tr}]$:	Interval III $[t_{tr}, t_{gr}]$:	Interval IV $[t_{gr}, \infty]$:
$\frac{dM_{sol}}{dt} = F_{tr} \cdot c_g$	$\frac{dM_{sol}}{dt} = F_{tr} \cdot c_g - k_{nu} (c_i - c_{sat})^g$	$\frac{dM_{sol}}{dt} = - k_{nu} (c_i - c_{sat})^n$	$\frac{dM_{sol}}{dt} = - k_{gr} (c_i - c_{sat})^g$
$\frac{dM_{pr}}{dt} = 0$	$\frac{dM_{pr}}{dt} = k_{nu} (c_i - c_{sat})^n$	$\frac{dM_{pr}}{dt} = k_{nu} (c_i - c_{sat})^n$	$\frac{dM_{pr}}{dt} = k_{gr} (c_i - c_{sat})^g$
$V_i = V_{i0} + F_{tr} \cdot t$	$V_i = V_{i0} + F_{tr} \cdot t$	$V_i = V_{i0} + F_{tr} \cdot t_{tr}$	$V_i = V_{i0} + F_{tr} \cdot t_{tr}$

Results of the nucleation and growth model

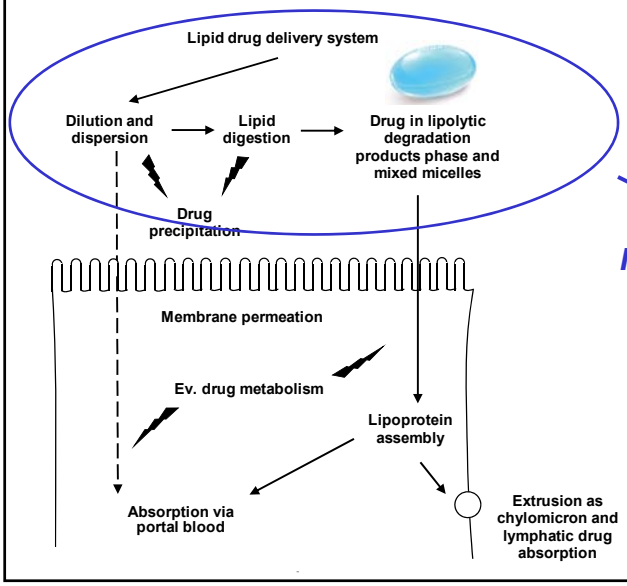
- Excellent agreement of model prediction with concentration profile obtained from HPLC analysis
- Fig. a) depicts the low transfer 4 ml/min and b) shows the 9 ml/min
- We found in all cases a nucleation exponent of 5 and a growth exponent of 1.5



Some conclusions from the novel transfer test

- The instrumented transfer test could also be used to study the influence of excipients on precipitation
- Drug precipitation is not just a first order process so that nucleation and particle growth should be considered. Power law models should be implemented in a PBPK model

B) The fate of lipid-based formulations

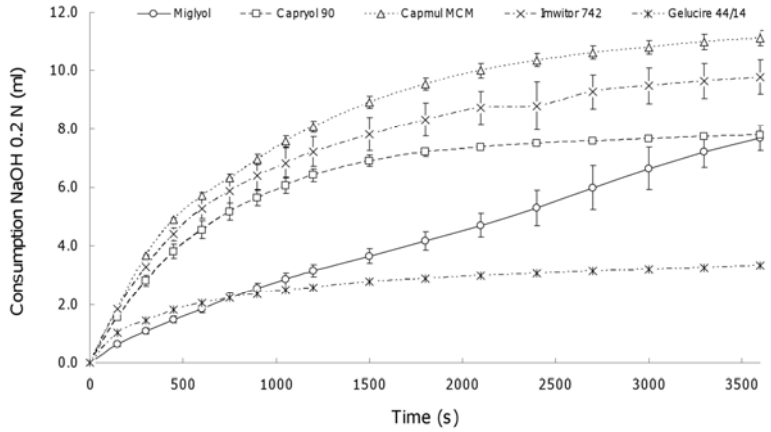


***In vitro* testing for the formulation development**

In vitro lipolysis to test formulation digestion

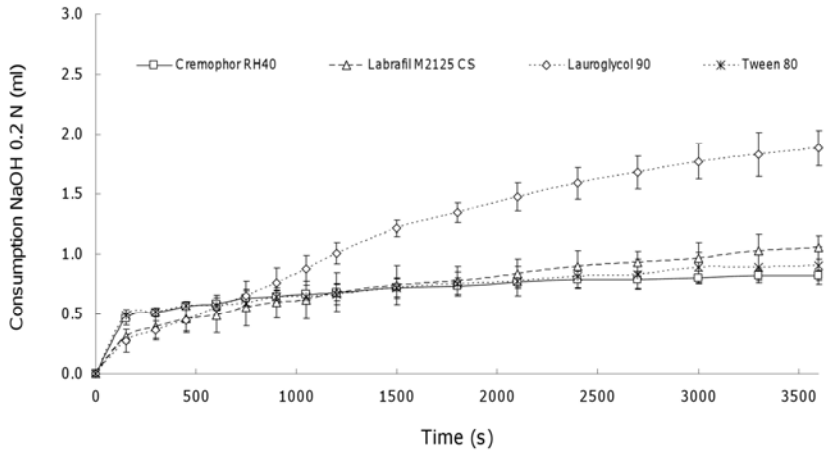
- **Pioneers were the groups at Monash University (C. Pouton/Ch. Porter) and Copenhagen (A. Müllertz)**
- **Performance of an excipient or a formulation can change upon digestion**
- **Excipients can loose their functionality leading to potential drug precipitation**

Some excipients are extensively digested (here in FaSSIF V2)



Ref, Arnold et al, DDIP 2011

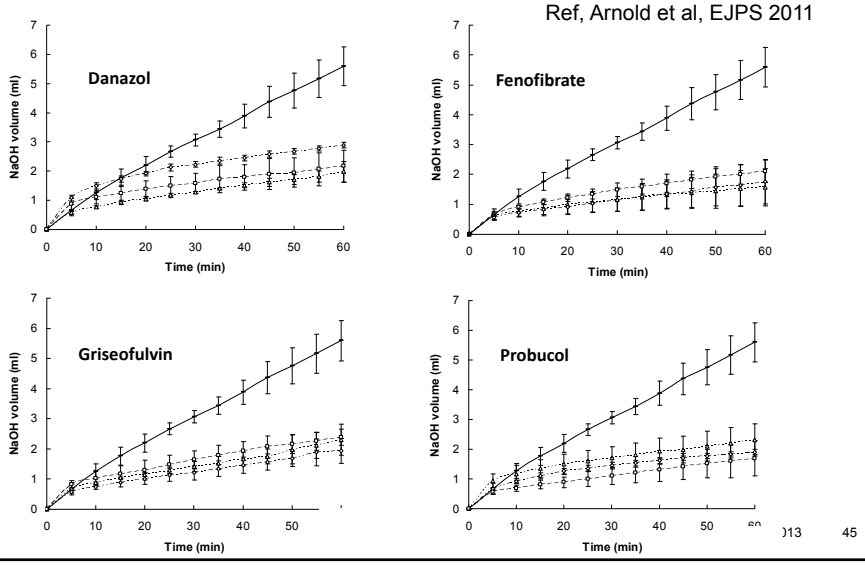
…other excipients are partially digested



Compare with total hydrolysable ester bonds to assess lipolysis potential

Presence of drug changed the lipolysis kinetics

Ref, Arnold et al, EJPS 2011

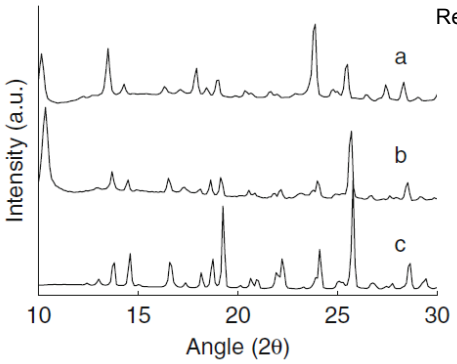


013 45

How does a drug precipitate during digestion (→ important for re-dissolution)

Ref, Stillhart et al, EJPS 2013

Example of fenofibrate



XRPD pattern of the pellet phase obtained upon ultracentrifugation and resulting from **a** the formulation with 80 mg/g fenofibrate, **b** the pellet phase of drug-free formulation spiked with crystalline fenofibrate, and **c** pure crystalline fenofibrate.

Some conclusions and comments

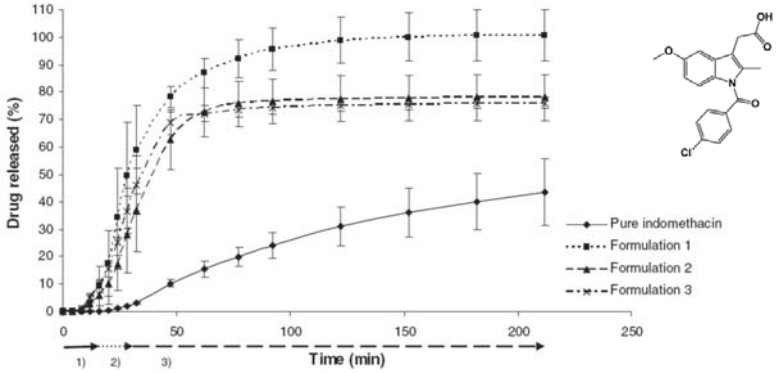
- *In vitro* lipolysis indicates formulation changes upon digestion
- A simple "test response" is to detect whether or not a drug precipitates → ranking of formulations
- Modeling of lipid-based formulations is still difficult since the excipients have often several biological effects (not only on lipolysis but also on permeability)
- However, if we still would like to use *in vitro* release data for PBPK modeling….

A dynamic USP 4 test

- Testing with dynamic pH change → can be beneficial for physiologically-based drug absorption modeling (see GastroPlus™)
- USP 4 dispersion/precipitation applying the pH cascade: 0.1 N HCl (15 min); phosphate buffer pH 6.0 (16 min); phosphate buffer pH 6.8 (182 min)

An example of comparing different self-microemulsifying drug delivery systems

- **Release of indomethacin from SMEDDS → how robust is the transit from the stomach to intestine for an acidic model drug?**



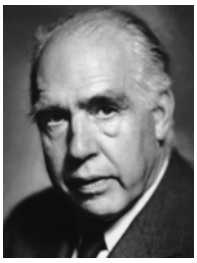
Ref, Arnold et al DDST, 2010

Some final remarks

- **Different options were shown how to anticipate risks in drug formulation development**
- **Tools range from the BCS, DCS to PBPK**
- **Any prediction of drug absorption should be primarily seen as a risk assessment….please keep in mind….**

"Prediction is very difficult, especially about the future."

Niels Bohr



Thank you for your Attention

- **Acknowledgements**

  - *Dr. P. Schirg (PS Prozesstechnik GmbH, Switzerland)*
  - *Dr. C. Uerpmann (Kaiser Optical Systems, Inc.)*

  - *Prof. Dr. G. Imanidis (Univ. of Appl. Sci. Northwest. Switzerland; Univ. of Basel)*
  - *Y. Arnold (Univ. of Appl. Sci. Northwest. Switzerland; Univ of Basel)*
  - *M. Cavegn (Univ. of Appl. Sci. Northwest. Switzerland; Univ. of Basel)*
  - *C. Stillhart (Univ. of Appl. Sci. Northwest. Switzerland; Univ. of Basel)*

Partners of our current research projects

Questions and discussion