Thermodynamic Modeling of Drug Solubilities

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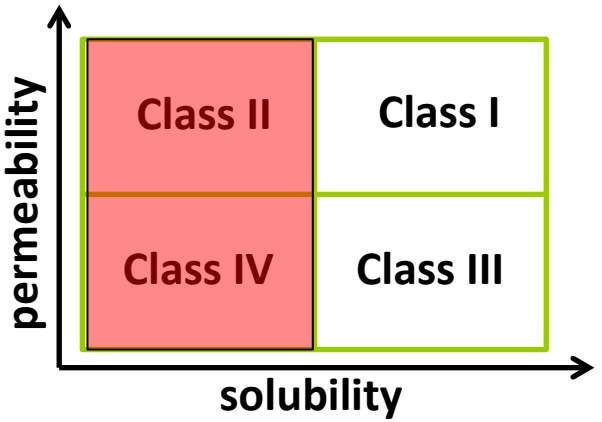
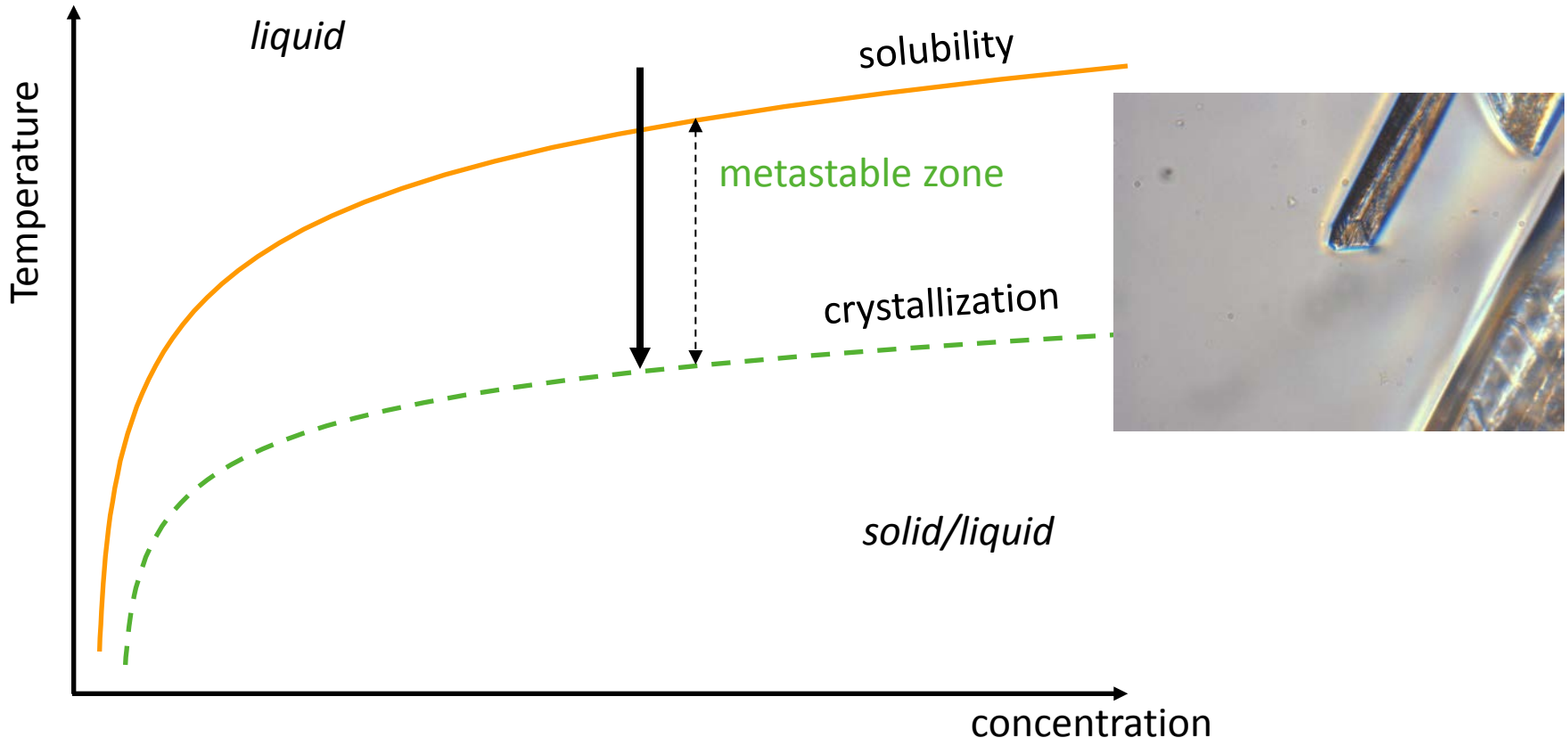
Motivation

- APIs are complex molecules
- Most APIs are classified in class II or IV of the Biopharmaceutics Classification System (BCS)
- Limited bioavailability due to
  - poor solubility and/or
  - low dissolution rate



- Strategies to improve solubility:
  - Cosolvents
  - Salt formation
  - Amorphous formulations
- Strategies to improve dissolution rate:
  - Particle-size reduction
  - Salt formation
  - Amorphous formulations
  - Cocrystals

Solubility as function of temperature



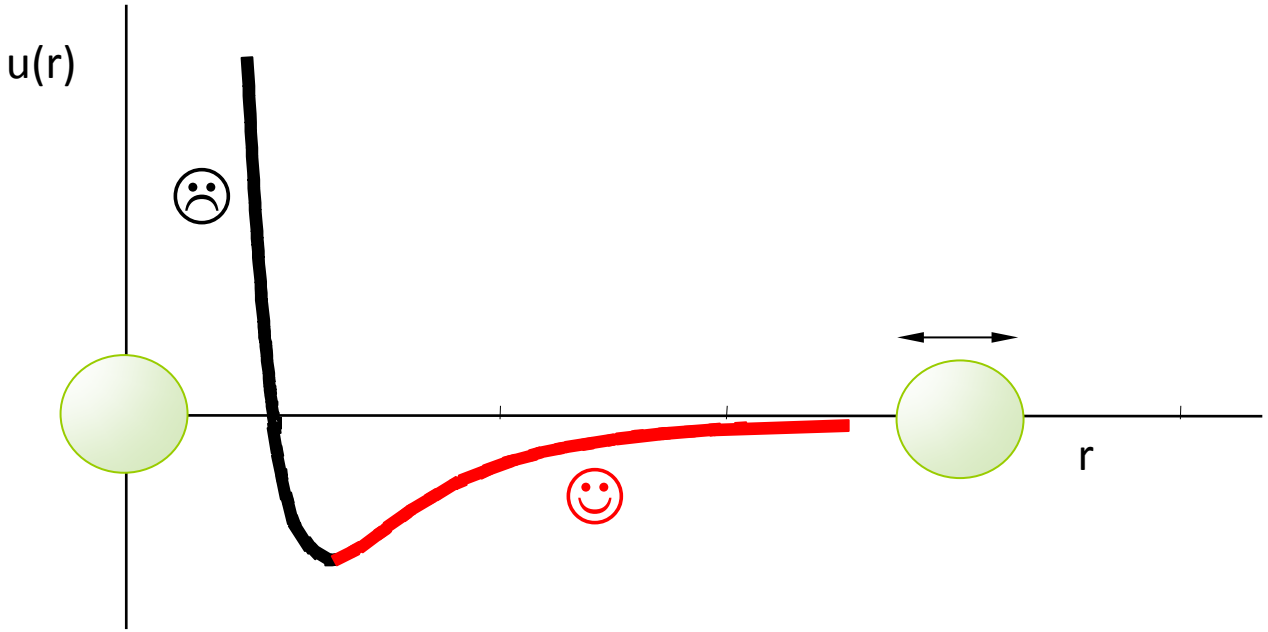
What determines solubility?

- **Attractive interactions**
  - van der waals attractions
  - Hydrogen bonds
  - Dipol-dipol interactions

  (Enthalpy)

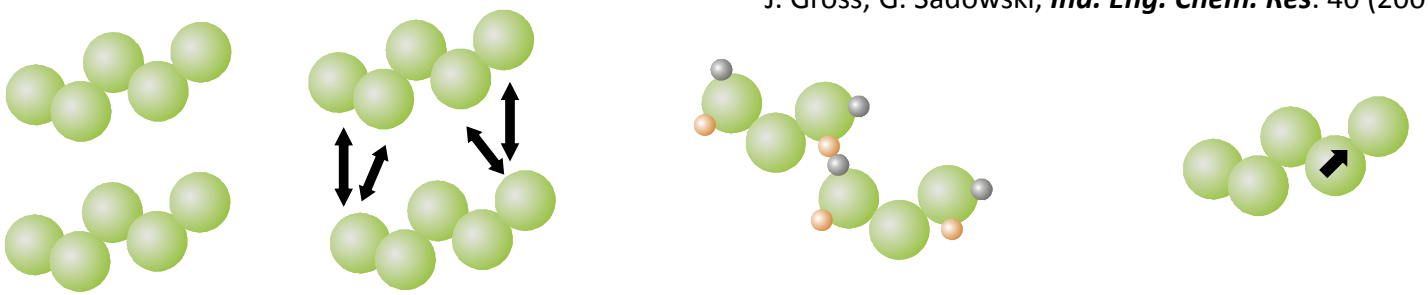
- **Repulsive interactions**
  - Size of the molecules
  - Shape of the molecules

  (Entropy)



Thermodynamic model PC-SAFT

J. Gross, G. Sadowski, ***Ind. Eng. Chem. Res***. 40 (2001) 1244-1260



$$A^{res} = A^{repulsion} + A^{vdW\ attraction} + A^{association} + A^{dipole/quadrupole}$$

Applicable to:

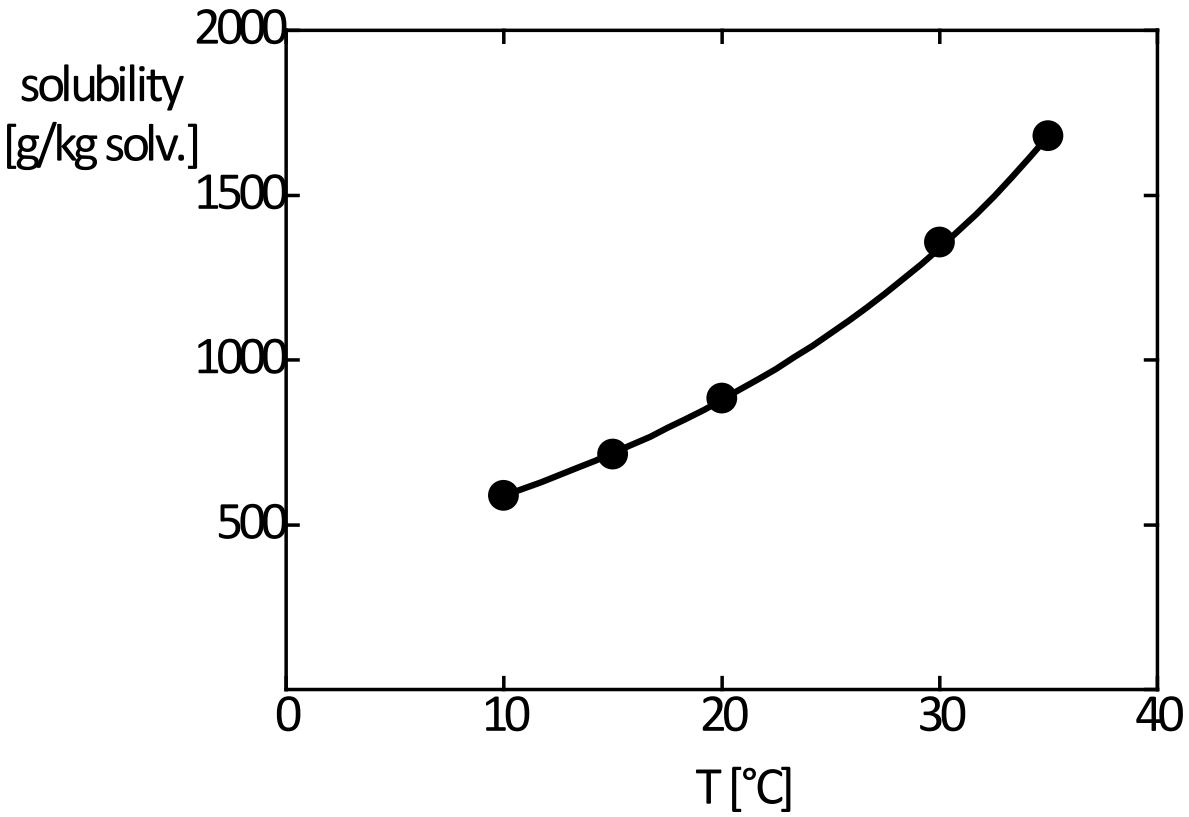
- alkanes
- olefines, alkenes
- non-polar solvents
- polyolefines
- polyesters
- non-polar gases
- ….

- water
- alkohols
- acids
- amines
- sugars
- pharmaceuticals
- ….

- ketones
- esters
- ethers
- aldehydes
- polar solvents
- carbon dioxide
- ….

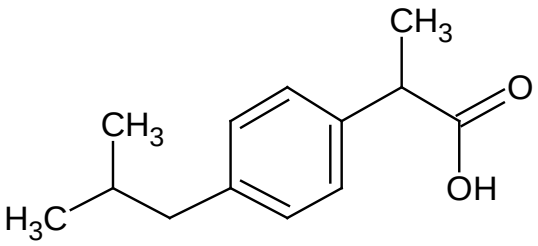
Solubility in pure solvents

- Determination of PC-SAFT parameters by fitting to solubility data (five data points)
- Example: **Ibuprofen** in acetone



symbols: exp. data

line: PC-SAFT

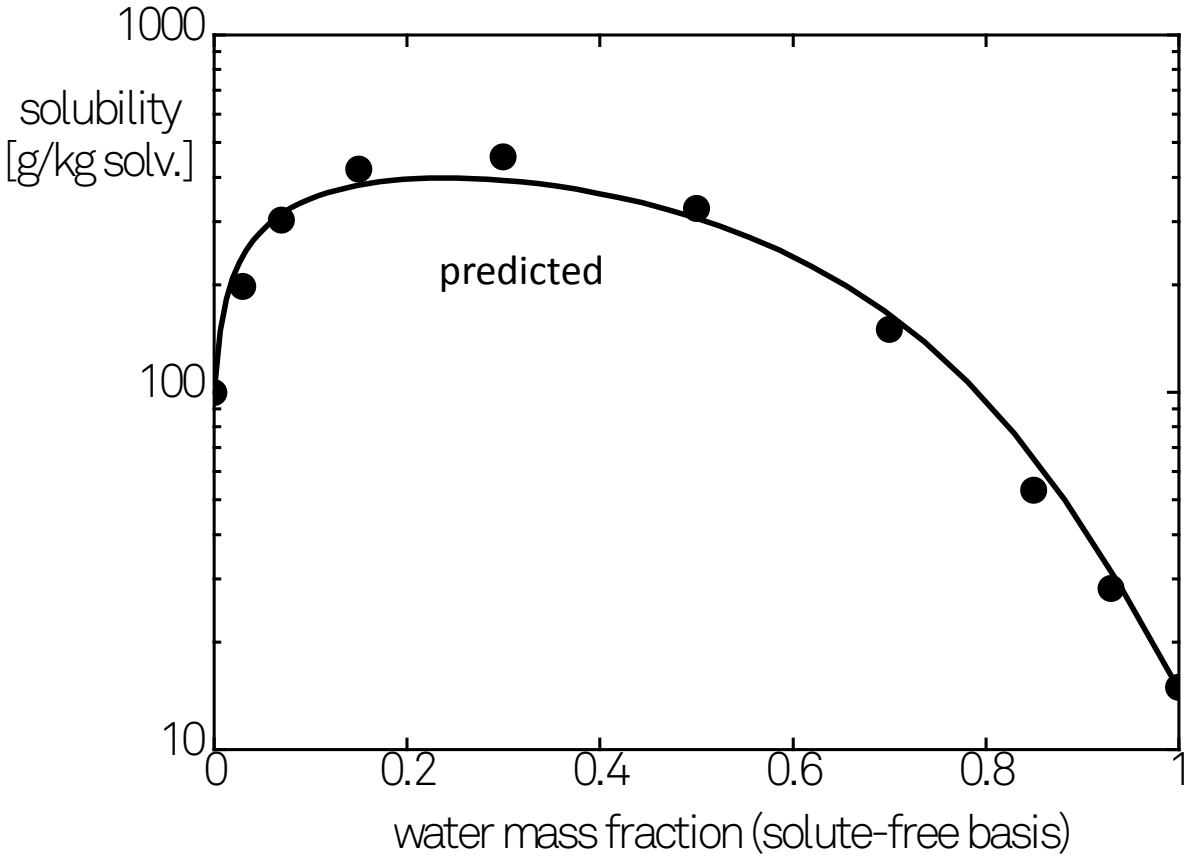


exp. data: Gracin and Rasmuson 2002

Ruether and Sadowski, J Pharma Sci 98 (2009) 4205-4215

Solubility in solvent mixtures

- Prediction possible based on solubility in pure solvents only
  - No additional experimental data required
- Example: **Paracetamol in water-acetone** mixtures at 25°C



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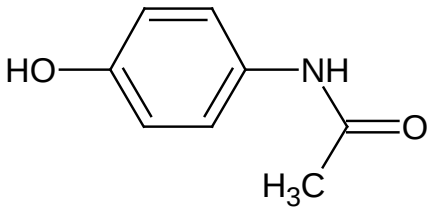
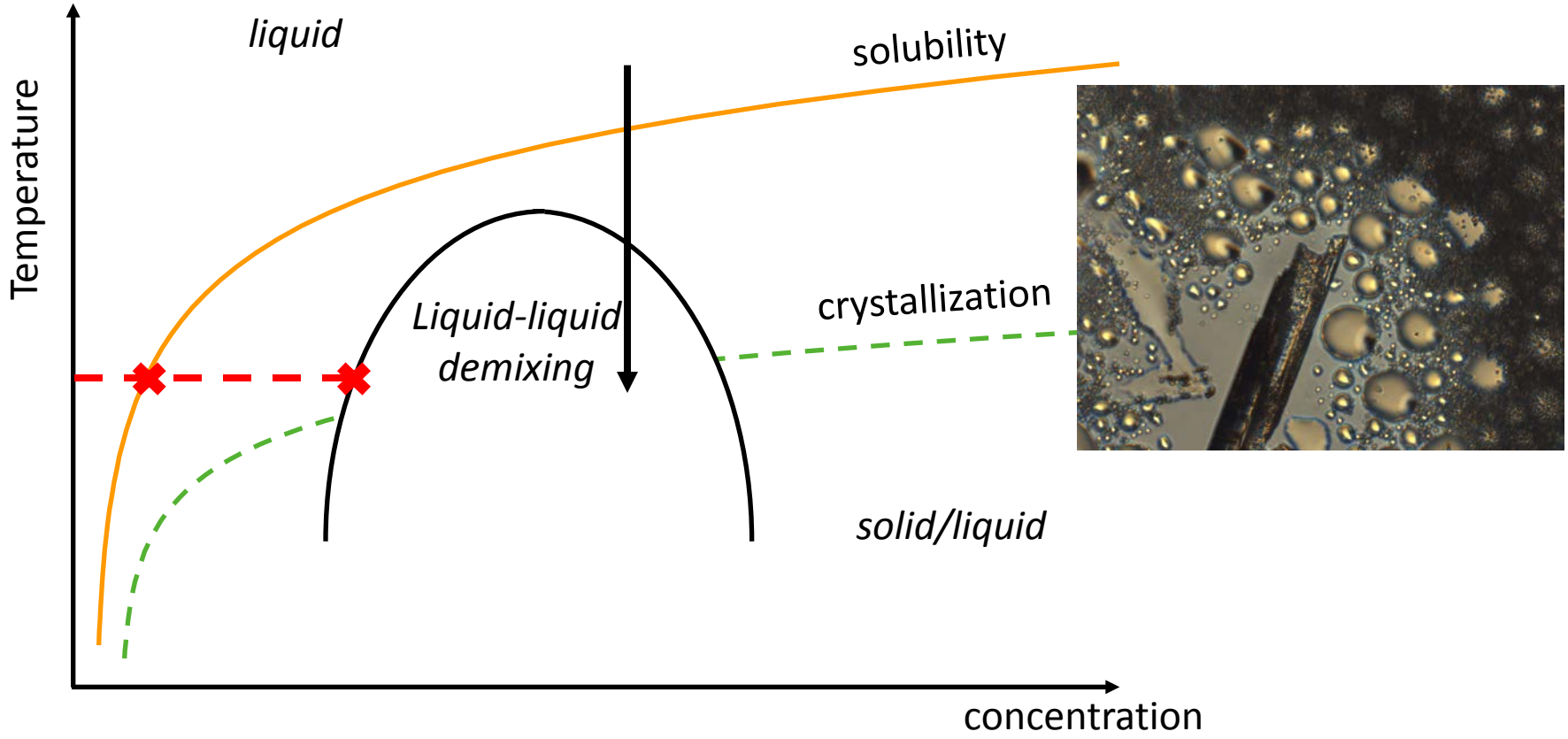


exp. data: Granberg and Rasmuson 2000

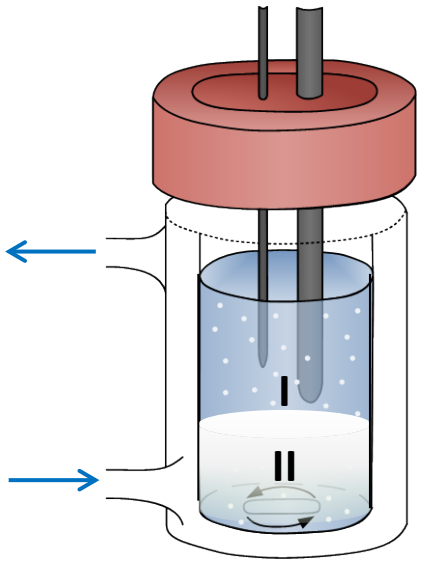
Ruether and Sadowski, J Pharma Sci 98 (2009) 4205-4215

Oiling out in API solutions

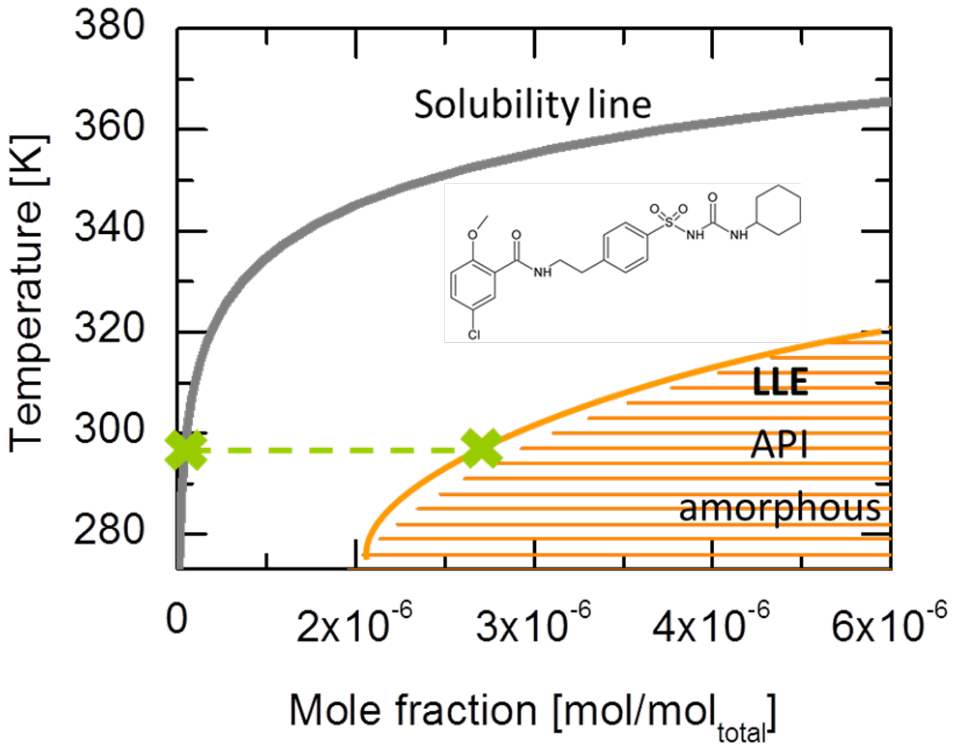


Phase-equilibrium approach

- crystalline solubility measured



Glibenclamide in water



- amorphous demixing predicted with PC-SAFT

✓ $x_{API}^{amorphous} / x_{API}^{crystalline} \approx 25$

Solubility of amorphous vs. crystalline API

- Prediction of the **solubility ratio** $x_i^{amorphous} / x_i^{crystalline}$ by PC-SAFT

Table 7. Predicted and Experimental Solubility Ratio for Amorphous to Crystalline Drug Forms.[a] [1;2]

drug	forms	calculated solubility ratio		experimental solubility ratio	temperature (°C)	medium
indomethacin	amorphous/ γ-crystal	15 – 40	19	4.5	25	water
glibenclamide	amorphous/crystal	100 – 1600	25	14	23	buffer
glucose	amorphous/crystal	15 – 50	18	21	20	ethanol
griseofulvin	amorphous/crystal	40 – 440	4	1.4	21	water
hydrochlorothiazide	amorphous/crystal	20 – 110	*	1.1	37	HCl and PVP
iopanoic acid	amorphous/I-crystal	12 – 20	*	3.7	37	buffer
polythiazide	amorphous/crystal	50 – 450	*	9.8	37	HCl and PVP

[a] Data taken from ref 35a.

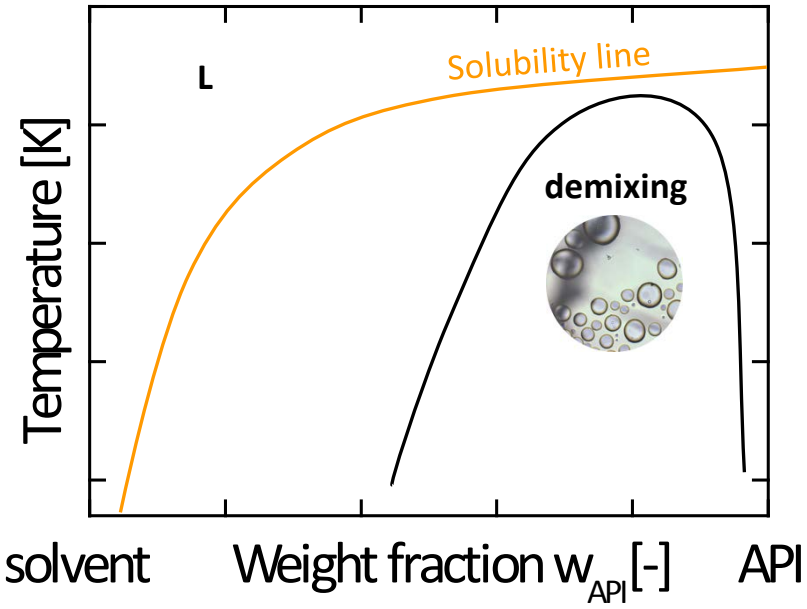
* On-going work

- Solubility ratios from PC-SAFT are more suitable than those from literature
- PC-SAFT accounts for the solvent influence

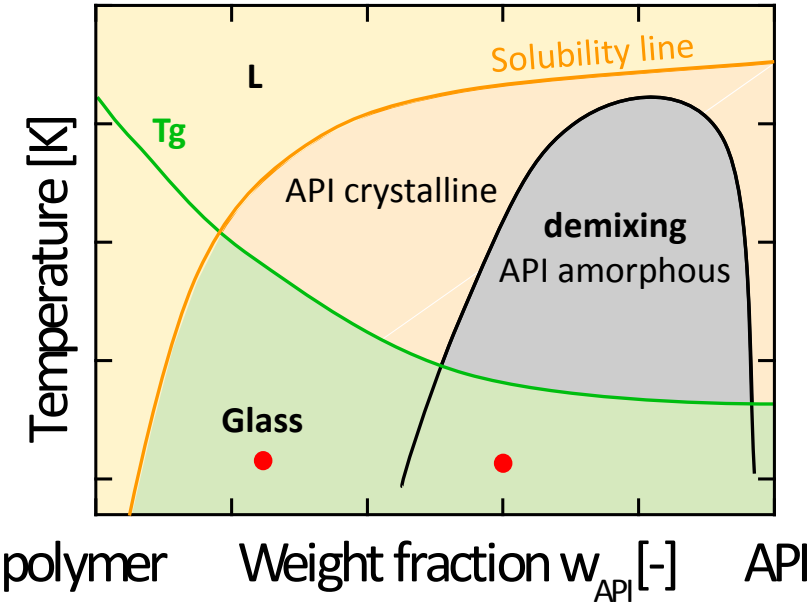
[1] Hancock, B. C. ; Parks, M. *Pharm. Res.* 17 (2000), Nr. 4, S. 397–404
[2] Hajime K., Tetsurou H., *European J. Pharmaceutics Biopharmaceutics* 70 (2008) 493–499

Phase behavior of API/polymer formulations

Crystalline/amorphous API in solvent

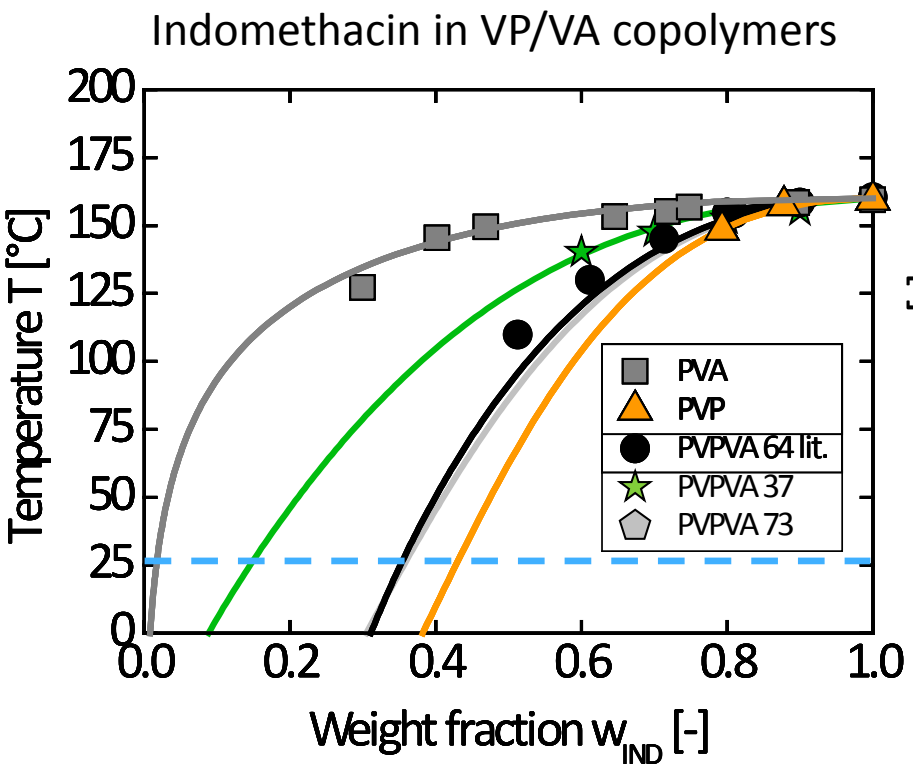


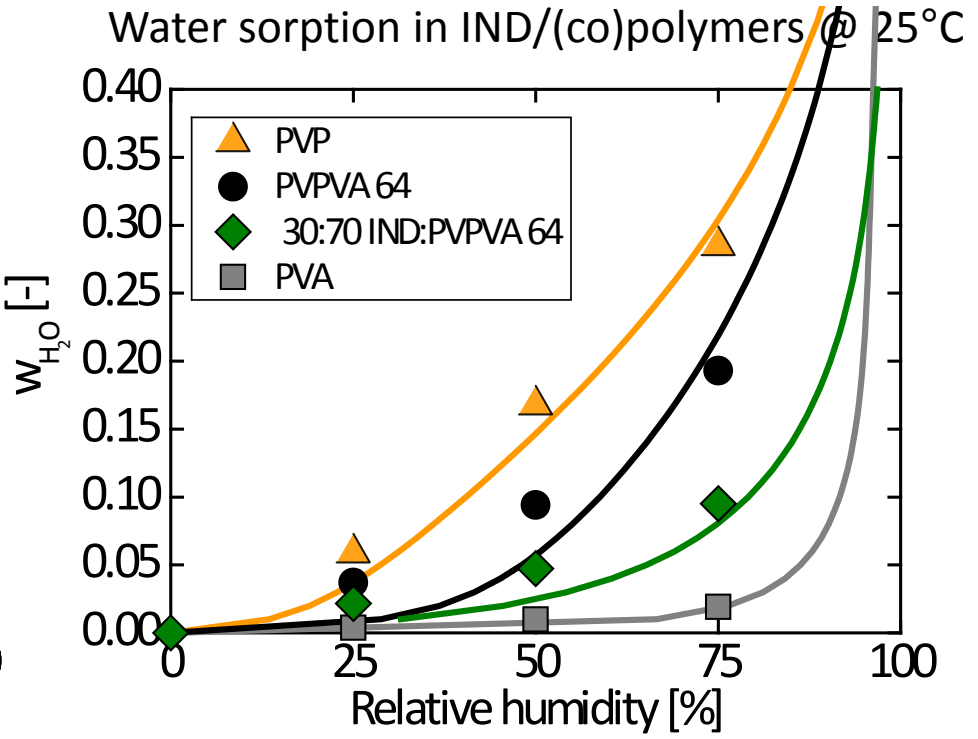
API/polymer formulation



- Phase behavior of API/polymer formulations is similar to that of API/solvent systems
- Experimental investigation and modeling/prediction by PC-SAFT

Solubility - influence of copolymer composition

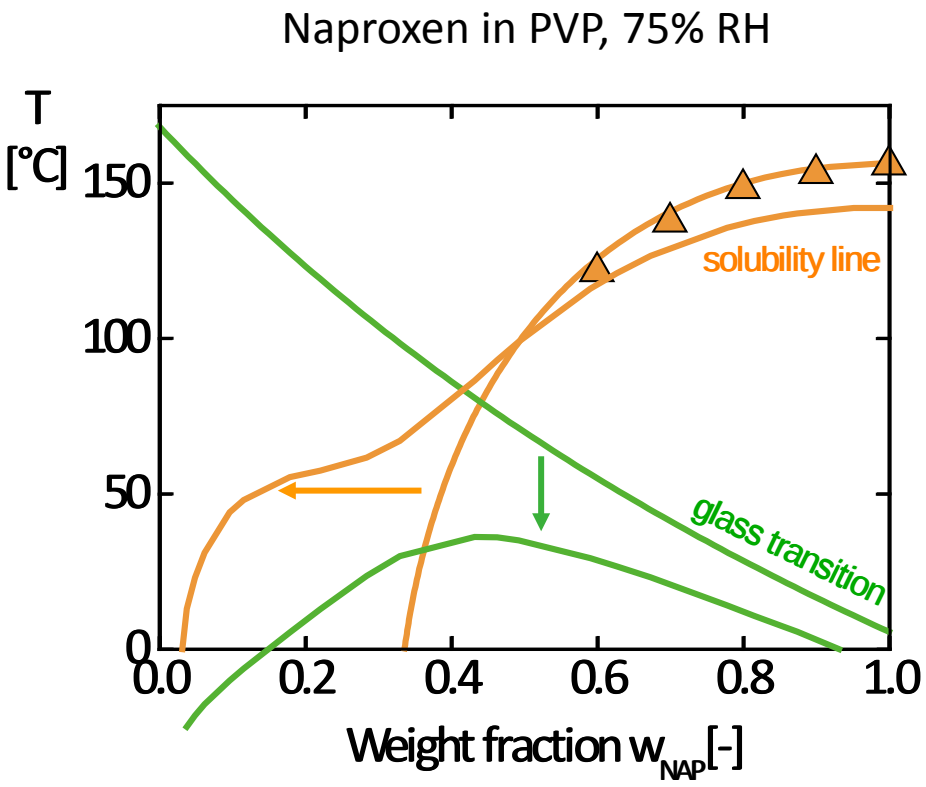




Lit. data: Sun et. al., J. pharm. Sci., 2010

- Solubility of indomethacin depends on the (co)polymer
- Solid dispersions often (can) absorb remarkable amounts of water

Phase behavior as function of RH



T_g calculation using Gordon-Taylor equation

Water absorption increases the probability of API recrystallization and therewith **decreases bioavailability.**

Conclusion

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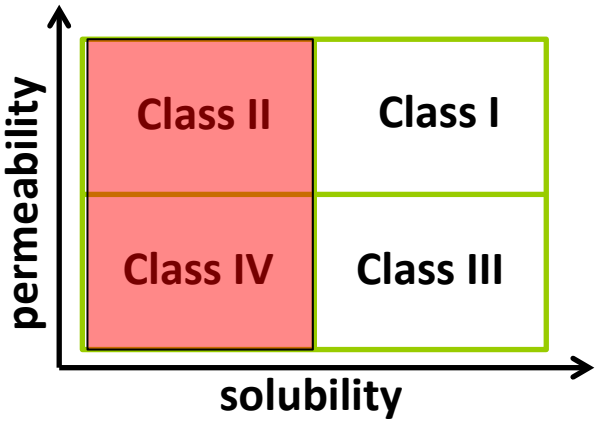
- Most APIs are classified in class II or IV of the Biopharmaceutics Classification System (BCS)
- Limited bioavailability due to
  - poor **solubility** and/or
  - low **dissolution rate**
- Strategies
  - **Cosolv**
  - **Salt fo**
  - **Amorphous formulations**



Thermodynamics is a powerful tool that helps to understand and to predict these phenomena

olution rate:

- **Amorphous formulations**
- **Cocrystals**

The TH group

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DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

Lonza

NOVARTIS

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