Approaches to measure equilibrium (intrinsic) and “transient” solubility, and the impact on dissolution and membrane transport kinetics.

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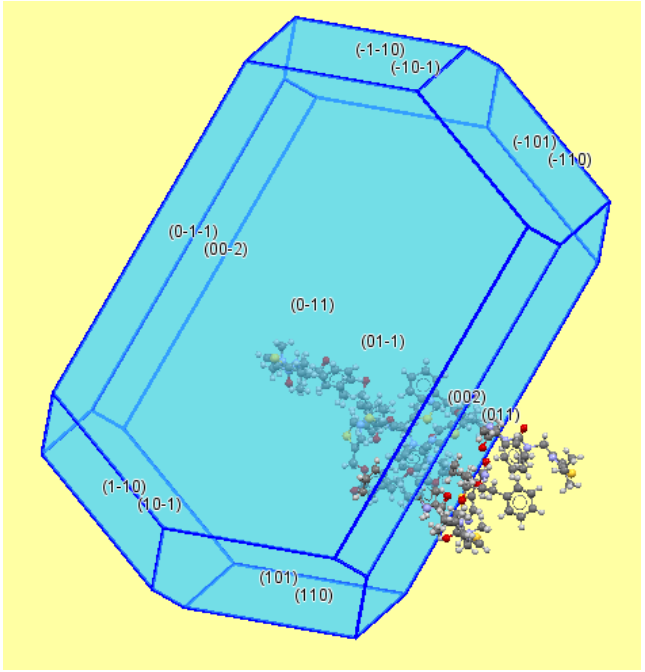
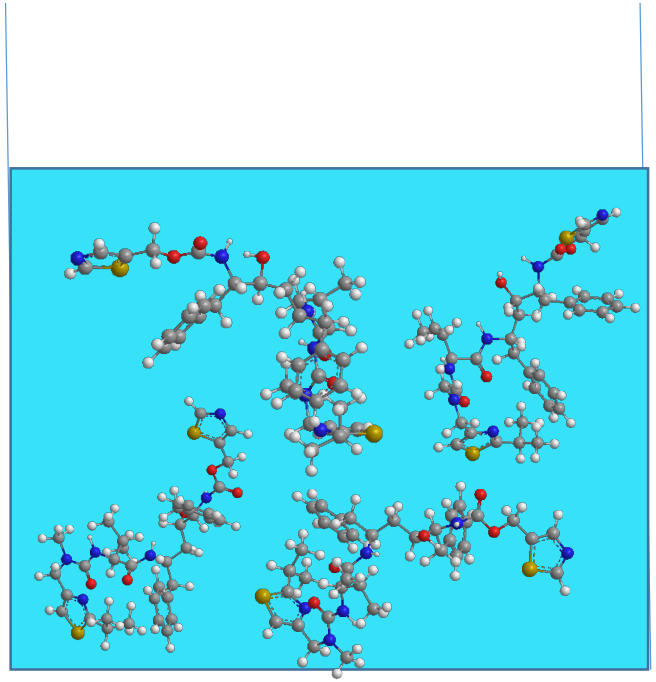
Outline

- Thermodynamics of solubility, crystalline and amorphous
- Solubility measurement
  - Experimental approaches
  - Media effects
  - Common issues in measurement
- Supersaturation – defining based on solubility measurements versus thermodynamic considerations
- Dissolution of different solid state forms and controlling factors
- Factors impacting membrane transport
- Supersaturation evaluation in different media and membrane transport

Solubility – Conventional Definition

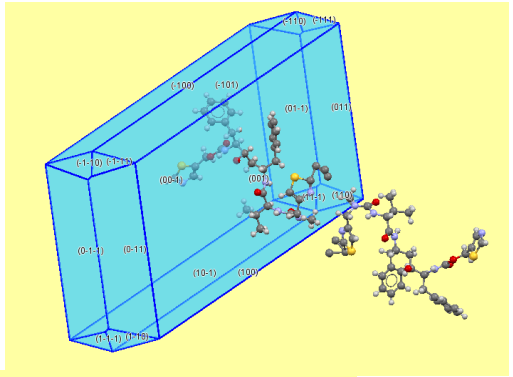




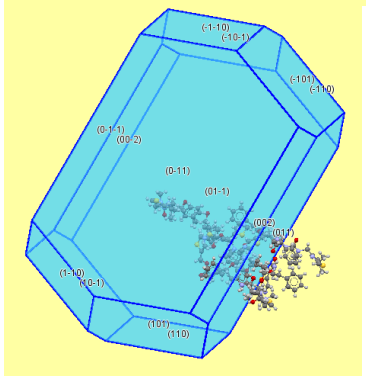
Thermodynamically Stable Form

Saturated Solution
Concentration = X mg/mL

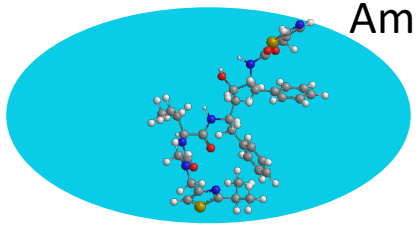
Solubility – extended definition



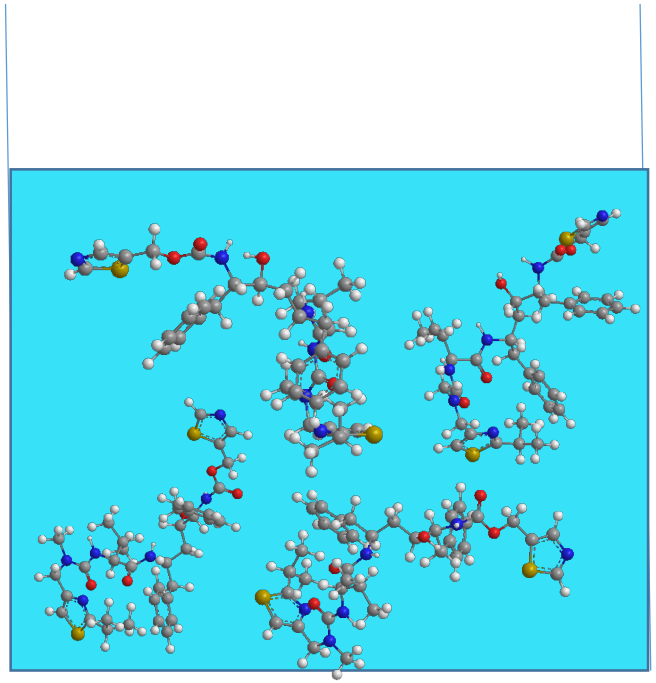
Polymorph x



Polymorph y

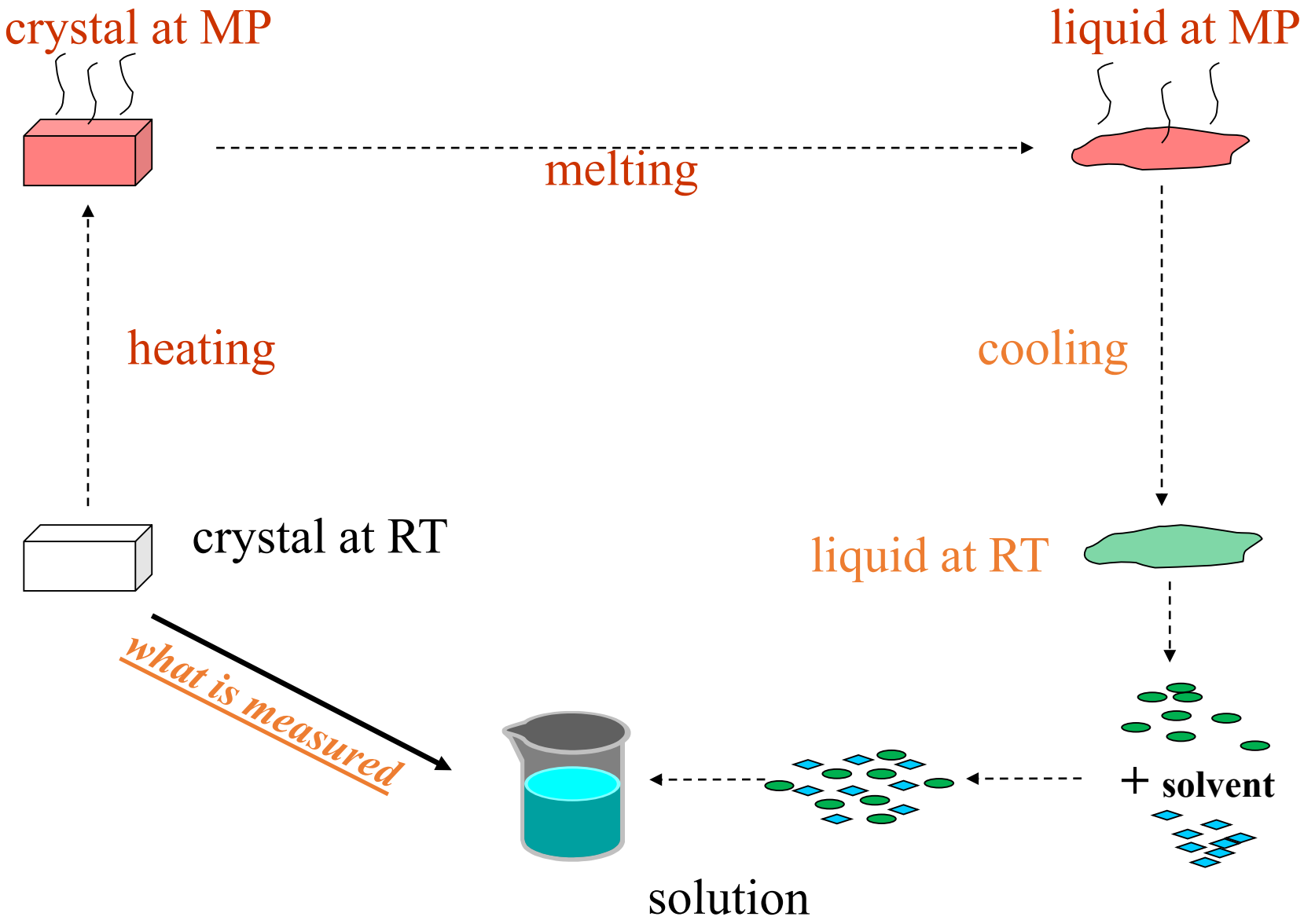


Amorphous z



Saturated Solution
Concentration = X mg/mL
Y mg/mL
Z mg/mL

What Factors Determine Crystal Solubility?



Simplified Thermodynamic Description

$$\ln a_{crystal} = \ln x\gamma = -\frac{\Delta G^{fusion}}{RT}$$

$$\ln x = -\frac{\Delta G^{fusion}}{RT} - \ln \gamma$$

Solid state properties

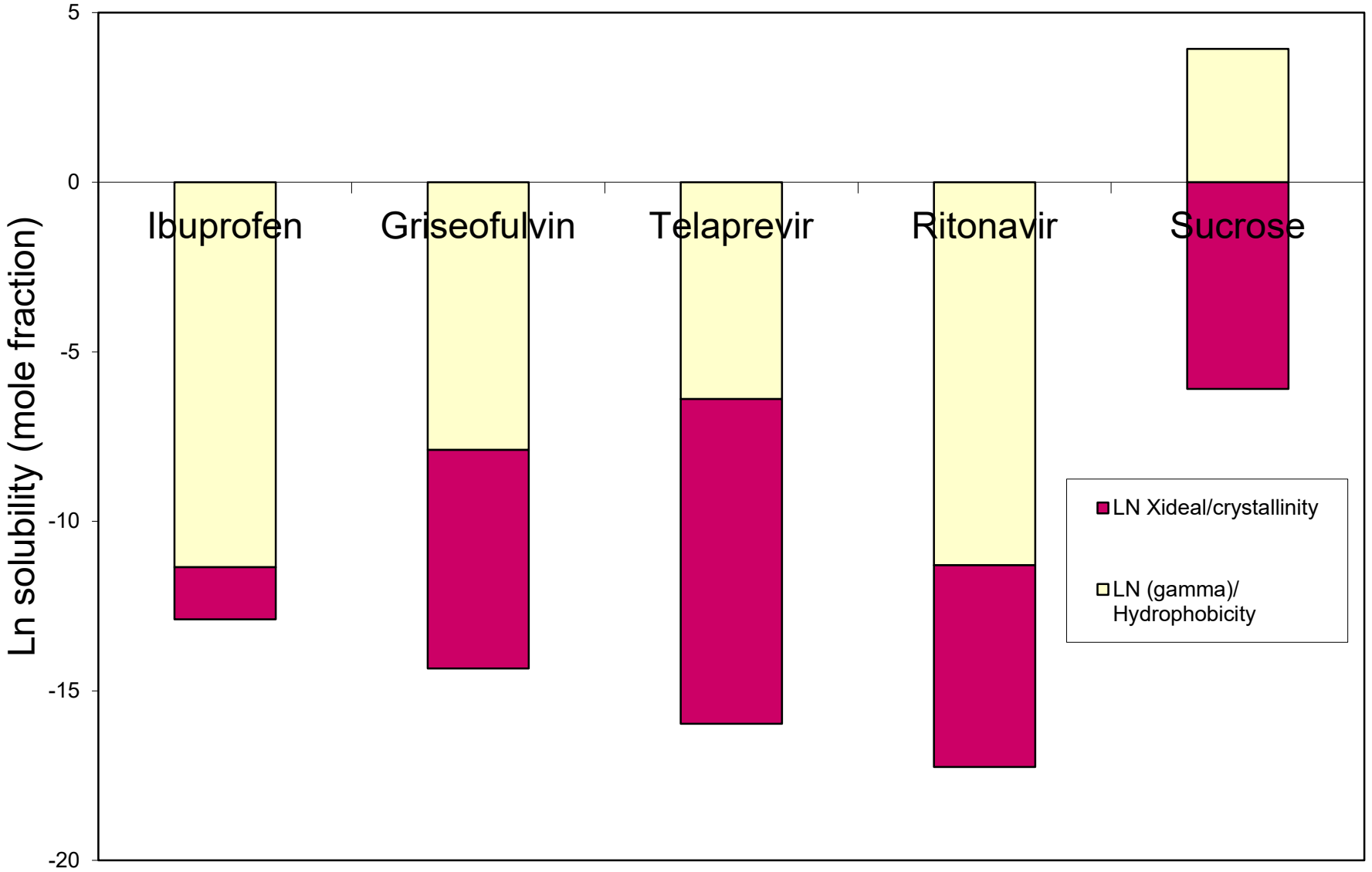
solute-solvent interactions

$$\log S_w^{solid} = 0.5 \ -\log P - 0.01(T_f - 298)$$

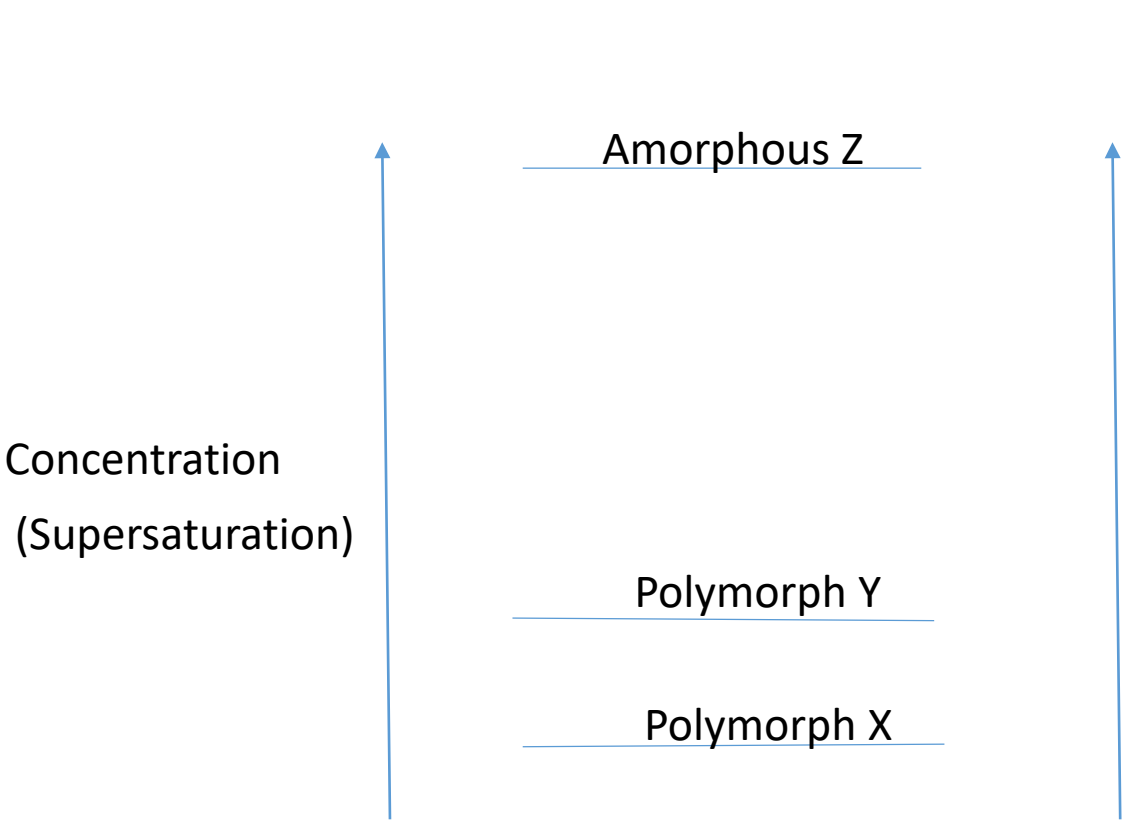
Yalkowsky's General Solubility Equation

Jain and Yalkowsky J. Pharm. Sci. 2001

Relative Contributions of Crystal Lattice and Hydrophobicity to Aqueous Solubility

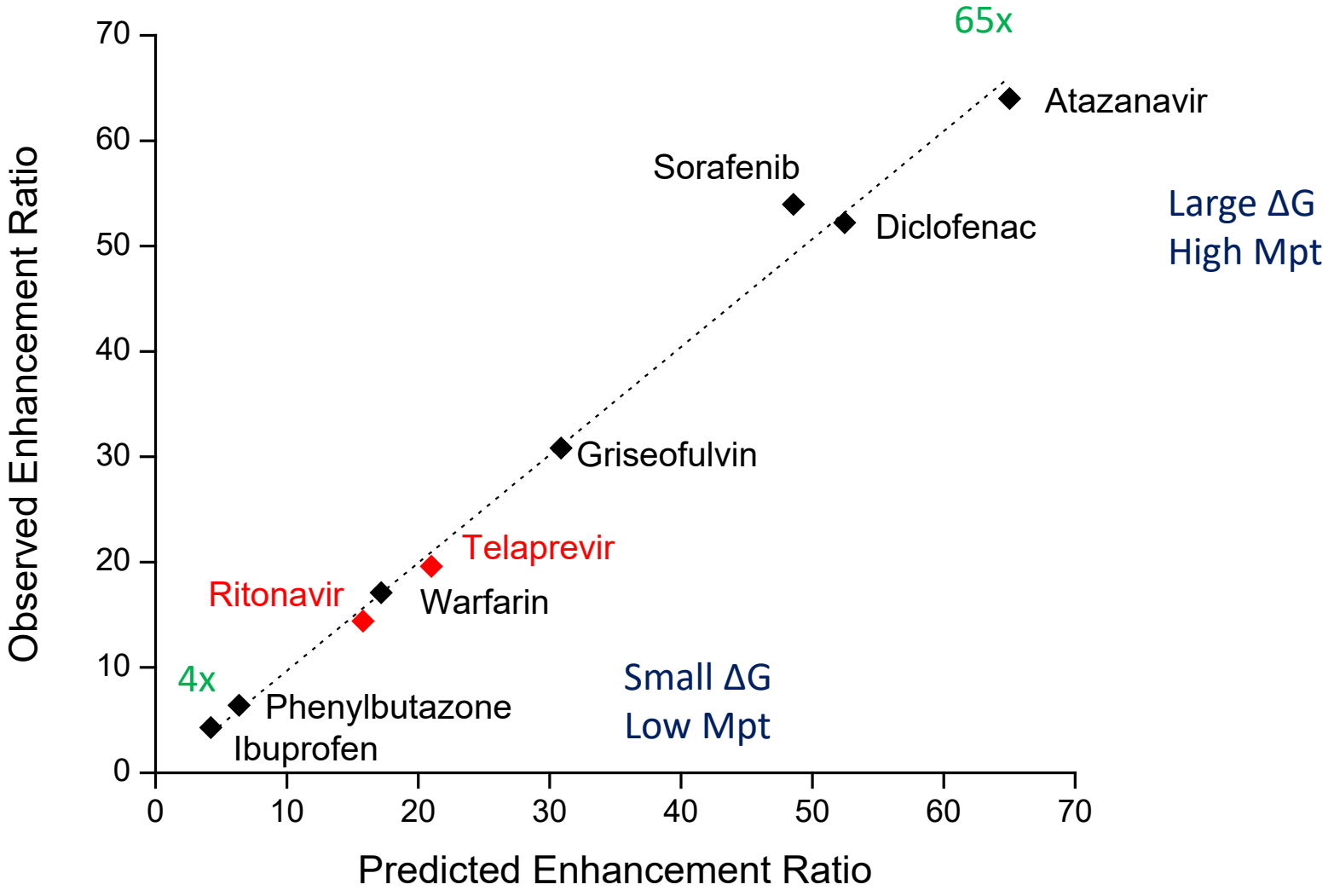


Changing the Solid State Form Changes Thermodynamic Activity and Solubility



$$\frac{S^Z}{S^X} \approx e^{\frac{\Delta G}{RT}}$$

Amorphous:Crystalline Solubility Ratios



Taylor, L. S.; Zhang, G. G. Z., *ADDR*. 2016 doi:10.1016/j.addr.2016.03.006

Key Points

- Solubility depends on solid properties
- The solubility also depends on the solvent
- The solvent does not impact the thermodynamic activity of the crystal*

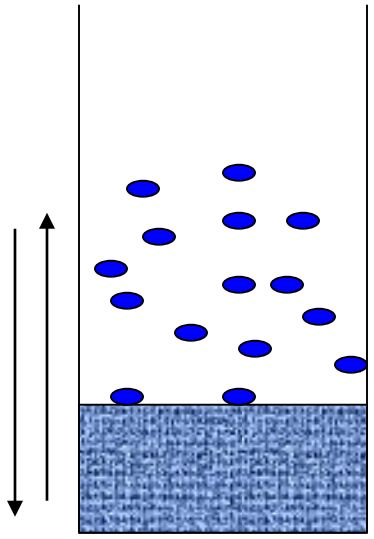
*true as long as the solvent does not mix with the crystal, e.g. solvate formation

Membrane flux depends on solute activity not concentration

Saturated solutions of methyl parabens in different solvents

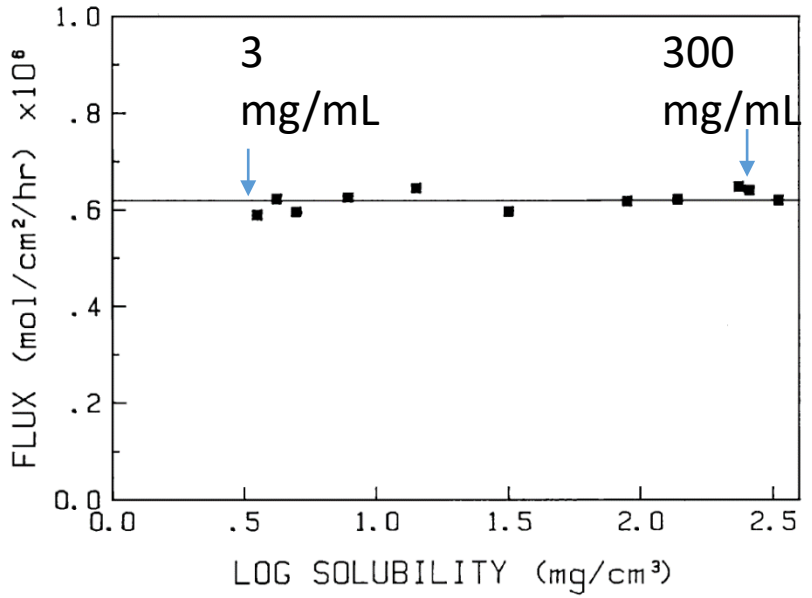
Large variations in concentration
Same flux value

Why?



saturated

activity solid = activity solution

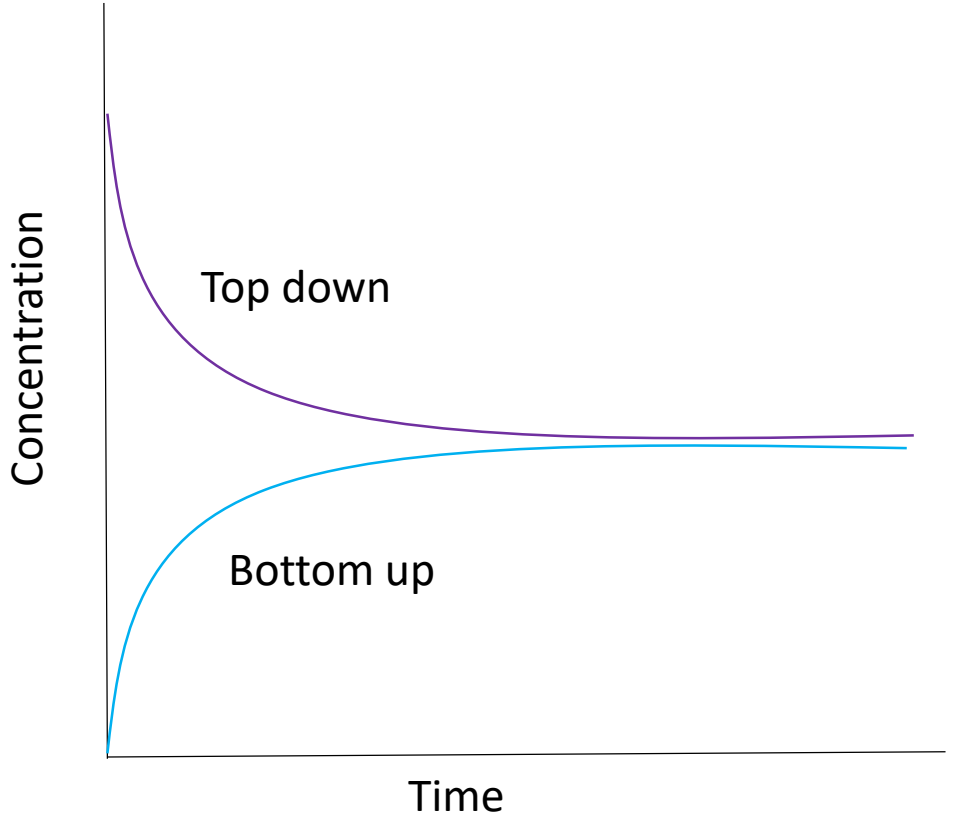


Increasing crystal solubility = constant flux

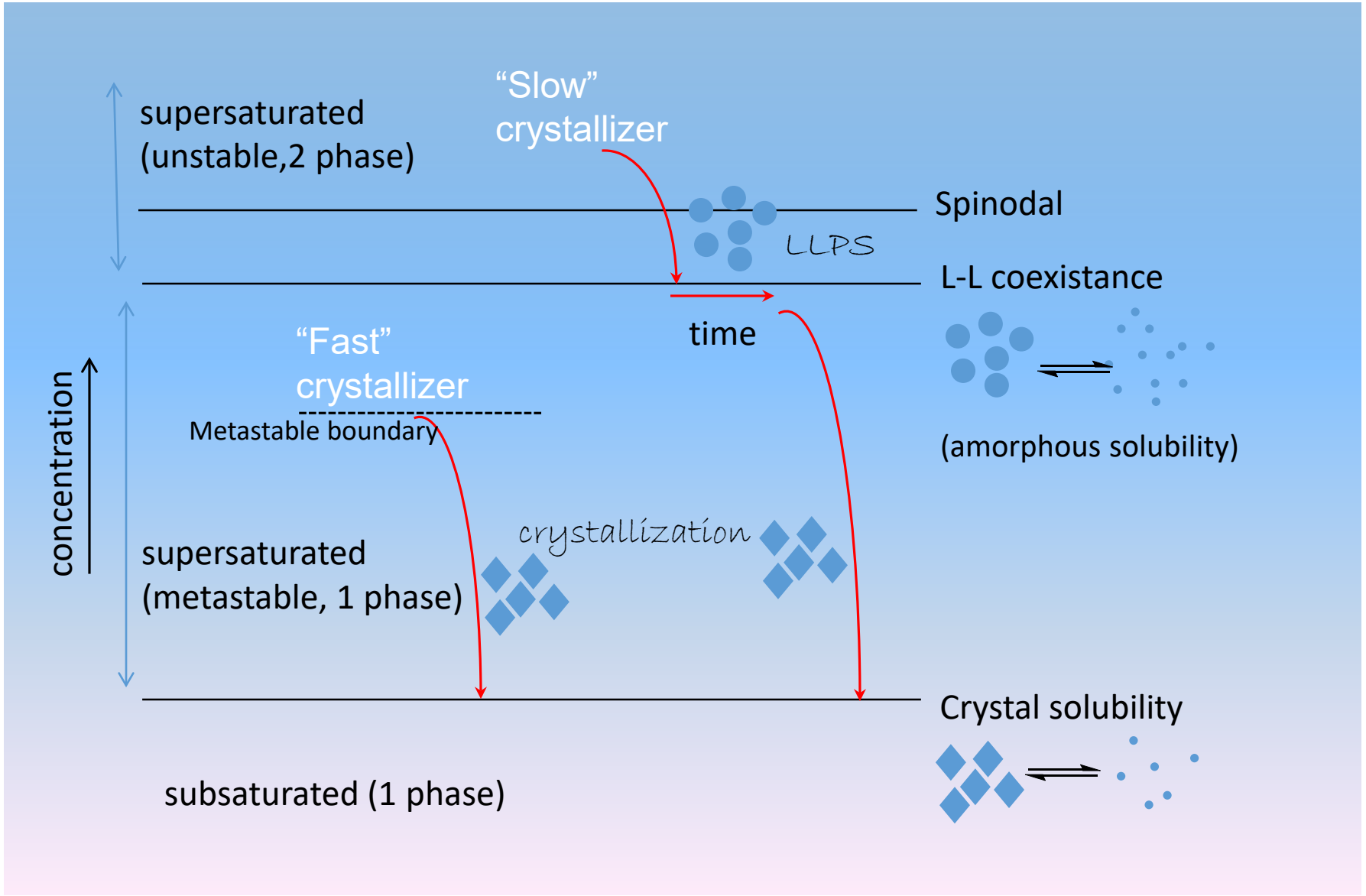
Twist and Zatz J. Soc. Cosmet. Chem. 1986

Solubility measurement

- Top down
  - Early phase solubility
  - Amorphous solubility
  - Risks
    - Unknown solid form
    - Solvent effects
    - True equilibration may not be reached
- Bottom up
  - Crystalline solubility
  - Concerns
    - Equilibration time
    - Solid phase at end of experiment
    - Separation of solid and supernatant
    - pH



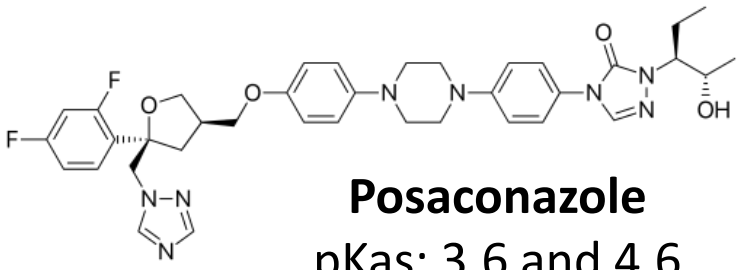
Phase Transitions in Supersaturated Solutions



Media Effects

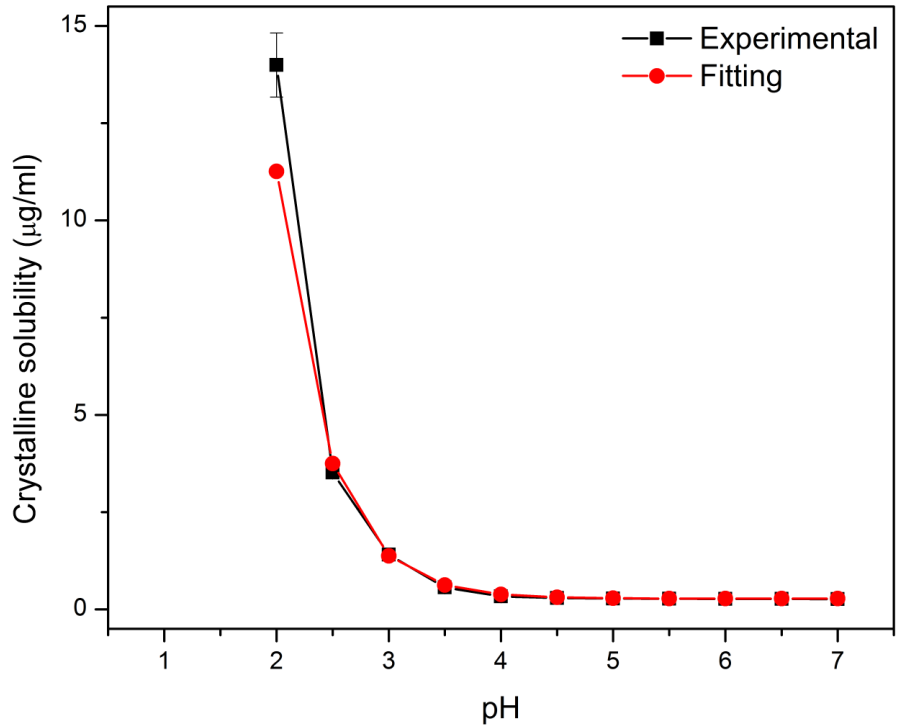
- pH
- Ionic strength
- Buffer species
- Solubilizing components (most commonly micelles)

pH-dependent Solubility –Crystalline Drug



Posaconazole

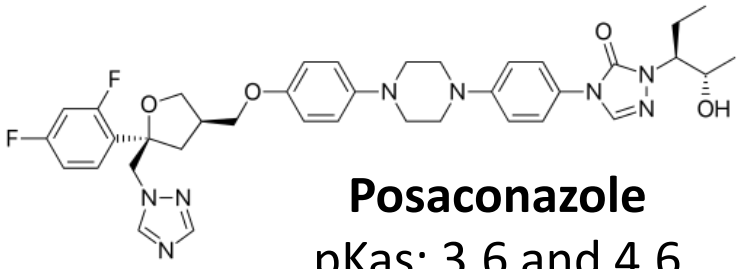
pKas: 3.6 and 4.6



$$S_{tot} = S_B(1+10^{(pK_a - pH)})$$

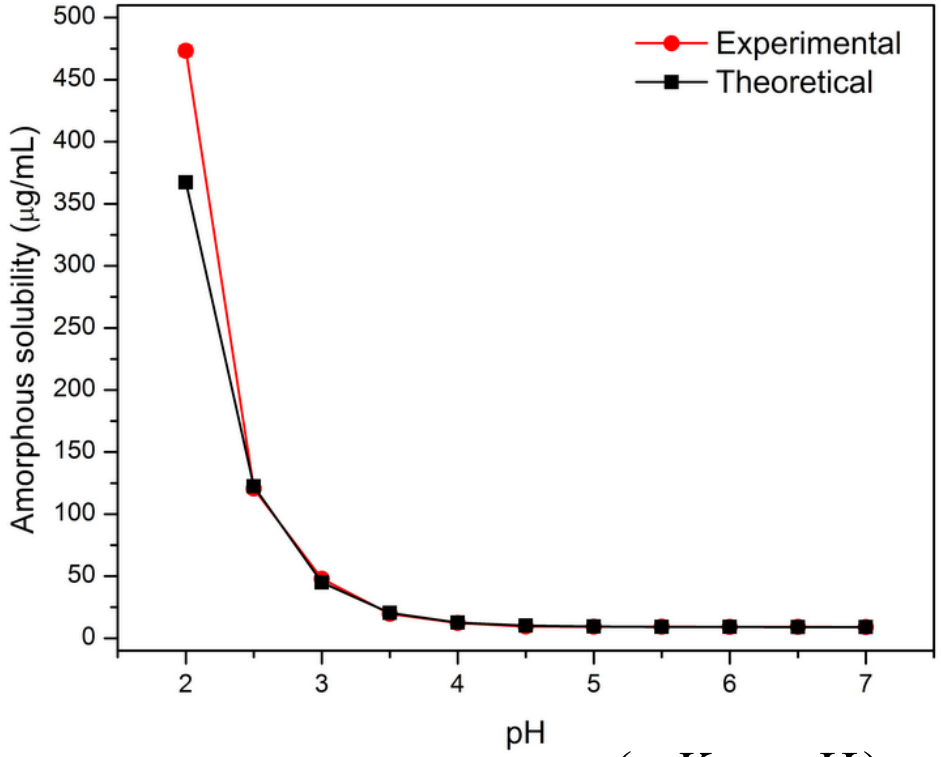
Crystalline solubility

pH-dependent Solubility –Amorphous Drug



Posaconazole

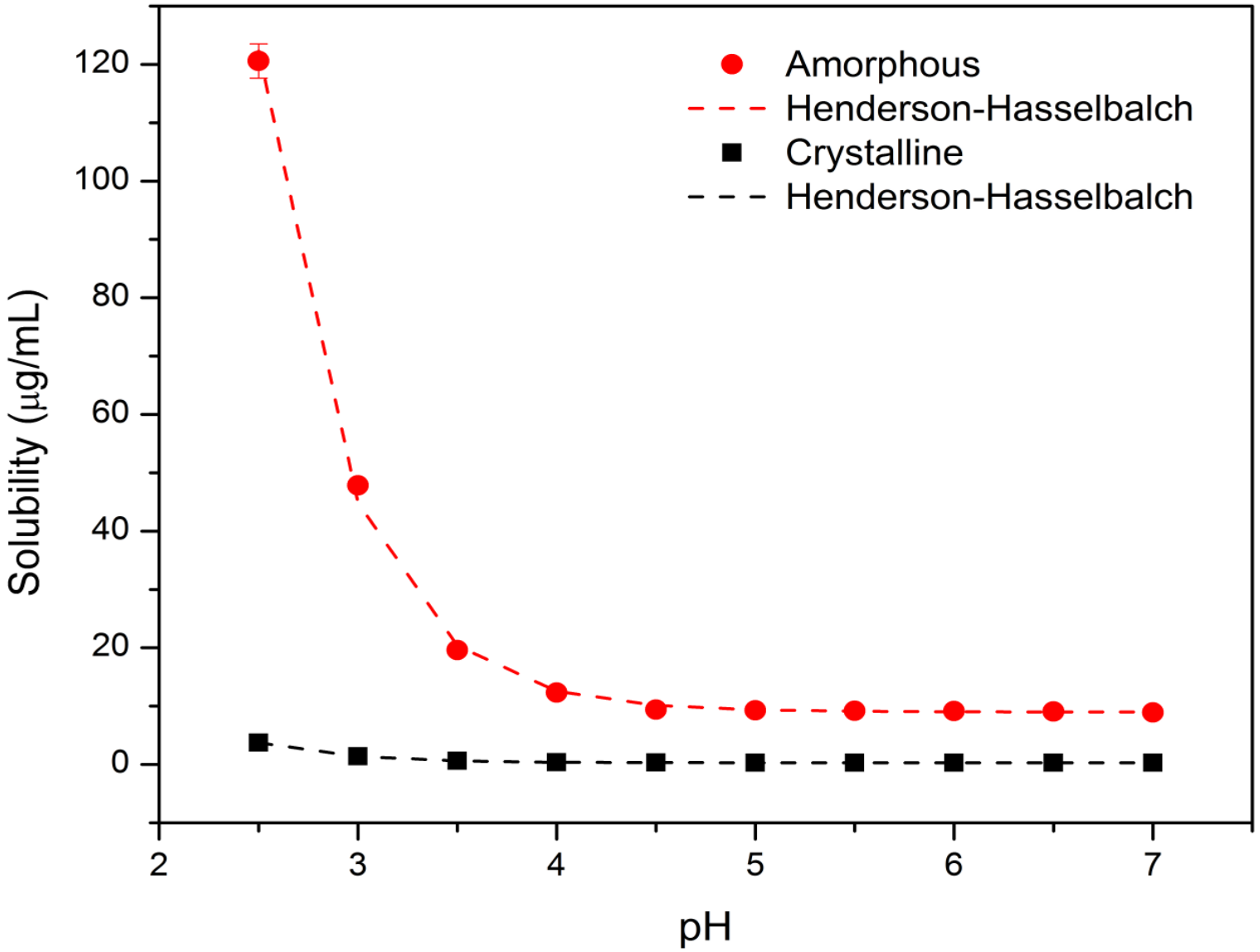
pKas: 3.6 and 4.6



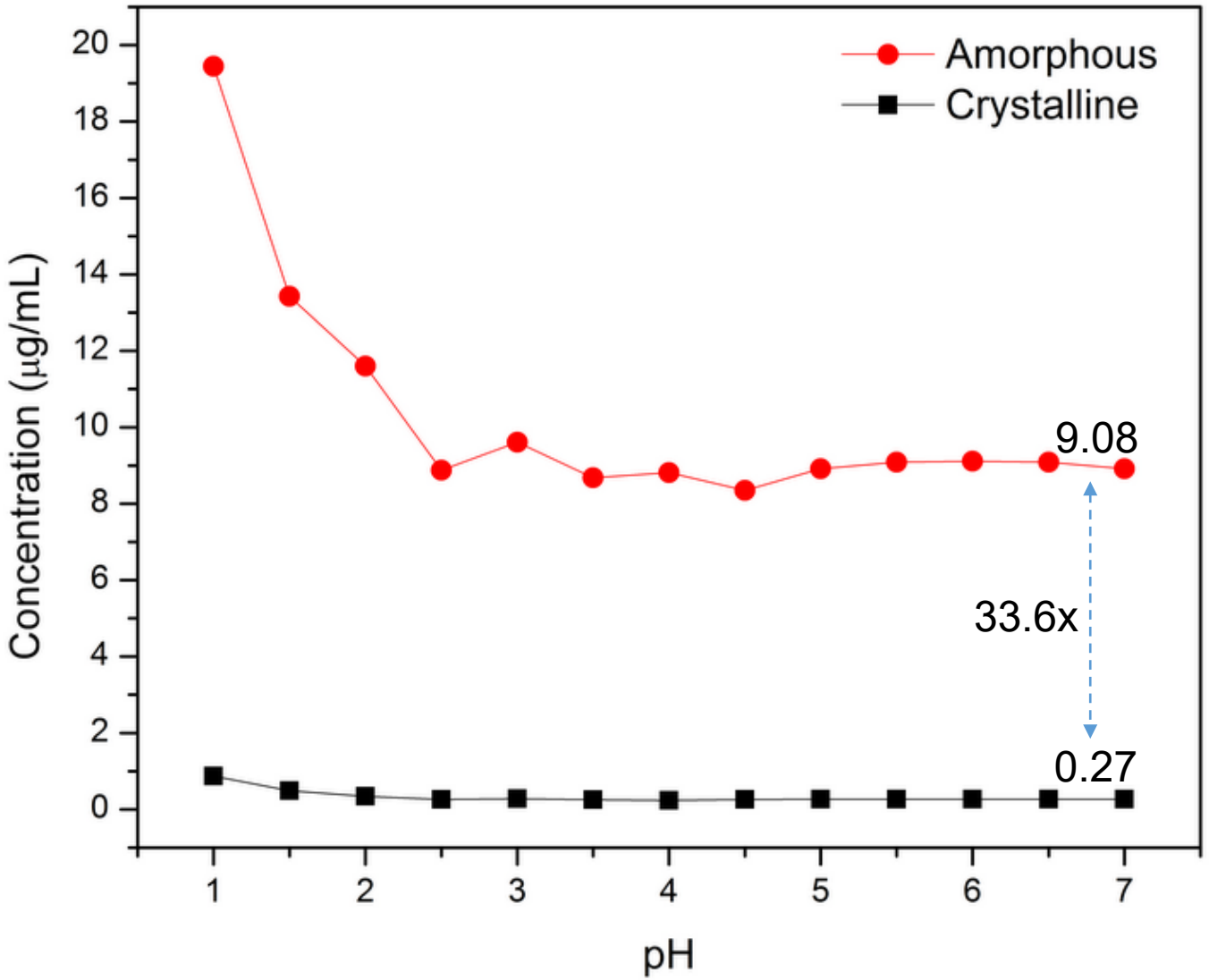
$$S_{tot} = S_B(1+10^{(pK_a - pH)})$$

Amorphous solubility

pH Solubility Profiles for Amorphous and Crystalline Posaconazole

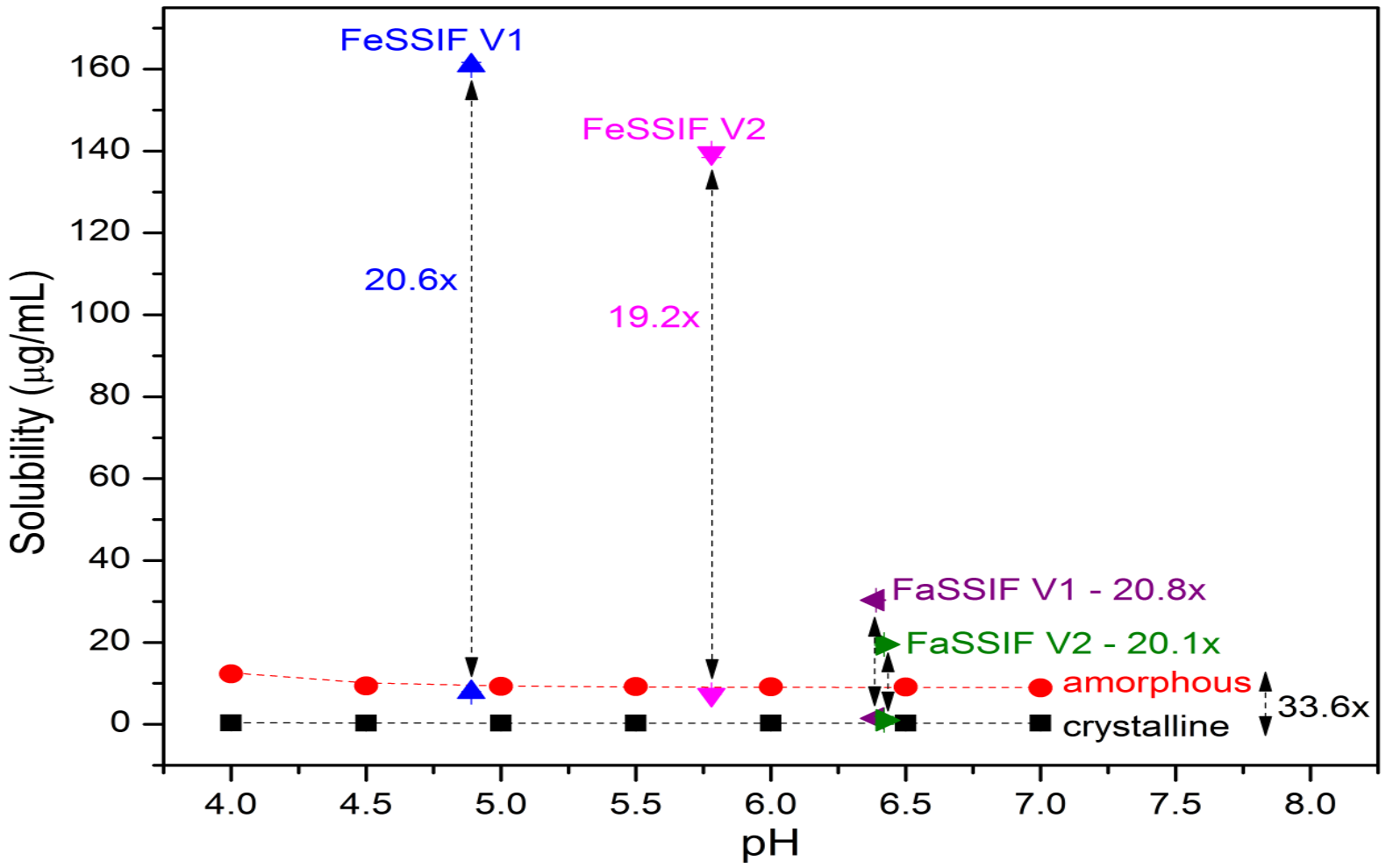


Concentration of unionized form as a function of pH



Supersaturation is ~ 33

Solubilizing Media Components



Some comments about solubility measurement

- Magnetic stirrers can grind material. This may reduce particle size and allow small particles to pass through a filter.
- Chemical stability in medium should be checked for equilibration period.
- Separation method should be carefully considered
- Ionic strength matters! Keep constant when measuring solubility as a function of pH.
- Check pH and adjust if necessary prior to equilibration point.
- Check solid state form of drug in equilibrium with solution (polymorph, salt, free form etc).

Avdeef A, Fuguet E, Llinàs A, Ràfols C, Bosch E, Völgyi G, Verbić T, Boldyreva E, Takács-Novák K. Equilibrium solubility measurement of ionizable drugs–consensus recommendations for improving data quality. ADMET and DMPK. 2016 Jun 29;4(2):117-78.

Impact of solid state form on dissolution rate

Noyes-Whitney equation:

$$\frac{dM}{dt} = \frac{DA}{h}(C_s - C) \approx \frac{DA\,C_s}{h}$$

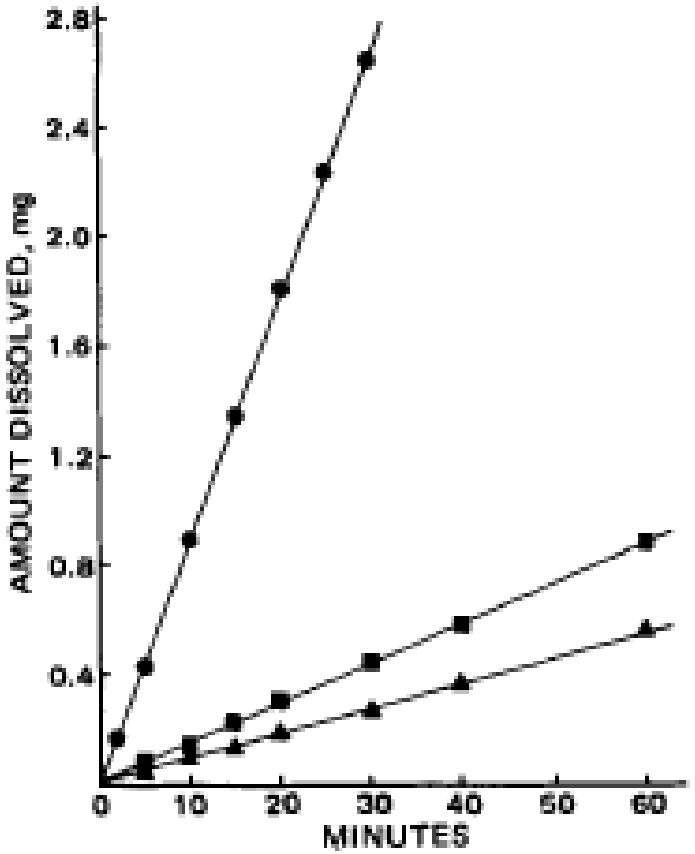
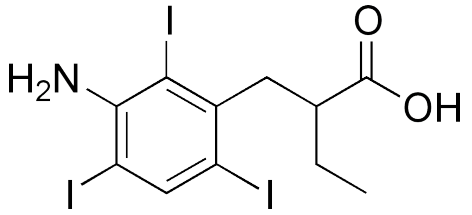


Figure 5—*Intrinsic dissolution of Form I (▲), Form II (■), and the amorphous form (●) of iopanoic acid.*

Iopanoic acid

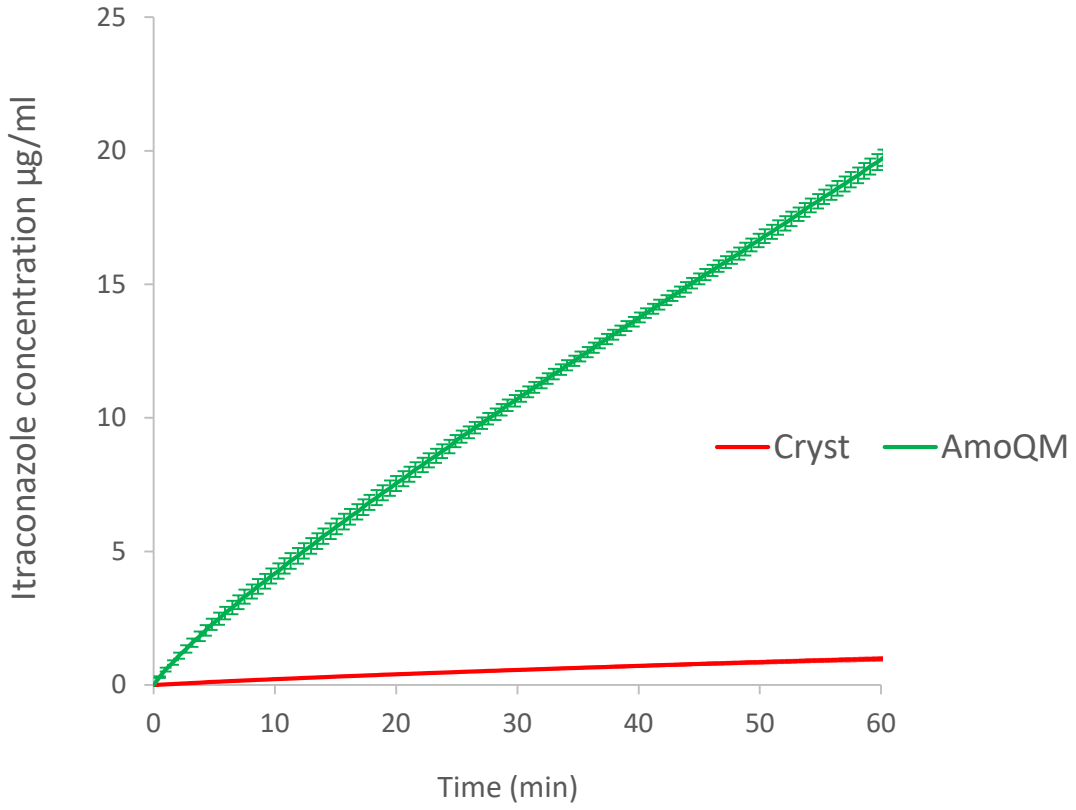


- Comparison of intrinsic dissolution rates of three solid forms: two polymorphs and amorphous solid
- IDRs are reflecting (apparent) solubility values of the solids

Stagner & Guillory, 1979, J Pharm Sci

Amorphous Form has a Faster Dissolution Rate than Crystal

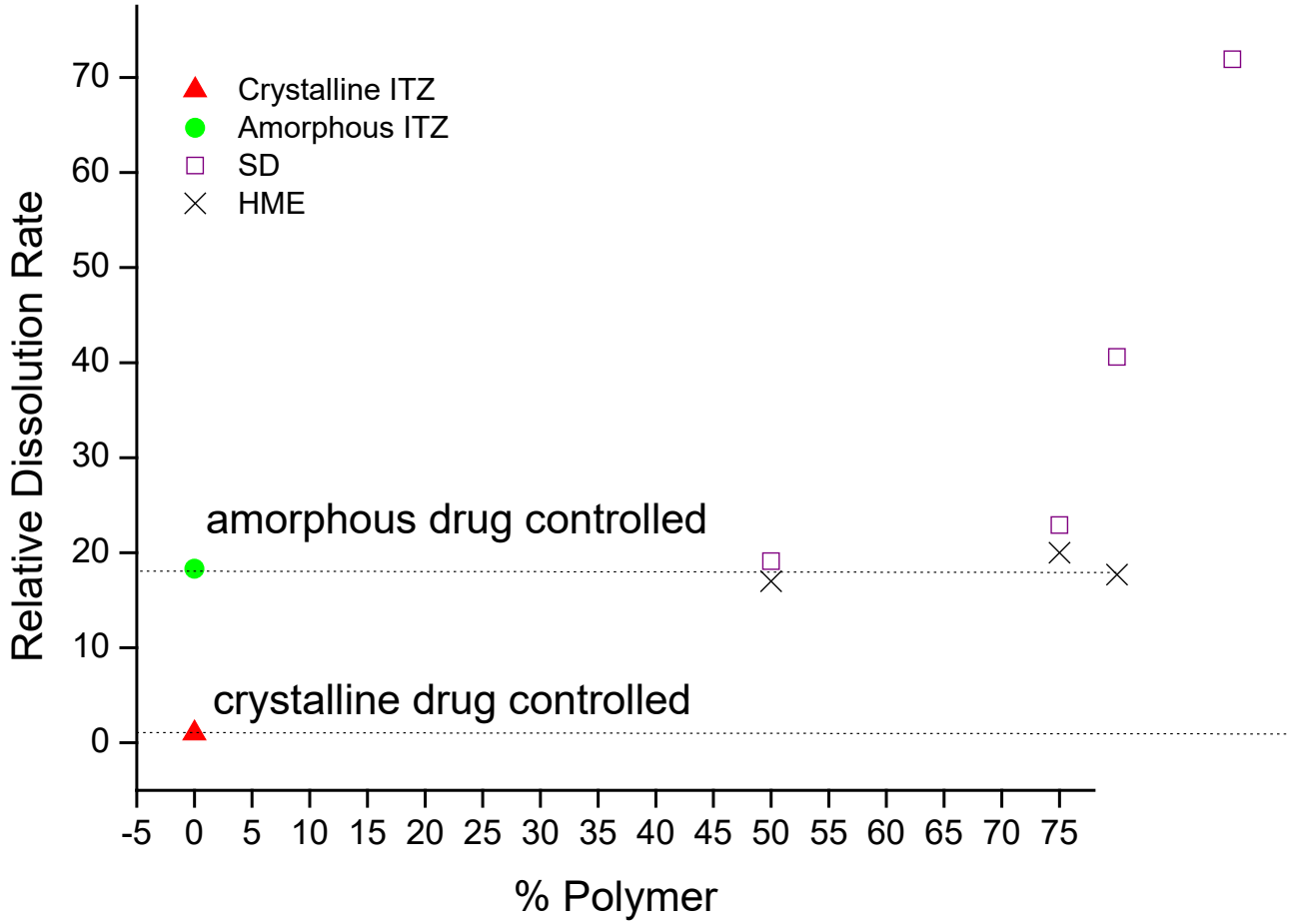
$$\frac{dM}{dt} = \frac{DA}{h}(C_s - C) \approx \frac{DA\,C_s}{h}$$



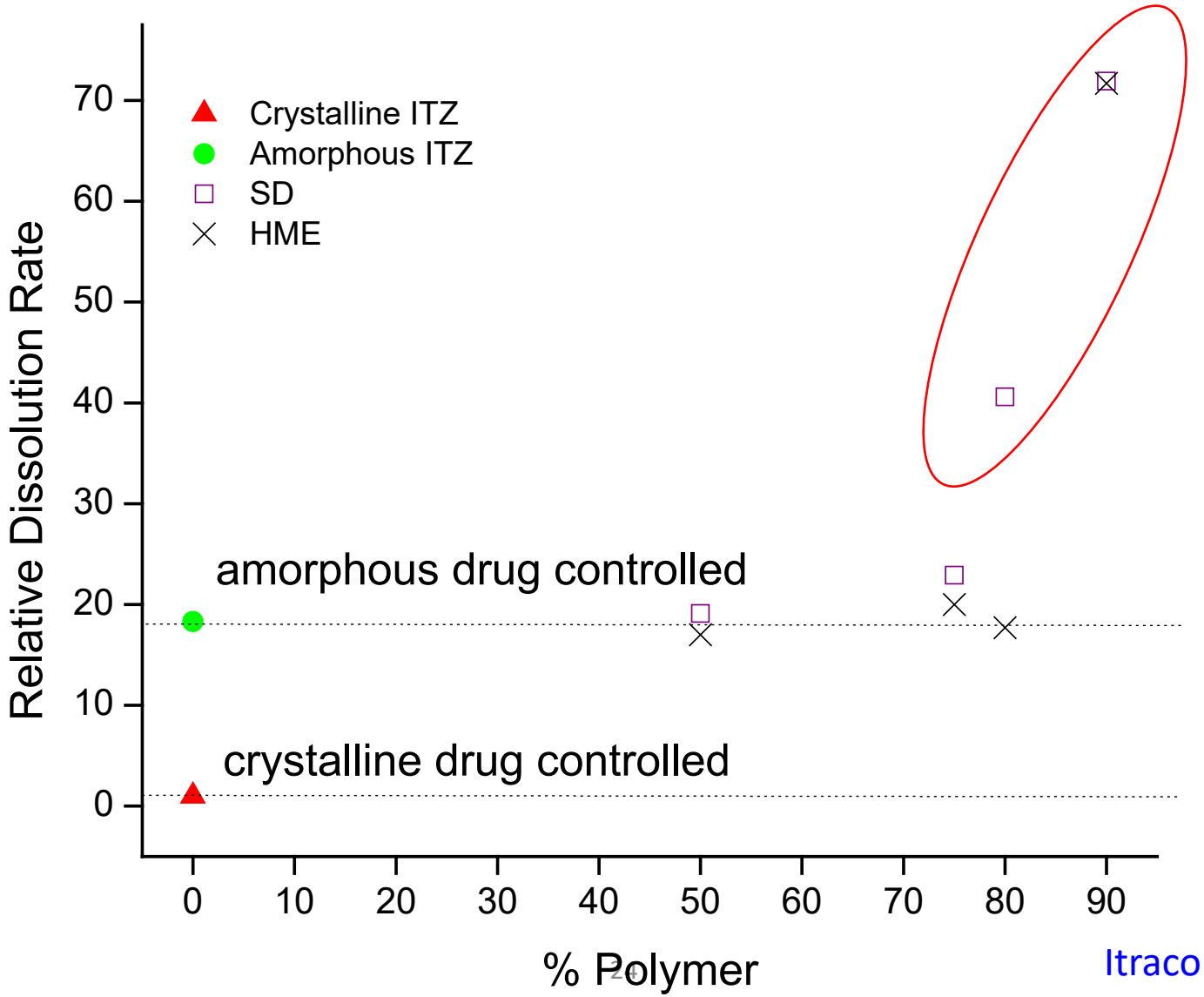
Slope of amorphous form ~ 20X crystal

Bhardwaj et al. (2018). Int J Pharm 540(1-2):106-119.

Dissolution of Amorphous Solid Dispersions



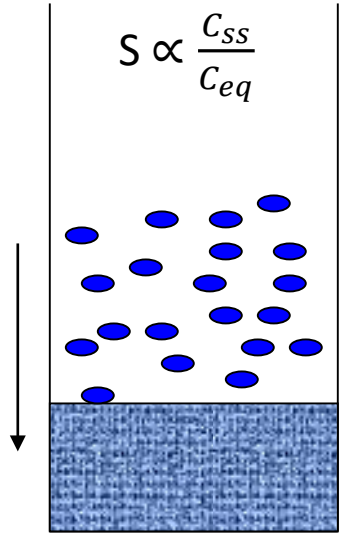
Dissolution rate of drug from an ASD can be **much** faster than from pure amorphous drug



No predictive models for these systems

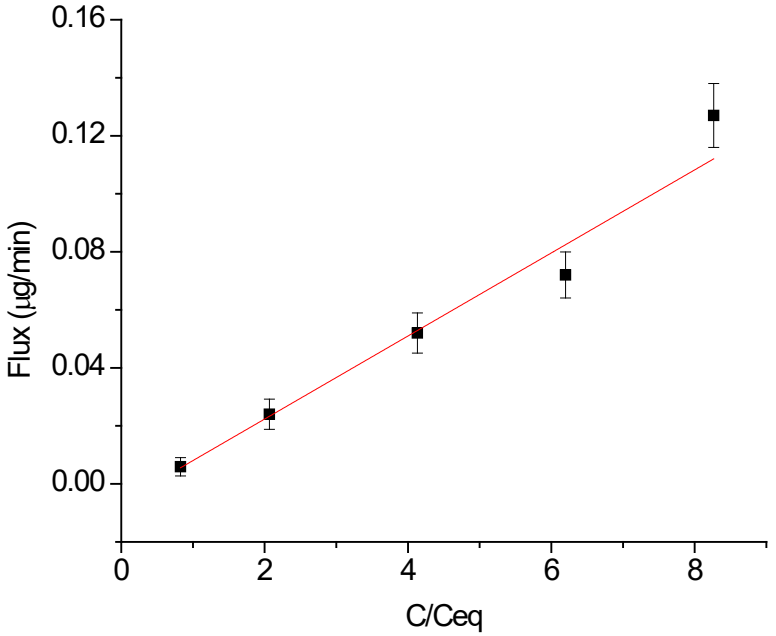
Itraconazole-PVPVA system

Supersaturation and Membrane Transport



supersaturated

activity solid < activity solute



Flux $\propto$ Supersaturation

Defining Supersaturation

$$S = \frac{a}{a_{eq}} = \frac{\gamma c}{\gamma_{eq} c_{eq}} \approx \frac{c}{c_{eq}}$$

$$S \approx \frac{c}{c_{eq}} \text{ is only valid when } \gamma \approx \gamma_{eq}$$

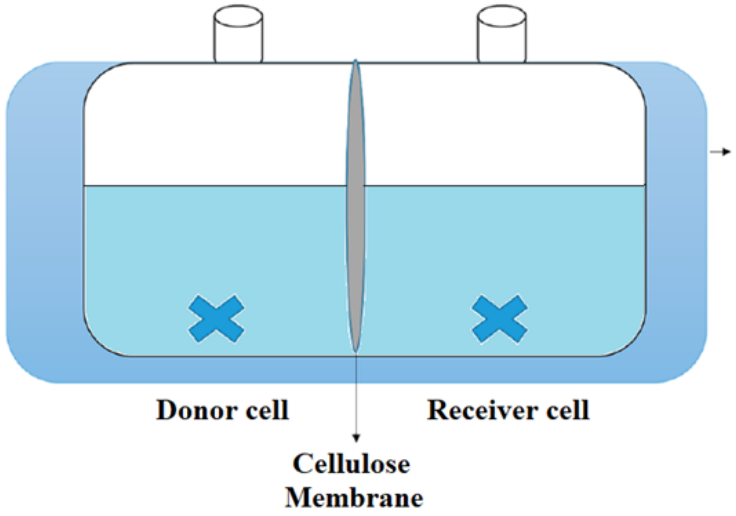
We can check this relationship by performing flux measurements

Supersaturation (activity based)

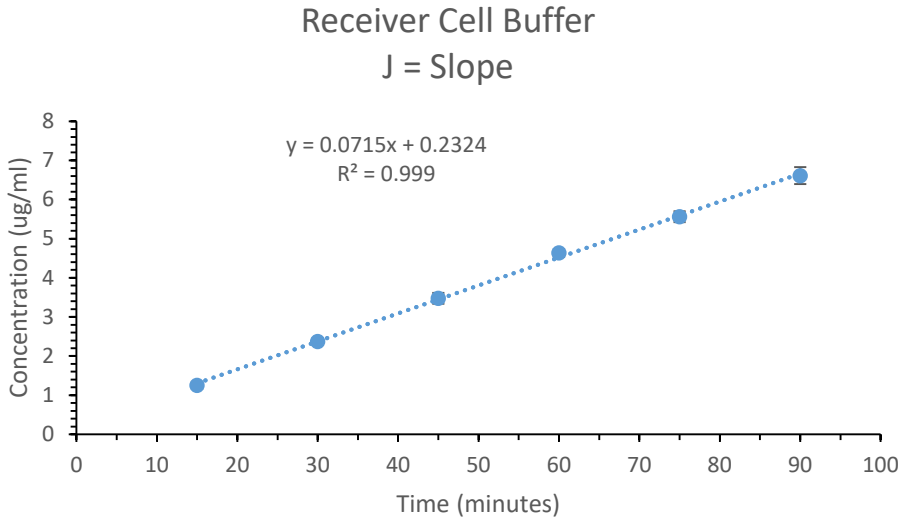
$$S = \frac{a}{a^*} \qquad J = \frac{Da}{h\gamma_m} \qquad S = \frac{J}{J^*}$$

J is the diffusive flux across a membrane and a is activity of the solute in the solution.

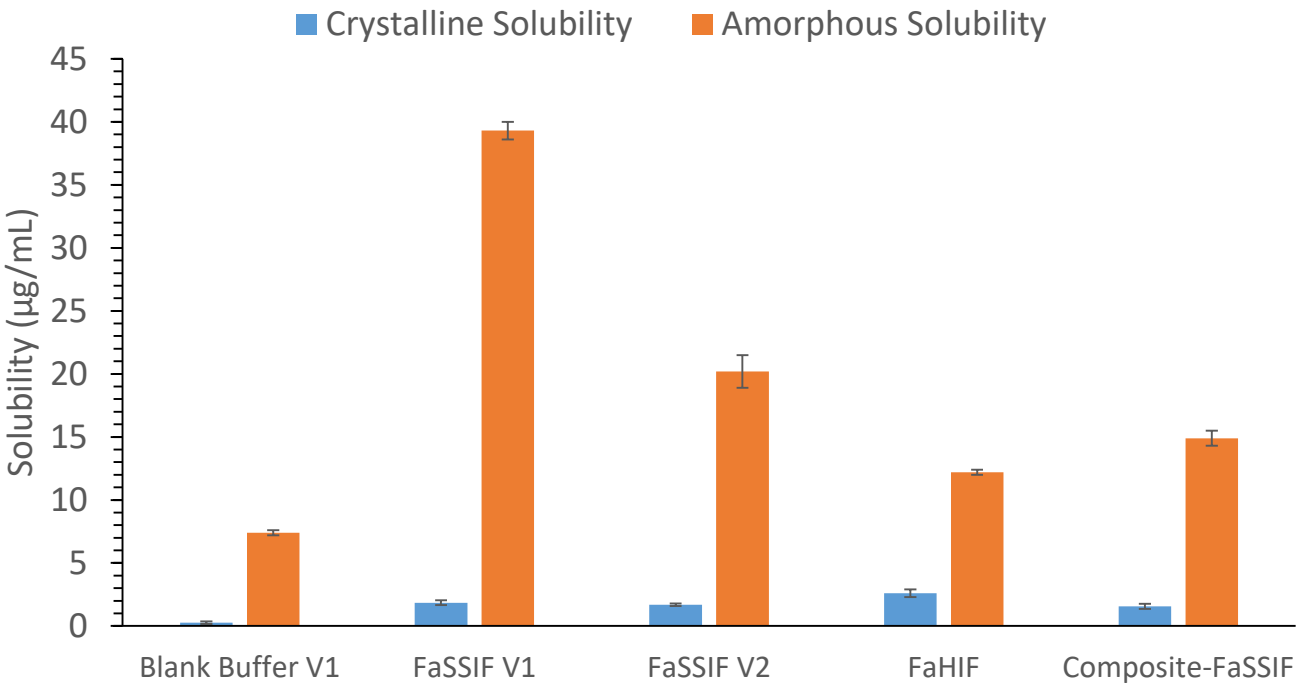
D is the diffusion coefficient of the solute, h is the thickness of the membrane and *γm* is the activity coefficient of the solute in the membrane.

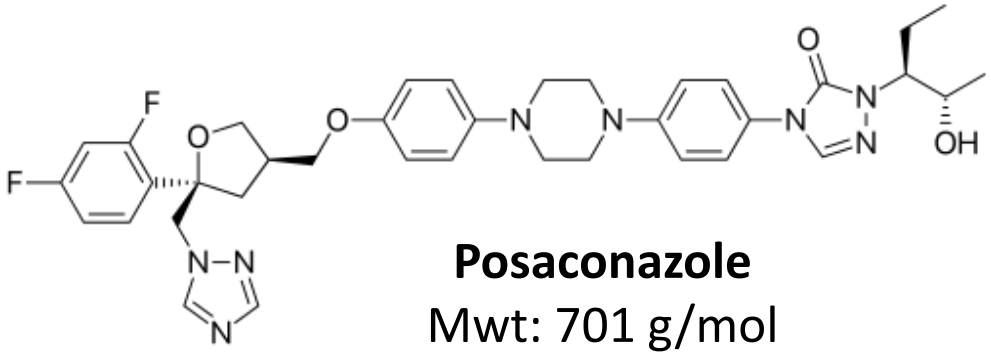


$$J = \frac{dm}{Adt}$$



Impact of Solubilizing Media on Crystalline and Amorphous Solubility



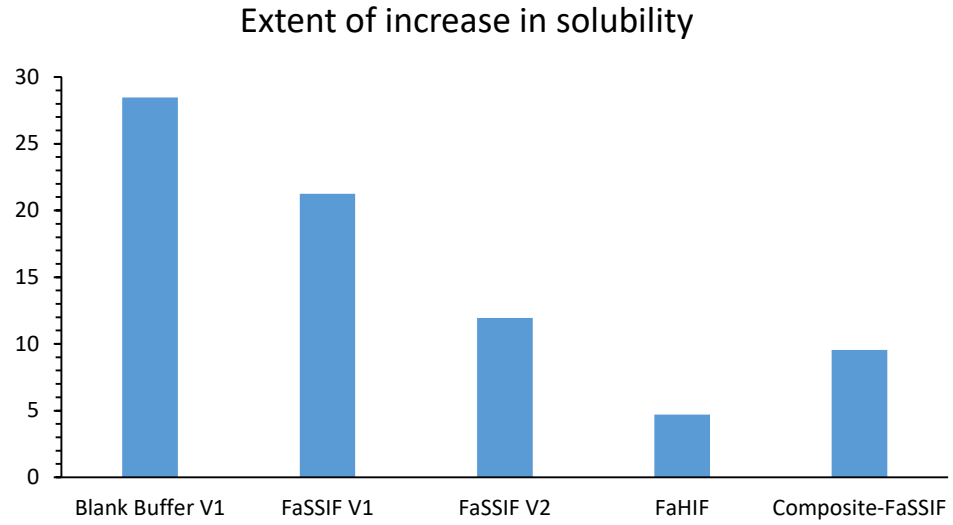


Posaconazole

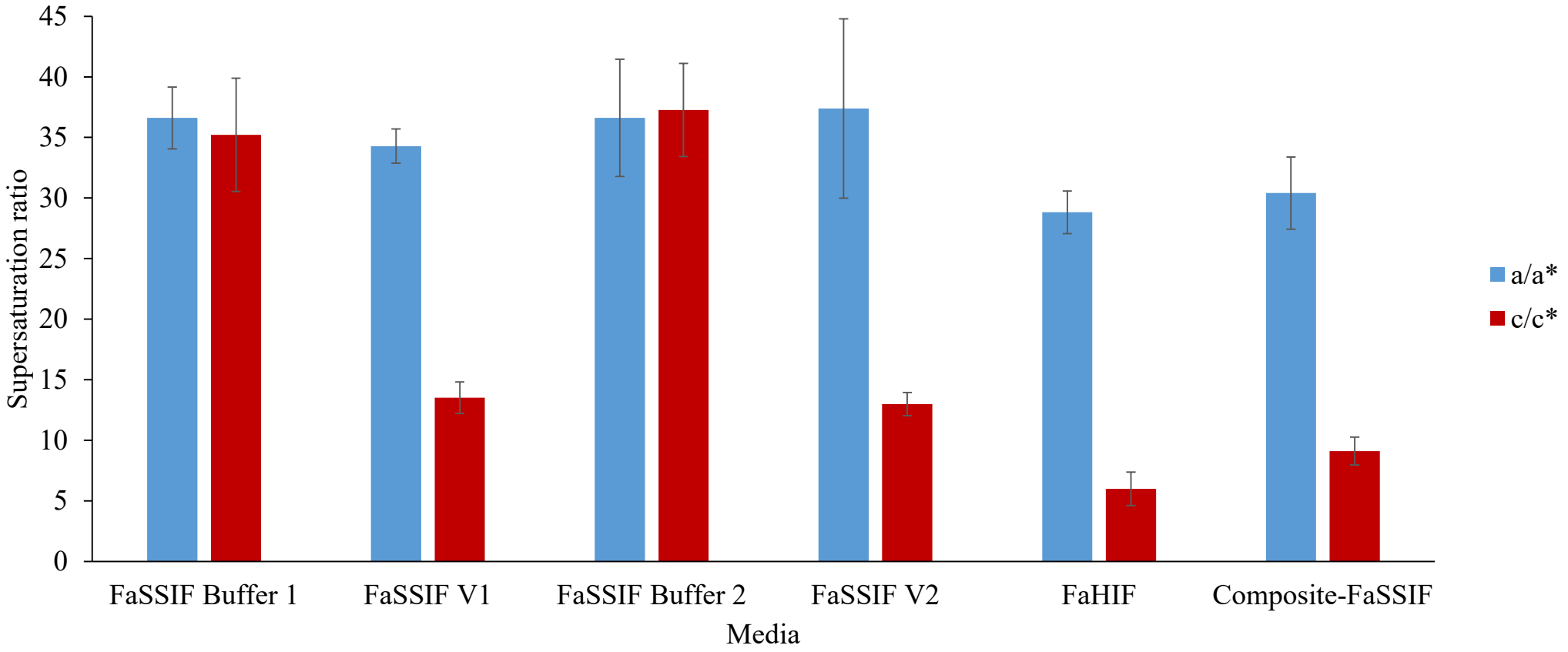
Mwt: 701 g/mol

Log P: 4.6

pKa: 3.6 and 4.6



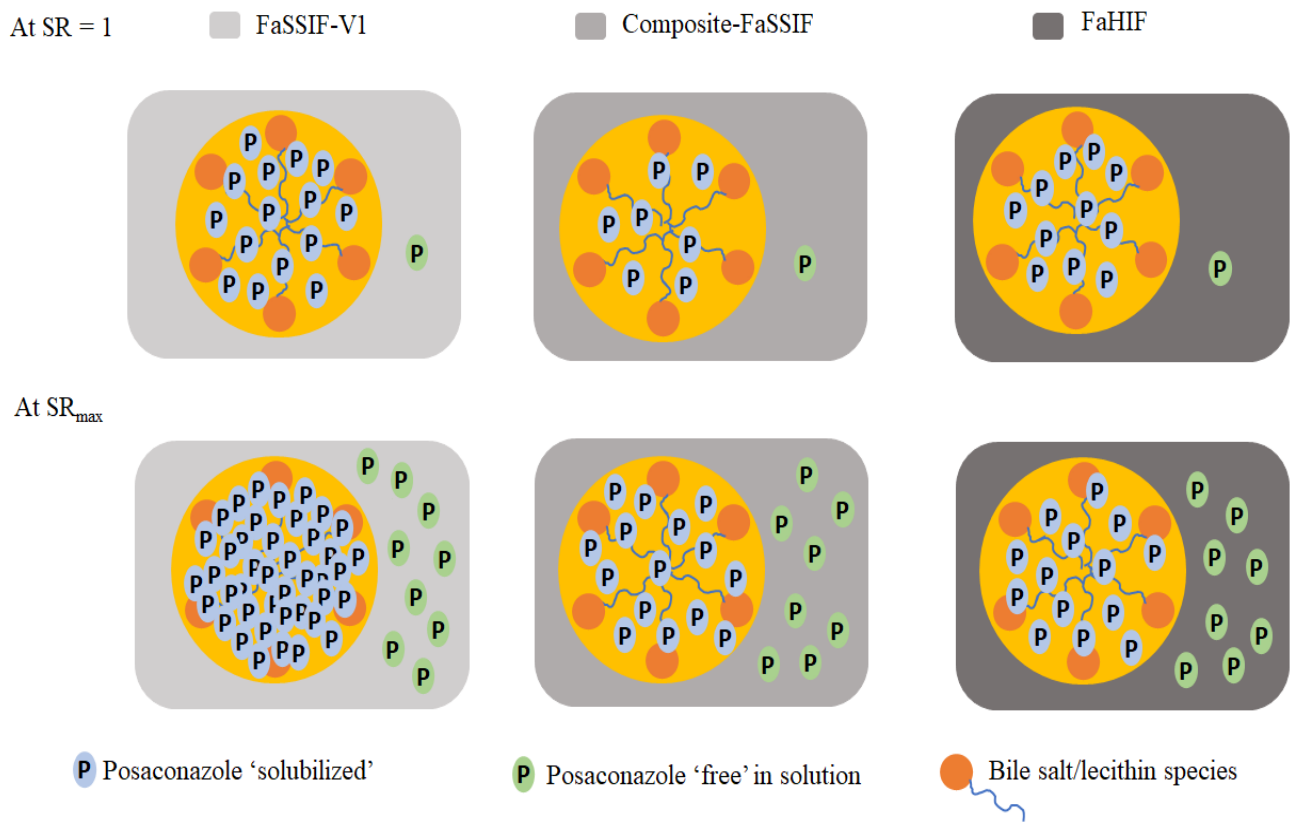
Activity versus Concentration-Based Supersaturation



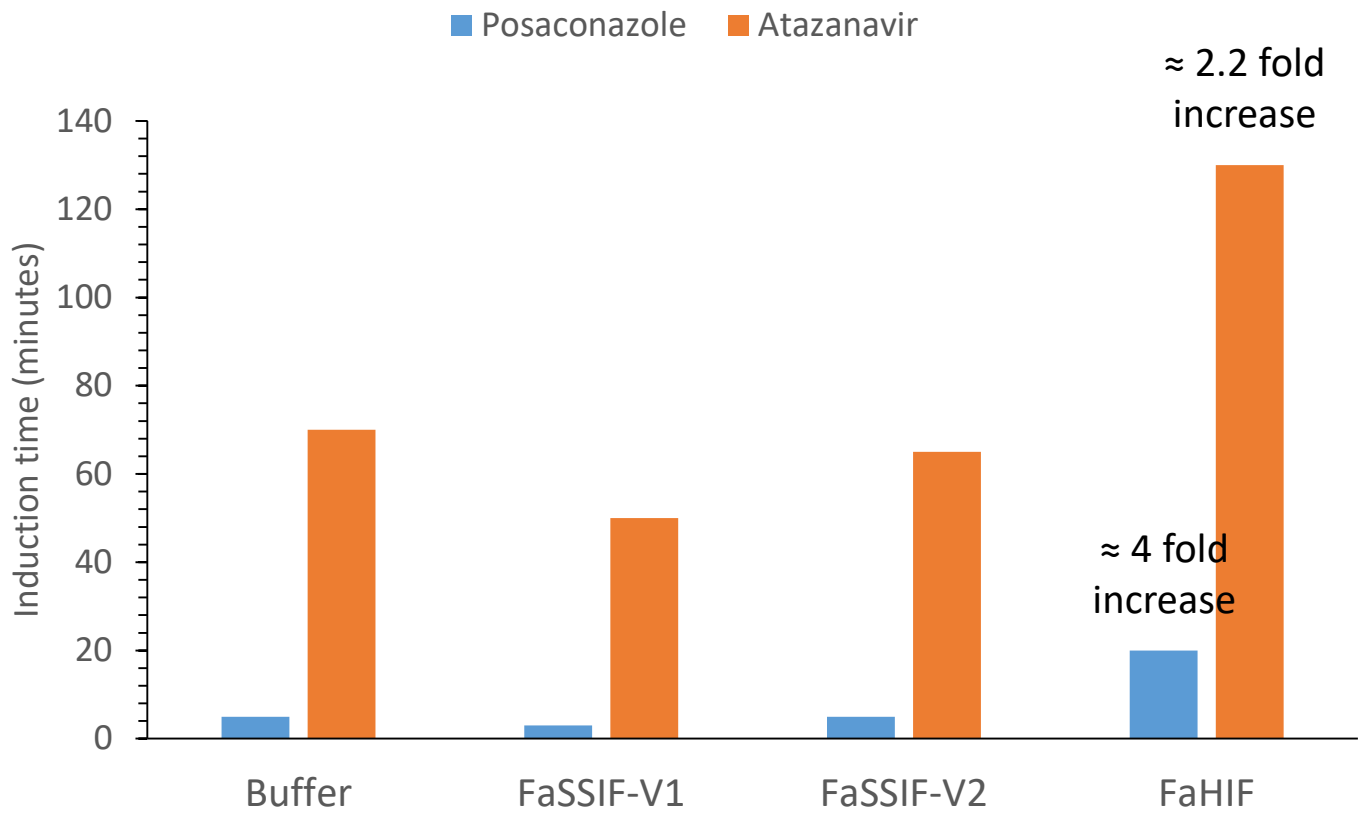
Flux measurements are similar for the different media. Concentration-based estimates are much lower in solubilizing media

Explanation – Micelle-water Partition Coefficient is not Constant with Solute Concentration

Medium	$K_{m/w}$ at crystalline solubility	$K_{m/w}$ at amorphous solubility
FaSSIF-V1	13.9	5.3
Composite-FaSSIF	7.4	1.9
FaHIF	11.3	1.6



Supersaturation Duration Also Depends on the Medium



Summary

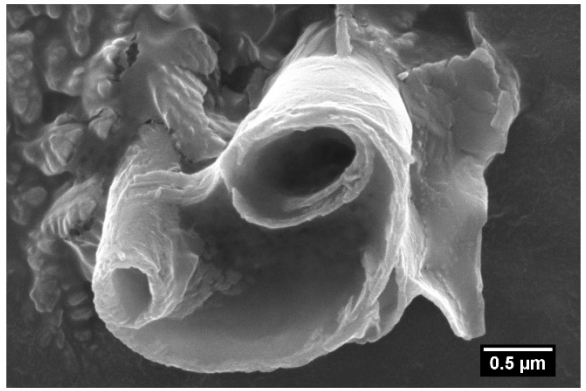
- Solubility is dictated by the solid and the solvent properties
- Many different values of solubility can be measured depending on experimental set-up. Which value is important?
- Current approach of defining supersaturation in complex medium is unlikely to be predictive of transport behavior
- Better estimates of supersaturation are also vital to understand crystallization kinetics. Impact of media components on crystallization kinetics are not well understood.

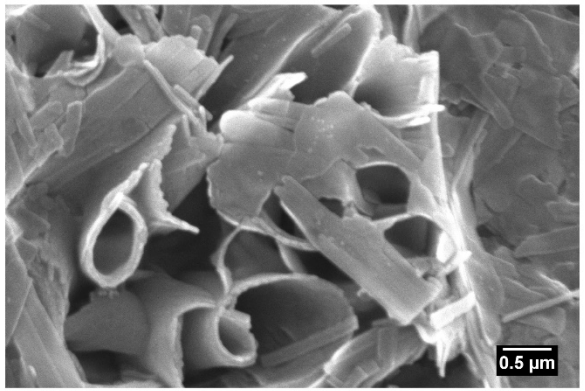
Acknowledgements

- Ahmed Elkhabaz
- Dana Moseson
- Anura Indulkar
- Geoff Zhang
- Gao Yi
- Tu van Duong
- Patrick Augustijns
- Joachim Brouwers
- Vivek Bhardwaj

- FDA
- NSF
- AbbVie

And for fun – some cool pictures!





Posaconazole crystallized from buffer and FaSSIF-V1 (with polymer)

Amorphous posaconazole precipitated in HIF