High throughput solubility measurement with crystalline/amorphous information

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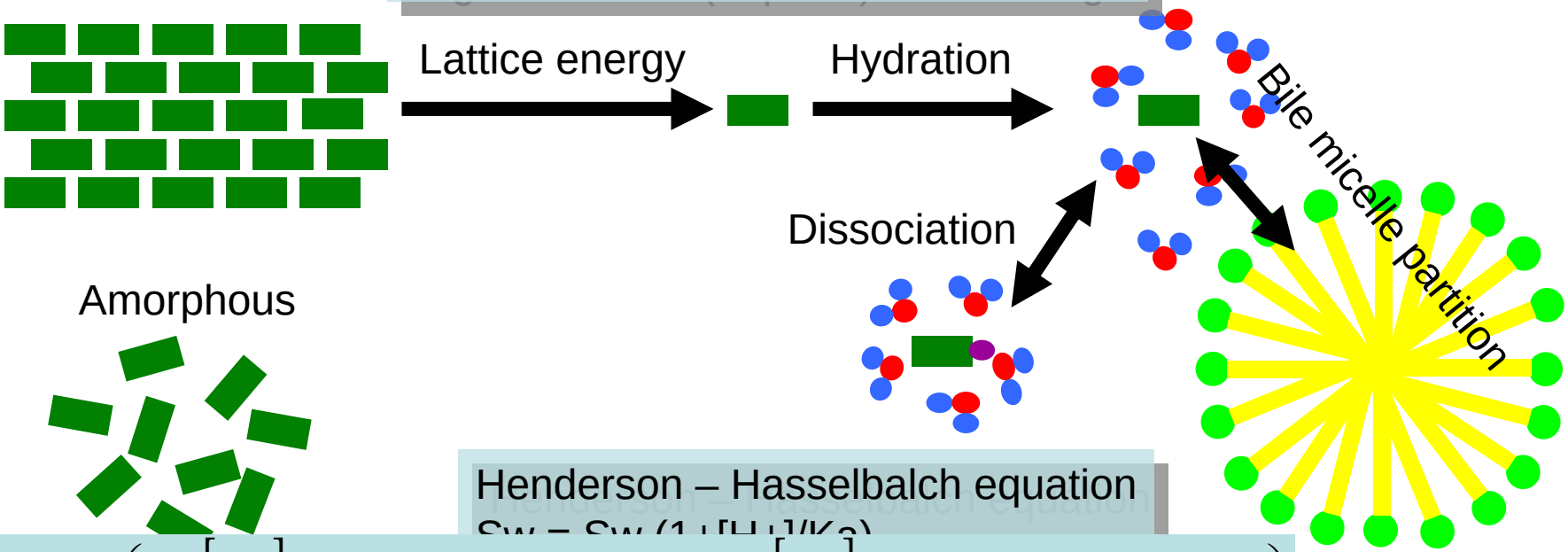
Outline

- Introduction of new solubility screen
- Results from 1700 measurements
- Strategy to apply the new method in drug discovery
- Solubility calculation for oral absorption simulation

What determines solubility?

Yalkowski's equation
$\log Sw0 = 0.8 - (m.p.-25) \times 0.01 - \log P$



Henderson – Hasselbalch equation

$$S_{tot} = S_0\left(1+\frac{[H^+]}{Ka}+\frac{C_{micelles}}{C_{water}}\cdot 10^{\log P_{micelles,undissociated}}+\frac{[H^+]}{Ka}\cdot\frac{C_{micelles}}{C_{water}}\cdot 10^{\log P_{micelles,dissociated}}\right)$$

Dressman's equation
$\log P_{mic,undissolved} = 0.74\log P + 2.29$

Traditional kinetic solubility

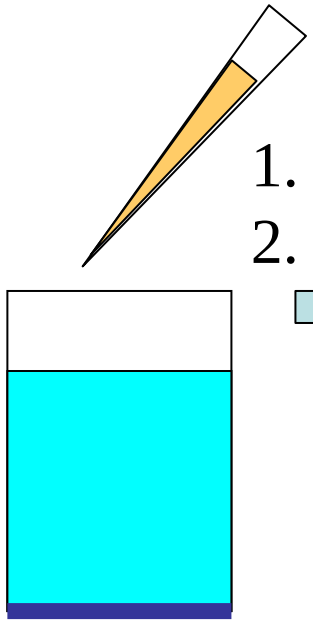
- Start with DMSO sample solution
- Short incubation time
- Detect turbidity by nephelometry
- *Precipitant is assumed to be amorphous*
  - *This assumption is wrong*

Kinetic solubility > thermodynamic sol

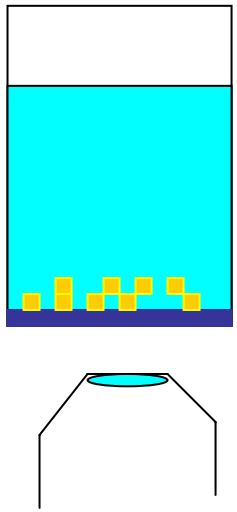
- Three possible reasons
  - ~~Solubilitization effect of DMSO~~
  - Short incubation time
  - Crystal/amorphous

New solubility assay

DMSO stock



1. Long incubation
2. Centrifuge



PLM

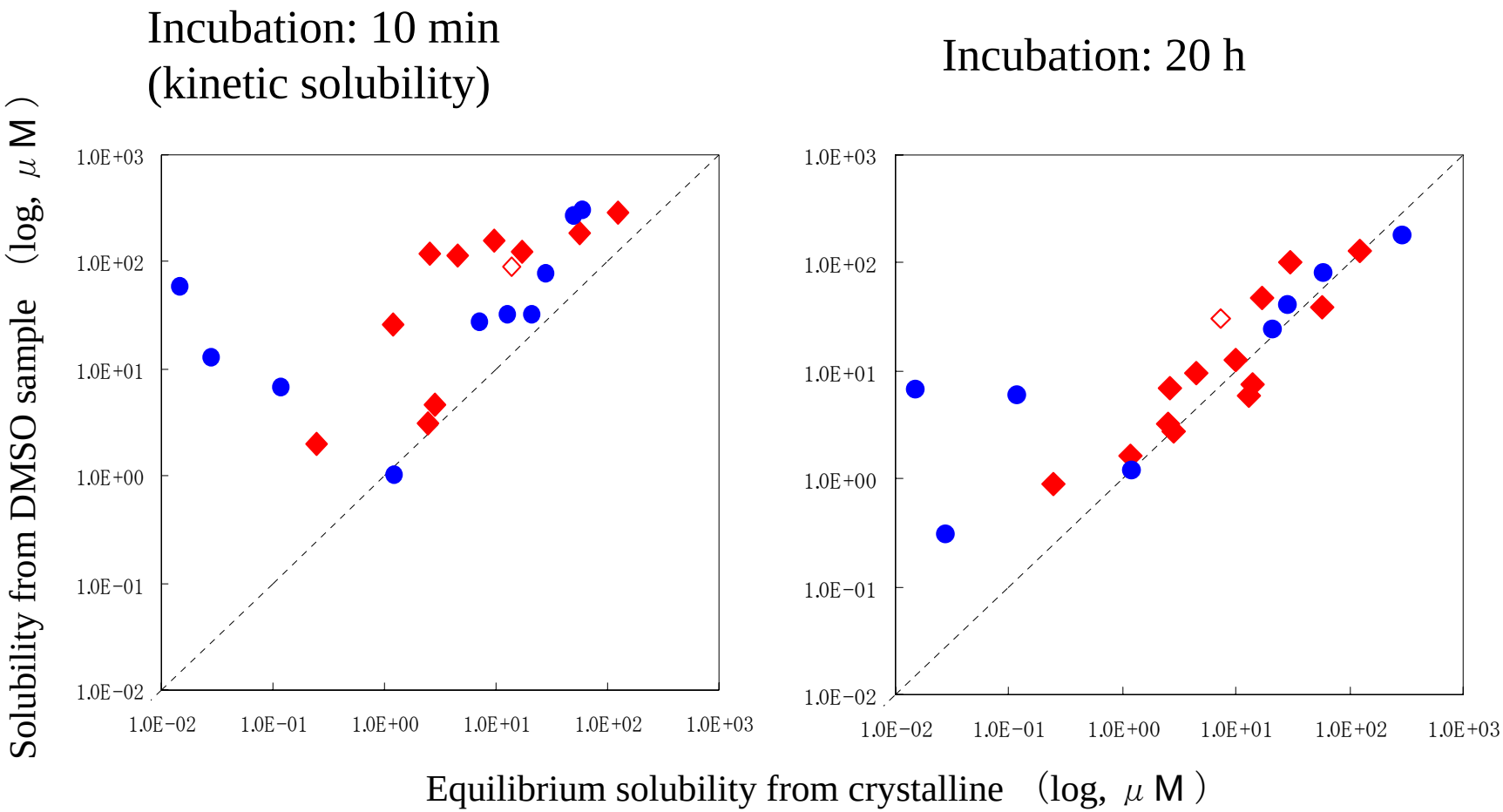
Filtration

- LC-MS
- HPLC

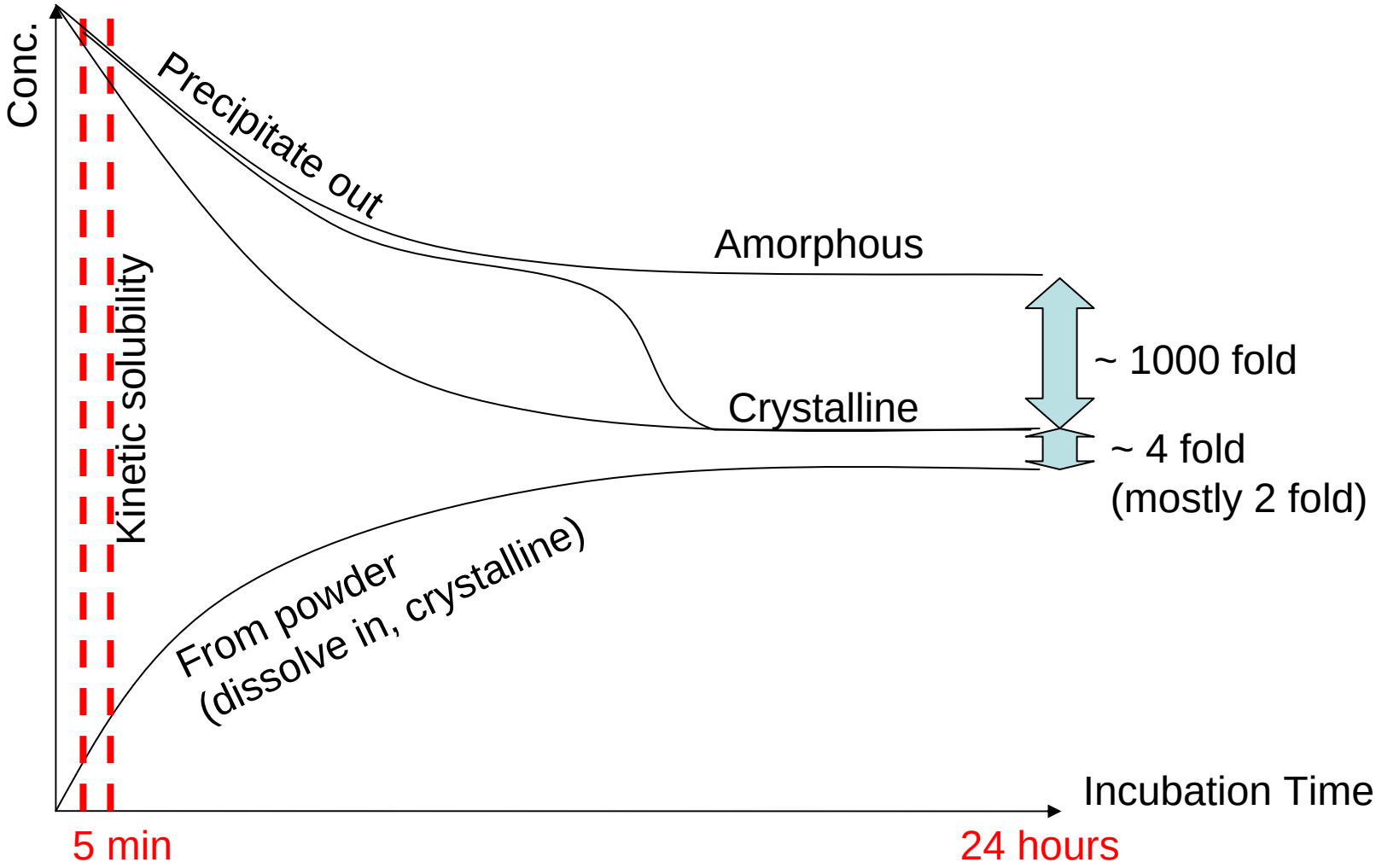
Final DMSO = 1%
(little effect on solubility)

Glass bottom plate

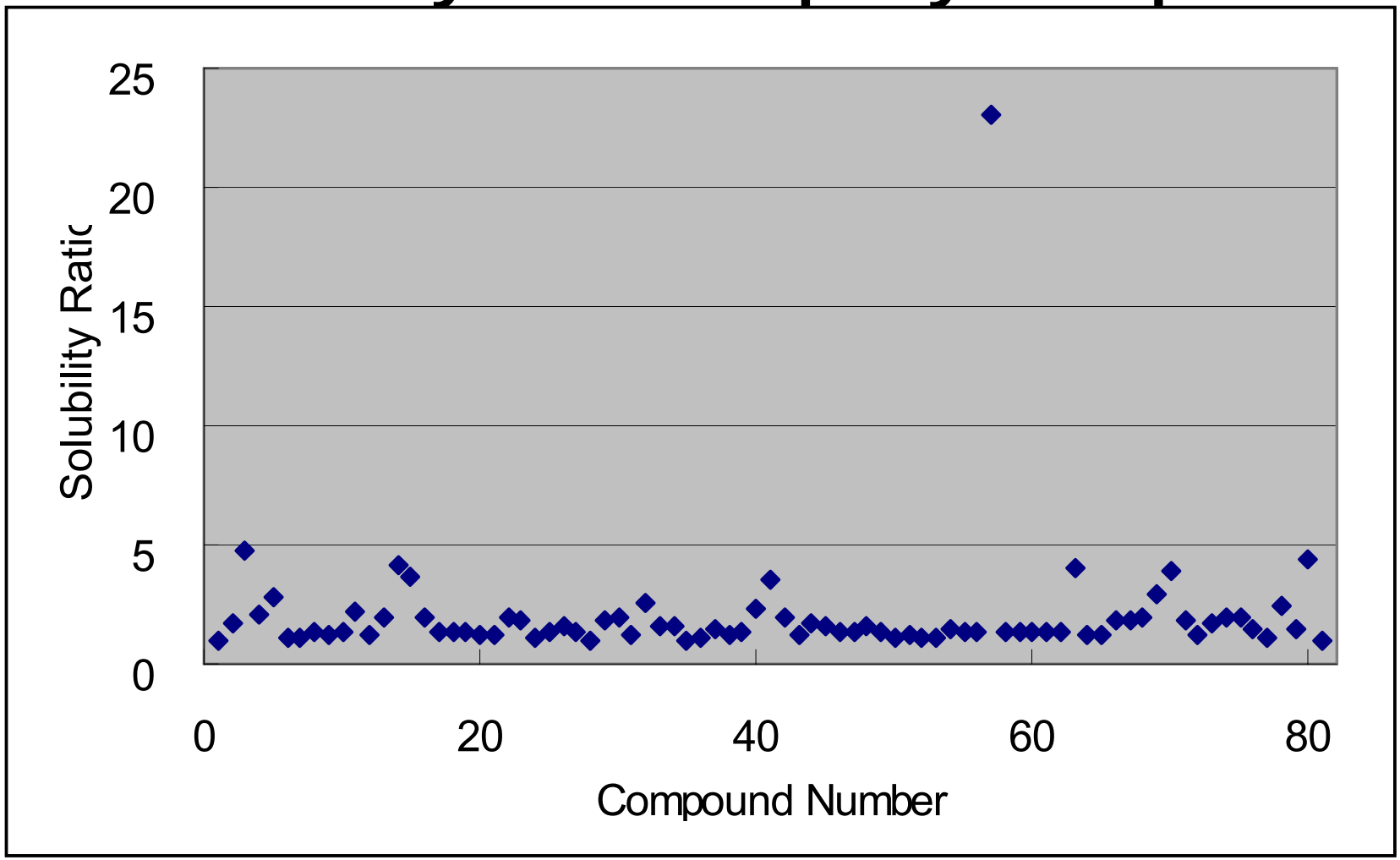
Validation using Marketed Drugs



Concentration time profile

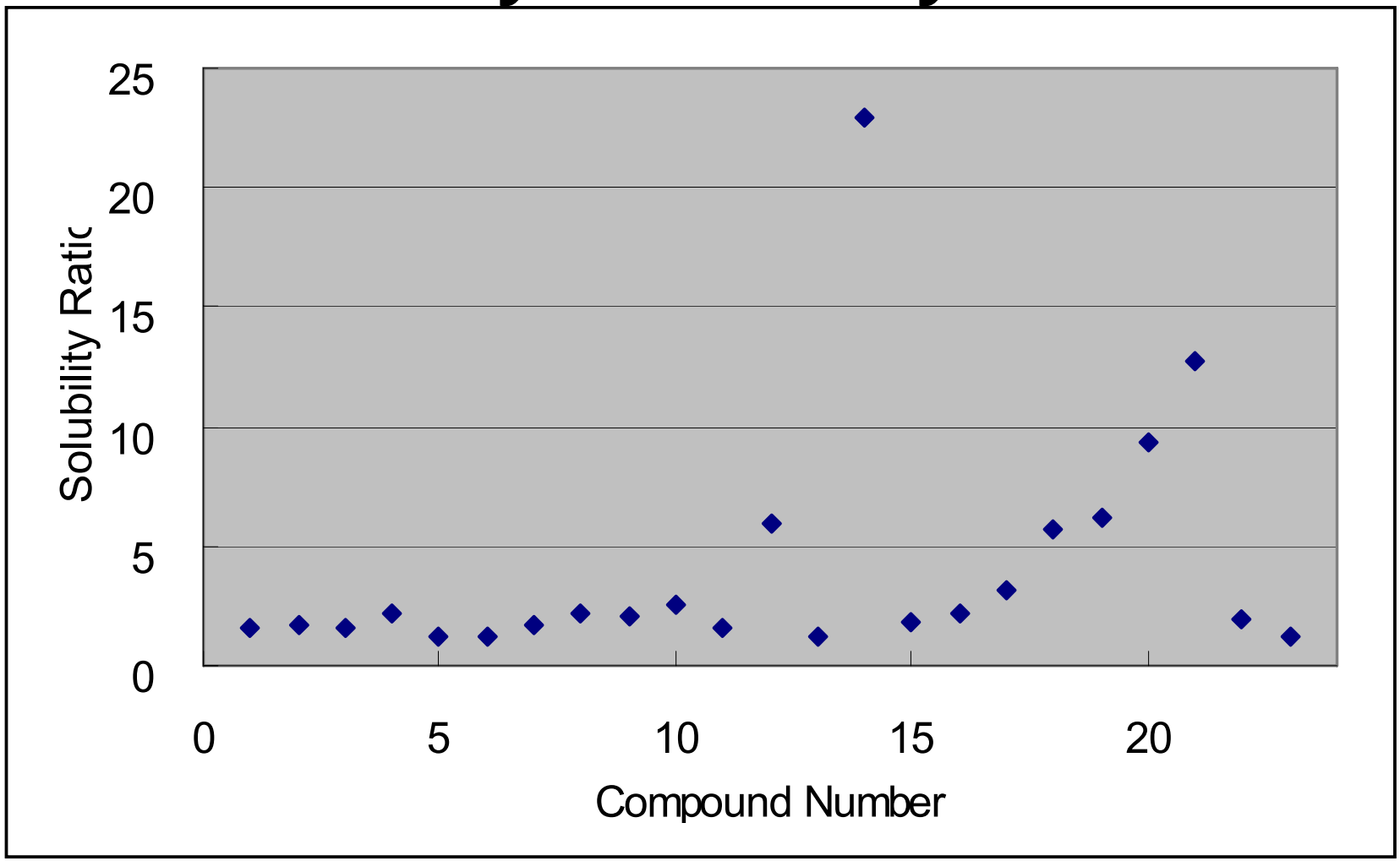


Solubility Ratio: polymorphs



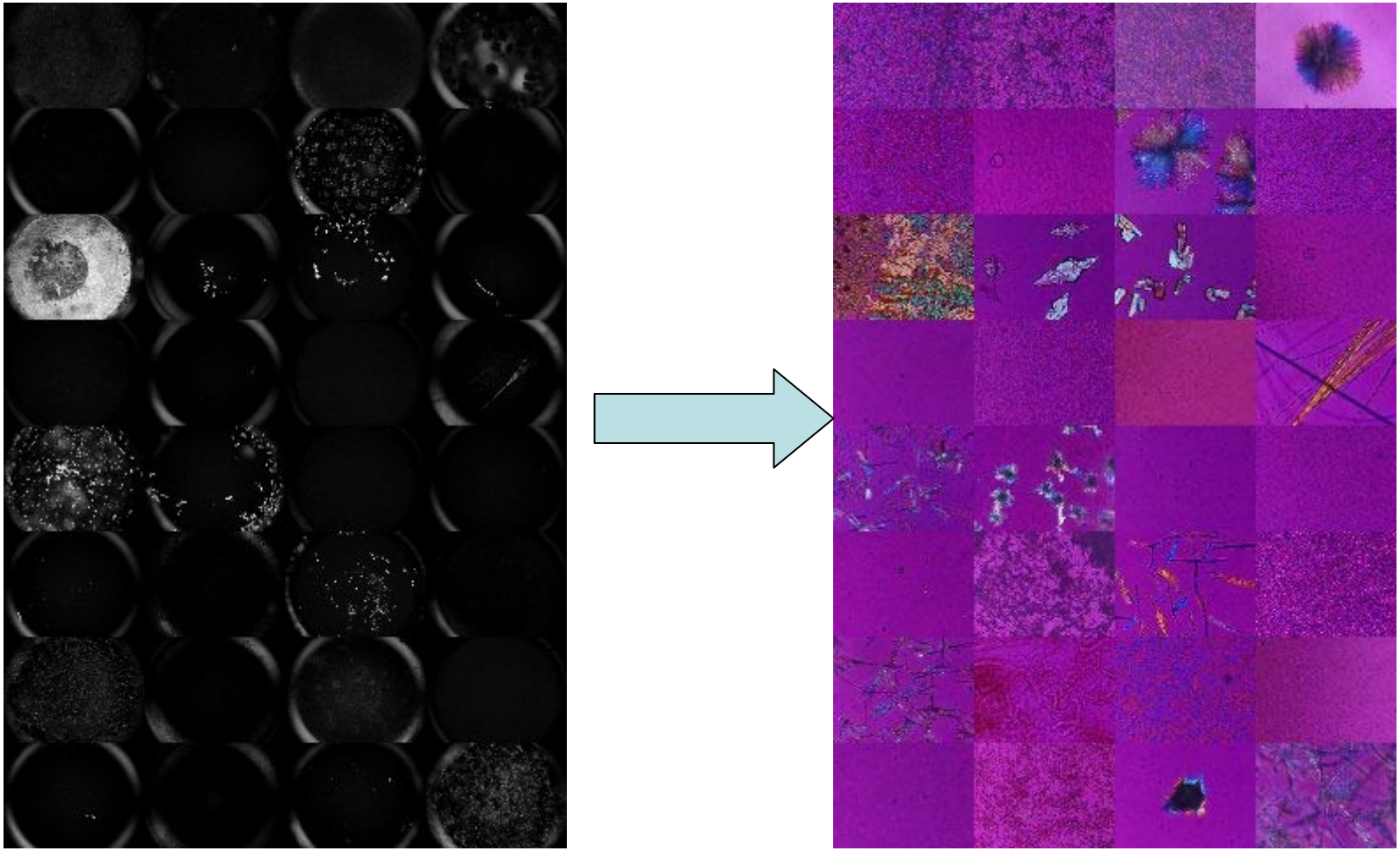
M. Pudipeddi, A. T. M. Serajuddin. *J. Pharm. Sci.* **2005**, *94*, 929–939.

Solubility Ratio: hydrates

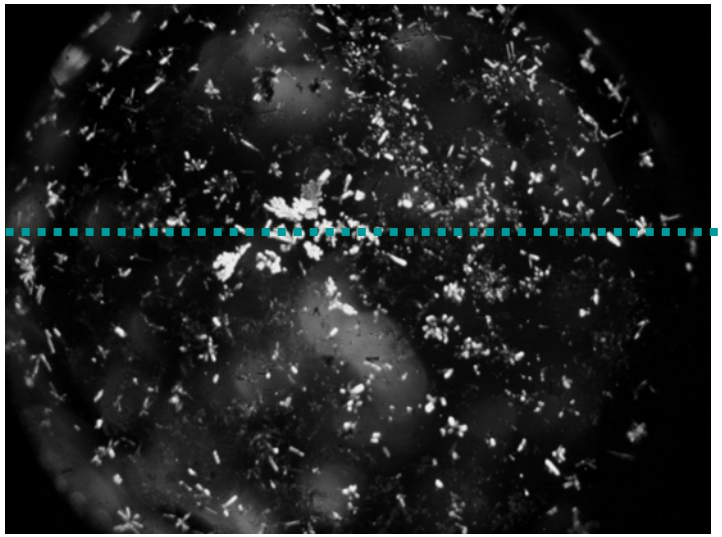


M. Pudipeddi, A. T. M. Serajuddin. *J. Pharm. Sci.* **2005**, *94*, 929–939.

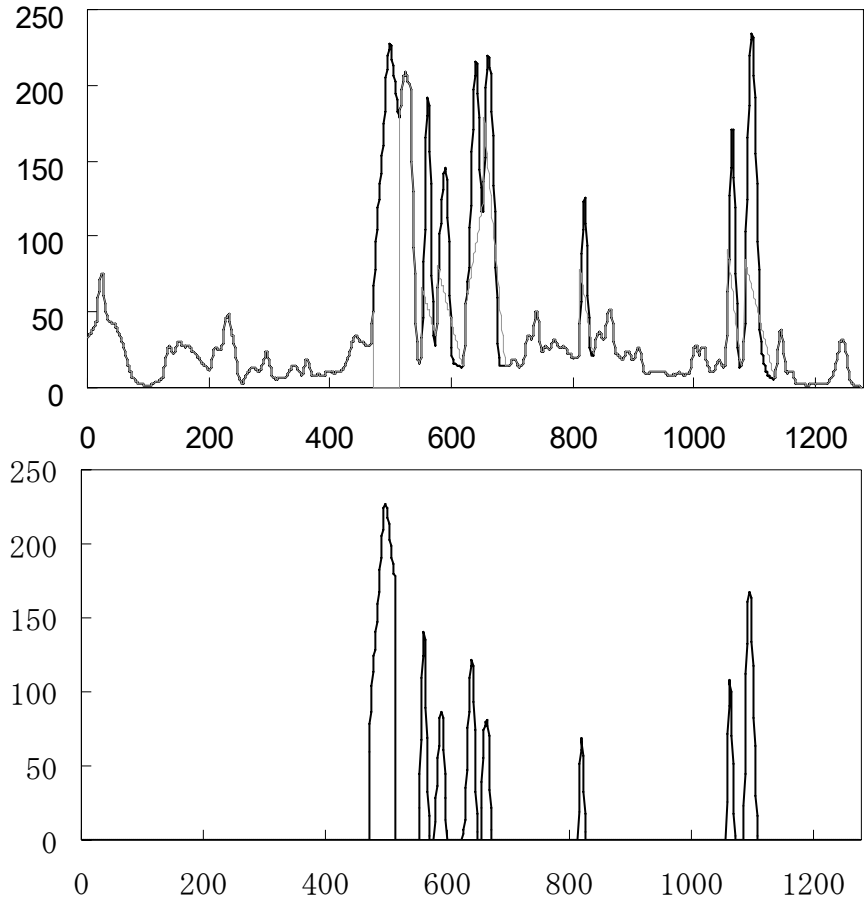
Photo of 96 well plate



Auto PLM diagnostic



Intensity – position



About 85% correct against human eye observation.

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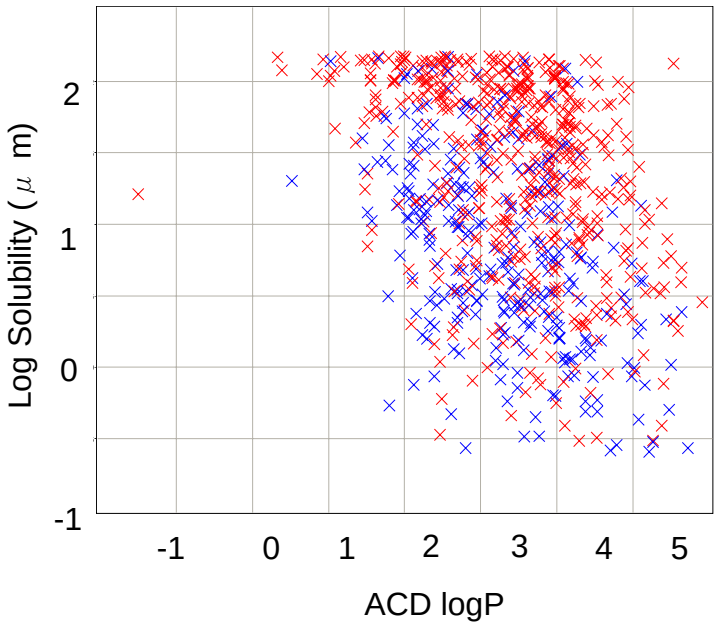
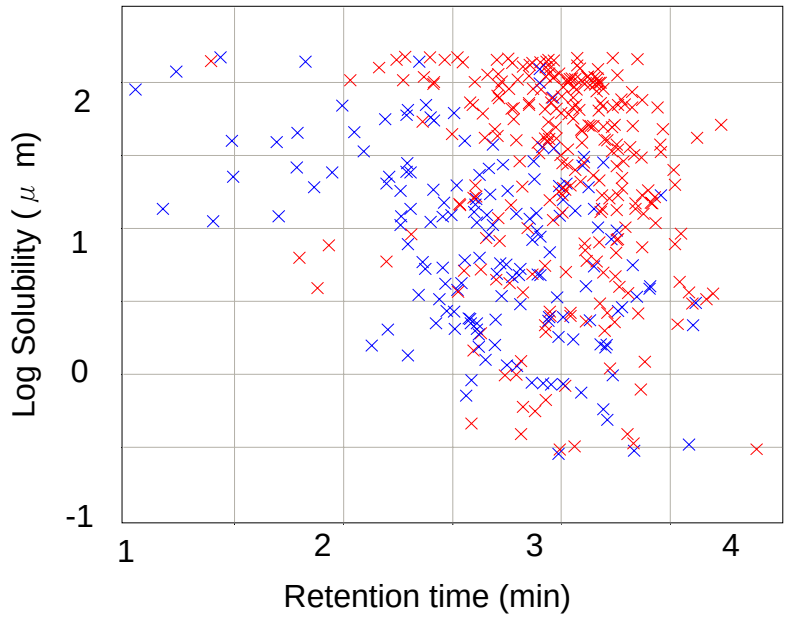
In real drug discovery, does it work?

- In 2006, > 1600 compounds measured
  - All pain project compounds at lead optimization
  - 0.6 person x day/once a week
  - Semi automation (No robot)
    - Eye observation of crystalline/amourphous

All compounds (ca. 1700)





Percentage of crystalline precipitant

	Compound number	Number of crystalline	Crystal %
All	1669	-	-
< 150 uM[a]	1219	434	36
Project A[a]	625	248	40
Project B[a]	341	82	24
Project C[a]	130	73	56
Project D[a]	85	14	16
Project E[a]	38	17	45

a Compounds with > 150 μ M solubility value were excluded from the analysis due to uncertainty of crystal detection by PLM.

Three findings from 1700 measurements

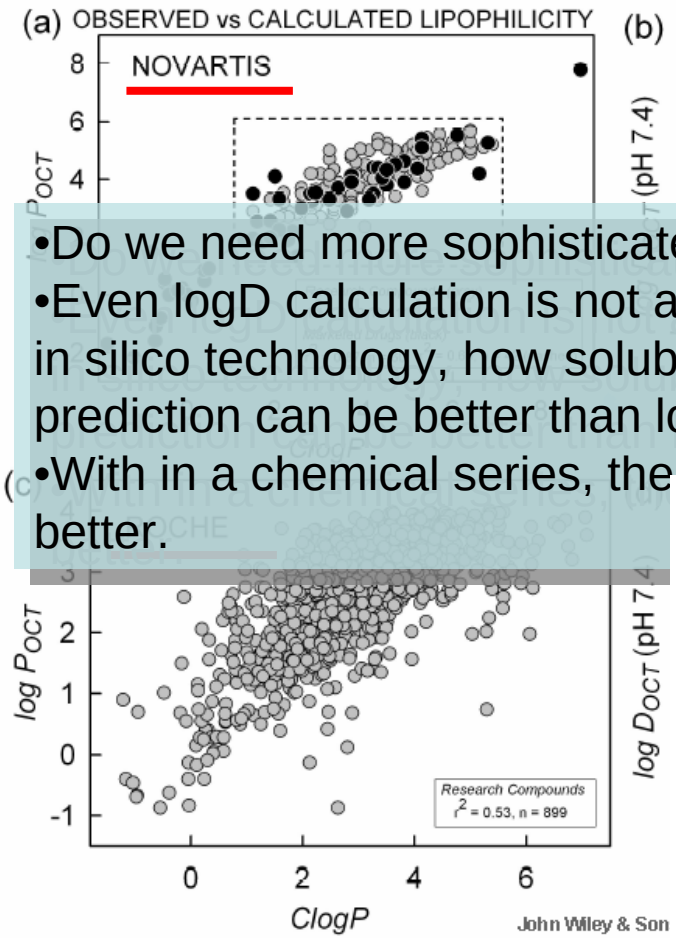
- Solubility of crystalline is lower than that of amorphous (Of course!).
- Solubility – lipophilicity relationship is vague.
  - Even when the precipitant was amorphous.
- Percentage of crystal differed among chemical scaffold.

Fact or Myth?

- In silico is good enough for solubility and permeability. Let’s quite these assays”
- Similar “Myth” is also found for oral absorption simulation
- Formulation is perfect. No worry about low solubility.

Even logP/D calculation is not accurate

Octanol shake flask vs in silico calculation (across all project)



- Do we need more sophisticated calculation principle?
- Even logD calculation is not accurate with the current in silico technology, how solubility, Caco-2,etc prediction can be better than logD prediction?
- With in a chemical series, the predictability may be better.

Alex Avdeef, Stefanie Bendels, Li Di, Bernard Faller, Manfred Kansy, Kiyohiko Sugano, Yukinori Yamauchi (Inter-company collaboration) J. Pharm. Sci., *2008, 2893-2909*

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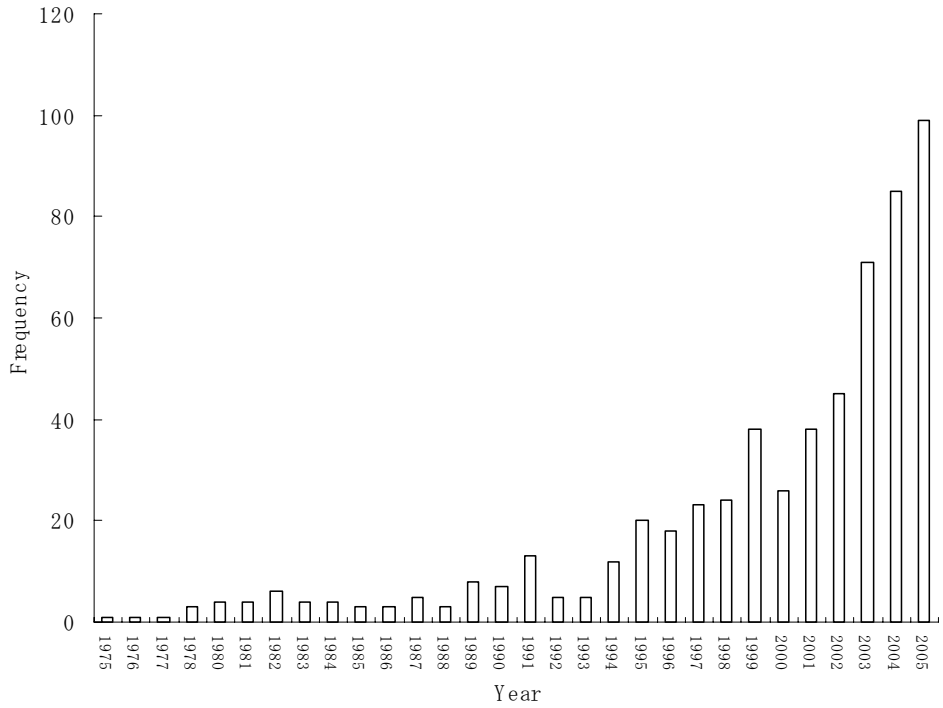
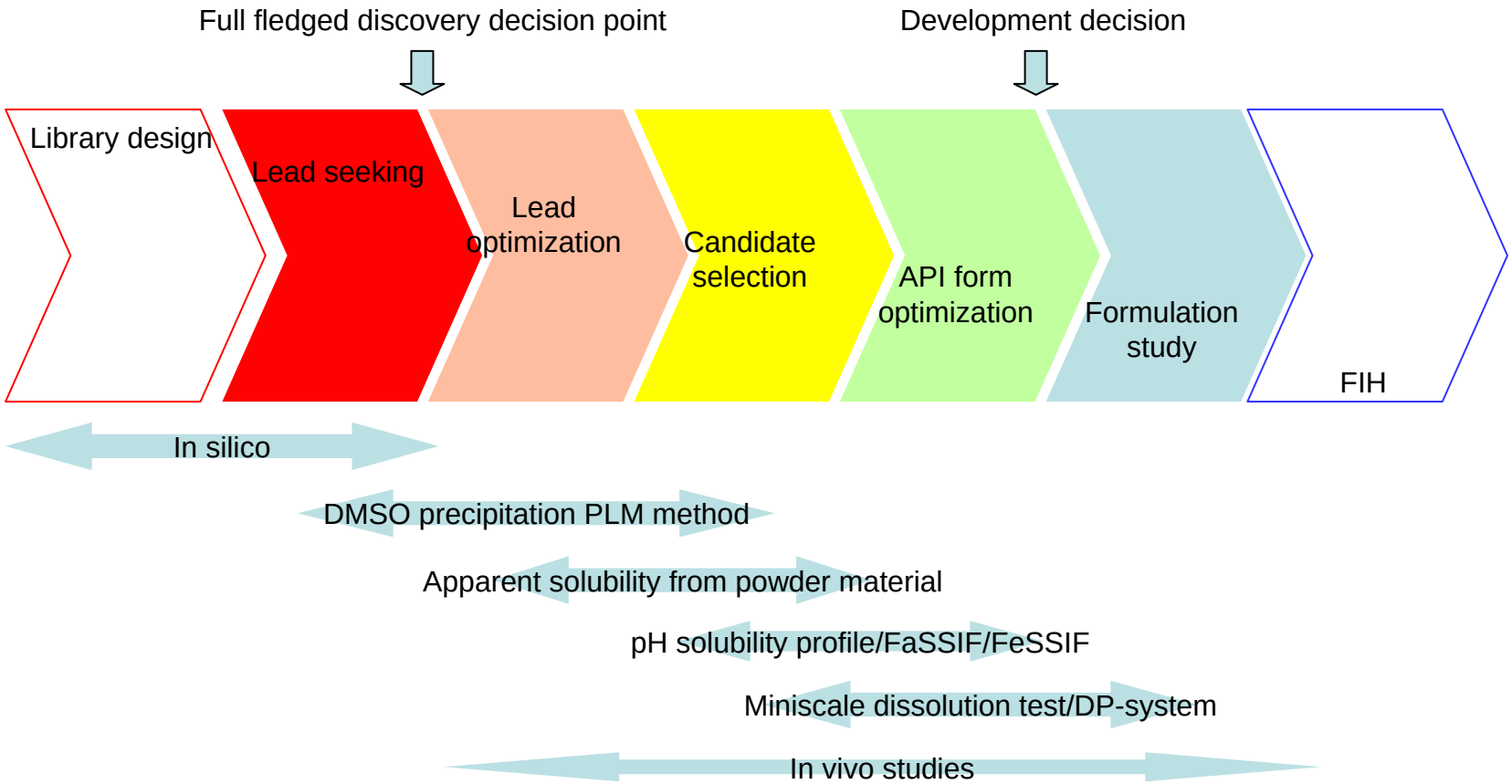
Low solubility compound increasing



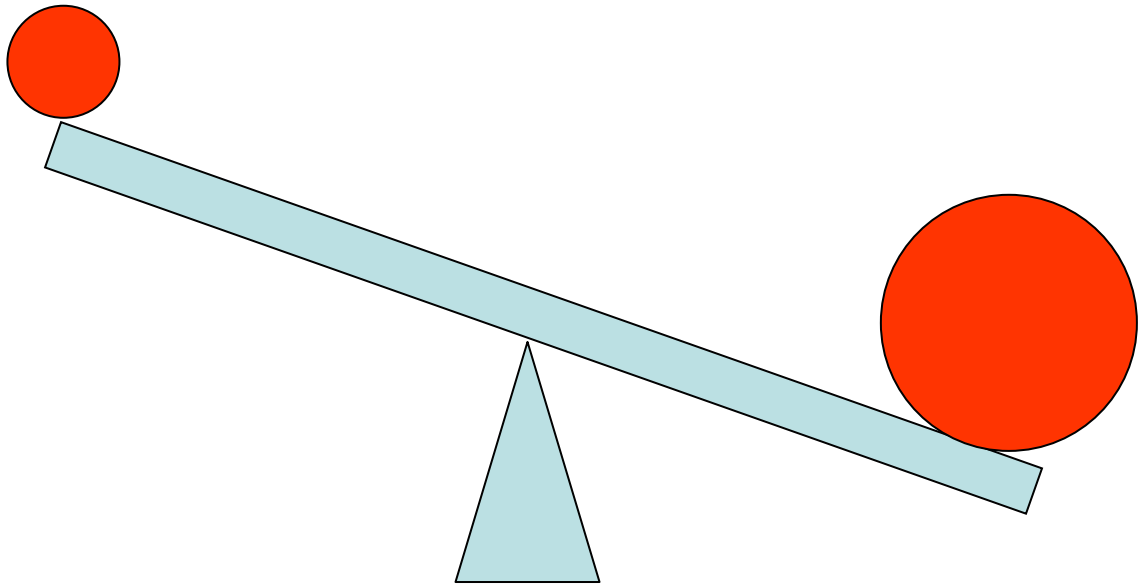
Number of publications containing the concept "poor solubility drug" as of December 2006. Carried out using SciFinder®

Sugano et al., DMPK, 2007, 225-254

Solubility line-up



Chemical modification or DDS?



Does standard formulation approach work? (Milling/Salts)
Is the compound suitable for DDS technique?
What is possible and what is not possible?
Which has higher success rate?
Which is faster to clinical trial and launch?
Which is less resource intensive (human, manufacture etc)?

Computational simulation might help to understand this.

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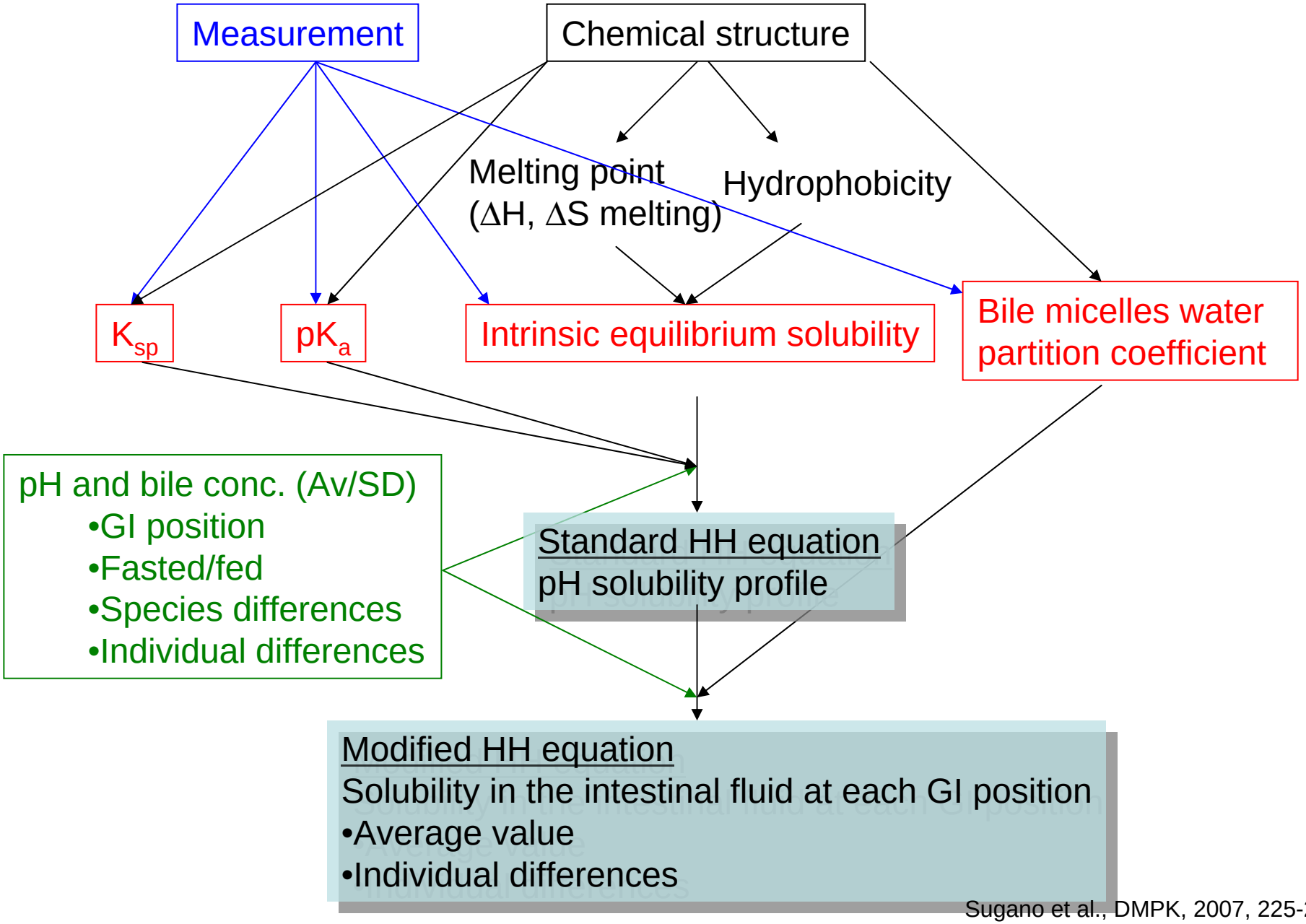
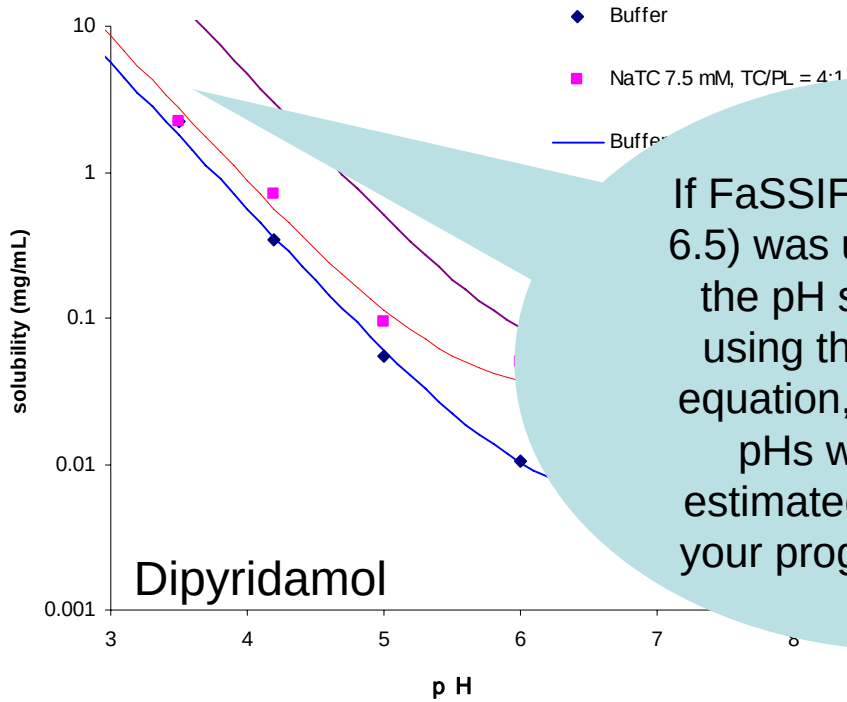
Scheme to calculate solubility in each GI tract



Sugano et al., DMPK, 2007, 225-254

Modified Henderson-Hasselbalch equation



If FaSSIF solubility (at pH 6.5) was used to calculate the pH solubility profile using the standard HH equation, solubility at low pHs would be over estimated. Please check your program simulation.

$$S_{tot} = S_0\left(1+\frac{[H^+]}{Ka}+\frac{C_{micelles}}{C_{water}}\cdot 10^{\log P_{micelles,undissociated}}+\frac{[H^+]}{Ka}\cdot\frac{C_{micelles}}{C_{water}}\cdot 10^{\log P_{micelles,dissociated}}\right)$$

$\log P_{micelles,undissociated} - \log P_{micelles,dissociated} \approx 1$ Base

$\log P_{micelles,undissociated} - \log P_{micelles,dissociated} \approx 2$ Acid

Glomme, A.; März, J.; Dressman, J.,. In Pharmacokinetic Profiling in Drug Research, Testa, B.; Krämer, S.; Wunderli-Allenspach, H.; Folkers, G., Eds. Wiley-VCH: Zurich, 2006; pp 259-280.

Avdeef, A.; Box, K. J.; Comer, J. E.; Hibbert, C.; Tam, K. Y.,. Pharmaceutical Research 1998, 15, (2), 209-215.

Other precautions for simulation

- pH change at solid surface
- Bile micelles diffusion coefficient
- Free fraction? Or drug in bile micelles absorbed?
- Precipitation
- GI fluid volume
- Hydrodynamics
- Species differences of bile conc
- …
- …

I will discuss these items at this British Pharmaceutical Conference @ Manchester.
Please come and see me again!!!

Conclusion

- The new solubility assay is a beneficial asset for drug discovery.
- Crystalline/amorphous information is important for drug design and compound selection.
- Strategic approach is required to fix the low solubility issues.
  - Computational simulation might help.
- The modified HH equation is required for oral absorption simulation
  - There are many other precautions for simulation

Acknowledgement

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  - Teruhisa Kato (Sandwich at present)
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  - Richard Manley
  - Hurst Kelly