

What are we actually measuring the solubility of?

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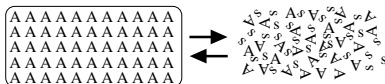
School of Pharmacy
Nottingham University

Thursday 19th June 2008

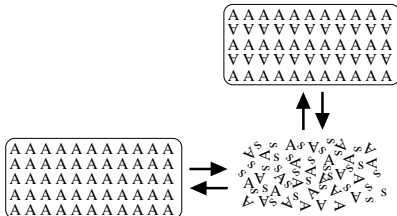
Solubility: Compound A in solvent s



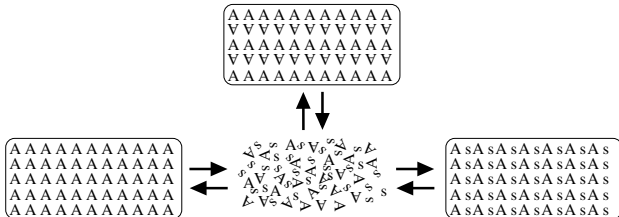
Solubility: Compound A in solvent s



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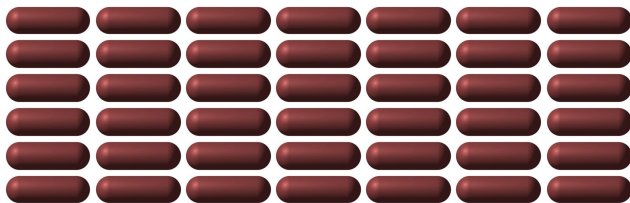
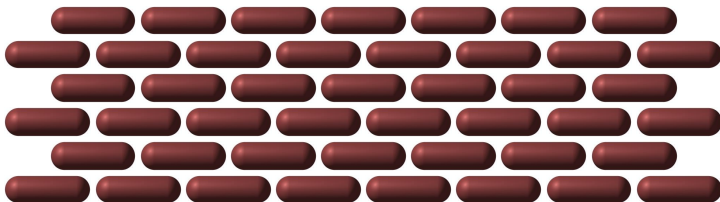
Polymorphism: definition

Materials made from same molecules, which have different crystal structures

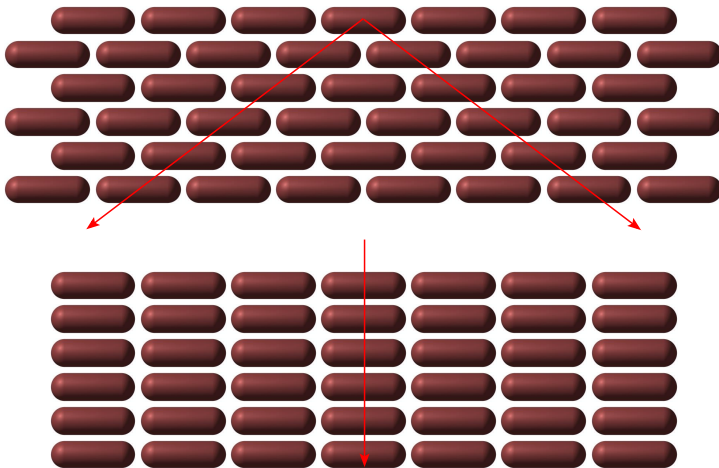
Equivalent of

Materials made from same building blocks but with different arrangements of building blocks

Example



Example

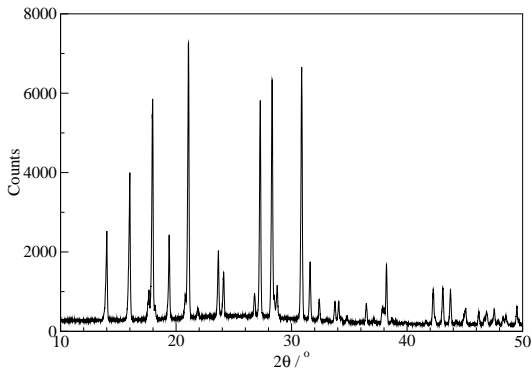


Analytical methods

- IR & Raman
- Calorimetry (TGA & DSC)
- Solid-state NMR
- Single crystal X-ray diffraction
- Powder diffraction

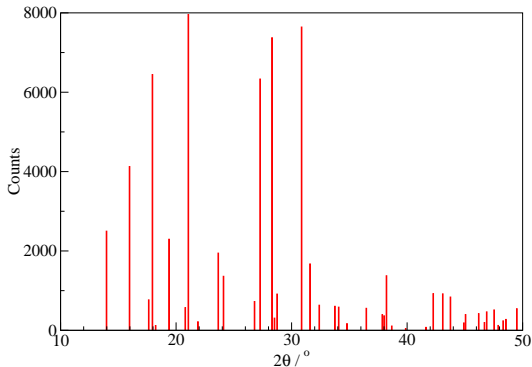
Information in XRPD pattern

Overall pattern



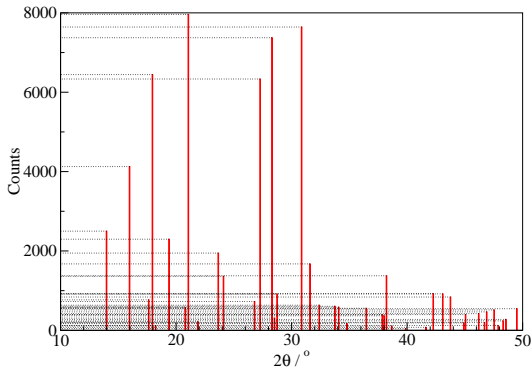
Information in XRPD pattern

Peak positions \rightarrow unit cell parameters



Information in XRPD pattern

Peak intensities \rightarrow atomic positions



XRPD analysis approaches

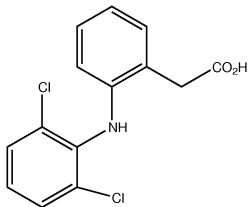
Simple comparison:

- Visually compare pattern with database
 - PDF4, CSD, in-house

More rigorous approaches:

- Automated comparison
 - Principal component analysis, dendrograms
- Full-pattern approaches
 - Rietveld, LeBail, Pawley etc

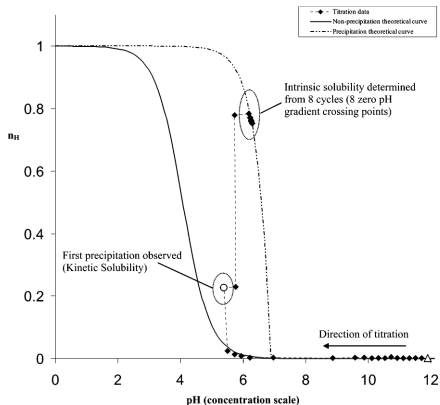
Diclofenac: structure



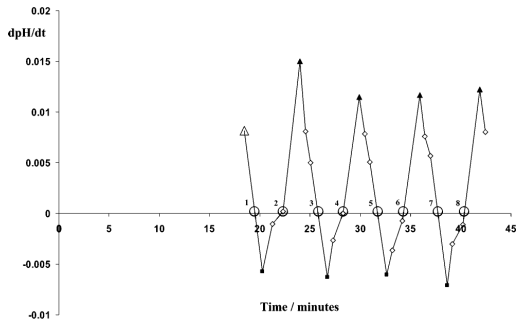
NSAID: uses include arthritis and acute injury

Single solubility for neutral form: $1.0 \pm 0.1 \mu\text{g. ml}^{-1}$

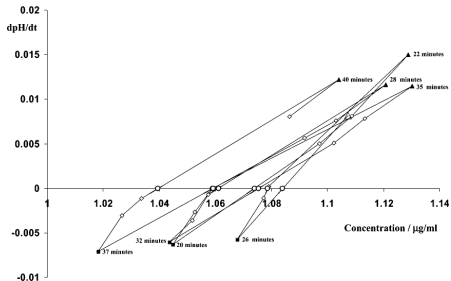
Diclofenac: solubility



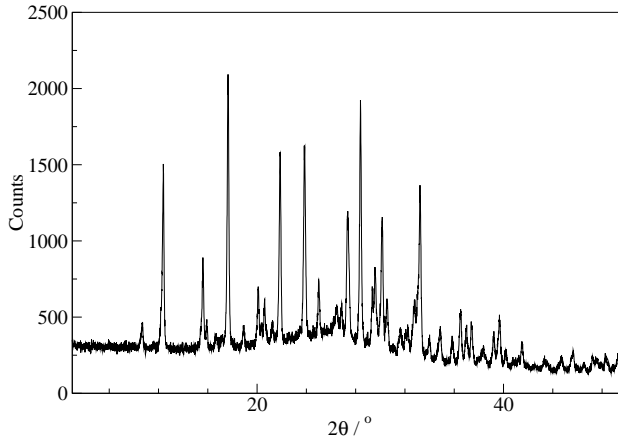
Diclofenac: chasing equilibrium



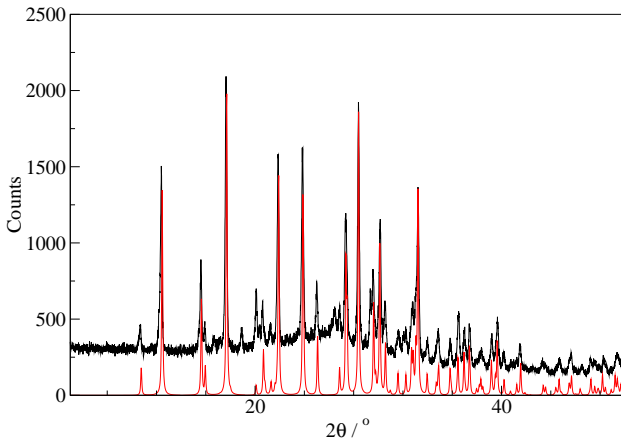
Diclofenac: chasing equilibrium



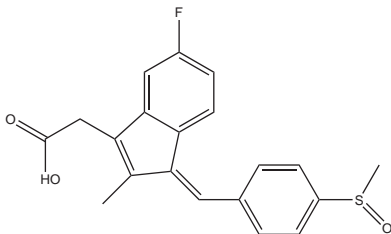
Diclofenac: neutral form XRPD



Diclofenac: neutral form XRPD, plus database hit

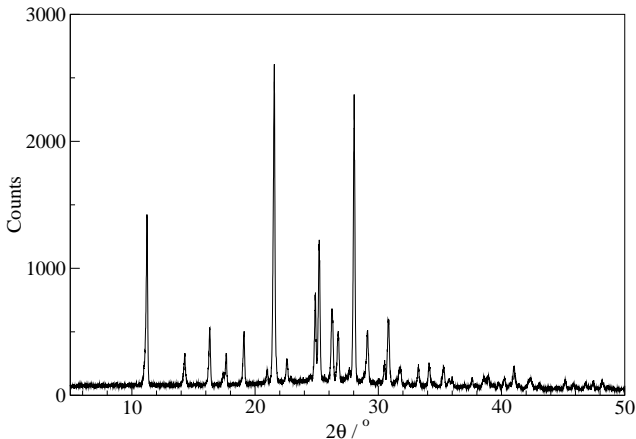


Sulindac: structure

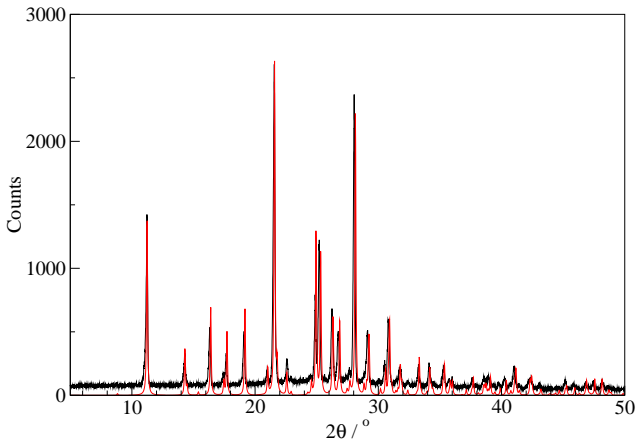


NSAID (prodrug) used to treat acute or chronic inflammation
After 20 minutes, solubility changes: $70 \mu\text{g.ml}^{-1} \rightarrow 10 \mu\text{g.ml}^{-1}$

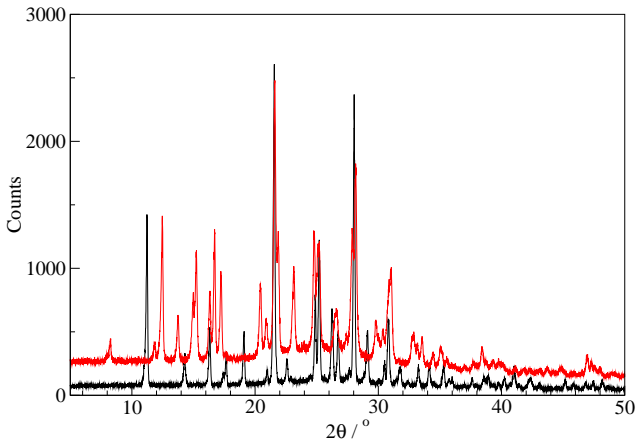
Sulindac: commercial form XRPD



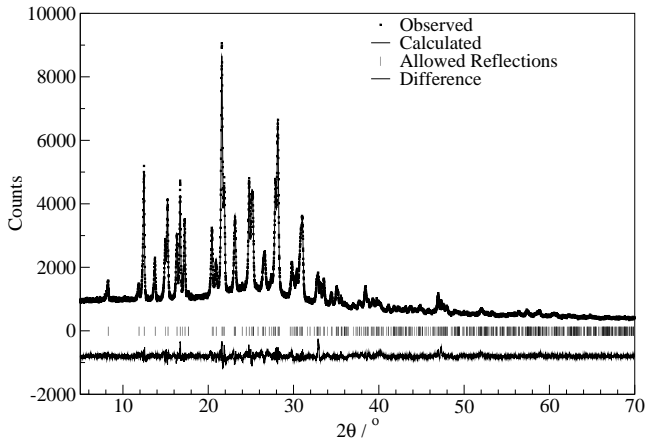
Sulindac: commercial form XRPD + database hit



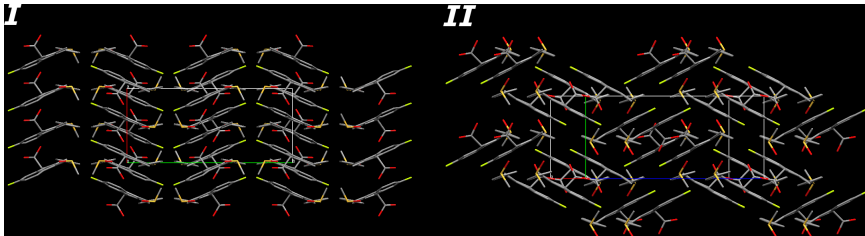
Sulindac: precipitate XRPD



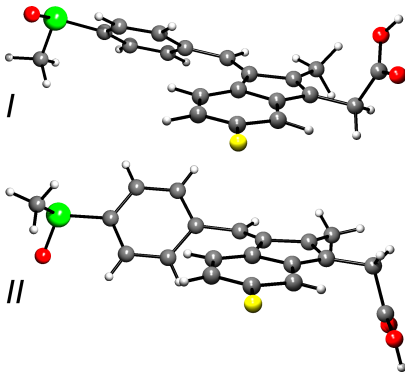
Sulindac precipitate: Rietveld



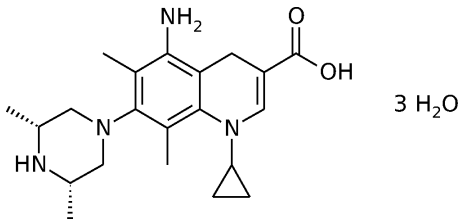
Sulindac: structures



Sulindac: structures

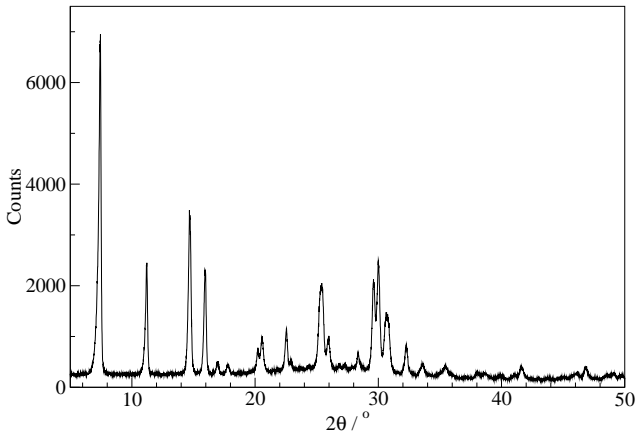


Sparfloxacin: structure

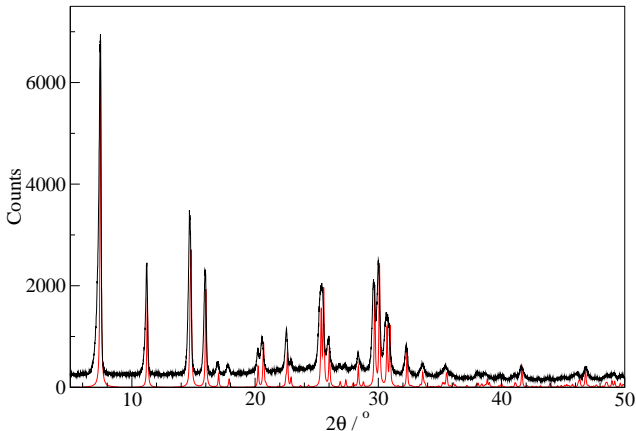


Antibiotic, single stable value for intrinsic solubility: 167 ± 14
 $\mu\text{g}\cdot\text{ml}^{-1}$

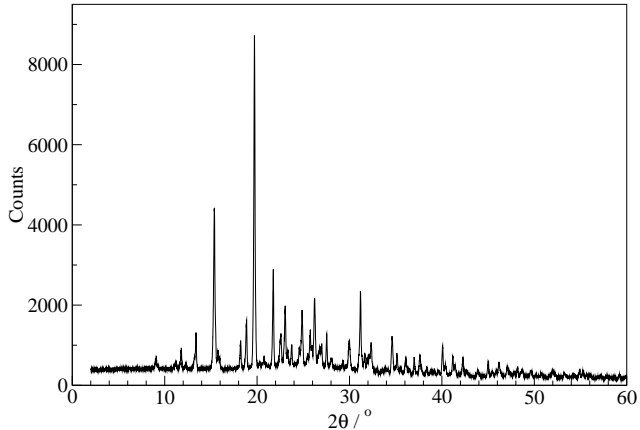
Sparfloxacin: commercial



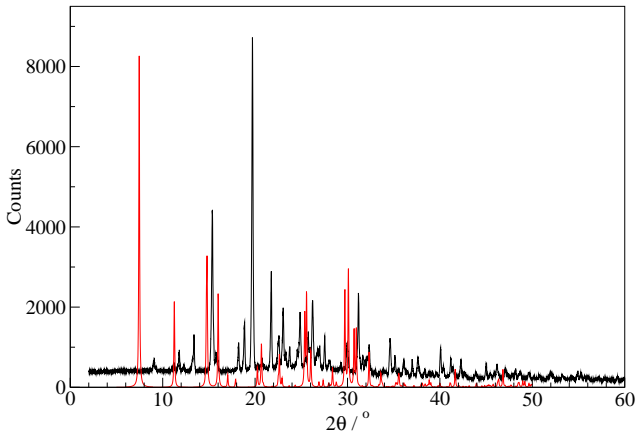
Sparfloxacin: commercial + calculated anhydrous



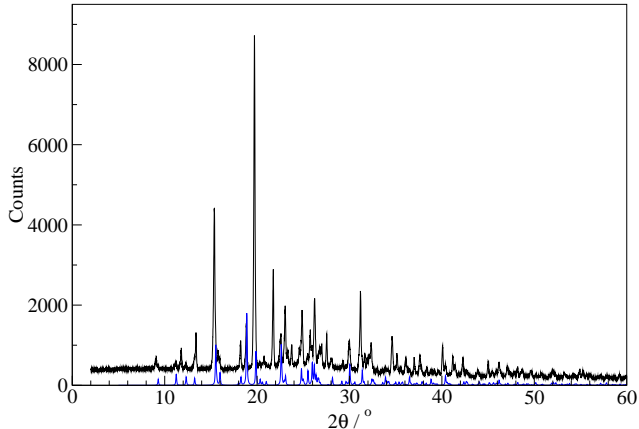
Sparfloxacin: precipitate



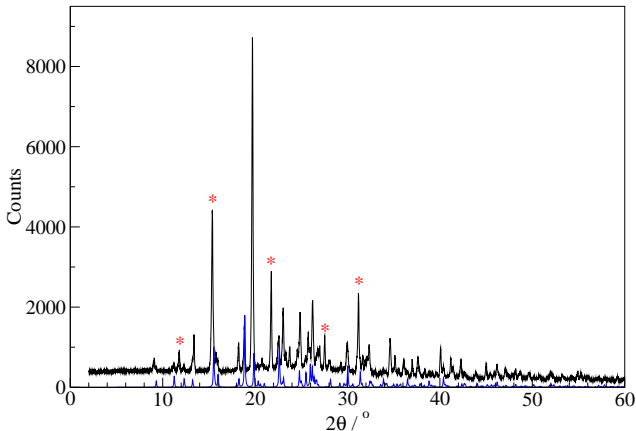
Sparfloxacin: precipitate, calculated anhydrous



Sparfloxacin: precipitate, calculated trihydrate

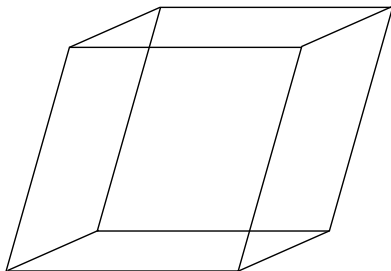


Sparfloxacin: precipitate, calculated trihydrate



Sparfloxacin: hydrate crystal structure

Form II

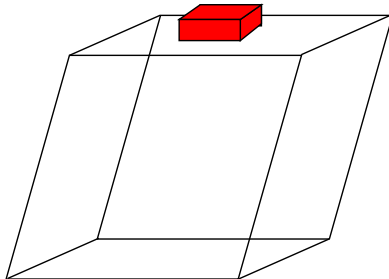


Single crystal microdiffraction, Station 9.8, Daresbury SRS

Sparfloxacin: hydrate crystal structure

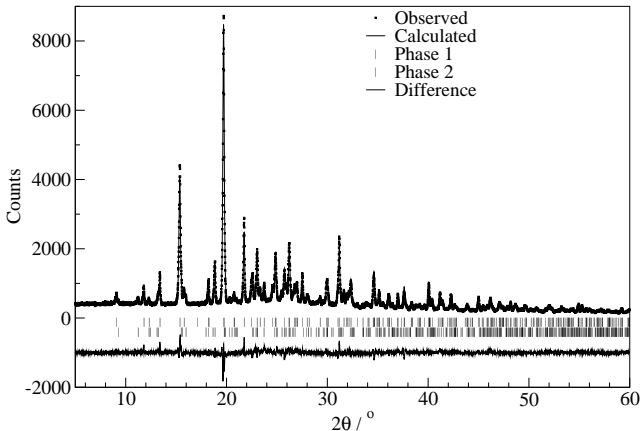
Form I

Form II

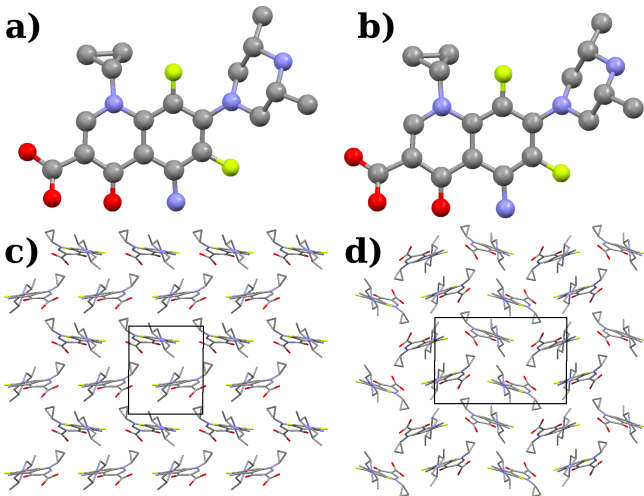


Single crystal microdiffraction, Station 9.8, Daresbury SRS

Sparfloxacin: precipitate, two trihydrates



Sparfloxacin: hydrate polymorphism

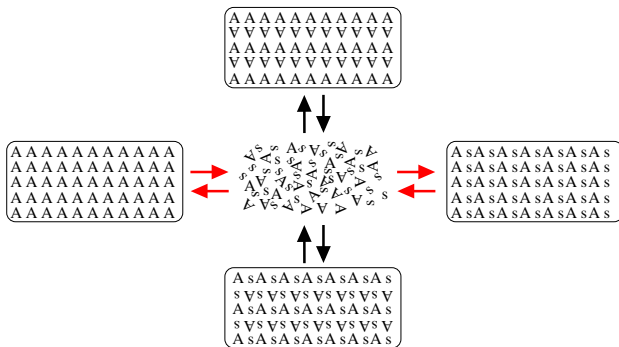


Various behaviours

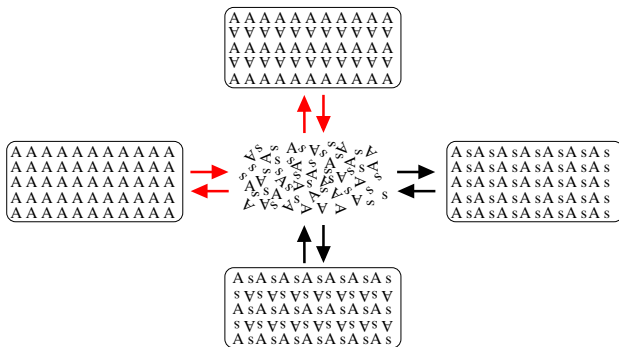
We have observed:

- Single solubility value due to single precipitate
- Two solubility values due to polymorphism of precipitate
- Single solubility value due to polymorphic hydrate!

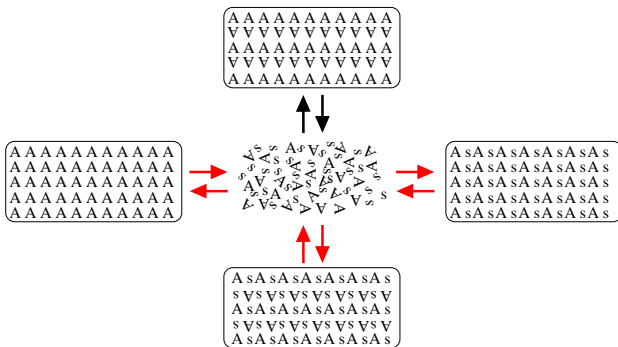
Solubility: Diclofenac



Solubility: Sulindac



Solubility: Sulindac



So, what are we measuring the solubility of?

We don't know until we look!

People involved with the work presented

Cambridge

- Toni Llinàs
- Jonathan Goodman
- Robert Glen

Sirius Analytical

- Karl Box

Daresbury Labs SRS

- Timothy Prior