FORMULATION STRATEGIES FOR LOW SOLUBLE DRUGS - AN OVERVIEW

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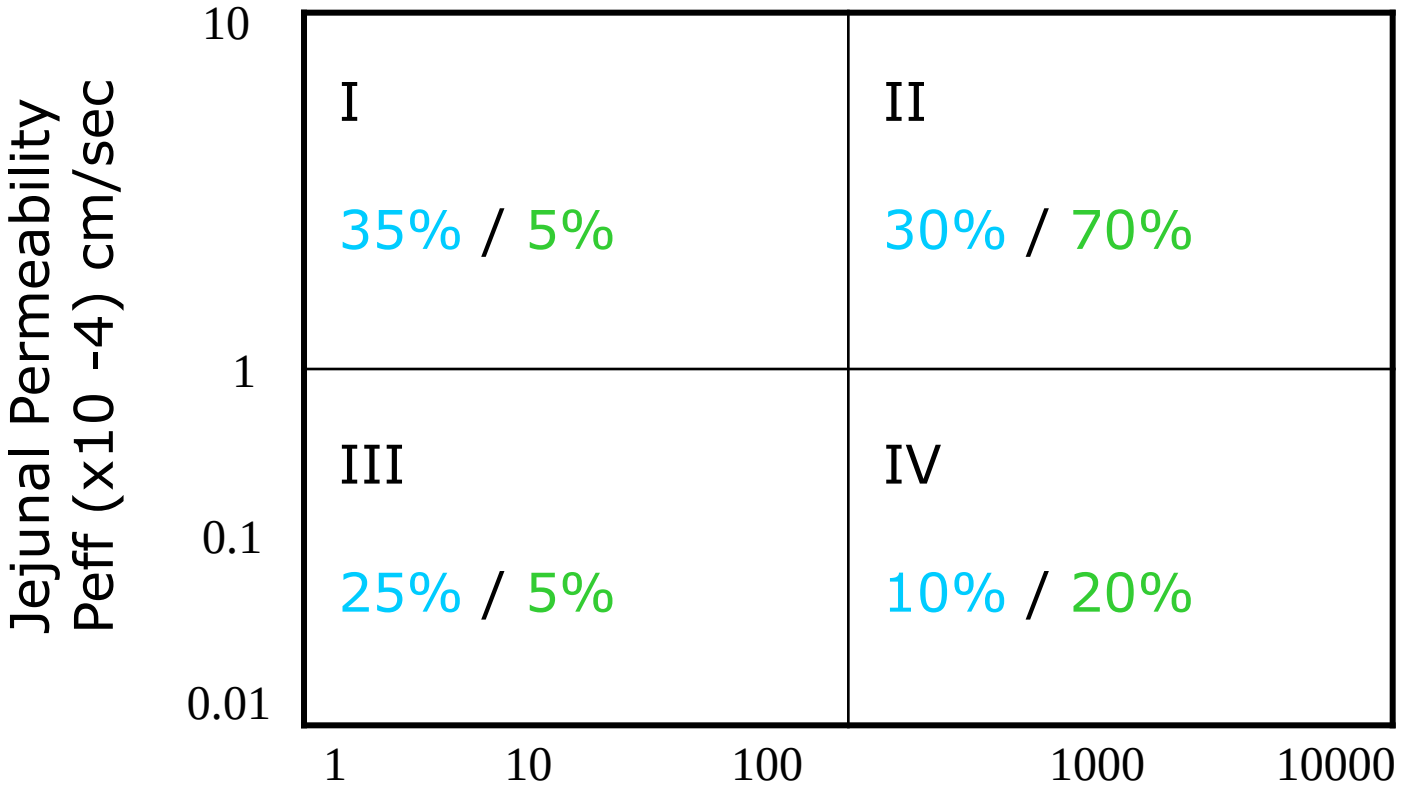
Presentation objectives

- Provide a general overview of the formulation strategies available for low soluble compounds
- Describe the scientific fundament behind the formulation strategies
- Consideration of pro/con of the selected options

BCS:

Blue: Marketed product; Green: Drug Candidates

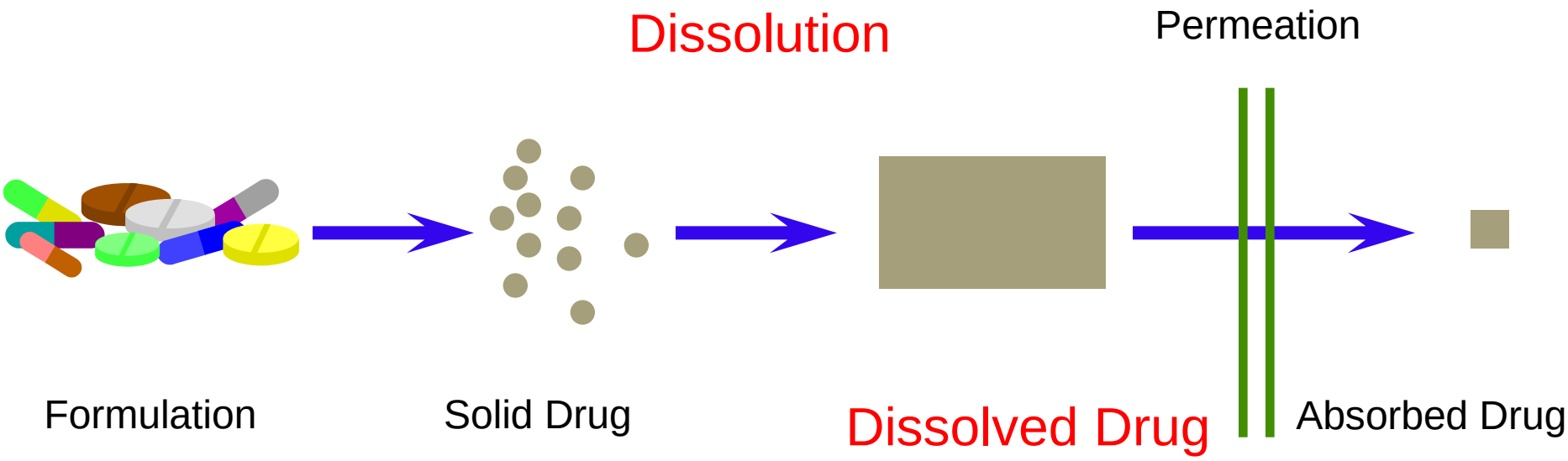


"Solubility": Volume (ml) of water required to dissolve the highest dose at the lowest solubility in the pH 1-7.5 range

Data from Müllertz, A.

The visual reality for pharmaceutical scientist in innovative industry

Does this matter to drug absorption and formulation?



Formulation strategies for insoluble drugs

Traditional Approaches

- Salts/cocrystals
- Solvents/co-solvent systems
- Wetting agents
- Emulsions
- Micronization
- Solid state modifications
  - Polymorphs/ amorphours

Advanced approaches

- Solid dispersions
- Microemulsions
- SEDDS/SMEDDS
- Complexation
- Liposomes
- Nanoparticles

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Formulation systems working by presenting the compound in solution

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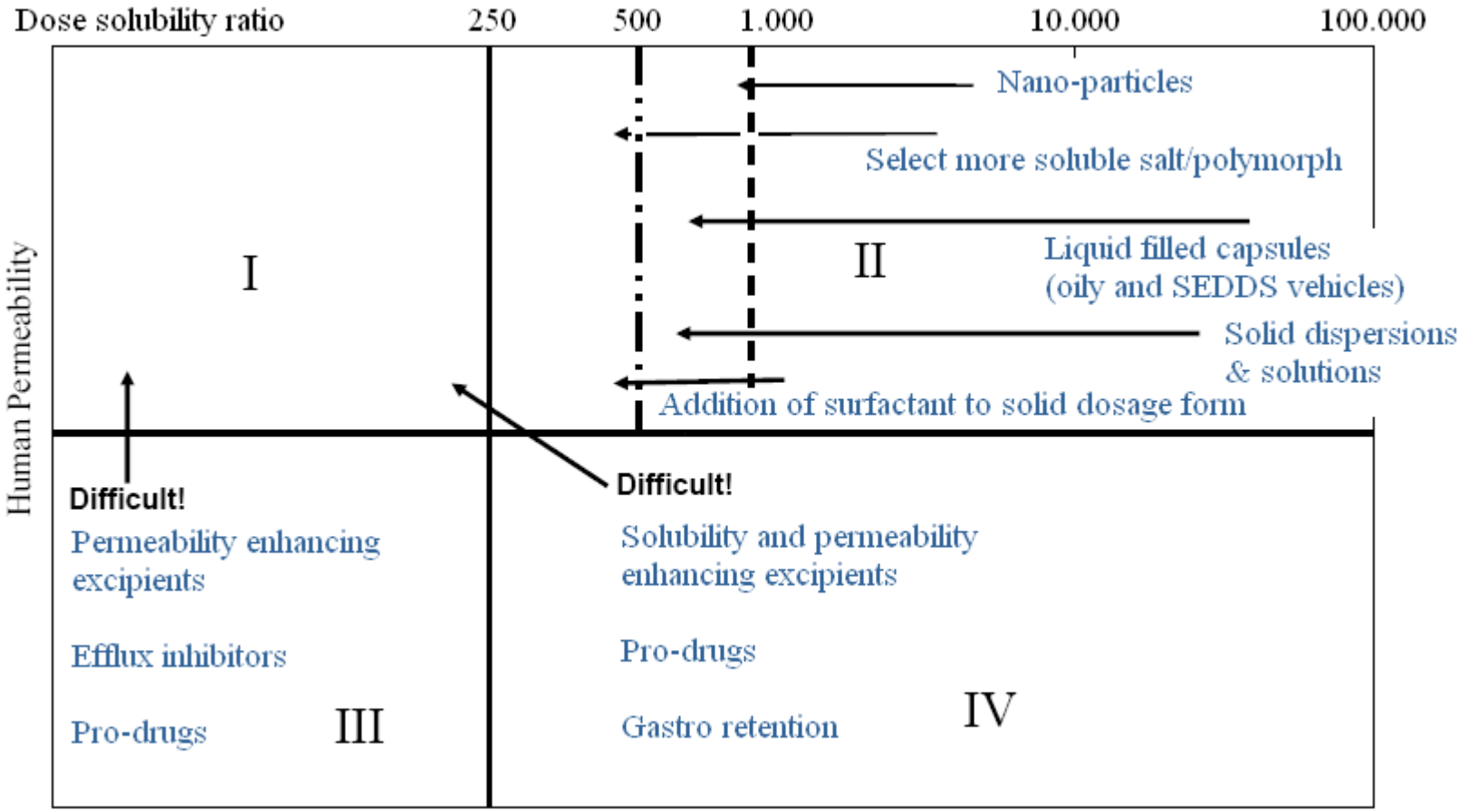
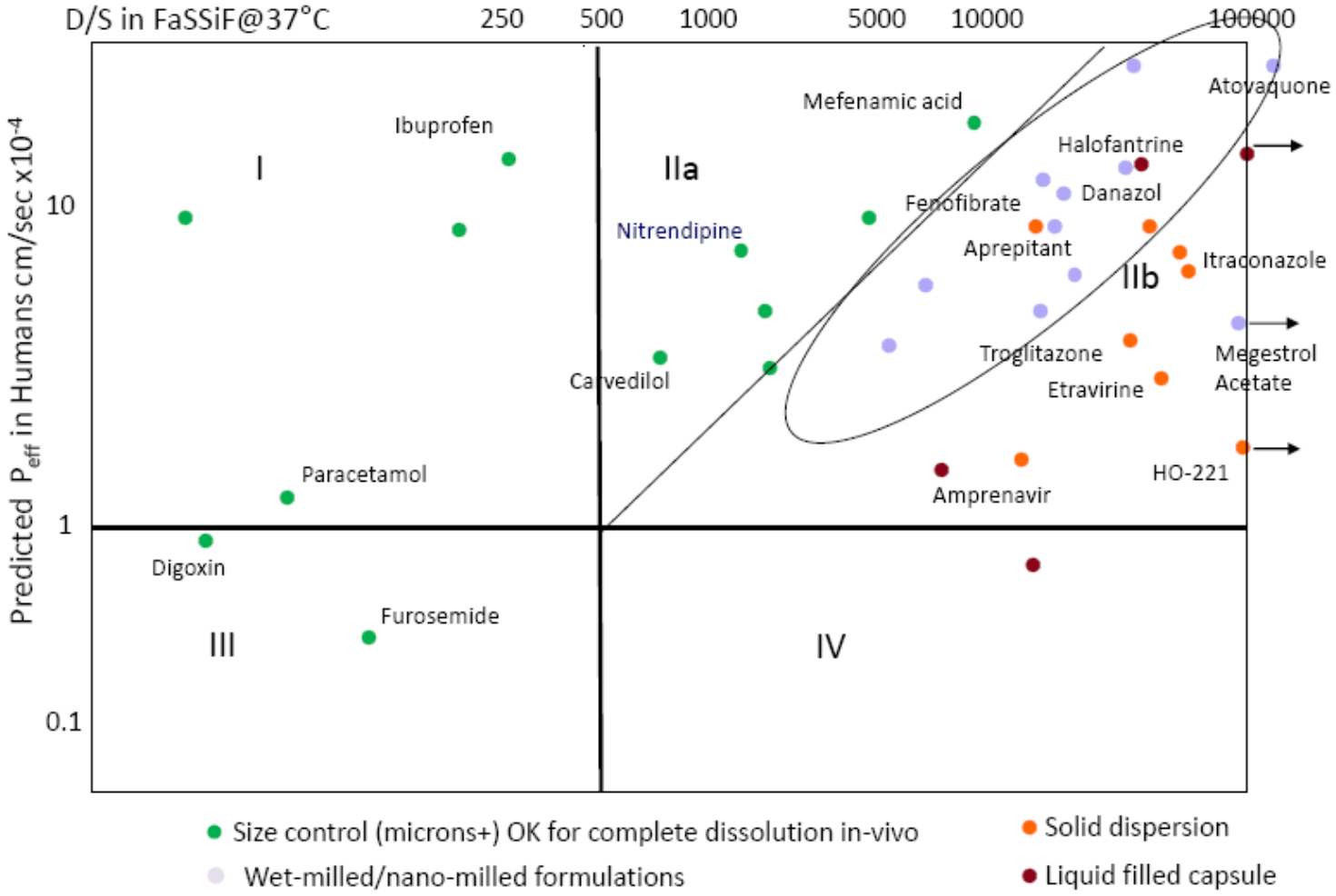
Formulation systems working by changing the dissolution rate

Formulation types



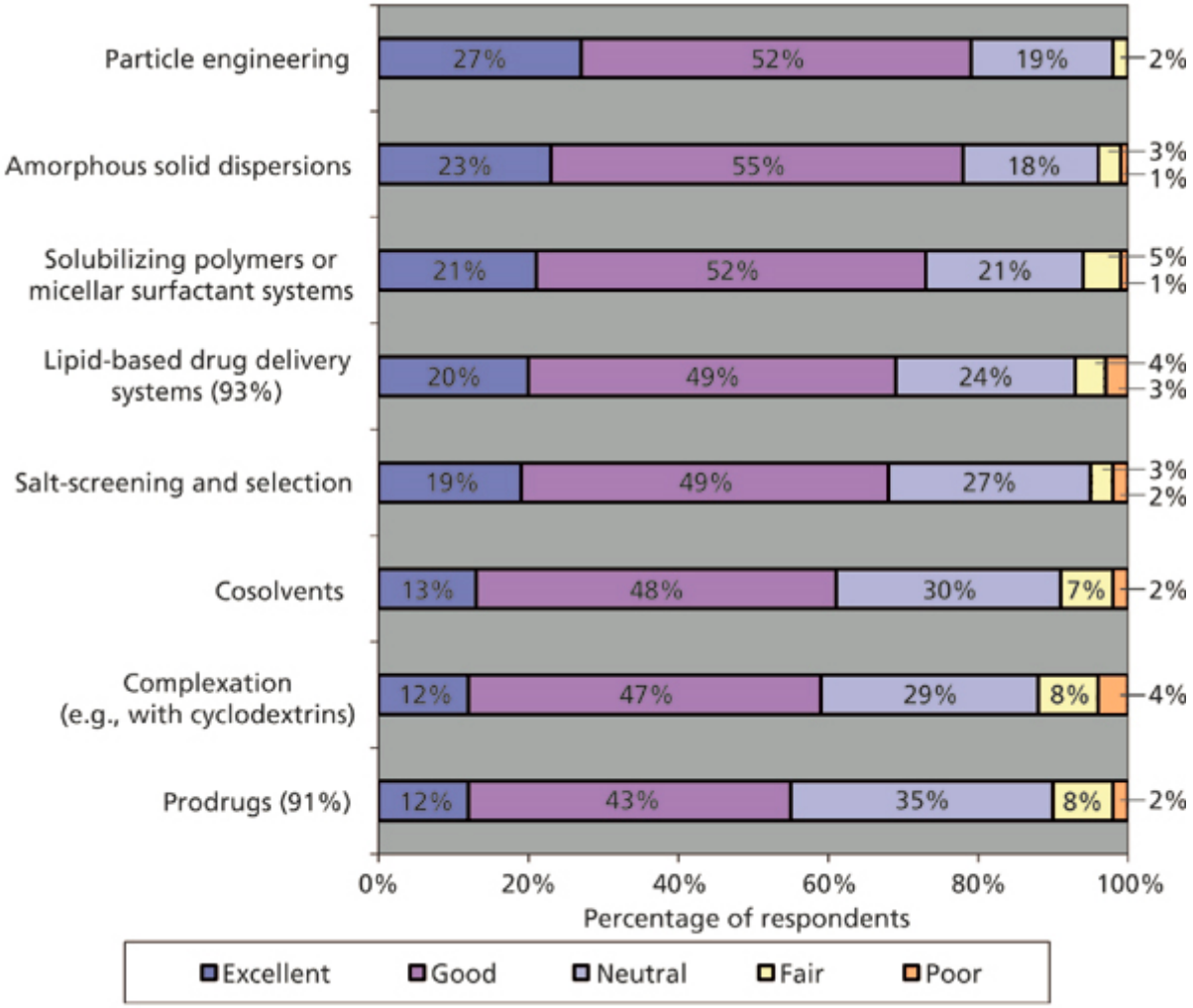
Dressman et al., 2001

DCS plot: Approximate position for selected drugs



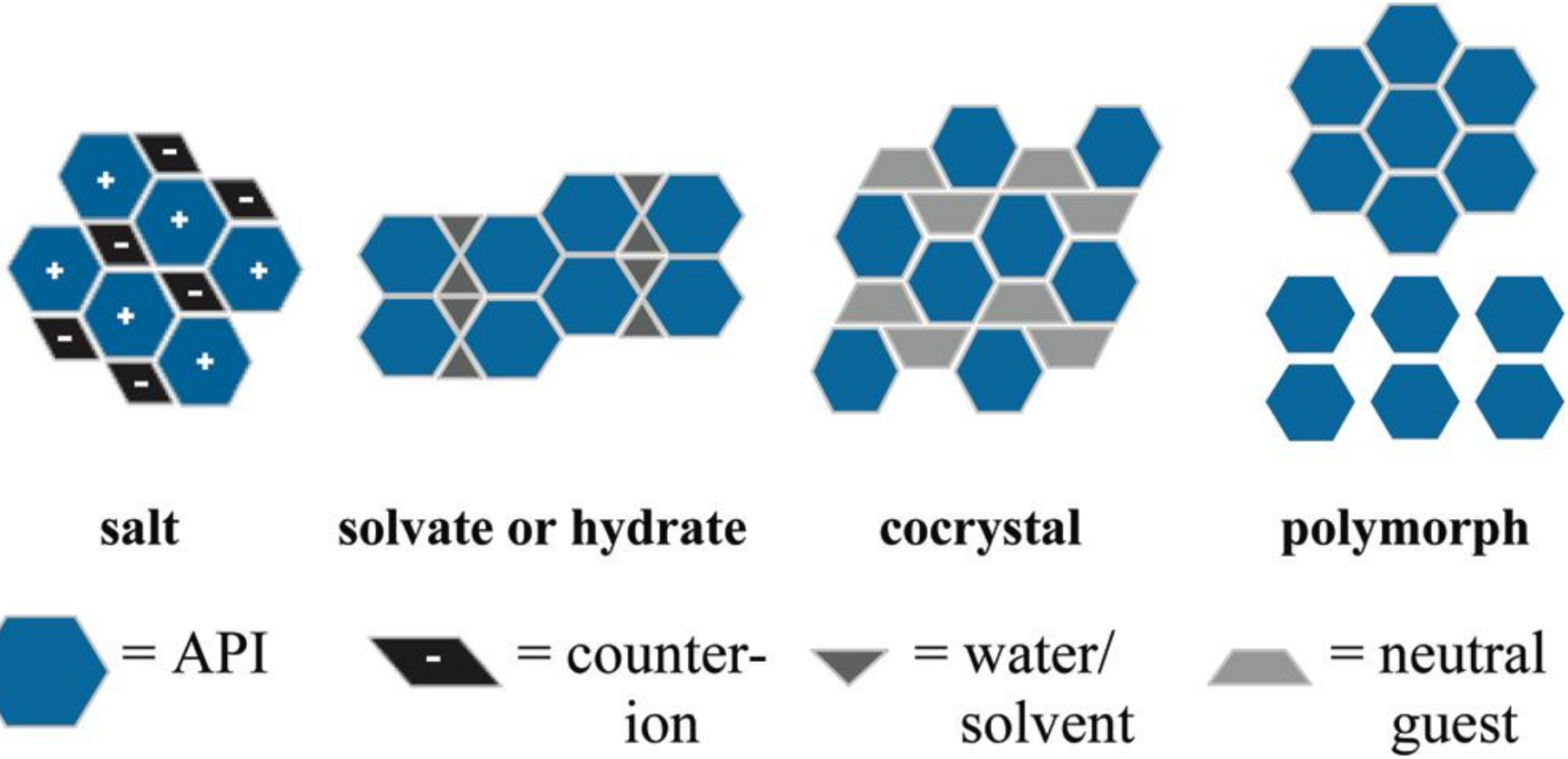
Slide from Karl Box, AAPS 2011

Evaluation of strategies for addressing poor solubility



Siew and van Arnum , 2013

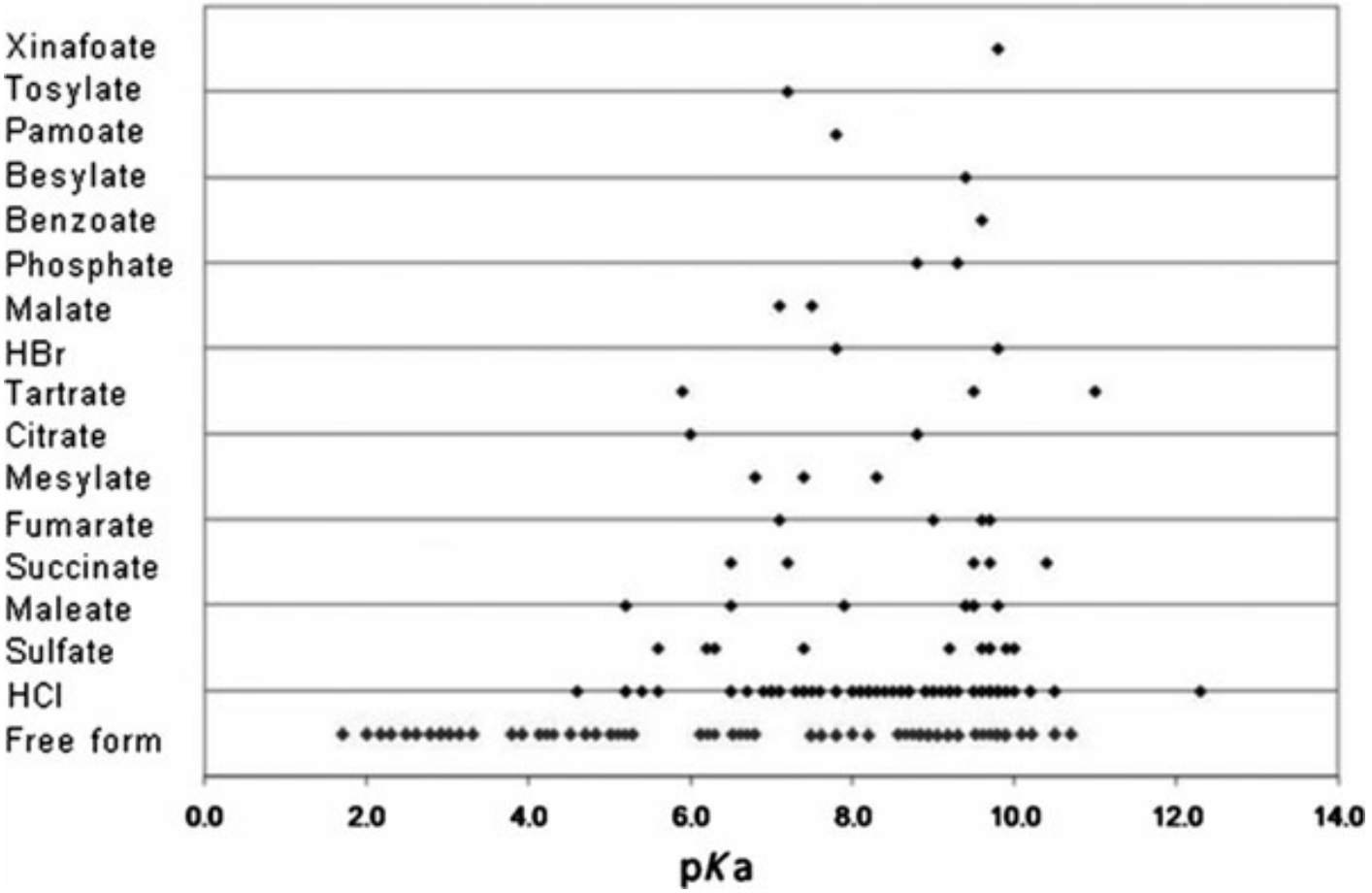
The solid form family picture



Schultheiss & Newman, 2009

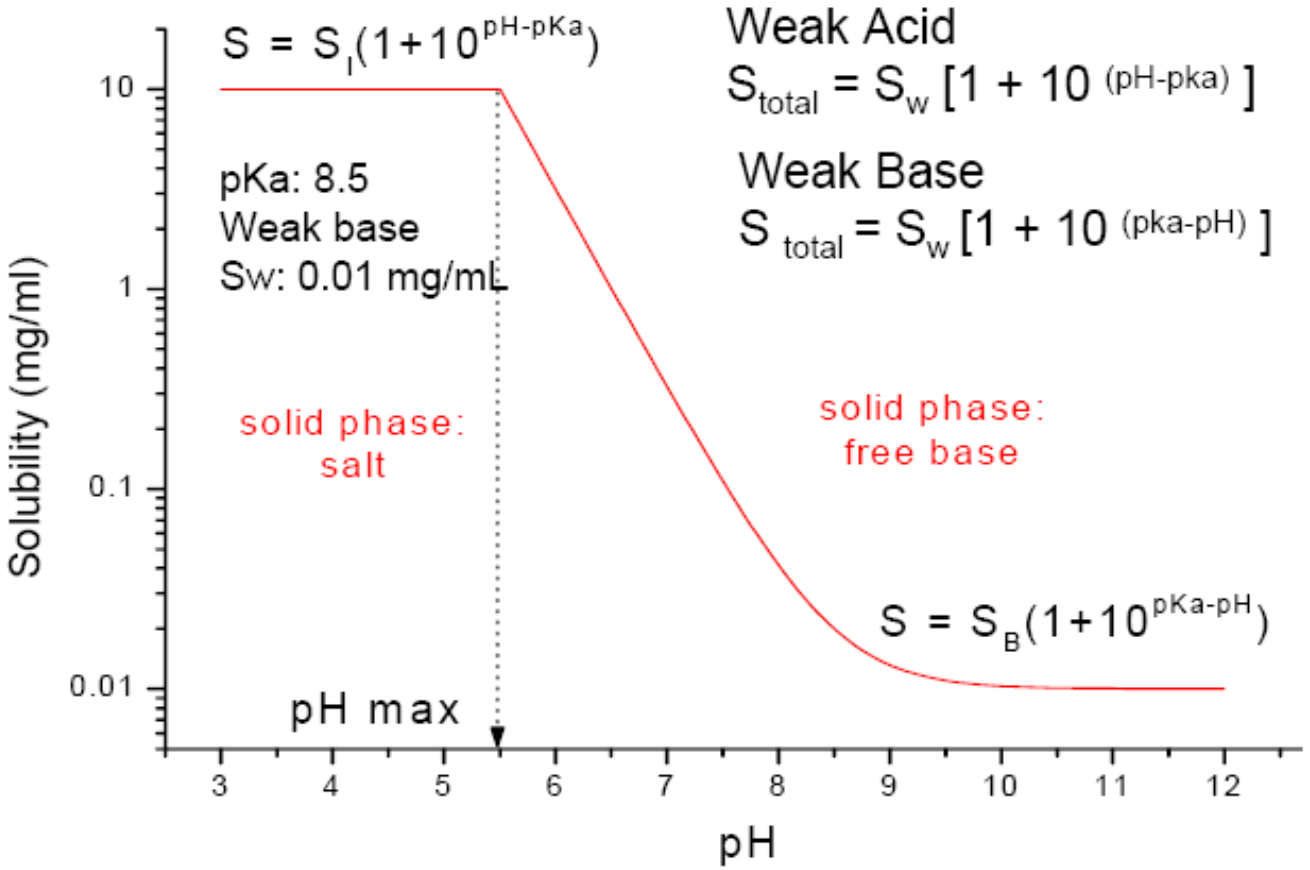
pKa needed for salt formation ?

- survey of 203 compounds



Stephenson et al., 2011

Solubilisation of ionisable compounds



Significance of substance properties

- Biopharmaceutical

Property of drug subst.	Requirement	Indicator	Effect of salt form
In-vivo dissolution	Timely and complete dissolution of dose administered	1. Solubility 2. Dissolution rate (IDR)	++
In-vivo permeation	Complete absorption of dose	1. LogP 2. Permeability in *in vitro* models	-

Significance of substance properties - Technical, 1

Property of drug subst.	Requirement	Indicator	Effect of salt form
Chemical stability in solid phase	Stable under isolation, purification and storage; compatability with pharmaceutical excipeients	Stability and compatability studies	+
Physical stability in solid phase	Manageable during pharmaceutical processing	Investigation of polymorphism and thermodynamic stability	++
Hygroscopicity	No change of hydration during storage and use	Water vapor sorption (DVS)	++

Significance of substance properties - Technical, 2

Property of drug subst.	Requirement	Indicator	Effect of salt form
Corrosiveness	Absent	Assesment of corrosiveness	++
Mechanical	Milling possible	1. M.p. >100°C 2. Milling tests	+
	Powder flow and compressibility	Specific pharmaceutical tests	+

Frequence of counter-ion

Anion	% *)
Hydrochloride	54
Methansulphonate	10 **)
Hydrobromide	8
Acetate	5
Fumerate	5
Sulphate/Bisulphate	3
Succinate	3
Citrate	2
Phosphate	2
Malate	2
Others	6

*) Data from Serajuddin, 2007; % is based on total number of anionic salts in late clinical phase (101 in total) 1995-2006

**) Some controversity on the use of methansulphonate exits; please consult Elder et al. (2010), J.Pharm.Sci., 99(7) 2941-47, for another perspective

Disadvantages of form slection

- Greater MW baggage
  - Significant issue for high dose compounds
- Reduced solubility/dissolution rate with HCl salts
  - Common ion effect
- Some salts have higher hydrate or polymorph formation potential
- Impact on secondary processing
  - Wet granulation – impact on hydrate/anhydrate
  - Spray drying can dissociate string acid salts
  - Wet milling can dissociate strong acid salts
  - HCl salts may cause corrosion of tooling

Size reduction strategies

$$\frac{dX_d}{dt} = \frac{DS}{\delta} \cdot (C_S - \frac{X_d}{V})$$

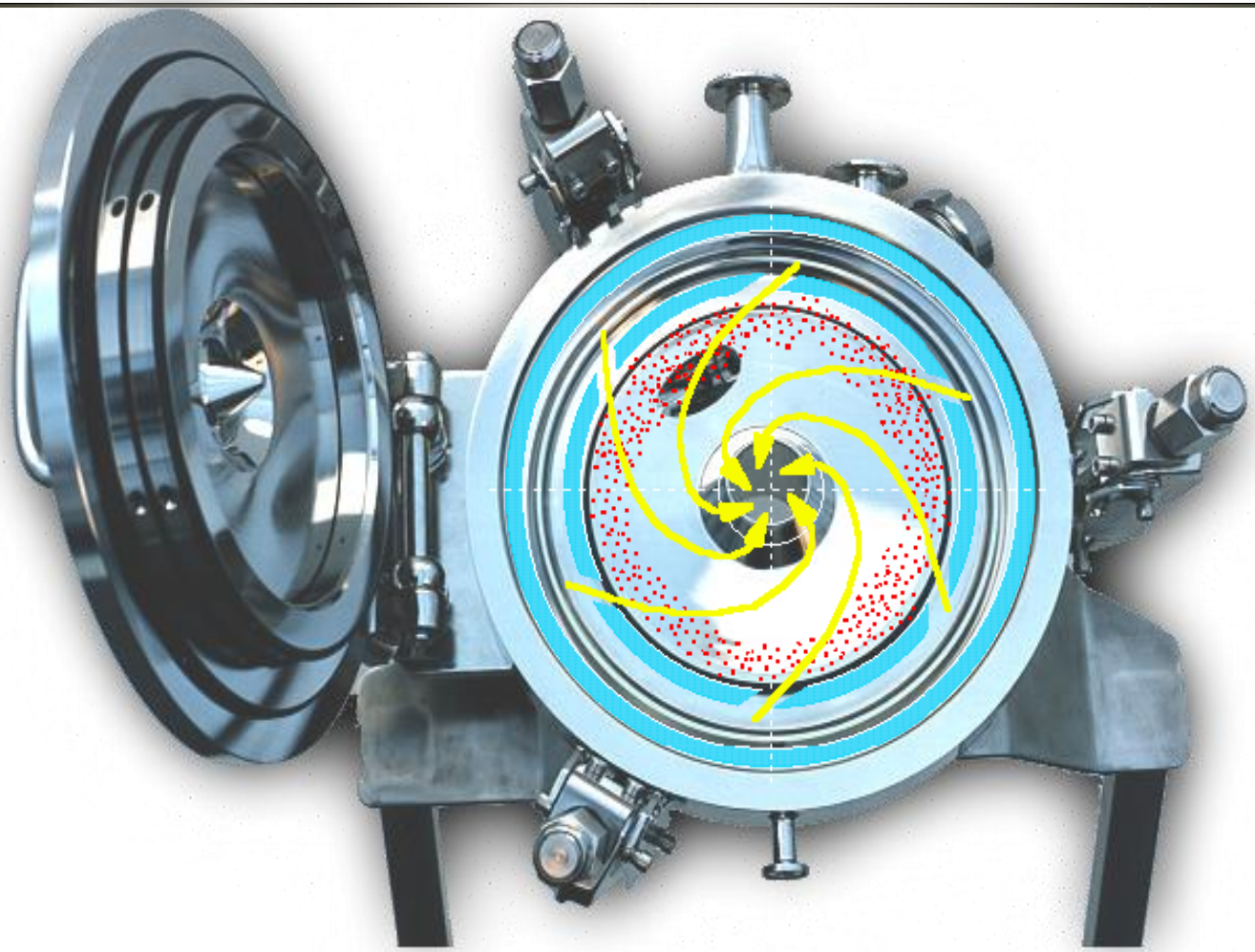
Increases the available surface area for solubilisation

Changes the dissolution rate, not the solubility

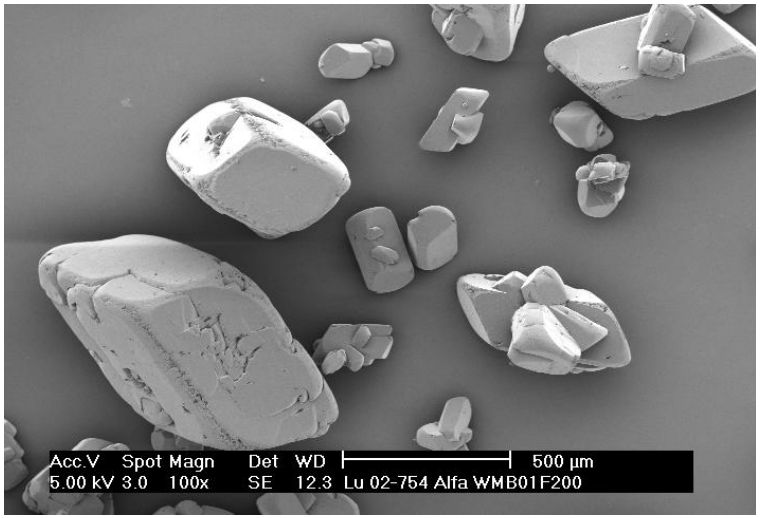
Size reduction strategies

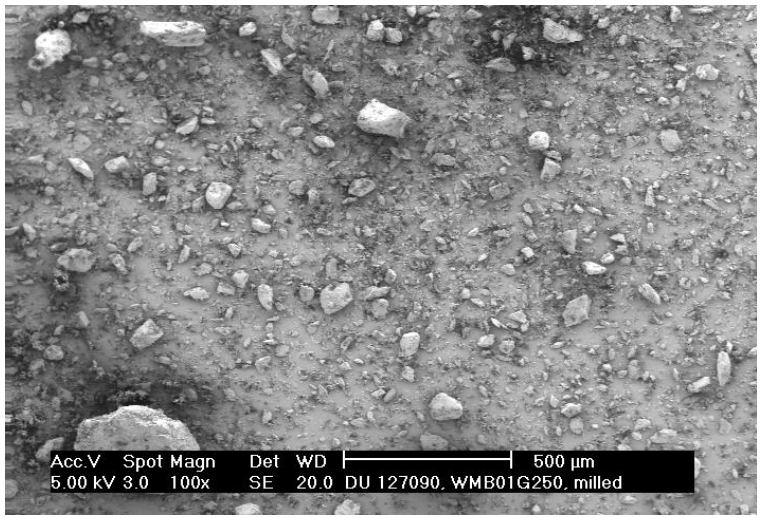
- Typical approaches:
  - Milling, typical d50 of app. 20 μm
    - Used to de-lump and improve processability
  - Micronisation, typical d50 of app. 2 μm
    - Used to enhance processability and improve dissolution performance
  - Surface stabilised nano-particles, typical d50 of app. <1 μm
    - Used to enhance exposure

Micronisation



Micronisation





Surface area 0,05 m^2/g

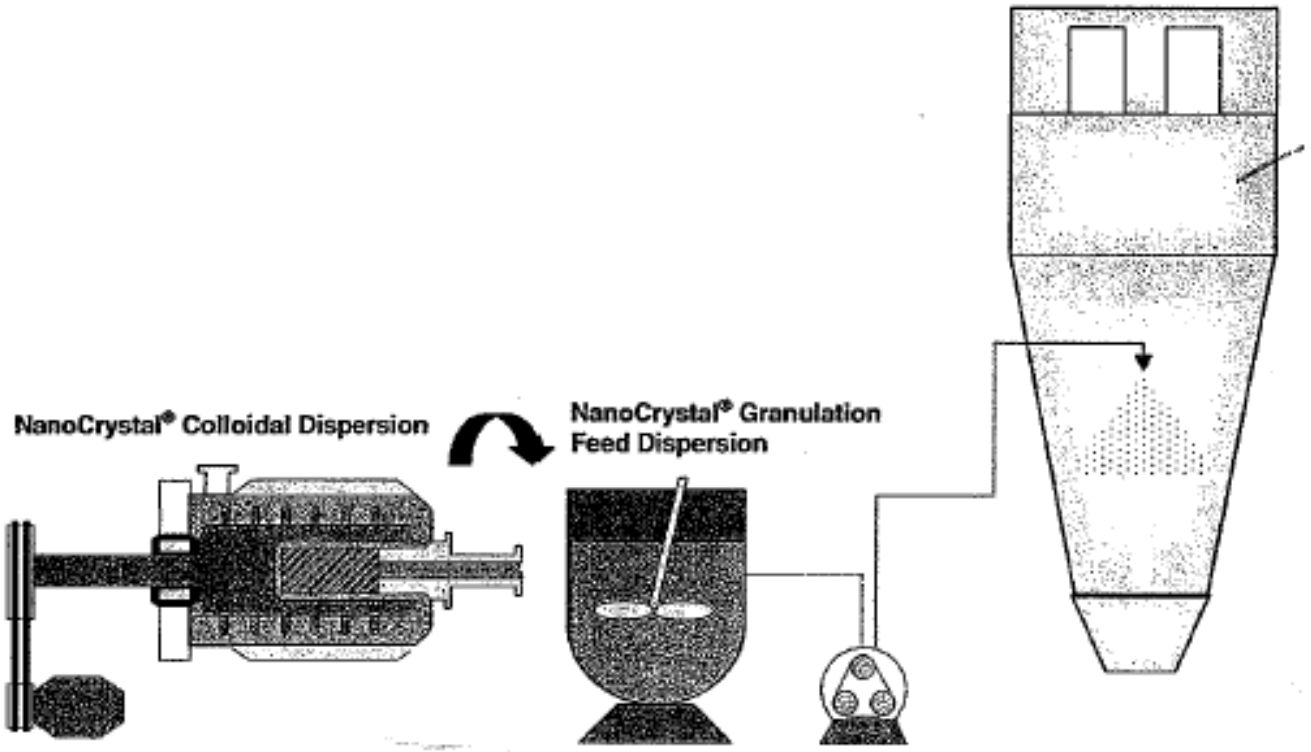
Particle size $X_{50\%}$ 269 µm

Surface area 1,21 m^2/g

Particle size $X_{50\%}$14,0 µm

NanoCrystals® - ELAN

- A suspension is obtained by milling and sprayed onto carrier particles



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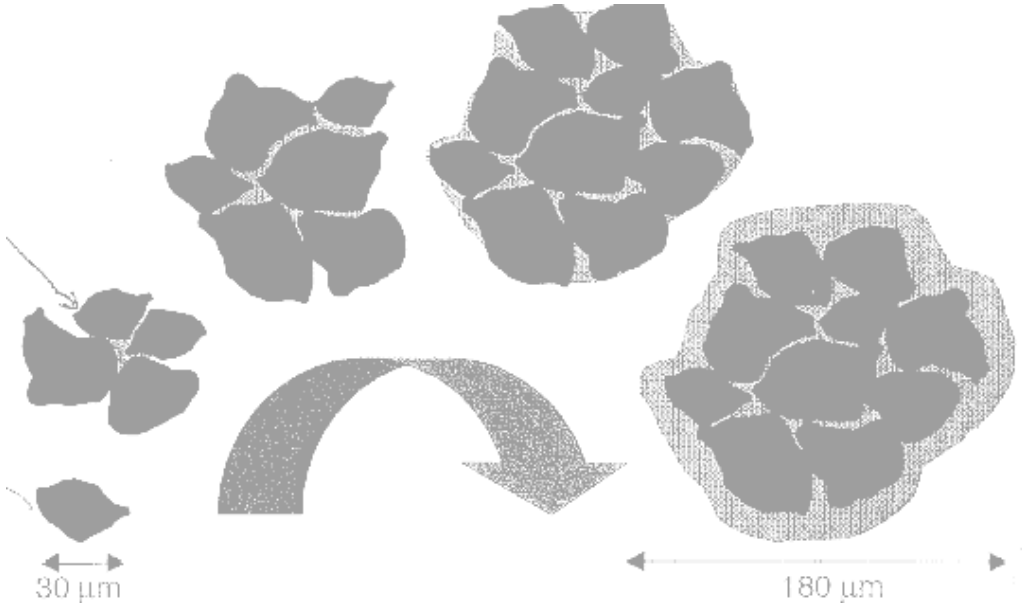
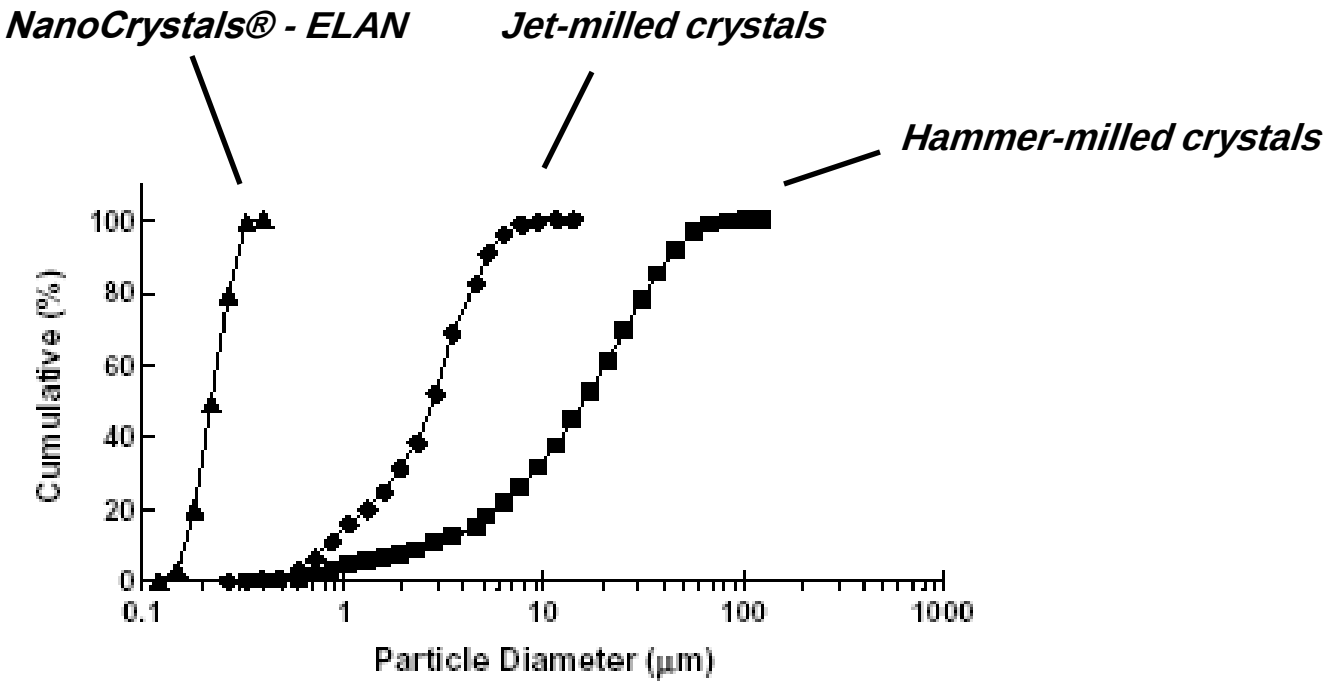


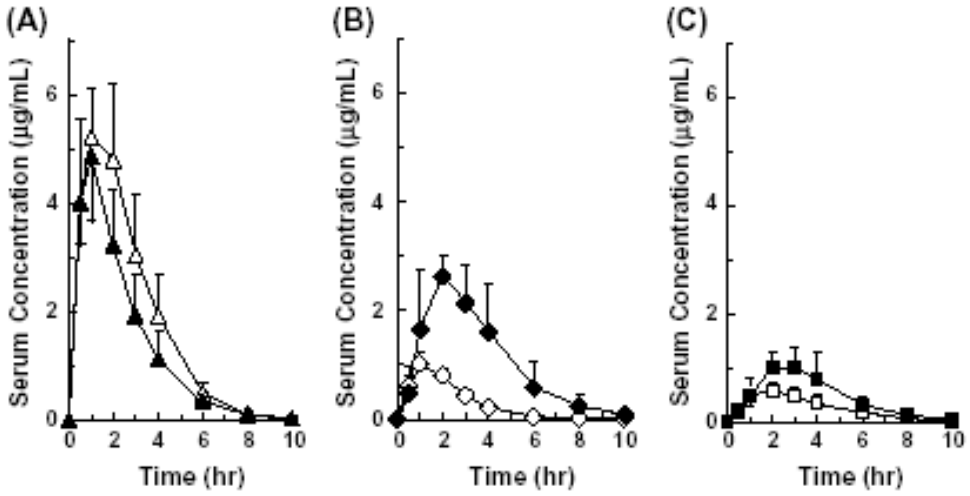
Nanoparticles

Cilostazol, aqueous solubility: 3 μg/ml



Jinno et al., 2006

Effect of particle size on bioavailability



Jinno et al., 2006

▲△ NanoCrystals® fed/fasted

◆◇ Jet-milled crystals fed/fasted

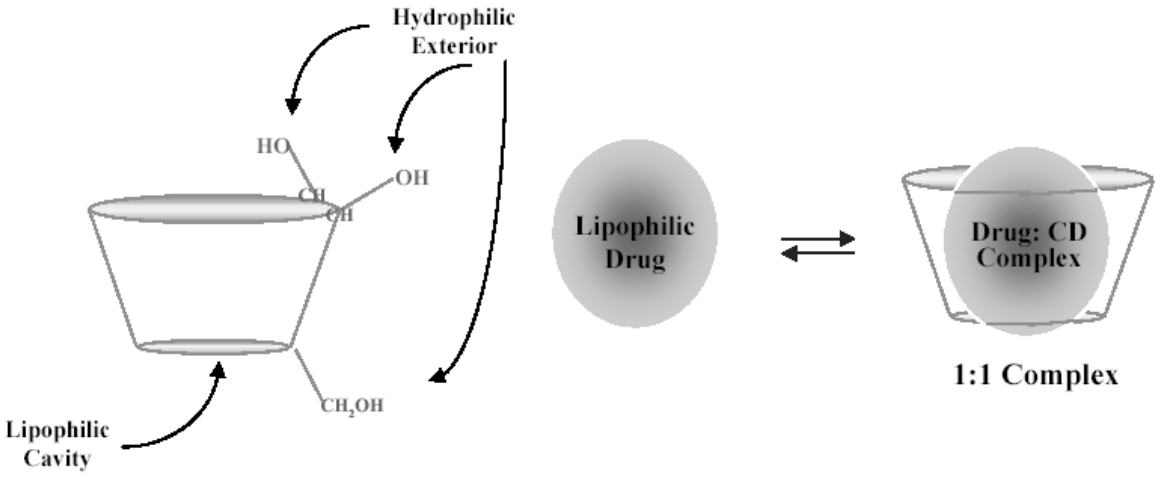
■□ Hammer-milled crystals fed/fasted

Size reduction: disadvantages

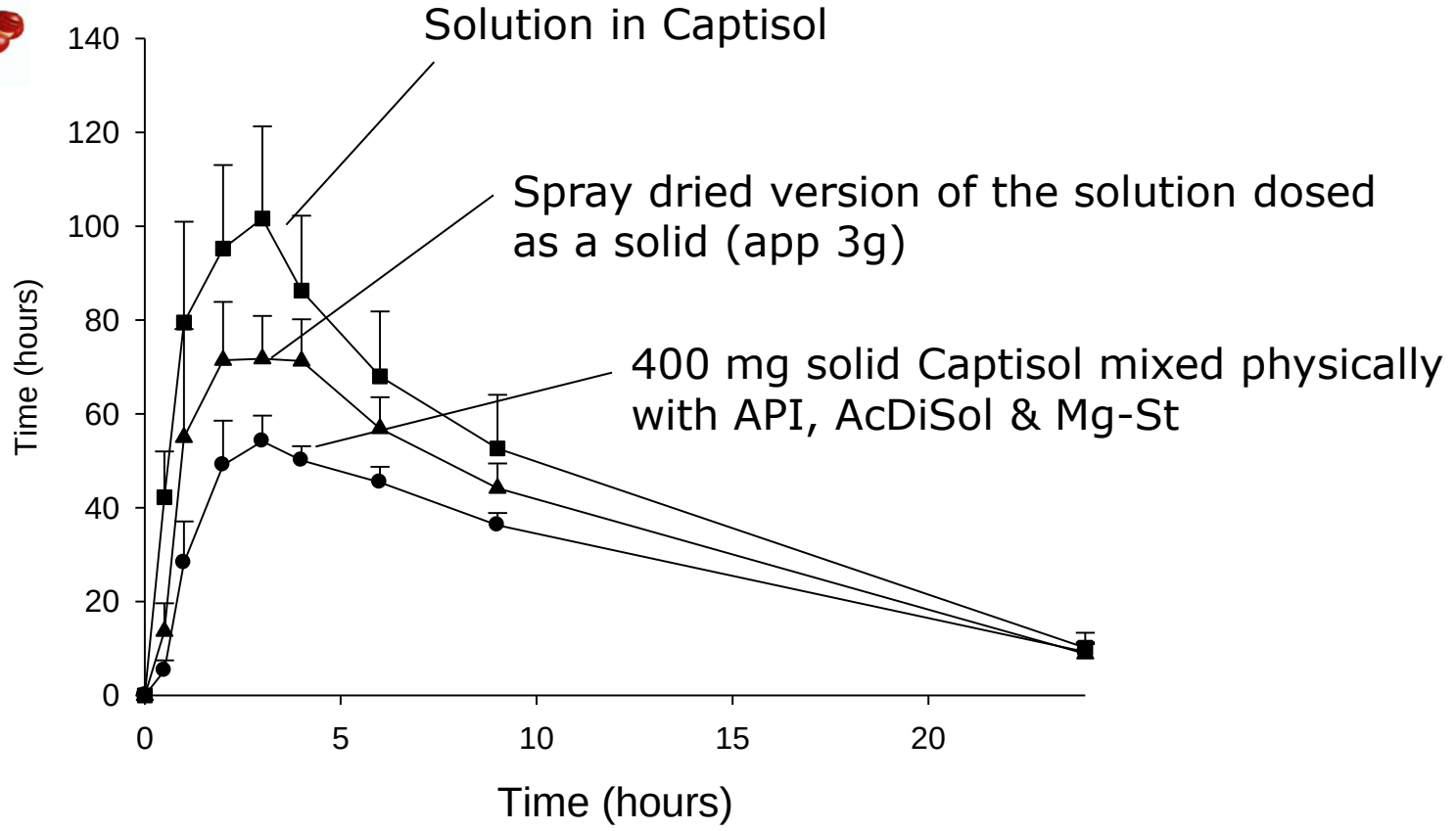
- Additional processing step, impact on CoGs
- Scale up not trivial
- Energetic process can introduce physical changes
  - Milling and particularly micronisation can introduce amorphicity
  - Wet bead milling may lead to stability issues
    - Chemical, e.g. hydrolysis
    - Physical (polymorphic changes)
    - Microbiological

Complexation/cyclodextrins

- Solubilisation of API through formation of inclusion complexes
  - At 1:1 complexes a large amount of CD required => large tablets, impact of CoGs
  - Royalty payment (for HPβCD and SBEβCD)
  - Enhances chemical stability

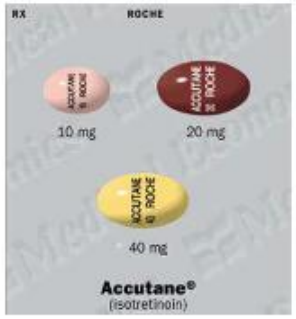


The power of CD's

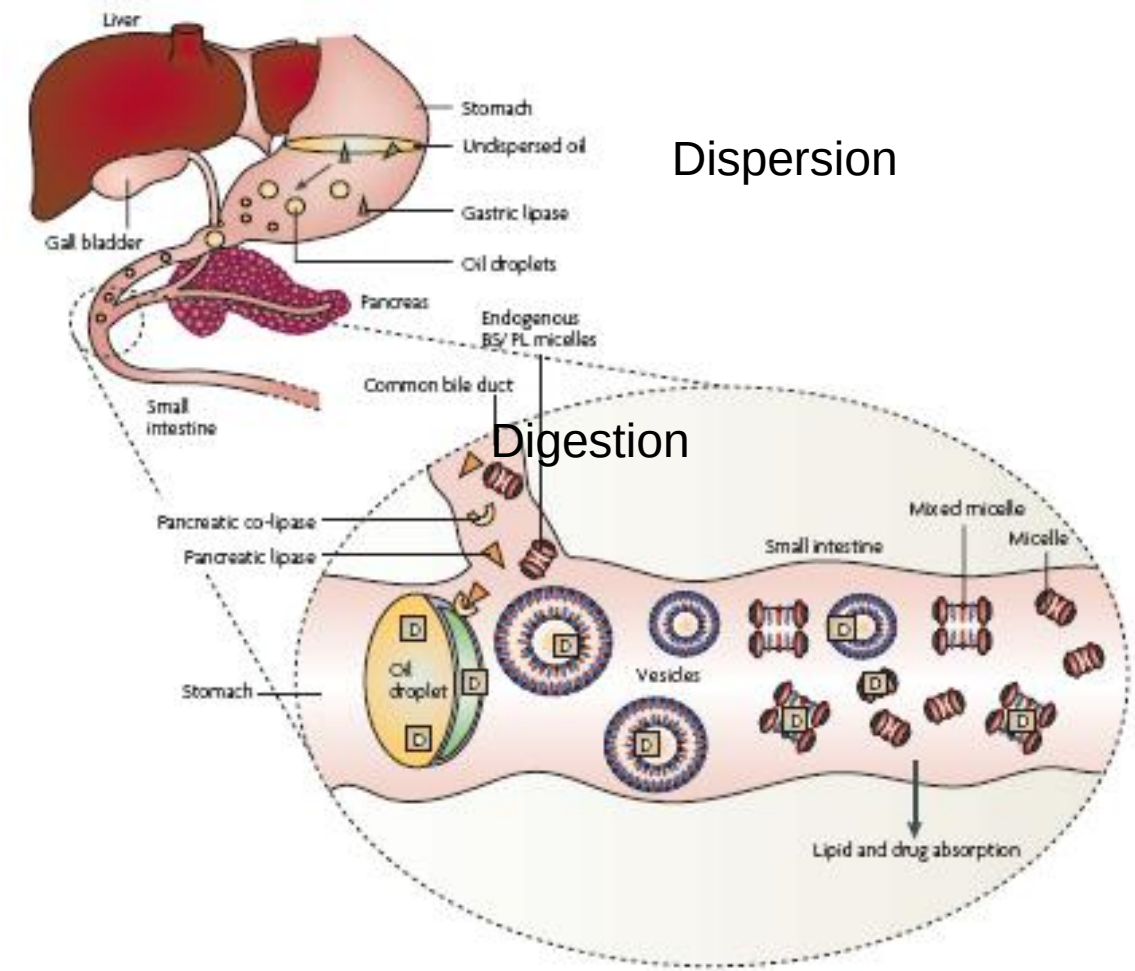


Commercial Lipid based formulations

- Accutane (Isotreinoin)
- Marinol (Dronabinol)
- Vesanoid (Tretinoin)
- Sandimmune (Cyclosporine)
- Neorale (Cyclosporine)
- Norvir (Ritnavir)
- Fortovase (Saqunovir)
- Gengraf (Cyclosporin)



Dispersion and digestion of lipids



Porter et al, 2007

Liquid filled capsules (soft and hard)

- Advantages
  - Improved bioavailability
  - More rapid rate of absorption
  - Lower PK variability
  - Can overcome food effects
  - Distinctive commercial image

- Disadvantages
  - Specialized filling equipment (slower than tablet production)
  - Excipients variability
  - Oxidation issues due to excipients
  - X-linking of capsules may cause dissolution issues
  - Low solubility in water ≠ high solubility in lipids

Amorphous strategies

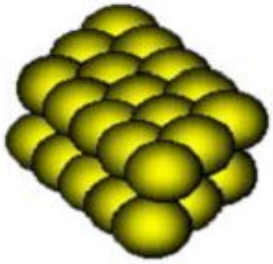
- Significant enhanced exposure can be attained from the amorphous form as the key constraint of lattice energy of the crystalline state is overcome

Amorphous compounds

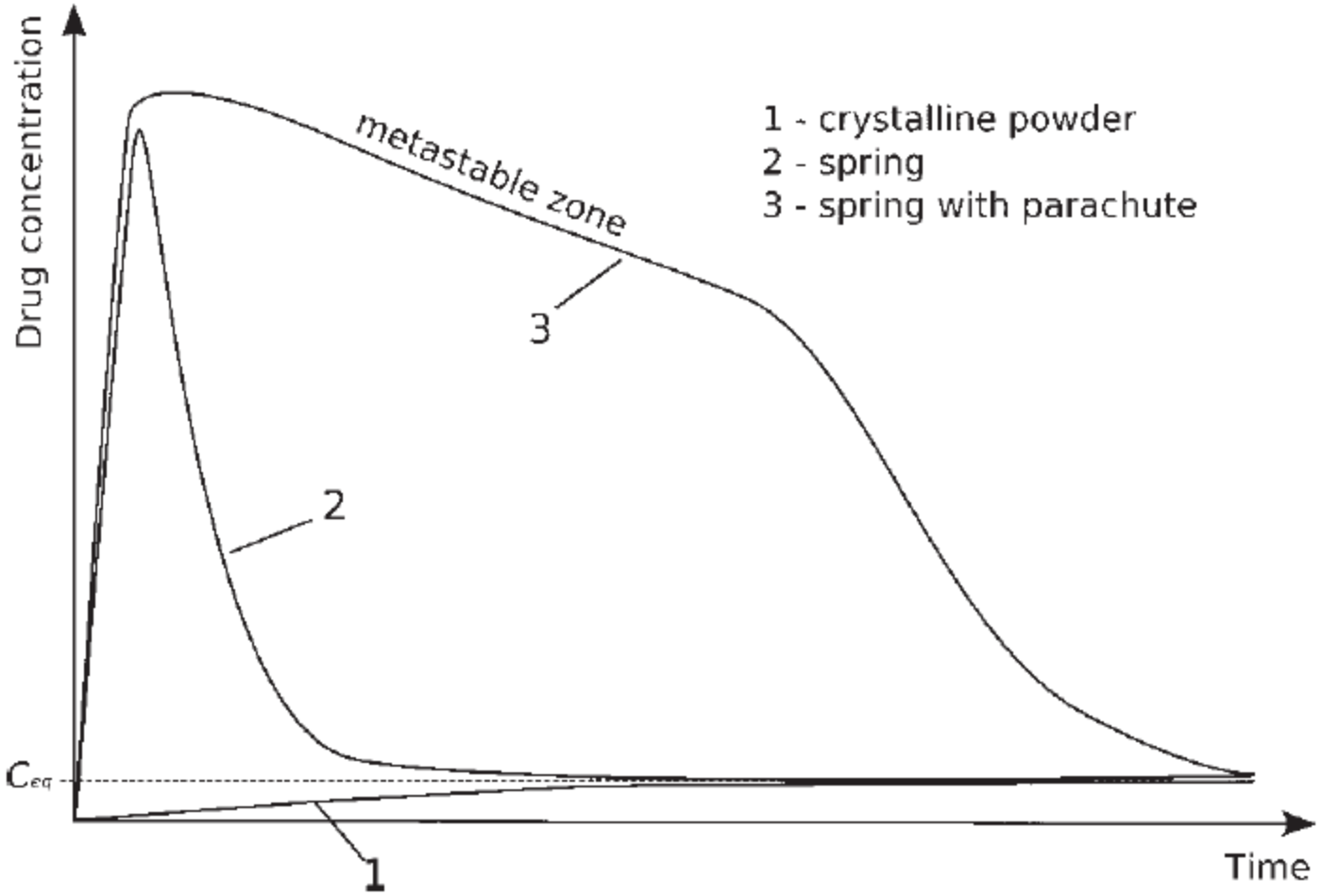
Solids with no orientation or positional long-range order

Crystalline compounds

Solids with orientation and positional long-range order in three dimensions



The parachute profile



Brouwers et al 2009

How parachute excipeints works

- Reducing the degree of supersaturation by increasing the solubility
- Increasing the viscosity, resulting in a reduced molecular mobility and diffusion coefficient
- Changing the adsorption layer at the crystal medium interface by, for example, adsorbing onto the crystal surface thereby hindering crystal growth

Brouwers et al., 2009

Parachute excipients

- Some polymers can increase the solubility, but their precipitation inhibition is most likely the result of direct interference of the polymer with nucleation and/or growth rate
  - Cellulose derivatives (MC, HPC, HPMC)
  - Vinyl polymers (PVA, PVP, PVPVA)
  - Ethylene polymers (PEG)

- Surfactants may completely solubile the drug, but also delay precipitation
  - SDS, vitamine E-TPGS, Tween 20, & 80, Cremophor RH40

- Cyclodextrin, increases the solubility through complexation

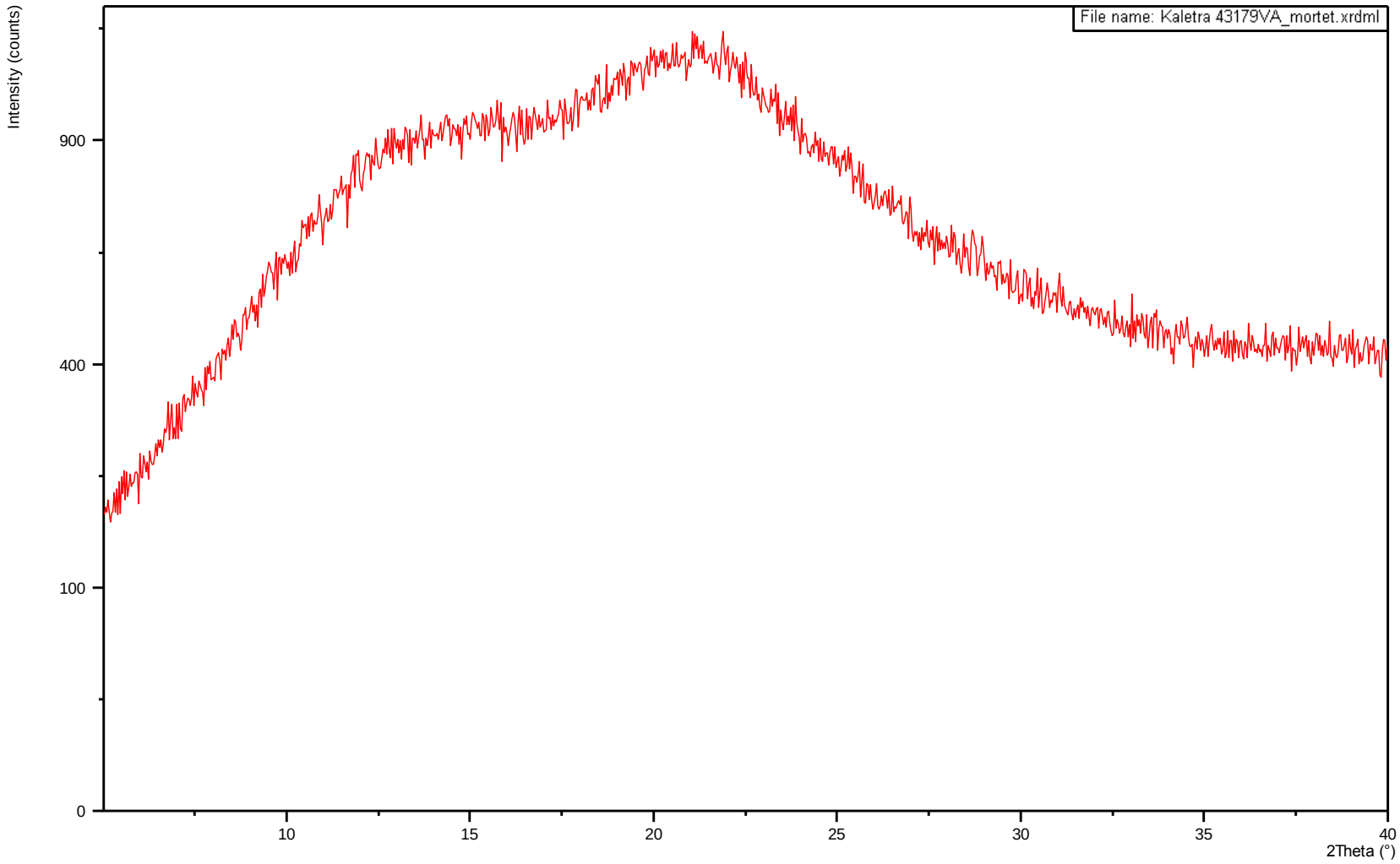
Kaletra – a commercial examle

- Ingredients
  - Ritonavir and Lopinavir (API)
  - Sorbitan laurate
  - Hydromellose
  - Hydroxypropylcellulose
  - Talc
  - Macrogol
  - Sodium stearyl fumerate
  - Silica
  - Copovidone

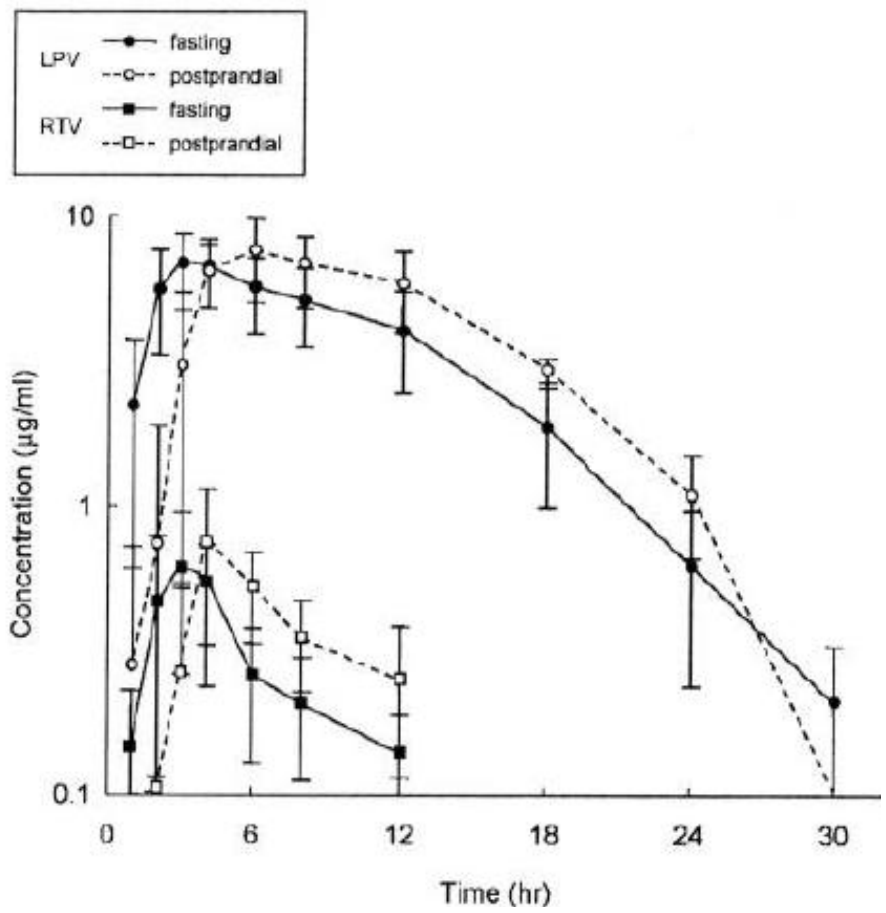
Production method of Kaletra

From: www.soliqs.com

XRPD of Kaletra



Kaletra in humans



Oki et al., 2004

Issues with Solid Solutions/dispersions: chemical stability

- Factors impacting the chemical stability are:
  - High molecular mobility of water acting as plasticiser
  - Greater reactibity of amorphous state
    - Greater impact of excipient and processing impuritis on stability

Issues with Solid Solutions/dispersions: physical stability

- The single most importan factor limiting the use of amorphous state is inadequate physical stability
  - Caused by higher mobility
  - Thermodynamic properties of the amorphous state
  - Recrystallisation leads to loss of bio-enhancement
  - Measurement of amorphicity/crystallinity not trivial and method dependent

Production methods of amorphous materials

Parameter	Hot melt	Spray drying	Freeze drying
Econimics	+++	++	+
Processing complexity/time	+++	++	+
Continious processing	+++	++	+
Heat labile compoinds	+	++	+++
Shear labile compounds	+	++	+++
Bioenhancement	++	+++	+++
Scale up	+++	++	+
High doses	+++	+	+

Final remarks

- A number of different formulation strategies exists for low soluble compounds
- No single preferred method – needs to be tailored with the compound
- What worked 10 years ago - may not work now