

Special Aspects of Nanomedicines

Viewpoint from the Industry

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Outline

- Definition
- Biopharmaceutical aspects
- Overview of different particle size reduction methods
- General process towards nanoformulations
- Product development
- Concluding remarks

Definition by EMA

- *Nanotechnology* is defined as the production and application of structures, devices and systems by controlling the shape and size of materials at nanometre scale. The nanometre scale ranges from the atomic level at around **0.2 nm** (2 Å) up to around **100 nm**.
- *Nanomedicine* is defined as the application of nanotechnology in view of making a medical diagnosis or treating or preventing diseases. It exploits the improved and often novel physical, chemical and biological properties of materials at nanometre scale.

Ref.: EMEA/CHMP/79769/2006

Pharmaceutical Nanotechnology

	Technology type	Size range
Established technologies	Liposomes	100 nm
	Drug nanocrystals/Nanoparticles	50 – 1000 nm
	Micelles, SMEDDS, SNEDDS	10 – 200 nm
	Polymer-based nanoparticles	5 nm – 5µm
	Lipid based nanoparticles (SLN, NLC)	20 – 200 nm
	Dendrimers	10 nm – 500 nm
Subject to current research	Fullerenes	0.7 nm
	Nanotubes	10 – 200 nm
	Quantum dots	2 – 10 nm
	Nanostructured biomaterials	50 – 500 nm
	Drug-Nanoparticle conjugates	
Future applications	Nanodevices	?

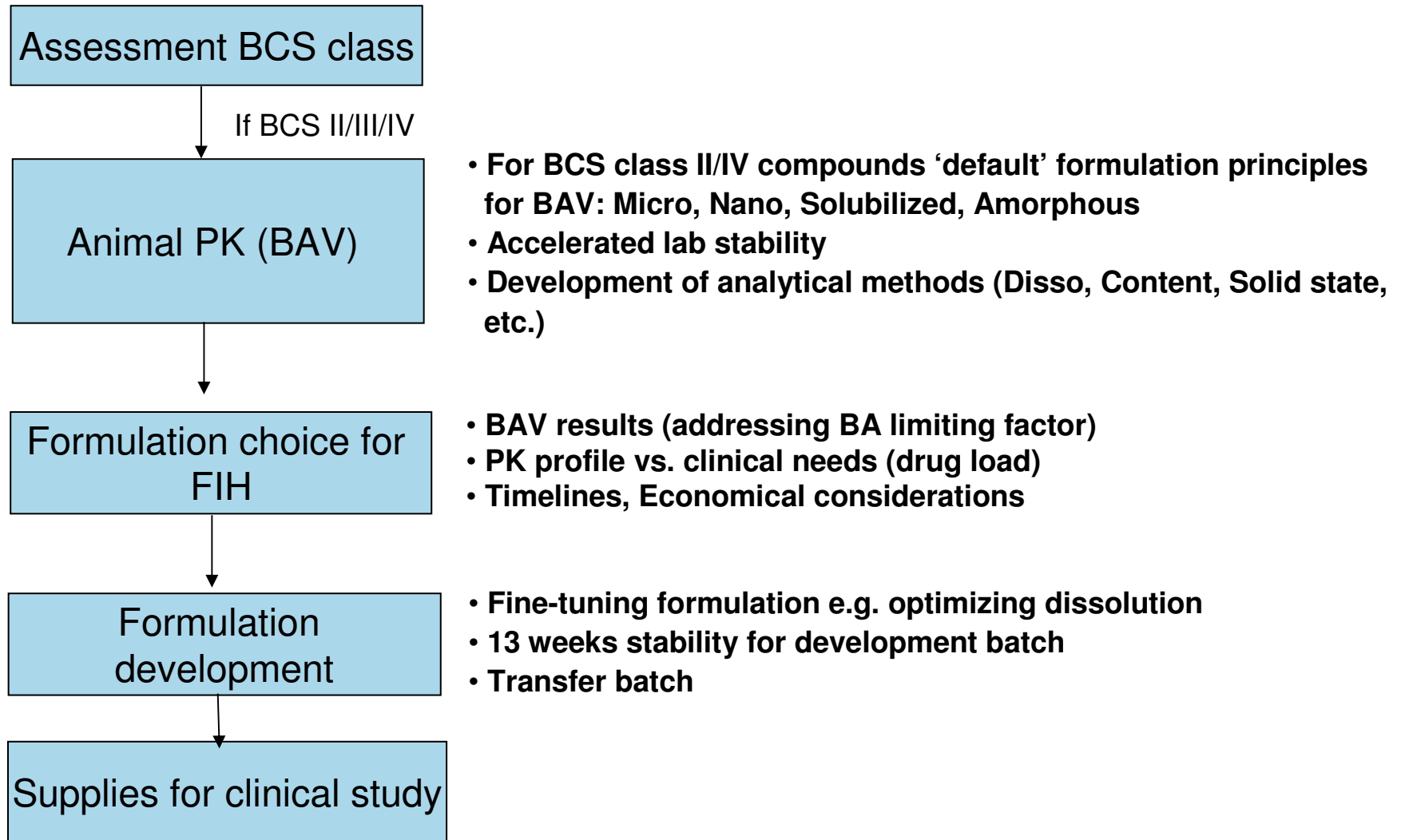
Working definition for Nanoparticles/Drug Nanocrystals for this presentation

- Nanoparticles/Drug nanocrystals are particles with a mean particle size between 1 nm to 1000 nm consisting of pure API stabilized with surfactants or other stabilizers. The solid state of the nanoparticulate API can range from pure crystalline, partially amorphous to fully amorphous.
- Nanosuspensions are colloidal dispersions of nanoparticles/drug nanocrystals.

Outline

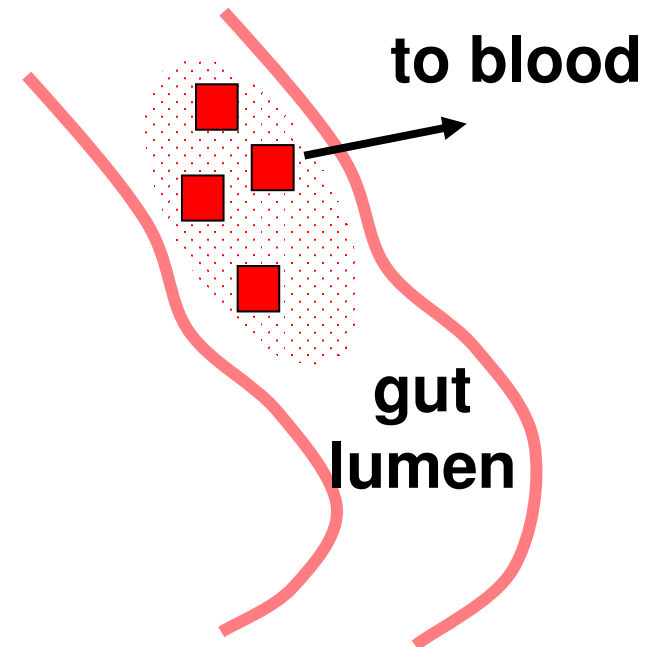
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Development strategy BCS class II/IV

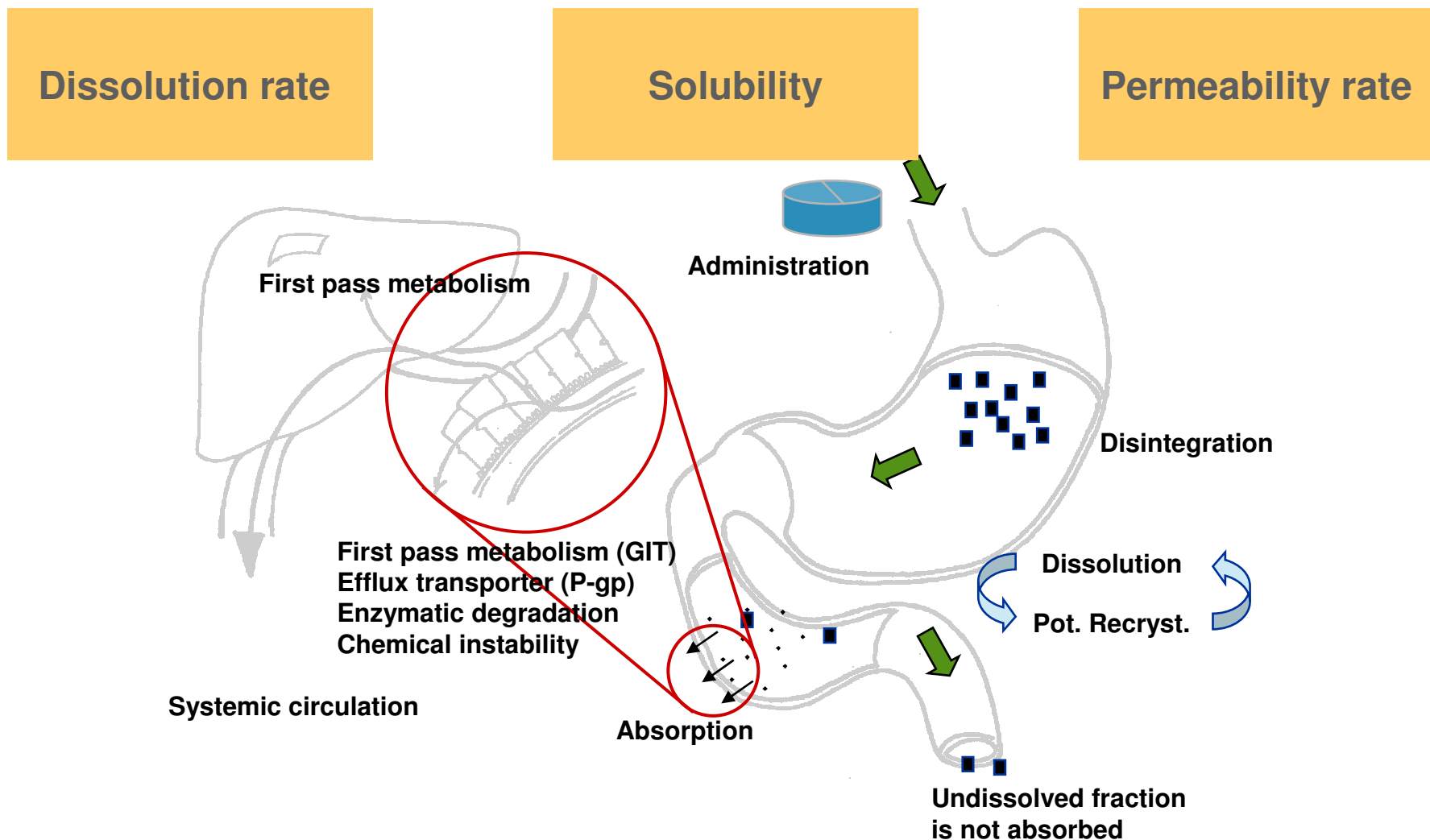


Challenges of poorly soluble drugs

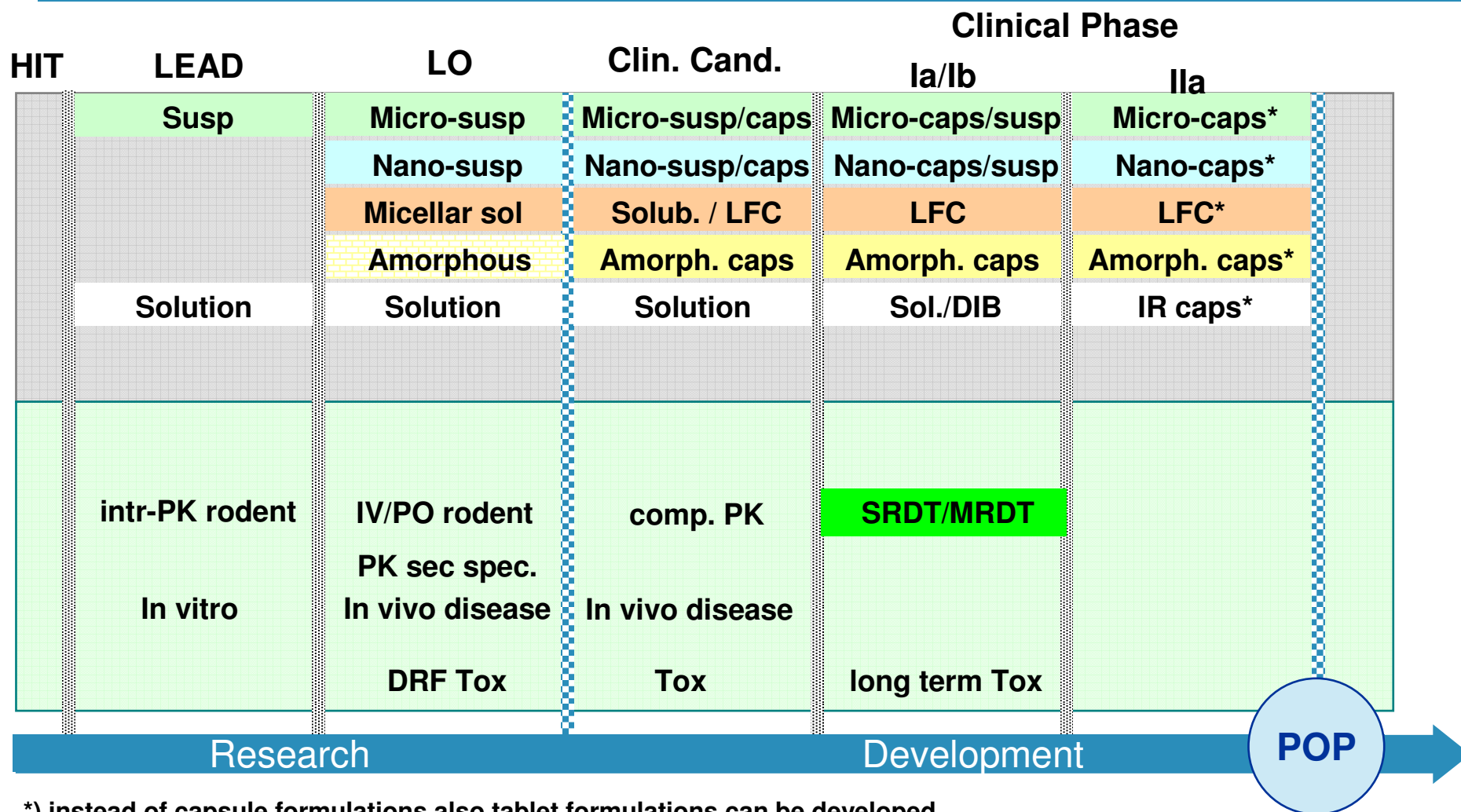
- incomplete or erratic absorption
- poor bioavailability
- slow onset of action
- patient-to-patient variability
- strong food effects
- high doses needed



Determination of BA limiting factor asap

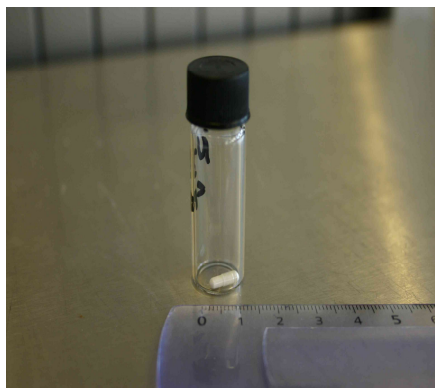


Strategy for BCS class II/IV

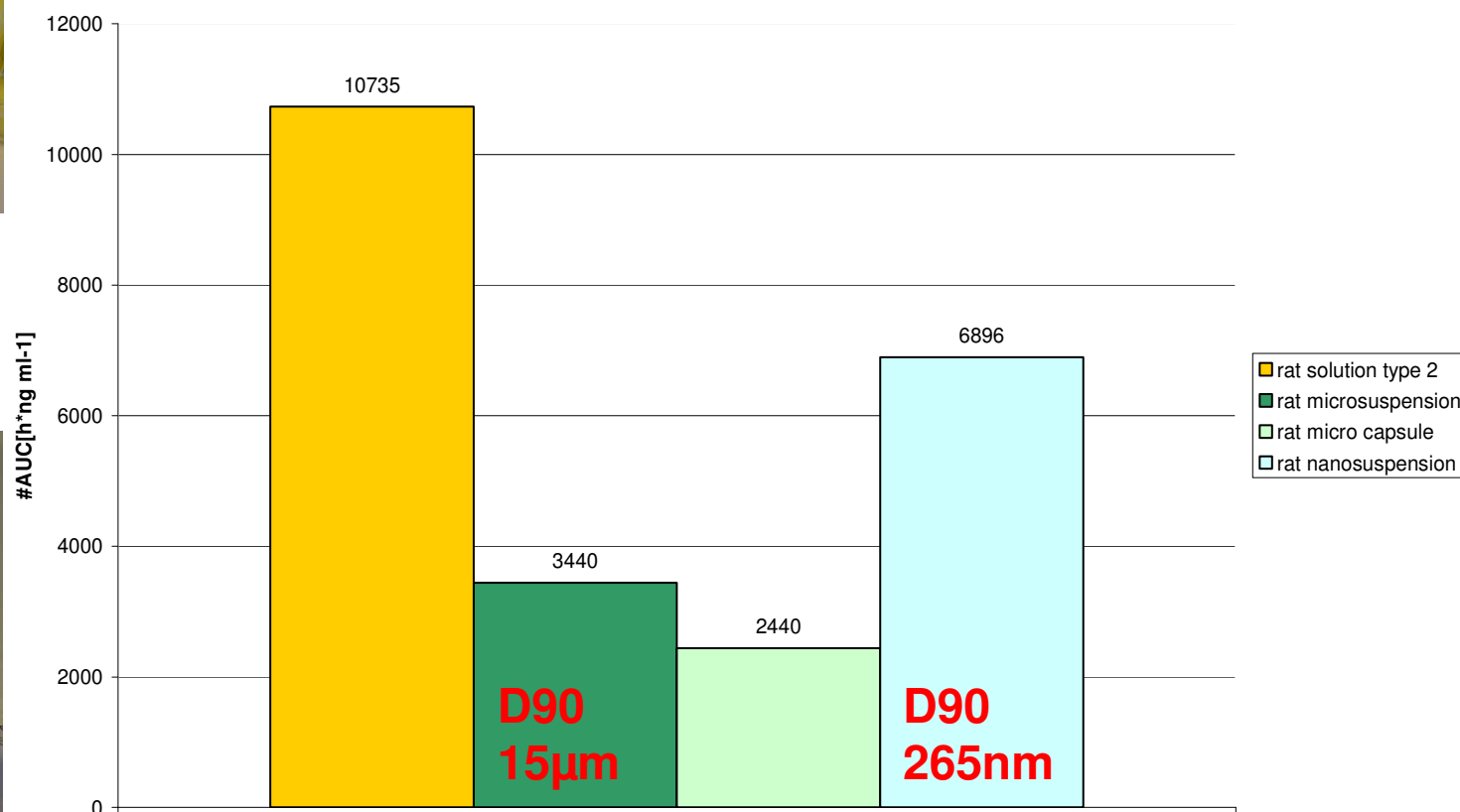


*) instead of capsule formulations also tablet formulations can be developed

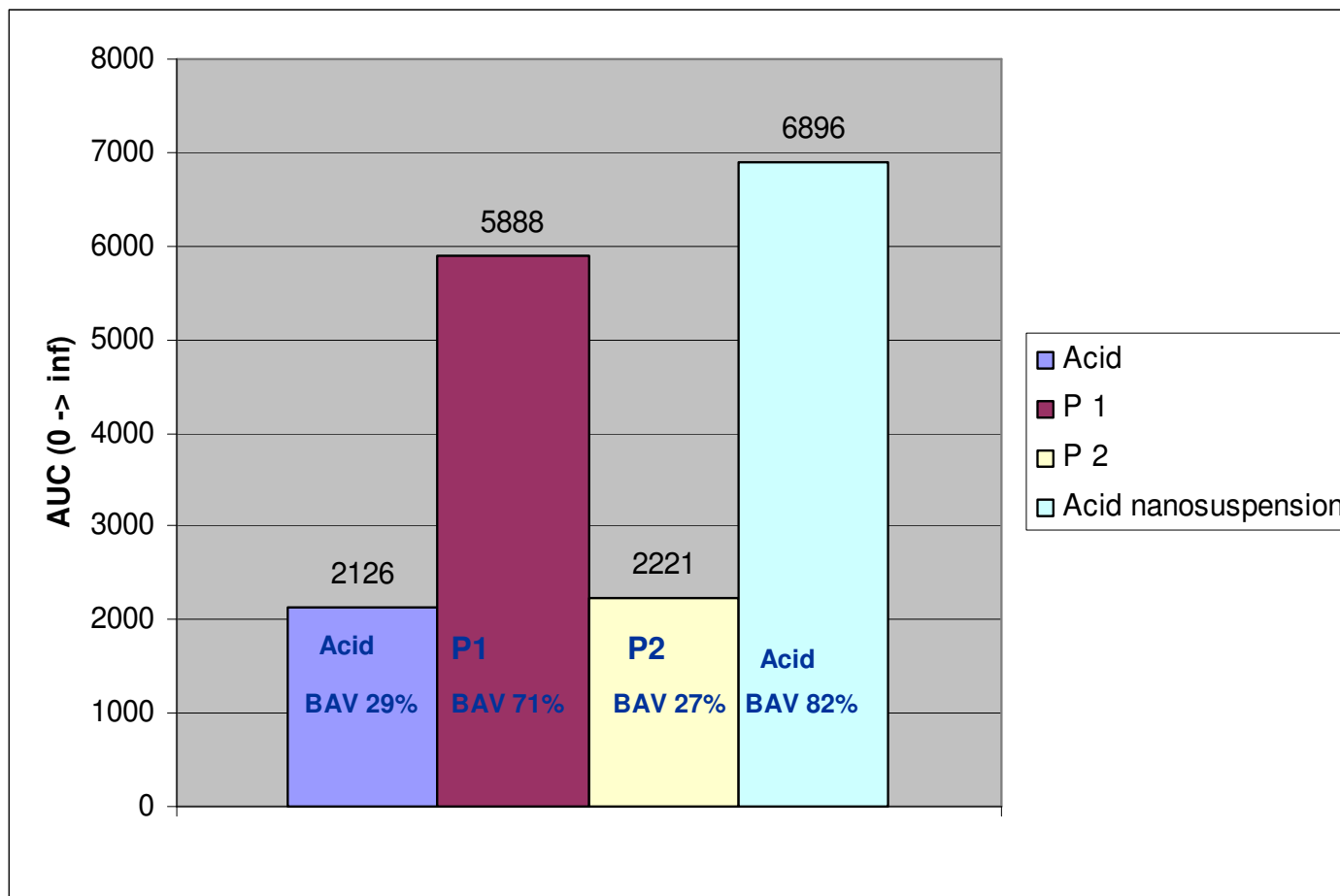
Comparison liquid and first solid forms in a rat PK study



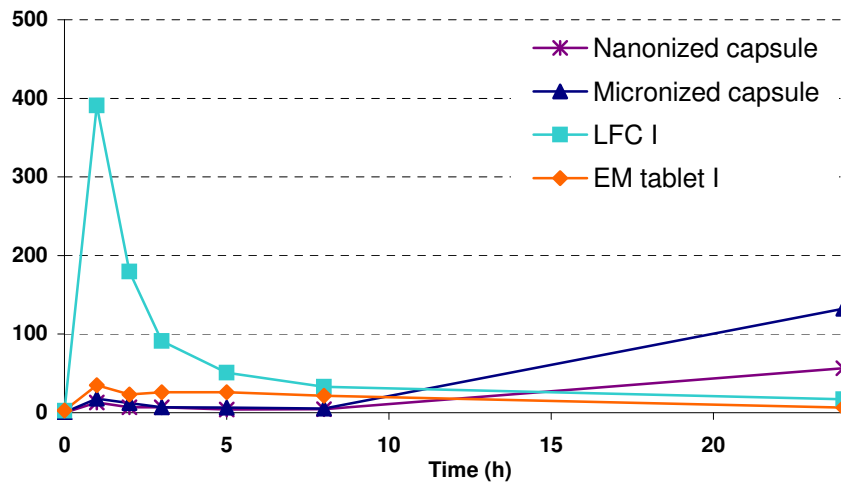
poorly soluble BCS II: exposure after application of different formulation types



Comparison of free acid, salts and nanosuspension



Solubility limited vs. Dissolution rate limited BA

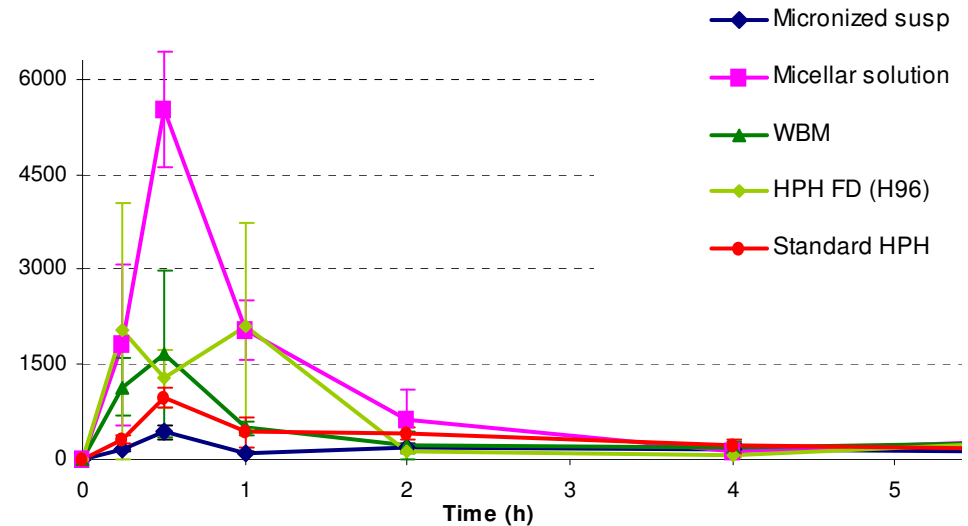


Solubility limited

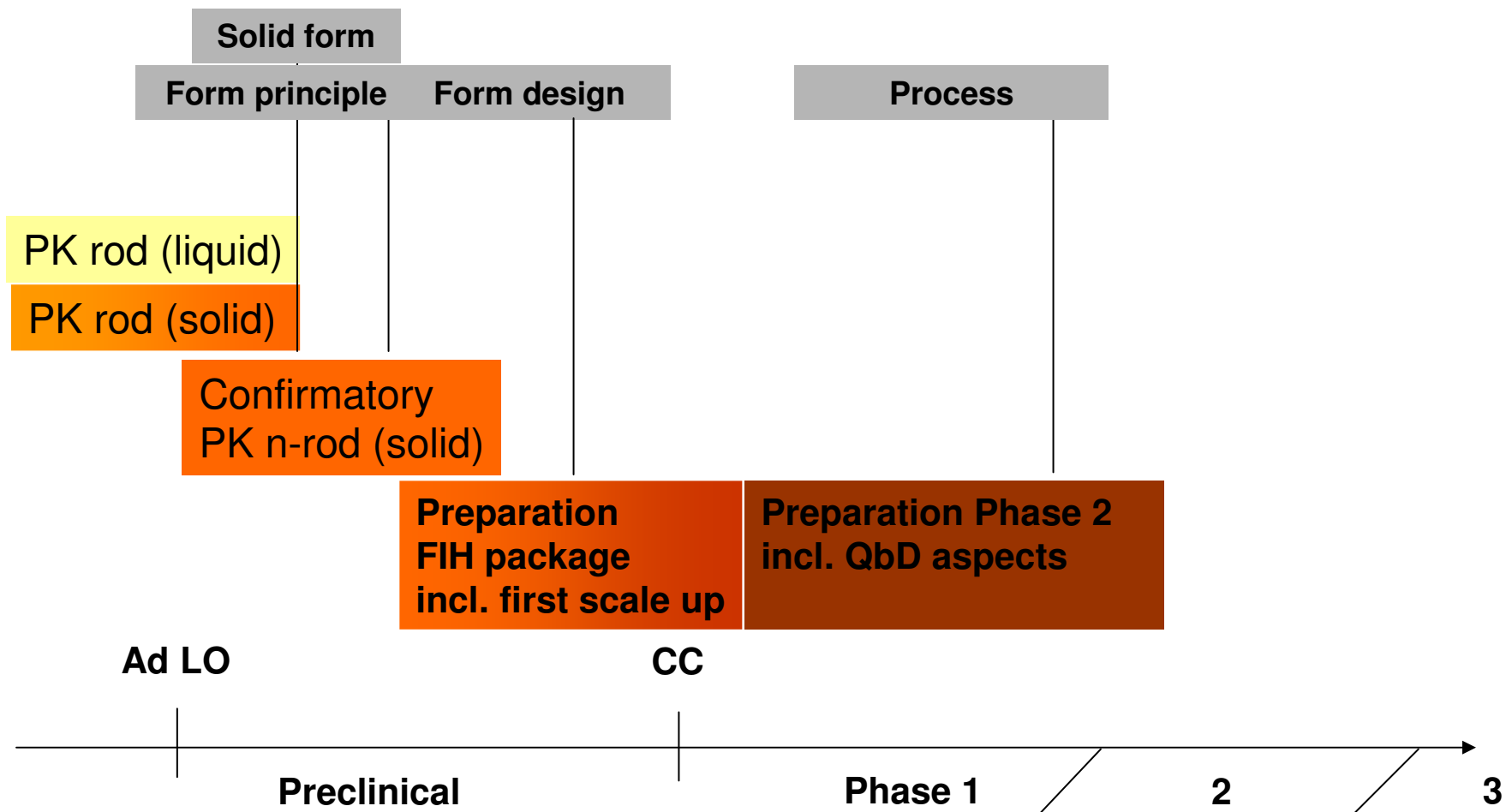
Sol >>> Nano/Micro

Dissolution rate limited

Sol > Nano > Micro



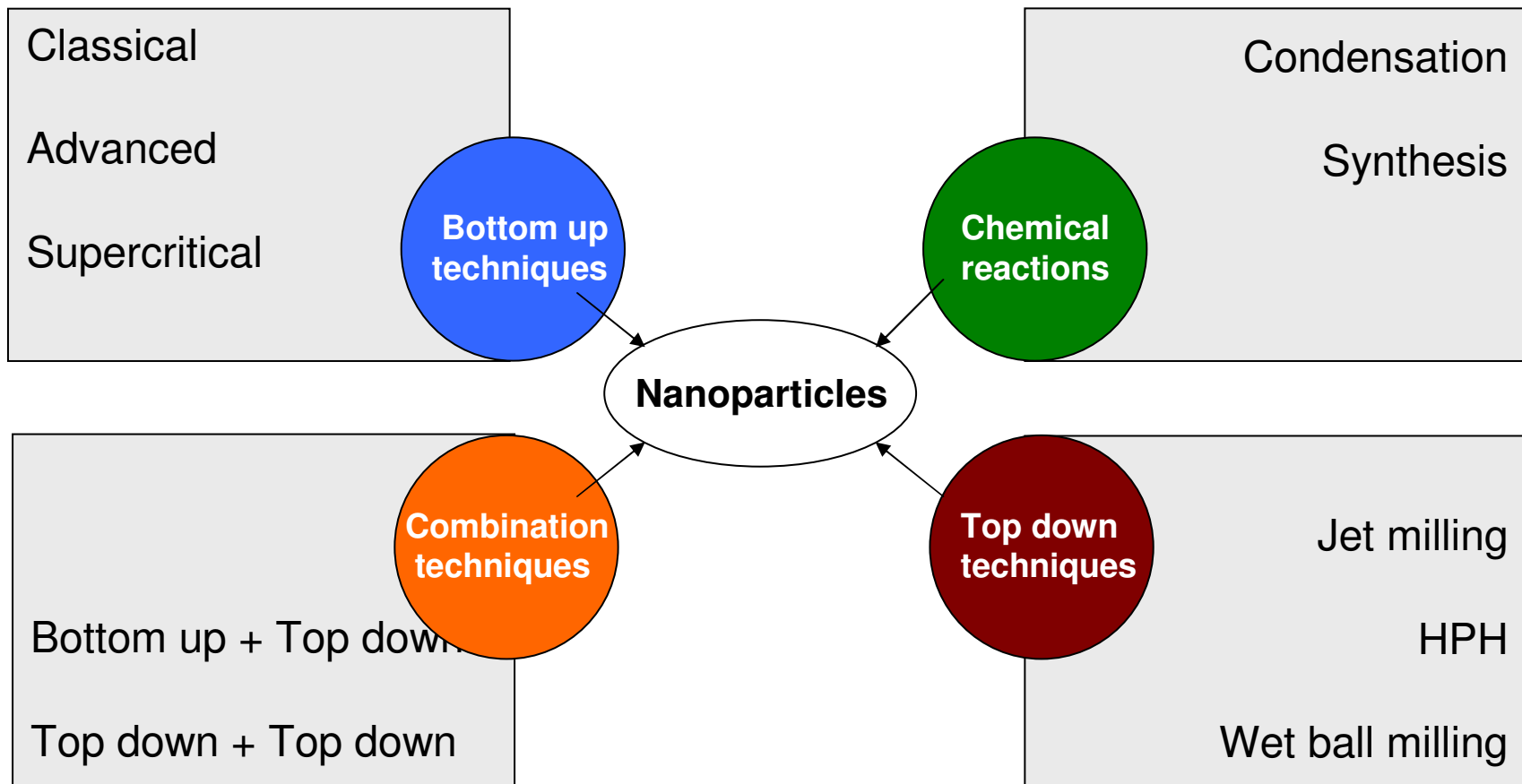
Summary Formulation Development



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Overview of Nanosizing Technologies



Overview Particle Size Reduction Techniques

Top down	Bottom up	Combinations
Wet milling HPH (Jet milling)	Precipitation SD, FD Supercritical Fl. Cryogenic Prec.	Prec. + HPH SD + HPH FD + HPH

Outline

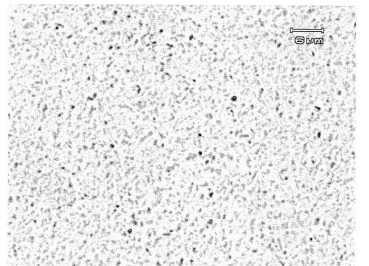
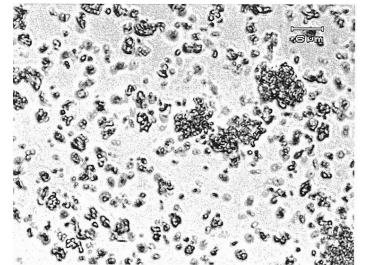
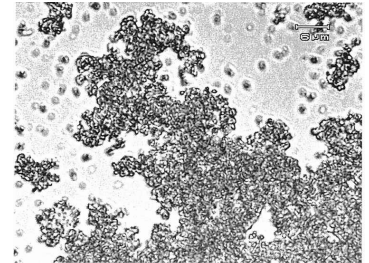
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General process towards nanoformulations

- Stabilizer screening, particle size reduction method
- Scale up nanosuspension
- Screening solidification methods
- Prototype formulations
- Stability testing (Intermediates, Final Drug Product)

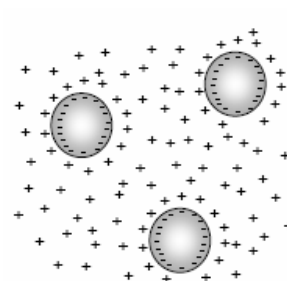
Stabilizer screening

- Still highly empirical
- Stabilizer choice depends on:
 - Application (Administration route and purpose)
 - Particle size reduction method
 - Physico-chemical properties of API
- Stabilizer should provide a robust, reliable
particle stabilization after production and administration

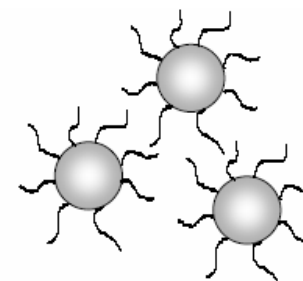


Stabilization principles

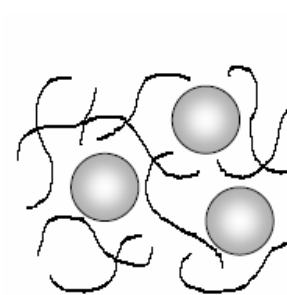
- Steric e.g. cellulose polymers, Poloxamers
- Electrostatic
 - non-ionic e.g. polysorbate
 - anionic e.g. SLS, DOSS
- Electrosteric e.g.
most common for oral administration
combi HPMC/SDS, HPMC/DOSS
- Depletion e.g. polymers



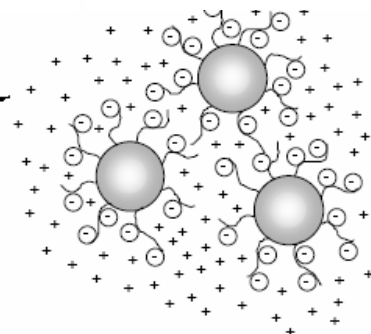
Electrostatic



Steric



Depletion



Electrosteric

Ref.: PhD thesis Heike Arndt, 2002

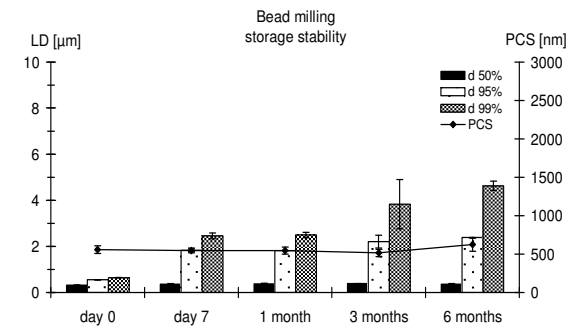
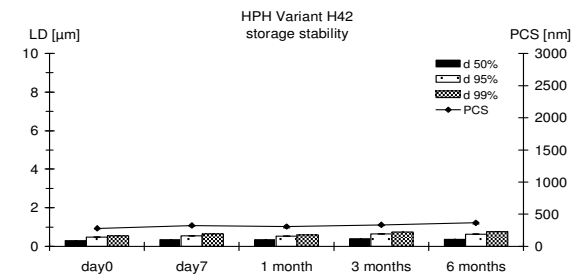
Stability testing Intermediates and finished DP

- Particle size

Nanosuspension: Ostwald ripening, aggregation

DP: Redispersion from solid dosage form

- Microbiological stability
- Chemical stability (Degrad., Content, etc.)
- Solid state properties (Degree of crystallinity)
- Dissolution testing



Dissolution testing

- 2 different methods
 - Standard QC method for release of DP
 - Discriminating method under non-sink conditions for formulation screening support
- Selection of Filter system/Centrifugation system
- Cave: Selection of appropriate media (pH, surfactant, electrolytes)

Particle characterization techniques

Structural and analytical techniques

Microscopy (Polarized light microscopy, CLSM, SEM, TEM)

Powder X-ray diffraction (PXRD)

Raman spectroscopy

Thermal techniques

DSC, TGA

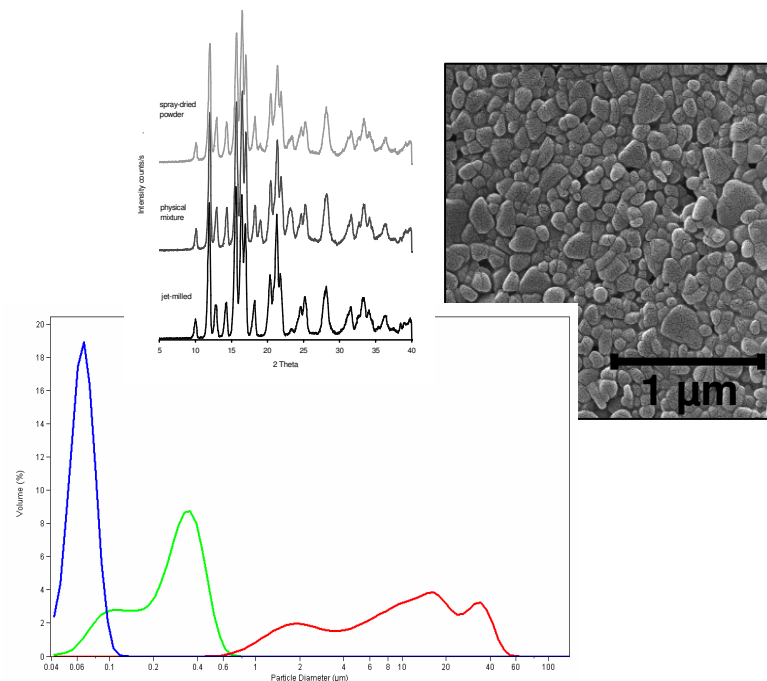
Hot stage microscopy

Particle size analysis

PCS, LD, (Coulter Counter)

others

Zeta potential



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Nanosuspensions in TOX

Milling equipment (Beaker method)

- Glass beads (4 mm)
- Milling beads(0.5 to 1.5 mm)
- Magnetic stirrer/stirrer bar

Dispersion medium

- Cellulose based polymers (MC, HPMC)
- Surfactants: Pol 188

Concentration

- API up to 10% w/w
- 1/10 to 1/2 milling media rel. to suspension

Scale

- 10 ml up to 1 liter



Nanoformulations for animal PK studies (oral route)

Milling equipment (Small scale)

- High pressure homogenizer (batch mode)
- Agitated ball mill with milling media

Dispersion medium

- Cellulose based polymers (MC, HPMC)
- Surfactants: Pol 188, SDS, TPGS, Tw 80

Concentration

- API up to 30% w/w

Solidification

- SD, HSG, FD followed by capsule filling or tableting

Scale

- 30 ml up to a few liters



Nanoformulations as CTM

Milling equipment (cGMP)

- High pressure homogenizer (batch mode, cont mode)
- Agitated ball mill with milling media in recirculation

Dispersion medium (only approved excipients)

- Cellulose based polymers (MC, HPMC)
- Surfactants: Pol 188, SDS, TPGS, Tw 80

Concentration

- API up to 30% w/w (HPH=10%; WBM=30%)

Solidification

- SD, HSG, FD followed by capsule filling or tableting

Scale

- up to several liters



Solid dosage forms containing drug nanocrystals



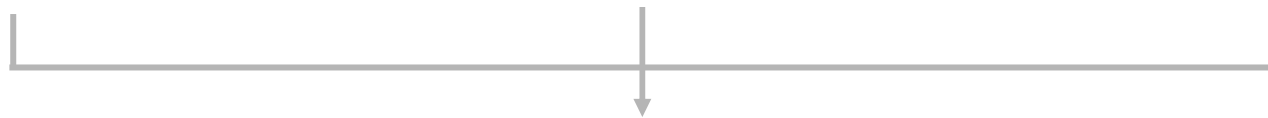
Spray-dried



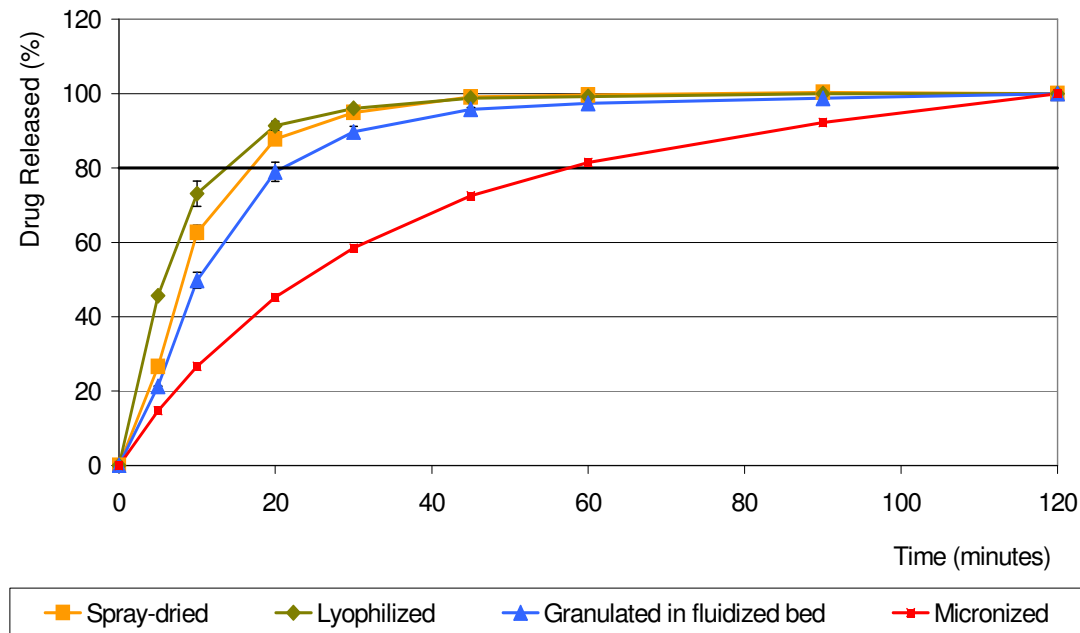
Granulated



Lyophilized



A comparison of lyophilization (FD), spray-drying (SD) and fluidized bed granulation (FBG)

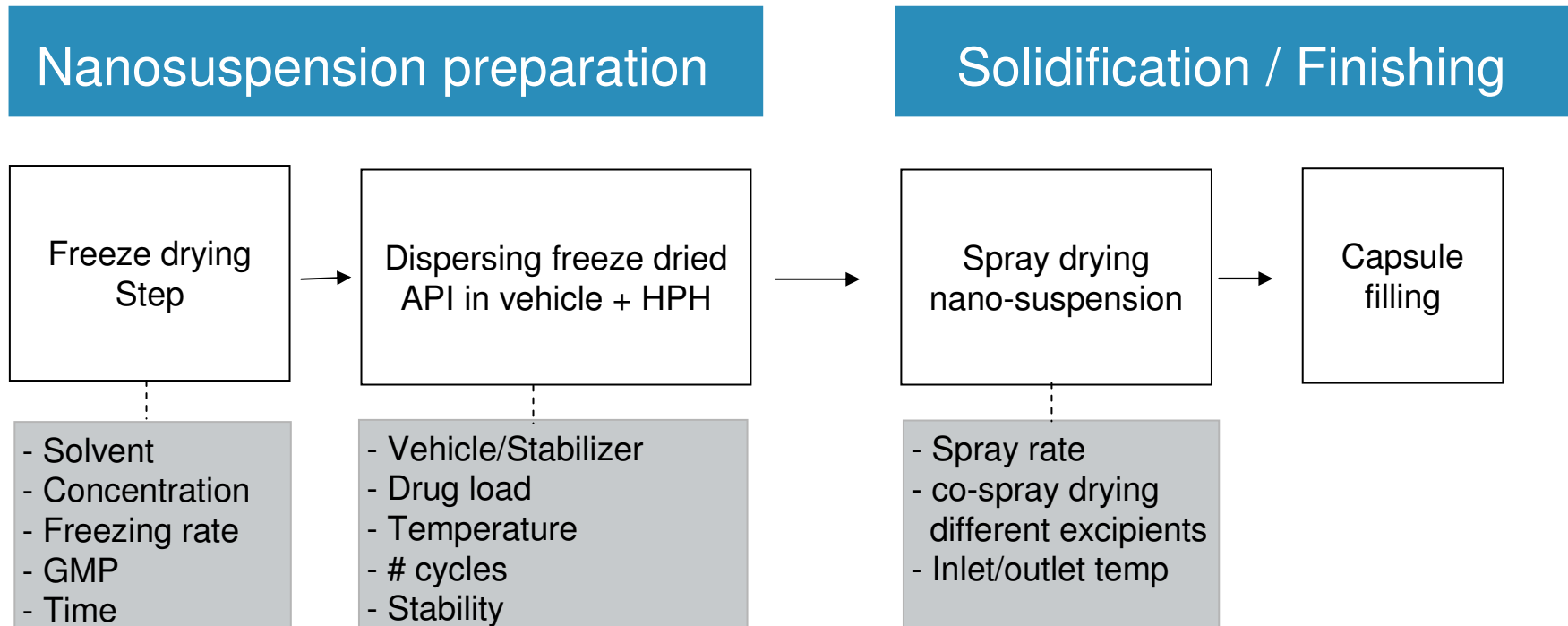


Lyophilization

Spray-drying

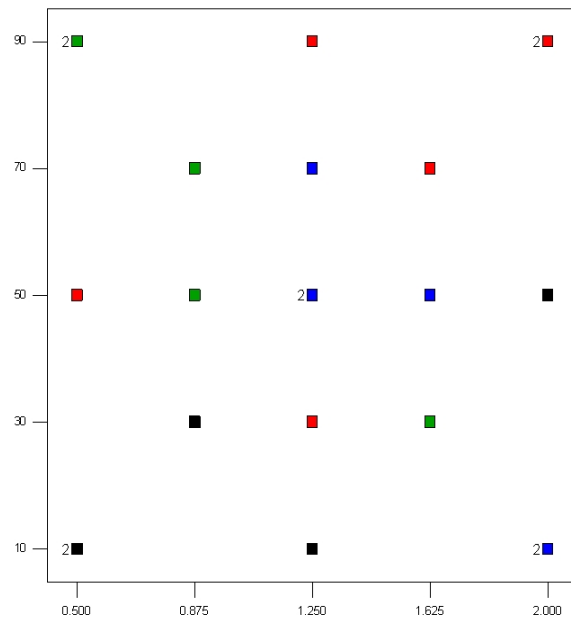
Fluidbed granulation

Typical process steps for a combined method (H96)

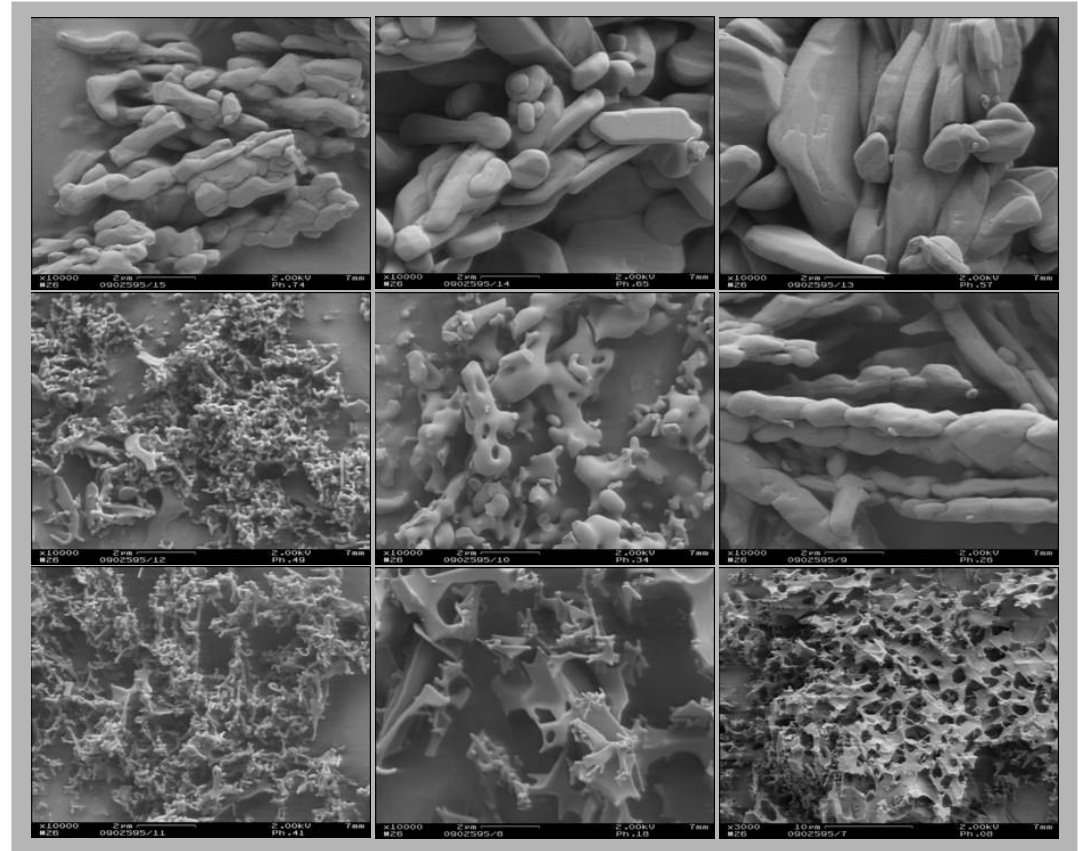


DOE: Identify optimal solvent and API concentration to obtain brittle starting material

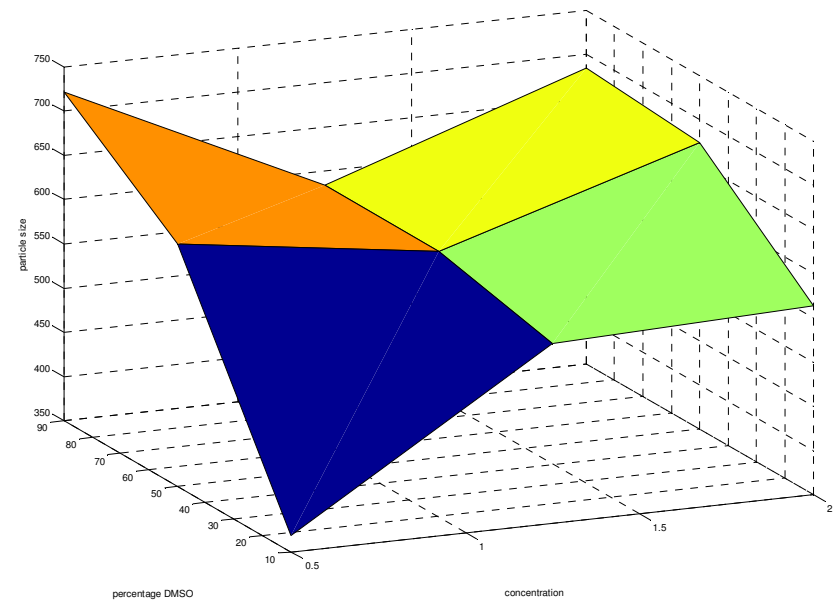
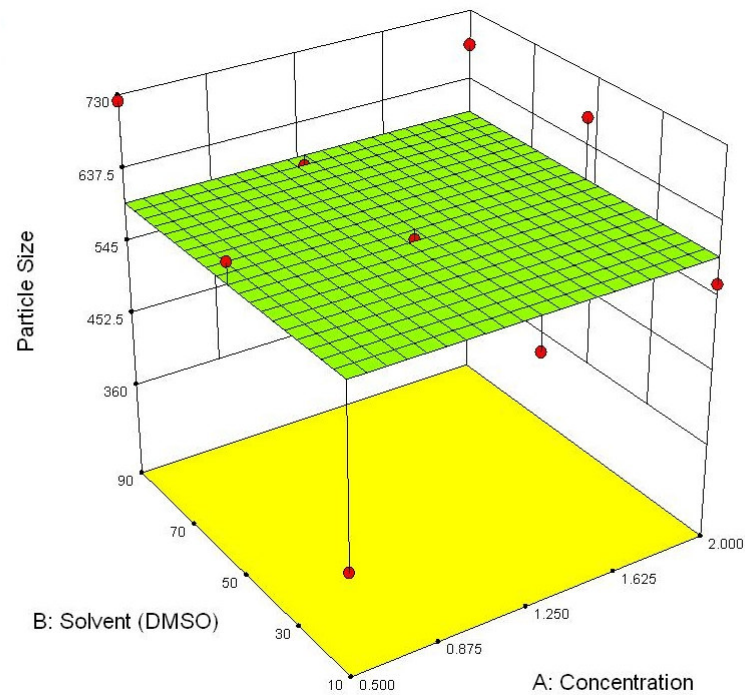
Solvent mixture



API concentration



Particle size as function of c(API) and FD solvent



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Concluding remarks

- Nanosizing can help for dissolution rate limited APIs
- Nanosizing is an established way (oral and parental products are on the market)

- Complex process needs a lot of expertise

Large variety of different nanosizing techniques available

Trend from empirical to more systematical procedures

Need for good guidance

- Still active academic research area – opportunities for new drug delivery systems

Acknowledgments

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