Recrystallization of poorly soluble drug from amorphous solid dispersion recognized by confocal Raman microscopy

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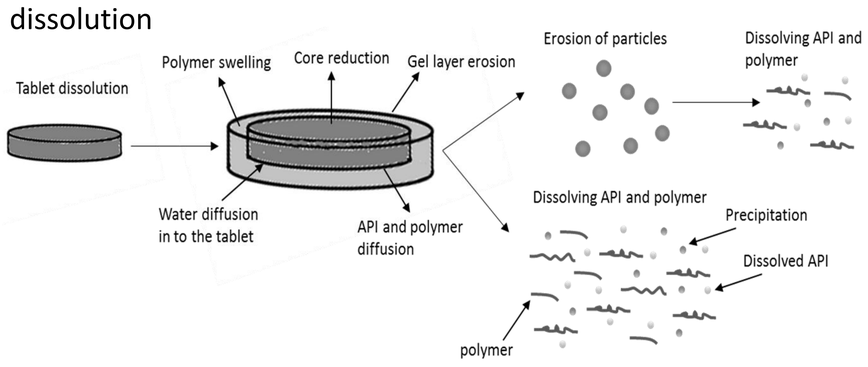
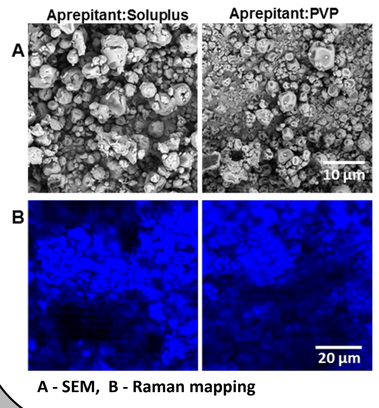
Purpose of study

1. Dissolution mechanism of amorphous solid dispersion
2. Recognition of recrystallization during dissolution
3. Specification of the crucial properties for preventing recrystallization during dissolution
4. Selection of suitable polymer matrix to prevent precipitation during dissolution



Amorphous solid dispersions [1, 2]

- Preparation – Spray drying (ratio 1:3)
- Poorly soluble drug – Aprepitant (II. BCS class)
- Polymer matrix – Soluplus, PVP



A - SEM, B - Raman mapping

Amorphous solid dispersion of initial material confirmed by:

- XRD
- DSC
- Raman mapping of bisected tablet

Confocal Raman microscopy

- Changes in the distribution of amorphous solid dispersion in gel layer on molecular level during dissolution

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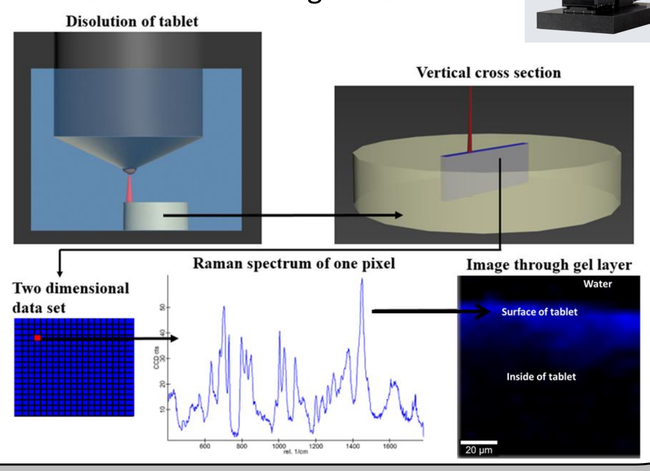
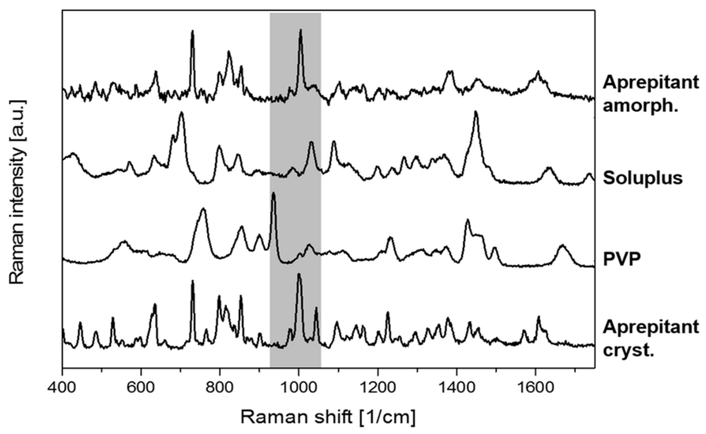
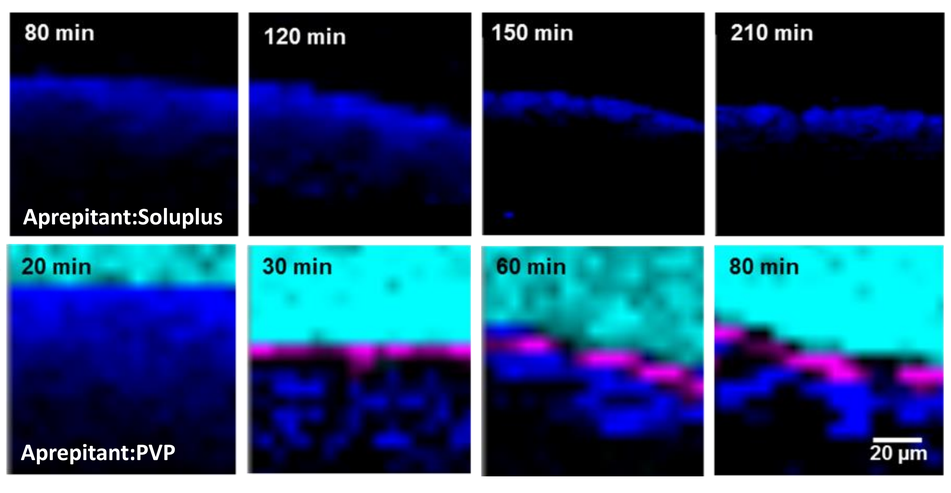


Raman spectra of individual compounds

Unique band for determination of each component



Mechanisms of dissolution determined by Raman depth scans



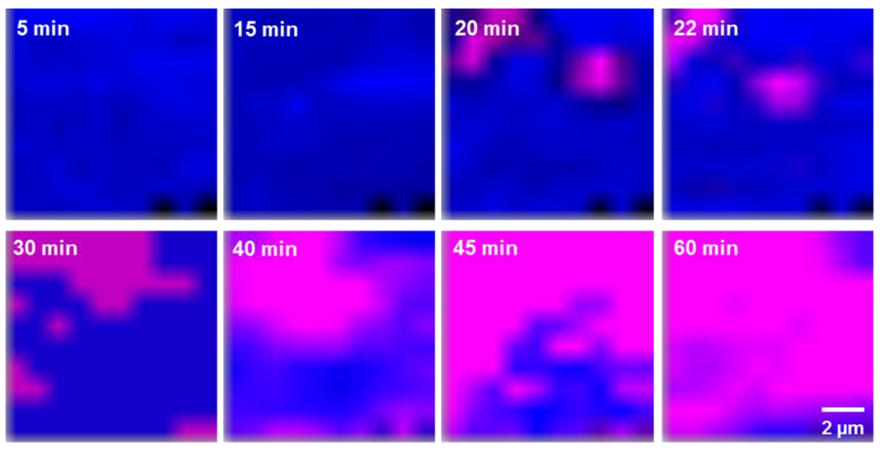
Amorphous solid dispersion
PVP
Crystalline Aprepitant

- Slow dissolution
- No segregation

- Fast dissolution of PVP
- **Highly hygroscopic polymer** – highly hydrated gel layer on the surface
- Separation of components
- Recrystallization

Visualization of Aprepitant crystals

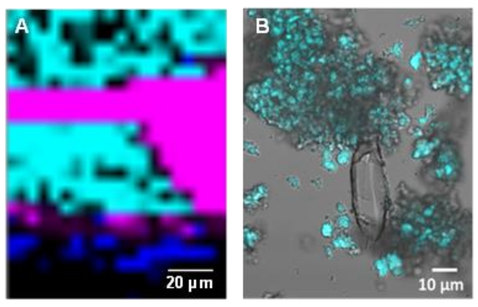
Evaluation of crystalline Aprepitant in PVP matrix



Amorphous solid dispersion
Crystalline Aprepitant

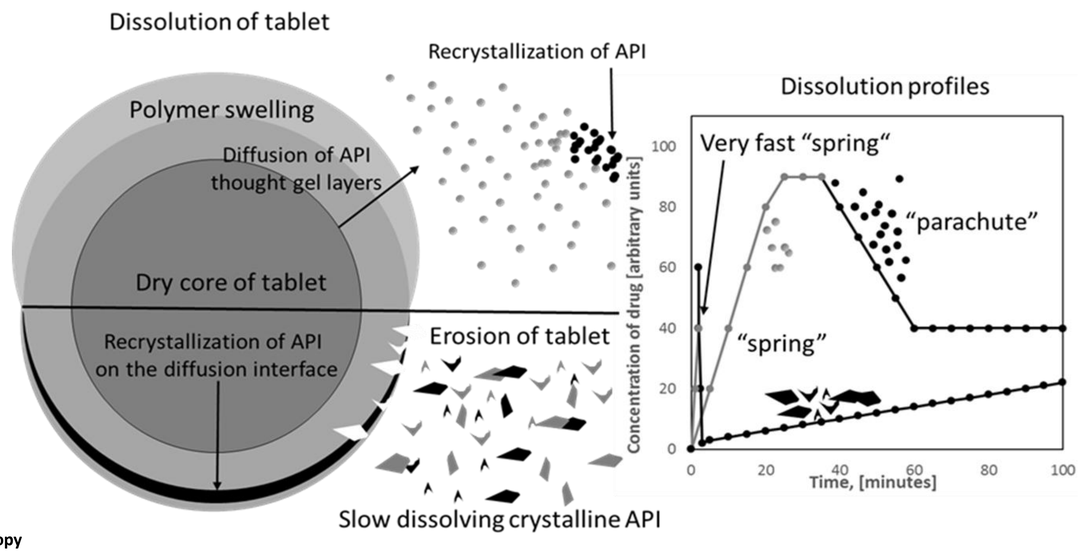
Raman images of a tablet surface, x-y scans

- Supersaturation not so large - Ostwald ripening leads to macroscopic crystals
- Viscous gel layer - Brownian movement reduced, the nucleation to **small crystals**



A – Confocal Raman microscopy B – Confocal fluorecsence microscopy

Dissolution mechanisms of amorphous solid dispersions

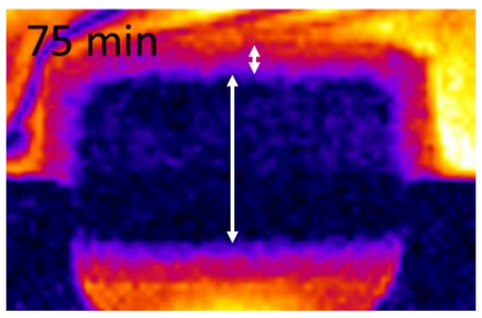


Combination of Imaging techniques during dissolution

Magnetic Resonance Imaging[2]

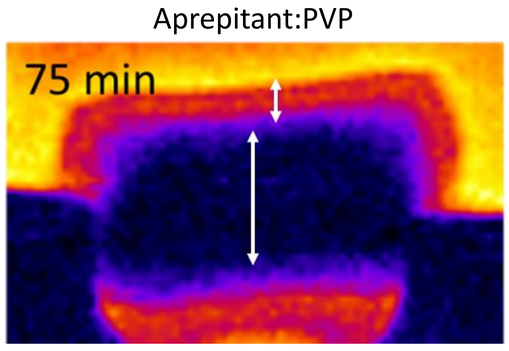
Swelling of polymers, thickness of gel layer, water penetration rate

Aprepitant:Soluplus



Slower water penetration rate

Aprepitant:PVP

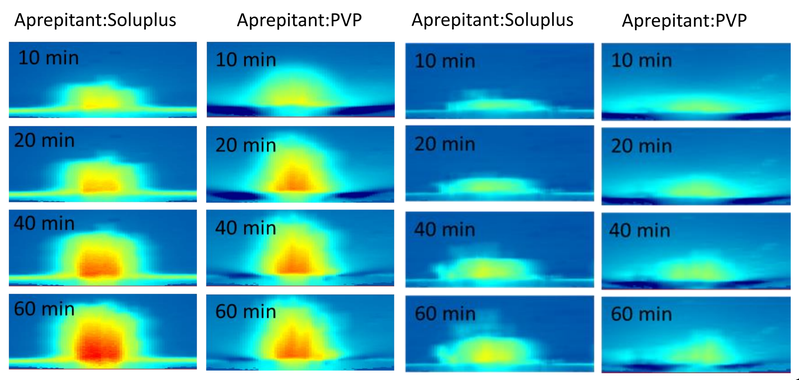


More significant swelling

UV Imaging

UV Imaging (SDI Sirius)

Release of drug from polymer matrix in static condition observed by UV Imaging (SDI Sirius)



Conclusions

- Different dissolution mechanisms recognized by Confocal Raman microscopy x similar properties of the initial amorphous solid dispersions
- Aprepitant:Soluplus solid dispersions
  - Gradual dissolution of both components
  - No phase segregation
  - High complexation effect
  - Dissolution of Aprepitant limited by water penetration rate and diffusion though the gel layer
- Aprepitant:PVP solid dispersions
  - Phase separation
  - Precipitation of Aprepitant on the surface of tablet
  - Two types of precipitated crystals
  - Dissolution rate of crystalline drug

References

1. Punčochová K., Heng J., Beránek J., Štěpánek F., International Journal of Pharmaceutics, 2014, 469 (1), 159-167.
2. Punčochová K., Ewing A. V., Gajdošová M., Sarvašová N., Kazarian S. G., Beránek J., Štěpánek F., International Journal of Pharmaceutics, 2015, 483 (1-2), 256-267.

Acknowledgments

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ZENTIVA

The effect of polymers on kinetics of nucleation and crystals growth of pharmaceutics

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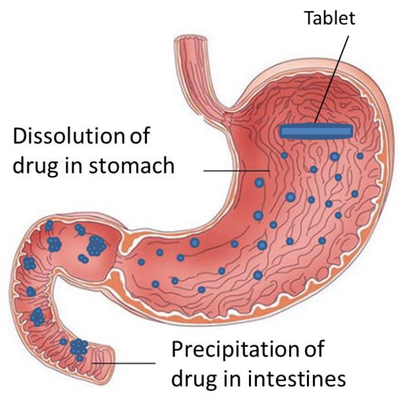
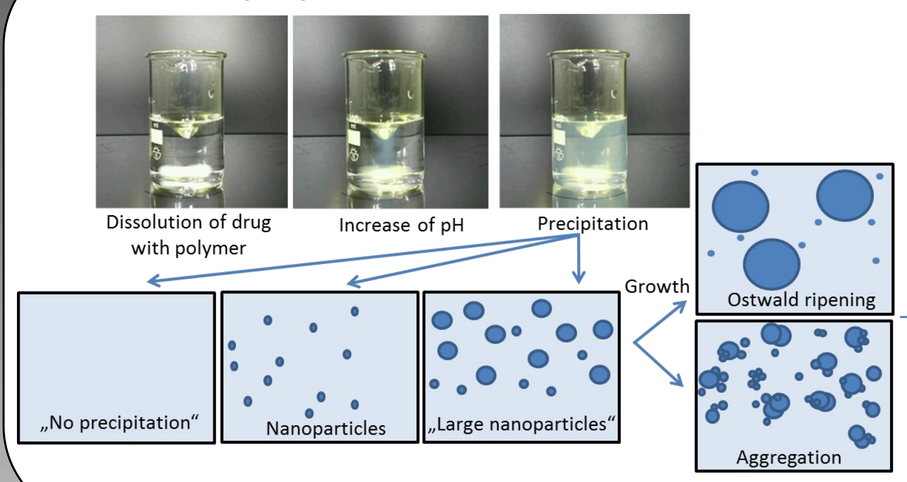
Purpose of study

1. Understand the behavior of poorly soluble drug after precipitation in dissolution medium
2. Effect of different excipients on kinetics of drug nucleation and crystals growth
3. Predict the suitability of combinations API-polymer for preparation of solid dispersion

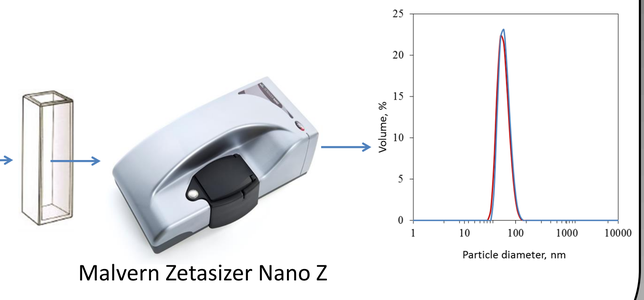


Effect of polymers on kinetics of nucleation



Distribution of particle size

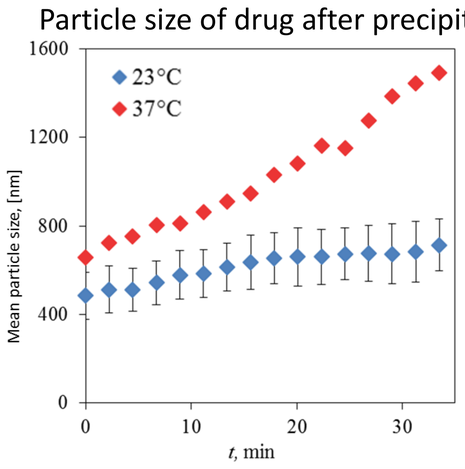
- Dynamic light scattering
- Brownian motion of particles
- Crystal size distribution in time



Characterization of initial materials

Drug - Poorly soluble drug from II. BCS class

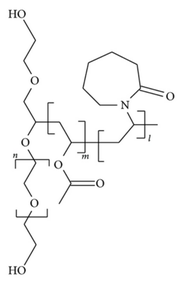
Particle size of drug after precipitation



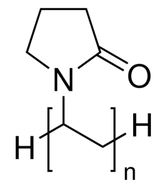
- Effect of temperature on growth rate
- Brownian motion supports the growth of particle

Polymers

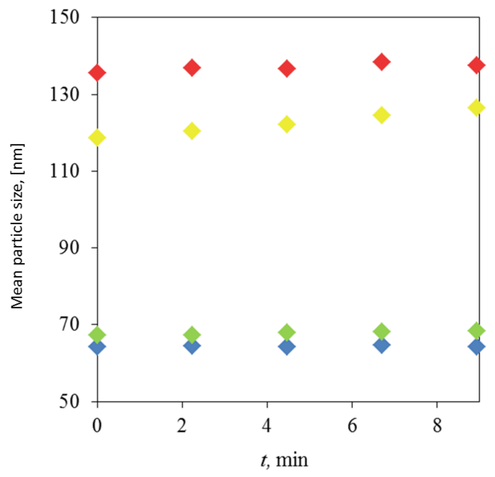
Soluplus
- Amphiphilic copolymer
- Solubilizing effect
- Micells in water



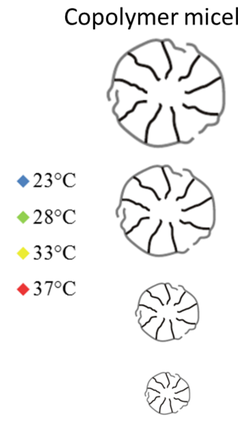
PVP K30
- Hydrophilic copolymer
- Improve solubility
- No formation of micelles



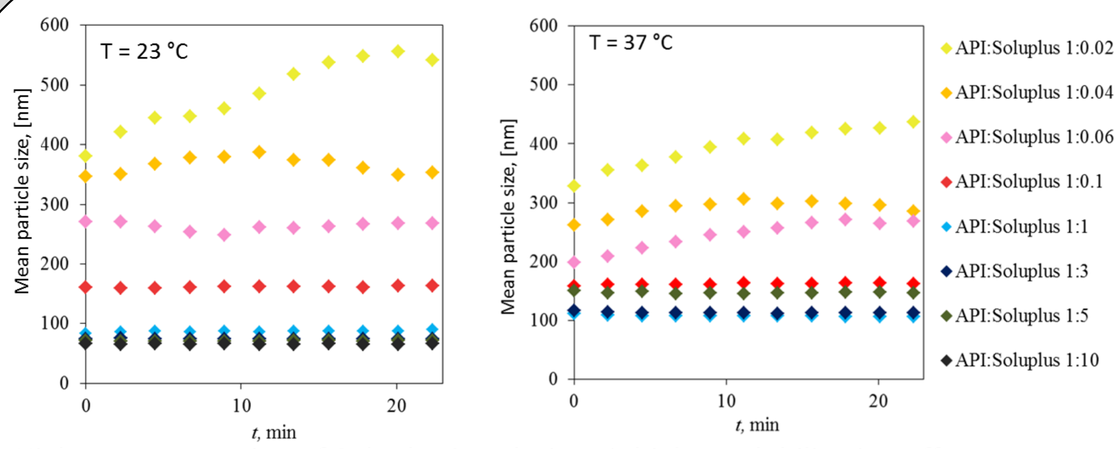
Soluplus



Copolymer micelles

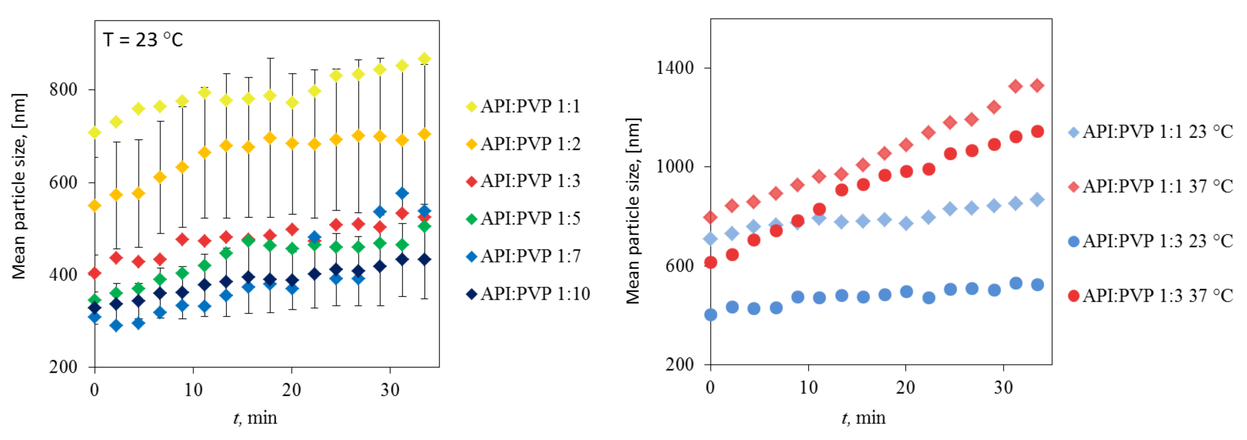


Effect of Soluplus on particle size of drug



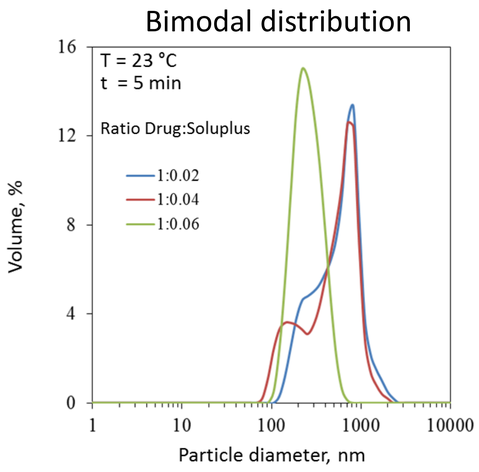
- Higher concentration of Soluplus in solution → higher solubilization effect
- Steady state of micelles size in time

Effect of PVP on particle size of drug



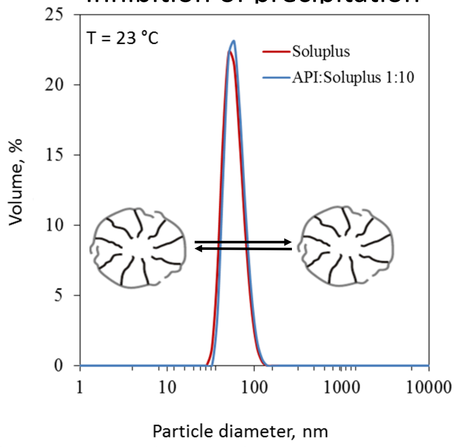
- t = 0 min effect of concentration on particle size (nucleation)
- Growth – similar rate
- Effect of temperature on growth rate

Bimodal distribution



- Ratio 1:0.02 below CMC

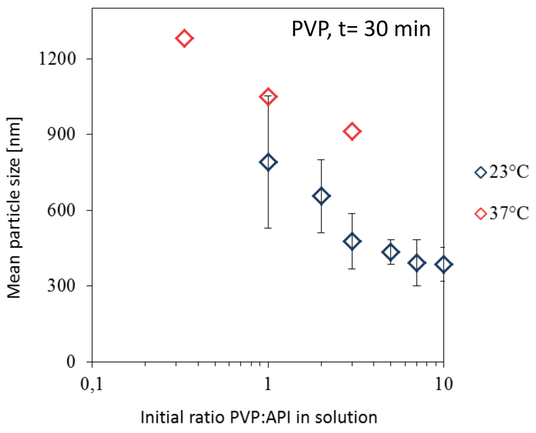
Inhibition of precipitation



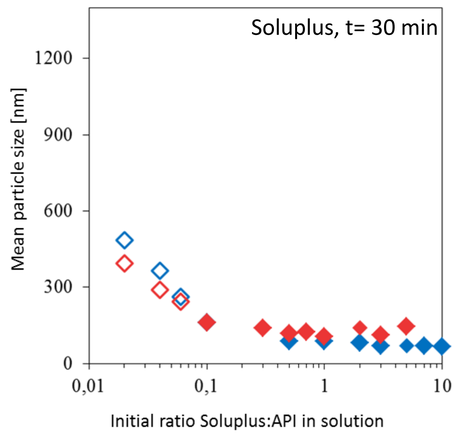
- Ratio 1:0.04 ~ CMC

- Ratio 1:0.06 above CMC

Comparison of polymers



- Concentartion above CMC: higher temperature → larger micelles
- High concentration of Soluplus → Inhibition of precipitation



- Higher temperature → faster Brownian motion → large particles
- Higher viscosity → slower Brownian motion → small particles

Conclusions

- Monitoring of drug precipitation – prediction of drug behavior during dissolution

PVP
- Higher viscosity leads to decrease of particle size
- Aggregation of particles – negative effect

Soluplus
- Solubilization of drug above CMC, stopping of growth
- Inhibition of precipitation in higher concentration of Soluplus in solution

Future work

- Morphology of precipitated particles – Microscopy, SEM
- Polymorphism of precipitated particles (crystalline from, amorphous form) – Raman, DSC
- Thermodynamic solubility – effect of polymers in different concentrations

Acknowledgments

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