W4226

Confocal Raman imaging provides evidence of a new release mechanism of poorly soluble drug from amorphous solid dispersion

UNIVERSITY OF CHEMISTRY AND TECHNOLOGY PRAGUE

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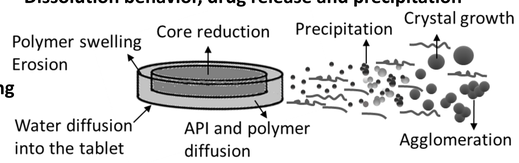
Selection of proper matrix for amorphous solid dispersions

- Enhance the **dissolution rate**
- Prevent or inhibit **precipitation**
- Understand the dissolution mechanisms
- Specify the crucial properties for **preventing recrystallization** during dissolution
- Develop the final formulation

Dissolution behavior, drug release and precipitation



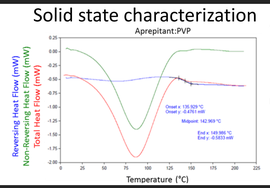
Preparation and characterization of amorphous solid dispersions

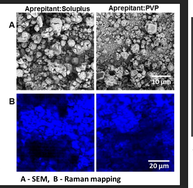
- Preparation – Spray drying (ratio 1:3)[1]
- Poorly soluble API – **Aprepitant** (II. BCS class)
- Polymer matrix – Soluplus, PVP

Soluplus
- Amphiphilic copolymer
- Solubilizing effect
- Micelles in water

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

Solid state characterization

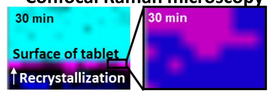




A - SEM, B - Raman mapping

Imaging methods – visualization of *dissolution*

Confocal Raman microscopy[3]

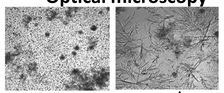


- Determination of precipitation
- Identification on molecular level
- Separation of phases

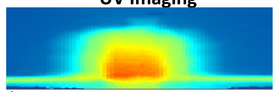
↑Depth scans ↓Surface of tablet

ATR-FTIR Imaging[2]
- Determination of precipitation
- Chemically specific information
- Water penetration rate

Optical microscopy

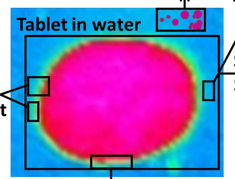


UV Imaging



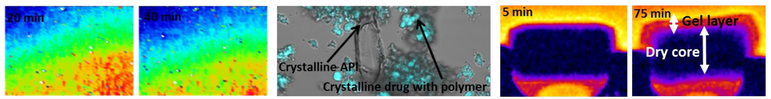
- Release of drug from the surface

Surface of tablet
Slice of tablet



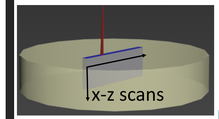
Magnetic resonance imaging (MRI)[2]
- 3D hydratation, swelling
- Erosion of tablet
- Water penetration

Confocal fluorescence microscopy[3]



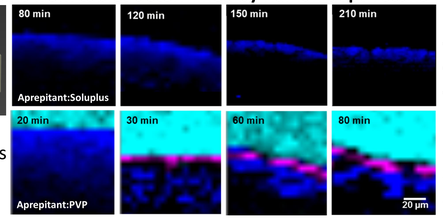
Optimizing the formulation in point of precipitation inhibition using imaging techniques

Dissolution mechanisms from tablet determined by Raman depth scans



- Raman images thought the gel layers

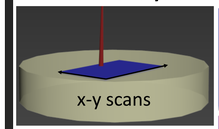
Amorphous solid dispersion
PVP
Crystalline Aprepitant



Soluplus matrix
- Slow dissolution
- No segregation
- No recrystallization

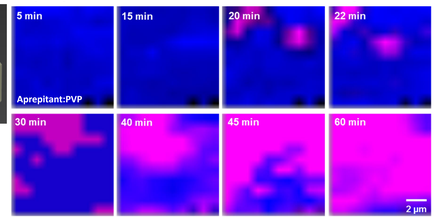
PVP matrix
- Gel layer on the surface
- Separation of components
- Recrystallization

Evaluation of crystalline Aprepitant in PVP matrix determined by Raman images



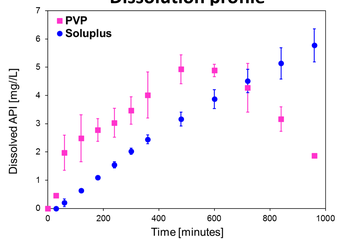
- Raman images of a tablet surface

Amorphous solid dispersion
Crystalline Aprepitant

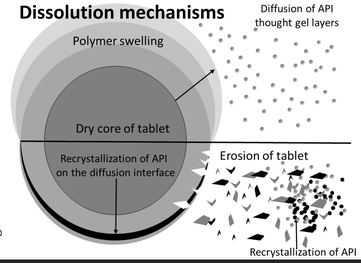


- Crystals detect after 20 minutes of dissolution
- Gradual crystal growth on the tablet surface
- Surface of tablet covers by crystalline Aprepitant after 60 minutes

Dissolution profile



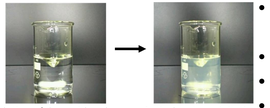
Dissolution mechanisms



Soluplus matrix
- Hydrated, forms a gel layer on the surface of the tablet
- Drug diffusion through the gel layer

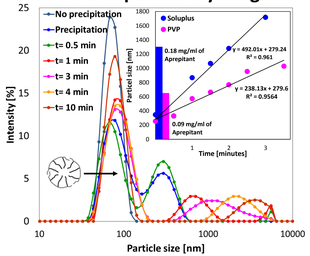
PVP matrix
- PVP dissolving
- Recrystallization of drug
- Erosion of tablet

Effect of different excipients on kinetics of drug nucleation and crystal growth

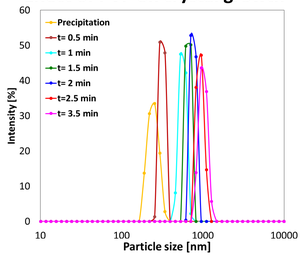


- Nucleation and crystal growth - Dynamic light scattering
- Morphology of precipitated particles - Microscopy
- Ability to postpone the precipitation
- Size of crystals

Effect of Soluplus on crystal growth

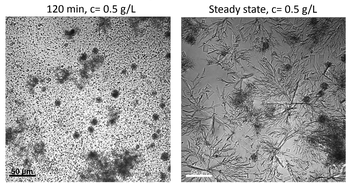


Effect of PVP on crystal growth



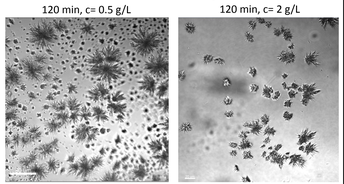
- No phase information (amorphous/crystalline) - possible dissolution
- High supersaturation - fast precipitation and crystal growth

Effect of Soluplus on crystal size



- Small particles for more than 4 hours
- Two types of crystals shapes

Effect of PVP on crystal size



- Fast formation of final crystals
- One type of crystal shape

Conclusions

- Different dissolution mechanisms recognized by Confocal Raman microscopy x similar properties of the initial amorphous solid dispersions
- Soluplus in formulation inhibits precipitation in small amount, solubilization effect
- Separation of phases in glass solution leads to precipitation of Aprepitant
- Improve supersaturation concentration (Soluplus > PVP > water), Slow precipitation rate (PVP > Soluplus > water)

Fundings & Reference

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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.
3. Punčochová K., Vukosavljevic B., Hanuš J., Beránek J., Windbergs M., Štěpánek F., European Journal of Pharmaceutics and Biopharmaceutics, Submitted (October, 2015).