PRECIPITATION OF POORLY SOLUBLE DRUG DURING DISSOLUTION DETERMINED BY MRI AND ATR-FTIR IMAGING

Kateřina Punčochová [a, b], Josef Beránek [b], Andrew Ewing [c], Sergei G. Kazarian [c] ♣, František Štěpánek [a] *

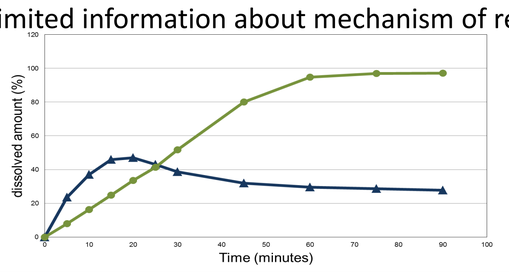
[a] Department of Chemical Engineering, Institute of Chemical Technology Prague, Czech Republic
[b] ZENTIVA k.s., U Kabelovny 130, Prague 10, Czech Republic
[c] Department of Chemical Engineering, Imperial College London, Great Britain
*Frantisek.Stepanek@vscht.cz
♣s.kazarian@imperial.ac.uk

Aim of the study

- **Enhancement of bioavailability of poorly soluble drugs**
- **Observation of drugs dissolution by ATR-FTIR Imaging and MRI**
- **Mechanism of dissolution**
- **Precipitation**

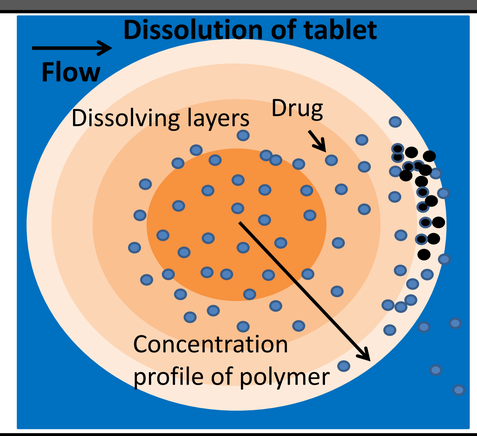
Introduction

Dissolution test
- Concentration of API as a function of time
- Rate of drug release
- Limited information about mechanism of release



Imaging methods
- What happened during dissolution?
- Selection of candidate formulations
- Effect of polymers, additives

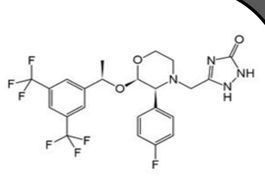
Precipitation of amorphous form to crystalline form
- local supersaturation of diffusing drug leads to precipitation of drug
- decreasing of bioavailability



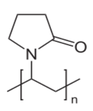
Materials

Aprepitant (Drug)

• molecular weight	534.4 g/mol
• logP	4.5
• pKa	3.5, 9.6
• solubility in water (20 °C)	0.02 mg/ml

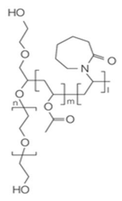


Polyvinyl pyrrolidone (PVP)
- hydrophilic polymer
- soluble in water



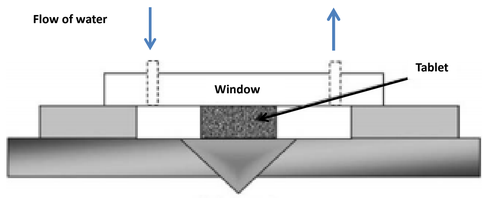
Soluplus
- amphiphilic polymer
- colloidal micelles in water

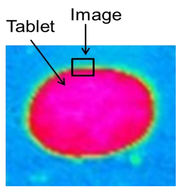
Solid dispersion preparation
- drug dispersed in polymer matrix
- preparation by spray drying
- ratio 1:3 (drug:polymer)
- amorphous form of drug

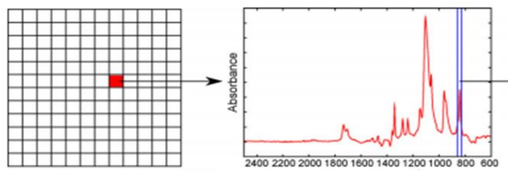


Imaging methods

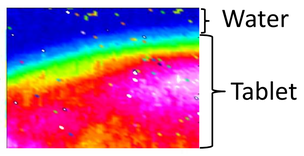
Attenuated total reflection (ATR) - FTIR Imaging
Bruker Equinox mid-IR imaging system in ATR mode [1,2]







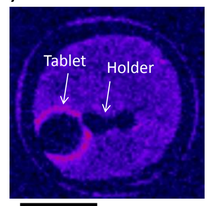
FPA detector pixels — Spectrum from one pixel

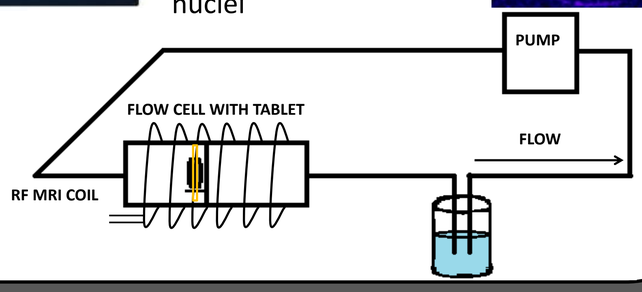


Integrated absorbance plotted for all pixels

Magnetic resonance Imaging (MRI)
MRI Desktop Systém Icon (BRUKER)

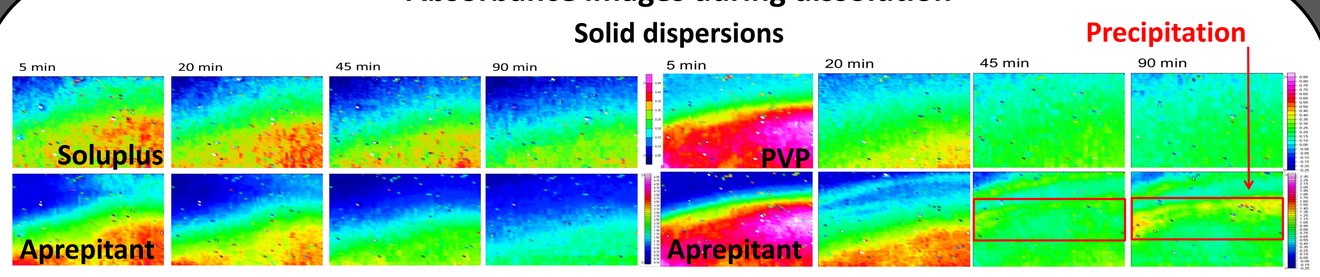
- Different principles of measurement based on NMR signal
- Concentration of ^{1}H nuclei



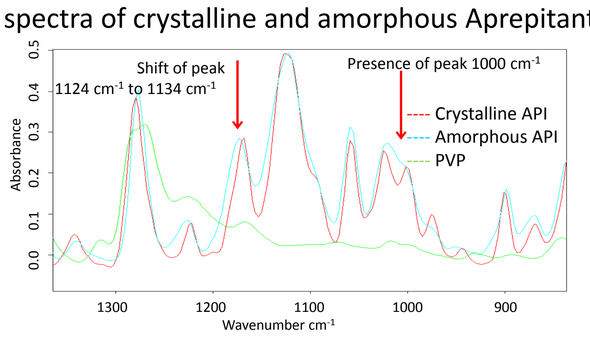


ATR-FTIR imaging recognizes crystallization in solid dispersion system

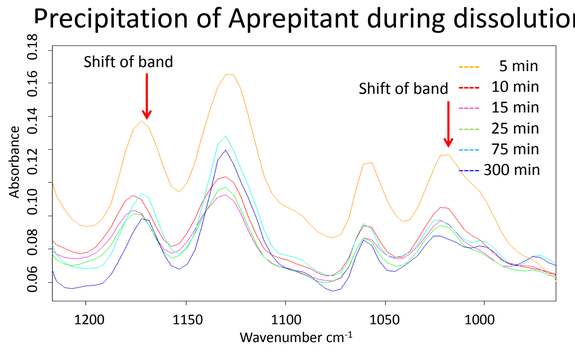
Absorbance images during dissolution



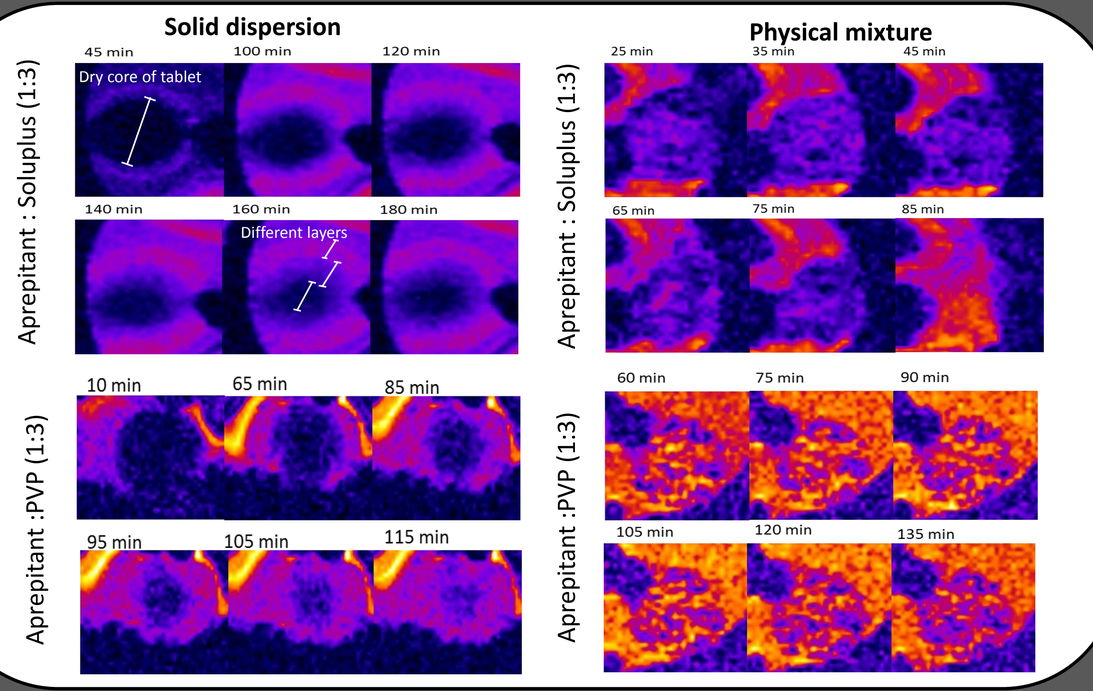
IR spectra of crystalline and amorphous Aprepitant



Precipitation of Aprepitant during dissolution

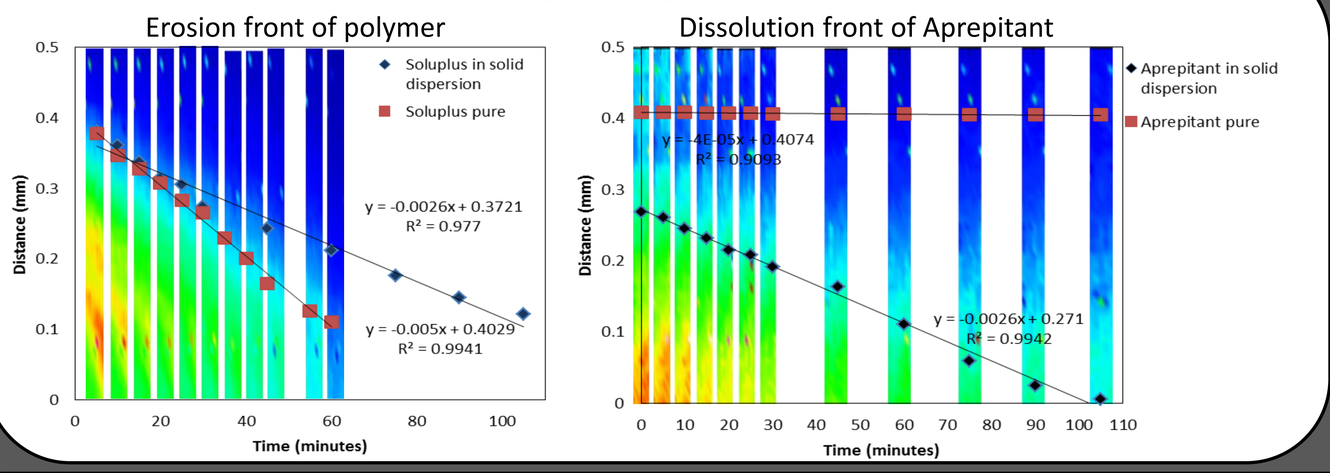


MRI recognizes different mechanism of water penetration to solid dispersion and physical mixture



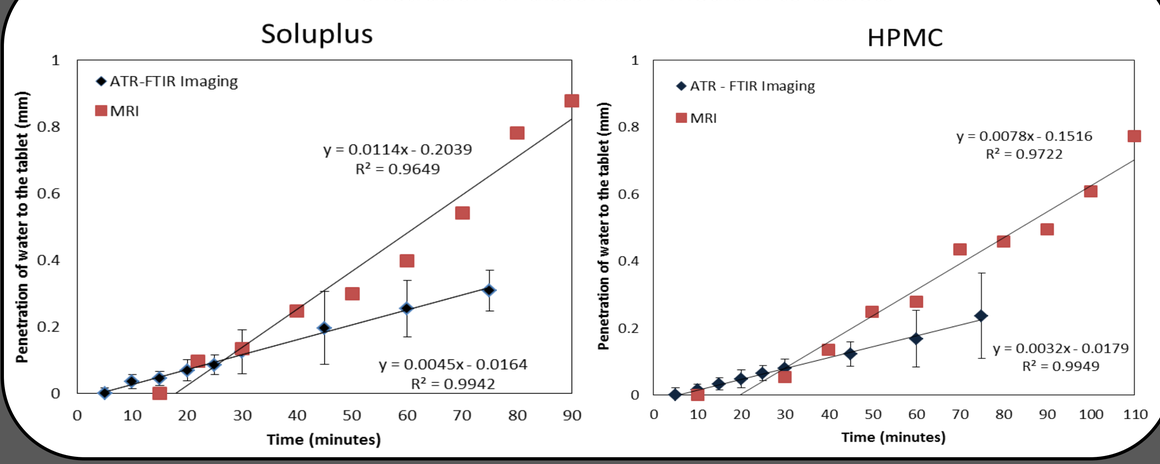
Different dissolution rate in solid dispersion

ATR-FTIR Imaging during dissolution



Comparison of MRI and ATR-FTIR Imaging

Penetration of dissolution medium to tablets



Conclusions

Dissolution process of poorly soluble drug in solid dispersion
- **Soluplus** stabilizes amorphous form by gradual slow dissolution, suitable for dissolution of poorly soluble drugs
- **PVP** does not stabilize amorphous form during dissolution, suitable for fast dissolution
- Precipitation detected by visual observation and IR spectra

Comparison of MRI and ATR-FTIR Imaging
- Slower water penetration in Absorbance Imaging caused by limitation of crystal
- Penetration of water to Soluplus – 2.53x faster in MRI
- Penetration of water to HPMC – 2.43x faster in MRI

Acknowledgment:
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[1] Kazarian S.G., Chan K. L. A., Macromolecules, 2003, 36, 9866-9872.
[2] Kazarian S.G., Ewing A. V., Expert Opin. Drug Deliv., 2013, 10(9), 1207-1221