

Crystallization of poorly soluble drug in solid dispersion during dissolution



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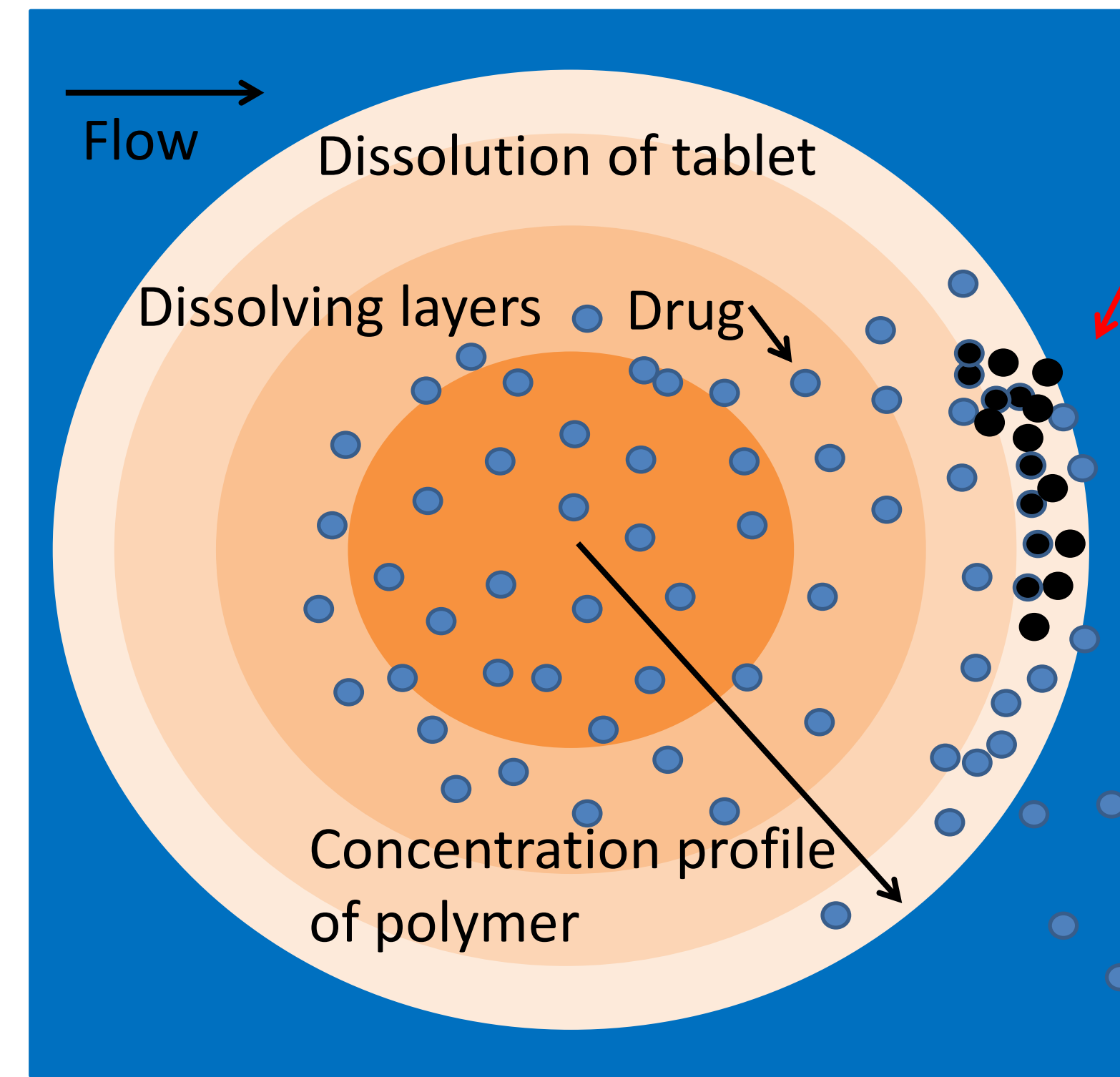
Aim of the study

- Enhancement of bioavailability of poorly soluble drugs
- Selection of polymers based on physico-chemical behavior
- Observation of drugs dissolution by ATR-FTIR Imaging
- Supersaturated concentration
- Crystallization

Introduction

Solid dispersion preparation

- drug dispersed in polymer matrix
- preparation by spray drying
- ratio 1:3 (drug:polymer)
- amorphous form of drug
- hollow spherical particle shape



Crystallization of amorphous form to crystalline form

- local supersaturation of diffusing drug leads to precipitation of drug
- decreasing of bioavailability

Influence of polymers to crystallization

Interfacial tension

$$B_{\text{hom}}^0 = A_{\text{hom}} \exp \left[- \frac{16\pi\gamma^3 v^2}{3k^3 T^3 (\ln S)^2} \right]$$

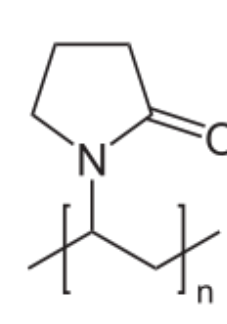
Supersaturation ratio c/c^*

Viscosity of solution

Materials

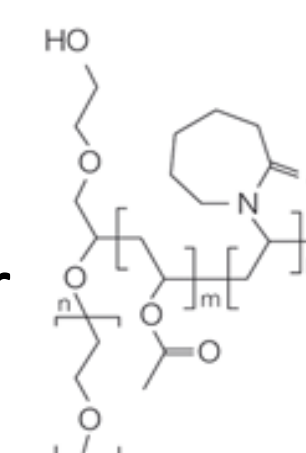
Polyvinyl pyrrolidone (PVP)

- hydrophilic polymer
- soluble in water



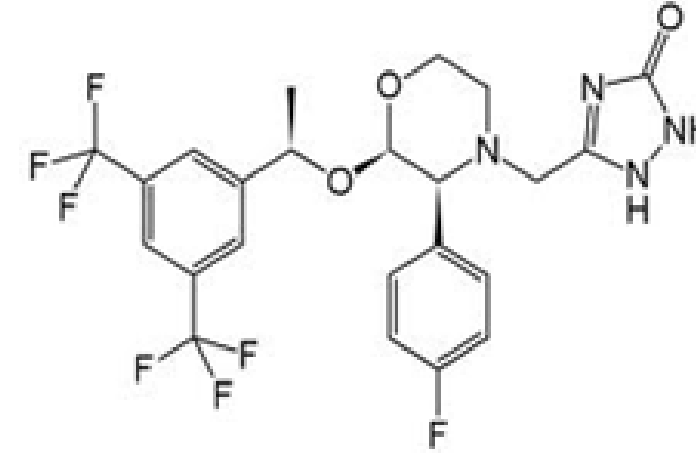
Soluplus

- amphiphilic polymer
- colloidal micelles in water



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



Sirius T3 instrument

- CheqsolTM 1, 2 method
- acid titration

Effectiveness of polymers

Soluplus

- increase of kinetic solubility
- prolong the duration of supersaturation

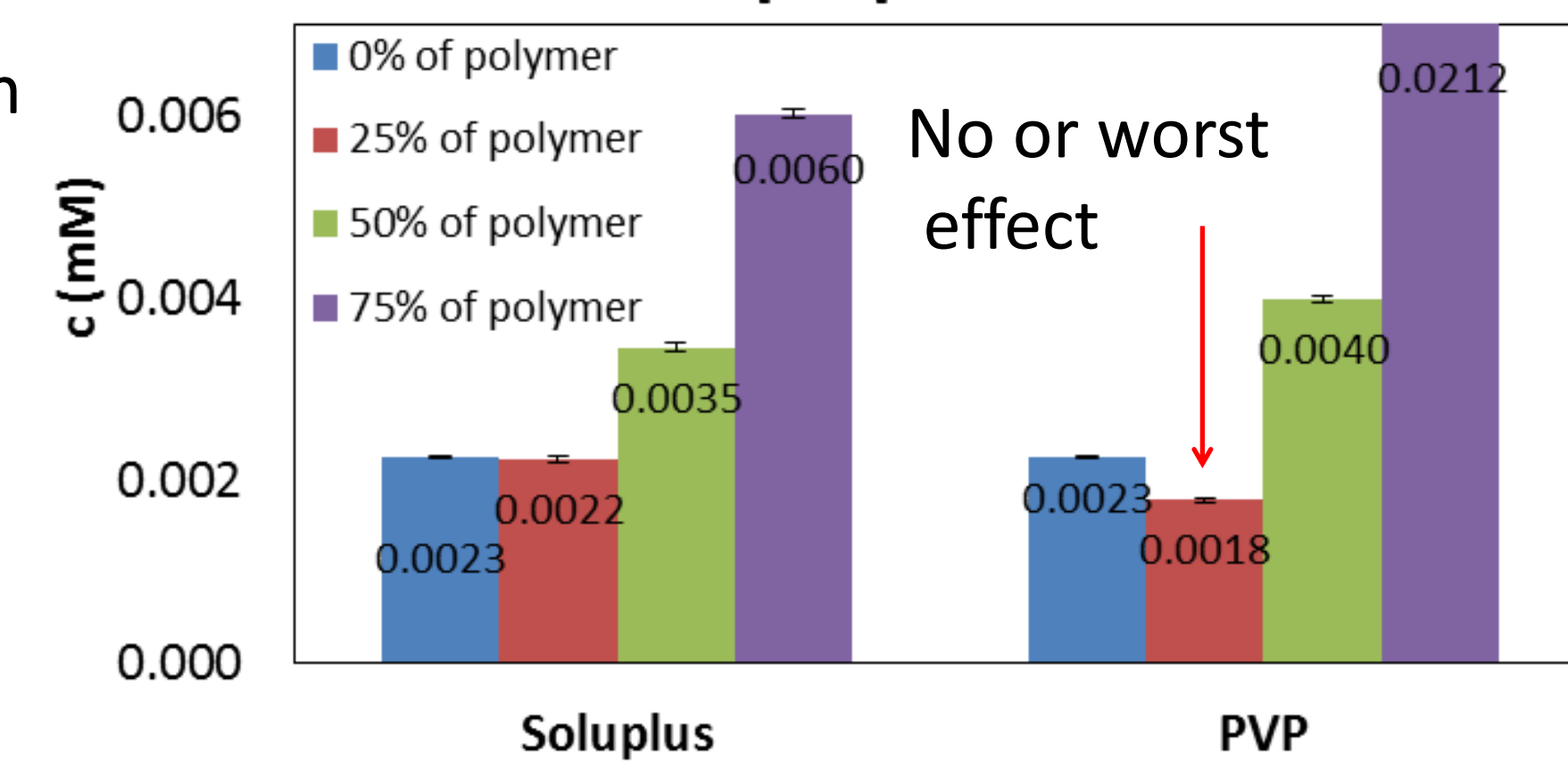
PVP

- increase of kinetic solubility in high concentration; risk of precipitation in low

Kinetic solubility

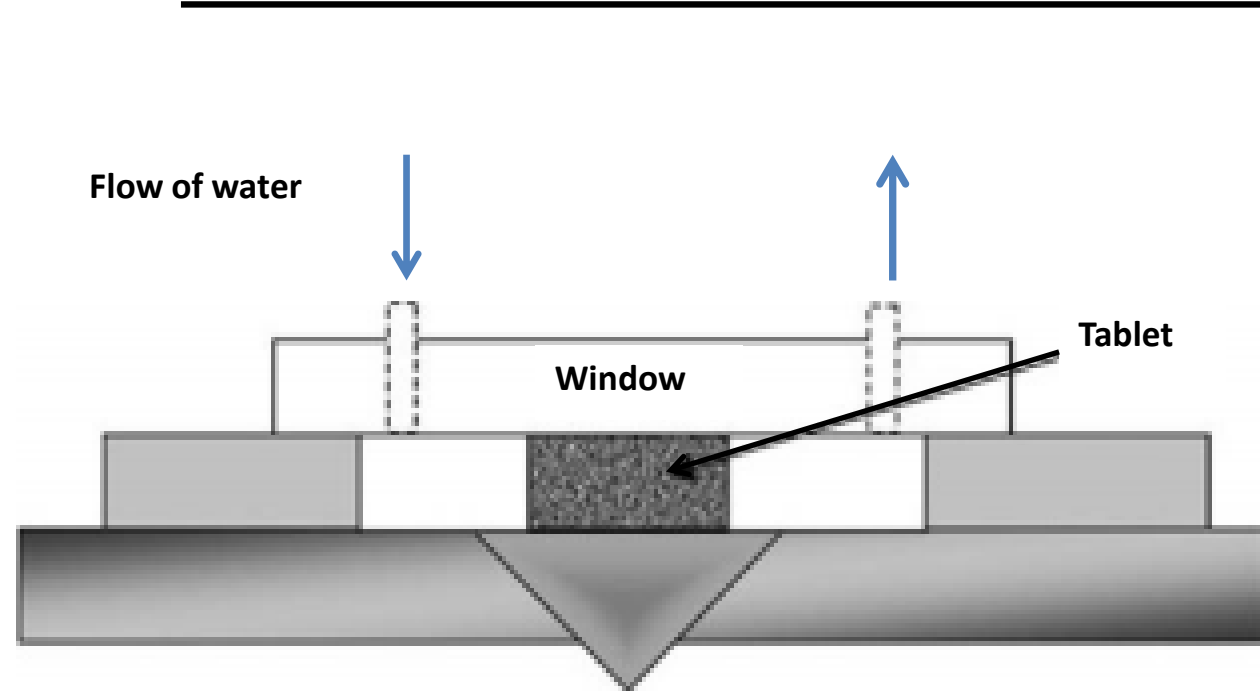
- concentration of Aprepitant at which precipitation is induced

Effect of polymers to kinetic solubility of Aprepitant



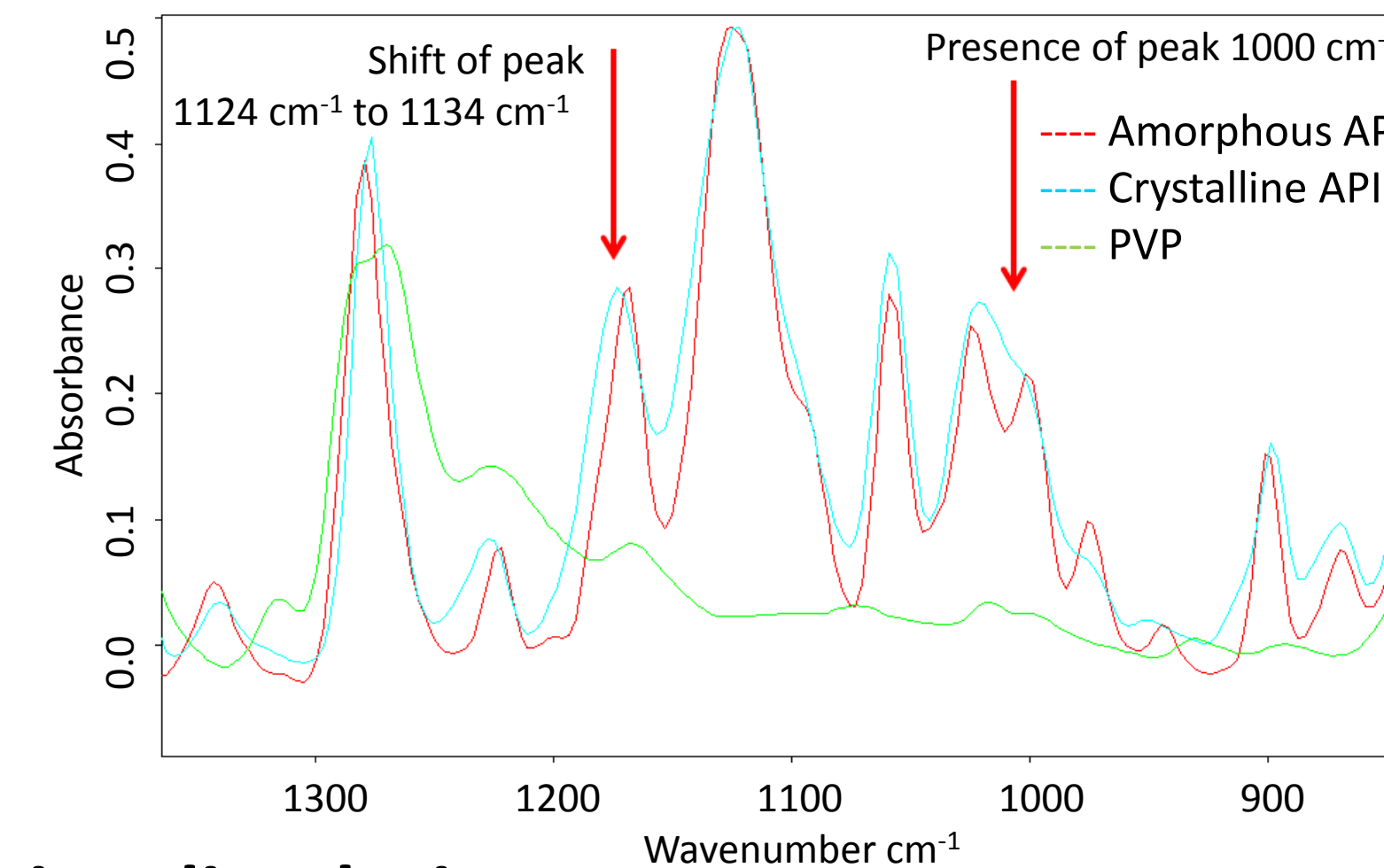
ATR-FTIR imaging recognizes crystallization in solid dispersion system

Attenuated total reflection (ATR) - FTIR Imaging



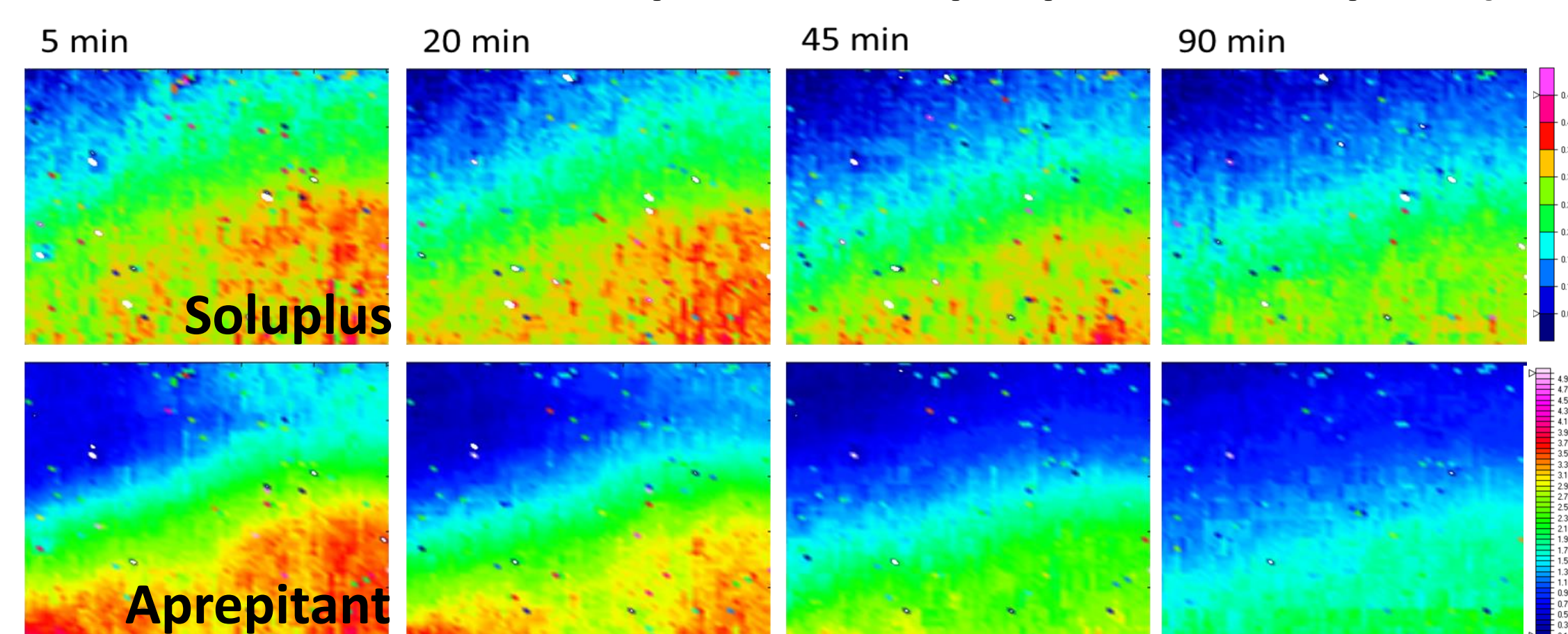
- Bruker Equinox mid-IR imaging system in ATR mode
- Golden Gate imaging accessory fitted with a diamond ATR crystal
- 64 x 64 pixels focal array (individual pixel size 40 x 40 μm)
- image size 635 μm x 525 μm (view of edge of tablet)
- spectral resolution of 8 cm⁻¹
- ATR imaging of dissolution has been introduced in Kazarian laboratory^{3, 4}

Comparison of ATR-IR spectra of crystalline and amorphous Aprepitant



- Integral absorbance of IR bands generates corresponding spectroscopic images
- Ideally, polymers stabilize amorphous form of Aprepitant during dissolution

Dissolution of solid dispersion - Aprepitant:Soluplus (1:3)



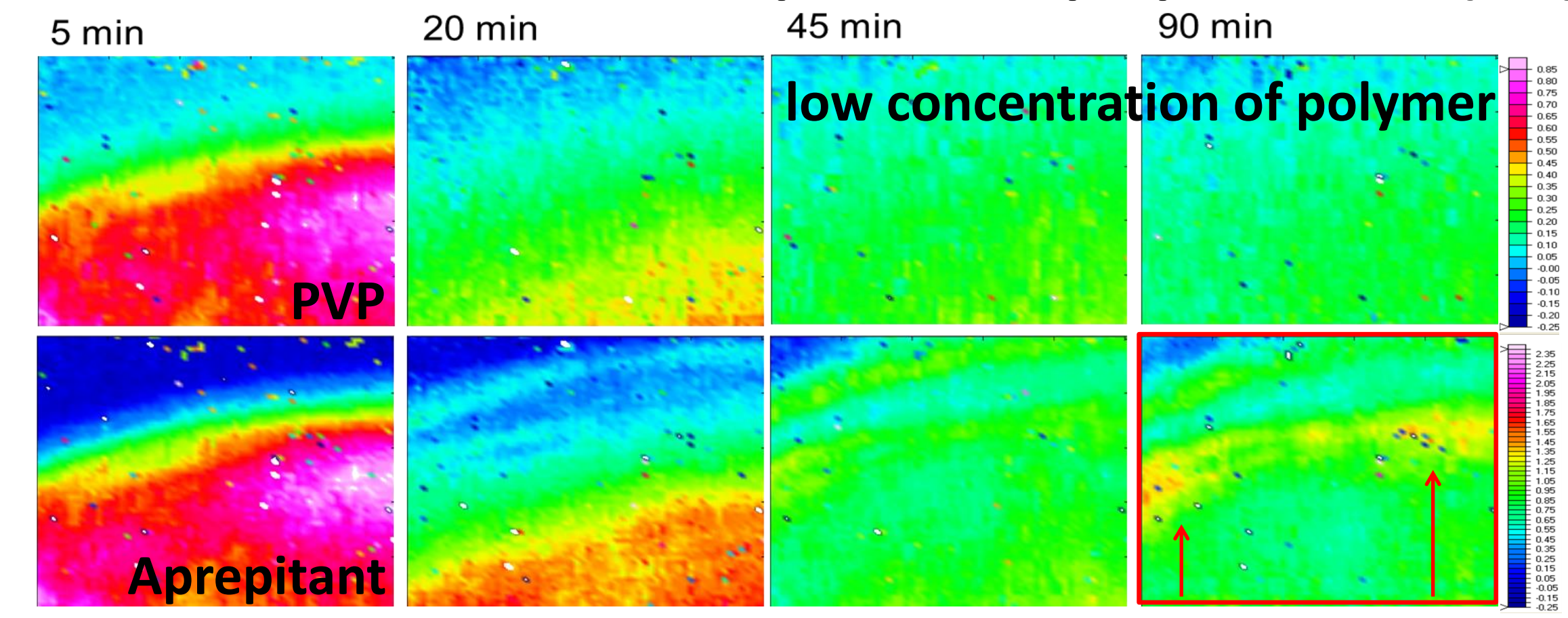
Absorbance images during dissolution

Effect of polymers

Soluplus
slow dissolution of polymer
gradual dissolving API
no crystallization of API

PVP
fast dissolution of polymer
fast dissolving API
crystallization of API
local supersaturation

Dissolution of solid dispersion - Aprepitant:PVP (1:3)

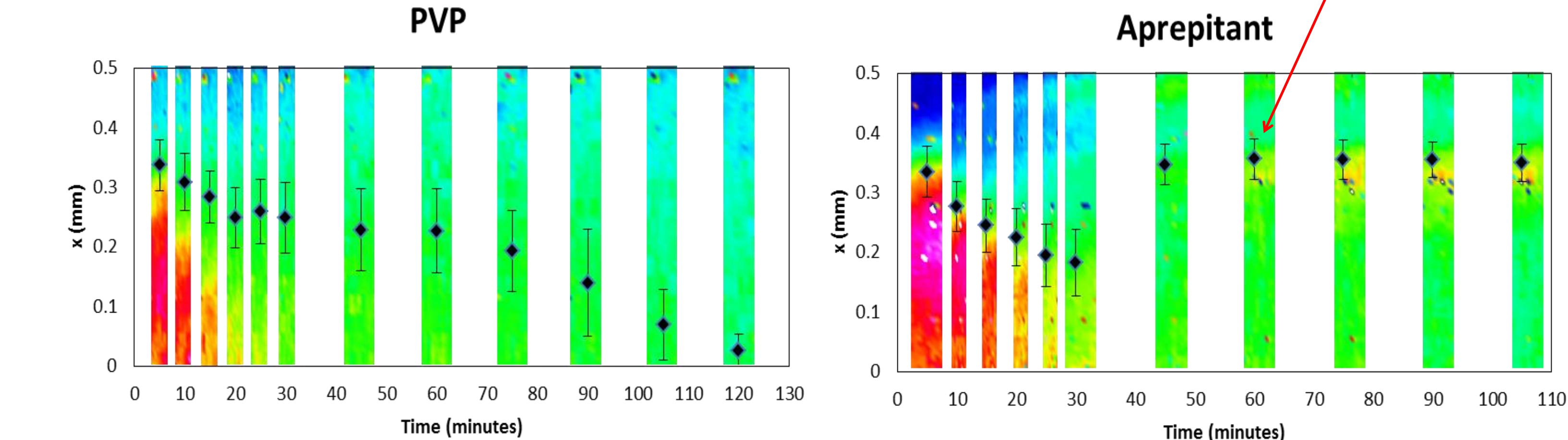
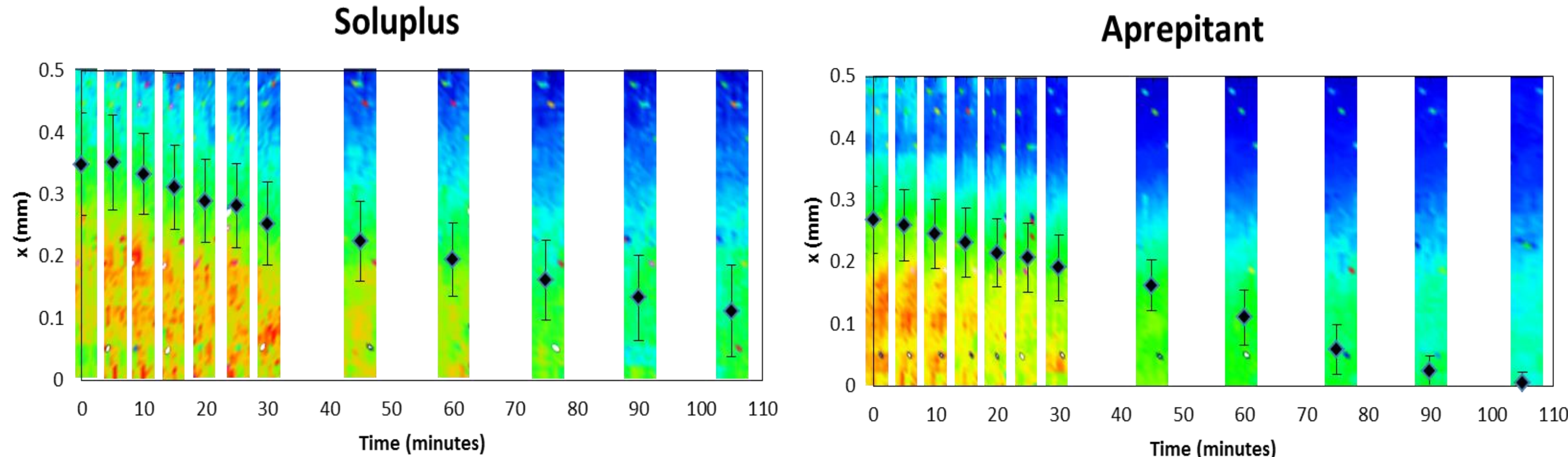


Movement of the diffusion layer in time

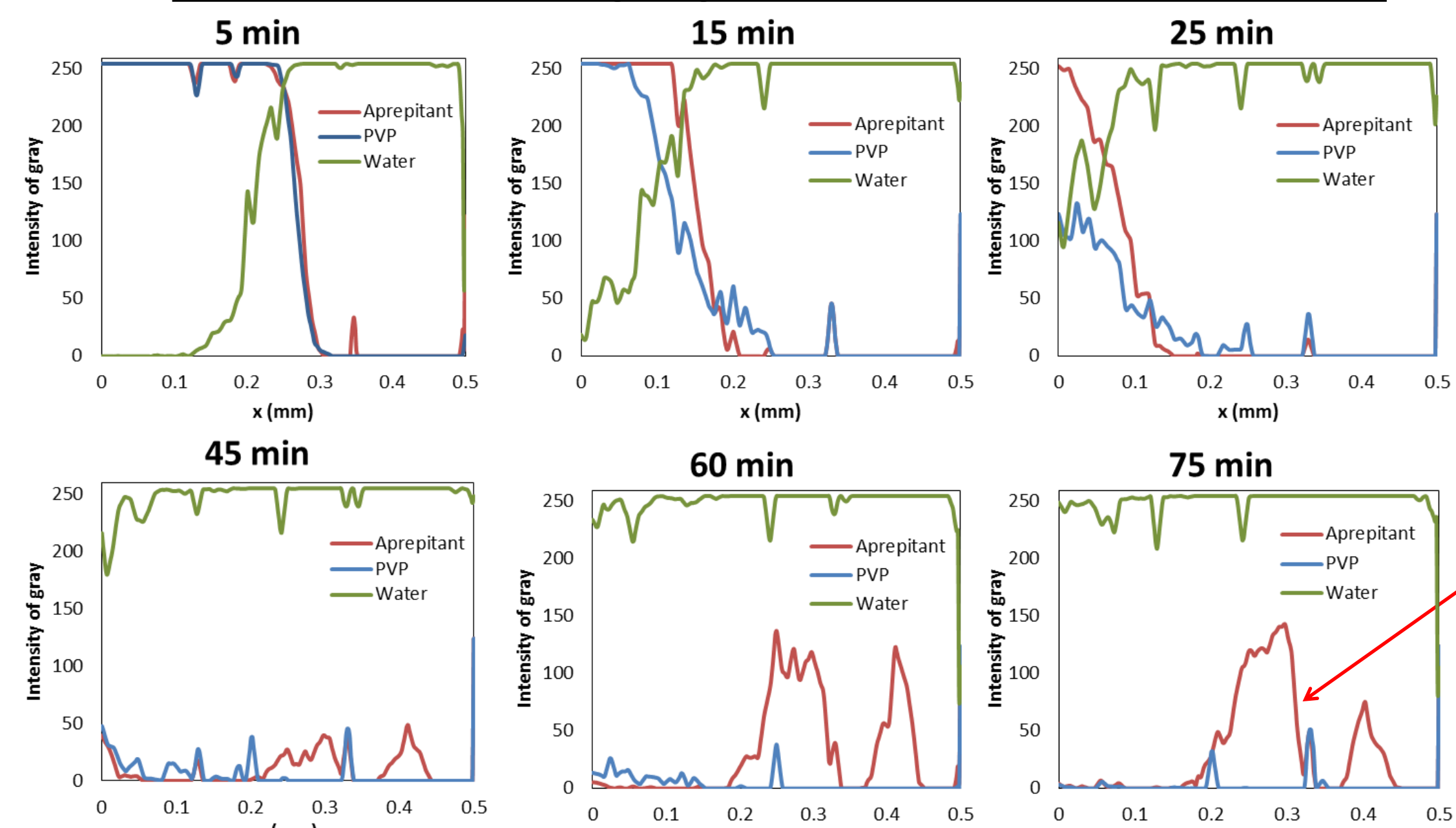
Effect of polymers

Soluplus
Slow movement with constant concentration of Soluplus in core of tablet

PVP
Slow movement with decreasing concentration of PVP in core of tablet

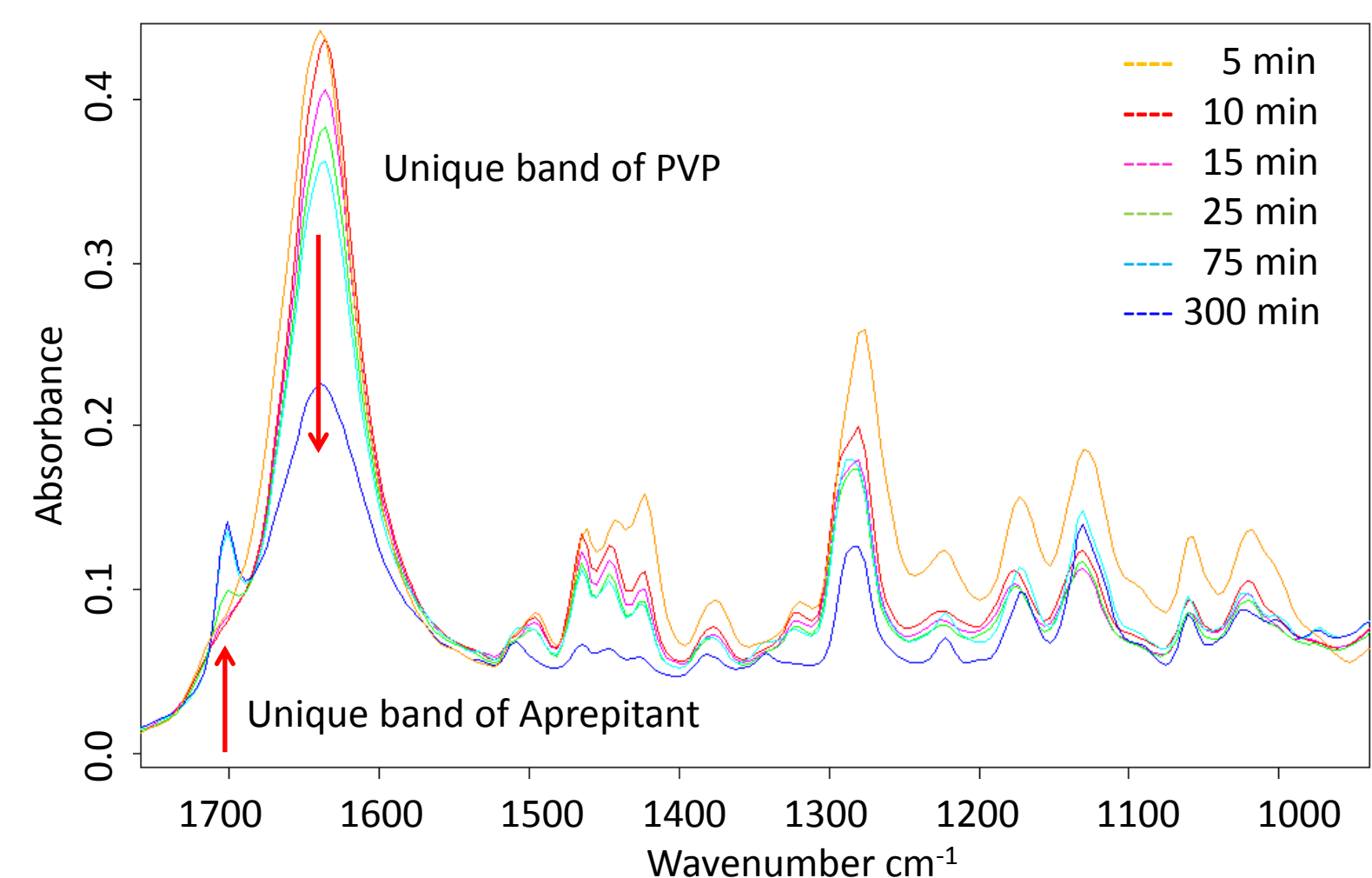


Profiles of PVP, Aprepitant and water over time



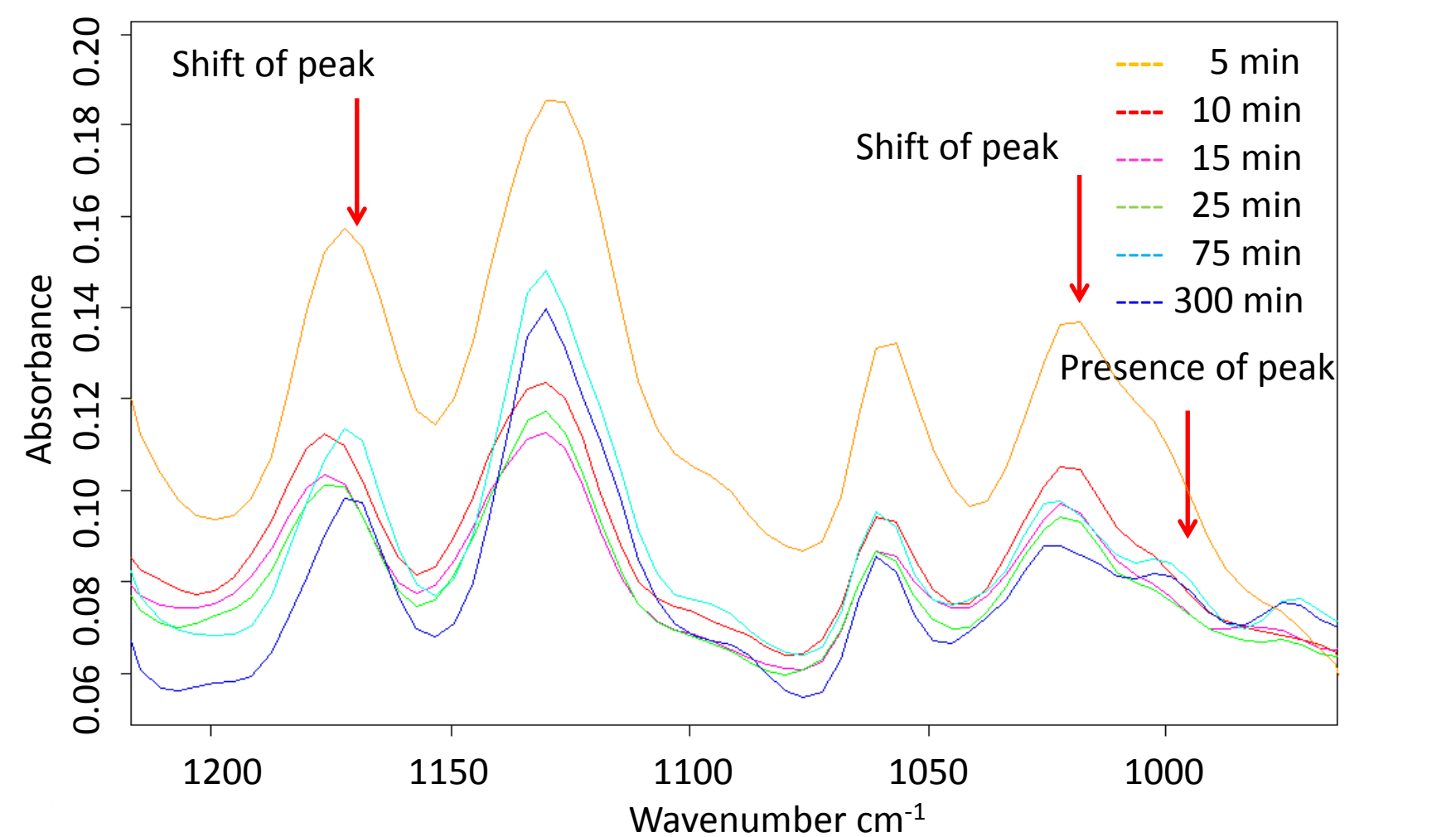
- movement of diffusion layer of all 3 components
- fast penetration of water
- low concentration of PVP and Aprepitant in 45 min crystallization of Aprepitant

Dissolution of Aprepitant:PVP



- decrease of PVP concentration (peak 1635 cm⁻¹)
- decrease and following increase of Aprepitant concentration (peak 1125 cm⁻¹)

Crystallization of Aprepitant during dissolution

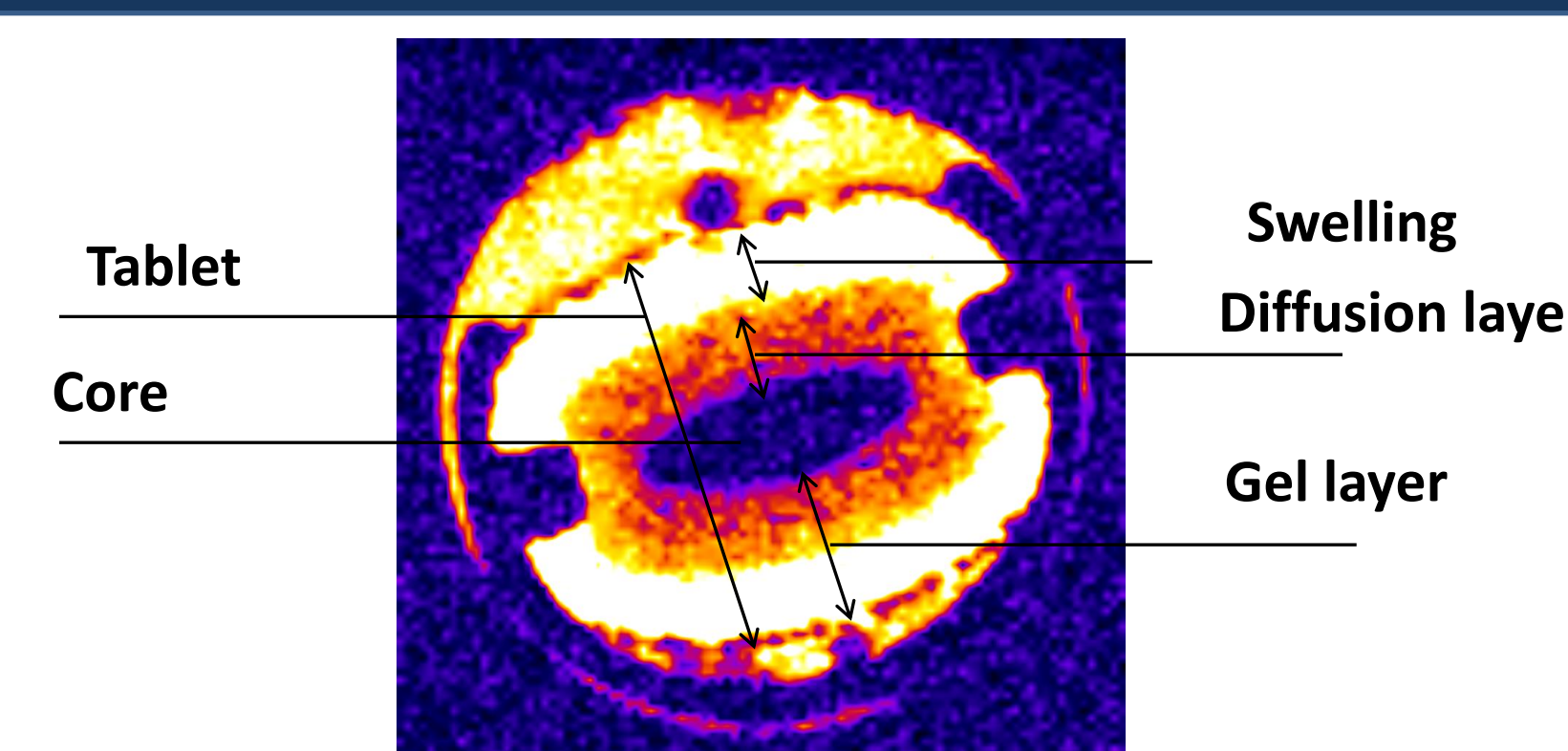


- Detection of crystalline form of Aprepitant

Conclusion and future work

Dissolution process of poorly soluble drug in solid dispersion

- Soluplus stabilizes amorphous form by gradual slow dissolving
- PVP does not stabilize amorphous form during dissolution
- crystallization detected by visual observation and IR spectra
- comparison of movement of diffusion layer



Future work

- MRI study of movement of diffusion layer
- prediction of the precipitation of API depending on the concentration of polymer

Acknowledgment:

Financial support from the Specific University Research (MSMT 2013/2014) is gratefully acknowledged.

¹ Stuart, M. and Box, K., Anal. Chem., 2005, 77(4), 983-990.

² Box, K.J., et al., J. Pharm. Sci., 2006, 95(6), 298-1307.

³ Kazarian S.G., Chan K. L. A., Macromolecules, 2003, 36, 9866-9872.

⁴ Kazarian S.G., Ewing A. V., Expert Opin. Drug Deliv., 2013, 10(9), 1207-1221