Monitoring and Optimization of Industrial Batch Crystallization Processes using NIR and ATR UV-vis Spectroscopy

Chun H. Hsieh

Literature Seminar

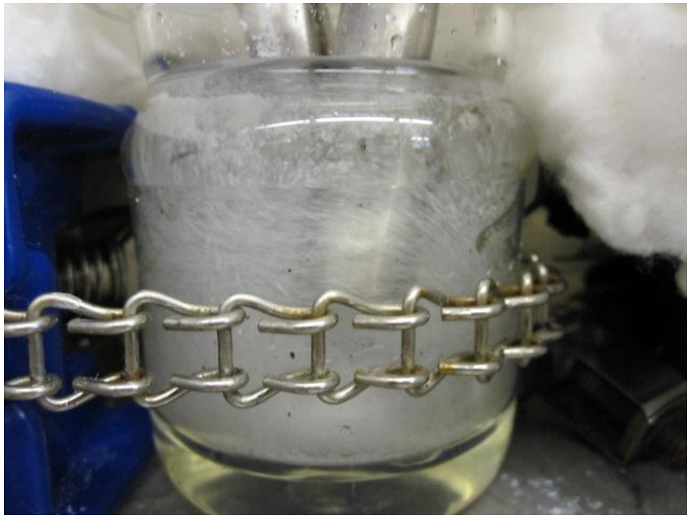
November 16th, 2010

Outline

- ❑ Motivations
- ❑ Use of Process Analytical Technology for the Optimization of Batch Crystallization Processes in Industry
- ❑ Monitoring and Analyzing of Crystallization Processes using NIR Spectroscopy
- ❑ Application of ATR UV-vis Spectroscopy for Monitoring the Crystallization

Motivations

- The Gemperline's group is interested in slurry reactions and the *modeling* of reactive dissolutions and reactive crystallization (e.g. API)
- Analytical techniques
  - Kinetic modeling and chemometrics
- Instrumental techniques
  - NIR Reflectance Spectroscopy
  - ATR UV-vis Spectroscopy
  - Raman Spectroscopy
  - Liquid Chromatography (HPLC)



A Review of the Use of Process Analytical Technology for the Understanding and Optimization of Production Batch Crystallization Processes

Paul Barrett *, Ben Smith*, Joerg Worlitschek*, Veronica Bracken*, Brian O’Sullivan**, and Des O’Grady**

* Mettler-Toledo Autochem, USA, ** University College Dublin, Ireland

Process Analytical Technologies (PATs)

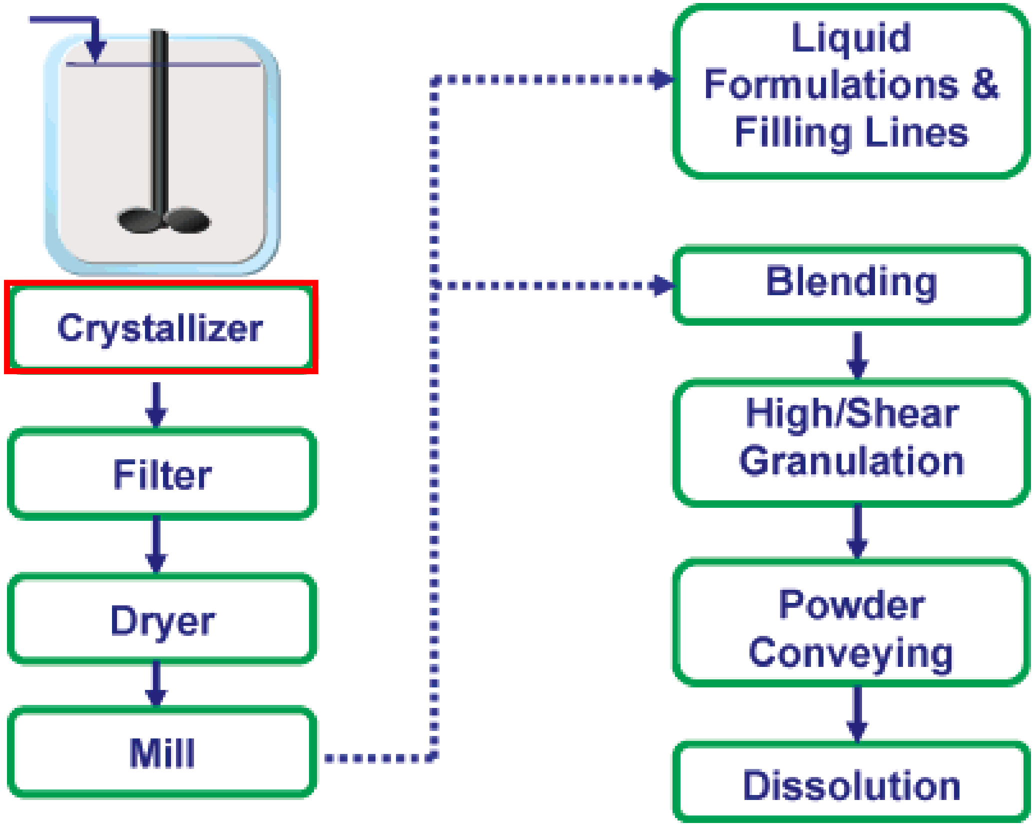
- ❑ Poor understanding of crystallization at production scale
- ❑ Significant impact on both product quality and downstream process unit operations

  filtration, drying, milling and product formulation
- ❑ Challenges within production crystallizers

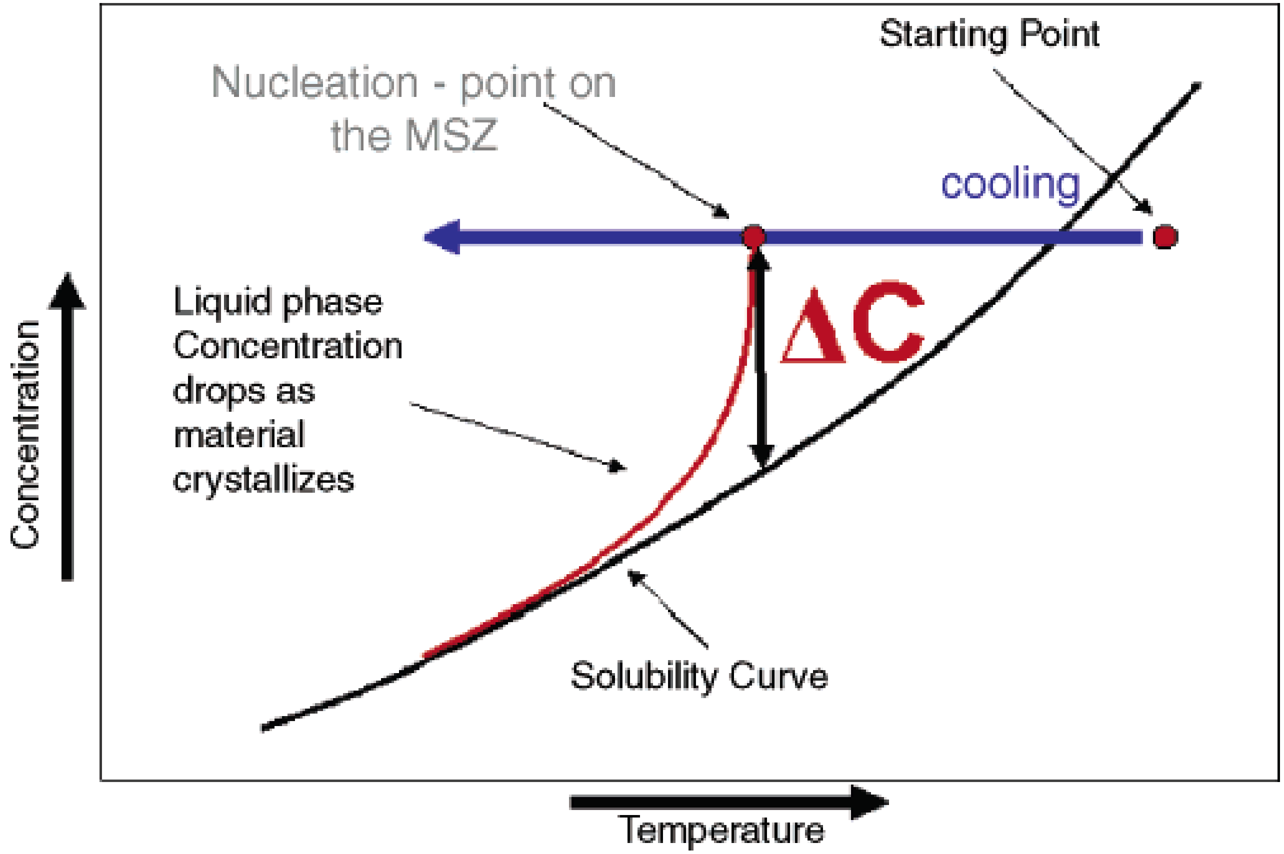
  inconsistencies of batch-to-batch; size and amount of crystals produced and purity profile
- ❑ Review typical problems encountered in production

  e.g. poor mixing

Particles in Pharmaceutical manufacturing



Solubility curve and metastable zone (MSZ)



Population balance equation

Nucleation (B)

$$J_{NI} = A_I \exp[\frac{-B_I}{(\ln \beta)^2}]$$

$$J_{NII} = A_{II} S \exp[\frac{-B_{II}}{\ln \beta}]$$

Crystal Growth (G)

$$G = \frac{dL}{dt} = \frac{\Phi_s M_s k_c}{3 d_s \Phi_v} \eta_r (C - C^*)^j$$

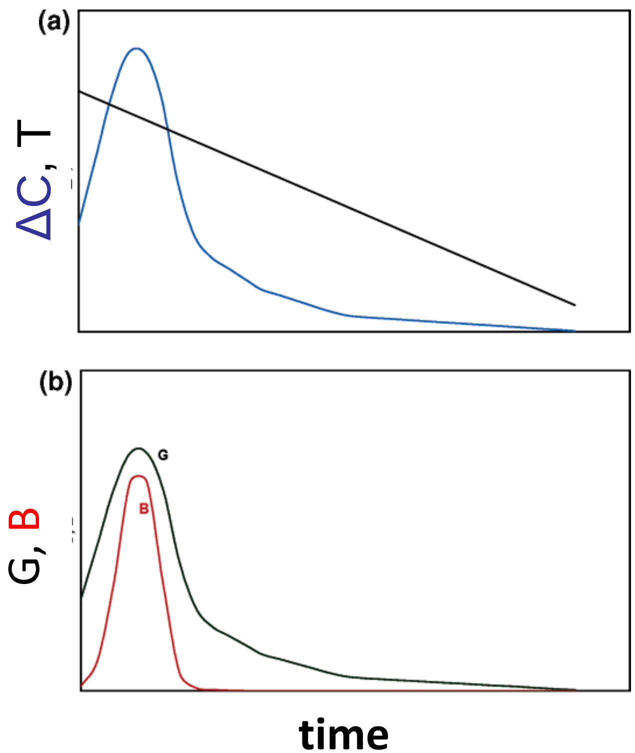
Population Balance Equation

$$\frac{1}{V}\frac{\partial \psi V}{\partial t} + \frac{\partial \psi G}{\partial L} = (J_{NI} + J_{NII})\delta(L - L^*)$$

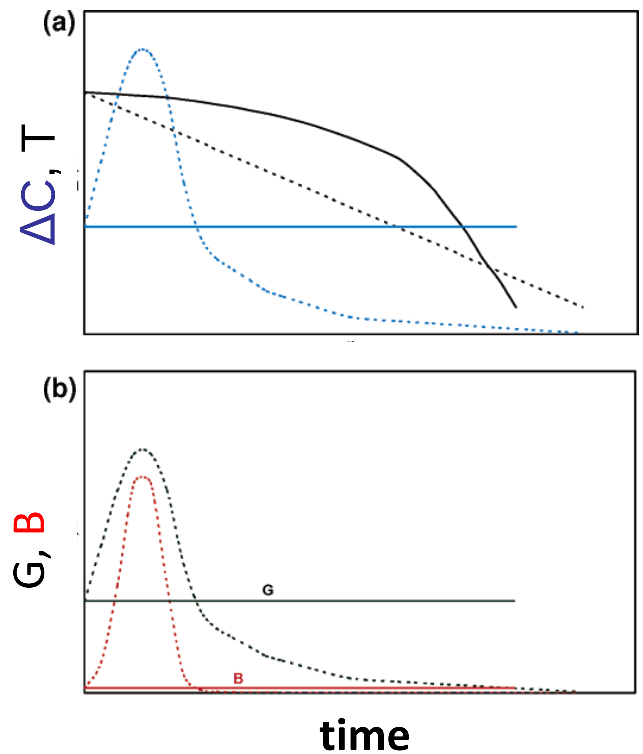
Blandin, A.; Mangin, D.; Nallet, V.; Klein, J.; Bossoutrot, J. *Chemical Engineering Journal*, **2001**, 81, 91-100

Comparison of gradient of temperature

Linear gradient of Temperature

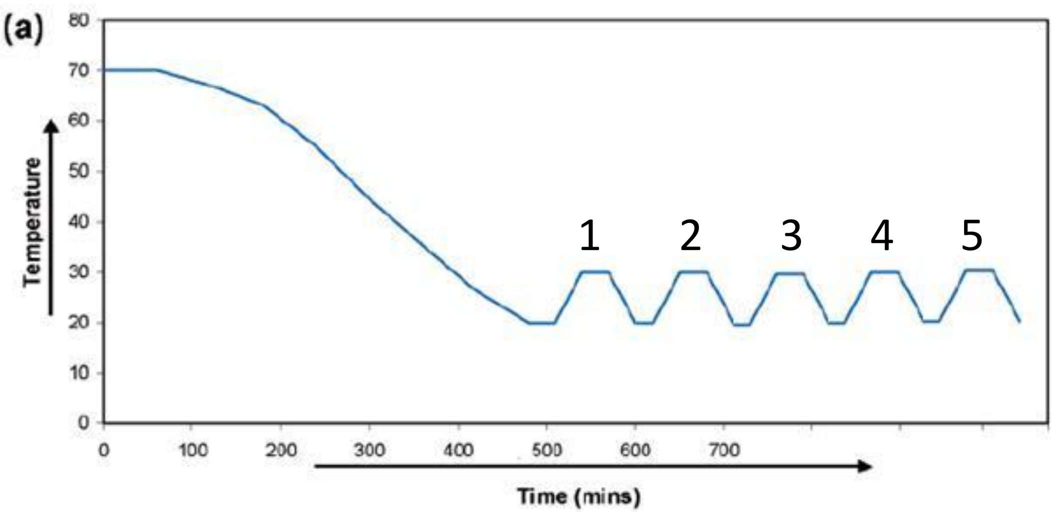


Optimised gradient of Temperature

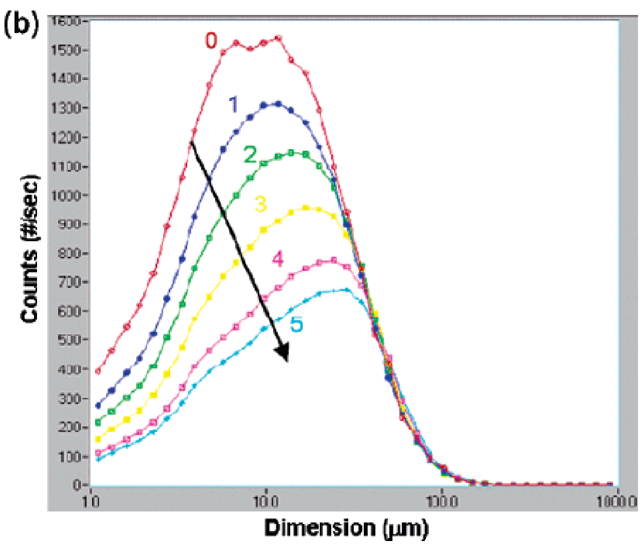


Temperature cycle optimization

Gradient of Temperature



Particle size distribution



Gibbs-Thomson effect: Smaller particles dissolve faster than larger particles

Applications of NIR Spectroscopy to Monitoring and Analyzing the Solid State during Industrial Crystallization Processes

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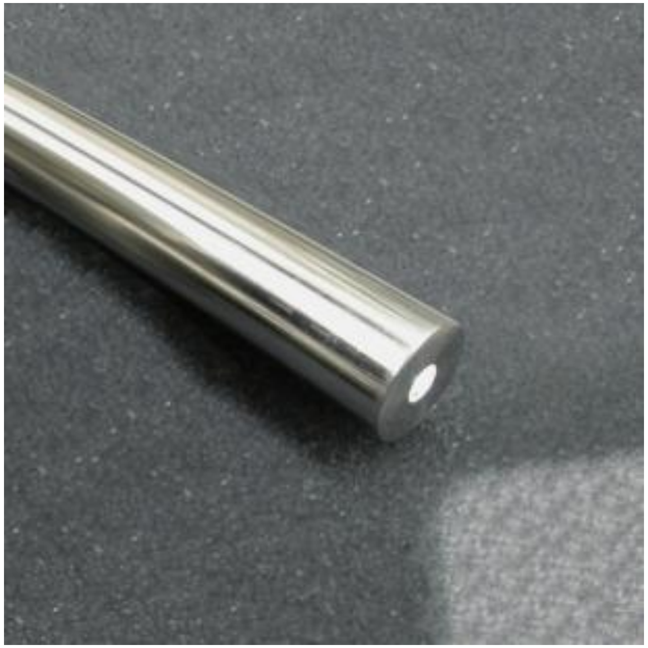
* Université Claude Bernard Lyon 1, France, ** SANOFI Chimie, France

Choices of NIR probes

Transflectance



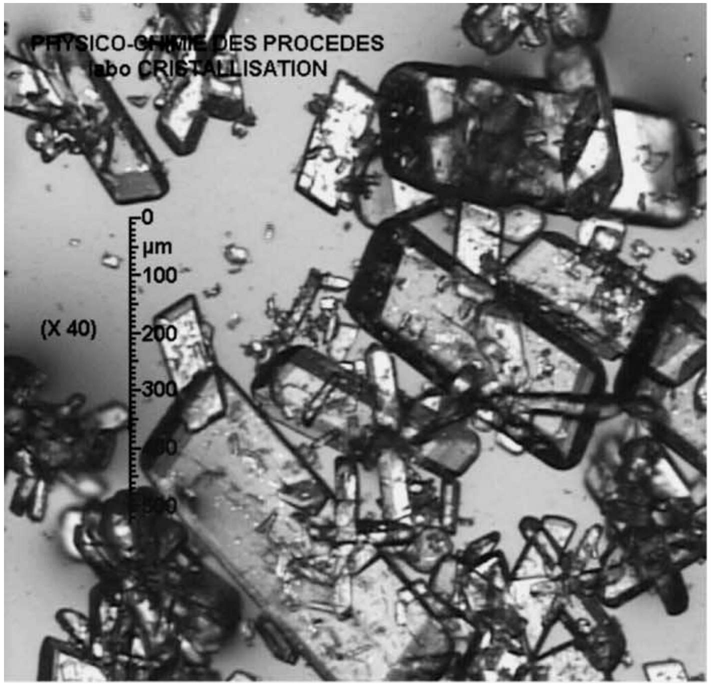
Diffuse Reflectance

Introduction

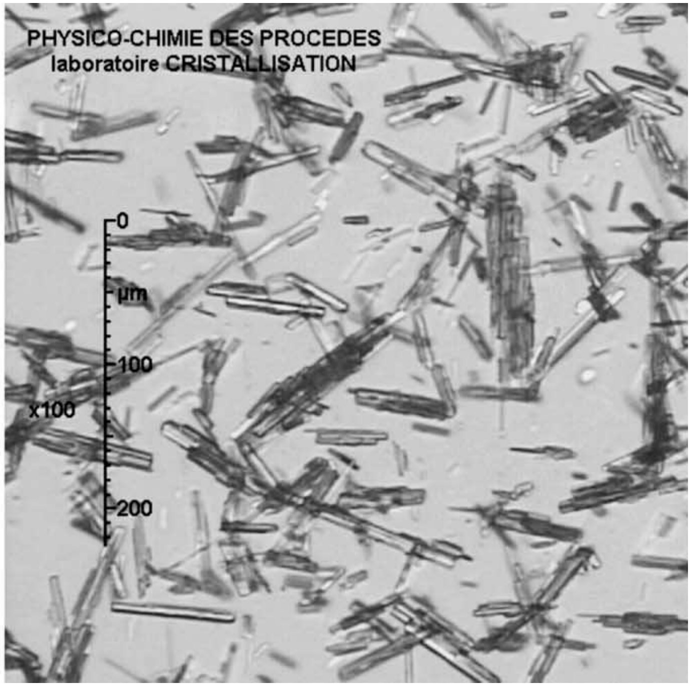
- Investigation of the polymorphic transitions of SaC during the crystallization and filtration
- Investigation of the kinetic behavior of the phase transition against different operating conditions using NIR spectroscopy
- Study the effect of residual water in the solvent on the transition during filtration

Two polymorphic forms of SaC

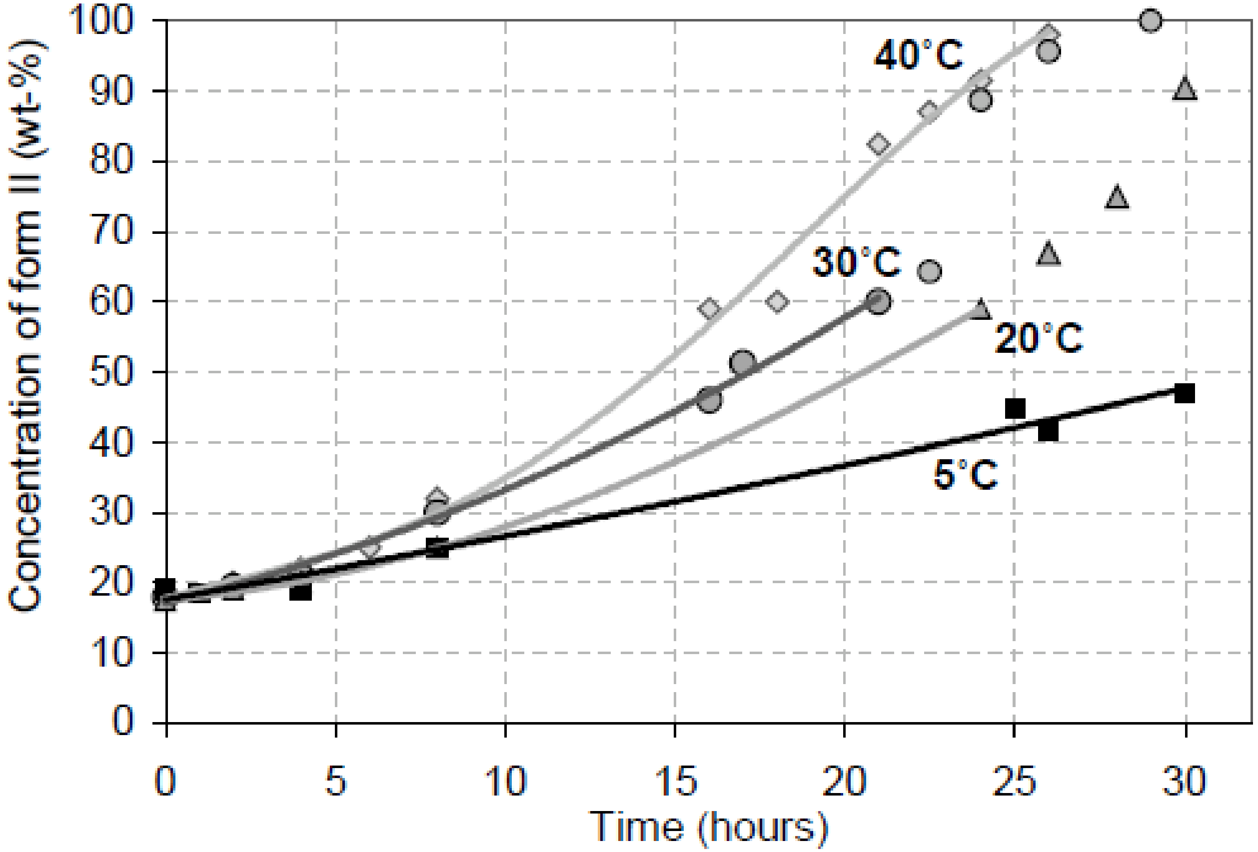
Form I: Parallelepipeds



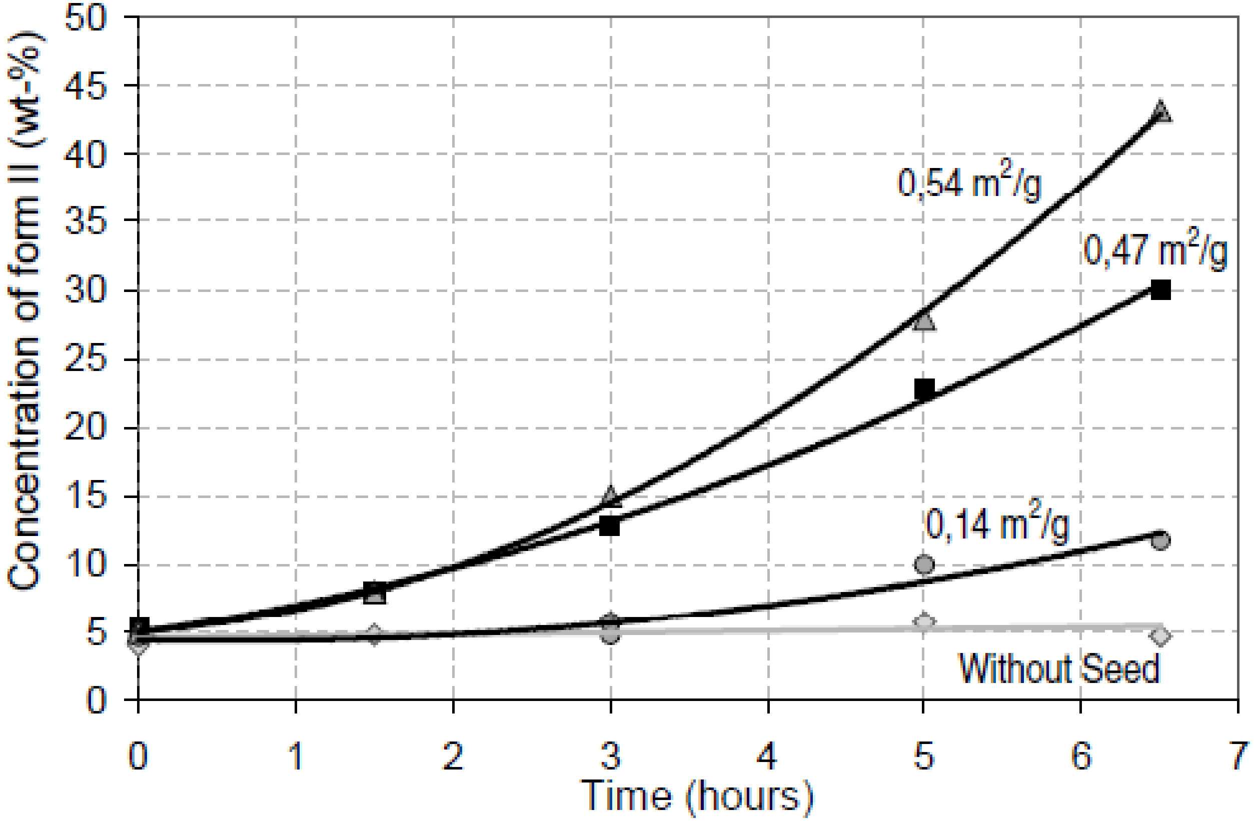
Form II: Needles



Temperature dependency of the transition kinetics

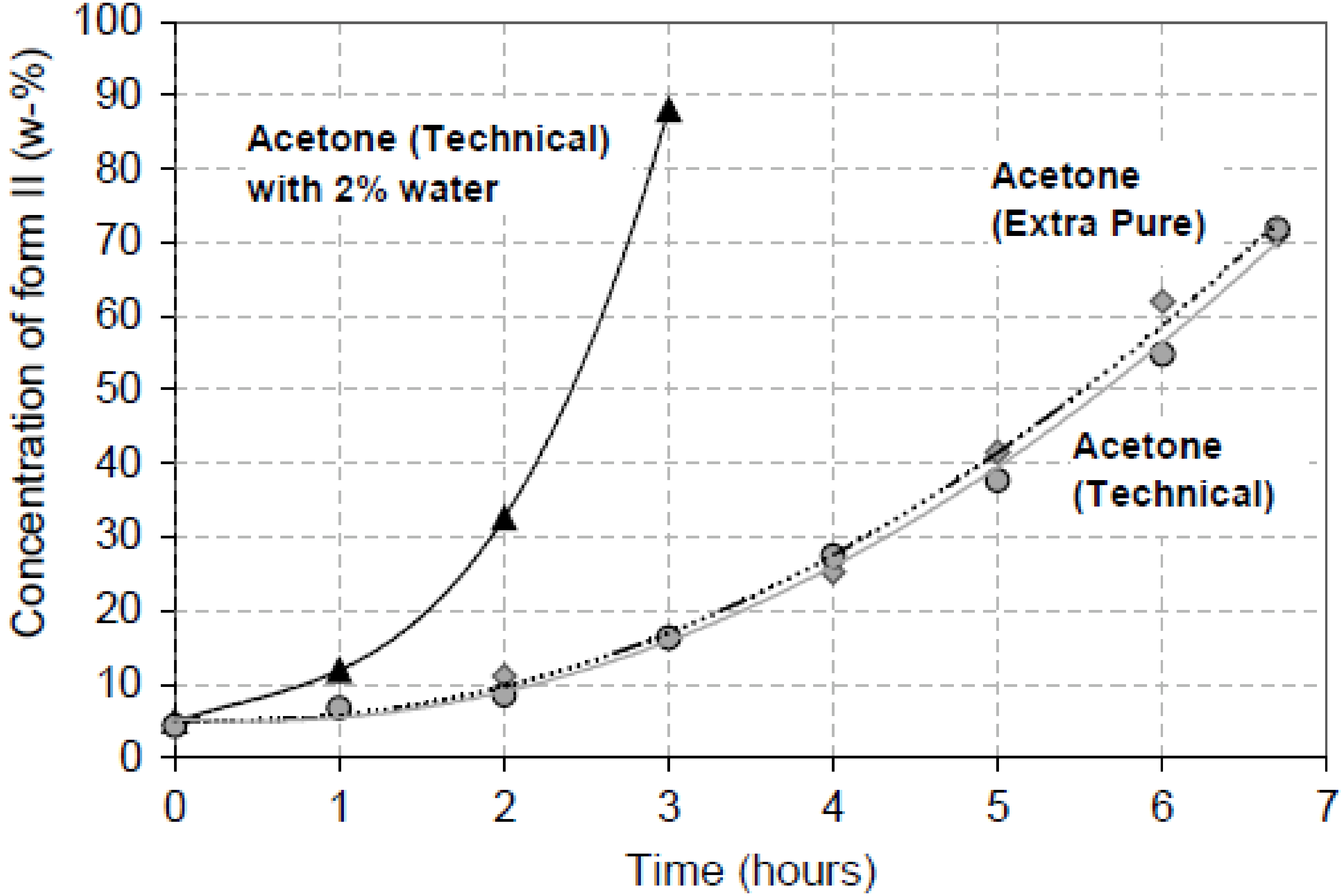


Effect of the size of SaC-II seed crystals on the transition kinetics



Transition kinetics at 20 ◦C, with 2% seed, as a function of the specific area of the seed form II crystals.

Effect of the water on the transition kinetics



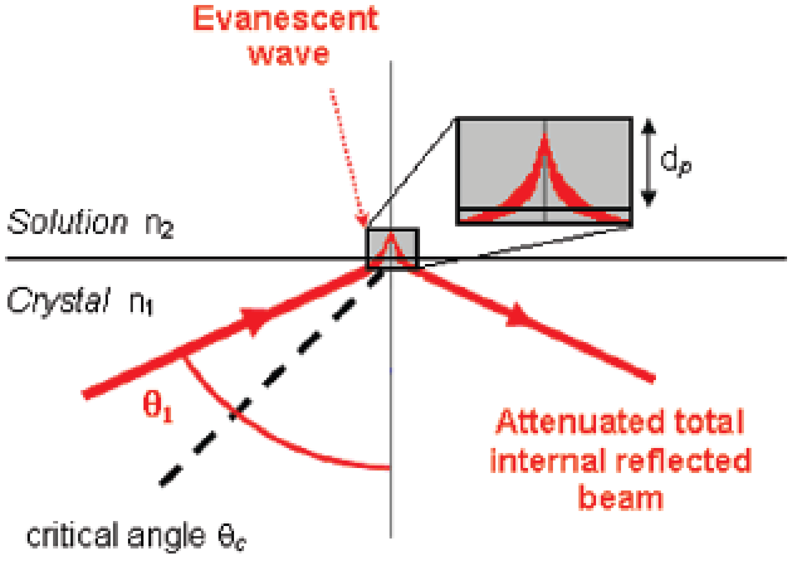
Application of ATR-UV Spectroscopy for Monitoring the Crystallization of UV Absorbing and Nonabsorbing Molecules

Pascal Billot*, Magdalena Couty*, and Patrik Hosek*

* Sanofi Aventis, France

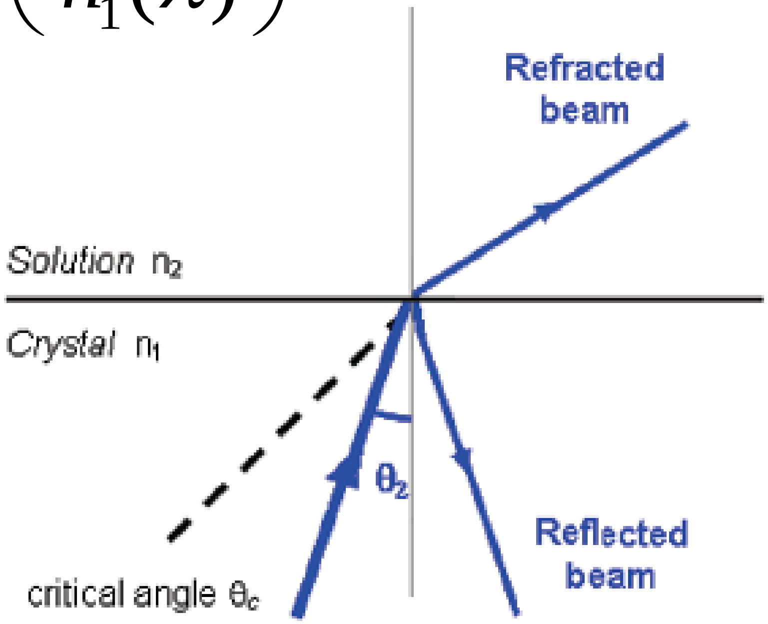
Principle of Attenuated Total Reflectance (ATR)

$$\theta_c(\lambda) = \arcsin\left(\frac{n_2(\lambda)}{n_1(\lambda)}\right)$$



(a)

Total Internal Reflection



(b)

External Reflection

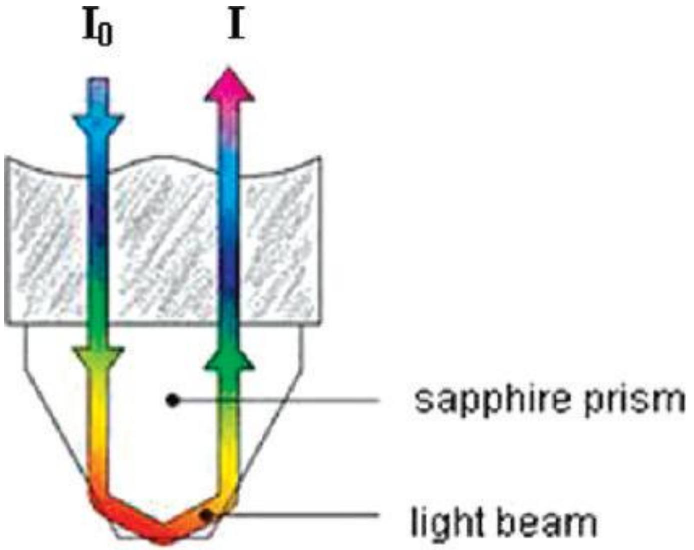
Principle of Attenuated Total Reflectance (ATR)

Critical Refractive Index $$n_{crit} = n_1 \sin\theta$$

Absorbance (attenuated) $$A = \log(\frac{I_0}{I})$$

Beer Lambert's Law $$A(\lambda) = \varepsilon(\lambda)Cl$$

$$l = zd_p$$

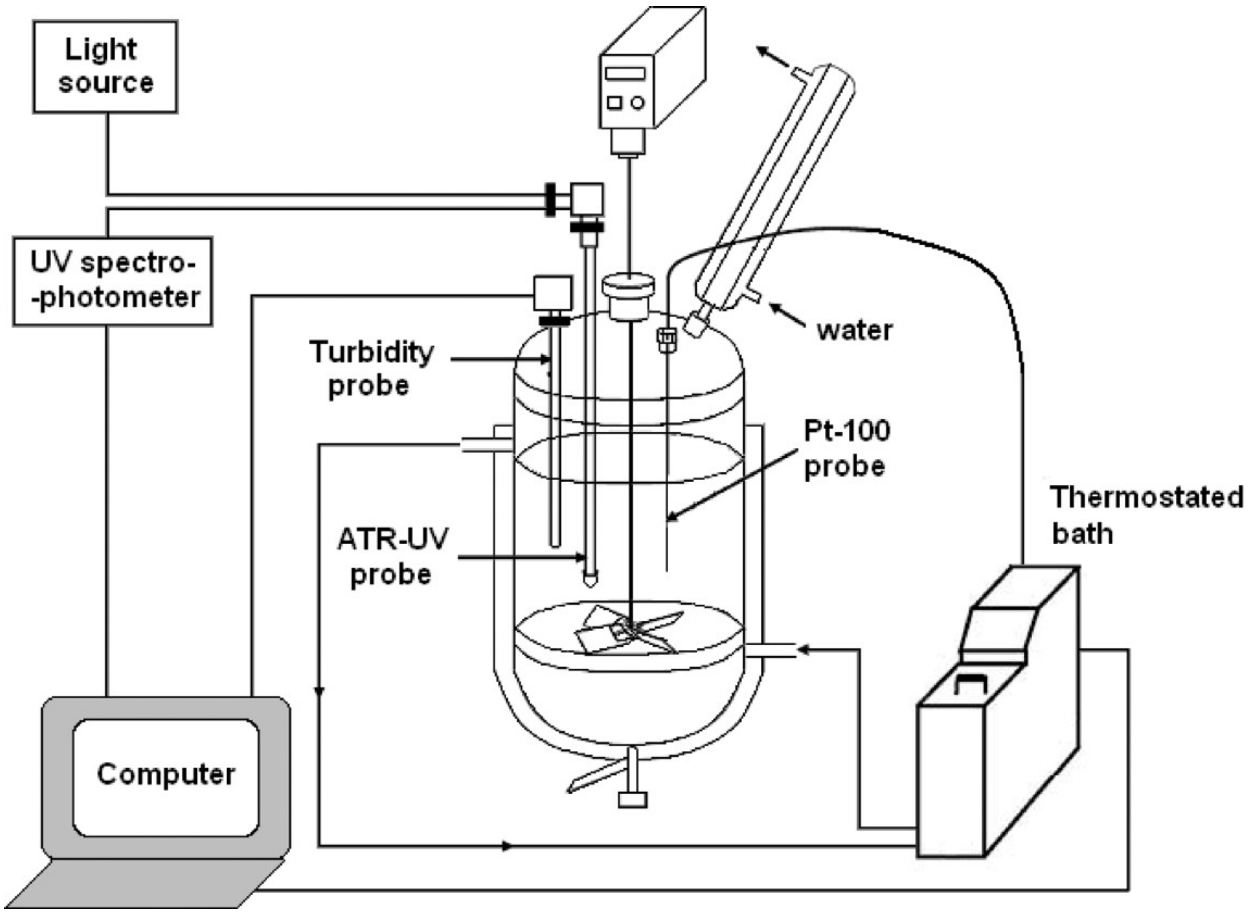


Depth of penetration $$d_p = \frac{\lambda}{2\pi\sqrt{(n_1)^2 \sin^2\theta - (n_2)^2}}$$

Introduction

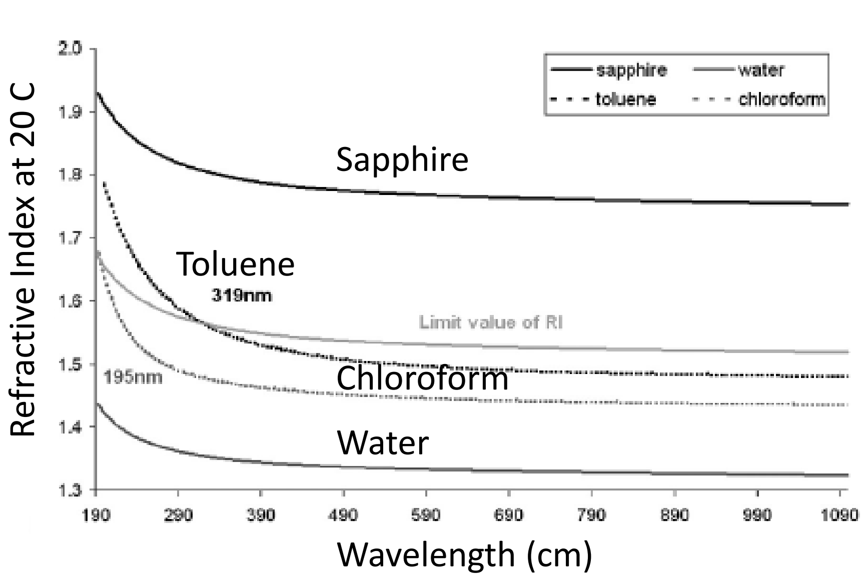
- Monitor crystallization process by using ATR UV-vis spectroscopy
- Advantages offered by the ATR UV-vis spectroscopy to measure supersaturation levels
- Feasible for monitoring crystallizations for non-UV-absorbing molecules

Instrumentation

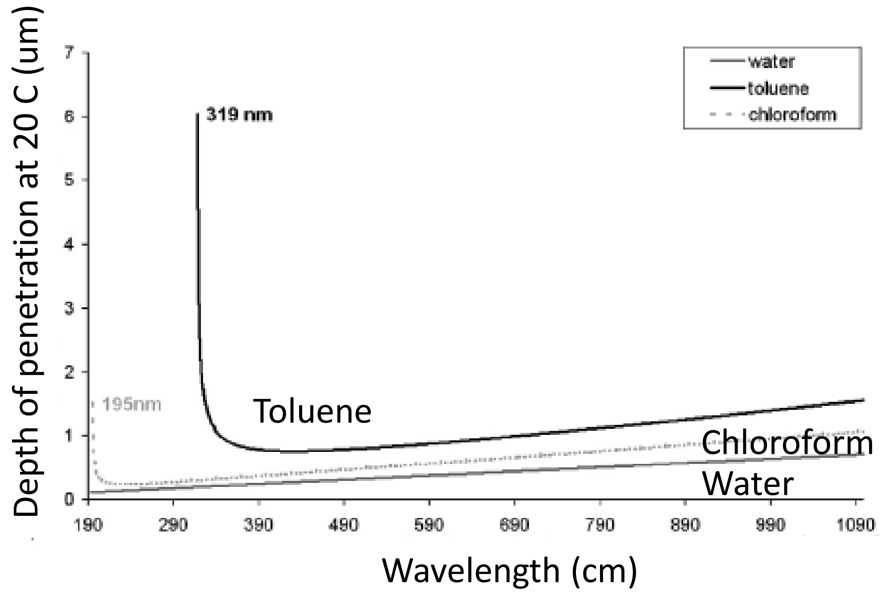


Variation of refractive index with wavelength

literature values



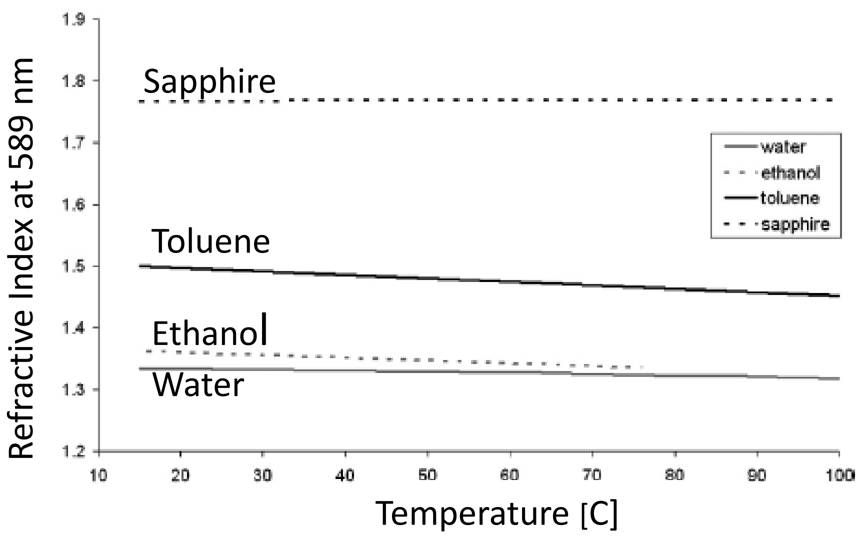
calculated depth of penetration (dp) values



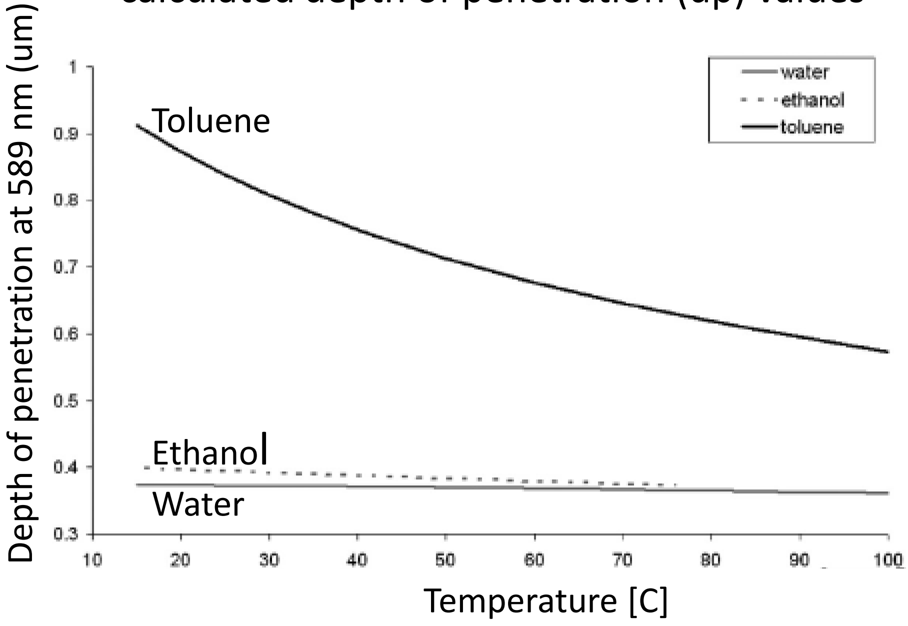
East Carolina University

Variation of refractive index with temperature

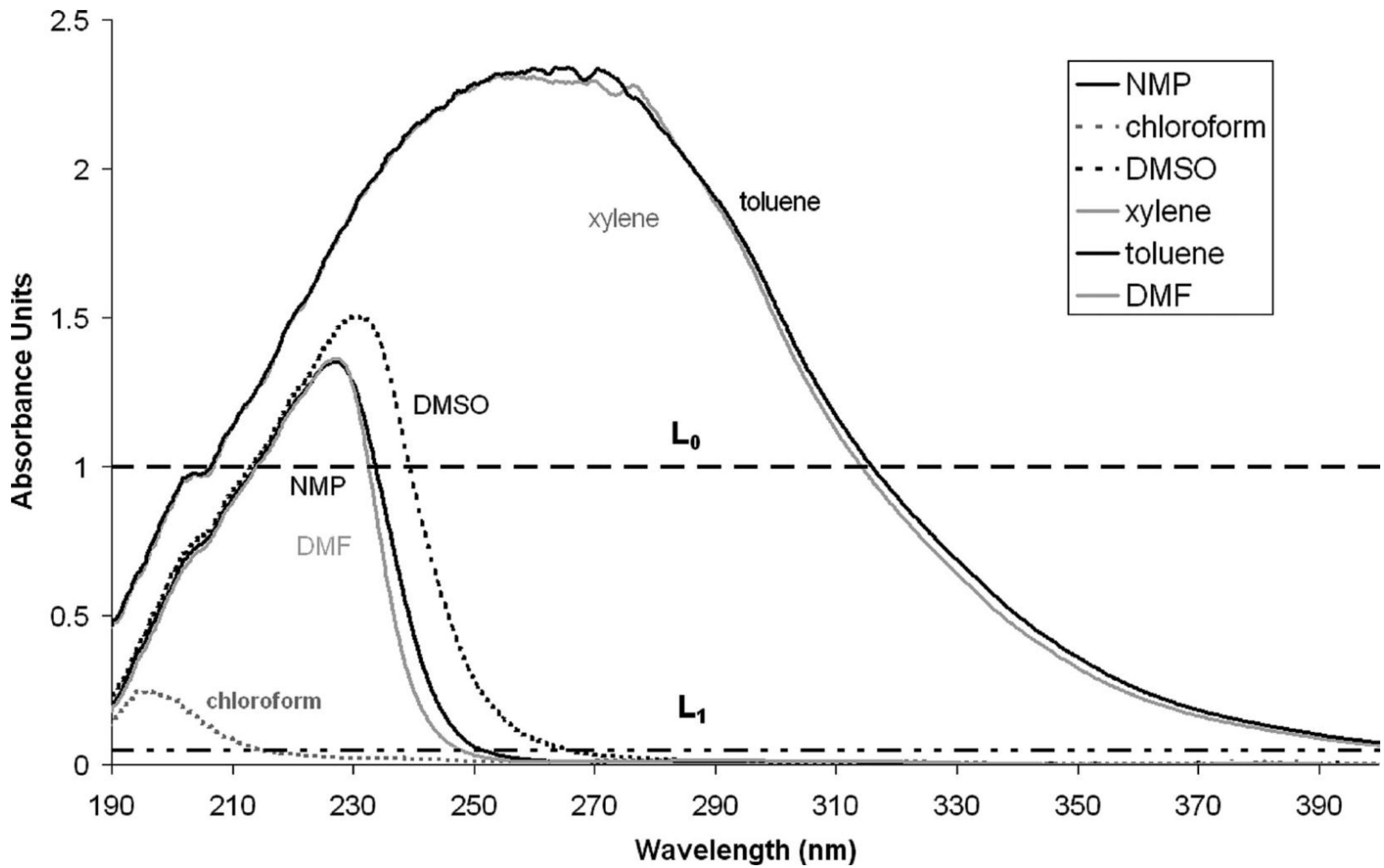
literature values



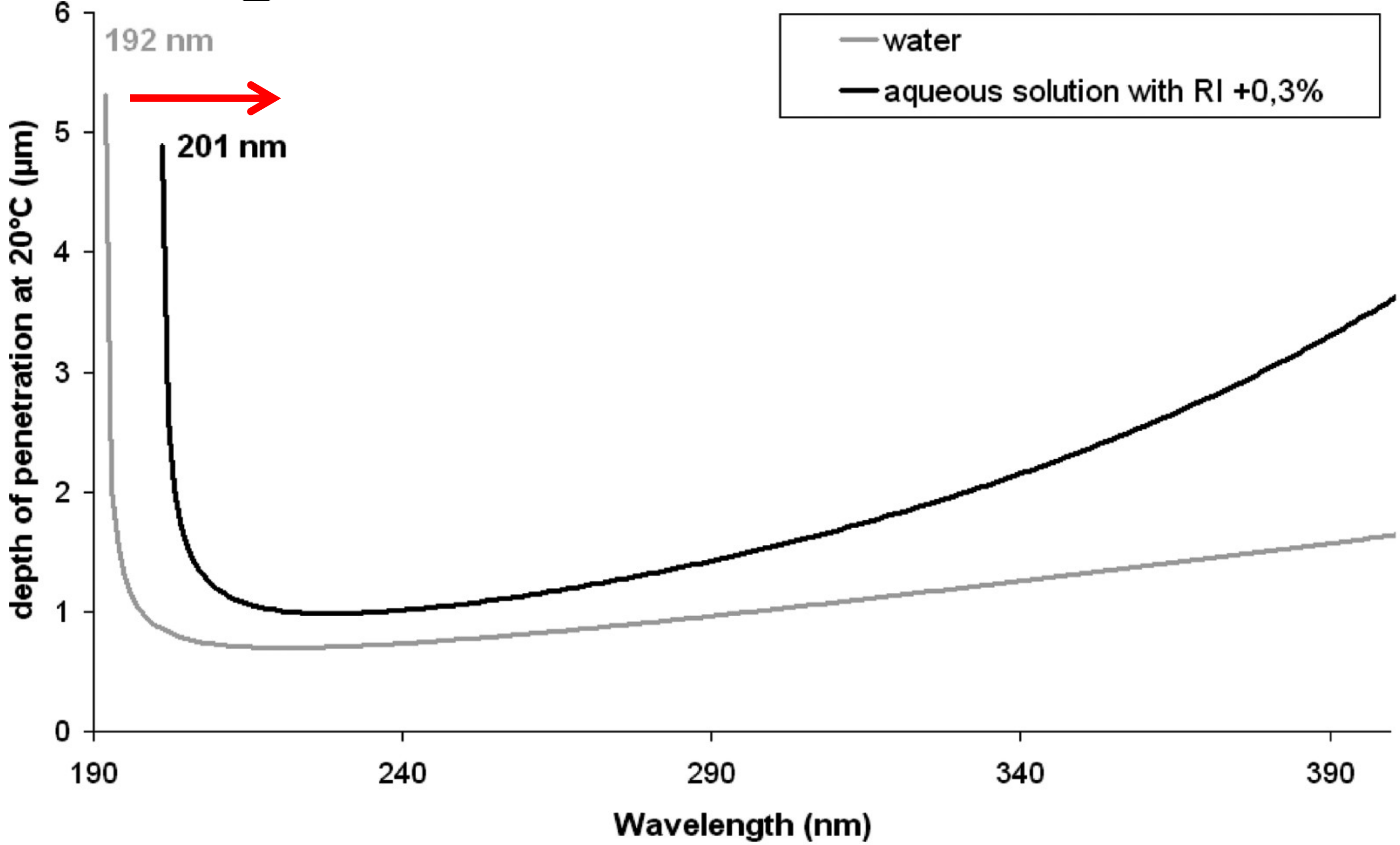
calculated depth of penetration (dp) values



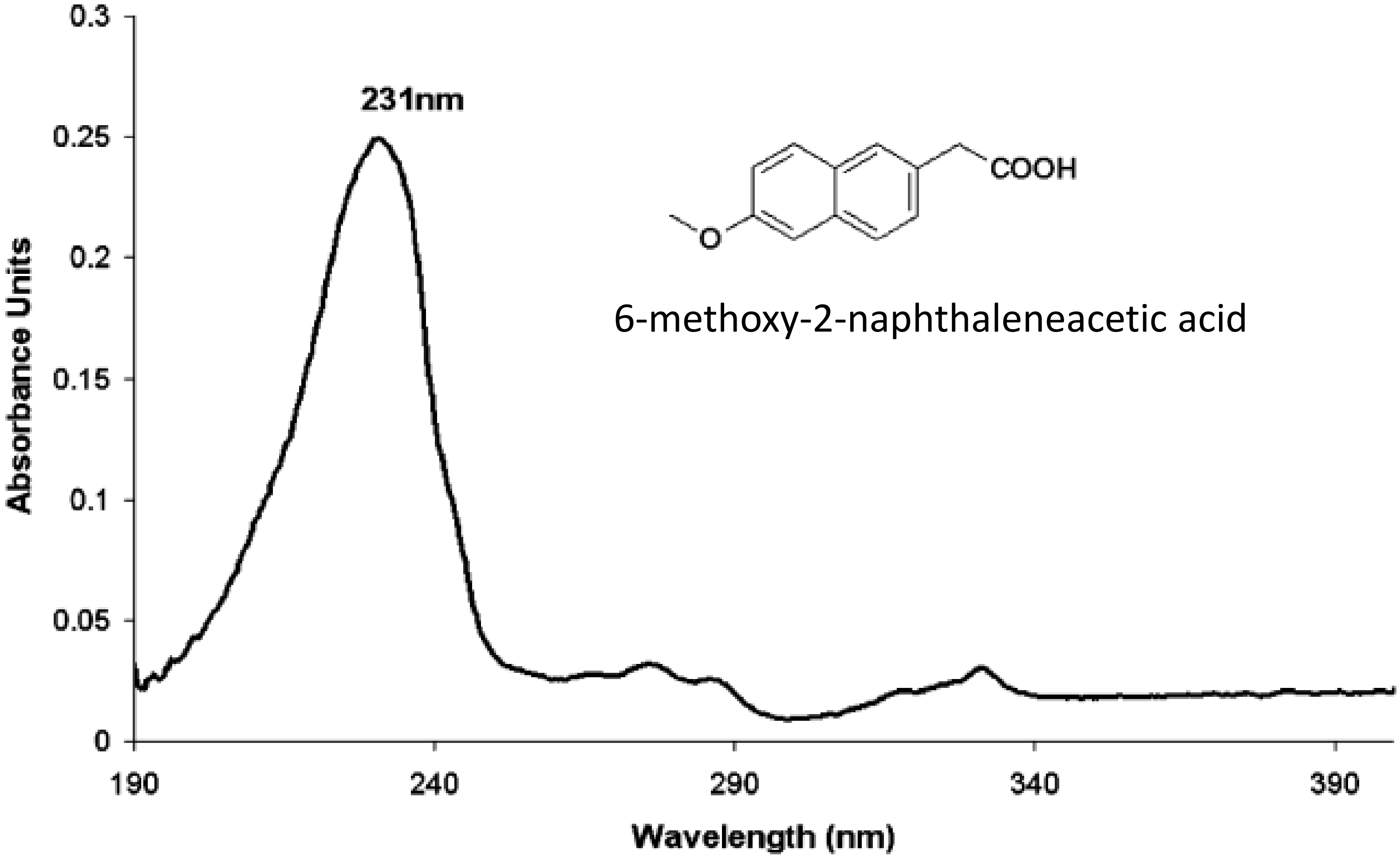
UV cut-off wavelengths



The depth of penetration for non-absorbing molecules

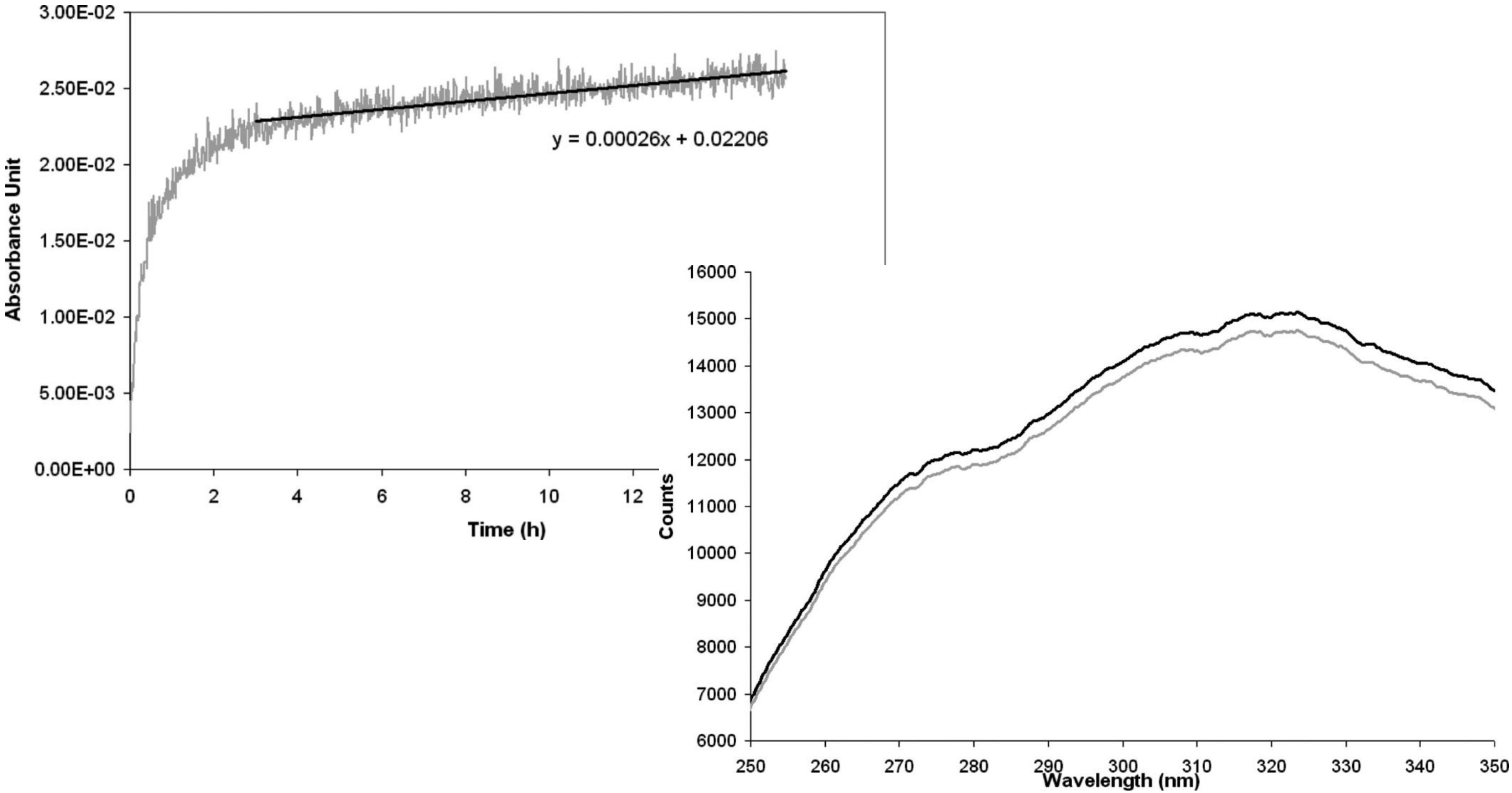


Choice of the test compound 6-MNA

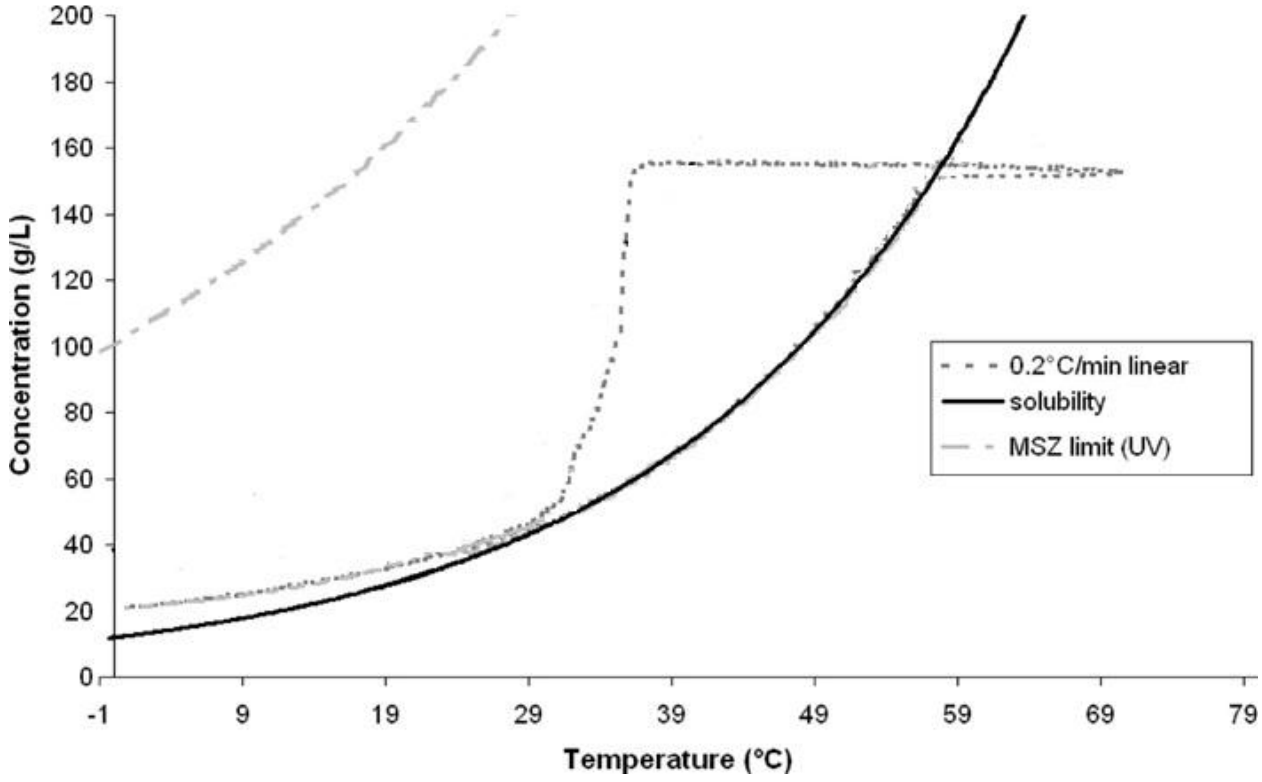


6-methoxy-2-naphthaleneacetic acid

Instrumental stability

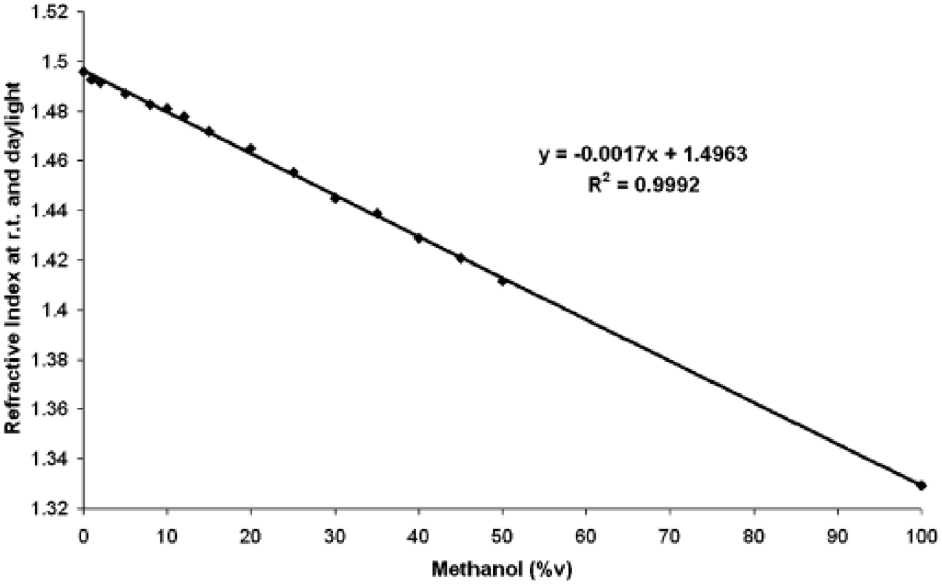


Determination of solubility curve and metastable zone width



Application to non-UV-absorbing substances

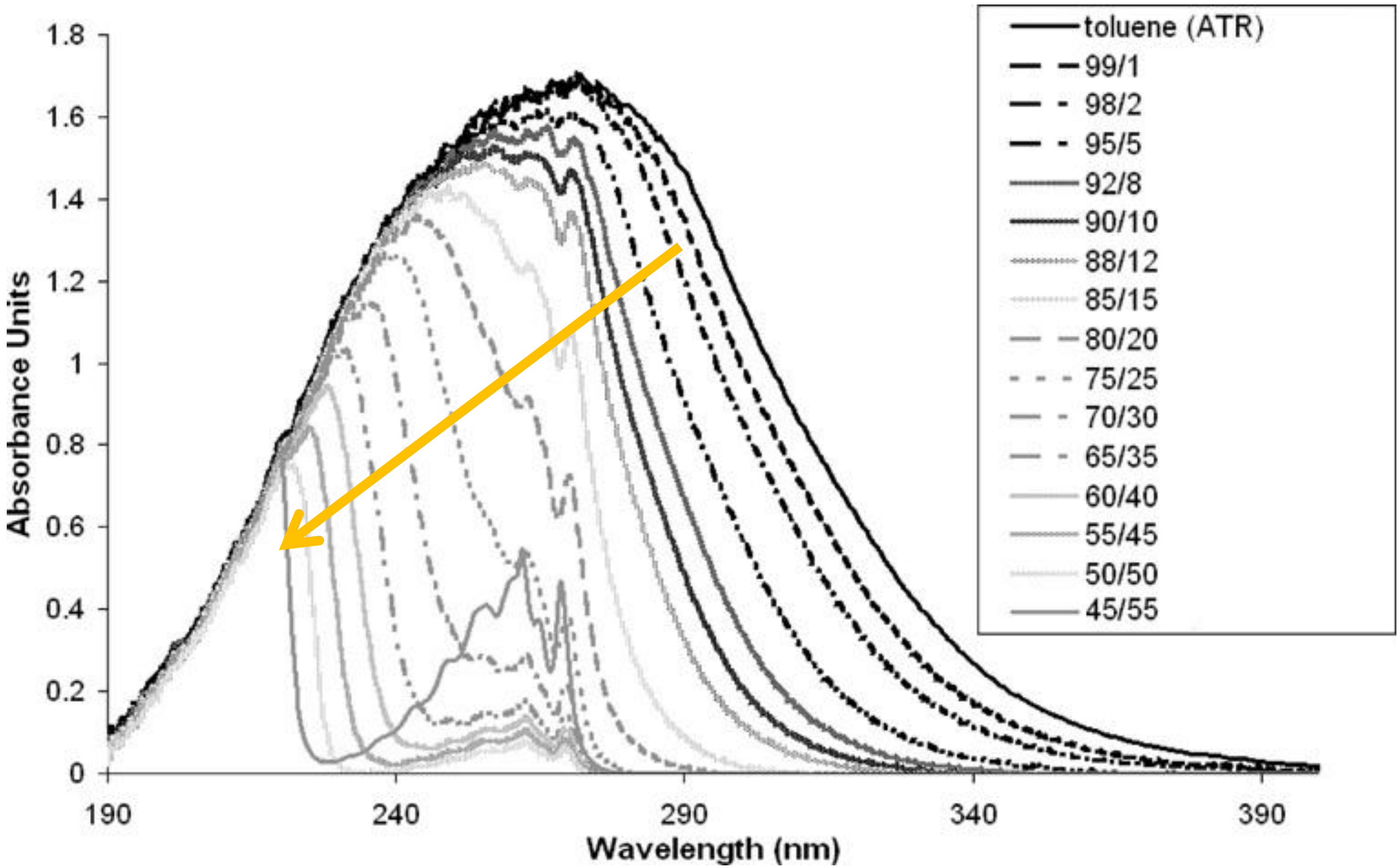
$$d_p = \frac{\lambda}{2\pi\sqrt{(n_1)^2 \sin^2\theta - (n_2)^2}}$$



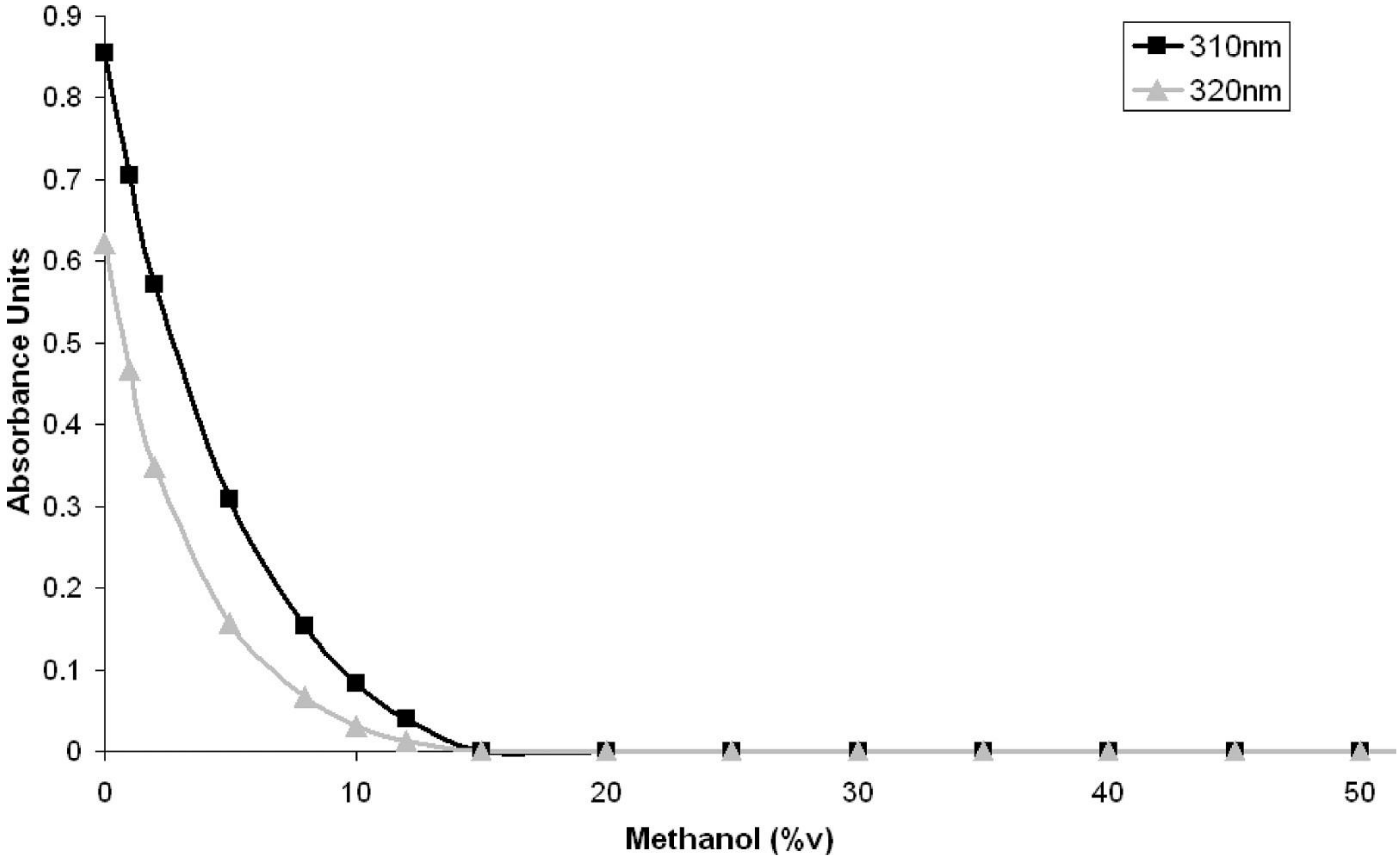
For non-absorbing species

1. Absorption (A) $A(\lambda) = \varepsilon(\lambda)Cl$
2. Optical path length (l) $l = zd_p$
3. Depth of penetration (dp)
4. Refractive index (n_2)
5. Concentration of non-absorbing species

Application to non-UV-absorbing substances



Application to non-UV-absorbing substances



Conclusion

- ❑ Demonstrated the NIR & ATR UV-vis spectroscopy can be used to monitor the crystallization processes
  1. NIR spectroscopy provided highly valuable information on the kinetic of polymorphic transitions of API and particles size distribution in the solid phase concentration
  2. ATR UV-vis spectroscopy provided the access to solubility curve, metastable zone width and the measurements in the liquid phase concentration

References

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