

In-situ Measurement of Solid Phase Transformations During Dissolution Testing

Jaakko Aaltonen^{1,2}, Leena Peltonen¹, Jouni Hirvonen¹, Clare Strachan², Jukka Rantanen^{2,3}

¹Division of Pharmaceutical Technology, University of Helsinki, Finland

²Drug Discovery and Development Technology Center, University of Helsinki, Finland

³Department of Pharmaceutics and Analytical Chemistry, The Danish University of Pharmaceutical Sciences

AIM

To combine *in-situ* solid phase analysis with intrinsic dissolution rate (IDR) measurements in order to achieve real-time molecular level information of solid phase behavior of APIs during dissolution testing.

KEY FINDINGS

The solid phase behavior cannot always be reliably derived from the IDR curve.

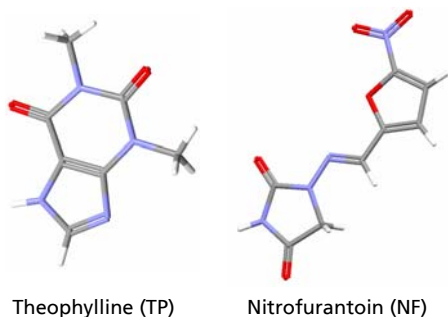
However, with *in-situ* solid phase analysis, direct information on possible solid phase changes can be obtained.

As a result, a deeper understanding of the phenomena related to overall dissolution is achieved.

INTRODUCTION

A solvent-mediated phase transformation from a metastable to a stable form can take place when a solid is in contact with a solvent, for example during dissolution testing. This can cause changes in solubility, dissolution rate and bioavailability. Traditionally, a change in the intrinsic dissolution rate (IDR) is linked to a solid phase transformation, but the information is not direct and can also be due to other factors. The purpose of this study was to apply *in-situ* solid-state analysis to IDR measurements, in order to get direct molecular level information of the reasons behind the dissolution rate changes.

MODEL DRUGS



TECHNICAL DETAILS

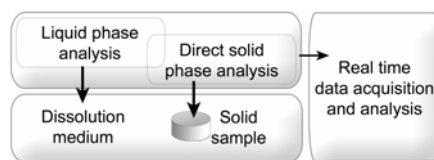
The solid phase analysis was performed using Raman spectroscopy *in situ* during the IDR test, while the concentration of the drug in the dissolution medium was measured with a UV-Vis spectrophotometer equipped with a flow-through cuvette. The dissolution medium used in the study was purified water ($t = 25\text{ }^{\circ}\text{C}$, $V = 500\text{ ml}$). (Scheme 1, Fig. 1).

Raman spectra were standard normal variate (SNV) corrected. Quantification of the solid forms was based on calibration curves constructed using anhydrate:monohydrate powder mixtures. Characteristic peaks for TP anhydrate, TP monohydrate, NF anhydrate and NF monohydrate were identified and a ratio of characteristic peak intensities was calculated for each calibration sample. Thereafter, the calculated ratios were correlated to the hydrate form contents of the samples.

REFERENCE

Aaltonen J et al.: *In-situ* measurement of solid phase transformations during dissolution testing. *J. Pharm. Sci.* In Press. doi:10.1002/jps.20725

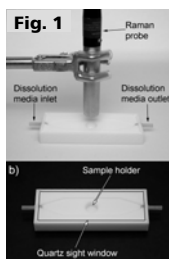
PROCEDURE



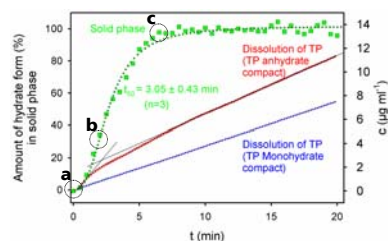
Scheme 1. The procedure: a solid sample is immersed in a liquid dissolution medium and both phases are analyzed simultaneously.

DISSOLUTION TESTING SET-UP

The dissolution tests were conducted with a channel flow intrinsic dissolution test apparatus in which only one surface of the powder compact is in contact with the dissolution medium. The compacts were placed in the sample holder, and Raman spectra were measured *in situ* through a quartz sight window (Fig. 1).



CASE 1. IDR / SOLID PHASE ANALYSIS OF THEOPHYLLINE



a) t=0 min:

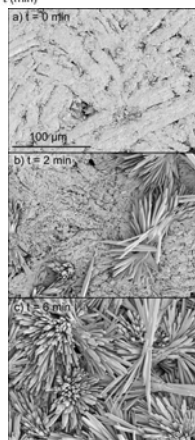
Only TP anhydrate crystals are seen on the surface of the compact.

b) t=2 min:

Crystals of the monohydrate form nucleate and grow while both forms dissolve.

c) t=6 min:

No crystals of the anhydrate form are present on the surface anymore. Dissolution of the monohydrate form occurs.



RESULTS

- TP anhydrate underwent a transformation to TP monohydrate during the dissolution test.
- The transformation started almost immediately after contact with the dissolution medium.
- The dissolution rate decreased as the amount of the stable hydrate form increased.
- An increase in the specific surface area was detected due to crystal growth of the monohydrate phase. Therefore, the dissolution rate of the transformed compact (initial anhydrate) was higher than that of initial monohydrate compact.

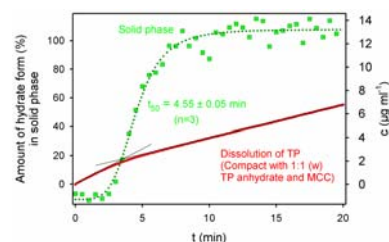
ACKNOWLEDGEMENTS

The Academy of Finland and Finnish Cultural Foundation (Elli Turunen fund) are acknowledged.

CONTACT

jaakko.aaltonen@helsinki.fi

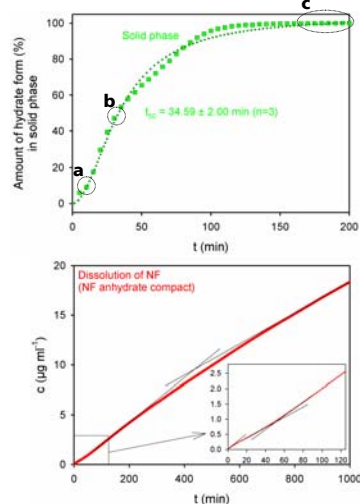
CASE 2. IDR / SOLID PHASE ANALYSIS OF THEOPHYLLINE:MCC



RESULTS

- The solid phase transformation was successfully measured in a mixture of an excipient and an API
- Presence of microcrystalline cellulose retarded the onset of the solid phase transformation, but MCC had no effect on the rate of transformation

CASE 3. IDR / SOLID PHASE ANALYSIS OF NITROFURANTOIN



a) t=10 min:

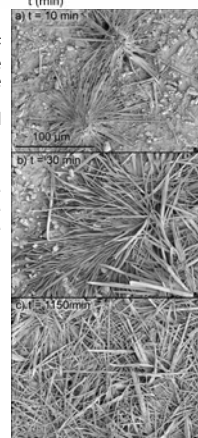
Small crystals of NF anhydrate dissolve while crystals of the monohydrate form nucleate, grow and dissolve.

b) t=30 min:

Both forms dissolve and the fiber-like crystals of the monohydrate form continue to grow.

c) t=1150 min:

The whole surface is covered with the monohydrate form. Dissolution of the monohydrate form occurs.



RESULTS

- NF anhydrate (form β) transformed to NF monohydrate (form II) during the dissolution test.
- The solid phase transformation during dissolution involves several overlapping factors, and therefore no clear correlation with the dissolution rate and the solid phase composition was found.
- The dissolution rate changed many times during the test. Possible reasons include:
 - Loose particles on the surface
 - Specific surface area changes
 - Wetting and dissolution of particles below the very surface