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Report:

This report describes the application of time-resolved x-ray diffraction techniques to investigate the kinetics of dehydration of crystalline pharmaceutical hydrates as a function of temperature and the pharmaceutical additive (excipient) polyvinylpyrrolidone (PVP).

The theophylline monohydrate samples were loaded in a alumium differential scanning calorimeter (DSC) pan which was injected by a stepper motor controlled purpose built sample stage into a pre-heated x-ray diffraction camera. Two-dimensional diffraction data was recorded every 0.48 seconds with a Photonic Science CCD detector. This diffraction data was converted to powder diffraction data format for the phase characterisation of theophylline monohydrate. A typical thermally induced phase transition of theophylline monohydrate (figure 1a) and theophylline monohydrate with PVP (figure 1b) at 130°C is shown in figure 1 and figure 2. It can be seen from these figures that the entire reaction is completed within 40 seconds for theophylline monohydrate and 50 seconds for theophylline monohydrate in the

presence of PVP. We have observed an intermediate phase, which is characterised by the reflection at a 2θ value of 9.3° prior to the development of the anhydrous phase, which is characterised, by the reflection at a 2θ value of 7.2°. We also observed that in the presence of
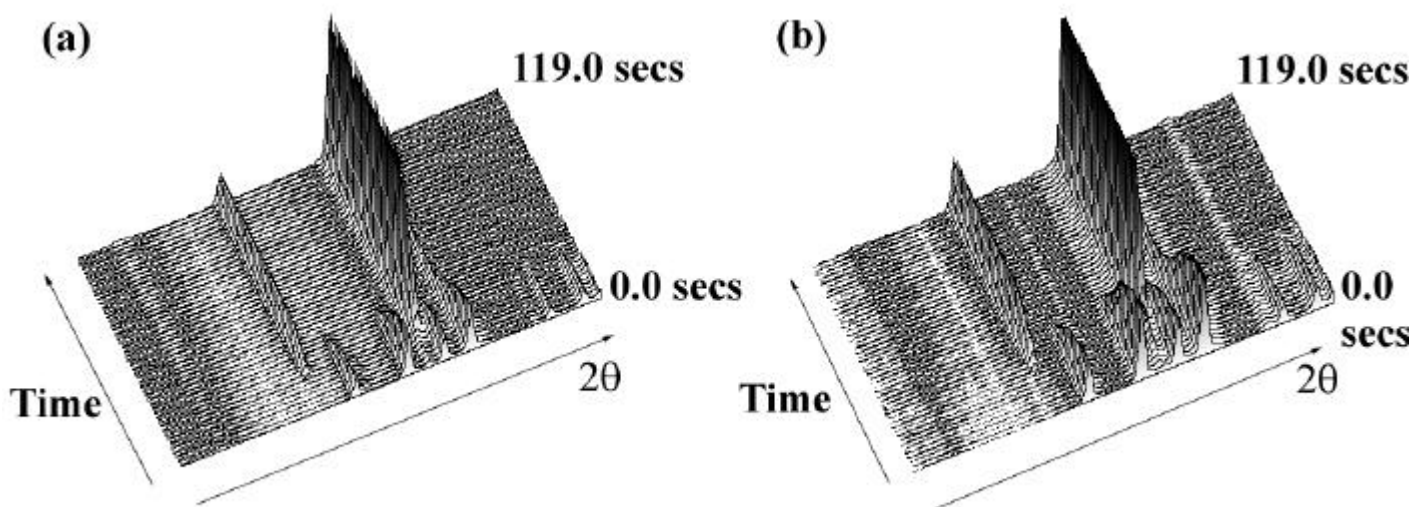

Figure 1

PVP the stability and the mass fraction of the intermediate phase increased and this intermediate phase has delayed the formation of the anhydrous phase. The high brilliance of the ESRF and the availability of a fast electronic detector meant that we were able to monitor these reactions simultaneously with a time resolution of ~0.5 seconds. It is important to emphasise that no other analytical technique is suitable for obtaining comparable information from such a rapid solid-state reaction. The decrease in the concentration of the crystalline hydrate phase was quantified based on the intensity of the reflection at a 2θ value of 8.8° while the increase in the crystalline anhydrate was monitored from the variation in the intensity of the reflection at a

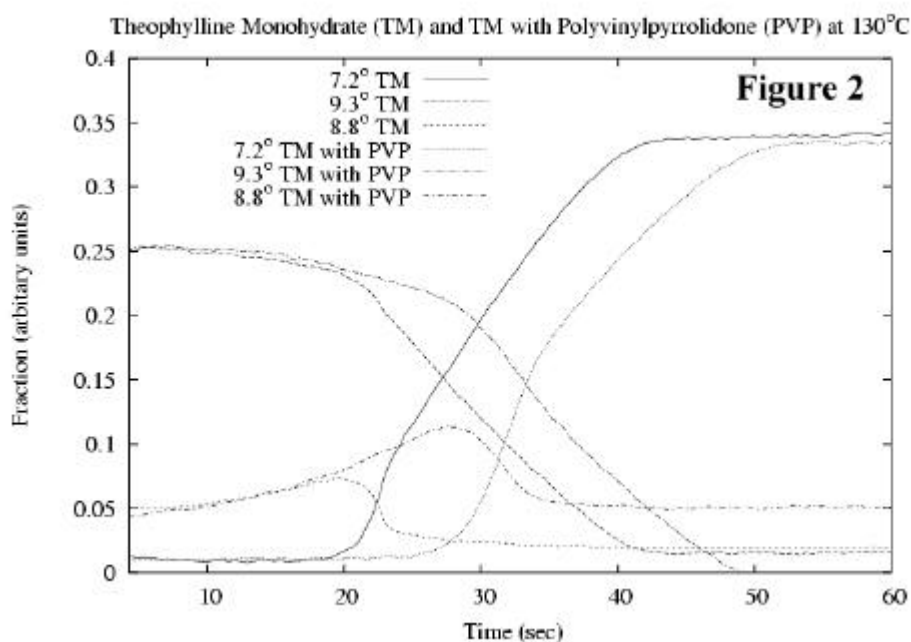2θ value 7.2° and the change in the intermediate phase is characterised by the reflection at a 2θ value 9.3° as shown in figure 2.