

# APPLICATION OF MICRO RAMAN SPECTROSCOPY TO PHARMACEUTICAL FORMULATIONS UNDER CONTROLLED HUMIDITY

K. L. A. Chan, O. S. Fleming, S. G. Kazarian\*

Department of Chemical Engineering and Chemical Technology, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom; E-Mail: [s.kazarian@imperial.ac.uk](mailto:s.kazarian@imperial.ac.uk)

**Keywords:** *nifedipine structure, drugs, polymorphism, crystallization, Raman spectroscopy, Infrared microscopy.*

**Abstract:** The polymorphism of nifedipine under controlled relative humidity has been studied by both Raman and FTIR spectroscopy. Amorphous nifedipine was found to be less stable at a high humidity and converted into thermodynamically more stable crystalline states.

The dissolution characteristic and the bioavailability of a poorly water soluble drug is a strong function of its molecular state.<sup>1</sup> It has been suggested that the relative humidity has a strong effect on the stability of the drug morphology.<sup>2</sup> It is therefore important to understand the effect of different environmental parameters on the properties of pharmaceutical formulations in the pharmaceutical industry. Such knowledge would facilitate new formula/manufacturing process designs for more effective and reliable drugs.

Raman and infrared spectroscopy are widely used analytical methods to study pharmaceutical formulations. Combining Raman/FTIR microscopy with a recently available vapour generating instrument provides the opportunity to study the effect of temperature and humidity on the morphology of samples in situ.

The polymorphism of nifedipine under controlled relative humidity has been studied by both Raman and FTIR spectroscopy. The Raman spectra were measured using a Renishaw system with a 20x ultra long working distance objective. The FTIR spectra were obtained with a Bruker system and a macro written in the OPUS software (Bruker) was used for automated sequential acquisitions. The effect of humidity on the stability of the amorphous nifedipine has been evaluated. We have recently shown that nifedipine can exist in three different major polymorphs and one transient polymorph.<sup>3</sup> Different polymorphs can easily be distinguished using the spectroscopic methods employed in this study. This study shows that the transition of amorphous nifedipine (g-NIF) into two forms of crystalline nifedipine ( $\alpha$ - and  $\beta$ -NIF) upon exposure to different controlled humidities. The experimental set up allows us to measure spectra at different locations of the sample during the exposure period without disturbing the environment of the sample. Figure 1 shows an example of the white light image of a crystallising nifedipine amorphous film. Raman spectra extracted from different areas indicate the type of crystallite formed at specific areas. Figure 2 demonstrates a progressive transition of nifedipine from g-NIF to  $\beta$ -NIF, monitored by infrared spectroscopy. This information can be used to estimate the speed of crystallisation as a result of exposure to various humidities. Both Raman and infrared results show a higher crystallisation rate when the amorphous sample is exposed to a higher relative humidity.

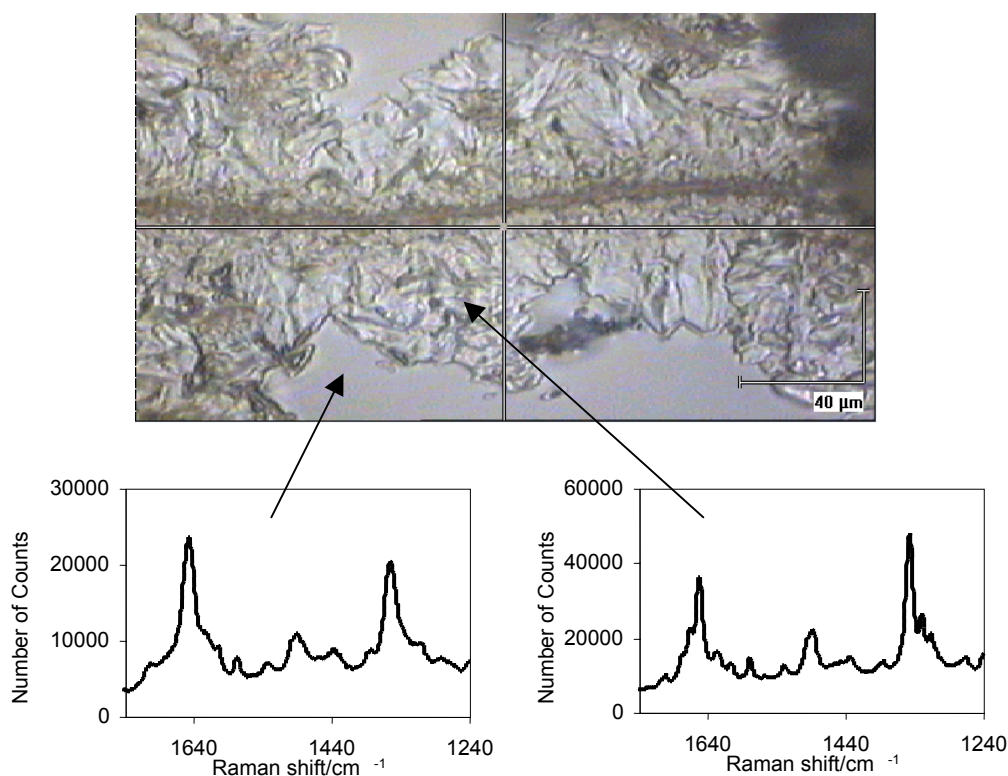


Fig. 1: White light image of g-NIF film crystallised upon exposure to 95% of RH at 25 °C for 30 minutes. The corresponding Raman spectra from the glassy and crystalline domain are also shown.

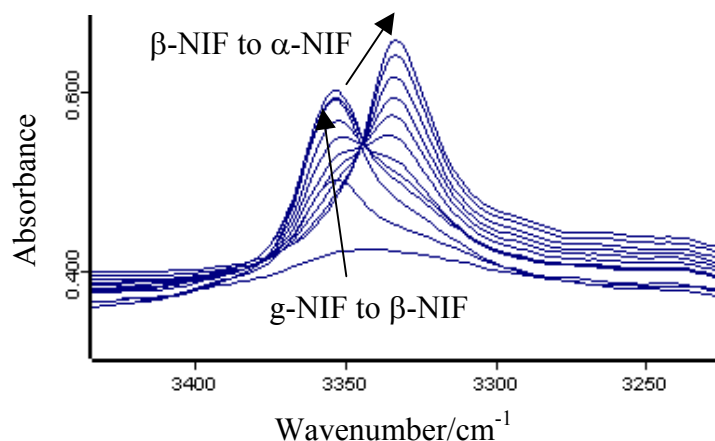


Fig. 2: Infrared spectra of NIF film measured with 1 hour time intervals.

#### Acknowledgement:

We thank EPSRC for support (GR/R57164) and SMS, Renishaw, plc and Bruker Optics for technical support. KLAC and OSF thank Pfizer and EPSRC for the studentships. We also thank Dr. G. D. Chrysikos for a sample of nifedipine.

#### References:

1. C. J. Frank, in *Analytical Applications of Raman Spectroscopy*, M. Pelletier, J., Ed.; Blackwell Science, pp 224-271 (1999).
2. V. Andronis, M. Yoshioka and G. Zograf, *J. Pharm. Sci.* **86**, 346 (1997).
3. K. L. A. Chan, O. S. Fleming, S. G. Kazarian, D. Vassou, G. D. Chrysikos and V. Gionis, *J. Raman Spectrosc.* **35**, 353-359 (2004).