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Monitoring ibuprofen–nicotinamide cocrystal formation during solvent free continuous cocrystallization (SFCC) using near infrared spectroscopy as a PAT tool

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ABSTRACT

The purpose of this work was to explore NIR spectroscopy as a PAT tool to monitor the formation of ibuprofen and nicotinamide cocrystals during extrusion based solvent free continuous cocrystallization (SFCC). Drug and co-former were gravimetrically fed into a heated co-rotating twin screw extruder to form cocrystals. Real-time process monitoring was performed using a high temperature NIR probe in the extruder die to assess cocrystal content and subsequently compared to off-line powder X-ray diffraction measurements. The effect of processing variables, such as temperature and mixing intensity, on the extent of cocrystal formation was investigated. NIR spectroscopy was sensitive to cocrystal formation with the appearance of new peaks and peak shifts, particularly in the 4800–5200 cm^{-1} wave-number region. PXRD confirmed an increased conversion of the mixture into cocrystal with increase in barrel temperature and screw mixing intensity. A decrease in screw rotation speed also provided improved cocrystal yield due to the material experiencing longer residence times within the process. A partial least squares analysis in this region of NIR spectrum correlated well with PXRD data, providing a best fit with cocrystal conversion when a limited range of process conditions were considered, for example a single set temperature. The study suggests that NIR spectroscopy could be used to monitor cocrystal purity on an industrial scale using this continuous, solvent-free process.

1. Introduction

Pharmaceutical cocrystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, where one of the constituents is an active pharmaceutical ingredient (API) (Schultheiss and Newman, 2009). Interest in cocrystals for pharmaceutical applications has increased dramatically in recent years, reflected by increasing numbers of patent registrations, journal publications and entries into the Cambridge Structural Database (Schultheiss and Newman, 2009; Childs and Zaworotko, 2009; Blagden et al., 2008). Chemistry of cocrystals has been investigated by many groups over the last decade demonstrating their advantages in improving dissolution rate, stability and processing properties. Our group reported a SFCC process which involves cocrystallization and simultaneous agglomeration in a twin screw extruder at temperatures near the melting point of lower melting component or the eutectic temperature (Dhumal et al., 2010; Paradkar et al., 2010). This technology offers advantages in terms of scalability, freedom from solvent, processing time, higher conversion and agglomeration over existing techniques such as solution crystallization (Chiarella et al., 2007), sonocrystallization (Aher et al., 2010, 2011; Paradkar and Dhumal, 2011), grinding (Trask et al., 2006) and Kofler melt (Berry et al., 2008).

The FDA now encourages process innovation in the pharmaceutical industry through better process understanding which is achieved by adopting quality by design (QbD) and process analytical technology (PAT) (CDER guideline). As a result, the pharmaceutical industry is working together with equipment manufacturers, analytical science experts and process engineers to enable existing as well as new processes with process analytics capability. Process analysers are an important component of the PAT framework. Different PAT analysers are employed in the area of crystallization (Yu et al., 2004). UV–visible, NIR and Raman spectroscopic techniques have been used for monitoring the percentage of API in the polymer melts (Wang et al., 2008; De Beer et al., 2011; Saerens et al., 2011). In SFCC, the generation of a new cocrystal phase is to be monitored. The objective of this work is to PAT enable SFCC technology. Challenges include a large number of process variables such as extruder screw rotation speed, screw geometry, processing temperature and feed rate, all of which can significantly influence the product quality and conditions encountered during extrusion. Therefore it is essential to carefully select the mode of process analytics in order to understand the effect of such variables

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on the quality of product, particularly with respect to the extent of conversion into cocrystal.

Fourier transform infrared spectroscopy has been used to measure cocrystal concentrations from solution and solid state (Yu et al., 2010; Maheshwari et al., 2009). DSC and hot-stage polarized microscopy have been used as techniques for studying and screening cocrystals; cocrystal formation of carbamazepine and nicotinamide from the amorphous state were studied using these complementary techniques (Seefeldt et al., 2007). Two distinct crystallization pathways were discovered, dependent upon the heating rate employed. Berry et al. (2008) used hot stage polarized microscopy to screen cocrystals of nicotinamide and found the method to form cocrystals more readily than unseeded solution crystallization. Raman spectroscopy has been reported as an alternative cocrystal characterisation technique which probes the effect of crystal structure on bond vibrations (Peterson et al., 2002; Hilfiker et al., 2003). This is a non-invasive and rapid measurement technique which can also be used for high throughput screening. Allesø et al. (2008) compared near infrared spectroscopy and Raman spectroscopy as a screening method for cocrystals using model cocrystal compounds of indomethacin. Principal component analysis showed NIR spectra of cocrystal forms to differ from that of physical mixtures of the components. The low selectivity of NIR was found to compromise screening efficiency whenever polymorphic APIs were employed, although NIR has also been reported as a reliable technique for polymorph screening (Aaltonen et al., 2003, 2007).

The aim of the current work was to investigate the ability of near infrared spectroscopy to monitor the formation of cocrystals produced continuously during twin screw extrusion. The ability to monitor and potentially control the purity of cocrystals in real-time would represent a highly useful process which would align well with the current regulatory drive towards continuous monitoring and real-time quality control. Ibuprofen and nicotinamide were used as a model cocrystal system in these experiments to study the effect of set processing conditions. Results were correlated with off-line evaluation of purity from PXRD.

2. Materials and methods

2.1. Materials

Ibuprofen was purchased from Jay Radhe Sales (Ahmedabad, India) and nicotinamide from Sigma Aldrich. All other solvents and chemicals were of analytical grade.

2.2. Cocrystallization in hot melt extrusion

Cocrystallization of ibuprofen and nicotinamide in 1:1 molar ratio (1.68:1 mass ratio) was carried out in a co-rotating twin screw extruder (Pharmalab, ThermoScientific, UK) with screw diameter 16 mm and length-to-diameter ratio 40:1. Ibuprofen and nicotinamide were mixed (in 0.2 kg batches) in a turbula mixer for 10 min before feeding at a rate of 0.2 kg/h through a gravimetric twin screw feeder (Brabender, Germany). The extruder was operated without a die and the product was collected directly on exiting the extruder screws. Extruder torque was monitored continuously during extrusion.

2.2.1. Effect of variables

A range of batches were produced to study the effect of temperature profiles (T80 and T90, as shown in Table 1), screw speeds (20, 30 and 40 rpm) and three different screw configurations (detailed in Dhumal et al., 2010) on the conversion of ibuprofen into cocrystal. The process has been described more fully in previous reports (Dhumal et al., 2010; Paradkar et al., 2010).

Fig. 1. Pharmalab HME16 extruder equipped with NIR probe connected to the Antaris II NIR spectrometer.

2.2.2. X-ray powder diffraction (XRPD)

Crystallinity of extruded material was assessed by X-ray powder diffraction using a Bruker D8 diffractometer (wavelength of X-rays 0.154 nm Cu source, voltage 40 kV, and filament emission 40 mA). Samples were scanned from 2° to 30° (2θ) using a 0.01° step width and a 1 s time count. The receiving slit was 1° and the scattering slit was 0.2°.

2.2.3. Off-line NIR spectroscopy

In addition to real-time measurements made at the end of the extruder barrel, for selected experimental conditions NIR spectra were also taken at several points along the length of the extruder screws to examine the dynamics of cocrystal formation. This was achieved by abruptly stopping the extruder screw rotation, removing the upper half of the extruder barrel and manually placing the NIR probe on static material located between the screw flights (taking approximately 300 s to complete). Off-line NIR spectra were also taken for ibuprofen (crystalline form), nicotinamide and ibuprofen:nicotinamide physical mixture in a 1:1 molar ratio.

2.2.4. In-line NIR spectroscopy

Near infrared spectrometry was performed during extrusion using an Antaris II NIR spectrometer (Thermo Scientific, UK). A high temperature probe with a sapphire window was fitted into a threaded port at the end of the extruder barrel, flush mounted so that the tip of the sensor was in contact with the extruded material. The probe was connected to the spectrometer via fibre optic cables as shown in Fig. 1. Each sample reading averaged 32 individual spectra at a resolution of 8 cm^{-1}, scanned over the region of 4000–10,000 cm^{-1} wave-numbers (2500–1000 nm wavelength) using Thermo Scientific RESULT software. Measured spectra were then stored for subsequent analysis.

3. Results and discussion

The extrusion trials were carried out to study the effect of variables including set temperature, extruder screw speed and screw configuration. In-line NIR measurements were performed and the extruded product was characterized by XRPD to measure conversion into cocrystal. The XRPD patterns of ibuprofen, physical mixture (PM) and cocrystal are shown in Fig. 2. The 2θ peak at 6.1 is characteristic of ibuprofen, while the peak at 3.1 is characteristic of the cocrystal. The ratio of 2θ peaks at 3.1 and 6.1

Table 1
Temperature profiles across the different zones of the extruder barrel.

Code	Temperature (°C)								
	Zone 10	Zone 9	Zone 8	Zone 7	Zone 6	Zone 5	Zone 4	Zone 3	Zone 2
T80	70	80	80	80	75	70	50	40	25
T90	80	80	90	90	80	75	50	40	25

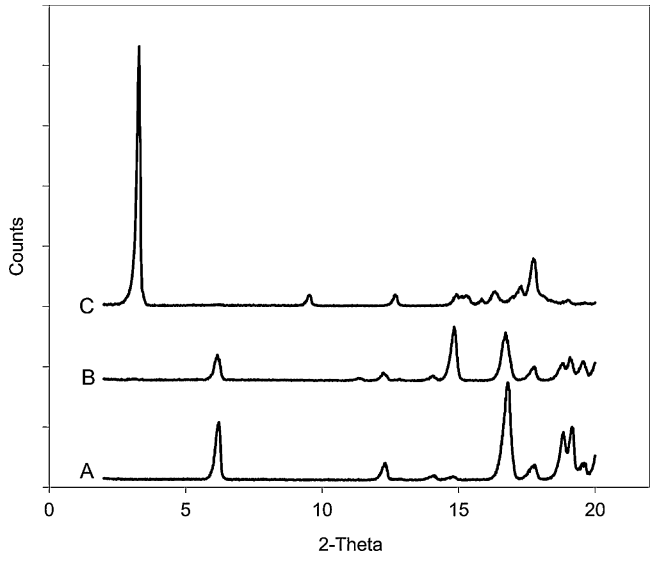

Fig. 2. PXRD patterns of ibuprofen (A), physical mixture of ibuprofen and nicotinamide (B) compared to extruded cocrystals (C).

was used as an indicator of ibuprofen conversion to cocrystal. XRPD has been used to determine relative levels of conversion into cocrystals (Ibrahim et al., 2011) and polymorphs (Kaneniwa and Otsuka, 1985). The results of our previous studies indicated that increase in temperature and reduction in screw speed was found to improve conversion of ibuprofen to cocrystals and reduce the amount of residual ibuprofen. Shear intensity was found to play a significant role with higher shear showing greatest conversion rates, as manipulated by changing the screw configuration. A summary of these effects on cocrystal purity is shown in Fig. 3 and has been discussed in more detail previously (Dhumal et al., 2010; Paradkar et al., 2010). Cocrystal purity was found to range from 20 to 99% depending on set extrusion conditions. Highest conversion was achieved at a set temperature of 90 °C with a high mixing intensity screw configuration and a low screw rotation speed to provide high process residence time.

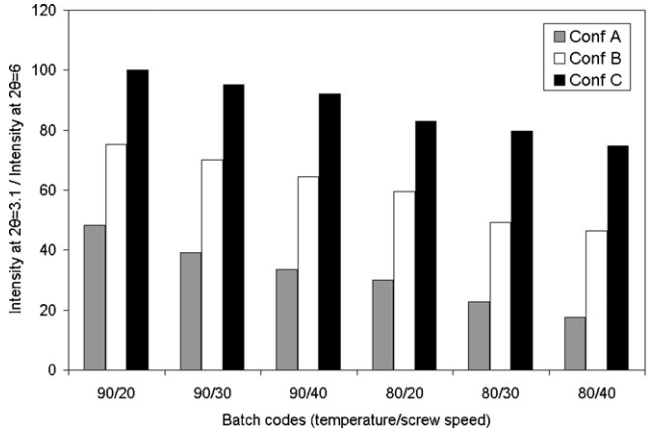

Fig. 3. Ratio of PXRD cocrystal peak to residual ibuprofen peak for extruded cocrystals.

3.1. Off-line NIR spectroscopy

NIR spectra of ibuprofen, nicotinamide, physical mixture and cocrystal were measured off-line so as to determine the characteristic peaks attributable to the cocrystal. The cocrystals used for this purpose were obtained using the SFCC conditions (90 °C, 20 rpm, high intensity mixing) causing maximum conversion as per our previous report (Dhumal et al., 2010; Paradkar et al., 2010). These NIR absorbance spectra are displayed in Fig. 4. Significant differences between the spectra of ibuprofen and nicotinamide were observed in a number of regions. The spectra of the physical mixture resembled an addition of the two individual components. Second derivatives of the NIR spectra of the two co-formers and their physical mixture are shown in Fig. 5, in the range between 4700 and 5200 wave-numbers. The spectra obtained for the physical mixture was found to consist of a combination of the drug and co-former spectrum. Fig. 6 compares the second derivatives of the physical mixture with extruded cocrystal. Cocrystals showed significant differences to the physical mixture. The second derivative peaks in the physical mixture at 5045, 4975, 4855 and 4764 cm^{-1} exhibited a frequency shift towards higher wave-numbers. These changes in the spectrum could be attributed to the hydrogen bonding involved in cocrystal formation between ibuprofen and nicotinamide. Fig. 7 shows the acid and amide end groups of ibuprofen and nicotinamide, which take part in hydrogen bonding during the cocrystallization process and shift the frequency at which these groups absorb. The 5045, 4975 and 4855 cm^{-1} peaks are due to N—H and N—H/C=O absorptions from the nicotinamide. The 4764 cm^{-1} peak is due to the O—H/C=O absorption from the ibuprofen. Once bonded together, the vibrations are modified and the peaks shift. This gives rise to the appearance of new peaks observed at 5083, 5018, 4873 and 4800 cm^{-1}.

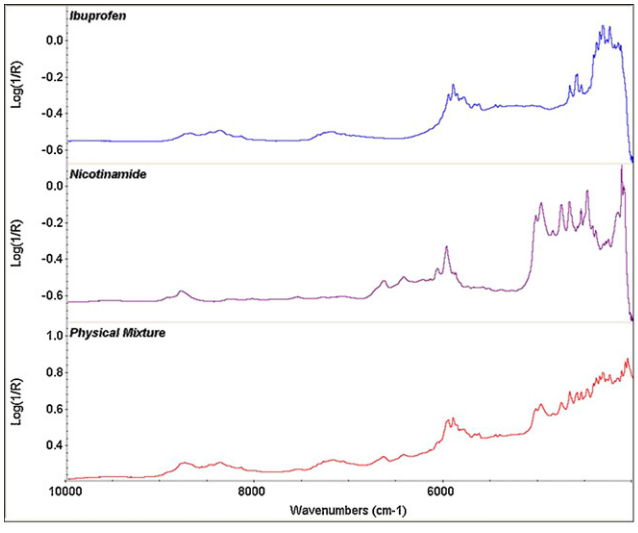

Fig. 4. NIR spectra showing ibuprofen, nicotinamide and a physical mixture of ibuprofen–nicotinamide.

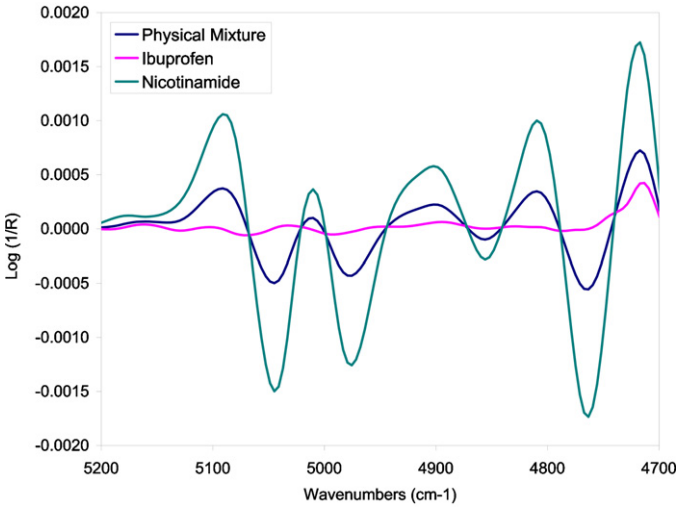

Fig. 5. Second derivatives of NIR spectra for ibuprofen, nicotinamide and physical mixture of ibuprofen nicotinamide measured off-line.

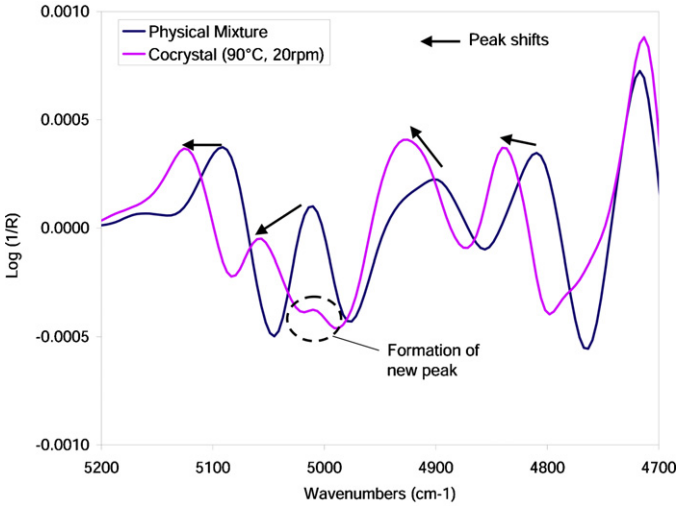

Fig. 6. Second derivative of NIR spectra between 4700 and 5200 wave-numbers; physical mixture and extruded cocrystal.

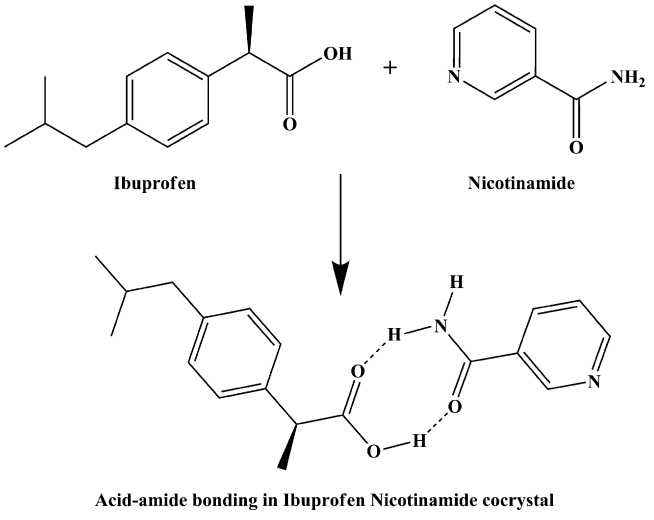

Fig. 7. Chemical structure of ibuprofen and nicotinamide; and typical cocrystal bonding.

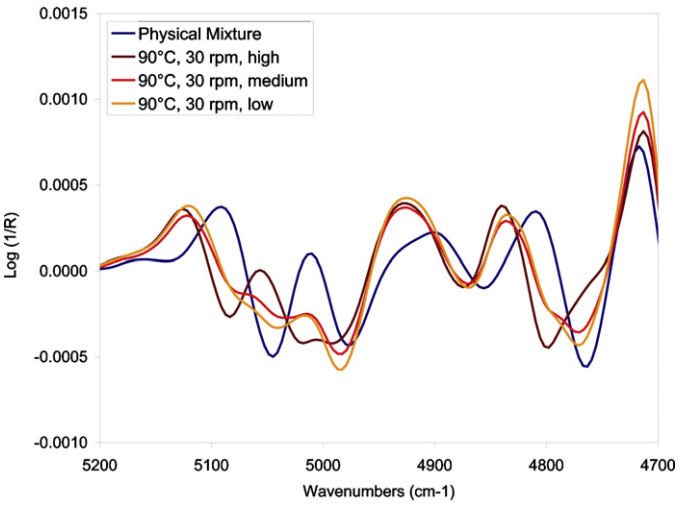

Fig. 8. Second derivative of NIR spectra between 4700 and 5200 wave-numbers; effect of screw configuration at 90 °C and 30 rpm screw rotation speed.

3.2. *Effect of process variables on the cocrystal purity by NIR*

The effect of extruder screw intensity on measured NIR spectra is shown in Fig. 8, at a set temperature of 90 °C and extruder screw speed 30 rpm. All measured in-process spectra showed characteristic peak shifts from the physical mixture at room temperature, in the regions described above. The high intensity screw configuration produced the most significant deviation from the spectra of the physical mixture, particularly between wave-numbers of 4980 and 5100, correlating the PXRD results showing screw configuration to significantly affect cocrystal purity. This provides confidence that NIR could be useful to detect levels of cocrystal content during processing. The effect of set extruder barrel temperature is shown in Fig. 9. Similar changes in spectra were produced by increasing temperature at a set temperature of 90 °C and extruder screw speed 30 rpm as were observed with increasing mixing intensity of the screw configuration. More pronounced deviation from the physical mixture spectra were observed at 90 °C around the 4980–5100 wave-number region. The effect of extruder screw speed at a set temperature of 90 °C and extruder screw speed 30 rpm on measured NIR spectra is displayed in Fig. 10. Relatively small changes

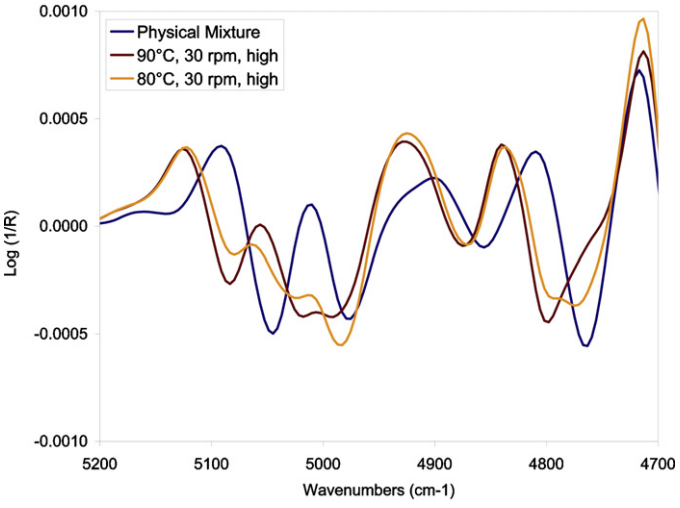

Fig. 9. Second derivative of NIR spectra between 4700 and 5200 wave-numbers; effect of set barrel temperature at 30 rpm screw speed, high intensity screw configuration.

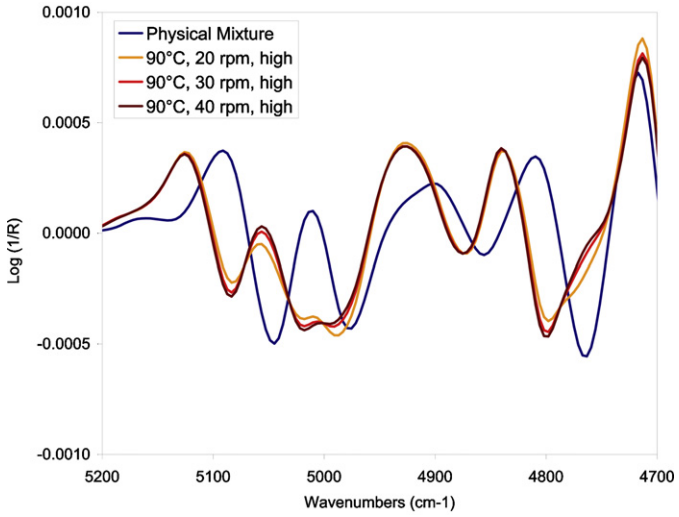

Fig. 10. Second derivative of NIR spectra between 4700 and 5200 wave-numbers; effect of screw speed at 90 °C, high intensity screw configuration.

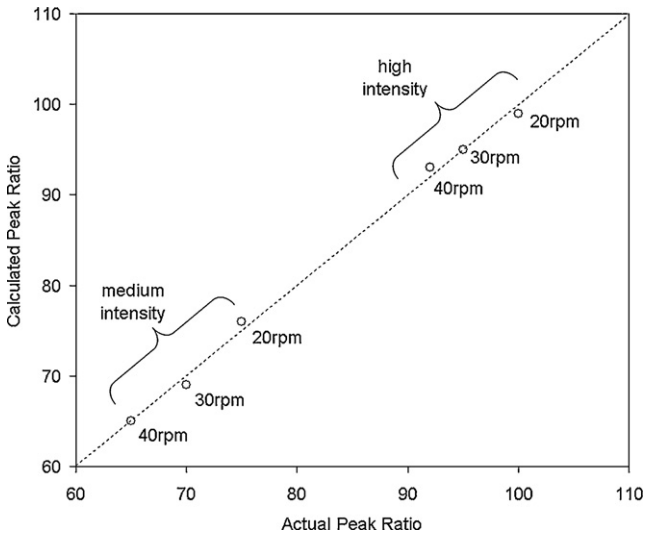

Fig. 12. Partial least squares calibration of NIR spectra (4959–5080 wave-numbers) for medium and high intensity screw configurations at 90 °C against measured PXRD cocrystal:ibuprofen peak ratio (correlation coefficient 0.999).

were observed in these spectra for 90 °C using the high intensity screw configuration. These results reflect the findings from PXRD which showed only a purity increase from 92 to over 99% as screw speed decreased from 40 to 20 rpm at 90 °C.

Fig. 11 shows the results of a partial least squares regression analysis of the NIR spectra for all extruded samples using the wave-number range 4959–5080 cm^{-1} which appeared to be the region most sensitive to cocrystal formation. In-line NIR spectra were calibrated against cocrystal purity measured by the PXRD peak ratio method described earlier. From this figure it can be seen that a reasonable correlation was observed between the measured and predicted purity (correlation coefficient 0.903) and that datasets from the three screw configurations were grouped together. However, this method failed to correlate the effect of different extruder screw rotation speeds adequately, and the sizable zero offset displayed in Fig. 11 suggested that the model was not optimized. Temperature is a well known factor that changes absorptions in the NIR region, so it was expected that calibrations over multiple temperature configurations would not give accurate results. The same partial least squares analysis was repeated using a smaller dataset, including only spectra obtained at a set temperature of 90 °C with medium and high screw intensity screw configurations. Results from this analysis are displayed in Fig. 12. A significantly better correlation between measured and predicted purity was achieved, producing a correlation coefficient of 0.999. These results suggest that the NIR method could effectively be used as a real-time monitoring tool to measure cocrystal purity during twin screw extrusion, providing that a careful calibration was first performed and that processing parameters were not varied excessively (e.g. change in set temperature or screw configuration). In practice, once an industrial process is set up it is likely that the set process conditions would be maintained at constant levels, for each product. This in-process application of NIR fits in well with the FDA's process analytical techniques (PATs) and quality by design (QbD) initiatives (ICH, Q8 guideline).

3.3. Progression of cocrystal formation

In order to understand the process of cocrystal formation in the extruder the material was sampled at different points along the

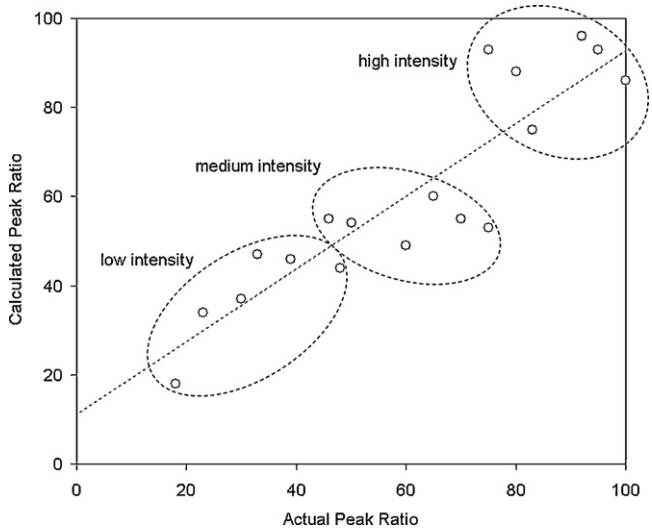

Fig. 11. Partial least squares calibration of NIR spectra (4959–5080 wave-numbers) for all extrusion variables against measured PXRD cocrystal:ibuprofen peak ratio (correlation coefficient 0.903).

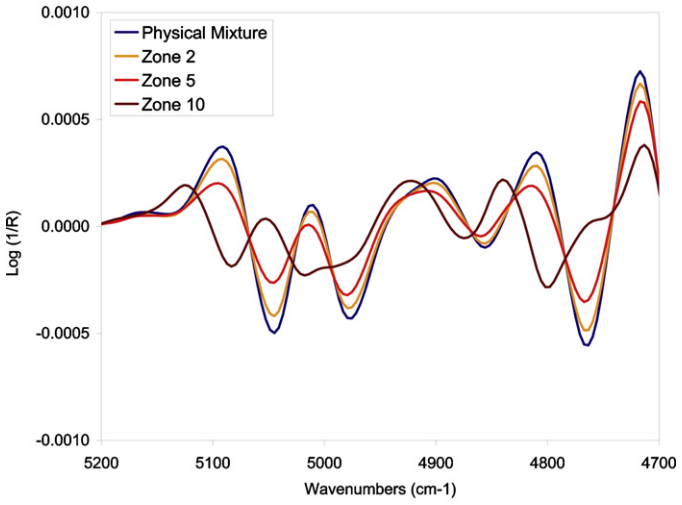

Fig. 13. Second derivative of NIR spectra between 4700 and 5200 wave-numbers; samples taken along the extruder barrel: close to the feed port (zone 2), midway (zone 5) and close to the exit of the screws (zone 10).

extruder barrel and NIR data was collected off-line. The data indicated that cocrystal formation occurred predominantly in the latter stages of the extruder screw, between zones 5 and 10 (Fig. 13). The characteristic peak shifts were not apparent in measurements made at extruder zones 2 and 5. This suggests that cocrystal formation is highly dependent on the length of extruder screws, residence time inside the process and the shear exhibited by the mixing elements across length of the barrel. Mounting multiple NIR sensors along the length of the barrel could represent a useful design in understanding and further studying the process of cocrystal formation in the extrusion. Further studies on this cocrystallization process are underway to quantify the dynamics of cocrystal formation using in-process NIR and Raman spectroscopy.

4. Conclusions

Twin screw extrusion was used to produce cocrystals of ibuprofen and nicotinamide in a continuous manner. Cocrystal purity was calculated from off-line PXRD and found to range from 20 to 99%, dependent upon set extrusion conditions. Cocrystal purity was shown to depend upon screw configuration, extrusion temperature and screw rotation speed; lowest speeds and hence highest residence time resulted in highest cocrystal content at the highest processing temperature with most intensive mixing screw. NIR spectroscopy using a high temperature probe placed in the extruder barrel was shown to detect cocrystal formation. Measured cocrystal purity from PXRD was used to calibrate NIR measurements using a partial least squares regression. A reasonable correlation was found between predicted and measured cocrystal purity for all extruded samples, which improved significantly when a less expansive set of extrusion conditions were included. The results highlight the potential for NIR as a real-time technique to monitor cocrystal formation during twin screw extrusion.

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