The Use of Transmission FT-NIR Analysis for the simultaneous analysis of Carbamazepine and PEG 2000 in Extrudates

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Drug Solubility, Near-infrared, Pharmaceutical Extrusion, Process Analytics

Introduction

Extrusion is a continuous manufacturing process which is used in the pharmaceutical industry to generate amorphous solid dispersions of poorly soluble drugs in polymer matrices. Many drugs exhibit poor solubility and as a result cannot readily be incorporated into a suitable oral delivery form. A number of approaches are available to improve drug solubility, including intimate mixing within a soluble polymer matrix. Twin screw extrusion is a highly efficient mixing process, whereby the polymer is gradually melted by the action of rotating screws. Depending upon the drug, polymer properties and applied process conditions, the cooled solid can take the form of a solid solution or solid dispersion. Typically the desired form of the drug is in an amorphous state.

Pharmaceutical extrusion is carried out at lower temperatures than conventional polymer processing because of the thermally sensitive nature of many drugs. Plasticizers are often added to the drug/polymer formulation to lower the extrusion temperature and improve processability. Careful choice of excipients and selection of processing conditions are necessary in order to produce a compound with optimized properties without inducing drug degradation.

There is an increasing drive in the pharmaceutical industry towards continuous processing and process analytical testing (PAT). Extrusion is well suited to process analytics; near-infrared (NIR) and Raman spectroscopy techniques have been applied to pharmaceutical extrusion, typically using high temperature sensors attached to the extruder die. However, many pharmaceutical polymer systems are transparent in the melt state and therefore cannot be measured by reflectance based techniques. The aim of this study was to apply transmission NIR spectroscopy to the extrusion of a transparent formulation consisting of a drug, polymer and plasticizer, in order to quantify both drug and plasticizer content.

Figure 1: The Antaris II MDS analyzer has the capability to collect in diffuse reflectance, transmission, and with the use of fiber optics

Figure 2: Powdered samples of each component were collected in the diffuse reflectance mode

Experimental

The extruder used for these experiments was a Thermo Scientific™ PRISM Pharmalab 16 HME twin screw extruder. It was run at 120 °C with a flow rate of 300 g/hr and a screw speed of 50 rpm.

The polymer used for the trials was Kollidon® VA64 and carbamazepine (CBZ) was used as a typical active pharmaceutical ingredient (API). PEG 2000 was also incorporated as a typical plasticizer. Various mixes of these three components were prepared ranging from 5–20% CBZ and 5–25% PEG 2000. Ten mixtures were used as a calibration set and two mixtures were run as validation samples.

FT-NIR spectra were recorded with a Thermo Scientific™ Antaris™ II Method Development System (MDS) instrument, see Figures 1 and 2.

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The powdered ingredients were scanned in disposable glass vials with the integrating sphere module. The extrudate was scanned using transmission extruder probes set in a custom made die using a path length of 2 mm. The implementation of the probes in the die is shown in Figures 3 and 4.

Figure 3: Extruder with transmission probes attached

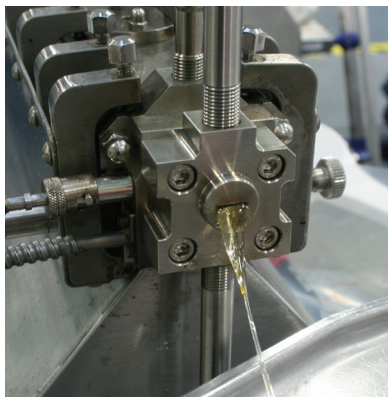

Figure 4: Close-up of the transmission die with probes

The operating conditions for the spectrometer were: scan range 4000–10,000 cm^{-1}, resolution 8 cm^{-1} and 32 scans averaged per sample. This resulted in a scan time of approximately 16 seconds per sample. The powder samples were run in off line mode as single samples. When collecting data from the extruder, the system was run in continuous mode, recording spectra every 30 seconds. The Thermo Scientific™ RESULT™ software was used to run the instrument and collect spectra, and Thermo Scientific™ TQ Analyst™ software was used to compute the calibration models.

Results

The NIR spectra of the three ingredients are shown in Figure 5. The spectra were converted to second derivative, see Figure 6.

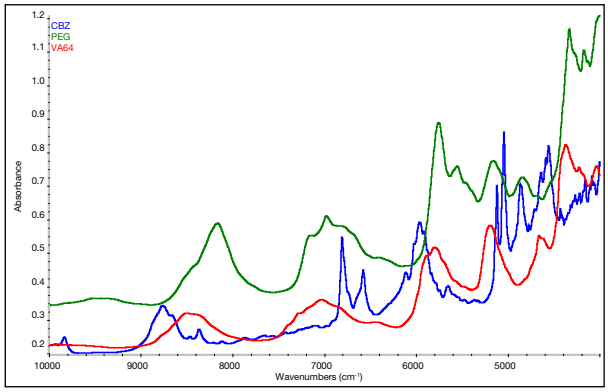

Figure 5: Pure Component spectra of Carbamazepine (blue), PEG 2000 (green) and Kollidon VA64 (red)

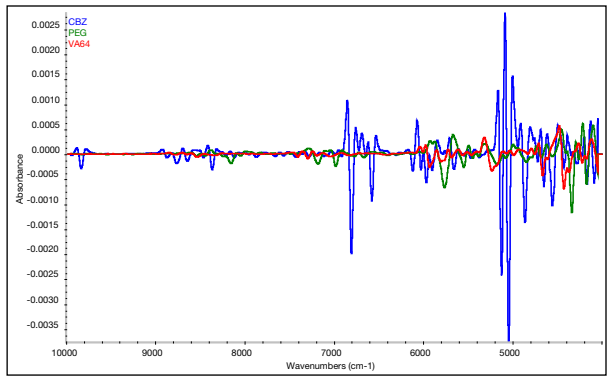

Figure 6: Second derivative spectra of CBZ (blue), PEG 2000 (green) and Kollidon VA64 (red)

Very strong peaks could be seen for CBZ and 5064 cm^{-1} was chosen as a good peak to monitor as there was little interference from the other components. PEG exhibited weaker peaks, but 5912 cm^{-1} proved a suitable place to monitor this component for this feasibility study, see Figure 7. However, there was still interference on this peak, so a more reliable calibration using partial least squares (PLS) regression and more samples, would improve the measurements.

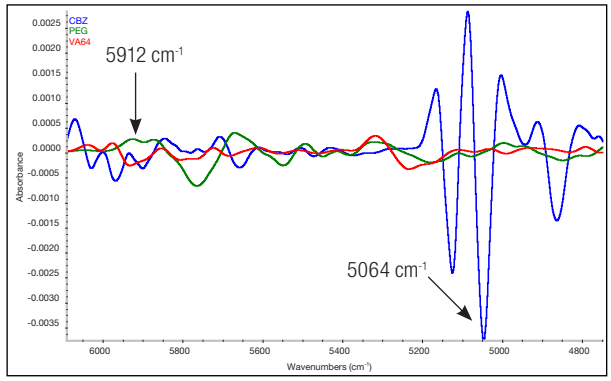

Figure 7: Peaks monitored during the extrusion process were 5064 cm^{-1} for CBZ and 5912 cm^{-1} for PEG 2000

Some representative spectra collected at the exit die of the extruder are shown in Figure 8. These spectra show samples with 5–20% CBZ with the PEG level constant at 10%. The melt became cloudy with 20% CBZ concentrations as the API was not fully dissolved in the polymer. This led to the spectra becoming quite noisy and an increasing shift in the baseline.

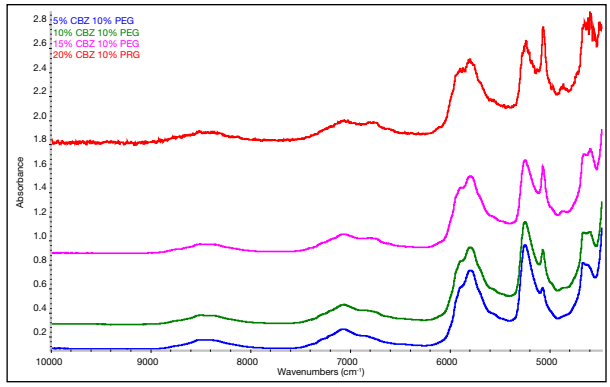

Figure 8: Transmission spectra of 5–20% CBZ with PEG 2000 held constant

The spectra were converted to second derivative to improve peak shape and to minimize the baseline shifts, see Figure 9. A clear increase in peak amplitude with CBZ concentration can be seen at 5064 cm^{-1}, corresponding to the peak highlighted from the pure spectra.

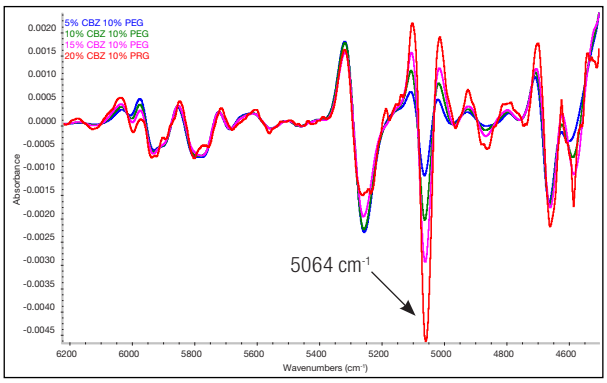

Figure 9: Second derivative spectra of 5–20% CBZ with PEG 2000 held constant

Figure 10 shows another set of extrudate spectra, this time with variance in the PEG concentration, 2.5–15%, and the CBZ concentration constant. Figure 11 shows the second derivative spectra.

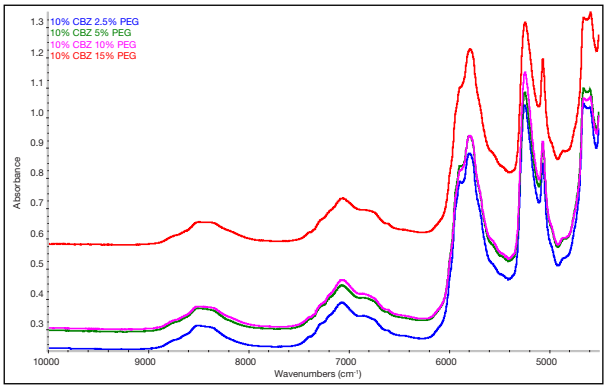

Figure 10: Absorbance spectra of 2.5–15% PEG with CBZ held constant

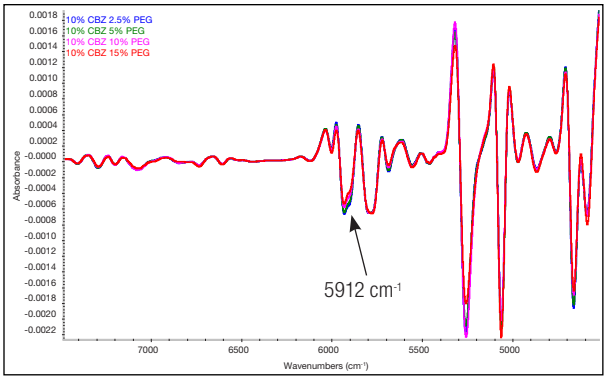

Figure 11: Second derivative spectra of 2.5–15% PEG with CBZ held constant

The progression in the PEG was convoluted by the other components as the PEG had overlapping absorptions with the other two components; but a change in peak height could be seen.

A single wavenumber multiple linear calibration was computed using the individual absorptions for each component highlighted previously. Figures 12 and 13 show the regression results. Excellent results were obtained for CBZ with a correlation coefficient of 0.99 and a reasonable calibration error of 0.48%. A good calibration was achieved for PEG, with a correlation of 0.97 and calibration error of 0.82%. There was a great deal of variability on the 10% PEG samples. This was mainly due to the sample that contained 20% CBZ and the noise in the spectra associated with that reading due to the melt being cloudy.

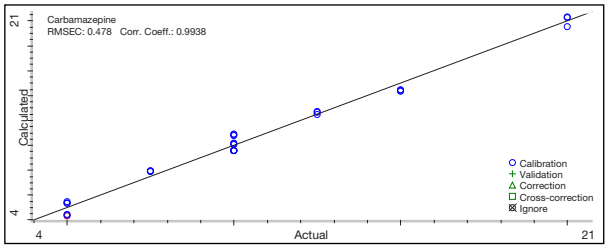

Figure 12: CBZ calibration

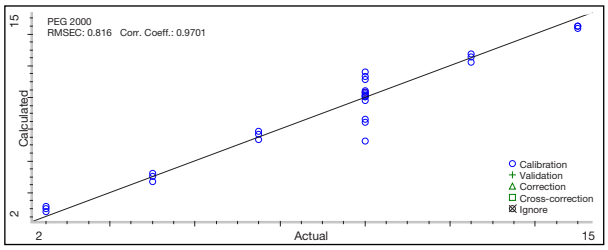

Figure 13: PEG 2000 calibration

These calibrations were then added into the RESULT workflow and used to predict two unknown extrudates in real time. Figure 14 shows the output for 7.5% CBZ/10% PEG batch. The previous run contained 12.5% CBZ and 10% PEG. The plot shows that 7 readings were taken (3.5 minutes) before the change in concentration reached the exit die. The final reading (another 11 minutes) had dropped to 8% before the sample ran out, but the trend was still downward. The results was within 0.5% of the nominal value however, which was within the calibration error. Under these extruder conditions, the melt composition had not stabilized after 14 minutes, but the trend was followed well. The PEG plot was more variable which was expected due to the higher variability in the calibration results. The reading was starting to settle back to the target value when the sample ran out. The final reading was 8.7%, but with a calibration error of 0.8%, this was quite close to the target value.

Figure 15 shows the results for the 15% CBZ/5% PEG batch. The previous batch contained 5% CBZ and 12.5% PEG, so the plot shows a nice trend changing from the low to high CBZ concentration. This batch ran for 18 minutes, and again, the concentration readings had not fully stabilized. The final value predicted of 15.9% was within the calibration error of the target value of 15.5%. The PEG values dropped from the initial values of 13% from the last batch down to around 6% at the end; close to the target value of 5%. There seemed to be some perturbation in the last six readings, presumably as the final change in concentration was coming through the extruder.

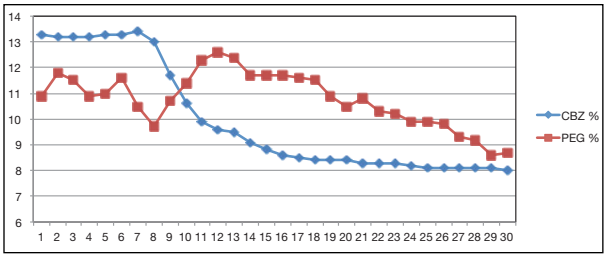

Figure 14: Stabilization of melt composition for CBZ (blue) and PEG 2000 (red)

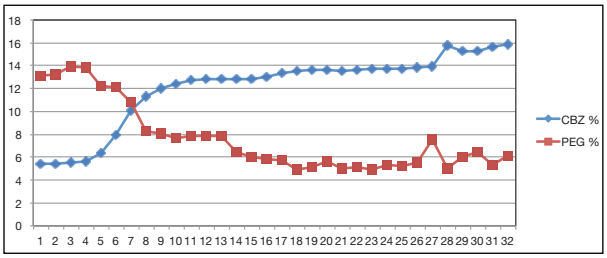

Figure 15: Stabilization of melt composition for CBZ (blue) and PEG 2000 (red)

Conclusions

FT-NIR spectroscopy has been successfully applied to the characterization of clear extrudates using transmission probes located in the extruder die. This study has demonstrated the feasibility of monitoring levels of two components simultaneously and in real-time, the API and plasticizer. Here, due to the limited number of calibration samples available, a simple one wavenumber calibration was applied to the data set. A greater number of samples would enable more robust calibrations to be performed by reducing the interference from overlapping absorptions using PLS regression.

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