A Novel Transflectance Near Infrared Spectroscopy Technique for Monitoring Hot Melt Extrusion

A L Kelly[1*], S A Halsey[2], R A Bottom[2], S Korde[1], T Gough[1], A Paradkar[1]

[1] Centre for Pharmaceutical Engineering Science, University of Bradford BD7 1DP, UK

[2] Thermo Fisher Scientific, Stafford House, Boundary Way, Hemel Hempstead HP2 7GE, UK

Corresponding Author:

Dr Adrian Kelly

Centre for Pharmaceutical Engineering Science,

University of Bradford, Bradford, BD7 1DP, UK

Tel: 00 44 1274 234532

Email: A.L.Kelly@Bradford.ac.uk

ABSTRACT

A transflectance near infra red (NIR) spectroscopy approach has been used to simultaneously measure drug and plasticiser content of polymer melts with varying opacity during hot melt extrusion. A high temperature reflectance NIR probe was mounted in the extruder die directly opposed to a highly reflective surface. Carbamazepine (CBZ) was used as a model drug, with polyvinyl pyrollidone-vinyl acetate co-polymer (PVP-VA) as a matrix and polyethylene glycol (PEG) as a plasticiser. The opacity of the molten extrudate varied from transparent at low CBZ loading to opaque at high CBZ loading. Particulate amorphous API and voids formed around these particles were found to cause the opacity. The extrusion process was monitored in real time using transflectance NIR; calibration and validation runs were performed using a wide range of drug and plasticiser loadings. Once calibrated, the technique was used to simultaneously track drug and plasticiser content during applied step changes in feedstock material. Rheological and thermal characterisations were used to help understand the morphology of extruded material. The study has shown that it is possible to use a single NIR spectroscopy technique to monitor opaque and transparent melts during HME, and to simultaneously monitor two distinct components within a formulation.

Keywords: Hot melt extrusion
Near infrared spectroscopy
Process analytical technology
Carbamazepine,
PVP-VA

1. INTRODUCTION

Hot Melt Extrusion (HME) is a continuous melt mixing process which can be used to generate amorphous drug forms in order to improve solubility. Typically, Active Pharmaceutical Ingredients (APIs) are dissolved or dispersed within a soluble polymer matrix (Crowley et al., 2007). Such approaches can be used to improve or control drug release and inhibit drug recrystallisation (Qi et al., 2008). HME generally refers to twin screw extrusion, which is a highly efficient mixing process whereby the polymer and additives are gradually melted by the action of rotating screws and heat transferred through the extruder barrel. Typically HME renders the drug amorphous, a state which can significantly enhance both drug solubility and bioavailability. The use of HME for manufacture of pharmaceuticals has been widely reported including applications such as pellets (Follonier et al., 1994), sustained release tablets (Tran et al., 2011; Crowley et al., 2004), implants (Bhardwaj and Blanchard, 1997) and transdermal films (Aitken-Nichol et al., 1996). A number of comprehensive reviews of the pharmaceutical HME process are available (Crowley et al., 2007; Repka et al., 2007; Repka et al., 2012).

During HME the API, polymer and other excipients are conveyed through a heated barrel by two closely intermeshing screws. The temperatures, mixing intensity and residence time to which the materials are subjected during the process can be varied by adjusting parameters such as set temperature, throughput, screw rotation speed and extruder screw configuration. Within the process the API and carriers experience high temperatures and levels of shear, which serve to melt the polymer and dissolve or disperse the API within the matrix. However, these harsh conditions can have adverse affects on many APIs, particularly those with thermolabile properties. Careful choice of excipients and optimisation of processing conditions are necessary in order to avoid degradation and produce a compound with the desired morphology and properties.

HME has the advantage of being a continuous process which means that following an initial start up and stabilisation period, a consistent output can be maintained indefinitely, providing that the input feed of materials is correctly maintained. Continuous processes are also well suited to in-line monitoring, or Process Analytical Technology (PAT). The FDA now encourages process innovation in the pharmaceutical industry through better process understanding achieved by adopting Quality by Design (QbD) and PAT (FDA Guidance for Industry, 2004). A range of techniques have been employed to monitor hot melt extrusion,

with spectroscopic measurements using high temperature probes most widely used (Saerens et al., 2013). Raman and near infra-red (NIR) spectroscopy techniques can provide qualitative and quantitative information about chemical and physical properties (De Beer et al., 2010). NIR spectroscopy is a rapid, non-destructive technique which refers to study of light absorption in the NIR region between 700-2500 nm and can be applied to the HME process (Wahl et al., 2013; Luypaert et al., 2007). The technique has been used to study melt extrusion of metoprolol tartrate at different loadings in a polyvinyl pyrollidone – polyvinyl acetate copolymer (Saerens et al., 2012). Results demonstrated that NIR could be used to monitor API concentration and polymer-drug inter-molecular interactions. NIR has also been successfully used to monitor extrusion co-crystallisation (Kelly et al., 2012; Moradiya et al., 2014a; Moradiya et al., 2014b). The use of Raman spectroscopy as a PAT tool for melt extrusion has also been reported, during extrusion of metoprolol tartrate and Eudragit, a commercial acrylic copolymer (Saerens et al., 2011). Raman and NIR spectroscopy have been used as complementary techniques to during HME of metoprolol tartrate with blends of polyethylene oxide and ethylene vinyl acetate (Almeida et al., 2012). Analysis of the spectroscopic data provided an improved understanding of the effects of process settings on the solid state of the API.

A limitation of NIR spectroscopy in HME applications is that molten API/polymer systems can exhibit varying levels of reflectivity. Extrudates may range between clear and opaque depending upon API concentration and set temperature. In such cases a single design of probe type, reflectance or transmission, may not be used to collect spectra for all melt types. Reflectance probes can only gather spectra from cloudy or opaque melts and transmission probes are only suitable for clear melts. The aim of the current work was to apply a novel transflectance measurement technique to characterise a range of melts with varying levels of reflectivity. The design of the measurement system is described and a case study used to demonstrate the application of the technique to simultaneously measure two components during HME.

2. MATERIALS AND METHODS

2.1 Materials

Carbamazepine (CBZ) was used as a model API, procured from Jai Radhe Sales India. This is an anticonvulsant and mood stabilising drug which has a molecular weight of 236 g/mol

and a melting temperature of 190°C. Polyvinyl pyrrolidone-vinyl acetate (PVP-VA) copolymer (Kollidon® VA 64) was used as a matrix polymer, supplied by BASF, Germany. This has a molecular weight of 45,000 – 70,000 g/mol, a glass transition temperature (Tg) of 101°C and a degradation temperature of 230°C. Polyethylene glycol (PEG) PEG2000 was used as a plasticiser, procured from Sigma Aldrich. This had a molecular weight of 2000 g/mol and a melting point of 50-53°C and was used to lower the viscosity of the materials to facilitate extrusion. PEG was introduced into the formulation to enable melt extrusion at a suitable temperature; CBZ alone added to PVP-VA was not found to provide sufficient levels of plasticisation. Physical mixtures of polymer, API and plasticiser were accurately weighed and mixed in a mortar and pestle prior to extrusion.

2.2 Methods

2.2.1 Hot Melt Extrusion

Extrusion was performed using a co-rotating twin screw pharmaceutical grade extruder (Pharmalab, Thermo Scientific, UK) with screw diameter 16mm and a screw length to diameter ratio of 40:1. The extruder barrel comprised 10 separately temperature controlled zones. Material feeding was achieved using a gravimetric twin screw feeder (Mini-twin, Brabender, Germany). A slit die was designed to fit onto the front of the extruder, housing two sensor probes, located directly opposite each other across the melt flow, across a 1mm gap (Figure 1). The transflectance measurement geometry comprised a high temperature reflectance NIR probe located in one port of the extruder die, and a stainless steel 'blank' sensor bolt with a polished tip located directly opposite the reflectance probe. This set up was designed such that opaque melts could be measured directly using the conventional reflectance probe whereas for transparent melts light passing through the melt would be reflected from the polished surface and be collected by the reflectance probe. Photographs of extrudates produced with different levels of CBZ and PEG are shown in Figure 2.

Physical mixtures of CBZ, PVP-VA and PEG were prepared by manually mixing the constituents between the ranges of 5.0 - 27.5 weight % CBZ and 5.0 – 20.0 weight % PEG, with the remainder of each composition being made up of PVP-VA. All extrusion experiments were performed at the same set temperatures, with temperature being profiled from 40°C at the feed end to 120°C at the extruder die as shown in table 1. Temperatures were selected following a series of initial extrusion trials at different set temperatures. The optimum set condition provided a good consistency of extrudate to be handled, whilst

generating a reasonable level of torque in the extruder drive. Blended physical mixtures were fed into the extruder at 360 g/hr and the extruder was operated at a screw rotation speed of 50 rpm.

2.2.2 Near Infrared Spectroscopy

NIR spectroscopy was performed using an Antaris II FT-NIR spectrometer (Thermo Scientific, UK). Off-line powdered ingredients were placed in clear glass vials and measured in reflectance mode using an integrating sphere. In-line measurements were made with a high temperature reflectance probe connected to the spectrometer using a fibre optic bundle. This probe was mounted in the extruder die as described above. For both off-line and in-line measurements, each sample reading averaged 32 individual spectra at a resolution of 8 cm^{-1}, scanned over the region of 4,000–10,000 cm^{-1}. The Thermo Scientific RESULT software was used to collect spectra. Off-line powder measurements were recorded singly and the in-line measurements were recorded continuously at the exit die. Data collection time was approximately 30 seconds per spectrum. Measured spectra were then stored for subsequent analysis with Thermo Scientific TQ Analyst software.

For each extrusion experiment, NIR spectra were collected in real time until the spectra were observed to stabilise. For the experimental conditions used, this took approximately 15-20 minutes. NIR spectra at stable conditions were then collected for a period of around 10 minutes before a new blend was introduced into the feeder and the process repeated. An experimental design was used to minimise the correlation, 0.14, between the components. In-line measurements on nineteen mixtures were used as a calibration set and four mixtures were analysed as validation samples.

2.2.3 Rheological Characterisation

Off-line rheological characterisation was carried out using a Physica MCR 501 rotational rheometer (Anton Paar, Austria) with parallel plate geometry of diameter 25mm. The gap between the two plates was set to 1 mm for all tests. Frequency sweeps were performed at a set temperature of 140°C and a constant strain of 3%; this value having been determined to be within the linear viscoelastic range by preceding strain amplitude tests. The angular frequency range tested was 0.1 - 100 s^{-1}. Samples were prepared by mixing the desired ratio of drug, polymer and plasticiser in a mortar and pestle before placing the powdered mixture

on to the heated lower plate of the rheometer. Approximately one minute was allowed for the material to soften prior to the upper plate being lowered to the desired gap width of 1mm and any excess material was removed. The effect of CBZ and PEG on the viscosity of the compound was quantified by examining physical mixtures containing a range of CBZ loadings between 7.5 and 20 wt% (with PEG fixed at 10 wt%) and a range of PEG loadings from 2.5 – 15 wt% (with CBZ fixed at 10 wt%).

2.2.4 Scanning Electron Microscopy (SEM)

Extruded samples were mounted on aluminium pin-stubs (Agar Scientific, Stansted, U.K.) using self adhesive carbon mounts (Agar Scientific). The mounted samples were examined using FEI Quanta 400 Scanning Electron Microscope (Cambridge, U.K.) in high vacuum operated at an acceleration voltage of 20 kV.

2.2.5 X-ray powder diffraction (XRPD)

The crystallinity of milled samples of extrudate and pure API were assessed by X-ray powder diffraction (XRPD) within 24 hours of extrusion, 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 scatter slit was 0.2°.

3. RESULTS AND DISCUSSION

3.1 Rheological Characterisation

Complex viscosity of physical mixtures containing varying levels of CBZ and PEG are displayed in Figure 3. PEG had a significant effect on melt viscosity over the range examined, with complex viscosity decreasing from 500 Pa.s at 2.5% PEG loading to 65 Pa.s at 15% PEG content. CBZ was observed to have a much less significant effect on melt viscosity, causing a relatively small decrease of 10% between 7.5 and 20% loading. These differences in flow behaviour were apparent during the extrusion experiments, as evidenced by extruder motor torque measurements shown in Figure 4. Motor torque reflects the levels of energy required to turn the extruder screws at the set rotation speed; these measurements were found to closely reflect the viscosity results show in Figure 3.

3.2 Structural Characterisation

X-ray diffractograms of extruded materials are compared to those of carbamazepine in figures 5a and 5b. The crystalline peaks evident in CBZ were not observed in any of the extruded compounds, even at a CBZ loading of 30 wt%. These results demonstrate that the crystalline CBZ was converted to an amorphous form during extrusion.

3.3. Morphological Characterisation

Scanning electron microscopy was performed on surfaces of extrudates in an attempt to understand the opaque nature of compounds with higher CBZ loadings. Figure 6 shows results from the fractured cross section (a) and outer surface (b) of an extruded strand containing 30% CBZ and 10% PEG. The polymer matrix (PVP-VA) being amorphous in nature is predominantly transparent. However, the presence of particulates with diameters in the range of 10-30 microns and a number of voids or bubbles are evident from these images. It is thought that amorphous particulates of API were formed during extrusion which led in some cases to voids forming around the particles. Due to the high melting temperature of the API (190 °C) a solid solution could not be formed during extrusion at higher API loadings. These particulates and voids explain the opaque appearance of the extrudates.

3.4. Near Infra-red spectroscopy

NIR spectra of the powdered feedstock materials were measured to determine the peaks of interest for both the CBZ and PEG, as shown in Figure 7. NIR spectra are typically broad and overlapping and are usually enhanced with a derivative mathematical treatment. A second derivative treatment was applied to these spectra, as shown in Figure 8. Strong and unique peaks could be seen for CBZ, but the PEG peaks were weaker and tended to overlap with the other two components. The 5600-6000 cm^{-1} region showed the most promise for the PEG measurement. For this reason, partial least squares (PLS) was selected for the regression method as this has been shown to have the ability to extract information from convoluted peaks (Faber and Kowalski, 1977).

Figure 9 shows the NIR spectra of some selected samples collected at the extruder exit die; the samples ranged from clear to opaque. It should be noted that the 4500-4000 cm^{-1} region was noisy due to energy losses along the fibre optic bundle. This region was left out of the calculations during method development. This figure also shows that the baseline of the spectra changed quite considerably with different sample compositions. This was due to the

samples having different scattering properties as samples varied widely in cloudiness. However, the use of the transflectance measurement technique allowed data to be collected for all sample types. During method development a derivative mathematical treatment minimised the effect of the change in baseline on the final measurements. The region chosen for regression was 6208-4754 cm^{-1} which incorporated peaks from both CBZ and PEG.

Figure 10 shows the change in the second derivative spectra for the CBZ concentration when the PEG was held constant. Several peaks were seen to increase in accordance with the CBZ concentration, the peak at 5064 cm^{-1} being particularly strong. Figure 11 shows the change in second derivative spectra for the PEG concentration when the CBZ was held constant. The 5600-6000 cm^{-1} region did exhibit some changes, but the PEG peaks were masked by the other components.

In-line measurements were used to calibrate the NIR instrument. Three or four spectra were used from each extrudate and the samples were split into calibration (66 samples) and validation (12 samples) sets. The results from the PLS regression are shown in Figure 12. Correlation coefficients of >0.99 were achieved between the NIR results and the weight data for CBZ measurements. Four factors were used for the CBZ calibration which gave good calibration (RMSEC) and validation (RMSEP) errors of 0.788% and 0.672% respectively. The PEG calibration was slightly less accurate with a calibration error of 0.633% and a validation error of 1.06%. The correlation coefficients dropped to 0.986 and 0.967 respectively. Six factors were required to achieve this calibration which was expected considering the PEG peaks were much less prominent than those for CBZ.

These calibrations were then used to monitor an extrudate in real time for both CBZ and PEG concentrations. A step change in the content of feedstock material was applied and calibrated NIR signals used to dynamically track these changes at the extruder die. CBZ level was changed from 22.5% to 16% and PEG loading from 9% to 11%. The concentrations of both components were measured simultaneously and plotted against time, as shown in Figure 13. A smooth transition can be seen from the two original concentrations to the two new concentrations; demonstrating that these measurements could be used for routine quality control of an extrudate. In addition, this data showed that it took approximately 15 minutes for the new batch of material to fully flush the previous sample through the extruder under these process conditions. However, it should be noted that these experiments were performed at relatively low throughput and screw rotation speed. Typical residence times in production are likely to be significantly lower.

4. CONCLUSIONS

A transflectance FT-NIR spectroscopy technique was developed for monitoring the hot melt extrusion process. A slit die was designed which enabled a reflectance NIR probe to be mounted directly opposite a highly polished surface, enabling measurements to be performed in both transmittance and reflectance modes. The technique was successfully applied to extrusion of carbamazepine in a polyvinyl pyrrolidone-vinyl acetate copolymer matrix with polyethylene glycol used as a plasticiser. At low API content the melt was transparent whereas at higher loadings it became opaque due to the presence of particulate API and voids which formed around these particles. Calibration of the NIR technique was performed using a wide range of API and plasticiser loadings. The calibrated technique was used to simultaneously monitor the loading of both API and plasticiser in real time, across transparent and opaque melt regions.

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Table I: Temperature profiles across the different zones of the extruder barrel (°C)

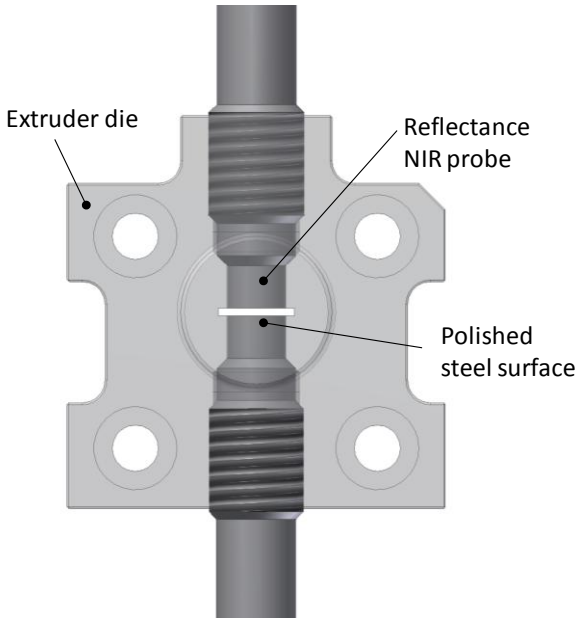
Zone 10	Zone 9	Zone 8	Zone 7	Zone 6	Zone 5	Zone 4	Zone 3	Zone 2	Zone 1
120	120	120	120	120	120	120	70	50	40

Table II: Formulation of batches used for PLS model calibration

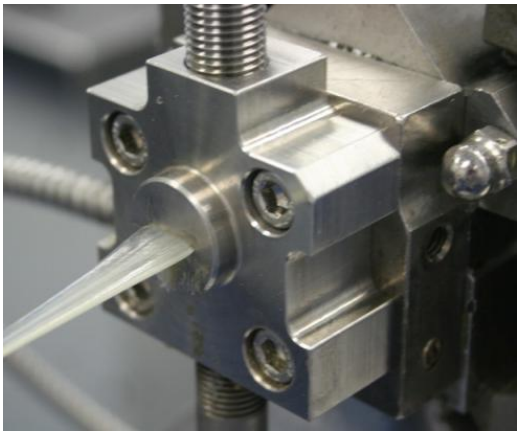
CBZ (%)	PEG (%)	PVP-VA (%)
5	10	85
6	14	80
7.5	12.5	80
8	7	85
10	10	80
11	13	76
12.5	7.5	80
15	10	75
14	8	78
18	12	70
20	10	70
20	5	75
20	15	65
20	20	60
20	7.5	72.5
21	18	61
25	10	65
27.5	17.5	55
30	10	60

Table III: Formulation of batches used for PLS model validation

CBZ (%)	PEG (%)	PVP-VA (%)
9	16	75
16	11	73
22.5	9	68.5
24	19	57



a) Model showing sensor location related to flowpath



b) Photograph of die during extrusion

379 Figure 1 Pharmalab extruder die designed to accommodate two opposing sensor ports across
380 a 1mm flow path

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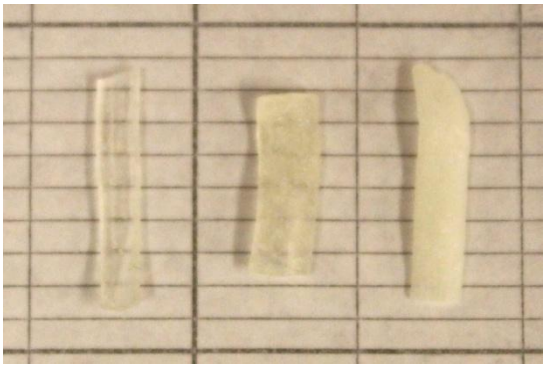
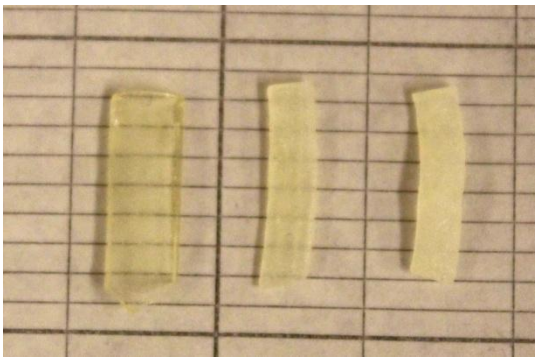


(a) 5, 15, 30% CBZ at 10% PEG



(b) 5, 15, 20% PEG at 20% CBZ

Figure 2 HME extrudate showing variation in opacity

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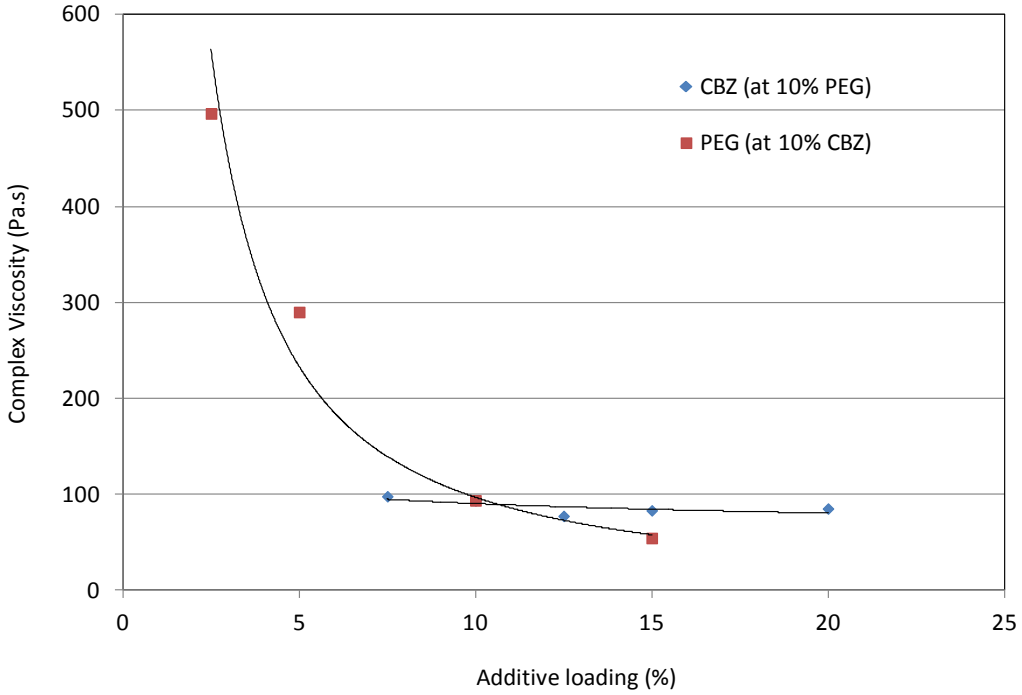

Figure 3 Complex viscosity of physical mixtures measured at $1s^{-1}$ showing the effect of carbamazepine and PEG loading

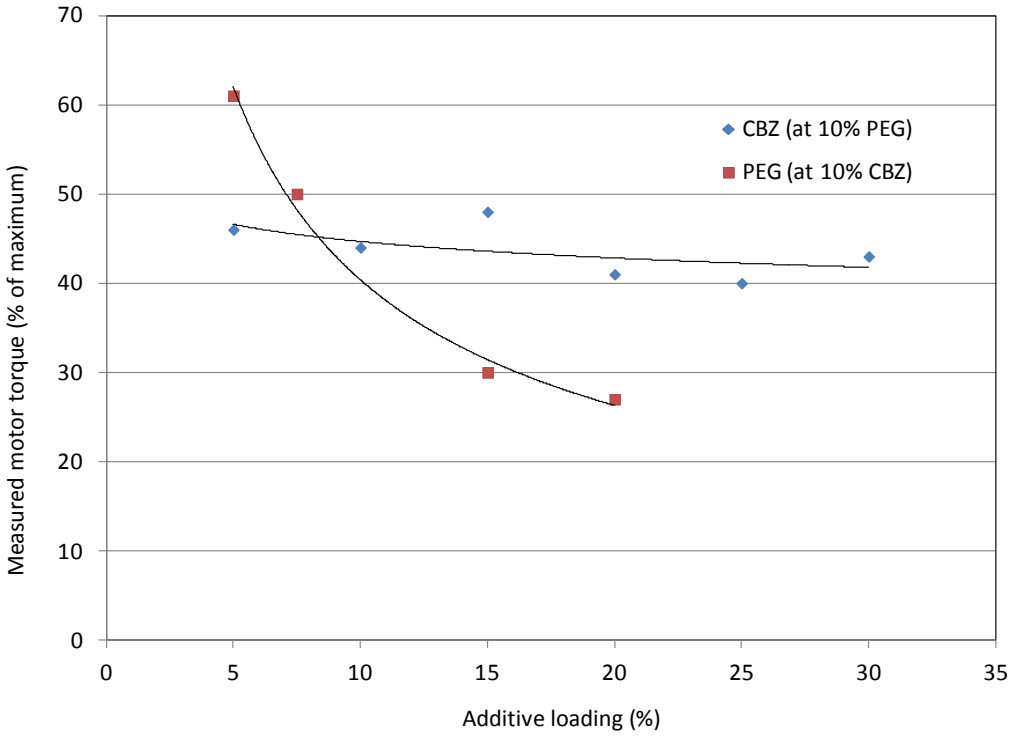

Figure 4 Measured extruder motor torque showing the effect of carbamazepine and PEG loading

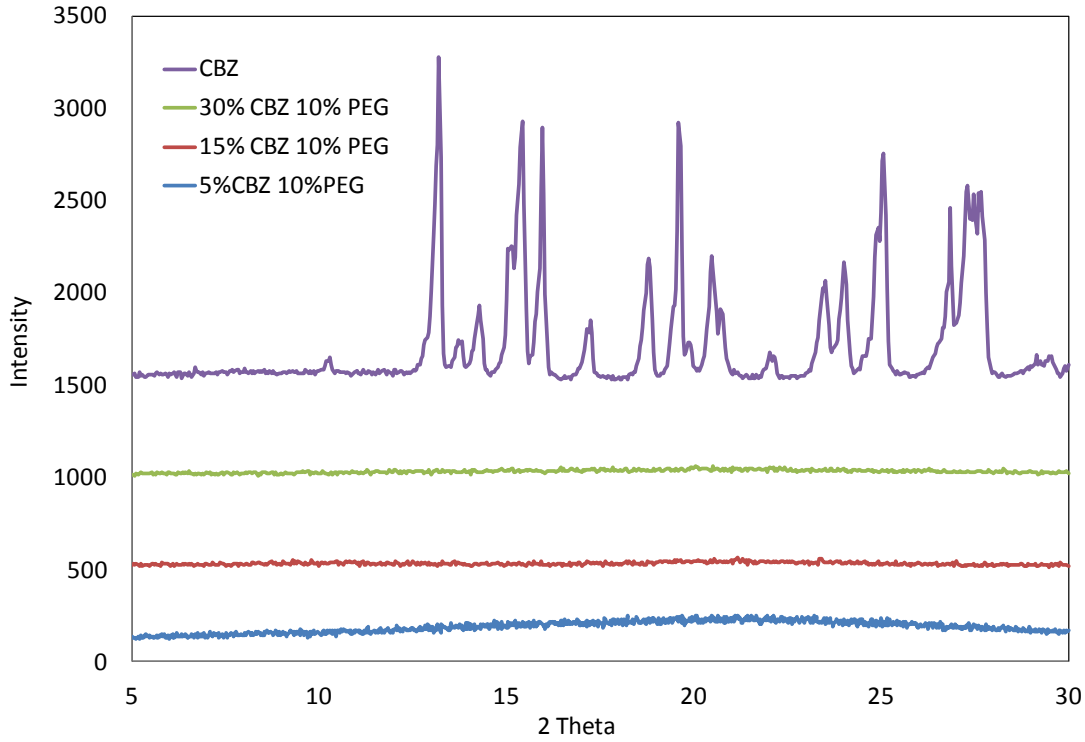

Figure 5a PXRD results showing the effect of CBZ content

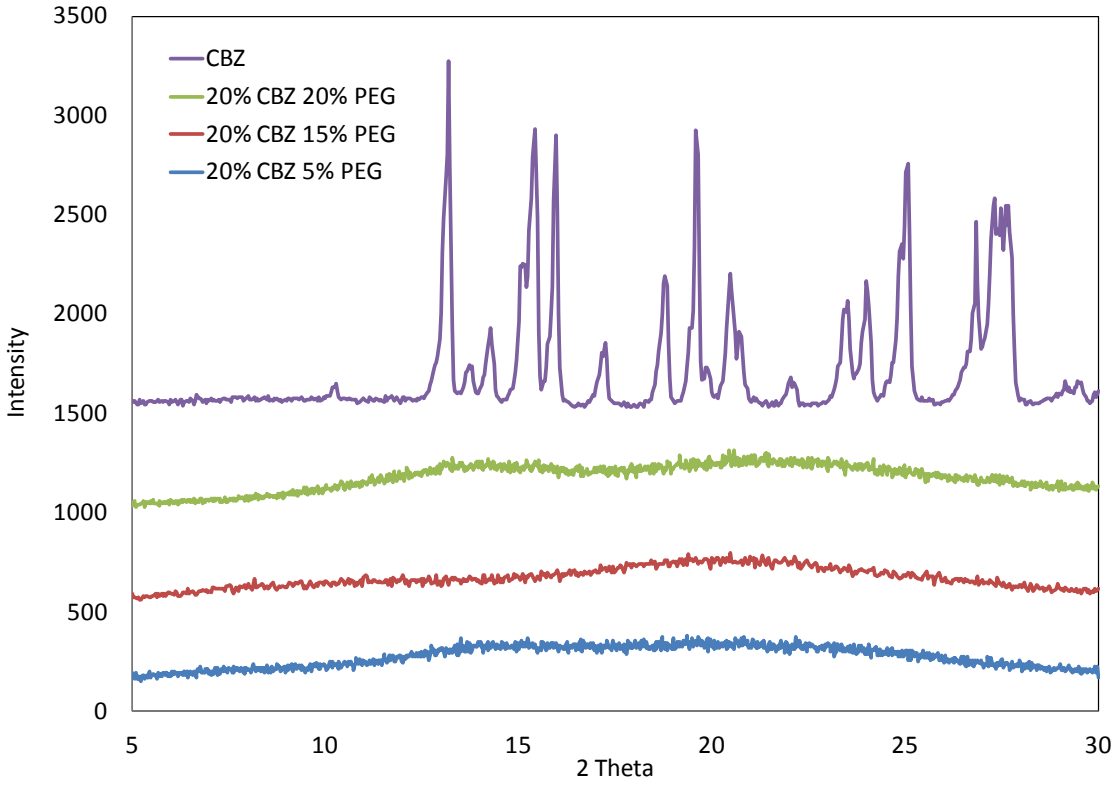

Figure 5b PXRD results showing the effect of PEG content

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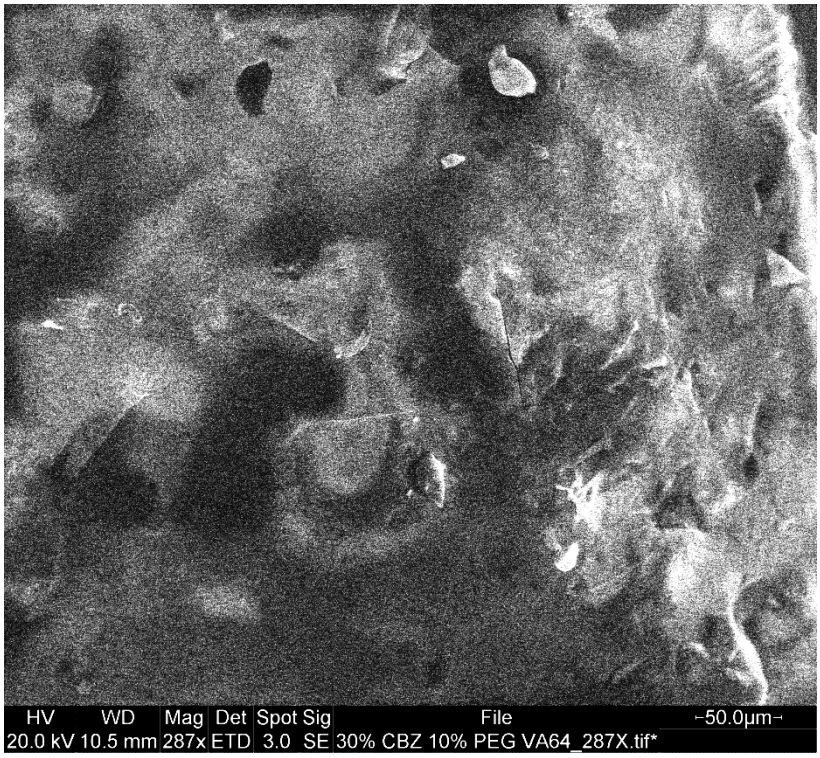
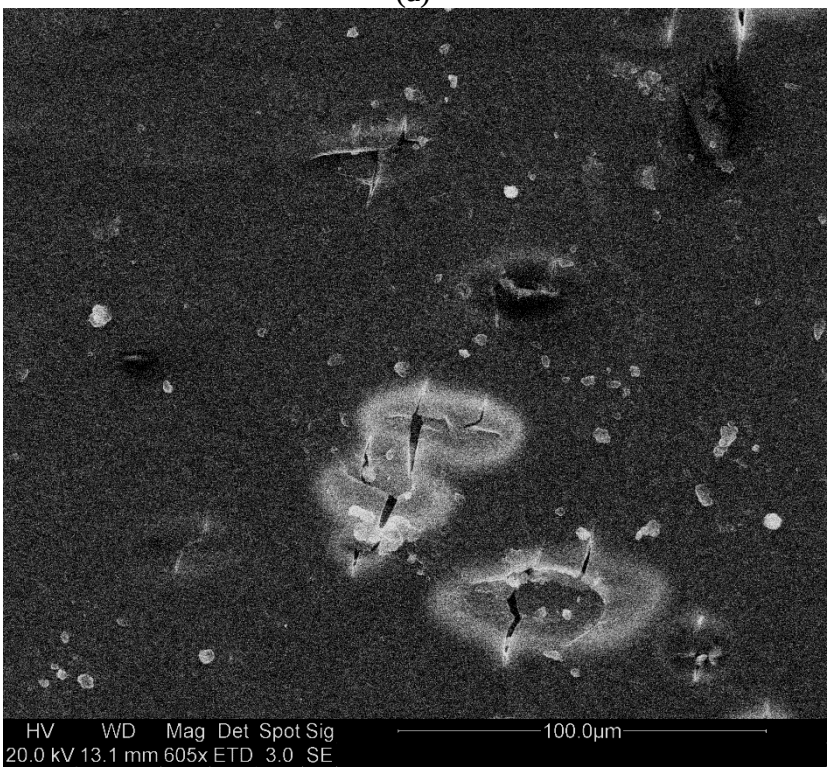


(a)



(b)

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405 Figure 6 SEM images of extrudate surfaces for 30% CBZ, 10% PEG;
406 a) fracture surface, b) top surface of extrudate

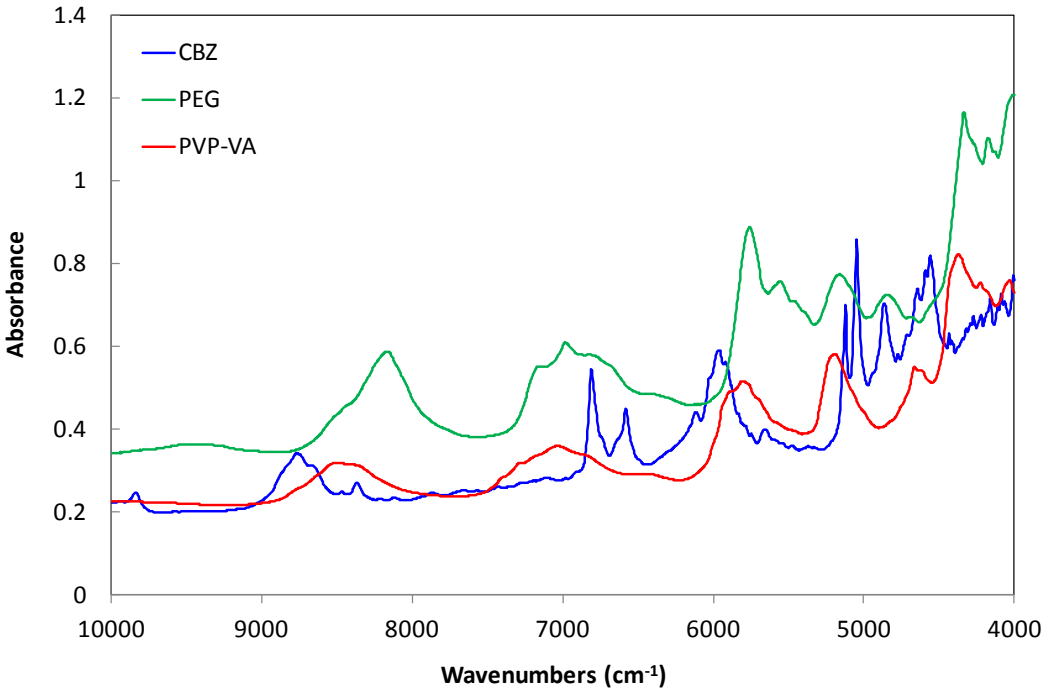


Fig. 7 Off-line FT-NIR spectra of pure components

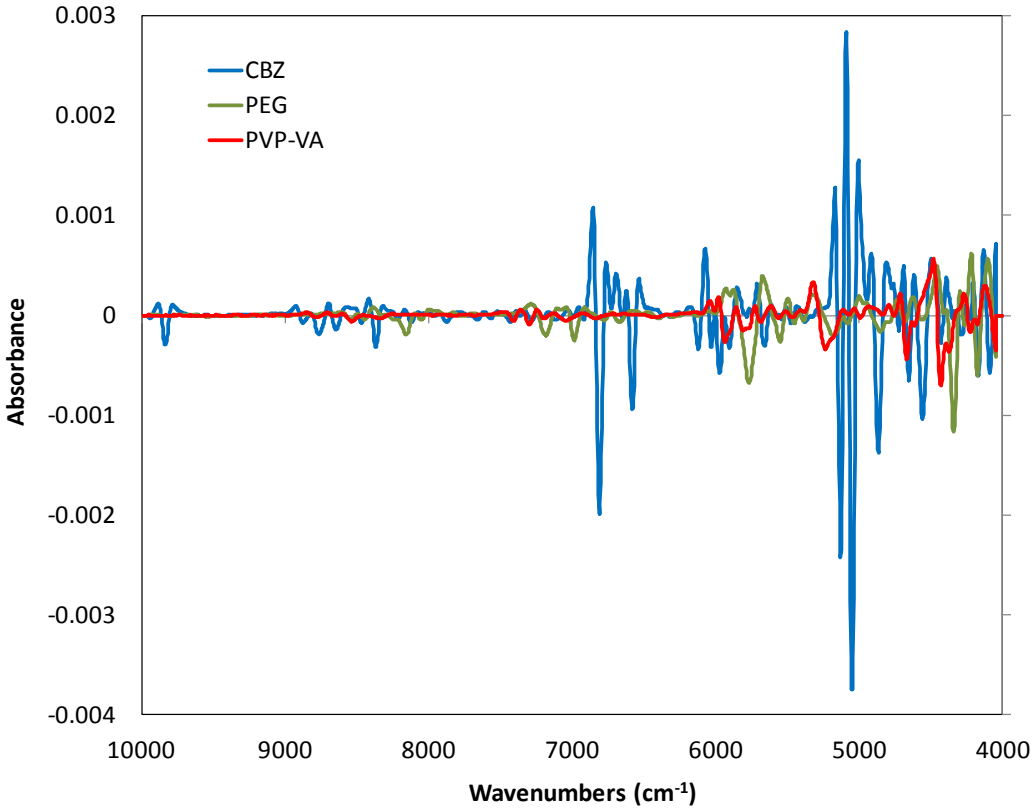
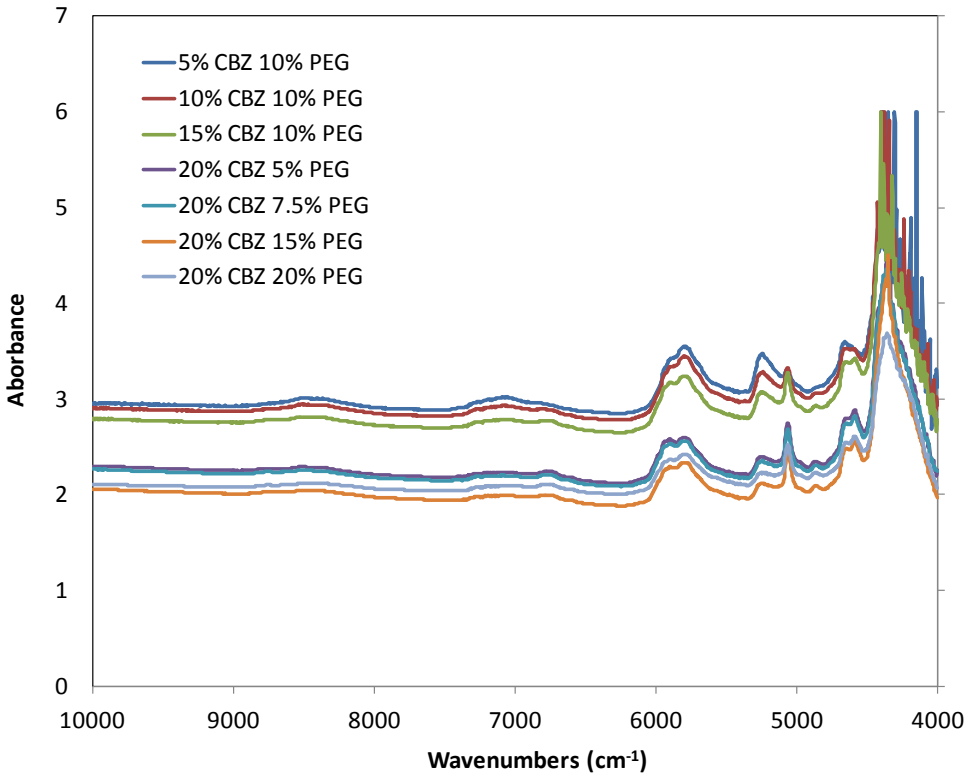


Fig. 8 Off-line second derivative spectra of pure components



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415 Fig. 9 In-line FT-NIR spectra of extrudates at the die exit

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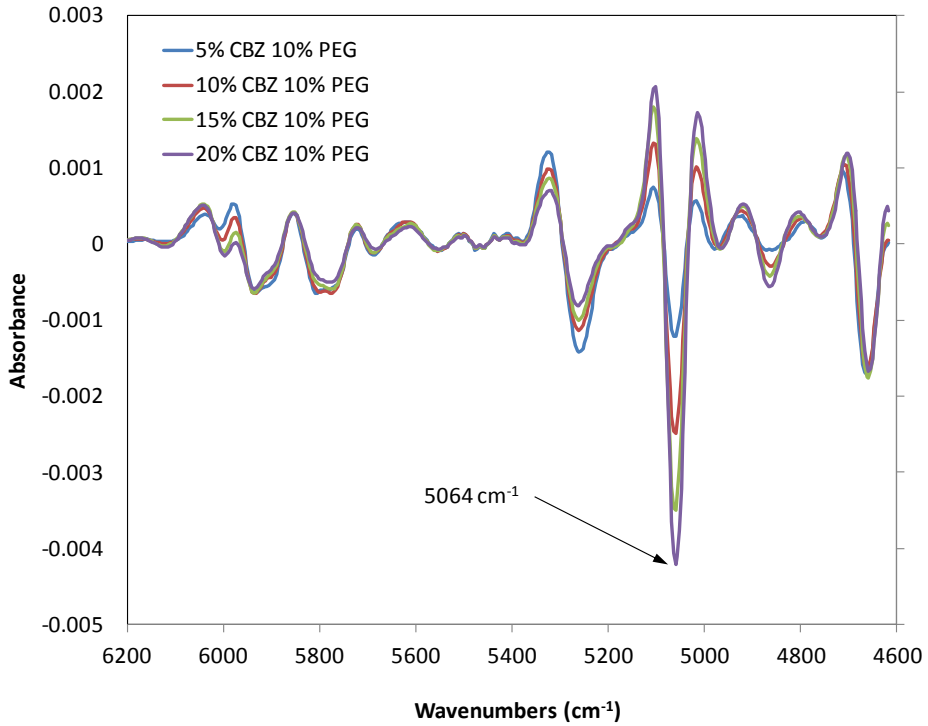

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419 Fig. 10 In-line second derivative spectra extrudates showing CBZ concentration changes,

420 PEG held constant at 10% by weight

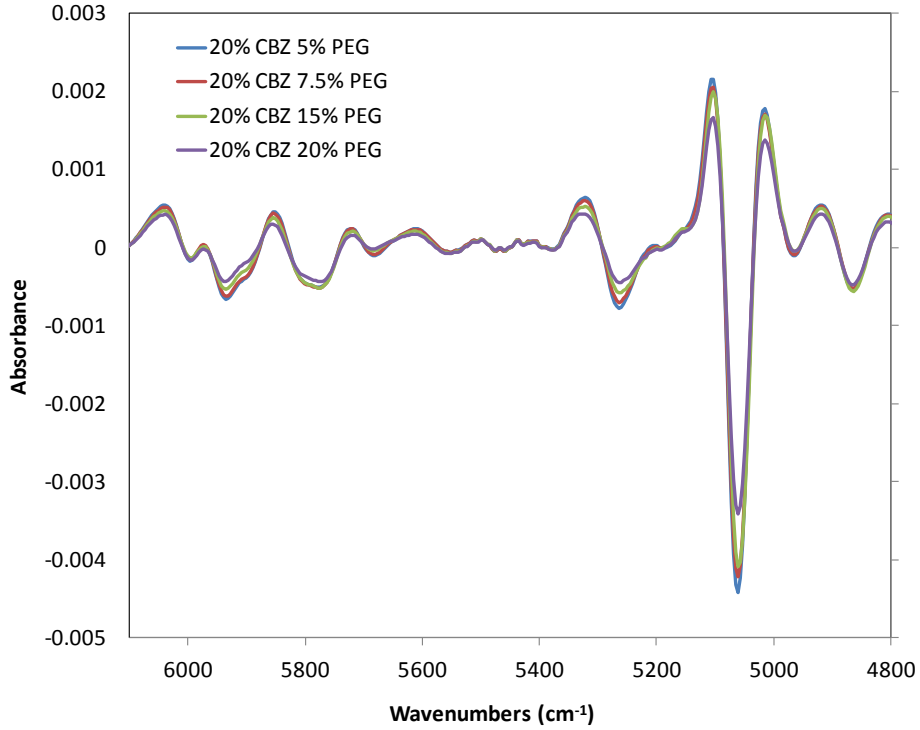
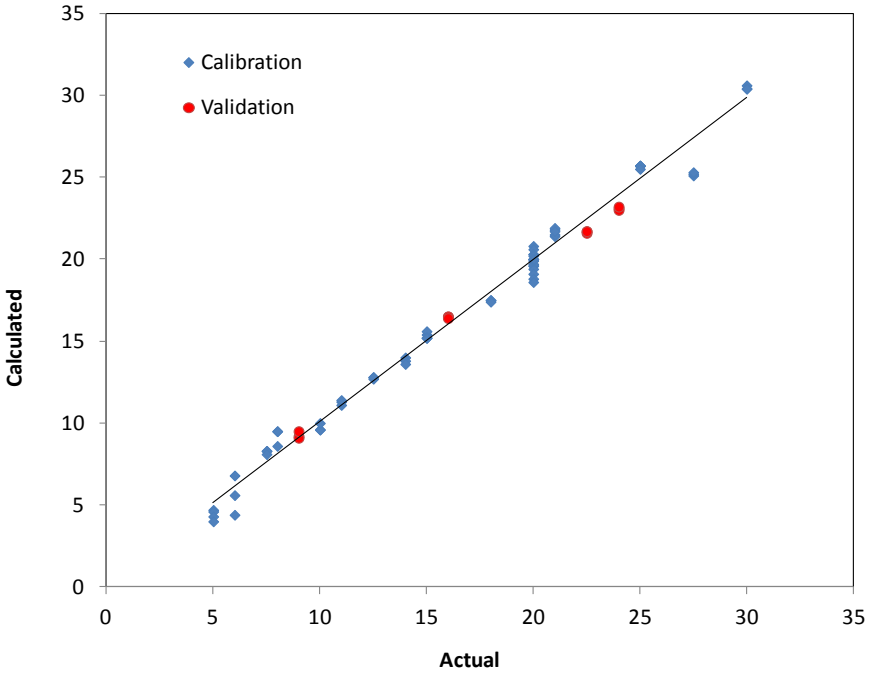


Fig. 11 In-line second derivative spectra extrudates showing PEG concentration changes, CBZ held constant at 20% by weight



427
428
429 Fig. 12a PLS regression results for CBZ
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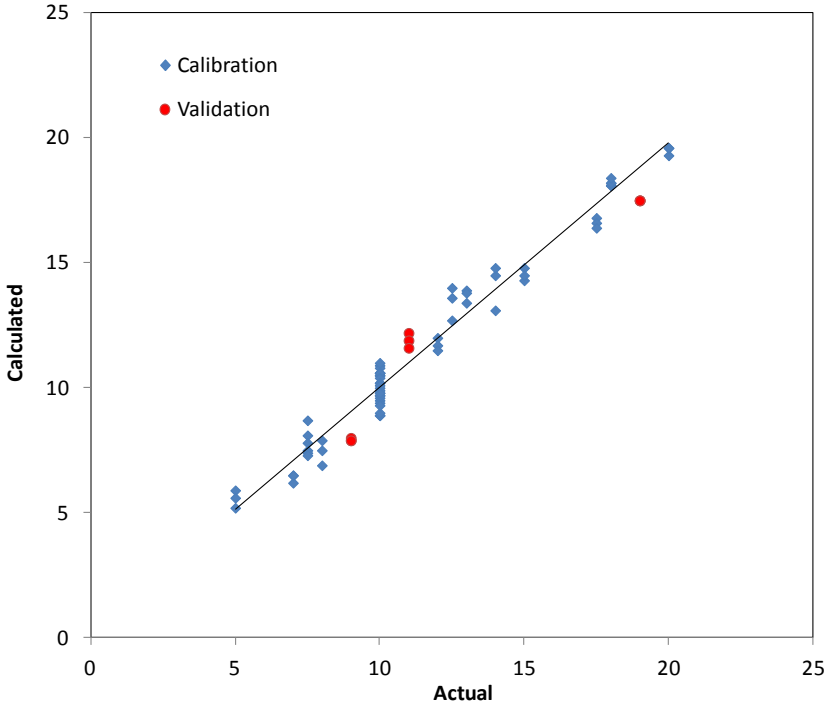

431
432
433 Fig. 12b PLS regression results for PEG
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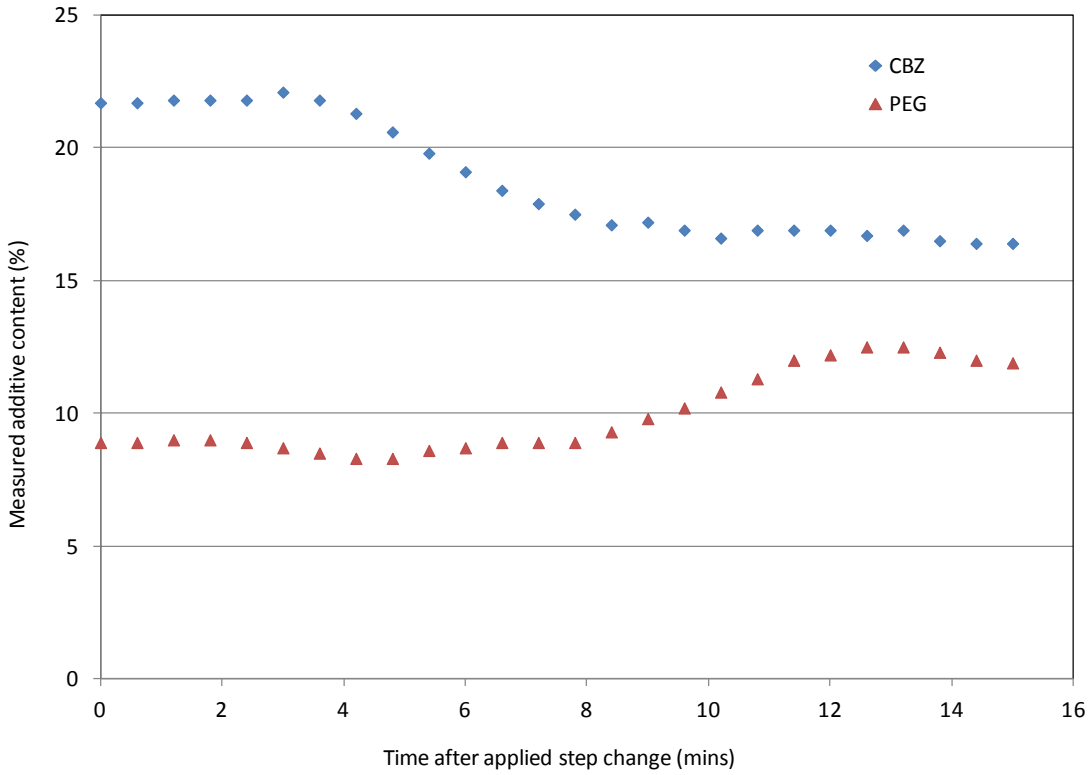

Fig. 13 Plot of CBZ and PEG concentrations measured in real time following an imposed step change in feedstock from 22.5% to 16% CBZ and 9% to 11% PEG