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A novel transflectance near infrared spectroscopy technique for monitoring hot melt extrusion

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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.

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

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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 and 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,b). 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

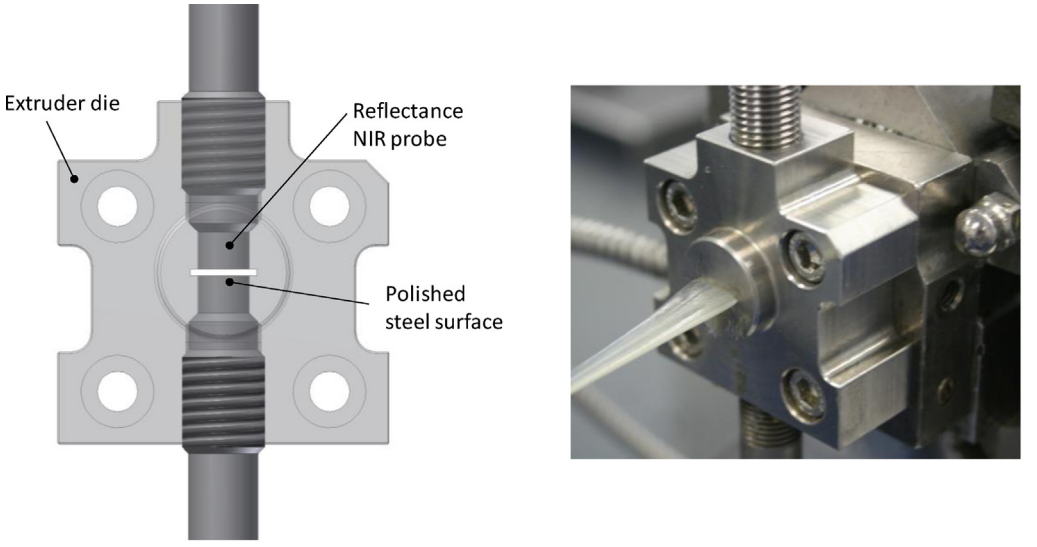
2.1. Materials

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 (T_g) 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 16 mm 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 1 mm gap (Fig. 1). The transflectance measurement geometry comprised a high temperature reflectance NIR probe located in one port of the extruder die,



a) Model showing sensor location related to flowpath

b) Photograph of die during extrusion

Fig. 1. Pharmalab extruder die designed to accommodate two opposing sensor ports across a 1 mm flow path.