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International Journal of Pharmaceutics 329 (2007) 62–71
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Preparation of monolithic matrices for oral drug delivery using a supercritical fluid assisted hot melt extrusion process

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Received 7 July 2006; received in revised form 10 August 2006; accepted 15 August 2006
Available online 30 August 2006

Abstract

The use of supercritical fluids as plasticisers in polymer processing has been well documented. The body of work described in this research paper outlines the use of a supercritical CO_2 assisted extrusion process in the preparation of a hot melt extruded monolithic polymer matrix for oral drug delivery. Several batches of matrix material were prepared with Carvedilol used as the active pharmaceutical ingredient (API). These batches were subsequently extruded both with and without supercritical CO_2 incorporation. The resultant matrices were characterised using steady-state parallel plate rheometry, differential scanning calorimetry (DSC), atomic force microscopy (AFM), micro-thermal analysis (μTA) and dissolution testing. Dissolution analysis showed that the use of supercritical CO_2 during the extrusion process resulted in a faster dissolution of API when compared with unassisted extrusion. The supercritical CO_2 incorporation also resulted in reduced viscosity during processing, therefore allowing for quicker throughput and productivity. The results detailed within this paper indicate that supercritical fluid assisted hot melt extrusion is a viable enhancement to conventional hot melt extrusion for the production of monolithic dosage forms.

Keywords: Supercritical fluid; Extrusion; Polymer; Drug release; Monolithic matrix

1. Introduction

Controlled release of therapeutic agents remains one of the biggest challenges in drug delivery. Repeated administration of a drug so as to maintain drug concentration within the therapeutic window may cause serious side effects, which in many cases necessitates the patient to stop taking medication (Geever et al., 2006). With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible adverse effects related to the transiently high concentration. An example is hypotension in patients taking rapid-release nifedipine products. Recently, the development of tablets, which can be swallowed and thereafter slowly release the drug in the gastrointestinal tract has garnered great interest. There are currently many different nomenclatures available for the aforementioned dosage forms, such as slow release, prolonged release, sustained release and extended release. The term extended release has been adopted by the European Pharmacopiea as the denominator for this type of device. The release pattern from such a device may vary from continuous to two or more pulses (Alderborn and Aulton, 2002). Over the past decade the use of biodegradable polymers for the administration of pharmaceuticals and biomedical devices has increased dramatically. The most important biomedical applications of biodegradable polymers are in the areas of controlled drug delivery systems (Holy and Fialkov, 2003), in the form of implants and devices for bone and dental repairs (Chasin and Langer, 1990; Ma and Zhang, 2001).

Hot melt extrusion of biodegradable polymers for extended release applications has received increased attention in the pharmaceutical literature recently. Hot melt extrusion is the process of converting a raw material into a product of uniform shape

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doi:10.1016/j.ijpharm.2006.08.028

and density by forcing it through a die under controlled conditions (Rauwendaal, 1986). Extrusion process technology can be divided into two categories; ram extrusion and screw extrusion. Ram extrusion consists of a positive displacement ram capable of generating high pressures forcing material through a shaping die while screw extrusion consists of a rotating screw or a set of rotating screws inside a barrel. In a pharmaceutical environment hot melt extrusion offers many advantages over more traditional tablet preparation methods; all the processing steps (mixing, melting and homogenising) are carried out on a single machine and neither water or solvents are involved in the process, thus due to the anhydrous nature of the process any potential drug degradation from hydrolysis can be avoided. The intensive mixing provided by a twin screw extruder causes suspended drug particles to de-aggregate in the polymer melt resulting in a more uniform distribution of fine particles. Hot melt extrusion offers a high throughput and a low material loss while preparing extrudates that possess excellent homogeneity.

The use of supercritical CO_2 as a solvent in the processing of various biodegradable/biocompatible polymers for pharmaceutical and medical applications in the forms of particles and microcellular foam has garnered much attention in the last decade. A supercritical fluid is defined as a substance for which both pressure and temperature are above the critical values (Kazarian, 2000).

CO_2 is a promising alternative to noxious organic solvents and chlorofluorocarbons. It has shown versatility as a supercritical fluid in the synthesis as well as processing areas for polymers owing to its attractive physical properties. It is non-toxic, non-flammable, chemically inert and inexpensive. Its supercritical conditions are easily attained ($T_c = 304.15\,K$, $P_c = 7.38\,MPa$) and it can be removed from a system by simple depressurization (Nalawade et al., 2006).

The processing of polymers is highly influenced by the viscosity of the bulk materials. Raising the processing temperature or the addition of volatile or harmful plasticisers is often seen as a solution in overcoming the inherent difficulties encountered when processing high molecular weight polymers. However, higher temperatures during processing can lead to thermal degradation. Also, added plasticisers remain in the product and thus alter its properties and performance. The low thermal stability of high molecular weight biodegradable polymers has led to the emergence of supercritical CO_2 as a useful processing aid. There are many examples in the literature of the use of pressurized gases to lower the melt viscosity of numerous amorphous and semicrystalline polymers. Polyethylene glycol (Daneshvar et al., 1990; Weidner et al., 1997; Gourgouillion et al., 1998; Gourgouillion and Nunes da Ponte, 1999; Lopez et al., 2000), polystyrene (Kiran and Sen, 1993; Kwag et al., 1999; Lee et al., 1999) and polydimethylsiloxane (Mertsch and Wolf, 1994; Xiong and Kiran, 1995; Bae and Gulari, 1997; Gerhardt et al., 1997) are examples of polymers where a viscosity reduction has been demonstrated upon the incorporation of supercritical CO_2. Biomaterials (Tuan et al., 1999), as well as polyethylene/polystyrene blends (Lee et al., 1998) have exhibited similar behaviour. Verreck et al. (2006) noted in a recent publication that although numerous examples describing the effect of supercritical CO_2 as a plasticiser for polymers can be found in the literature, there are relatively few publications dealing with pharmaceutically acceptable polymers.

This work reports on the use of supercritical CO_2 as a plasticiser during the processing of a hot melt extruded dosage form based on polyethylene oxide. The impact on the production of hot melt prepared matrices, in addition to the release rate of an active pharmaceutical ingredient from the prepared matrices both with and without the utilization of supercritical CO_2 during compounding was investigated.

2. Experimental

2.1. Hot melt extrusion

All the melt compounding detailed herein was carried out on a bench-top Prism^{TM} twin screw extruder with 16 mm diameter screws and a 25/1 length to diameter ratio (Thermoprism, 2006). Prism^{TM} co-rotating extruder screw configurations are designed and manufactured in a modular construction, the screws are made up of individual sections that slide onto a keyed or splined shaft. Therefore, different screw configurations using narrow disk bi-lobal kneading elements can be arranged at any location along the shaft to generate controlled shear or mixing effects.

Injecting CO_2 into the extruder barrel may cause leakage of the gas resulting in a limited building up of pressure during processing. Therefore, the screw configuration was carefully considered in order to be able to mix the CO_2 with the polymer melt at appropriate pressures. Lee et al. (1998) suggested a number of different aspects which must be taken into account when designing the extruder set up and screw configuration for supercritical CO_2 assisted compounding: (a) at the injection port of the carbon dioxide, the pressure fluctuations should be minimised to obtain a stable injection. Therefore, transport elements instead of kneading elements should be used at the site of injection; (b) injected CO_2 should not be allowed to leak from upstream orifices, requiring the use of a melt seal using reversed elements; (c) the pressure downstream should be maintained at a sufficiently high level to ensure that the supercritical CO_2 remains dissolved in the polymer. This can be obtained by providing high die resistance; (d) complete dissolution of CO_2 can be assured by using kneading elements to improve mixing downstream of the supercritical fluid introduction.

For the compounding detailed in this work, the screws were assembled in the co-rotating intermeshing mode with a long continuous mixing section made up of 30°, 60° and 90° bi-lobal kneading elements that ensured that the transition from conveying to high shear mixing was very gradual. The mixing section was positioned towards the die end of the extruder downstream from the supercritical CO_2 injection port. The required compounding temperature profile was established on the Prism^{TM} extruder by means of four temperature controllers placed along the length of the barrel. A fifth temperature controller was used to regulate the temperature at the die. Extrudate was cooled via two cool air fans and was subsequently granulated using a Prism^{TM} granulator. The extrusion conditions used are outlined in Table 1. The positions of the heating zones, mixing sections and injec-

Table 1
Extrusion temperatures at a screw speed of 35 RPM

Temperature (°C)	
Zone 1	50
Zone 2	130
Zone 3	130
Zone 4	130
Die	140

tion port are visible on the schematic diagram of the barrel of the Prism^{TM} twin screw extruder in Fig. 1. Batches of material were prepared with and without the assistance of supercritical CO_2: a full list of the batches prepared can be seen in Table 2. The matrices under investigation in this work were chosen as part of ongoing research at Pharmaplaz Ltd. For the batches prepared using the assistance of supercritical CO_2, a P50 reciprocal high pressure pump from Thar^{TM} technologies was used. The pump was connected via a high pressure line to the extruder at E port 2 (see Fig. 1), and was controlled using a hand held display.

The compounding process was optimised for supercritical CO_2 assisted extrusion prior to the compounding of the batches used in this trial. The optimisation process concluded that the use of a melt seal generated by reverse mixing elements as suggested by Lee et al. (1998) and Verreck et al. (2006) was unnecessary in this instance due to the flow behaviour of the materials used, which precluded leakage of CO_2 upstream through the barrel. The design of the strand die used in this work was found to produce sufficiently high resistance so as to ensure that the supercritical CO_2 remained dissolved in the polymer during compounding.

The active pharmaceutical ingredient (API) incorporated in this work was Carvedilol obtained from Pharmaplaz Ltd. Polyethylene oxide ($M_w = 200{,}000$) was obtained from Polysciences Ltd. Eudragit EPO was donated by Degussa Ltd.

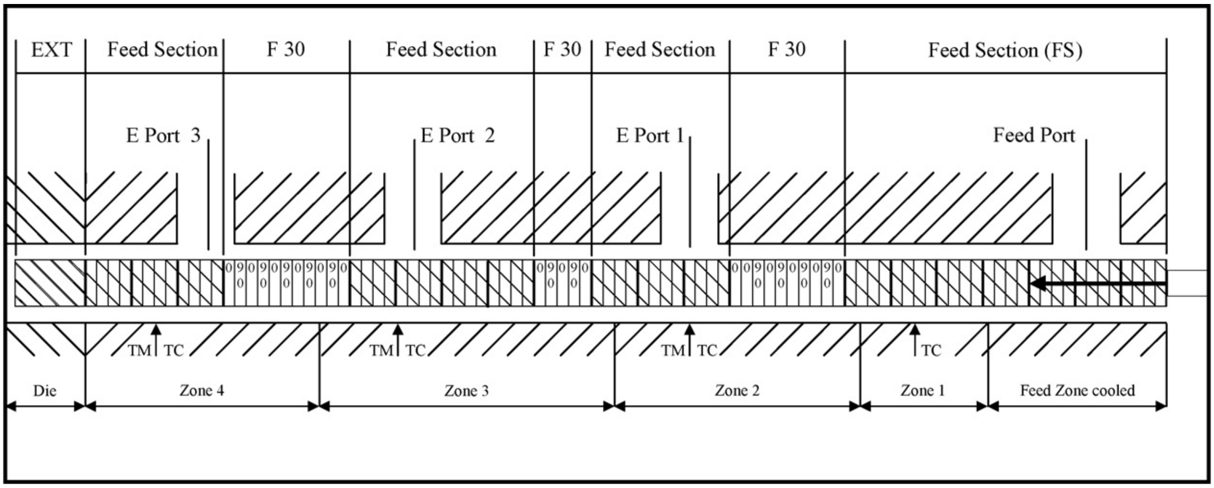

Fig. 1. Schematic representation of Prism^{TM} twin screw extruder barrel.

Table 2
Batches prepared during this study

Batch no.	PEO, $M_w = 200{,}000$ (wt.%)	Eudragit EPO (wt.%)	API (wt.%)	Supercritical CO_2 assisted (1200 psi)
1	86	0	14	No
2	64.5	21.4	14	No
3	43	43	14	No
4	89.5	0	10.5	No
5	67.125	22.375	10.5	No
6	44.75	44.75	10.5	No
7	92.5	0	7.5	No
8	69.375	23.125	7.5	No
9	46.25	46.25	7.5	No
10	86	0	14	Yes
11	64.5	21.4	14	Yes
12	43	43	14	Yes
13	89.5	0	10.5	Yes
14	67.125	22.375	10.5	Yes
15	44.75	44.75	10.5	Yes
16	92.5	0	7.5	Yes
17	69.375	23.125	7.5	Yes
18	46.25	46.25	7.5	Yes

2.2. Modulated differential scanning calorimetry (MDSC)

The DSC method was among the techniques used for examination of the extruded pellets. The analyses were preformed using a DSC 2920 Modulated DSC (TA Instruments) coupled with a refrigerated cooling system. Samples of between 9.0 and 9.8 mg were weighed out using a Sartorius scales having a resolution of 0.00001 g. Samples were then placed in non-perforated aluminum pans, which were crimped before testing, with an empty crimped aluminum pan being used as the reference cell. Calorimetry scans were carried out from 20 to 190 °C for each extruded pellets. All DSC measurements were carried out at a scanning rate of 1 °C/min. Volatiles were removed from the purging head with nitrogen at a rate of 30 ml/min. Calibration of the instrument was preformed using indium as standard. After each scan was completed the melting points were analysed to determine heats of fusion and T_m of each batch.

2.3. Steady-state parallel plate rheometry

The method used to study the rheological properties of the samples detailed in this study was a steady-state parallel plate viscometer, the AR1000^{TM} rheometer from TA Instruments$^{©}$. It is a versatile research-grade rheometer designed for rapid characterization of mobile and viscous liquids. It is fitted with an environmental test chamber (ETC), for use as the temperature control environment in the analysis of polymer melts using parallel plate or cone/plate measurement geometries with provision for nitrogen purging.

The following is the procedure used in all of the rheological studies detailed herein. The air and nitrogen supplies were turned on and the air bearing guard was removed. The instrument was calibrated for inertia and the geometry was set for the 25 mm steel parallel plates being used. The instrument was mapped and with the ETC closed the rheometer was brought to test temperature of 140 °C. The gap between the plates was zeroed, the doors were opened and the sample was loaded. The amount of sample loaded has an effect on the accuracy of the results, and so extreme care was taken during sample loading to ensure the correct fill. The apparatus was set to take 10 points per decade with 5% tolerance. After each test a bronze scraper was used to remove the sample from the plates, before the machine was brought back to temperature for the next sample.

2.4. Micro-thermal analysis

Micro-thermal analysis (μTA) is a materials characterisation technique combining the visualisation power of atomic force microscopy (AFM) with the characterization capabilities of thermal analysis. A 2990 micro-thermal analyser incorporated into a Topometrix explorer AFM was used to characterise all of the blends in this study. Characterisation was carried out in two modes: micro-modulated thermal analysis (μMDTA) in which thermal transitions are measured in a way analogous to MDSC and micro thermomechanical analysis (μTMA), which can be used for the measurement of expansion, softening, melting and glass transitions. Surface visualisation scans were acquired on a cross-section of the extruded granules with a constant probe temperature of 40 °C. The PID settings were optimised for each scan in order to ensure accurate data acquisition. The scan range was set to 100 μm with a scan rate of 200 μm/s, and the set point used was 10 nA. μMDTA and μTMA measurements were taken at various surface points at a rate of 20 °C/min from ambient temperature to 350 °C. About 150 points per second were recorded using a frequency of 2.2 kHz and a heating amplitude of 3 °C.

2.5. Dissolution testing

Dissolution testing was carried out using a Sotax AT7 smart dissolution system from Carl Stuart Ltd. The test was carried out in triplicate using the Basket method (USP XXV). Test specimens of constant size and external surface area were produced by cutting the extrudate strands manually to give granules of constant length 0.5 cm. At the request of the funding body, the test specimens were tested in dissolution medium of pH 7.2 and 0.2 M HCl. The test was carried out at 37 ± 0.5 °C. The stir rate was set to 100 rpm with 600 ml of dissolution media being used per vessel. The wavelength of 100% drug concentration for the drug (Carvedilol) was determined using a Perkin-Elmer Lambda 40 UV/vis spectrometer, and was found to be 285.64 nm. This value was entered into software calculations prior to commencement of testing. Samples were automatically taken every 15 min, filtered and passed through a Perkin-Elmer Lambda 20 UV/vis spectrometer, before being returned to the dissolution chamber. The dissolution profile was observed from a plot of time versus absorbance.

3. Results and discussion

3.1. Hot melt extrusion

Extruder torque is a measure of the resistance that the motor experiences as a consequence of the melt viscosity inside the barrel. Verreck and Brewster (2004) discussed the use of the extruder torque values as a method of measuring relative viscosities of polymer melts at set values of processing temperature, feed rate and screw speed. In a previous paper Lyons et al. (2006) used a similar method as an indicator for melt viscosity during processing, in that contribution, the extruder torque reading was supplemented with measurement of die head pressure. Die head pressure is a measurement obtained by a pressure transducer, which records the pressure exerted by the polymer melt at the shaping die. Higher viscosity melts will exert more pressure than melts with lower viscosities. During the hot melt extrusion process the values for torque and die head pressure were recorded several times, the average observed values are presented in Table 3.

As the residence time of the supercritical CO_2/matrix mixture in the extruder is relatively short, an estimate of the time required to form a single-phase solution is important prior to continuous processing. Diffusion theory has been used in the literature as a method of making such an estimate (Park and Suh, 1996a,b), for a typical polymer viscosity of 200 Pa s, this

Table 3
Recorded torque and die head pressure readings obtained during processing

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9
Batches processed using conventional extrusion									
Die head pressure (bar)	35	50	62	42	59	72	50	61	75
Extruder torque (N/m)	3	5	12	5	7	15	8	11	16
	Batch 10	Batch 11	Batch 12	Batch 13	Batch 14	Batch 15	Batch 16	Batch 17	Batch 18
Batches processed using supercritical fluid assisted extrusion									
Die head pressure (bar)	25	38	43	32	45	54	40	50	62
Extruder torque (N/m)	2	4	5	3	5	9	6	8	12
Ratio's of recorded values (supercritical fluid assisted extrusion/conventional extrusion)									
Die head pressure (bar)	0.714	0.76	0.693	0.762	0.763	0.75	0.8	0.82	0.83
Extruder torque (N/m)	0.667	0.8	0.417	0.6	0.714	0.6	0.75	0.73	0.75

method suggests that single-phase solution formation can be achieved sufficiently quickly so as to allow for industrial scale up (Park and Suh, 1996b). Shear action in the extruder causes the breakup of larger CO_2 bubbles into smaller ones and hence, enhanced mass transfer that shortens the time for formation of a single-phase solution.

The recorded values for torque and die head pressure indicate that at constant temperature and screw speed, a drop in the melt viscosity of the polymer melt occurs upon addition of supercritical CO_2 to the hot melt extrusion process. The ratio's of the observed values for torque and die head pressure show that supercritical fluid incorporation resulted in a drop to at least 0.83 times that of the values observed using conventional extrusion methods for each polymer matrix processed. Chiou et al. (1985) describes the primary methods by which supercritical fluid effects placticisation in the barrel of the extruder. Firstly, carbon dioxide is absorbed between the polymer chains causing an increase of free volume and a decrease in chain entanglements. Secondly, carbon dioxide acts as a molecular lubricant that reduces melt viscosity. Supercritical CO_2 induced plasticisation of polymers has been widely studied in the literature using a wide range of methods including: positron annihilation lifetime spectroscopy (Yuan et al., 1998), chromatography (Edwards et al., 1998), dynamic mechanical response (Fried et al., 1989), high pressure DSC (Chiou et al., 1985), FTIR (Kazarian et al., 1996), and X-ray diffraction (Houde et al., 1992). The reduction in motor load and head pressure observed with the addition of supercritical CO_2 are akin to what would be expected to occur when melt processing temperatures are increased. This possible improvement in throughput without the risk of thermal degradation is one of the most favorable properties of supercritical fluid assisted hot melt extrusion. Incorporation of the API is also seen to plasticise the polymer matrix with reduction in the motor load and die head pressure occurring with increasing API loading. This behavior has previously been reported by Ozeki et al. (1997) and Lyons et al. (2006).

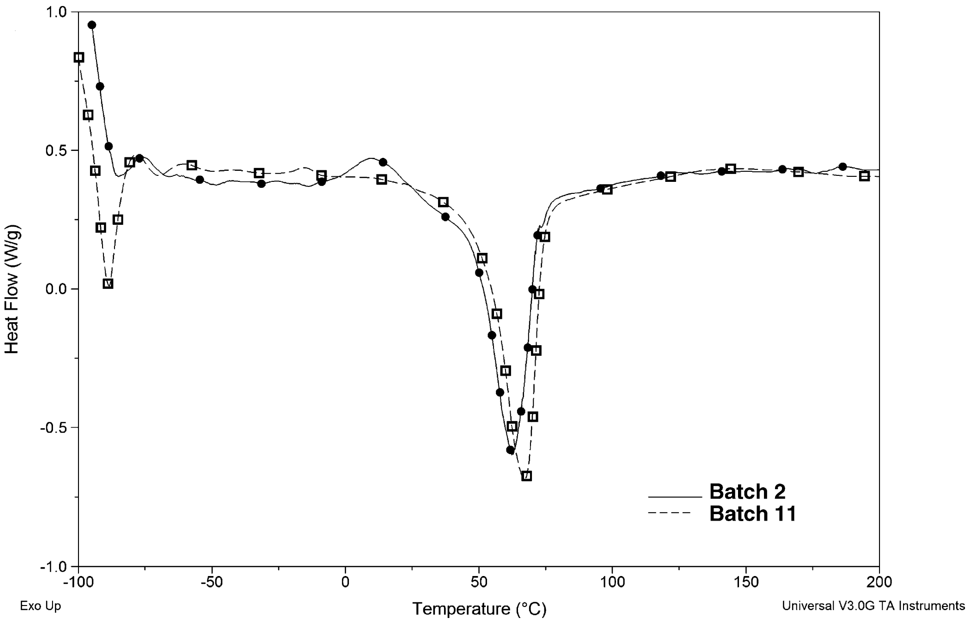

Fig. 2. MDSC thermograms obtained for extruded batches 2 and 11.

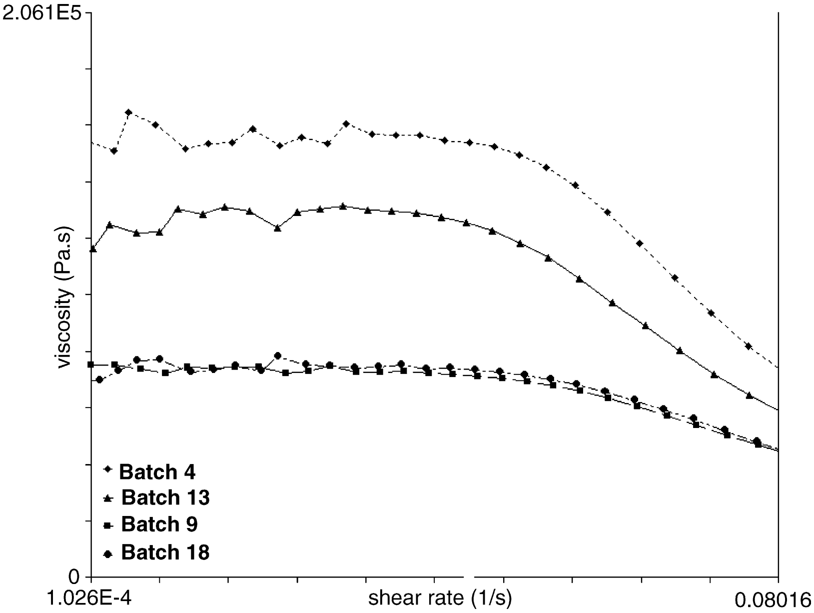

Fig. 3. Steady-state viscosity data recorded for batches 4, 9, 13 and 18.

3.2. Modulated differential scanning calorimetry (MDSC)

MDSC scans were carried out on all the batches of extrudate produced, in order to ascertain if the use of supercritical CO_2 during the processing of the polymer matrices had any lingering effect on their thermal properties.

Fig. 2 shows two of the thermograms typical of those obtained in this work. The results obtained indicate no significant change in the melting behavior of the extrudate produced in the supercritical CO_2 assisted process occurs when compared to extrudate of the same composition produced via a conventional hot melt extrusion process. As noted in previous work by Lyons et al. (2006) and Ozeki et al. (1997), and in agreement with values observed in the torque and die head pressure readings obtained in the processing of the polymer matrices, the API is observed to have a plasticising effect on the polymer matrices tested. The plasticising effect is manifested by a depression in the melting point of the polymer matrices, the magnitude of which increases with increasing API inclusion: at 14% by weight, the average observed depression in matrix melting point was 3.43 °C.

3.3. Steady-state parallel plate rheometry

As previously stated the melt viscosity during processing was monitored using torque and die head pressure data. Steady-state parallel plate rheometry was carried out to ascertain if the viscosity reduction occurred only in the barrel during supercritical CO_2 assisted processing or if the mobility of the polymer blends remained heightened after processing.

The data obtained indicated that the viscosity reducing effect of supercritical CO_2 occurs only in the barrel of the extruder during supercritical CO_2 assisted processing. Fig. 3 illustrates the viscosity curves obtained for four of the batches produced in this study. These results are typical of those obtained. Batches 4 and 13 have identical composition; similarly batches 9 and 18 have identical composition. Batches 13 and 18 were produced using supercritical CO_2 assisted processing while batches 4 and 9 were produced using conventional processing: negligible difference in the viscosities of the extrudates is observed when compar-

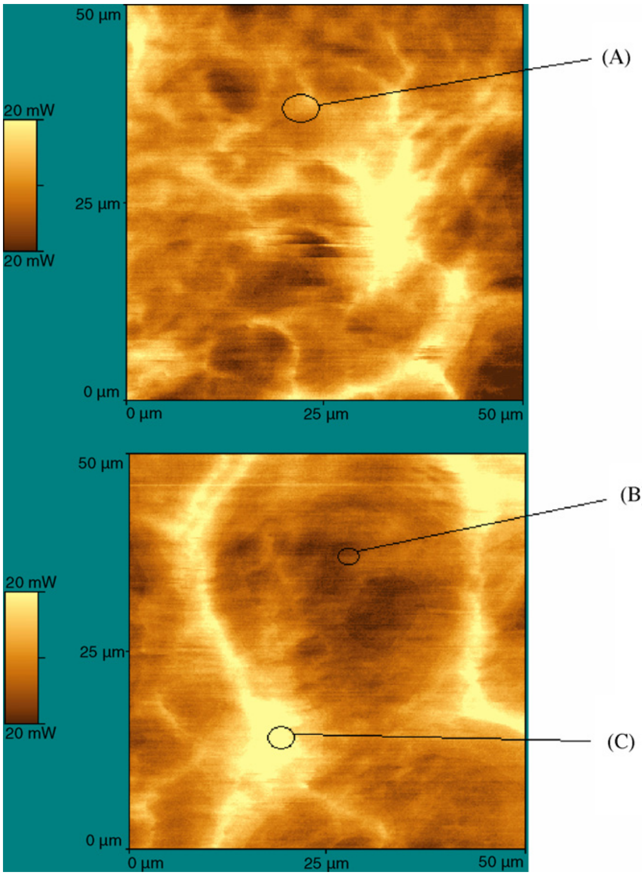

Fig. 4. Surface conductivity images for sample 8 (upper image) and sample 17 (lower image).

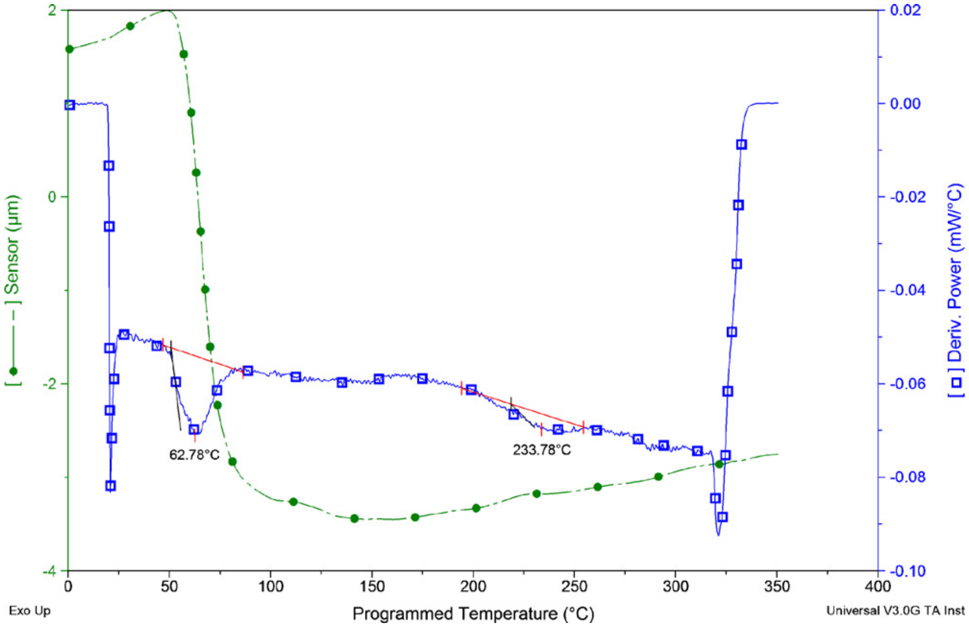

Fig. 5. µMDTA and µTMA scans obtained for area 'A' indicated in Fig. 4.

ing those produced via a supercritical CO_2 assisted process and those produced using conventional processing.

3.4. Micro-thermal analysis

Micro-thermal analysis was used to characterise the surface of the polymer matrices produced. Thermal conductivity images for batches 8 and 17 are shown in Fig. 4. Although the conductivity image is dominated by surface topography in the image presented, PEO spherulites are clearly visible in sample 17. µMDTA and µTMA measurements were taken at the positions indicated in Fig. 4. Fig. 5 shows the µMDTA and µTMA trace obtained on the surface of batch 8. A melting point at 62 °C is visible, as is a transition at 233 °C, which is typical of depolymerisation and functional group instability in EPO. A melting point at 67 °C, typical of PEO, is observed when µMDTA and µTMA scans are obtained on the spherulite as can be seen in Fig. 6. In both Figs. 5 and 6 rapid softening of the polymer occurs at the melting point as can be clearly seen in the µTMA sensor trace. Fig. 7 is taken from the interspherulitic region of batch 17 and shows transitions at 59 and 222 °C which are typical of EPO, thus indicating that the incorporation of the supercritical CO_2 results in a higher crystallinity of PEO than non-supercritical CO_2 assisted extrusion, with the EPO material in the matrix

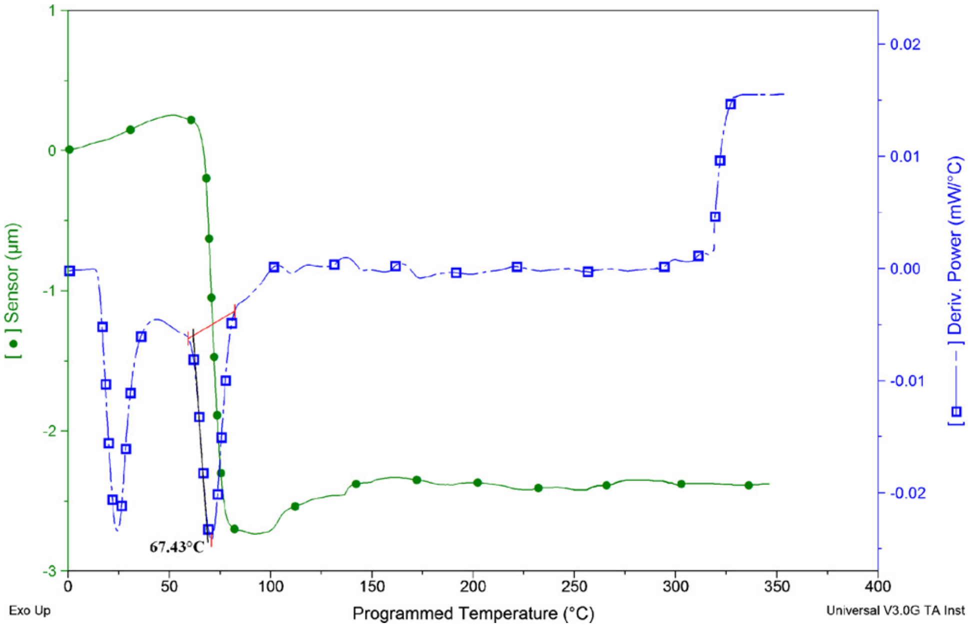

Fig. 6. µMDTA and µTMA scans obtained for area 'B' indicated in Fig. 4.

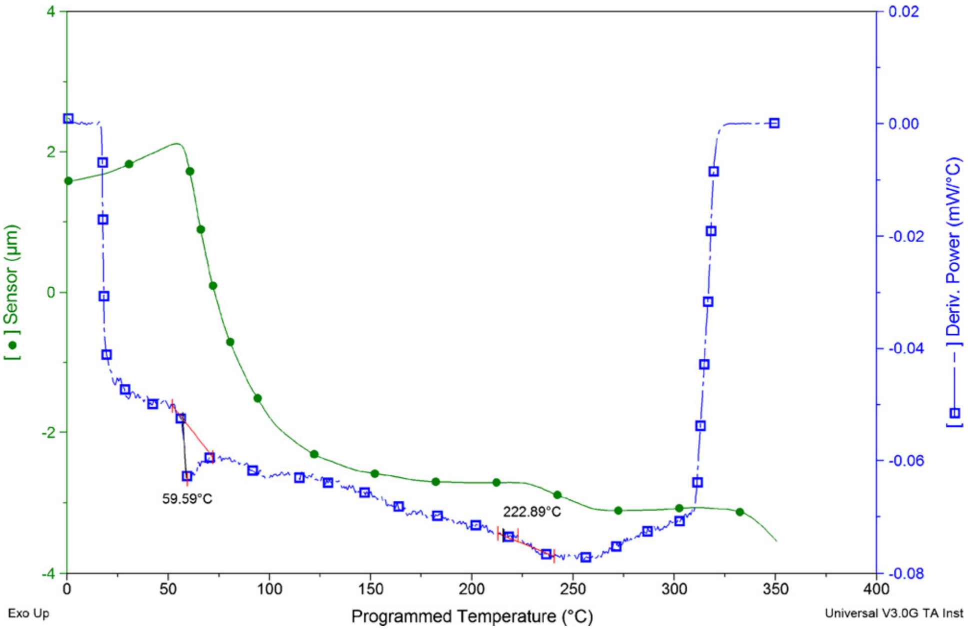

Fig. 7. µMDTA and µTMA scans obtained for area ‘C’ indicated in Fig. 4.

Table 4
Dissolution times in 0.2 M HCl of the batches under investigation

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9
Matrices prepared using conventional extrusion									
$t_{25\%}$ (min)	15	35	35	10	20	35	5	5	35
$t_{50\%}$ (min)	35	65	65	20	30	60	15	25	60
$t_{75\%}$ (min)	55	110	100	50	70	90	45	70	100
	Batch 10	Batch 11	Batch 12	Batch 13	Batch 14	Batch 15	Batch 16	Batch 17	Batch 18
Matrices prepared by supercritical fluid assisted extrusion									
$t_{25\%}$ (min)	15	35	35	10	20	30	5	20	30
$t_{50\%}$ (min)	30	60	60	20	30	55	15	30	55
$t_{75\%}$ (min)	50	100	90	40	60	80	35	70	80

being restricted to the interspherulitic regions of the matrix. The increased crystallinity of the PEO occurs due to the supercritical CO_2 induced mobility of the PEO chains, allowing them to rearrange into kinetically favoured configurations. These effects were also noted for PET (Zhong et al., 1999) and PC (Gross et al., 2000).

3.5. Dissolution testing

In vitro dissolution testing was carried out in two media: 0.2 M HCl and pH 7.2 buffer. The $t_{25\%}$, $t_{50\%}$ and $t_{75\%}$ dissolution values obtained are displayed in Tables 4 and 5. Dissolution of the polymer matrix proceeds at a slightly faster rate as the per-

Table 5
Dissolution times in pH 7.2 buffer of the batches under investigation

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9
Matrices prepared using conventional extrusion									
$t_{25\%}$ (min)	10	30	60	10	20	60	10	30	45
$t_{50\%}$ (min)	25	130	210	30	70	210	30	130	190
$t_{75\%}$ (min)	50	310	510	55	250	530	50	330	510
	Batch 10	Batch 11	Batch 12	Batch 13	Batch 14	Batch 15	Batch 16	Batch 17	Batch 18
Matrices prepared by supercritical fluid assisted extrusion									
$t_{25\%}$ (min)	10	20	45	10	15	45	10	20	30
$t_{50\%}$ (min)	20	90	140	25	50	150	20	90	120
$t_{75\%}$ (min)	40	210	330	40	110	350	40	210	310

centage of drug contained in the polymer matrix is increased. This is thought to be as a direct result of less rate controlling polymer being present in the matrix at higher drug loadings. The drug release occurs at a much quicker rate in the 0.2 M HCl than in the pH 7.2 buffer solution. In all cases studied, samples prepared via supercritical CO_2 assisted processing reached 75% dissolution quicker than those prepared by conventional extrusion. It is proposed that the quicker dissolution is due to a higher internal surface area in the more foam like supercritical CO_2 produced samples. Eudragit EPO does not dissolve above pH 5.5, but swells. This resulted in slower release of API from batches containing EPO in the buffer solution. Samples containing EPO did not release 100% drug in the buffered solution over the length of the experiment. This is most likely a result of active agent remaining entrapped in un-dissolved EPO regions.

4. Conclusion

The work presented described the use of supercritical CO_2 as a plasticiser in the hot melt production of a range of polymer matrices for sustained oral drug delivery. Several batches of matrix material were prepared incorporating an active pharmaceutical ingredient and processed both with and without supercritical CO_2 incorporation. Torque and die head pressure readings taken from the extruder during processing indicate that supercritical CO_2 acts as a placticiser during the extrusion process, thus allowing for higher extrusion speeds to be achieved. Characterisation of the resultant matrices revealed that the placticising effect occurs only in the barrel of the extruder and no viscosity reduction is observed after processing. The matrices were seen to be thermally stable with the incorporation of supercritical CO_2 having no effect on the thermal properties of the matrix when measured post processing. μTA revealed that the incorporation of supercritical CO_2 leads to a higher propensity for crystalisation in PEO. Dissolution analysis showed that the use of supercritical CO_2 during the extrusion process resulted in a faster dissolution of API when compared with unassisted extrusion. The results detailed within this paper indicate that supercritical fluid assisted hot melt extrusion is a viable enhancement to conventional hot melt extrusion for the production of monolithic dosage forms.

Acknowledgements

This study was supported in parts by Pharmaplaz Ltd. and grants from Enterprise Ireland.

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