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The significance of variation in extrusion speeds and temperatures on a PEO/PCL blend based matrix for oral drug delivery

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Abstract

The body of work described in this research paper outlines the use of PEO/PCL blends in the production of monolithic matrices for oral drug delivery. Several batches of matrix material were prepared with carvedilol used as the active pharmaceutical ingredient. The matrices were prepared using various extrusion parameters to investigate the effect of screw speed and barrel temperature on the properties of the drug delivery devices. The resultant extrudate was characterised using steady state parallel plate rheometry, differential scanning calorimetry (DSC) and dissolution testing. Higher screw speeds were observed to result in slightly lower matrix melt viscosity when compared with matrices compounded using lower screw speeds. Dissolution testing showed that the incorporation of the hydrophobic PCL polymer into a PEO matrix results in a retarded drug release profile.

Keywords: Extrusion; PEO; PCL; Drug delivery; Matrix; Temperature

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 a 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) and in the forms of implants and devices for bone and dental repairs (Chasin and Langer, 1990; Ma and Zhang, 2001).

After the discovery of the major commodity and engineering plastics materials in the early to mid part of the 20th century, the cost of bringing a new polymer material to market began to rise dramatically. As a result, both the polymer industry and academia began to focus on developing polymer blends with novel and valuable properties, in order to enlarge the spectrum of available polymers. Various polymeric materials are known for specific or unique characteristics and melt blending of polymers during extrusion is a useful method combining the desired properties of different polymers. A polymer blend can be defined as a combination of two polymers without any chemical bonding between them (Paul, 1978). However, in practice, some blends involve copolymers and there are cases where some chemical interaction occurs between components. Processing of polymer

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blends requires that the compounding equipment quickly melts each polymer (concurrently or sequentially), and then rapidly and efficiently affects distributive and dispersive mixing of the melt components. Co-rotating twin screw extruders are capable of easily satisfying these elementary steps in blending operations. Twin screw extruders are commonly used to mix together two or more materials into a homogeneous mass in a continuous process (Rauwendaal, 1986).

The work described herein investigates the production of monolithic matrices by melt blending PEO with a biodegradable poly(ester) in varying ratios. The work was carried out in order to enable a polymer such as PEO to be melt processed easily by addition of a polymer that is less viscous (without the use of liquid plasticiser systems) and also to determine if simple blending will allow reproducible 'tuning' of the degradability of the resultant matrices. Poly(e-caprolactone) (PCL) is widely used in drug delivery applications (Chasin and Langer, 1990). PCL is much more resistant to chemical hydrolysis and is achiral, a feature that limits the possibility of property modulation through the configurational structure of polymer chains. It is a highly hydrophobic crystalline polymer that degrades very slowly *in vitro* and *in vivo*. High permeability to many drugs and a lack of toxicity has made PCL well suited to controlled drug delivery. Variables such as processing temperature and screw speed could potentially have an effect on the properties of the blends produced via hot melt extrusion. In order to investigate the effect of process variables on the properties of monolithic matrices, PEO/PCL blends were compounded over a range of processing temperatures and screw speeds.

2. Experimental

2.1. Materials

The active pharmaceutical ingredient (API) incorporated in this work was carvedilol obtained from Pharmaplaz Ltd. (Ireland). Polyethylene oxide (MW 1 million) was obtained from Polysciences Ltd. (Germany). Tone 767 PCL was obtained from Dow Ltd. (U.K.).

2.2. Hot melt extrusion

The compounding of materials for this work was carried out on a Micro 27 labscale twinscrew extruder (Leistritz Ltd.) with a 27 mm screw diameter and a 38/1 length to diameter ratio. The required compounding temperature profile was established on the labscale extruder by means of nine temperature controllers placed along the length of the barrel. A tenth temperature controller was used to regulate the temperature at the die. The extrusion conditions used are outlined in Table 1. The batches of polymer extrudates prepared are outlined in Table 2.

2.3. Differential scanning calorimetry

The DSC method was among the techniques used for examination of the extruded pellets. The analyses were preformed using a 2010 DSC (TA Instruments). 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. DSC measurements were carried out at a scanning rate of 10 °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 the heat of fusion and T_m of each batch.

Table 1
Extrusion conditions used to examine the effect of variations in processing conditions on PEO/PCL blends

	Screw speed (RPM)	Temperature (°C)			
		Feed	Metering 1	Metering 2–8	Die
Temperature profile 1	25	50	75	85	95
	50	50	75	85	95
	100	50	75	85	95
Temperature profile 1	25	50	95	110	120
	50	50	95	110	120
	100	50	95	110	120

Table 2
Batch compositions used to determine the effect of processing conditions on PEO/PCL blends

Batch No.	PCL (% by weight)	PEO Mw 1 million (% by weight)	API (% by weight)
1	49	49	2
2	73.5	24.5	2
3	24.5	73.5	2
4	40	40	20
5	60	20	20
6	20	60	20

2.4. Steady state parallel plate rheometry

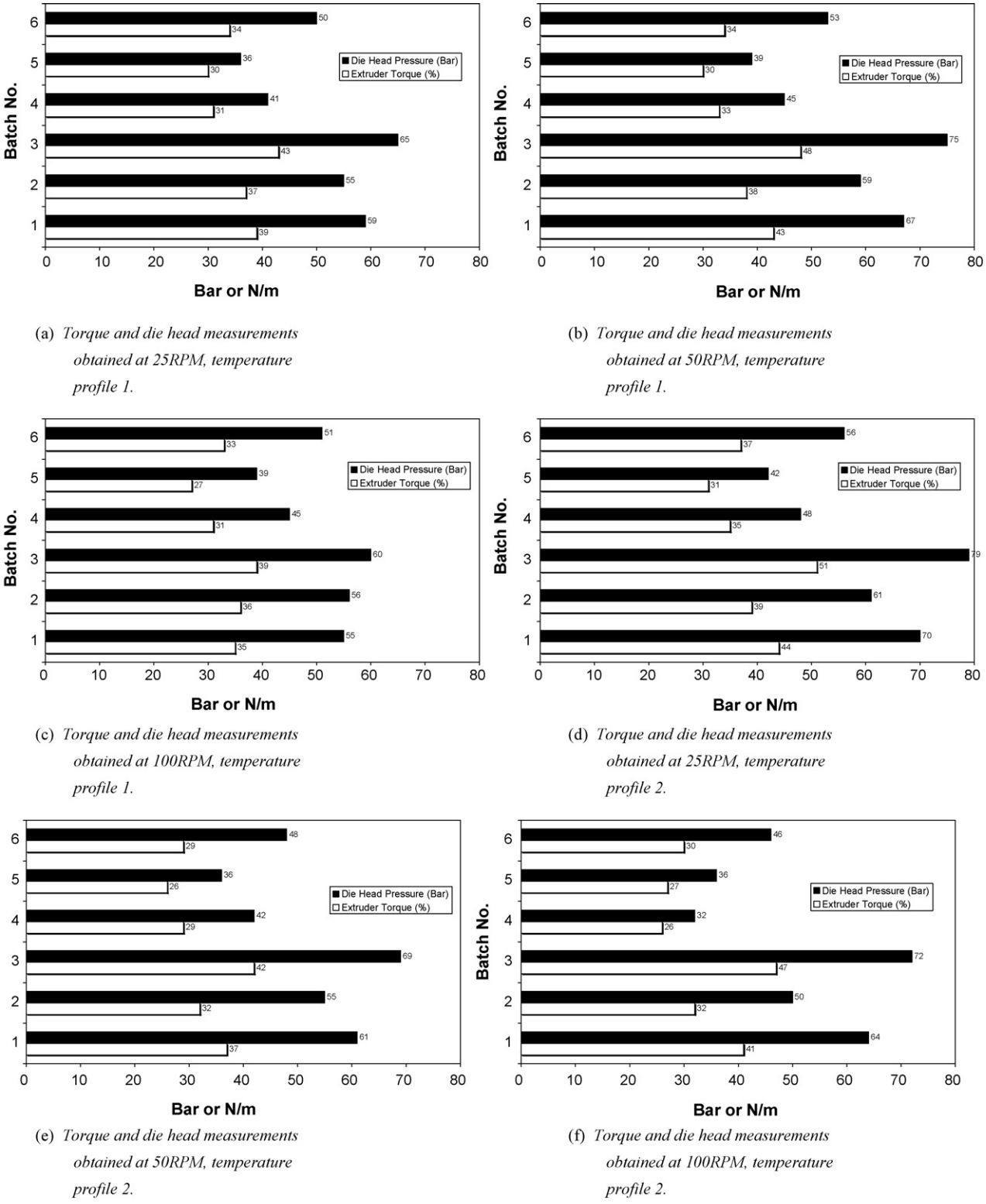
The rheological properties of the samples detailed in this study were measured using a steady state parallel plate viscometer, the AR1000^{TM} rheometer (TA instruments).

All of the tests detailed herein were carried out at a test temperature of 140 °C using an environmental test chamber. 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.

2.5. 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 surface area were pro-

duced by manually cutting the extrudate strands to the desired dimensions. These test specimens were tested in an acidic dissolution medium (0.2 M hydrochloric acid, pH 1.2). The test was carried out at 37 ± 0.5 °C. The stir rate was set to 100 rpm with 900 ml of dissolution media being used per vessel. The wavelength and absorption of a 100% drug concentration for the drug (carvedilol) was determined using a Perkin-Elmer Lambda 40 UV/Vis spectrometer. These values were entered into software calculations prior to commencement of testing. Samples were automatically taken every 15 min, filtered and



(a) *Torque and die head measurements obtained at 25RPM, temperature profile 1.*

(b) *Torque and die head measurements obtained at 50RPM, temperature profile 1.*

(c) *Torque and die head measurements obtained at 100RPM, temperature profile 1.*

(d) *Torque and die head measurements obtained at 25RPM, temperature profile 2.*

(e) *Torque and die head measurements obtained at 50RPM, temperature profile 2.*

(f) *Torque and die head measurements obtained at 100RPM, temperature profile 2.*

Fig. 1. Torque and die head measurements obtained during the compounding of PEO/PCL blends.

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

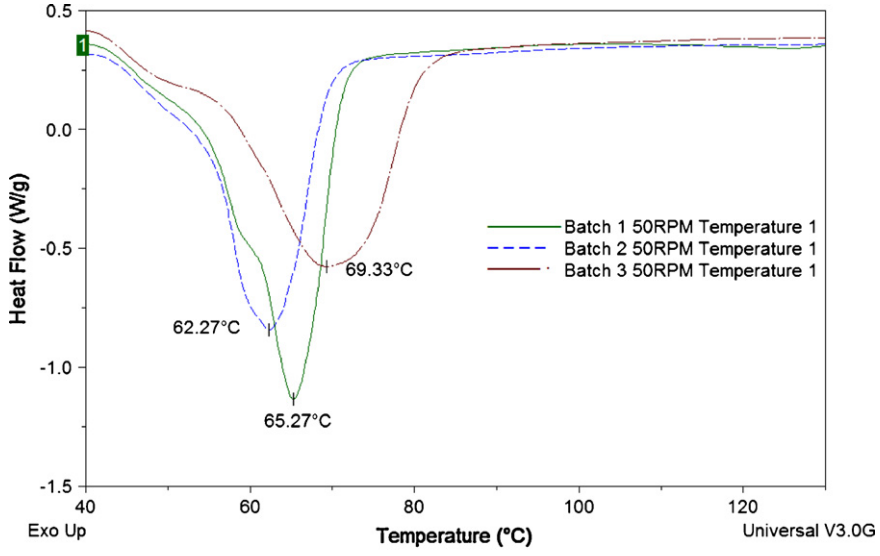
3.1. Processing observations

Extruder torque is a measure of the resistance that the motor experiences as a consequence of the melt viscosity inside the barrel. Verreck (Verreck et al., 2006) 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 previous work, our research group (Lyons et al., 2006, 2007a,b) 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. Fig. 1 shows the torque and die head pressure readings recorded during processing of the PEO/PCL blends over a range of temperatures and screw speeds.

Several trends are apparent in the presented torque and die head pressure data. At the higher processing temperature, lower values for die head pressure and torque are noted as a result of the temperature dependency of polymer melts. Melt viscosity is inversely related to the fractional free volume in the polymer melt, which increases from a small value at the glass transition temperature (T_g) linearly with increasing temperature. Inclusion of higher percentages of API results in lower viscosity of the polymer melt and higher processability of the extrudate. Incorporation of PCL to the polymer matrix also results in lower melt viscosity during extrusion, as the percentage inclusion of PCL increases, the observed values for torque and die head pressure show an incremental proportional decrease. In all cases, higher screw speeds result in higher values of torque and die head pressure as would be expected due to the higher volumes of material being processed per unit time.

3.2. Thermal analysis

Thermal analysis of the batches was carried out to investigate the effects of melt blending PCL and PEO on the thermal properties of the resultant monolithic matrices. Fig. 2 shows the thermograms of batches 1, 2 and 3 processed using temperature profile 1 at 50 RPM. Both virgin PEO and virgin PCL exhibit the T_m as a well defined exothermic peak. The PCL polymer used herein melts at 60 °C, compared with a melting point of 69 °C for the PEO material used in this work. However, in the blended materials, there is one melting peak and one shoulder corresponding to the T_m of the two components, with the shape of the melting peak changing with blend composition. The inclusion of PCL is seen to result in a depression of the melting point of the matrix. The depression in the melting point becomes more substantial with increasing percentage inclusion



Batch number	PCL (%wt)	PEO Mw 1 million (%wt)	API (%wt)
1	49	49	2
2	73.5	24.5	2
3	24.5	73.5	2

Fig. 2. Overlaid thermograms of batches 1, 2 and 3.

Table 3
Melting temperatures of the PCL/PEO blends compounded at a range of temperatures and screw speeds

Screw speed (RPM)	Batch 1 (°C)	Batch 2 (°C)	Batch 3 (°C)	Batch 4 (°C)	Batch 5 (°C)	Batch 6 (°C)
Processed using temperature profile 1						
50	65.105	63.635	67.675	64.47	63.85	66.985
100	66.325	64.215	67.535	64.04	62.195	65.625
Processed using temperature profile 2						
25	63.91	61.465	67.465	63.69	61.39	66.615
50	64.445	62.98	66.545	63.6	61.58	65.18
100	65.015	64.425	66.795	62.685	60.255	63.365

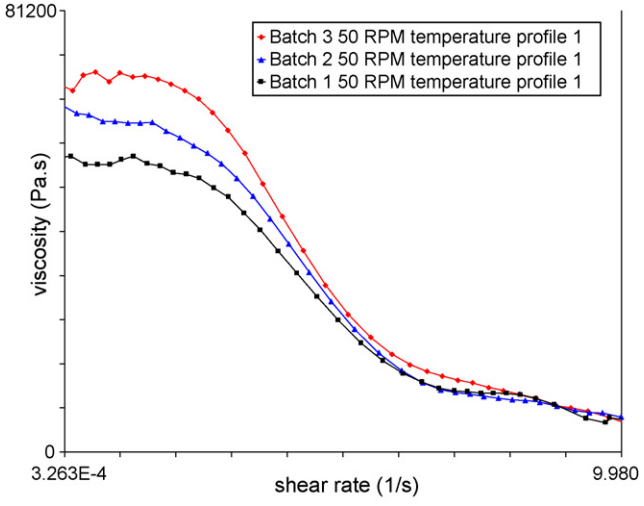
of PCL. This behaviour has been noted in the literature (Qiu et al., 2003).

Processing variables are not seen to have any discernable impact on the melting points of the resultant matrices. The melting points for all the matrices under investigation are presented in Table 3. Batches 4, 5 and 6 comprise the same polymer ratios as batches 1, 2 and 3; however batches 4, 5 and 6 are loaded with 20 wt% API. The batches containing higher percentages of API were seen to exhibit depressed melting points compared to matrices with lower drug loadings. This phenomenon is due to the API acting as a plasticiser in the matrix. This has been noted in the literature in previous work by Ozeki et al. (1997). This is also in agreement with values observed in the torque and die head pressure readings, obtained during processing of the polymer matrices.

Miscibility of polymer blends is generally studied using DSC. A single glass transition temperature is the most widely and conventionally used criterion for determining the miscibility of a polymer blend. A single composition dependant T_g indicates full miscibility conversely, an immiscible polymer blend exhibits more than one T_g. However, because the melting and glass transition temperatures of PEO and PCL are relatively close, determination of miscibility by conventional DSC is not possible in this case. Kuo et al. (2002) reports that PEO and PCL are miscible by studying the crystallisation temperatures of the blends, compared with those of the homopolymers. A recent study (Qiu et al., 2003) showed that PEO/PCL blends are immiscible. In that work the investigators questioned the validity of the findings of Kuo et al. In the case of the matrices in this work, miscibility of PCL and PEO is not a requisite for the matrices to function as drug delivery vehicles and was therefore not investigated further.

3.3. Steady state rheometry

Steady state rheometry was carried out on all the matrices under investigation in order to ascertain the rheological effects of incorporation of PCL into the polymer matrix. The effect of altering the process parameters on the flow behaviour of the matrices was also investigated in this manner. Fig. 3 shows the data obtained from steady state testing of batches 1, 2 and 3 processed at 50 RPM using temperature profile 1. The data presented shows a trend typical of that obtained in all the batches under investigation. The batches containing higher proportions



Batch number	*PCL (%wt)*	*PEO Mw 1 million (%wt)*	*API (%wt)*
1	*49*	*49*	*2*
2	*73.5*	*24.5*	*2*
3	*24.5*	*73.5*	*2*

Fig. 3. Steady state data for batches 1, 2 and 3.

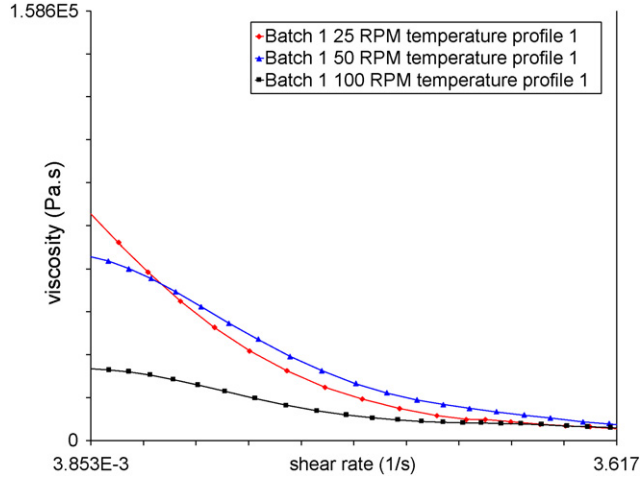
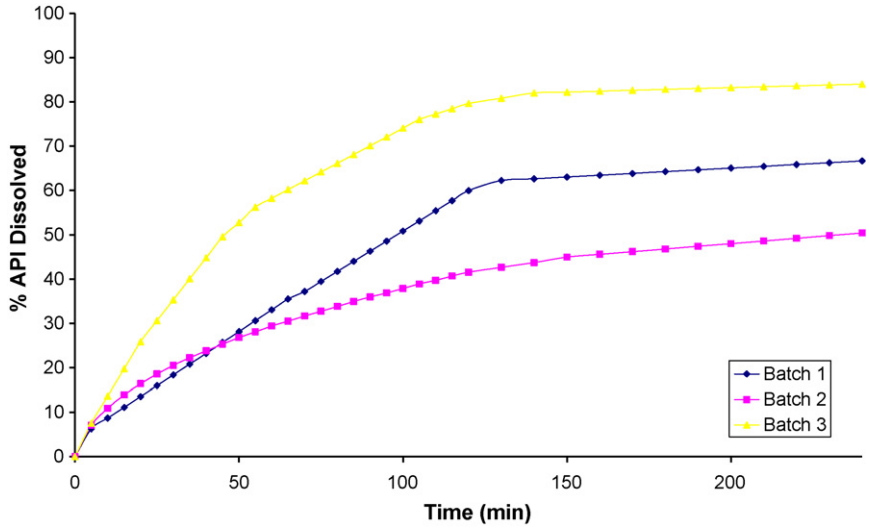


Fig. 4. Steady state data for batch 1 (a 49 wt%:49 wt% PEO/PCL blend, loaded with 2 wt% API) after processing at varying screw speeds.

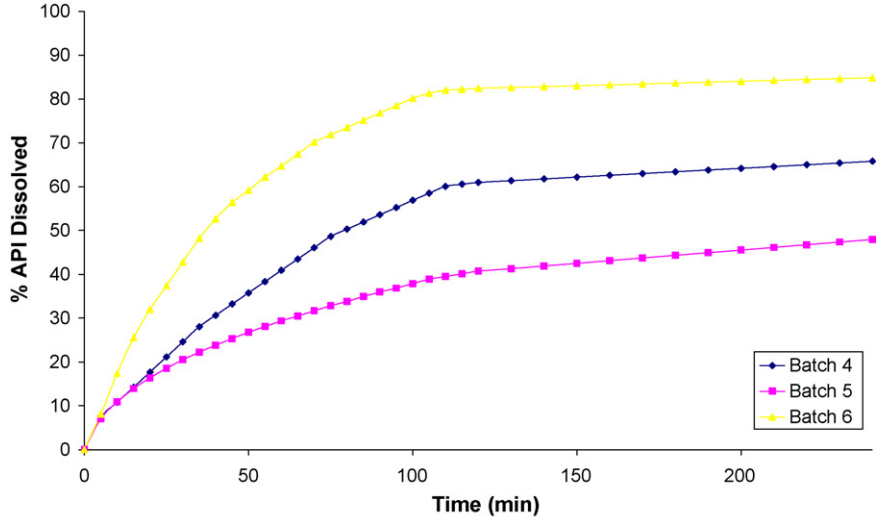


Batch number	PCL (%wt)	PEO Mw 1 million (%wt)	API (%wt)
1	49	49	2
2	73.5	24.5	2
3	24.5	73.5	2

Fig. 5. Dissolution results obtained from batches 1, 2, and 3 processed at 25 RPM using temperature profile 1.

of PEO are seen to be more viscous than the batches containing higher loadings of PCL. This is in agreement with observations made during processing of the blends, which showed that the blends containing PCL were easier to process.

The effect of processing at different temperatures was not seen to have any discernable effect on the rheological properties of the resultant matrices. However, the effect of processing at different screw speeds is seen to have a slight effect on the



Batch number	PCL (%wt)	PEO Mw 1 million (%wt)	API (%wt)
4	40	40	20
5	60	20	20
6	20	60	20

Fig. 6. Dissolution results obtained from batches 4, 5 and 6 processed at 25 RPM using temperature profile 1.

Table 4
Summarised drug release data obtained from dissolution testing of the processed using temperature profile 1, where t25%, t50% and t75% represent the time taken in minutes for 25%, 50% and 75% of the total API contained in the matrix to become dissolved in the test medium, respectively

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Processed at 25 RPM using temperature profile 1						
t25% (min)	45	45	20	35	45	15
t50% (min)	100	240	50	80	–	40
t75% (min)	–	–	105	–	–	85
% API released after 240 min	66.68	50.42	84.04%	65.79	47.95	84.83
Processed at 50 RPM using temperature profile 1						
t25% (min)	50	45	20	30	40	15
t50% (min)	110	235	45	85	235	40
t75% (min)	–	–	115	–	–	90
% API released after 240 min	64.35	51.01	79.32	63.84	50.56	85.37
Processed at 100 RPM using temperature profile 1						
t25% (min)	45	45	20	30	45	15
t50% (min)	95	–	50	90	–	35
t75% (min)	–	–	110	–	–	85
% API released after 240 min	68.16	48.09	81.93	67.54	49.63	81.36

flow behaviour of the matrices. Fig. 4 displays the rheological data for batch 1 processed at different screw speeds. It can be seen from the data presented that processing at 100 RPM results in a slight drop in the viscosity of the matrix. This is likely to be as a result of the mechanical shearing of polymer chains at the higher screw speed. This is consistent with findings in the literature (Homminga et al., 2005; Lyons et al., 2007a). This slight drop in viscosity is not seen to be significant enough to adversely affect the matrices as no corresponding drop in the melting point of the matrices processed at 100 RPM was noted during thermal analysis. The percentage inclusion of API was seen to have an effect on the viscosity of the matrices. Higher loadings of API resulted in reduced viscosity of the matrices consistent with the API acting as a plasticiser, as suggested during analysis of the thermal behaviour of the matrices.

3.4. Drug release

PCL–PEO block copolymer micelles have been reported as efficient drug carriers (Allen et al., 2000; Aliabadi et al., 2005; Geng and Discher, 2006). In addition, PEO/PCL blends have been used as microspheres for drug delivery (Lin et al., 1999; Park et al., 2005) as drug loaded biodegradable nerve guides (Verreck et al., 2005) and as porous scaffolds for tissue engineering using co-extrusion (Washburn et al., 2002;). In this work the drug release profiles from the prepared monolithic matrices were examined in 0.2 M HCl (pH 1.2). Figs. 5 and 6 show dissolution profiles typical of those obtained. Drug release from the monolithic matrices was found to vary substantially as the amount of PCL in the matrices was altered. The incorporation of PCL in the matrices was seen to retard the drug release from the polymer matrices, with the degree of retardation being propor-

Table 5
Summarised drug release data obtained from dissolution testing of the batches processed using temperature profile 2, where t25%, t50% and t75% represent the time taken in minutes for 25%, 50% and 75% of the total API contained in the matrix to become dissolved in the test medium, respectively

	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
Processed at 25 RPM using temperature profile 2						
t25% (min)	40	50	25	35	40	15
t50% (min)	95	–	50	80	235	45
t75% (min)	–	–	110	–	–	85
% API released after 240 min	68.50	46.31	81.69	64.39	50.61	85.69
Processed at 50 RPM using temperature profile 2						
t25% (min)	45	45	20	35	50	20
t50% (min)	100	–	50	80	–	40
t75% (min)	–	–	105	–	–	95
% API released after 240 min	66.31	48.37	85.13	65.06	45.32	81.51
Processed at 100 RPM using temperature profile 2						
t25% (min)	40	45	20	35	45	15
t50% (min)	105	235	45	75	240	40
t75% (min)	–	–	95	–	–	85
% API released after 240 min	63.23	50.96	87.07	66.37	50.19	86.38

tional to the amount of PCL in the matrix. This is to be expected, as PCL is a highly hydrophobic polymer.

The matrices prepared in this work show that the rate of drug release in a PEO/PCL monolithic matrix can easily be tailored by simply altering the composition of the binary blend. Matrices with higher loading of API were seen to release the active agent at a slightly quicker rate than those with lower loadings. This is thought to be due to less rate controlling polymer being present in the matrices with higher drug loading.

Tables 4 and 5 show summarised data for the dissolution tests carried out in this work. Neither the screw speed nor the temperature profiles employed in the compounding of the matrices were seen to have a significant effect on the drug release profiles from the matrices.

The drug release profiles in this work would not appear to be useful for a commercial controlled release system as the drug release occurs over such a short period. However, the use of PCL as a plasticiser for PEO systems of higher molecular weight produced by hot melt extrusion may prove to be an attractive option for increasing processability without the use of liquid plasticisers which may be prone to leaching.

4. Conclusion

The work presented describes both the use of PEO/PCL blends as monolithic dosage forms and also the effect of extrusion process variables on the properties of the resultant matrices. The percentage inclusion of PCL in the matrices was altered in order to investigate the effect of PCL on the properties and processability of the matrix. Both processing temperature and screw speed were varied during the production of the matrices described in this work to ascertain if the process parameters used could affect the end properties of the matrices. Torque and die head pressure measurements taken during processing, indicate that inclusion of PCL renders the matrices more easily processable. Higher processing temperatures also resulted in easier processing of the matrices due to lower polymer melt viscosity. Higher screw speeds resulted in higher observed values of torque and die head pressure due to the higher shear being generated during the extrusion process. Thermal analysis of the blends indicated that as the blend composition varied, so too did the melting behaviour. No adverse thermal effects were associated with varying the processing conditions. Steady state rheometry of the matrices indicated that the blends incorporating higher levels of PCL were less viscous than those consisting of higher levels of PEO. This result might prove useful in the production of PEO based matrices with higher molecular weights, as PCL could be used to act as a plasticiser in the system, without the usual drawbacks inherent in some plasticiser systems. Higher screw speed was observed to result in slightly lower matrix melt viscosity when compared with matrices compounded using lower screw speeds. Dissolution testing showed that the incorporation of hydrophobic PCL polymer into a PEO matrix results in a retarded drug release profile. The greater the amount of PCL, the slower the drug release.

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