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Poly(ethylene glycol) layered silicate nanocomposites for retarded drug release prepared by hot-melt extrusion

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ABSTRACT

Composites of paracetamol loaded poly(ethylene glycol) (PEG) with a naturally derived and partially synthetic layered silicate (nanoclay) were prepared using hot-melt extrusion. The extent of dispersion and distribution of the paracetamol and nanoclay in the PEG matrix was examined using a combination of field emission scanning electron microscopy (FESEM), high resolution transmission electron microscopy (HRTEM) and wide-angle X-ray diffraction (WAXD). The paracetamol polymorph was shown to be well dispersed in the PEG matrix and the nanocomposite to have a predominately intercalated and partially exfoliated morphology. The form 1 monoclinic polymorph of the paracetamol was unaltered after the melt mixing process. The crystalline behaviour of the PEG on addition of both paracetamol and nanoclay was investigated using differential scanning calorimetry (DSC) and polarised hot-stage optical microscopy. The crystalline content of PEG decreased by up to 20% when both drug and nanoclay were melt blended with PEG, but the average PEG spherulite size increased by a factor of 4. The time taken for 100% release of paracetamol from the PEG matrix and corresponding diffusion coefficients were significantly retarded on addition of low loadings of both naturally occurring and partially synthetic nanoclays. The dispersed layered silicate platelets encase the paracetamol molecules, retarding diffusion and altering the dissolution behaviour of the drug molecule in the PEG matrix.

1. Introduction

For almost four decades polymer layered silicate (nanoclay) nanocomposites have attracted intense research interest with the promise of applications across many industries. The literature in the field is now substantial and numerous review articles have been published on the topic (Alexandre and Dubois, 2000; Ray and Bousmina, 2005). However, the proposed widespread commercial use of this technology has not been fully realised, with a few notable exceptions in automotive, barrier (packaging), fire retardant and structural applications. This slow progress is in part due to the difficulties in melt blending nanoclays and polymers at elevated temperatures to achieve a homogeneous dispersion of nanoclay platelets in the polymer matrix without degradation of both polymer and nanoclay. This constraint is in part eliminated for low melting point biodegradable polymer/biopolymer layered silicate nanocomposites, such as those with poly(caprolactone) (Calberg et al., 2004; Chen and Evans, 2006; Lepoittevin et al., 2002), poly(ethylene glycol) (Chen and Evans, 2005), poly(ethylene-oxide)PEO (Choi et al., 2001; Zhao and Samulski, 2003), polylactides (Chang et al., 2003; Nam et al., 2003; Paul et al., 2003) and poly(vinylpyrrolidone) (Koo et al., 2003), where improved mechanical and functional stability of biopolymers can be achieved. Concomitant with the development of polymer nanocomposites, there has been renewed interest in the area of hot-melt extrusion as a technique for the preparation of polymer/bio-molecule composite materials for drug delivery (Brietenbach, 2002). The main advantage of using extrusion technology is the ability to move from batch processing normally used for polymer/drug manufacture to a continuous process. This enables consistent product flow at relatively high throughput rates, such that a drug loaded polymer can be extruded, for example, into a sheet or thin film for patches or into a tube for catheters or other medical tubing. Furthermore, the bioactive molecule loaded extrudate can be pelletised followed by secondary melt processing, such as injection moulded into heart valves. A number of researchers have examined the use of hot-melt extrusion to prepare biomedical polymer–drug mixtures, for example, Eudragit (Bruce et al., 2005), hydroxypropylcellulose (Repka et al., 2005), PEO (Crowley et al., 2002) and a commercially available melt-extruded formulation, Kaletra (Rosenburg et al., 2005). Other groups have used solution cast methods to produce drug loaded polymer nanocomposites in

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the form of hydrogels (Lee and Chen, 2004), nanoparticles (Dong and Feng, 2005) and solution cast nanocomposites (Cypes et al., 2003) although the latter has limitations with regard scale-up of the process and is not environmentally friendly. Drug release from polymeric matrices has been modelled by different researchers (Siepmann et al., 2002), and the mechanisms of drug release from solid dispersions in water-soluble polymers has been reviewed by Craig (2002). Molecular interactions between the drug molecule and polymer chains also affect the mechanism of drug release. Layered silicates alone have also been used in pharmaceutical applications as adsorbents, thickeners and excipients (Carretero, 2002) and recent research has outlined the use of layered silicates (Lin et al., 2006), mesoporous silicates (Cavallaro et al., 2004) and double layered hydroxides as drug and gene delivery vehicles (Desigaux et al., 2006). Here we report the facile preparation of paracetamol loaded PEG and PEG nanocomposites using hot-melt extrusion and demonstrate the potential to manipulate the release of bio-active molecules from PEG using nanoscale layered silicates (nanoclays). The time taken for 100% release of paracetamol from the PEG matrix increased almost 7-fold on inclusion of 5 wt.% of a partially synthetic fluoromica. The dispersed layered silicate platelets encase the paracetamol molecules retarding diffusion of the drug molecule throughout the PEG matrix.

2. Materials and methods

2.1. Materials

Poly(ethylene glycol) Polyglykol 20000S was supplied by the Clariant (Horsforth, UK), paracetamol (acetaminophen, USP purity >99%, referred to as P) was purchased from Sigma–Aldrich (Dorset, UK) and Cloisite 20A (referred to as M) was purchased from Southern Clay Products Inc. (USA), and is a natural montmorillonite modified with a dimethyl, dehydrogenated tallow, quaternary ammonium surfactant. Somasif MEE (referred to as S) was supplied by CBC Co Ltd. Japan and is a partially synthetic layered silicate, a fluoromica (Somasif ME100) modified with bis(2-hydroxylethyl methyl dodecylammonium chloride).

2.2. Preparation of nanocomposites

PEG, paracetamol(5 wt.%) and the layered silicate(1, 3 and 5 wt.%) were melt compounded in a Collin Zk25 twin screw extruder with 6 heater zones set at 55, 60, 60, 60, 60, and 60 °C and a screw speed of 60 rpm. The extrudate was air cooled using a gun blowing air onto the extrudate just after the die exit and further cooled along a customised conveyor belt, (Collin CR 136/350),).

2.3. Characterisation

Wide-angle X-ray diffraction (XRD) patterns were recorded using a PANanalytical X'Pert Pro MPD XRD (Almelo, The Netherlands) instrument using Cu Kα radiation (λ = 1.54 Å) generated at 45 kV and 40 mA. The samples were scanned at 0.63°/min in the range of 2θ = 1–40° and a step size of 0.02°. The surface morphology of all samples was examined using a JEOL JSM-6500F Field Emission Scanning Electron Microscope at 10 keV, both cryo-fractured and surface samples were sputtered with a thin layer of gold prior to imaging. Samples for examination using transmission electron microscopy were obtained using a Reichert-Jung Ultracut E (FC-4E cryo-unit) ultramicrotome with a diamond knife at −117 °C and collected onto 400 mesh copper grids. Images were obtained using a FEI Tecnai F20 field emission high-resolution transmission electron microscope (Philips) at 200 keV.

Non-isothermal crystallisation and melting experiments were conducted on thin specimens (~1 mm) of the composite systems placed between microscope glass slides and in turn placed on a hot stage (Mettler Toledo FP90) attached to a LSL Leica-Toleda PP polarizing microscope equipped with a video camera capture system. The samples were heated at 5–80 °C then cooled at 5 °C to room temperature. Differential scanning calorimetry (PerkinElmer high speed Diamond DSC) was used to measure the thermal properties of the PEG, paracetemol and extrudates (~5 mg) of the composite materials using a heating and cooling rate of 10 °C/min between 20 and 100 °C. The crystalline content of all materials was calculated using 197 J/g for a theoretically 100% crystalline PEG and corrected for blend composition.

Test specimens for drug release studies were prepared by compression moulding disks (diameter 18 mm; height 1.2 mm). Dissolution studies were performed using a Copley DIS 8000 USP standard dissolution apparatus with paddle stirrer (Nottingham, UK). The dissolution medium (900 ml of distilled water) was maintained at 37 ± 0.5 °C and stirred at 50 rpm. At predetermined intervals, 5 ml of sample was withdrawn (5 ml syringe Terumo syringe without needle) and replaced with the same volume of fresh dissolution medium at 37 ± 0.5 °C to maintain constant volume. The samples were filtered with a Millipore 0.45 m Millex syringe driven filter unit and analysed by UV spectroscopy using a Hitachi U2000 UV Spectrophotometer at 243 nm using 10 mm silica cells (VWR International Ltd. 307 370002). The results reported are an average of 4 measurements ±S.D. and a paracetamol calibration curve was prepared for this system.

3. Results and discussion

Composites of PEG with 5 wt.% P and 1, 3 and 5 wt.% of either a naturally derived montmorillonite (M) or partially synthetic fluoromica (S) were prepared using a twin-screw extruder. The extent of the dispersion of both paracetamol and nanoplatelets of layered silicates and the morphology of the nanocomposites were investigated using a combination of wide-angle X-ray diffraction (WAXD), field emission scanning electron microscopy (FESEM) and high resolution transmission electron microscopy (HRTEM). Fig. 1a and b show the WAXD patterns for PEG, PEGP5, PEGP5M and PEGP5S nanocomposites respectively. The d-spacing for the d_{001} basal space reflection for M, S and the respective nanocomposites were determined using Bragg's equation:

$$n\lambda = 2d \sin\theta \quad (1)$$

where n is an integer (n = 1), λ is the wavelength of the incident X-ray beam (λ = 1.5406 Å), θ is the angle of incidence of the X-ray beam and d is the inter-atomic distance between silicate layers.

The d_{001} spacing for M was 2.54 nm which on addition of 5 wt.% M to PEG increased to 4.19 nm, suggesting a highly intercalated structure. Addition of 5 wt.% paracetamol to PEGM composites resulted in a slight decrease in d_{001} spacing, from 4.19 to 3.77, 3.73 and 3.69 nm with increasing amounts of M, from 1 to 3 and 5 wt.%, respectively. For S, the d_{001} spacing was determined to be 2.05 nm which again increased, to 3.10 nm on addition of 5 wt.% S to PEG, again implying intercalation of the polymer chains in the inter-gallery spacing of the layered silicate S. However, in contrast to the PEGM composites, addition of 5 wt.% paracetemol to PEGS, irrespective of the loading of S, did not yield a reduction in d_{001} spacing. The differences in expansion of the galleries of the 2 nanoclays used can be attributed to the different conformations and arrangements of the surfactants on the layered silicates in addition to the larger aspect ratio of the fluoromica (S).

The morphology of the composite materials was examined using FESEM, see Fig. 2. The porous surface of PEG shown in (a) was

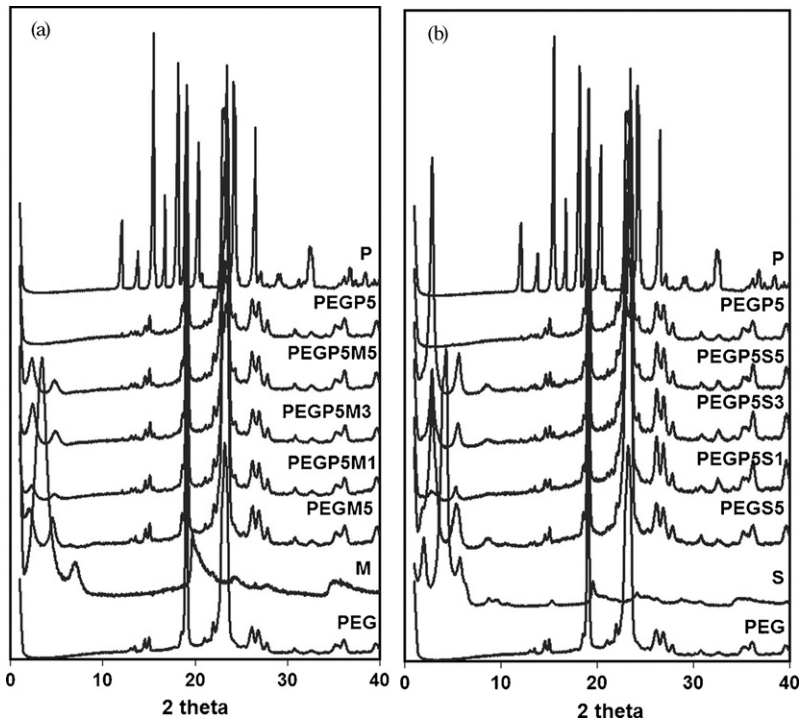

Fig. 1. WAXD patterns for PEG (a) montmorillonite (M) and b) fluoromica (S) based nanocomposites.

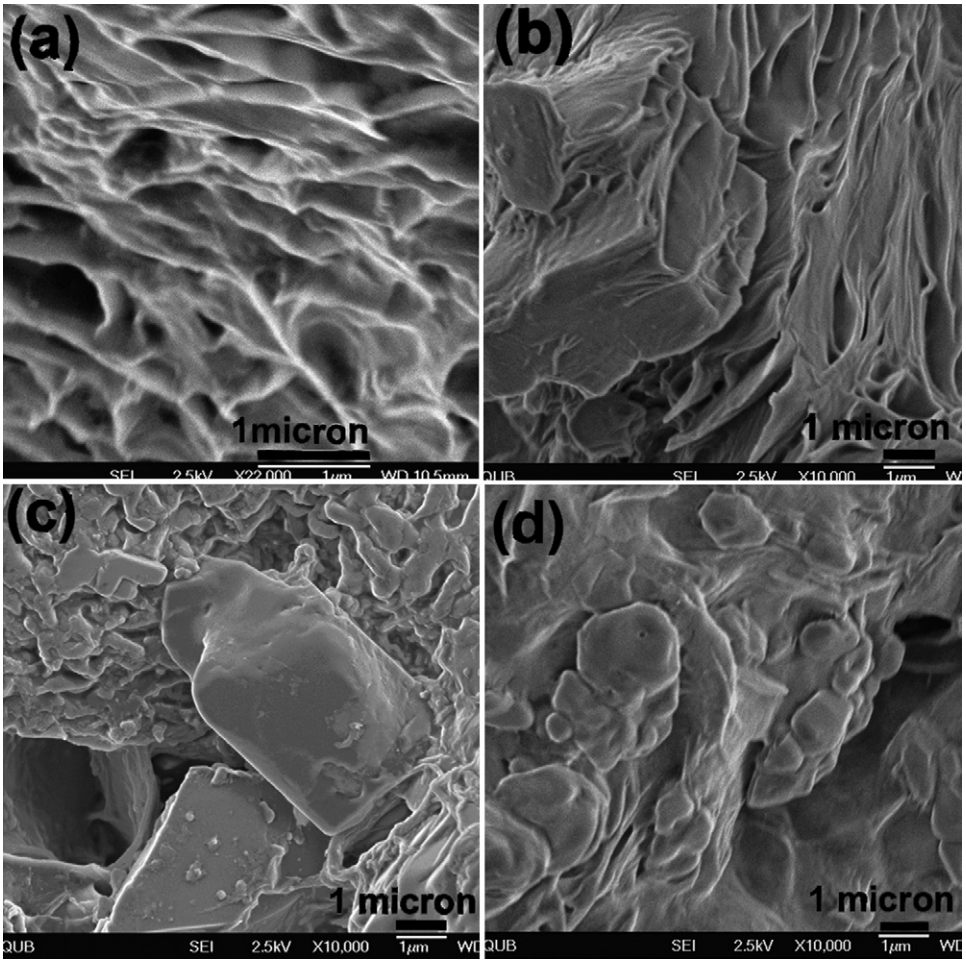

Fig. 2. FE-SEM images of fractured surfaces of (a) PEG, (b) PEGP5, (c) PEGP5M1 and (d) PEGP5S5.

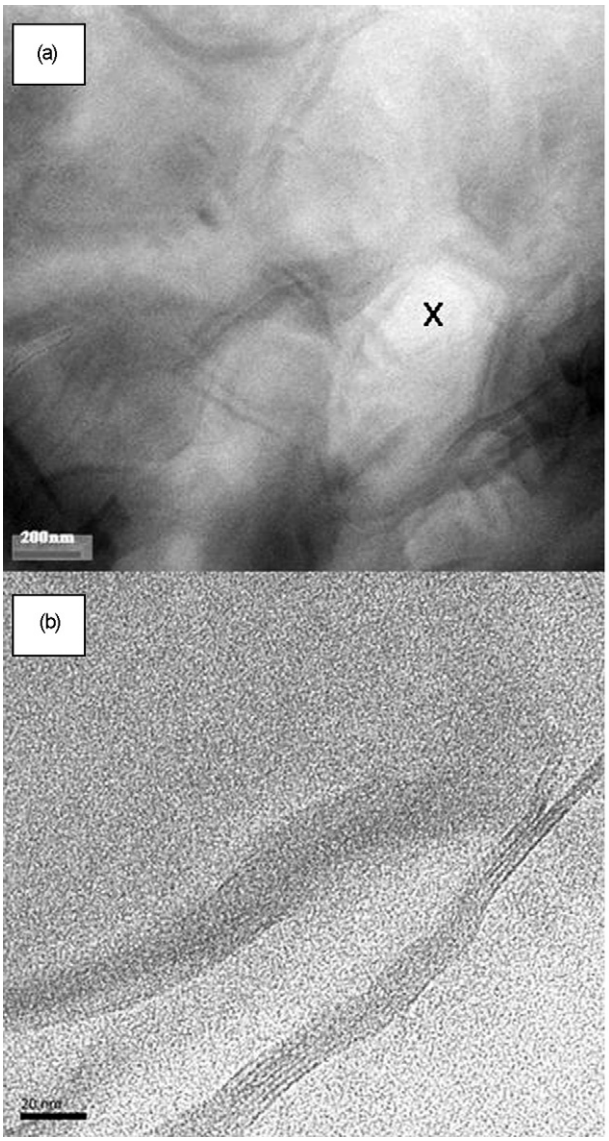

Fig. 3. Bright field HRTEM images of PEGP5S5 showing (a) paracetamol crystal surrounded by layered silicates dispersed in a PEG matrix (scale bar 200 nm) and (b) sub-20 nm groups of platelets in PEG matrix (scale bar 20 nm).

unaffected by addition of paracetemol (b), however, the platelet structure of both the natural montmorillonite (c) and partially synthetic fluromica (d) are clearly evident, resulting in a less porous surface. The entrapment of the paracetemol molecules by the clay platelets is obvious from the HRTEM image shown in Fig. 3a. The drug molecule (marked X) is surrounded by layered silicate platelets, the latter structures confirmed by energy dispersive X-ray analysis. Further evidence is also provided from HRTEM studies for a highly intercalated, partially exfoliated morphology, as many sub-20 nm thick groups of platelets were readily observed, as shown in Fig. 3b.

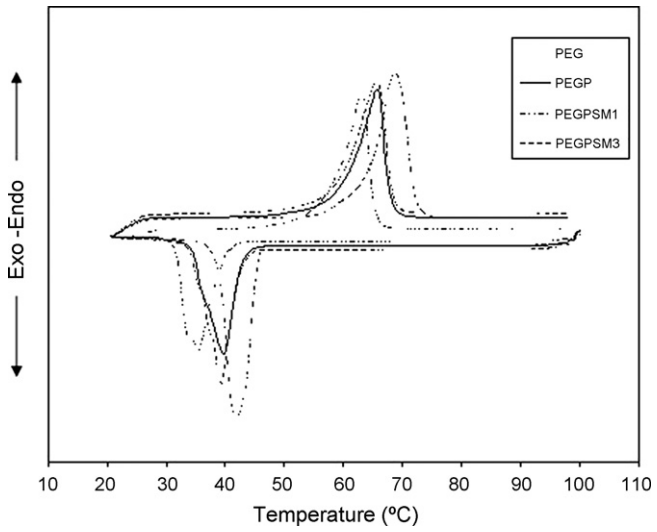

Fig. 4. DSC thermograms of PEG, PEGP, PEGP5M1 and PEGP5M3.

The thermal and crystallisation behaviour of PEG after addition of paracetamol and nanoclays was examined using DSC. By way of example, the thermograms for PEG, PEGP and the nanocomposites containing 1 and 3 wt.% M are shown in Fig. 4 and the heats of mixing (ΔH), onset of melting and crystallisation, T_g, T_m and crystalline content for all materials listed in Table 1. Typically, the melting point (T_m, °C) of the PEG decreased by 3 °C on addition of either 5 wt.% paracetamol and either nanoclay and the temperature of crystallisation (T_c, °C) by approximately 4 °C. The crystalline content of the PEG decreased by 8% on addition of paracetemol, 9% on addition of the montmorillonite but was unchanged when synthetic fluromica was added. The nucleation effect of M on PEG is clearly evident from the thermogram for PEGP5M1 in that the crystallisation peak has broadened and started to split into 2 peaks, the presence of M alters the crystallisation kinetics of PEG producing less perfect more poorly packed crystallites. Interestingly, this effect was not observed when 3 wt.% M was added, perhaps as a consequence of the increased concentration of M being less well dispersed, thus less effective surface area available for nucleation. However, when both drug and either montmorillonite or partially synthetic fluoromica were blended with PEG, the crystalline content fell by 15 and 20%, respectively. While the DSC measurements were performed in triplicate and the changes in T_m and T_c are on the limits of instrument error, the significant changes in crystalline con-

Table 1
Time to release and diffusion coefficients (D) for paracetamol release from PEG and PEG nanocomposites.

Sample	Onset crystal (°C)	Onset melt (°C)	T_c (°C)	T_m (°C)	ΔH_c (J/g)	ΔH_m (J/g)	Crystallinity (%)
PEG	47.2	54.2	41.8	68.7	−182.0	161.4	81.9
PEGP5	47.2	48.9	39.8	65.7	−155.8	156.9	75.6
PEGM5	45.8	52.5	37.4	64.7	−162.4	154.9	74.7
PEGP5M1	42.9	43.3	35.3	63.0	−161.4	155.8	74.3
PEGP5M3	46.3	48.5	39.2	65.5	−173.2	153.5	71.7
PEGP5M5	43.2	43.4	37.3	64.5	−168.7	151.2	69.1
PEGS5	49.0	53.0	40.5	68.2	−181.8	168.2	81.7
PEGP5S1	44.0	48.0	37.1	64.9	−168.3	153.0	73.0
PEGP5S3	45.7	46.8	39.5	64.9	−156.5	140.4	68.0
PEGP5S5	47.5	45.5	38.4	64.9	−148.6	148.8	65.6

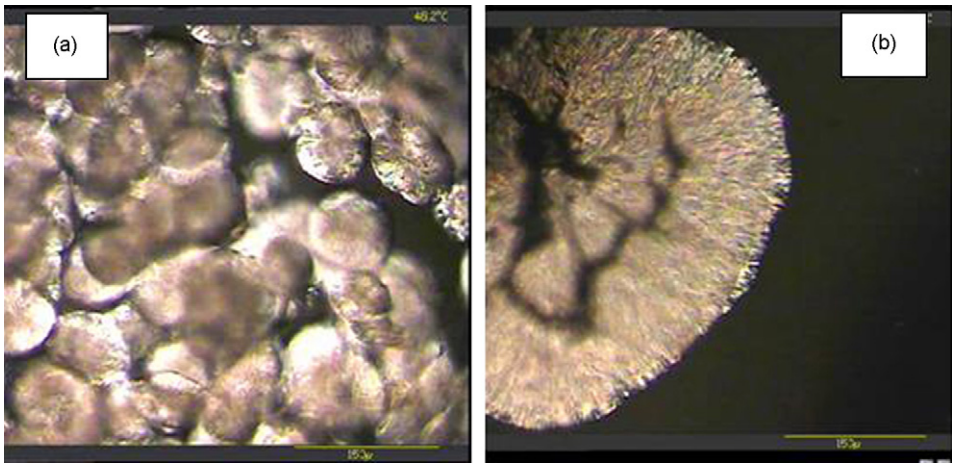

Fig. 5. Optical micrographs captured taken from the hot stage microscopy videos of the onset of crystallization for (a) PEG (scale bar 150 μm) and (b) PEGP5 (scale bar 150 μm).

tent after melt blending PEG with paracetamol and nanoclay further support the evidence from HRTEM and WAXD that a highly intercalated and partially exfoliated morphology predominates, in that, the mobility of the PEG chains is constrained by the clay platelets, thus hindering PEG crystallisation. From DSC, the paracetamol used in this study had a melting point of 170 °C, typical of the form 1 monoclinic polymorph of paracetamol, in agreement with our and previous SEM and WAXD observations (Nichols and Frampton, 1998). Polarised light hot-stage optical microscopy experiments were performed and showed that the crystal structure of paracetamol was retained after melt mixing with PEG at 60 °C. Concomitant with the reduction in the crystalline content of PEG on addition of paracetamol, the spherulite size of the PEG was significantly altered. Fig. 5 shows images captured during videoing the cooling of PEG and PEGP5 demonstrating the addition of paracetamol to PEG results in spherulites with larger diameters, on average increasing from 75 μm to about 300 μm and illustrates the effect paracetamol has on the crystallisation behaviour of PEG.

The *in vitro* dissolution and drug release kinetics of paracetamol from PEG with and without nanoclay was investigated. Fig. 6 shows the percentage paracetamol release as a function of time. There are three distinct steps in drug release from a matrix; liquid penetration into the matrix, dissolution of the drug and diffusion. Within the first 15 min the release rate is significantly altered by the presence of the nanoclays, the effect more pronounced for S and with increasing concentration of S in the composite. Liquid penetration and the dissolution behaviour of paracetamol have been retarded. The time for 50, 80 and 100% release of paracetamol from each formulation was measured and the diffusion coefficients determined using classical Fickian diffusion theory, see Table 2. As paracetamol is poorly soluble in water the release profile of the paracetamol powder is also included in both sets of results as a control. Furthermore, to aid the accuracy of the dissolution experiments the composite materials were compression moulded into disks having uniform dimensions. Eq. (2) can be used to describe the diffusion controlled release behaviour of drugs which have an assumed diffusion coefficient (D) for one dimensional diffusion:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(n+1)^2}\left\{-\frac{(2n+1)^2 D\pi^2}{l^2}t\right\} \quad (2)$$

where M is defined as the mass of drug released at time t, M_∞ is the mass of drug released as time approaches infinity and l is the thickness of test sample. Taking the first term from the summation series Eq. (2) can be reduced to Eq. (3)

$$\ln\left(1 - \frac{M_t}{M_\infty}\right) = \ln\frac{8}{\pi^2} - \frac{D\pi^2}{l^2}t \quad (3)$$

From a linear regression of Eq. (3) a plot of $\ln(1 - M_t/M_\infty)$ against t can be constructed and D determined from the slope of the line ($D\pi^2/l^2$), see Fig. 6. One of the assumptions made in calculating the diffusion coefficients is that sink conditions are maintained, (i.e. saturation solubility is at least 3 times more than the drug concentration in the dissolution medium as outlined in USP (US Pharmacopeia, 2005). By using 900 ml of dissolution medium and standard USP apparatus this condition has been fulfilled. The time taken for 50, 80 and 100% paracetamol release from PEG increased on addition of either natural or partially synthetic nanoclay. For both systems the time to release increased significantly with increasing addition of layered silicate from 1 to 3–5 wt.%. In particular, the time for 100% release for the PEGP5M1 was 45 min, this increased to 120 then to 300 min on addition of 3 and 5 wt.% montmorillonite, respectively, almost a 7-fold retardation of paracetamol release from PEG. Similar behaviour was also observed for the composites prepared with fluoromica in that the time for 100% release for PEGP5S3 and PEGP5S5 was the same as that for PEGP5M5. That the time for 100% release was similar for 3 wt.% fluoromica (S) and 5 wt.% montmorillonite (M) is as a consequence of the larger aspect ratio of the partially synthetic

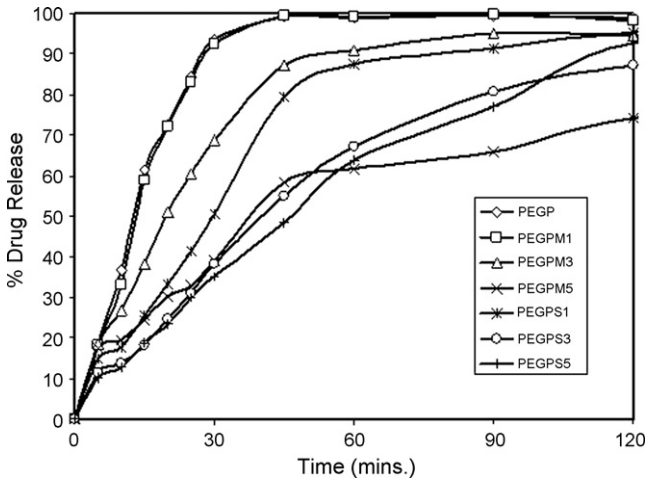

Fig. 6. Drug release profiles for paracetamol loaded PEG nanocomposites.

Table 2
Thermal behaviour of PEG, paracetamol loaded PEG and PEG nanocomposites

Sample	Time 50% release (min)	Time 80% release (min)	Time 100% release (min)	Diffusion coefficient (10^{-7} cm^2 s^{-1})
P Powder	2.65 ± 0.1	4.2 ± 0.1	5 ± 0.2	–
PEGP5	12.5 ± 1.6	23 ± 1.46	45 ± 0.6	13.1 ± 1.4
PEGP5M1	13 ± 1.7	23 ± 1.16	45 ± 0.78	13.1 ± 0.01
PEGP5M3	20 ± 0.7	35 ± 1.4	120 ± 1.9	8.8 ± 0.3
PEGP5M5	40 ± 1.1	180 ± 5.6	300 ± 6.5	4.4 ± 0.2
PEGP5S1	30 ± 2.4	45 ± 1.3	120 ± 3.3	5.8 ± 0.15
PEGP5S3	40 ± 1.45	90 ± 3.15	300 ± 2.5	4.4 ± 0.05
PEGP5S5	45 ± 3.4	95 ± 8.5	300 ± 2.7	4.4 ± 0.2

fluoromica. For both nanoclays the diffusion coefficients (D) decreased by a factor of 3 with increasing nanoclay loading up to 5 wt.%, but again lower loadings of fluoromica were as effective at decreasing D as higher loadings of montmorillonite.

4. Conclusions

In summary, we have reported the facile preparation of drug loaded polymer layered silicate nanocomposites using hot-melt extrusion. For a model drug (paracetamol), efficient distribution and dispersion of layered silicate nanoplatelets alters the dissolution behaviour of paracetamol in the polymer (PEG) and provides a torturous path for paracetamol diffusion throughout the PEG matrix. Using this approach, the release and dissolution behaviour of bioactive molecules, including but not limited to, pharmaceuticals, antimicrobials, nutraceuticals and proteins from polymer matrices can be manipulated.

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