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Ibuprofen-loaded poly(ε-caprolactone) layered silicate nanocomposites prepared by hot melt extrusion

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Abstract Ibuprofen loaded poly(ε-caprolactone) (PCL) layered silicate nanocomposites were prepared by hot-melt extrusion. The morphology and extent of dispersion of ibuprofen and layered silicate was studied using a combination of wide-angle X-ray diffraction (WAXD), field emission scanning electron microscopy (FESEM) and high resolution transmission electron microscopy (HRTEM). Exhaustive examination across the length scales revealed the composite to have both an intercalated and exfoliated morphology. The ibuprofen was well dispersed and distributed throughout the PCL matrix. Most significantly, the static tensile and dynamic mechanical properties of PCL can be manipulated as a function of nanoclay loading and is dependent on the aspect ratio of clay platelets. The glass transition of PCL increased by up to 16°C on addition of nanoclay, as determined from dynamic mechanical thermal analysis (DMTA). This behaviour was attributed to the constrained mobility of PCL chains intercalated between clay platelets and to the tethering of PCL chains by hydrogen bonding with platelet edges. As a consequence, PCL crystallisation was inhibited and confirmed from non-isothermal crystallisation experiments using differential scanning calorimetry (DSC). The fraction of PCL that was crystalline (X_c) decreased by 15% on addition of ibuprofen and nanoclay, although the temperature of crystallisation (T_c) did not change significantly. The dissolution of ibuprofen from PCL can be retarded by addition of layered silicates (nanoclays) to the polymer matrix.

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1 Introduction

Polymer layered silicate nanocomposites are hybrid materials where an inorganic phase (layered silicate/nanoclay) which has at least 1 dimension between 1 and 100 nm is dispersed in an organic phase (polymer). The layered silicates (nano-platelets) can have high aspect ratios and surface areas approaching 1000 m^2/g, see Pavlidou et al. and references therein [1]. Effective dispersion and distribution of these platelets in a biopolymer can provide a tortuous path for diffusion of drugs from polymer matrices, although the literature in this area is sparse [2–5]. However, the use of layered silicates, particularly montmorillonite to retard drug release from tablets and hydrogels has been reported previously [6–8]. Recently, there has been a renewed interest in using hot-melt extrusion (HME) to prepare, in a continuous process, polymer-drug formulations [9–13]. In particular, HME is being developed as an efficient method to disperse poorly water soluble drugs in polymers for enhanced delivery. Ibuprofen (2(4-isobutylphenyl)propanoic acid) is a non-steroidal anti-inflammatory drug having both analgesic and anti-pyretic activity. Ibuprofen can exist in different crystalline polymorphs and is also poorly water soluble and used regularly as a model drug [14, 15]. Previously we reported the preparation and dissolution of another model drug, paracetamol, from PCL and poly(ethylene glycol) (PEG) layered silicate nanocomposites [16, 17]. In this paper and for the first time, we describe the preparation and characterisation of a poorly water soluble drug (ibuprofen) loaded PCL layered silicate nanocomposite using hot-melt extrusion. We show that for

a well dispersed nanoclay system the release of ibuprofen from the polymer matrix can be retarded and most significantly the mechanical and thermal properties of PCL can be manipulated as a function of nanoclay loading.

2 Materials and methods

2.1 Materials

Poly(ε-caprolactone) (PCL) CAPA6500 (average Mol. Wt. 50,000) was supplied by the Solvay Chemical Company (Cheshire, UK). Ibuprofen (I): (USP purity >99%) was purchased from Voigt Global Distribution (Kansas City, USA). Cloisite 20A (referred to in this paper as M) was purchased from Southern Clay Products Inc. (Texas, USA), and is a natural montmorillonite modified with a dimethyl, dehydrogenated tallow, quaternary ammonium surfactant. Somasif MEE (referred to in this paper as S), was supplied by CBC Co. Ltd (Tokyo, Japan) and is a partially synthetically prepared layered silicate (synthetic fluoromica—Somasif ME100) modified with bis(2-hydroxylethyl methyl dodecylammonium chloride).

2.2 Composite and test specimen preparation

PCL, ibuprofen (5 wt%) and layered silicate (M: 1, 3 and 5 wt%; S: 1, 3 and 5 wt%) were melt compounded in a Collin Zk25 twin screw extruder using a temperature profile along the extruder with six heater zones set at 70, 80, 80, 75, 70 and 60°C from the feed to the die end, and a screw speed of 60 rpm. The extrudate was cooled using an air gun positioned just after the die exit and further cooled along a customised conveyor belt, (Collin CR 136/350), then pelletized using a strand pelletizer (Collin teach-line (CSG 1715)). Some of the extrudate was injection moulded into BS EN ISO Standard Standard 527 (75 × 50 × 30 mm) tensile bars using a mini injection moulder (Rondol High Force 5) with a screw speed of 50 rpm, a barrel temperature of 90, 125, 130°C and a water cooled mould temperature of 24°C. Test specimens for drug release were compression moulded into disks (diameter 18 mm and height 1.2 mm). For each composite formulation, 5 wt% ibuprofen and 1, 3 or 5 wt% layered silicate was added. Therefore, a composite with 3 wt% Somasif ME100 would have the following nomenclature, PCLI5S3 and so forth.

2.3 Nanocomposite characterisation

Powder diffraction patterns were recorded using a PANanalytical (originally Philips Analytical) X'Pert Pro MPD XRD (Almelo, The Netherlands) with Cu-Kα radiation ($\lambda = 1.54$ Å) generated at 45 kV and 40 mA. The samples were scanned at 0.63°/min in the range $2\theta = 1$–40^{o} and a step size of 0.02°. With regard to the sample preparation, powder clay samples were lightly pressed and flattened to obtain a smooth surface before testing and the composite samples compression moulded into disks having a diameter of 32 mm, to ensure uniformity in the sampling techniques.

The surface morphology of composite materials was examined using a JEOL JSM-6500F Field Emission Scanning Electron Microscope (FESEM) at 10 keV. There were several different types of samples prepared for analysis by SEM, cryo-fractured tensile bars and samples taken to study the surface topography of the disks before and after dissolution, in all instances samples were sputtered with a thin layer of gold (approx. 10 nm) prior to imaging. Samples (60–90 nm) for TEM examination were prepared using a Reichert-Jung Ultracut E (FC-4E cryo-unit) ultramicrotome with a glass knife at −117°C and collected onto 400 mesh copper grids. Images were obtained with a FEI Tecnai F20 field emission high-resolution transmission electron microscope (HRTEM) at 200 keV.

2.4 Static and dynamic mechanical testing

Tensile testing was performed using an Instron 5564 universal tester (Instron Corp, Canton, MA) with a 2000 N load cell on injection moulded dumbbells BS EN ISO Standard 527-2-1996 (75 × 50 × 30 mm) with six replicates of each. The crosshead speed was 200 mm/min and self-tightening grips were used to prevent slippage. The maximum stress, elongation at break, and Young's modulus were determined at room temperature. Dynamic viscoelastic properties of moulded nanocomposites were measured with a Triton Trilec 2000 Dynamic Mechanical Analyser. The analysis was performed on moulded samples (50 × 50 × 30 mm^3) in dual cantilever mode. The storage modulus and loss modulus were measured at a range of 5 frequencies from 0.316 to 31.6 Hz for a scanning rate of 3°/min from −100 to 30°C.

2.5 Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to characterise the thermal properties of PCL and the composite materials. The DSC experiments were performed using a high speed Perkin-Elmer Diamond DSC. The samples (5 mg) were heating at 10°C/min from 20 to 100°C, held at 100°C for 3 min, then cooled and reheated 10°C/min to remove thermal history effects.

2.6 In-vitro drug release

Dissolution studies were completed using a Copley DIS 8000 USP standard dissolution apparatus with paddle

(Nottingham, UK). The dissolution medium (900 ml of phosphate buffer pH 7.2) was maintained at 37 ± 0.5°C and stirred at 100 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 analyzed using UV spectrophotometery (Hitachi U2000 Spectrophotometer) at 222 nm using 10 mm silica cells (VWR International Ltd 307 370002). The results reported are an average of 4 measurements ± standard deviation. An ibuprofen calibration curve was prepared for this system.

3 Results and discussion

The extent of the dispersion of M, S and ibuprofen in the PCL matrix was studied using a combination of WAXD, FESEM and HRTEM. Figure 1a and b show the diffraction patterns for M (montmorillonite) and S (synthetic fluoromica) based composites, respectively. For M itself a doublet of peaks are observed below 10^{o} on the 2θ scale, the main peak corresponding to a d_{001} spacing of 2.54 nm. On addition of M or S to PCL, the d-spacing increased from 2.54 to 3.36 and 3.13 nm, respectively. The presence of these peaks having lower 2-theta peak maxima confirms that PCL chains have penetrated between the silicate layers, expanding them to form an intercalated structure. An increase in basal spacing of 0.4 nm in PCL nanocomposite systems was attributed by Chen et al. [18] to be equivalent to a monolayer of PCL molecules inserted within the inter-gallery spaces of the layered silicate. For the nanocomposites prepared in this study, the inter-gallery space expanded by more than two mono-layers indicating that the PCL may have adopted a planar bi-layer conformation within the galleries. The differences in expansion of the galleries can also be attributed to the different conformations and arrangements of the surfactants on the layered silicates in addition to the larger aspect ratio of the S silicate. Addition of M or S and ibuprofen (I) to the PCL matrix also resulted in an increase in the d-spacing relative to the clay itself, the magnitude of which increased with increased addition of M or S, as I was kept constant at 5 wt%. The largest increases were obtained when 5 wt% M or S and 5 wt% I was added to PCL, the d-spacing increased from 2.54 nm (M) and 2.05 nm (S) for the clays alone to a maximum of 3.58 nm and 3.29 nm for the M and S based composites, respectively. PCL is a semi-crystalline polymer and the three peaks obtained between 20 and 25 2θ, correspond to d-spacing of 0.414, 0.374 and 0. 325 nm and can be assigned as the 110, 111 and 200 crystal planes, respectively. These peaks decreased in intensity, particularly for the S based composites as a consequence of increased concentration of the larger sized S platelets, PCLI5S1,

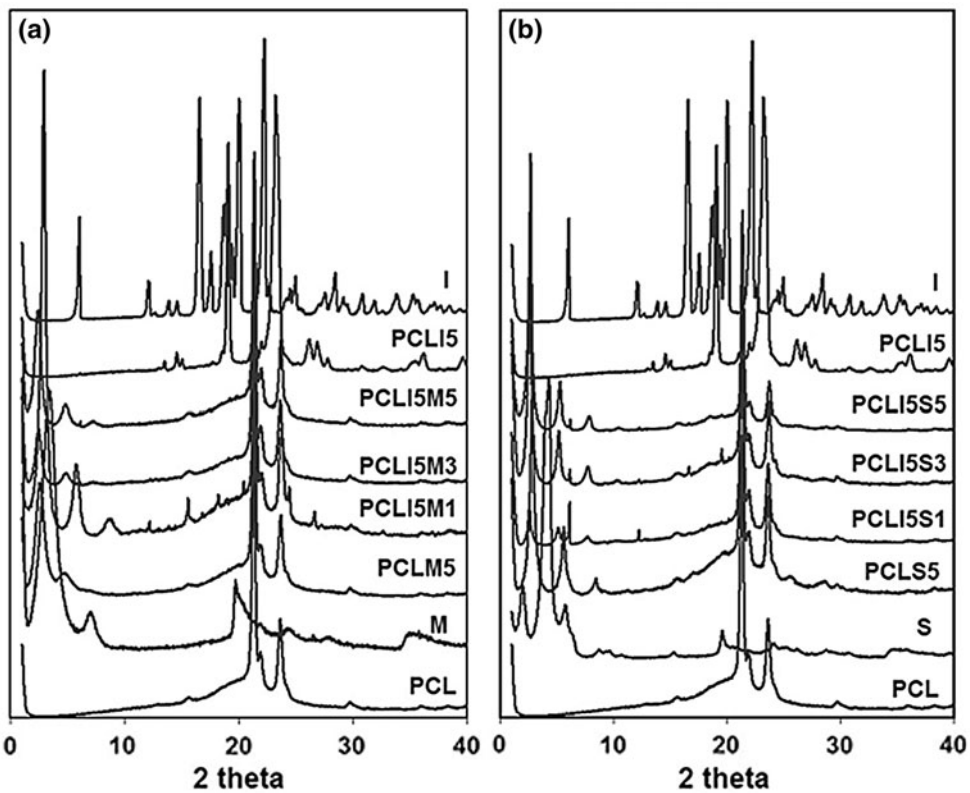

Fig. 1 X-ray powder diffraction patterns for **a** M (montmorillonite) and **b** S (partially synthetic fluoromica) based PCL-ibuprofen nanocomposites

PCLI5S3 and PCLI5S5 having the lowest crystallinity. It is postulated that for the PCLI5S composites the mobility of the PCL chains within the silicate layers is more constrained by the larger aspect ratio S platelets which in turn alters the crystallization behaviour of PCL by inhibiting chain folding. Ibuprofen is a highly crystalline molecule and multiple peaks were obtained in its powder X-ray diffraction pattern, see Fig. 1. The diffraction pattern obtained for ibuprofen prior to melt mixing is characteristic of the phase 1 form of ibuprofen [14]. Most of the peaks associated with ibuprofen have decreased in intensity, particularly above $2\theta = 30^{o}$ or changed in shape after melt mixing with PCL [19], indicating the crystalline form of ibuprofen has been altered (phase 11), as a consequence of the shear forces and temperatures applied during the extrusion process. Further studies are required to elucidate the effect of processing, if any, on ibuprofen efficacy.

The morphology and extent of dispersion of M, S and I in the PCL matrix was investigated by exhaustive examination using FESEM and HRTEM. Figure 2a shows the structure of the ibuprofen used in this study. The average size of the ibuprofen crystals was estimated to be 15 μm. The surface of the PCL itself (control), for the magnification shown, has a smooth texture, see Fig. 2b. However, on addition of ibuprofen to the PCL matrix a fibrillar like morphology was observed with irregular ibuprofen particles randomly dispersed in the PCL matrix. For composites containing both nanoclay (M or S) and I, such as PCLI5M3 in Fig. 2d, a different morphology was obtained which revealed smaller particles of both M and I. Examination of the composites at higher magnification using HRTEM showed the ibuprofen to well dispersed in the PCL matrix. Figure 3a and b shows HRTEM images of PCLI5M3 and PCLI5S5 composites, respectively. The white areas are ibuprofen crystals which are surrounded by clay platelets. The stacks of inorganic layered silicate, of varying thickness and length, encase the ibuprofen molecules and provide a tortuous path for diffusion. Prior to melt mixing, the layered silicate stacks are typically many hundreds of layers thick. However, during melt mixing with PCL and I, the shearing forces and temperature applied cause delamination of these stacks. By way of example, Fig. 3c and d shows, for PCLI5S5, individual single platelets and stacks of intercalated platelets. Image analysis of these clusters of

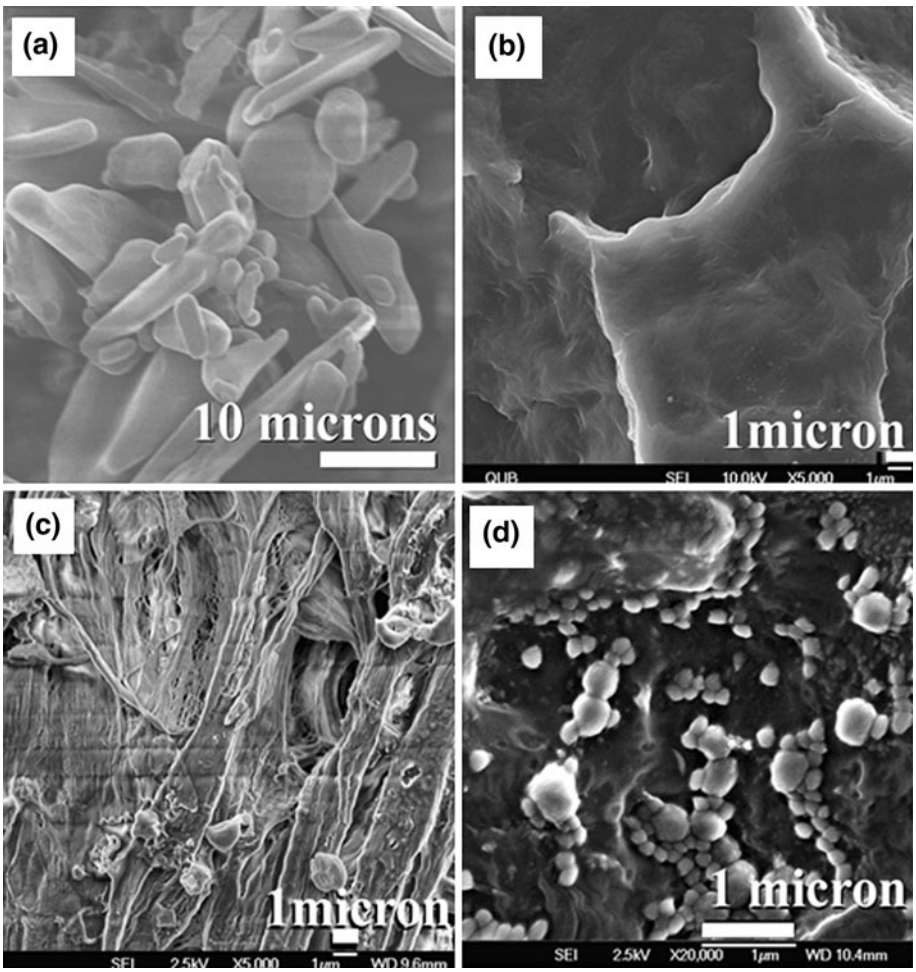

Fig. 2 FESEM micrographs of **a** ibuprofen powder, **b** PCL (control), **c** PCLI5, **d** PCLI5M5, and **b–d** were taken of cryo-fractured surfaces

platelets revealed an average of two platelets per stack with 16 exfoliated platelets and stacks of up to six platelets. This confirms that the layered silicate was well dispersed throughout the PCL matrix. The aspect ratio of the platelets was measured and was between 50 and 200 nm in length with an average value of approximately 110 nm.

The static and dynamic mechanical properties of the composites were measured. Tensile testing was performed on the samples to determine the modulus, elongation at break and ultimate tensile strength, see Fig. 4a–c. Within experimental error the addition of ibuprofen or M to PCL did not change the tensile strength, extensibility or modulus of PCL. In contrast, addition of S to PCL resulted in a decrease in tensile strength and elongation at break compared to neat PCL, however the modulus increased by over 400%. The is associated with S having a much larger aspect ratio than M, as determined from TEM observations, 500 nm as opposed to 100 nm. Addition of M or S and I to PCL resulted in a decrease in tensile strength and elongation at break relative to neat PCL, typically by about 30%.

By way of example, Fig. 5 shows the dynamic mechanical thermal properties of the M based nanocomposites. Figure 5a displays the variation in tan delta as a function of temperature, measured at 1 Hz. In the range −70°C to 0°C, an α-relaxation (T_g process) was observed centred at −40°C, with a corresponding drop in storage modulus, see Fig. 5b. Addition of M or I to PCL resulted in a decrease in storage modulus, by between 1 and 2 orders of magnitude in the temperature range studied. Successive additions of M from 1 to 5 wt% resulted in further significant decreases in storage modulus. By convention the glass transition temperature (T_g) was measured by taking the peak maximum in tan delta. The T_g for neat PCL was determined to be −54°C, this decreased to −56°C on addition of 5 wt% I. Addition of M alone to PCL resulted in a 16°C increase in T_g of PCL to −38°C. Interestingly, when M and I together were added to PCL, the increase in T_g was much less pronounced than when M alone was added. The T_g increased to −53, −52 and −50°C on addition of 1, 3 and 5 wt% M to PCLI, respectively. This increase in T_g on successive additions of M originates from the increased thermal energy required to move the polymer chains whose mobility is constrained physically by the addition of clay or by tethering of polymer chains via hydrogen bonding with hydroxyl groups on the edges of M. Similar trends were obtained for the S based composites (not shown), but the increase in T_g was less significant than that obtained for the M based composites. For example, the T_g for PCL

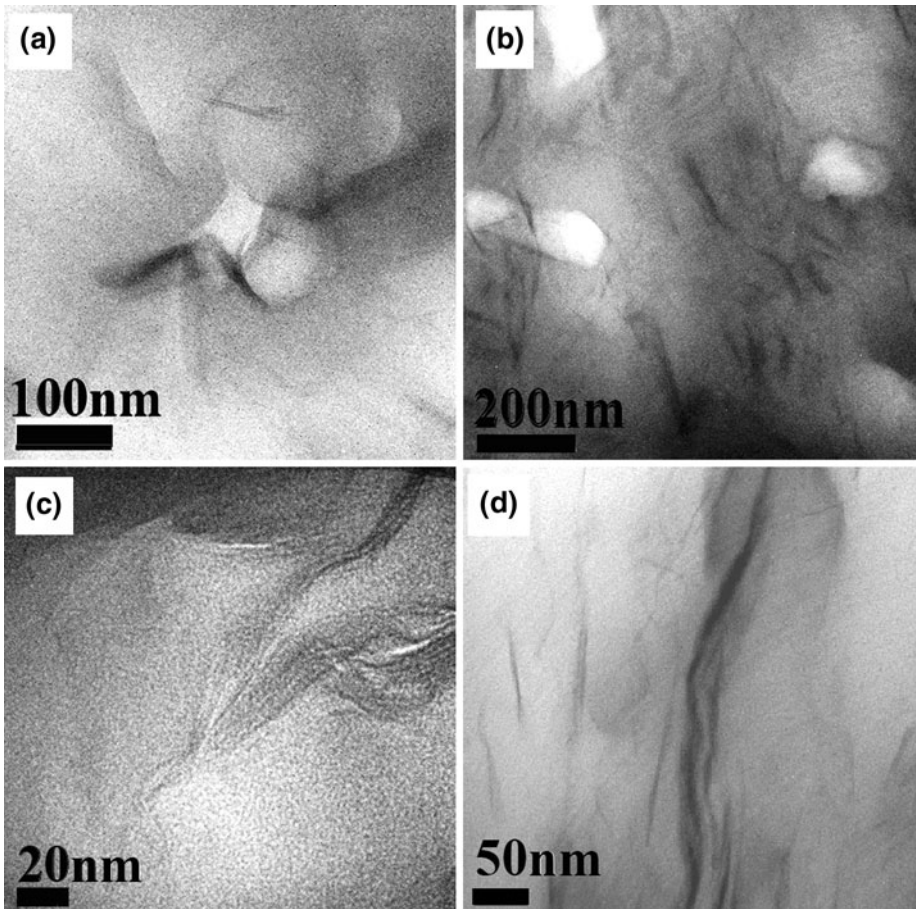

Fig. 3 Bright field HRTEM images of **a** PCLI5M3 and **b** PCLI5S5 showing a ibuprofen crystal (*white areas*), and **c**, **d** showing different degrees of layered silicate platelet delamination for PCLI5S5

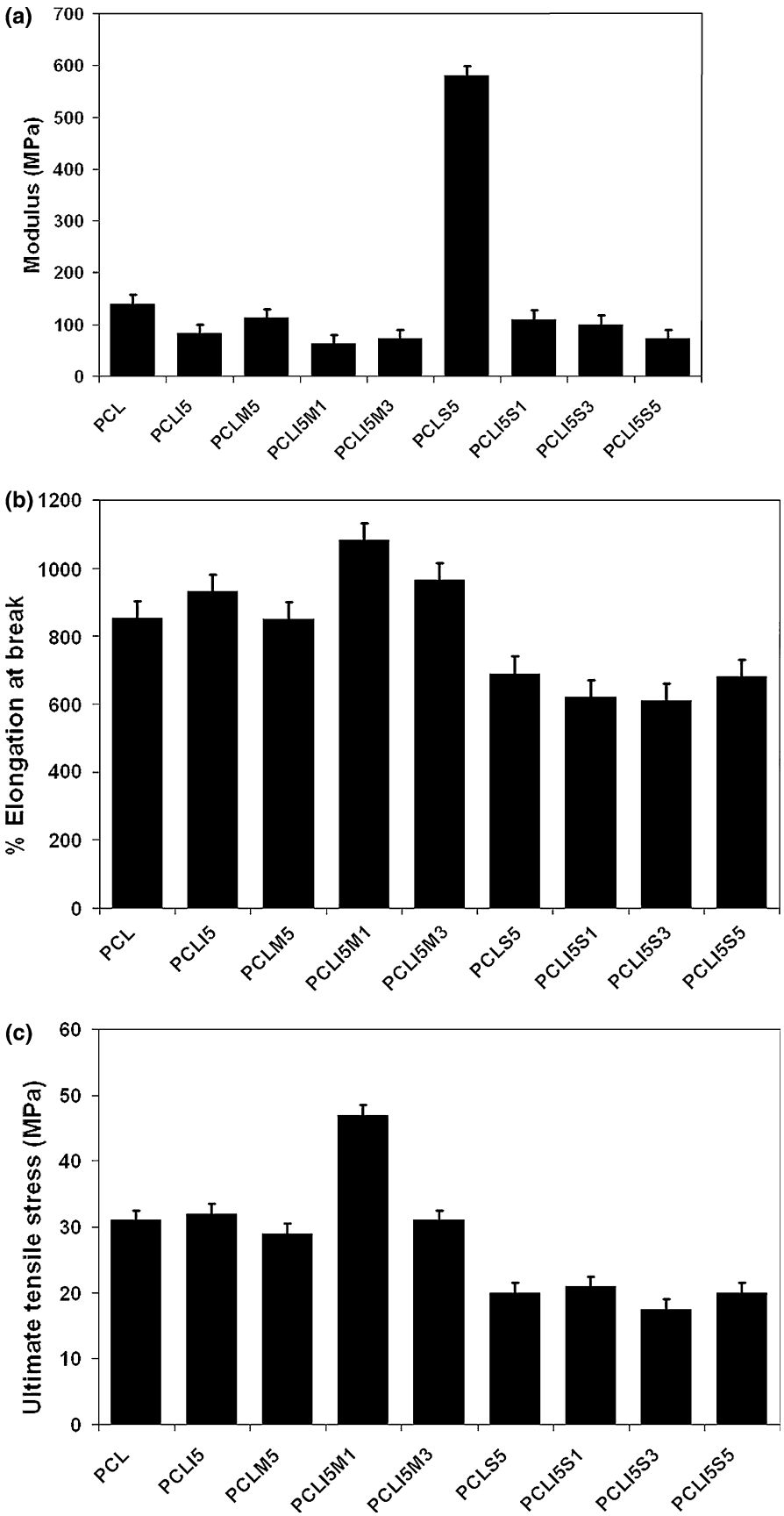

Fig. 4 Variation in **a** Young's modulus, **b** % elongation at break and **c** ultimate tensile stress for all composite materials relative to neat PCL

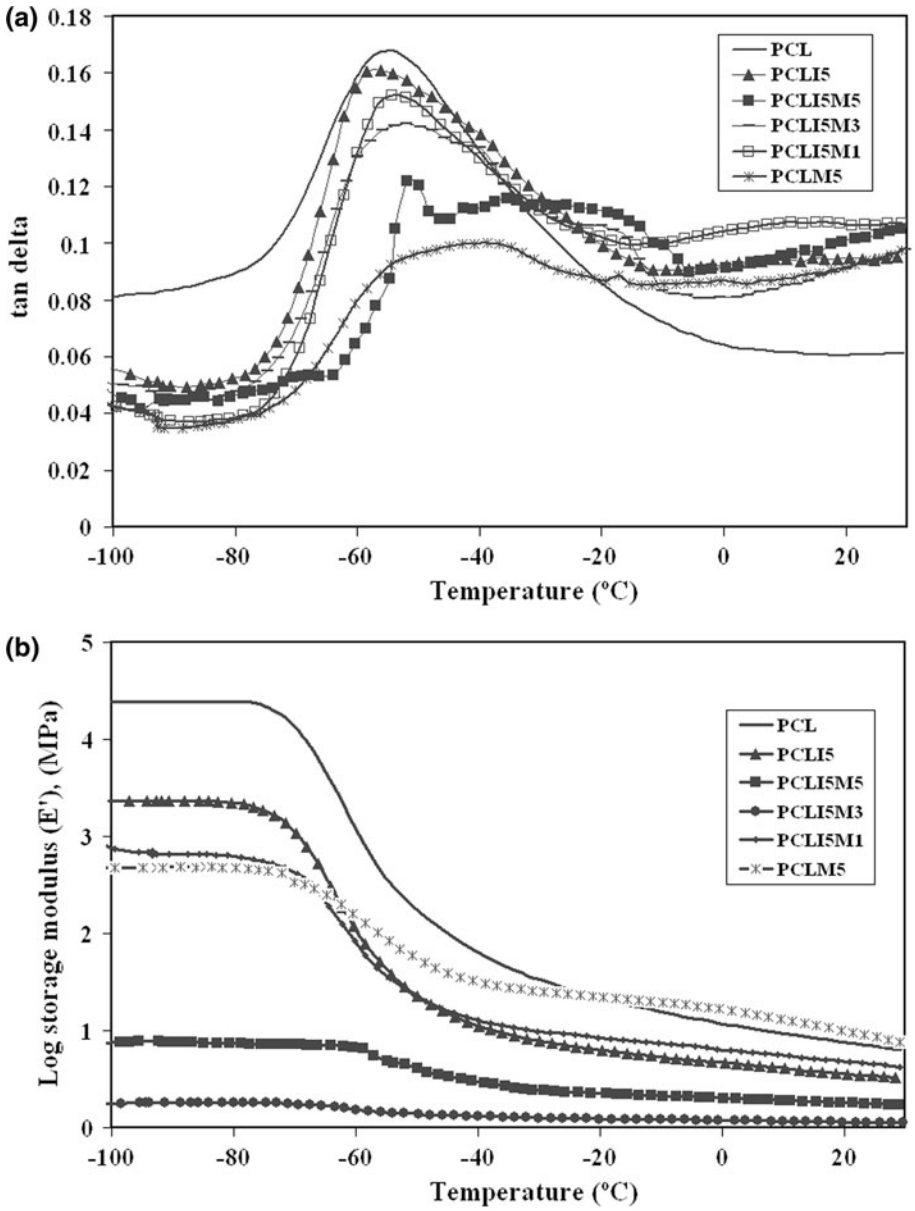

Fig. 5 Variation in **a** tan delta and **b** storage modulus (E′) as a function of temperature for PCL, PCLI and PCLI nanocomposites. — PCL, -▲- PCLP5, -*- PCLS5, -*- PCLM5; -□- PCLP5M1, PCLPMS3, -■- PCLP5SM5

increased from −54 to −45°C when S was added to PCL compared to −38°C when M was added to PCL.

The thermal properties for all the composites prepared were studied using DSC. The heat flow data for the non-isothermal melting and crystallization is listed in Table 1, including temperature of crystallisation, T_c (°C); temperature of melting, T_m (°C); enthalpy of crystallisation, ΔH_c (J/g); enthalpy of melting, ΔH_m (J/g) and crystalline content, X_c (%). Allowing for instrument error, T_c of PCL did not change significantly for the M based composites, but there was a decrease of 3.5°C in T_c for the S based composites The percentage crystallinity (X_c) was calculated using a value of 136 J/g [18] for a theoretically 100% crystalline PCL and compensating for blend composition.

Table 1 Thermal properties of PCL, PCLI and PCLI nanocomposites

	T_c (°C)	T_m (°C)	ΔH_c (J/g)	ΔH_m (J/g)	X_c (%)
PCL	32.8	55.5	47.9	42.0	35.2
PCLI5	29.4	53.4	56.4	53.4	39.2
PCLM5	31.1	55.9	46.0	51.1	35.7
PCLI5M1	31.1	52.5	54.6	50.8	37.5
PCLI5M3	31.5	53.8	56.0	51.2	37.9
PCLI5M5	31.1	53.8	46.2	48.8	30.6
PCLS5	31.5	55.5	47.5	49.2	34.4
PCLI5S1	28.6	52.5	46.4	45.8	32.1
PCLI5S3	28.6	50.8	49.5	47.5	33.5
PCLI5S5	29.4	53.8	46.7	43.7	30.9

X_c for neat PCL increased by 4% when I was added to PCL, but did not change significantly when either M or S alone was added to PCL. However, the addition of I and M to PCL yielded a modest increase in X_c, except for PCLI5M5, where X_c decreased from 35.2% for neat PCL to 30.6%. There is a limit (<10 wt%) to the amount of layered silicate and other additives which can be added to PCL above which crystallisation (chain folding) is inhibited. This behaviour has been observed previously and was attributed to the competing effects of the layered silicate acting as a nucleating agent increased X_c, whilst the PCL chains trapped within the silicate layers is amorphous, thus X_c decreases [18]. Ray et al. proposed that only exfoliated silicate platelets are able to act as effective nucleating agents, thus causing the formation of smaller crystallites [20]. Therefore, X_c may be related to the extent of clay dispersion in the PCL matrix. For PCL-ibuprofen-nanoclay composites, the system is further complicated by the addition of ibuprofen to the matrix and its effect on crystallinity.

The in-vitro release of ibuprofen from the composite materials was measured over 8 days using the method described above. There are three distinct steps in the drug release from a matrix tablet, liquid penetration into the matrix, dissolution of the drug and diffusion. For accuracy small compression moulded disks of uniform dimensions were made for all samples and the percentage ibuprofen released as a function of time measured, see Fig. 6. Figure 6a shows the initial release profile up to 170 min and Fig. 6b the longer term release up to 4 days. In the

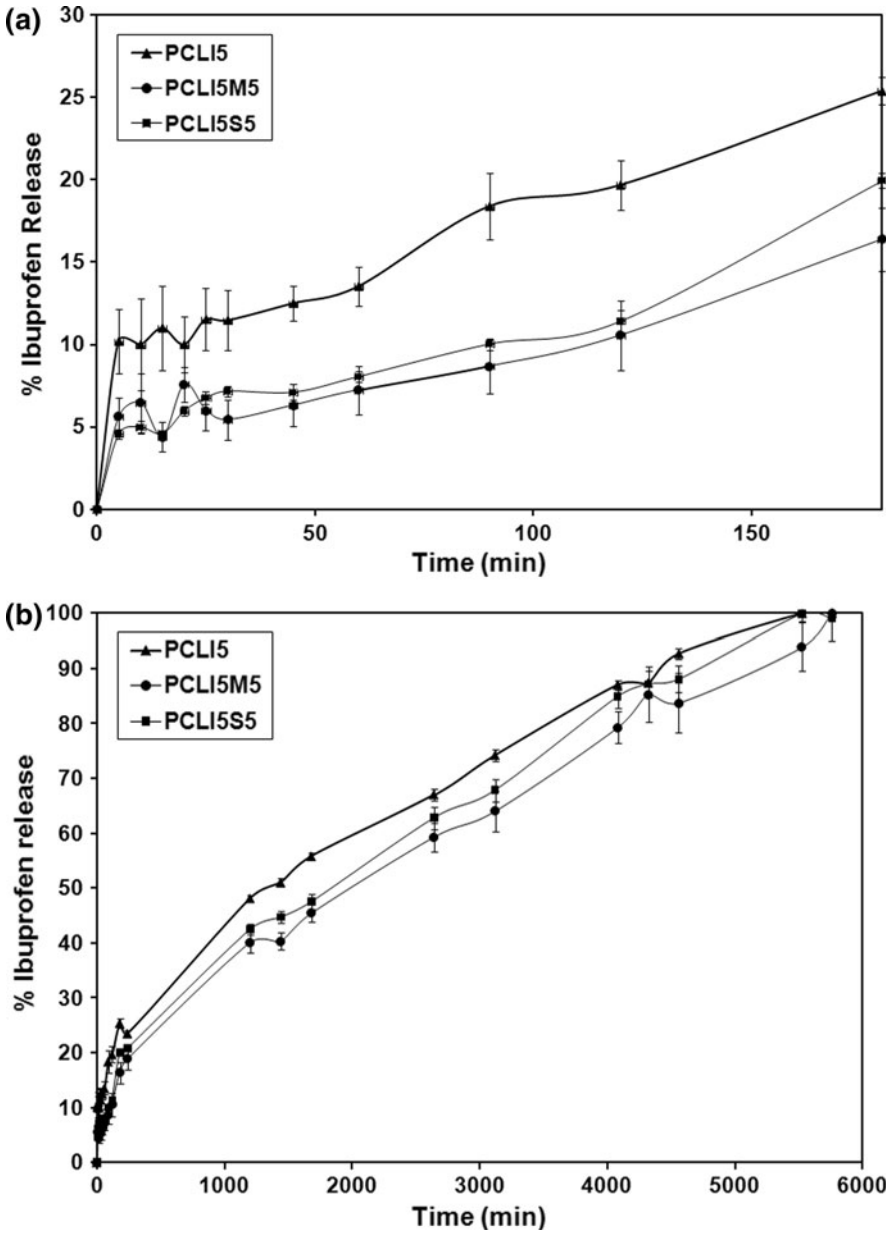

Fig. 6 Percentage ibuprofen release from PCL (at 37°C) as a function of time, **a** to 170 min and **b** up to 4 days

initial stages there is a burst effect where in the first few hours approximately 5% of ibuprofen was released. This can be attributed to the fraction of ibuprofen crystals that populate close to the surface of the test specimen and was confirmed by FESEM, see Fig. 7. Figure 7a, c and e are micrographs of the surface of PCLI5, PCLI5M5 and PCLI5S5 prior to the dissolution studies where ibuprofen crystals can be readily seen on the surface. Figure 7b, d and f are images of the surface topography of same three composites 6 days into the dissolution experiment and illustrate how the addition of M and S effects composite morphology and drug dissolution. Image analysis (not shown) of further FESEM images of the composites after dissolution revealed that the amorphous phase was preferentially dissolved leaving small crystallites of PCL, typically having dimensions of 50–100 nm. The time to release for ibuprofen from PCL at 25, 50, 80 and 100% is listed in Table 2. In particular, the time to 25 and 50% release increased, by 230 and 133%, respectively. The diffusion coefficient (D) for each formulation was determined using classical Fickian diffusion theory. D decreased from 5.8×10^{-7} cm^2 s^{-1} for PCLI5 by over two orders of magnitude to 10.2×10^{-9} cm^2 s^{-1} when even 1 wt% M or

Table 2 Time to release for ibuprofen from PCL nanocomposites

Time (min)	PCLI5	PCLPIM5	PCLI5S5
25% release	175	400	400
50% release	1350	1800	1800
80% release	3500	3800	3800
100% release	5000	5750	5525

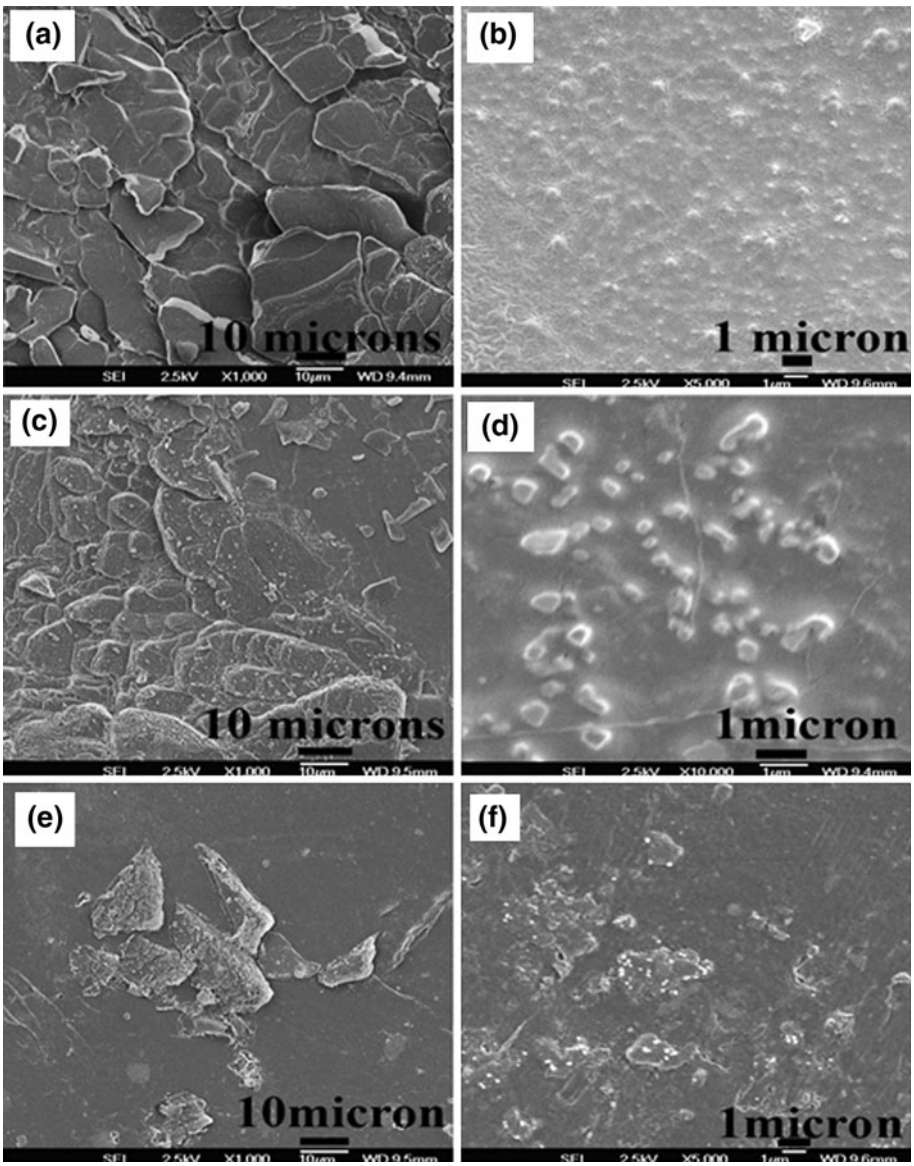

Fig. 7 Surface topography of compression moulded disks of **a** PCLI5 before **b** PCLI5 after **c** PCLI5M5 before **d** PCLI5M5 after **e** PCLI5S5 before and **f** PCLI5S5 after in-vitro dissolution experiments

S was added to PCLI5. To test how well the release curves obeyed Fickian behaviour, the diffusional exponent, n, was determined using $M_t/M_\infty = kt^n$, where M_t/M_∞ is the fraction of drug released from the polymer matrix, k is a constant, t is time, n is dependent on release kinetics and sample geometry, and a plot of M_t/M_∞ versus $\sqrt{t}$ gives a slope equal to n [21]. A value of $n \leq 0.5$ indicates Fickian diffusion. For all ibuprofen loaded PCL nanocomposites studied n was <0.5, the fastest diffusion observed for the initial burst effect for PCLI where $n = 0.35$ and $n \leq 0.1$ for all other samples.

4 Conclusions

Composites of PCL with ibuprofen and either naturally occurring or partially synthetic layered silicates were readily prepared using conventional hot-melt extrusion techniques. In all cases an intercalated and partially exfoliated composite morphology was attained. Ibuprofen molecules were well dispersed and distributed throughout the PCL matrix. Addition of clay platelets can be used to manipulate the mechanical properties of PCL and is dependent on the aspect ratio of the clay particles. The incorporation of both ibuprofen and M or S alters the crystallisation behaviour of PCL. PCL crystallisation is disrupted as polymer chain dynamics is restricted for those chains that diffused between clay platelets or are tethered to clay particles, thus an increased fraction of PCL is in the amorphous phase. The constrained mobility of PCL chains also resulted in an increase in T_g by up to 16°C. Furthermore, the storage modulus for all composites decreased relative to neat PCL, by about two orders of magnitude for the composites with 10 wt% additives. The release of ibuprofen from PCL was retarded when both M and S was dispersed in the PCL-ibuprofen blend. That the mechanical properties of such polymer matrices can be manipulated by addition of nanoclays may present opportunities for easier subsequent milling or compression of drug loaded biopolymers.

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