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Paracetamol-Loaded Poly(ε-Caprolactone) Layered Silicate Nanocomposites Prepared Using Hot-Melt Extrusion

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ABSTRACT: Composites of paracetamol loaded poly(ε-caprolactone) with layered silicates (nanoclays) were prepared using hot-melt extrusion. The paracetamol crystals and layered silicates formed both intercalated and partially exfoliated nanocomposite morphologies depending on composition. The dissolution and initial burst effect were retarded slightly by the nanoclay. T_m and T_c of poly(caprolactone) (PCL) were unaffected by the presence of nanoclay, but the crystalline content decreased. The highly dispersed nanoplatelets hindered the mobility of PCL chains and alter the crystallization behavior of PCL. The T_g of PCL increased by up to 15°C on addition of a synthetic fluromica, as the nanoclay constrained chain motion and tethered PCL chains through hydrogen bonding to hydroxyl groups on the edges of the clay platelets. The tensile mechanical properties of PCL were unaffected when a naturally derived clay (montmorillonite) and paracetamol were blended. In contrast, the modulus of PCL increased by 500% and the stress and elongation at break decreased by 30% for composites prepared with a partially synthetic fluoromica. The study has therefore demonstrated that nanocomposite formation is a potentially highly useful means of manipulating the mechanical properties of melt extrusion systems. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: poly(ε-caprolactone); paracetamol; layered silicates; nanoclay; nanocomposite; nanotechnology; extrusion; polymeric drug delivery; dissolution; biodegradable polymers

INTRODUCTION

Nanocomposites are materials that consist of particles of one compound with a mean diameter in the nano-size range (1–100 nm) dispersed throughout another material, commonly a modified inorganic clay dispersed within an organic polymer. There has been considerable interest in the polymer and biopolymer science literature regarding nanocomposites based on layered silicates, including those containing poly(caprolactone) (PCL),[1–3] poly(ethylene glycol)(PEG),[4] poly(ethylene oxide) (PEO),[5,6] poly(lactides),[7–9] and poly(vinylpyrrolidone) (PVP).[10] This interest has arisen due to the need to improve the poor structural and functional stability[11] and lack of abrasive resistance[12] of many polymers and biopolymers. In parallel to this there has also been renewed interest in the pharmaceutical sciences in the area of hot-melt extrusion (HME) as a technique for the preparation of polymeric drug delivery systems.[13,14] This technique has several distinct advantages over conventional methods, one of the main advantages being the ability to move from a batch to a

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Journal of Pharmaceutical Sciences

continuous process allowing consistent product flow at relatively high throughput rates. A number of researchers have examined the use of melt extrusion with different biomedical polymers and drug mixtures, including commercially available Eudragit,[15] and Kaletra,[16] as well as hydroxypropylcellulose,[17] PEO[18] and PVP.[19] The focus of the work here is to combine these two technologies in order to explore nanocomposites as HME excipients.

Nanocomposite systems have been previously explored as drug delivery systems, notably using solution cast methods to produce drug loaded polymer nanocomposites in the form of hydrogels,[20] pellets,[21] nanoparticles,[22] and solution cast nanocomposites.[21] Layered silicates have also been used in pharmaceutical applications as adsorbents, thickeners, and excipients.[23] Furthermore, recent research has outlined the use of layered silicates,[24] mesoporous silicates[25] and double layered hydroxides[26] as drug and gene delivery vehicles. For example, Carretero[23] described the use of clay minerals in pharmaceutical formulations and their use administered orally as gastrointestinal protectors and antidiarrhoeaics, administered topically as dermatological protectors and as excipients, such as lubricants and delivery systems. More recently, Cavallaro et al. reported the ability of mesoporous silicate to entrap and release non-steroidal anti-inflammatory agents[25] and Lin et al.[24] described the use of a hexadecyltrimethylammonium (HDTMA) modified montmorillonite (M) as a non-viral vector for gene delivery.

Here we explore the use of PCL nanocomposites as HME excipients. Poly(ε-caprolactone) is a biocompatible and biodegradable semi-crystalline polyester that has a relatively low melting point, typically around 55°C and has a very high decomposition temperature (350°C)[27] but can be readily processed using HME techniques. It is degraded by microorganisms in the body by hydrolytic degradation of the PCL backbone, one of the reasons it is used as scaffolds in tissue engineering and for the controlled release of drugs.[28] A number of researchers have analyzed the release of drugs from PCL and PCL copolymer matrices.[29,30] For example, Rich et al.[29] showed how the release of toremifene citrate from a poly(ε-caprolactone/DL-lactide) can be manipulated by varying the molecular weight of the copolymer or incorporating the tormifene citrate in a silica xerogel. The authors reported that the release rate could be adjusted from 3 months to up to 1 year and proposed it maybe possible to formulate a device for long-term treatment of breast cancer after surgery. Likewise, Chang et al.[30] reported that the kinetics of progesterone delivery from PCL matrices made by precipitation casting could be controlled by altering processing conditions, such as drug loading and matrix density.

The purpose of this work is to demonstrate a combined novel approach to the preparation of drug loaded poly(α-caprolactone) layered silicate nanocomposites using HME, a continuous process in contrast to the normal batch type processing used to prepare polymeric drug delivery systems, and most significantly the use of high surface area, large aspect ratio inorganic nanoplatelets. In particular we explore the effects on the mechanical and drug release properties of these systems. The methodology and results described in this article are significant and could equally be applied to the controlled/retarded release of any bio-active molecule (pharmaceutical, nutraceutical, protein, DNA/iRNA, anti-microbial, anti-coagulant, etc.) from biopolymers. As these biocomposite systems (biopolymer/bio-active molecule/nanoclay) are prepared using conventional polymer processing techniques they can be readily formed into medical devices. The published literature in this field is sparse and to the best of our knowledge minimal articles have been published by other groups on melt-extruded drug loaded polymer layered silicate nanocomposites.[31] Previously, we reported the effect of nanoclays on the properties and release profile of drug loaded PEG.[32] In this article, we describe the preparation and characterization of paracetamol loaded PCL layered silicate nanocomposites using melt compounding, discuss the effect of nanoclay loading on thermal, static and dynamic mechanical properties of PCL and report the *in vitro* dissolution and diffusion behavior of these bio-composite materials.

MATERIALS AND METHODS

Materials

PCL CAPA6500 (average Mol. Wt. = 50,000) was supplied by Solvay Chemical Company (Warrington, UK) Paracetamol (acetaminophen, referred to as P in this article), (USP purity >99%) was purchased from Sigma Aldrich (Dorset, UK). Cloisite 20A (referred to as M in this article) was purchased from Southern Clay Products, Inc.

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(Gonzales, TX) and is a natural montmorillonite modified with a dimethyl, dehydrogenated tallow, quarternary ammonium surfactant which renders the clay organophilic. Somasif MEE (referred to as S in this article) was supplied by CBC Co. Ltd. (Tokyo, Japan) and is a partially synthetic layered silicate (i.e., synthetic fluoromica (Somasif MEE) modified with bis(2-hydroxylethyl methyl dodecylammonium chloride)).

Nanocomposite Preparation

PCL, paracetamol and the layered silicate were melt compounded in a Collin Zk25 co-rotating intermeshing twin screw extruder (L/D ratio = 30) fitted with six heater zones set at 70, 80, 80, 75, 70, and 60°C and a screw speed of 60 rpm. The extrudate was air cooled by a gun blowing air onto the extrudate just after exiting the die and further cooled along a customized 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 527 (75 mm × 50 mm × 30 mm) tensile bars using a mini-injection moulder (Rondol High Force 5) using a screw speed of 50 rpm and a barrel temperature profile of 90–125–130°C and a mould which was water cooled to a temperature of 24°C. Test specimens for drug release were prepared by compression moulding disks (diameter 18 mm; height 1.2 mm). The composition and codes used throughout this article to describe the nanocomposites produced are listed in Table 1.

Table 1. Matrix Formulations Prepared

Code	PCL (wt%)	Paracetamol (wt%)	Layered Silicate (wt%)
PCL	100	0	0
PCLP5	95	5	0
PCLM5	95	0	5
PCLP5M1	94	5	1
PCLP5M3	92	5	3
PCLP5M5	90	5	5
PCLS5	95	0	5
PCLP5S1	94	5	1
PCLP5S3	92	5	3
PCLP5S5	90	5	5

M, montmorillonite (Cloisite 20A); S, fluoromica (Somasif MEE).

Characterization of Composite Formulations

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 of $2\theta = 1$–40° and a step size of 0.02°. Powder samples were lightly pressed and flattened to obtain a smooth surface before testing and the polymer nanocomposite samples were compression molded into disks having a diameter of 32 mm to ensure uniformity in the sampling techniques.

The surface morphology of samples was examined using a JEOL JSM-6500F Field Emission Scanning Electron Microscope operated at 10 keV. Different types of samples were prepared for analysis by SEM, cryo-fractured tensile bars, samples taken to study the surface topography of compression molded disks, before and after dissolution, and samples taken from the center of an uniaxially deformed tensile bar. In all cases specimens were sputtered with a thin layer of gold (~10 nm) prior to imaging.

Specimens for examination using HRTEM 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 using a FEI Tecnai F20 field emission high-resolution transmission electron microscope (Philips) and an operating voltage of 200 keV.

Non-isothermal crystallization and melting experiments were conducted on thin pieces of the composite materials placed between microscope glass slides, then placed on a hot stage (Mettler Toledo FP90) attached to a LSL Leica-Toleda PP polarizing microscope, equipped with a video camera system. The samples were heated at 5–80°C then cooled at 5°C to room temperature.

Tensile measurements were performed on an Instron 5564 universal tester (Instron Corp, Canton, MA) using a 2000 N load cell on injection moulded dumbbells (BS EN ISO Standard 527-2-1996—75 mm × 50 mm × 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.

Differential scanning calorimetry (DSC) was used to characterize the thermal properties of the drugs, polymers, and extrudates. The DSC

experiments were performed on a high speed Perkin-Elmer Diamond DSC with 5 mg samples weighed and sealed in aluminium pans. A heating and cooling rate of 10°C/min from 20 to 100°C was used.

The dynamic viscoelastic properties of nanocomposites were measured with a Triton Trilec 2000 Dynamic Mechanical Analyser. The analysis was performed on moulded samples (50 mm × 50 mm × 30 mm) in a dual cantilever mode. The storage modulus and loss modulus were measured at a range of five frequencies from 0.316 to 31.6 Hz and a scanning rate of 3°/min from −100 to 30°C.

In Vitro Drug Release

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 (Watford, UK) 0.45 μm Millex syringe driven filter unit and analyzed by UV spectroscopy using a Hitachi U2000 UV Spectrophotometer at 243 nm using 10 mm silica cells (VWR International Ltd., Lutterworth, UK 307 370002). The results reported are an average of four measurements ± standard deviation. A paracetamol calibration curve was prepared for this system.

RESULTS AND DISCUSSION

The extent of dispersion of paracetamol and layered silicates (nanoclays) in the PCL matrix and the morphology of the composite materials were investigated using a combination of XRD, SEM, and HRTEM. Figure 1a and b shows the diffraction patterns for the nanocomposites based on montmorillonite (M) and synthetic fluoromica (S), respectively.

The d_{001} basal spacing of the layered silicates (nanoclays) was estimated using Bragg's Law:

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

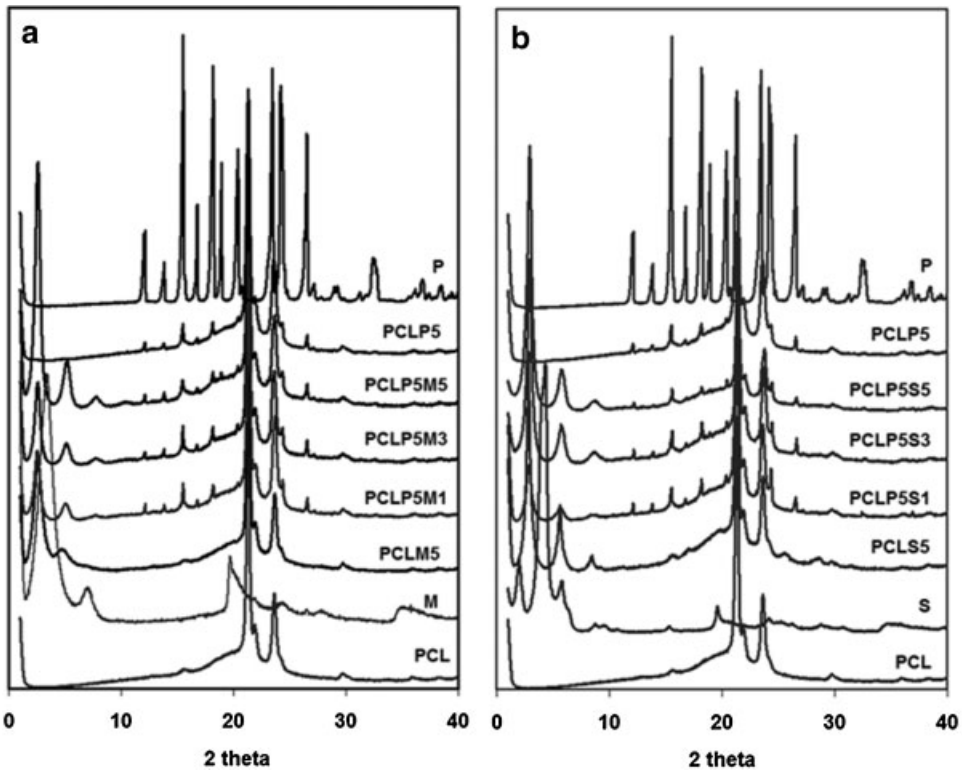

Figure 1. X-ray diffraction patterns for composites based on (a) montmorillonite (M) and (b) synthetic fluoromica (S).

where n is an integer ($n = 1$), λ the wavelength of the incident X-ray beam ($\lambda = 1.5406$Å), θ the angle of incidence of the X-ray beam and d the interatomic distance between silicate layers. M itself displays two diffraction peaks, associated with long range order, a more intense peak having a maximum at 3.34 ($d_{001} = 2.54$ nm) and a much smaller less intense peak at 7.28 2θ. When M was melt blended with either PCL or PCL and paracetamol both maxima shifted to lower values of 2θ and the d_{001} spacing for the main diffraction peak increased from 2.54 to 3.40 nm. The diffractogram obtained for S had three peaks below 10 2θ at 2.00°, 4.31°, and 6.05°, the main peak at 4.31° corresponding to a d_{001} spacing of 2.05 nm. Similar to what was observed with M, when S was melt blended with PCL or PCL and paracetamol, the d-spacing increased from 2.05 to 3.13 nm when mixed with PCL only and to 3.02 nm when extruded with PCL and paracetamol. The shifting of these d_{001} peaks to lower 2θ values and the increased spacing between silicate layers is representative of an intercalated morphology, whereby the polymer chains diffuse between the layers thus increasing the interlayer spacing. The increased inter-gallery spacing suggests the molten polymer has 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.[1] to be equivalent to a monolayer of PCL molecules inserted within the galleries of the layered silicate. In the nanocomposite systems described above each sample expanded by more than two monolayers (>0.8 nm) indicating that the PCL may have adopted a planar bilayer 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 partially synthetic fluoromica (S).

The crystalline region of the PCL matrix is defined by three peaks between 20 and 25 2θ with basal spacings of 0.414, 0.374, and 0.325 nm which can be assigned as the 110, 111, and 200 crystal planes, respectively.[33] These peaks decreased in intensity with increased loading of the larger sized S type layered silicate, the composites consisting of 5 wt% S having the lowest crystalline content. From XRD the addition of 5 wt% paracetamol alone does not have a significant effect on the crystallinity of PCL. The motion of the PCL chains which have diffused within the larger aspect ratio layers of the fluoromica (S) is restricted and unable to crystallize fully, thus a greater proportion of PCL is in the amorphous phase.

The micro- and nano-structure of PCL, paracetamol and the composite materials were examined across the length scales using SEM and HRTEM. Figure 2a–c shows SEM images of the paracetamol (average length of the paracetamol crystals was ~15 μm) and the fractured surfaces of neat PCL and PCLP, respectively. The effect of the addition of paracetamol to PCL can be seen in Figure 2c compared to pristine PCL (Fig. 2b). The fractured surface of PCLP5 shows an evenly distributed pattern of distinct shaped bodies ~15 μm in size where the PCL has coated the paracetamol crystals. For the nanocomposites, by

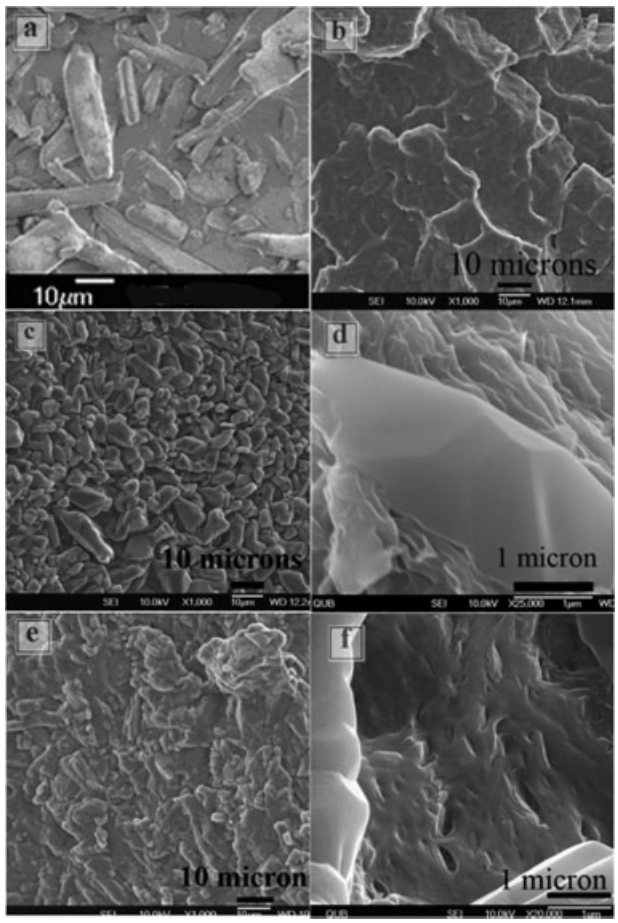

Figure 2. SEM micrographs: (a) paracetamol (P) powder, (b) cryo-fractured surface of PCL (control), (c) PCLP5, (d) PCLP5M1 sample showing the prismatic shaped crystal of paracetamol in the composite, (e) PCLP5M1, and (f) fractured surface of PCLP5M1.

way of example, Figure 2d–f shows different aspects of the microstructure of PCLP5M1. In Figure 2d, a prismatic crystal of paracetamol, about 4 μm in diameter can be observed. This crystal type of paracetamol, monoclinic form I, has been described by Nichols[34] as a prismatic to platy crystal structure which is elongated in the c-axis direction. The presence of this type of crystal confirms that the paracetamol has not changed crystal type to the other orthorhombic polymorph (form II) during processing in the extruder.

Figure 2e illustrates how the addition of a small amount of layered silicate 1 wt% (PCLP5M1) also changes the morphology of the fractured surface of the PCL matrix, a less fragmented morphology obtained. The good dispersion of the clay platelets in PCLP5M1 can be seen in Figure 2f, at higher magnification the voids observed were formed by the ejection of poorly bound clay tactoids during cryo-fracturing.

Further evidence for an intercalated and possible partially exfoliated morphology was obtained from exhaustive examination of the composite materials across the length scales using HRTEM. Figure 3a shows a HRTEM micrograph of PCLM5. Individual single platelets and sub-10 nm stacks of intercalated platelets can be seen. Image analysis of these clusters of platelets in this image revealed an average of 2 platelets per stack with 16 exfoliated platelets and stacks of up to 6 platelets thick. This, in combination with the data from the XRD, confirmed the layered silicate is well dispersed and distributed throughout the PCL matrix. The aspect ratio of the M platelets was measured and was between 50 and 200 with an average of ~110.

The TEM micrograph in Figure 3b shows a paracetamol crystal (marked X) surrounded by the layered silicate platelets in the PCL matrix. It is postulated that this type of morphology, where the paracetamol crystals are entrapped within the 3D matrix of the nanoplatelets retards the release of the drug by introducing a tortuous path for diffusion.

Energy dispersive X-ray (EDX) analysis was performed on the samples under examination and in this instance a spectrum collected for the region marked X in Figure 3b is shown in Figure 4. Analysis of this spectrum shows a large peak originating from the carbon content of the paracetamol crystal and a large peak associated with the copper grid on which the ultramicrotomed sample was positioned on. In the area examined a trace amount of silicon and iron was present from the background signal of montmorillonite, but this is not significant. The absence of significant silicon peaks, the major elemental constituent of layered silicates, confirms that the large crystal in the TEM micrograph is paracetamol and not a tactoid of clay.

Addition of nanoclays is known to alter the mechanical properties of polymeric materials. Static and dynamic mechanical testing was performed on all samples. Figure 5a–c shows the variation in Young's modulus, tensile stress and elongation at break of PCL on addition of paracetamol and either M or S.

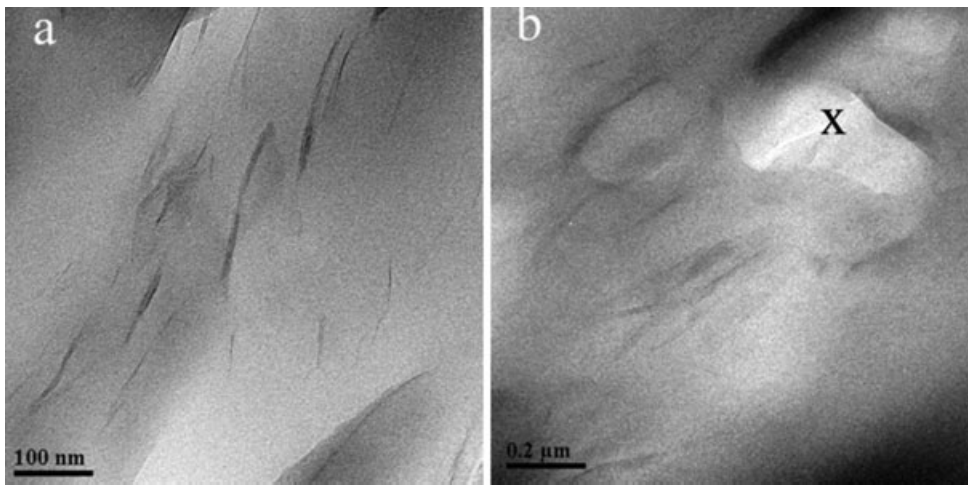

Figure 3. Bright field HRTEM images: (a) PCLM5 showing both an intercalated and exfoliated morphology and (b) PCLP5M1 showing a paracetamol crystal (X) surrounded by layered silicate platelets.

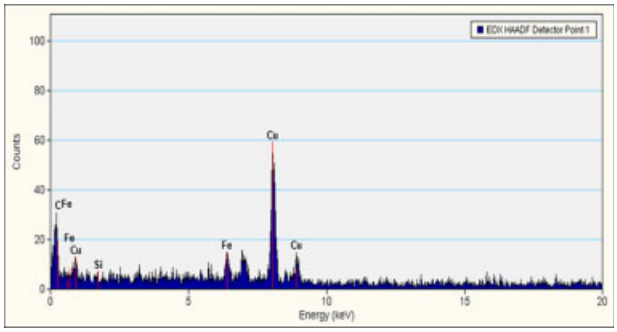

Figure 4. EDX spectrum of the crystalline region at X in Figure 3b.

Within experimental error the addition of either paracetamol (P) and/or montmorillonite (M) to PCL had little effect on the modulus, tensile strength, and extensibility of PCL. This is somewhat surprising given the observations made from the microscopy studies, that addition of even 5 wt% of micron sized paracetamol crystals had little effect on mechanical properties of PCL. A recent article by Chawla et al.[35] on 3D visualization and microstructure-based modeling of deformation in particle reinforced composites proposed that the prismatic structure of paracetamol allows the transfer of stress from the crystal to polymers more efficiently compared to spherical or plate like fillers. This in part explains why the addition of 5 wt% paracetamol did not enhance the mechanical properties of PCL. Evidence to support this hypothesis was found by examining the test specimens before and after tensile testing by SEM. By way of example, the effects of deformation on the surface topography of some of the composites are shown in Figure 6. For pristine PCL, no voids were obvious but a collection of ripples of different dimensions, with the larger ones about 2 μm apart and smaller ones ~200 nm apart, all oriented along the direction of tensile deformation. Similar results were reported previously by Rezgui et al.[36] who observed grooves of 0.5 μm, which they attributed to the semicrystalline nature of PCL. This morphology allows the rubber like amorphous matrix to deform without extensive cavitation at higher strains and crystalline fragmentation occurs under the effect of lamellar bending. A similar microstructure was obtained when paracetamol was added to PCL, however, the paracetamol crystals have broken into smaller fragments due to deformation, and the average size of these crystals is now between 2 and 5 μm in length. Moreover, the fibrillation

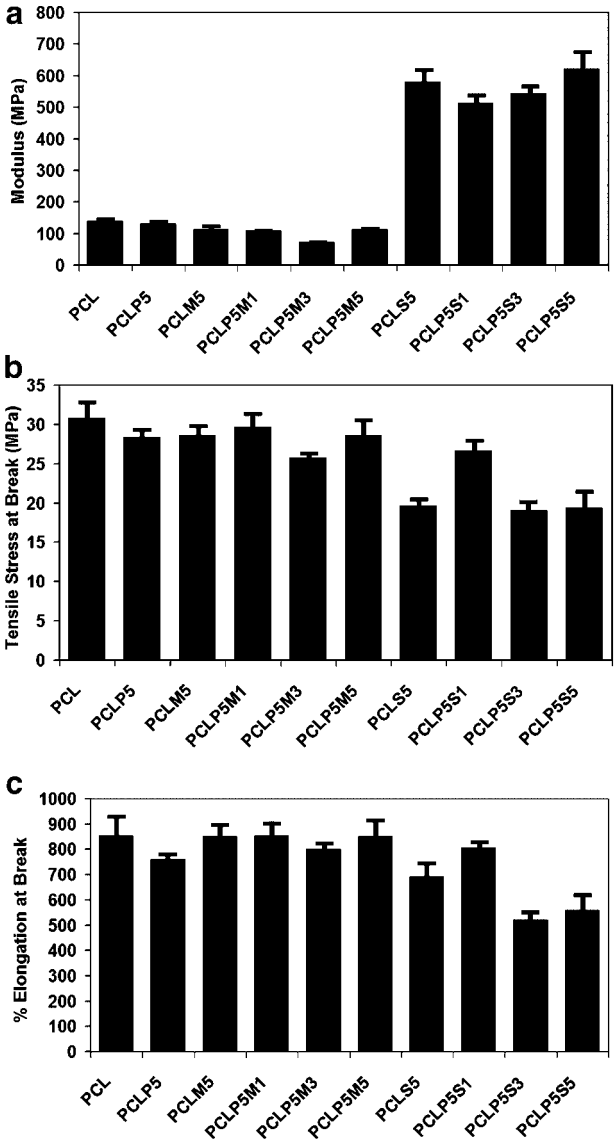

Figure 5. Variation in (a) Young's modulus, (b) tensile stress, and (c) % elongation at break of PCL as a function of paracetamol (P) and montmorillonite (M) or fluromica (S) loading.

observed for neat PCL in the tensile direction was also seen for PCLP5, but the presence of voids through cavitation was obtained. Figure 6c shows the surface morphology of the composite when 5 wt% M was added to PCLP5 (PCLP5M5), the fibril or lamellar morphology has been altered across all length scales, the surface topography obtained was much smoother. The addition of M and drug to PCL again results in the fragmentation of the paracetamol crystals, but the extent of void formation was much less than when no clay

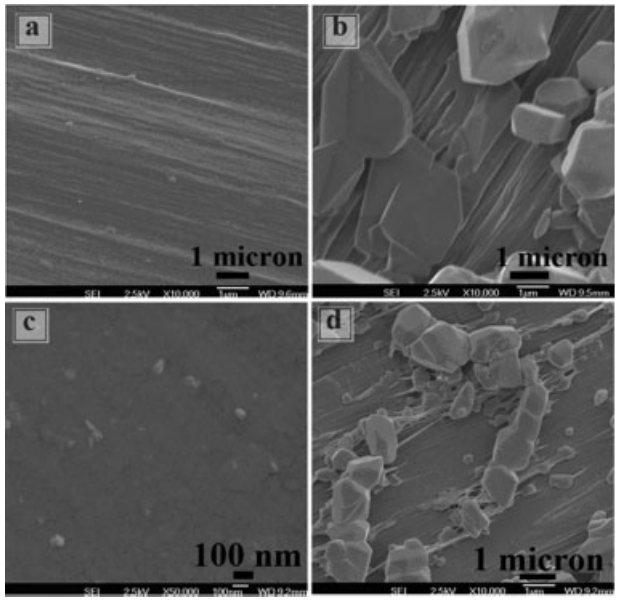

Figure 6. Surface topography of tensile test specimens: (a) PCL, (b) PCLP5, (c) PCLM5, and (d) PCLP5M5 stretched to over 800% extension and allowed to relax.

was added, that is, when the composite consisted of PCL and drug only.

In contrast, the addition of the partially synthetic layered silicate (S) to PCL resulted in a 500% increase in the modulus relative to PCL, see Figure 5a. The increased modulus of the composite with layered silicate S compared to M is a consequence of the larger platelet size of S. The average aspect ratio of montmorillonite (M) platelets, determined from TEM measurements, is ~100[37,38] whilst for Somasif MEE (S) it's around 500.[38] The increase in modulus obtained here is greater than that reported by Pantoustier et al.[39] who achieved a maximum of a 1.3-fold increase (130%) in modulus for a 3 wt% montmorillonite based PCL nanocomposite. Addition of S caused a decrease in tensile strength and elongation at break compared to neat PCL. Similarly, when both S and paracetamol were mixed with PCL a reduction in tensile strength and elongation at break was recorded, the decrease in both properties was greater when the S loading was increased from 1 to 3 or 5 wt%.

Many additives including layered silicates are known to alter the crystallization kinetics of some semicrystalline polymers. A significant reduction in the amount of PCL crystalline phase would grossly affect the rate of dissolution and diffusion of drug molecules from the PCL matrix. All materials and composites used in this study were

Table 2. Thermal Characteristics of PCL and PCL Nanocomposites

	T_c (°C)	T_m (°C)	ΔH_c (J/g)	ΔH_m (J/g)	X (%)
PCL	32.8	55.5	47.9	42.0	35.2
PCLP5	34.0	53.8	44.6	40.6	31.2
PCLM5	31.1	55.9	46.0	51.1	32.1
PCLP5M1	32.4	54.6	48.9	43.2	33.8
PCLP5M3	31.5	54.6	47.5	35.7	32.1
PCLP5M5	31.1	55.5	46.2	42.0	30.6
PCLS5	31.5	55.5	47.5	49.2	33.2
PCLP5S1	29.1	54.0	48.6	41.4	33.6
PCLP5S3	29.8	54.6	47.6	40.2	32.2
PCLP5S5	29.8	54.6	45.2	40.7	30.0

characterized using DSC, the heat flow data for the non-isothermal melting and crystallization are listed in Table 2, including the onset temperatures for melting T_m (°C) and crystallization T_c (°C), enthalpy of crystallization ΔH_c (J/g), enthalpy of melting ΔH_m (J/g) and crystalline content (X). The crystalline content in the composites was determined using a value of 136 J/g for a theoretically 100% crystalline PCL[1] and compensating for blend composition. There is minimal change in both T_m and T_c on addition of either layered silicate (M and S) or paracetamol (P) to PCL. In all cases a decrease in crystalline content was recorded, the layered silicates altering the crystallization behavior of PCL. At most a 10% reduction in crystalline content was obtained for the composite having the largest loading of S (5 wt%). It has been observed previously that the crystallinity of nanocomposites first increases with increasing organosilicate content then decreases.[1] These authors attributed this behavior to the competing effects of the layered silicate which can act as a nucleating agent to increase crystallinity as well as hinder crystallization by restricting the mobility of the poly(ε-caprolactone) chains trapped within the silicate layers.[1] It was suggested by Ray et al.[9] that only the exfoliated silicate platelets were able to act as effective nucleating agents, thus causing the formation of smaller crystallites.

The dynamic mechanical behavior of the composite materials as a function of temperature was investigated using dynamic mechanical analysis (DMA). Figure 7a shows the variation in tan delta with temperature for the materials containing M layered silicate, measured at 1 Hz. By convention the T_g was measured from the α-transition peak maximum at 1 Hz. Addition of

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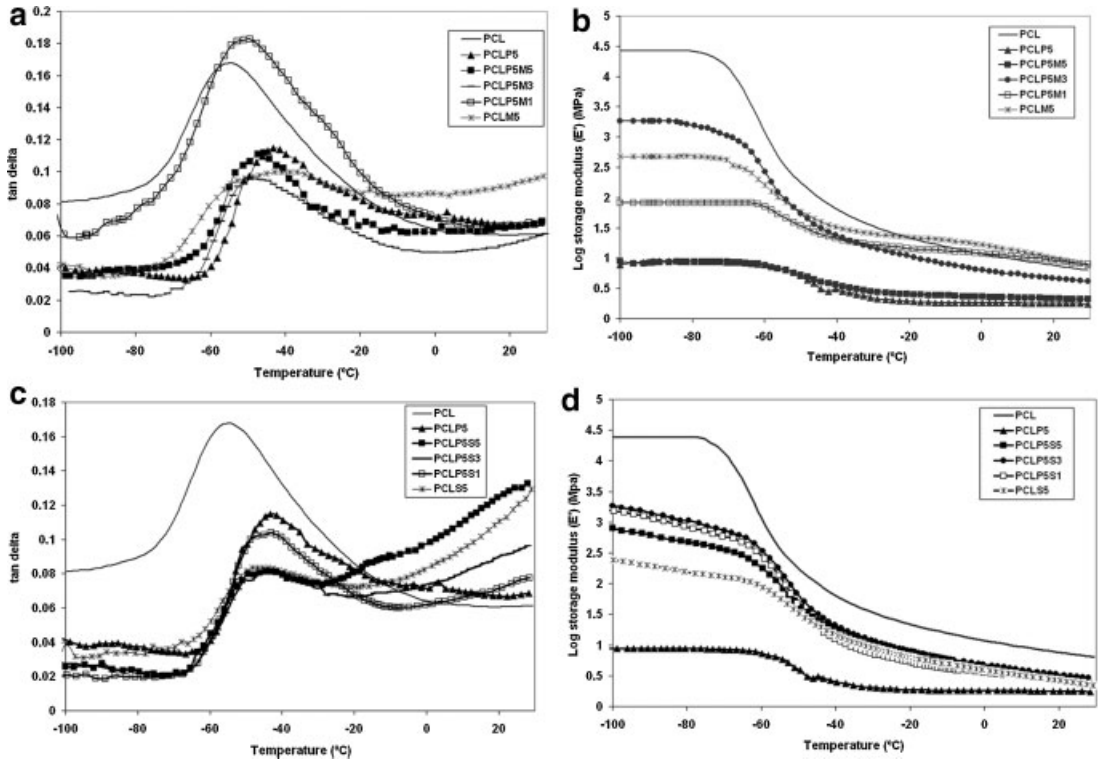

Figure 7. Variation in (a) tan delta of montmorillonite (M) based nanocomposites, (b) storage modulus of M based nanocomposites, (c) tan delta of fluoromica (S) based nanocomposites, and (d) storage modulus of S based nanocomposites as a function of temperature at 1 Hz.

either paracetamol (P) or M alone resulted in an increase in T_g, from −54 to −43°C and −39°C, respectively. Similar behavior was also obtained when S was added to PCL, in this case the T_g increased by 9°C, from −54 to −45°C, see Figure 7c.

Interestingly, when both paracetamol and M nanoclay were added together to PCL, there was also an increase in T_g, but to a lesser extent than when either component was added separately. In contrast, when paracetamol and S nanoclay were blended with PCL, the increase in T_g was greater than when either was added separately. In all cases, that the T_g of PCL increased further supports the hypothesis that the mobility of the polymer chains is constrained by the dispersed silicate layers either as a consequence of the diffusion of polymer chains into the limited space between layers or the tethering of chains to the edges and surface of the platelets. The effect is greater for S due to the larger aspect ratio of the fluoromica platelets and tethering of the PCL chains to S as a consequence of hydrogen bonding between PCL and hydroxyl groups on the edges of the S nanoplatelets. Furthermore, the intensity (damping) and shape of the tan delta peaks for both series of composites is less than that for PCL alone, suggesting strong interactions between PCL and nanoclay.[40] The higher the nanoclay loading in the composite the less intense, but more broad the tan delta peak. Figure 7b and d shows the variation in storage modulus (E') of PCL and the composite materials in the temperature range −100 to 30°C. In this temperature range addition of paracetamol to PCL resulted in approximately a fourfold decrease in the storage modulus below the T_g of PCL. Above the T_g the storage modulus of PCLP was also less than that for PCL. However, addition of M or S to PCLP resulted in an increase in the storage modulus, the magnitude of which increased threefold with successive increased loadings of nanoclay, such that for the composite with 5 wt% M, E' was one order of magnitude below that of neat PCL.

The effect of layered silicate content on the dissolution behavior and release kinetics of

paracetamol from PCL was investigated. One of the assumptions made in calculating diffusion coefficients is that sink conditions are maintained (i.e., saturation solubility is at least three times more than the drug concentration in the dissolution medium) as outlined in USP[41] and by using 900 mL of dissolution medium and standard USP apparatus, this condition has been fulfilled. To ensure uniformity of results, compression molded disks of uniform dimensions were made of all samples for *in vitro* measurements. In the initial stages, there is a "burst effect" where ~5–10% of the paracetamol is released. This has been attributed to the paracetamol crystals close to the surface being released as the surface is dissolved first, and has been confirmed by SEM, see Figure 8.

Figure 8a and b are SEM micrographs of the surface of the PCLP5 before and after dissolution, respectively. Initially, paracetamol crystals can be seen embedded in the PCL matrix, however, after 6 days of the dissolution experiment the sample was full with cavities. In complete contrast, when nanoclay was added, for example, for PCLP5S5 (Fig. 8c and d), prior to the dissolution the surface of the sample was smooth, but even after 6 days of the drug release experiment no cavities or voids were observed. Further image analysis of the FESEM images of the composite materials indicated that some of the surface PCL amorphous phase also dissolved leaving small crystalline spherullites of PCL, measured to be from 50–100 nm in size. In the long-term degradation of PCL (18 months) Pena et al.[42] attributed this to the crystallization of the amorphous regions where the autocatalytic cleavage of the ester bond forms shorter chains which can crystallize more easily.

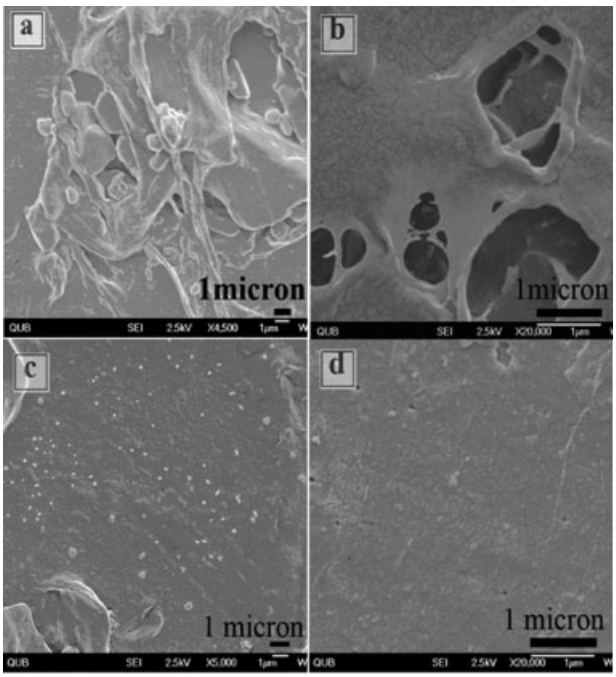

Figure 8. SEMs of the surface topography of compression molded disks of (a) PCLP5, (b) PCLP5 after 6 days drug release experiment, (c) PCLP5S5, and (d) PCLP5S5 after the 6 days drug release experiment.

Paracetamol was used as a model drug due to its well characterized properties and also as it has a reasonable, if not high, solubility in water (circa 17 g/kg at 25°C).[43,44] The release of paracetamol from the PCL matrix was retarded when either the M or S layered silicate was a constituent of the formulation (see Figure 9). The percentage paracetamol released as a function of time decreased slightly when the loading of either layered silicate (M or S) added was 5 wt%, this effect being more pronounced for the S layered silicate which has the greater aspect ratio (surface area). This behavior was not observed for low loadings of either M or S (1 wt%). We suggest that the large aspect ratio of the inorganic clay platelets provide a more tortuous path for paracetamol diffusion.

Diffusion coefficients for each formulation were calculated using classical Fickian diffusion theory, as outlined in a recent article by Liu et al.[45] Eq. (2) can be used to describe the diffusion controlled release behavior of drugs which have an assumed

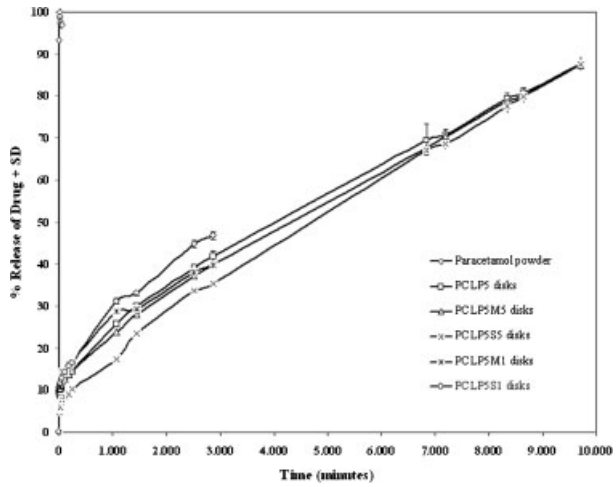

Figure 9. Comparative dissolution profiles of binary paracetamol/PCL solid dispersions and paracetamol loaded PCL-layered silicate solid dispersions prepared by hot-melt extrusion.

diffusion coefficient D, in one dimensional diffusion

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

where M is defined as the mass of drug released at time t, M_∞ the mass of drug released as time approached infinity, and l the thickness of the disk. By taking the first term in the summation series Eq. (2) can be reduced to Eq. (3) and from a plot of $\ln(1-M_t/M_\infty)$ against t, D can be determined from the slope, $D\pi^2/l^2$.

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

The diffusion coefficients (D) were calculated for all formulations and are listed in Table 3. It is noteworthy that the inclusion of the clays retarded the dissolution of the paracetamol in a manner that was compatible with the observations made regarding the distribution of the clay within the nanocomposite structure. The retarding effect was greater for the larger aspect ratio of partially synthetic fluoromica nanoclay.

DISCUSSION

Paracetamol loaded PCL layered silicate nanocomposites were prepared using conventional melt extrusion techniques. Both the paracetamol and layered silicate nanoplatelets were well dispersed and distributed throughout the PCL matrix. The shear forces and temperature regime used during the extrusion process did not alter the prismatic monoclinic form I crystal of the paracetamol. The inclusion of high aspect ratio nanoplatelets in the formulation changed the dissolution behavior of the drug in PCL and had a retarding effect on the diffusion of paracetamol from the polymer matrix when higher loadings of M or S were added (5 wt%), although these effects were comparatively modest. The melting and crystallization temperatures of PCL was unaffected by the addition of drug and nanoclay, but the crystalline content decreased by about 10% for those blends with 5 wt% layered silicate added. The dispersed, large surface area nanoplatelets, restrict the mobility of PCL chains and hinder the crystallization process. Further evidence for the constrained motion of PCL chains was obtained from DMTA, the T_g of PCL increased by 9 and 15°C when 5 wt% S and M were added, respectively. The tensile mechanical properties of PCL were relatively unchanged when montmorillonite (M) was added to the formulations. In contrast, when the partially synthetic fluoromica (S) was blended, the tensile stress and elongation at break decreased by about a third, but the modulus increased by 500%.

Overall, therefore, the use of nanocomposites appears to be a potentially highly useful means of manipulating the mechanical properties of hot melt extrudates, while not necessarily having a profound effect on the dissolution properties. This is of considerable potential significance in that hot melt extruded systems may be comminuted to a powder form prior to use, which may include inclusion in tablet formulations whereby the mechanical properties are critical. Perhaps surprisingly, the presence of the clay only has a modest effect on the dissolution properties, albeit one which is fully in keeping with the structural studies. A further interesting finding is the marked difference between systems including synthetic fluoromicra (S) and montmorillonite (M), with the former involving much more profound changes in mechanical, structural, and drug release properties. It is therefore evident from these studies that the inclusion of this and similar materials present an opportunity for manipulating the properties of HME formulations in a tailored and controlled manner.

CONCLUSIONS

In this study we have examined the possibility of using layered silicate nanocomposites as drug

Table 3. Comparison of the *In Vitro* Drug Release Profiles

Diffusion Coefficients	PCLP5	PCLP5M1	PCLP5M5	PCLP5S1	PCLP5S5
1st stage surface effect D ($\times 10^{-7}$ cm^2 s^{-1})	4.4 ± 0.04	5.8 ± 0.5	5.8 ± 0.1	5.8 ± 0.15	2.9 ± 0.06
2nd stage up to 180 min D ($\times 10^{-9}$ cm^2 s^{-1})	11.7 ± 0.4	11.7 ± 0.6	10.2 ± 0.6	11.7 ± 0.3	8.75 ± 0.2
3rd stage after 180 min D ($\times 10^{-9}$ cm^2 s^{-1})	2.9 ± 0.01	2.9 ± 0.07	2.9 ± 0.3	2.58 ± 0.1	2.39 ± 0.2

delivery systems, particularly in the context of hot melt extrusion. We have demonstrated that it is indeed possible to prepare drug-loaded nanocomposites, with a high level of clay dispersion, using paracetamol as a model and that retardation of dissolution is similarly possible. A key finding is the observation of a direct relationship between nanocomposite structure, dissolution behavior and mechanical properties in terms of both aspect ratio/surface area of the clay used and also the distribution of the clay within the matrix, the most marked effect being on the mechanical properties of the systems. A challenge remains in rendering the retardation of dissolution more extensive, although this may not necessarily be desirable, particularly for low solubility drugs whereby improved release may be required. Indeed, the ability to substantially modify the mechanical properties, thereby potentially aiding processing, without causing marked effects on dissolution may well be prove to be a highly applicable possibility, given the wide range of dosage forms for which HME formulation is now being employed within the pharmaceutical sciences.

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