Polyoxypropylene–Montmorillonite Nanocomposites for Drug-Delivery Vehicles: Preparation and Characterization

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ABSTRACT: Polyoxypropylene–montmorillonite (MMT) nanocomposites were prepared by an ion-exchange process of sodium montmorillonite (Na-MMT) and $-NH_3^+$ groups in polyoxypropylene amine hydrochlorides with three different molecular masses (D_{230}, D_{400}, and D_{2000}). Wide-angle X-ray diffraction (XRD) confirmed the intercalation of the polymer between the silicate layers. Electrostatic interaction between the positively charged NH_3^+ groups and the negatively charged surface of MMT was observed. Acidic ibuprofen and basic theophylline drugs were intercalated into the nanocomposites and characterized by infrared spectroscopy, XRD, transmission electron microscopy, and thermogravimetric analysis. The amount of drugs in the nanocomposites was calculated by calcination measurement. The *in vitro* drug release from the nanocomposites was studied in colon and intestinal pHs and compared with drug release from Na-MMT. The nanocomposite is expected to achieve *in situ* release for colorectal therapy in future applications. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 125: E157–E166, 2012

Key words: drug delivery systems; organoclay; nanocomposites

INTRODUCTION

Biologically active agents are normally administered, systemically or topically, at a site somewhat remote from the target. This procedure results in nonspecific and periodic application. Remote application, besides increasing the cost of treatment, often produces undesirable side effects, either in the target or in the environment around the target.

The main concept of modified delivery technology is that any pharmaceutical dosage form should be designed to provide therapeutic levels of drug to the site of action and maintain them throughout the treatment.[1] These goals may be achieved by modification of the rate and/or time and/or site of drug release in comparison with conventional formulations. Such modification in the release of active substances is provided to reduce toxic effects or for some other therapeutic purposes.

One class of drug-delivery vehicles that has received more attention in recent years is layered materials, which can accommodate polar organic compounds between their layers and form a variety of intercalated compounds.[2–7] Because the release of drugs in drug-intercalated layered materials is potentially controllable, these new materials have great potential as delivery hosts in the pharmaceutical field.

Silicate minerals are naturally occurring inorganic cationic exchangers characterized by a layered structure, and they exhibit properties such as good water absorption, swelling, adsorbability and cation-exchange ability that are considered beneficial from the viewpoint of the synthesis of pharmaceutical products, as both inactive and active substances.[8,9] In this regard, clay minerals have been used as stabilizers or emulsifying agents for the formulation and liquid drugs. It was observed that the bioavailability of drugs was reduced.[10,11] This led to the suggestion that an interaction between the drug and clay mineral inhibited or delayed release of the drug. Depending on the cation-exchange capacity (CEC) of the clay, the presence of cationic groups of the drug and the pH of the release medium determine the kinetics of drug release. Apart from electrostatic forces, there also exists the possibility of other interactions, including hydrophobic, hydrogen-bonding, ligand-exchange, and water-bridging interactions. These properties have encouraged the use of clay minerals for the sustained release of drugs and improved drug dissolution.[12–15] Smectites, especially montmorillonite (MMT) and saponite, have been the more commonly studied because of their higher CEC compared to other pharmaceutical silicates.

Different technological procedures have been reported for obtaining clay–drug interaction products. Commonly, clay mineral particles are dispersed in aqueous drug solutions, and finally, the solid

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phases are recovered and dried.[16] A way to entrap bioactive molecules by inducing coagulation in MMT dispersions was also described.[17] Dry procedures (specifically helpful for poorly soluble molecules) were also reported and consisted of grinding the clay and the drug together or putting them in contact at the melting temperature of the drug.[18]

One important consequence of the charged nature of the clays is that they are generally highly hydrophilic species and are, therefore, naturally incompatible with a wide range of nonpolar systems. Organophilic clay can be obtained simply by the ion-exchange reaction of hydrophilic clay with organic cations, such as alkyl ammonium or phosphonium ion. The great advantages of these materials is that by a suitable choice of organic compounds, it is possible to increase the gap between the single sheets, enabling organic cations chain to move between them and change the surface character from hydrophilic to hydrophobic. When the hydrophobicity of the clay mineral surface is increased, the adsorption of hydrophobic molecules is expected to increase and attain extended release in aqueous solutions. Organically modified smectites are widely used as adsorbents of nonpolar bioactive substances. The success of this approach has been shown with alachor,[19] norflurazon,[20] and hexazinone.[21] Finally, surfactant-modified MMTs also showed a higher affinity for anionic species, such as Cr (VI) derivatives, compared to unmodified clay minerals.[22]

Theophylline is used in therapy for respiratory diseases. It has some anti-inflammatory effect. Ibuprofen is an important nonsteroidal anti-inflammatory drug used to treat rheumatoid arthritis, osteoarthritis, and moderate pain. Its use is often limited by frequent side effects, which affect the gastrointestinal tract and the central nervous system and the ulcerogenic effect, in addition to its short half-life (1.8–2 h). These problems could be reduced by a formulation able to control drug release.

Site-specific drug delivery to the colon has attracted increasing attention, both for the therapy of colon-related diseases and systemic drug delivery. For this purpose, it is necessary to incorporate the drug in a formulation able to minimize premature release in the upper part of the gastrointestinal tract and then optimize drug release in the colon. In this study, we intercalated theophylline and ibuprofen into MMT modified by three molecular masses of polyoxypropylene to increase and attain extended release in aqueous solutions and direct drug release into the colon.

EXPERIMENTAL

Materials

The clay mineral used in this study was sodium montmorillonite (Na-MMT; colloid BP) from Southern Clay Products, Inc. (Gonzales, TX), with a CEC of 114.8 mequiv/100 g. It was received as fine particles. The interlayer or interlamellar spacing (d_{001}) spacing was 9.6 Å after the clay was dried in a vacuum oven at 100°C for 24 h. Three kinds of polyoxypropylene diamine were obtained from Huntsman Corp. (TX, USA): (1) polyoxypropylene diamine having an average molecular mass of 230 (D_{230}) and a primary amine content of 8.2 mequiv/g, (2) polyoxypropylene diamine having an average molecular mass of 400 (D_{400}) and a primary amine content of 4.3 mequiv/g, and (3) polyoxypropylene diamine having an average molecular mass of 2000 (D_{2000}) and a primary amine content of 0.97 mequiv/g. Theophylline (1,3-dimethyl-7H-purine-2,6-dione) and ibuprofen [α-methyl-4-(2-methylpropyl) benzene acetic acid] as model basic and acidic drugs, respectively, were purchased from Aldrich and were used as received without further purification. Silver nitrate ($AgNO_3$) was purchased from Aldrich and was used as received. Dimethylformamide (DMF) and ethanol were supplied by El-Naser pharmaceutical chemicals, Egypt and were used as received. The structures of the polyoxypropylene diamines and drugs are shown in Figure 1.

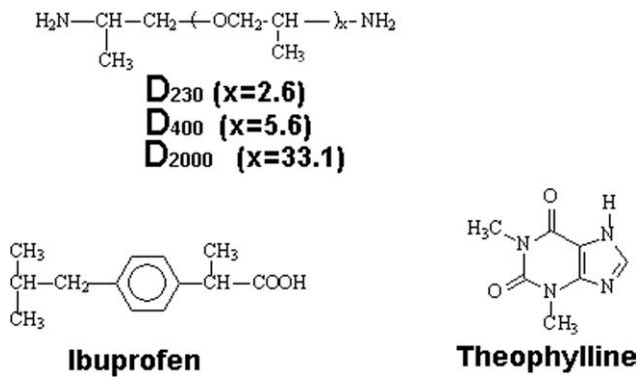

Figure 1 Structures of polyoxypropylene, ibuprofen, and theophylline.

Preparation and swellability of the polyoxypropylene–MMT nanocomposites

The intercalation of polyoxypropylene diamine hydrochloride into Na-MMT galleries was carried out by a cationic-exchange process following a previously described procedure.[23] MMT (15 g) was dispersed into 1000 mL of hot, distilled water under continuous stirring for 3 h at 60°C followed by stirring for several hours at room temperature. An aqueous solution of 3.5 g of D_{230} was added to the swelled Na-MMT with constant stirring. Then, the dispersion was heated at 60°C. To promote the ion-exchange reaction, protonation of the polymer was carried out by the addition of hydrochloric acid, and the pH was adjusted to 8. The mixture was then

TABLE I
Composition Data of Polyoxypropylene–MMT Nanocomposites

Code	Na-MMT weight (g)	Polyoxypropylene diamine weight (g)	Yield weight (g)
D_{230}–MMT	15	3.5	13
D_{400}–MMT	15	6	15
D_{2000}–MMT	15	30	20

stirred for an additional 24 h. The precipitate was filtered and washed with water several times until no chloride ions were detected in the filtrate by testing with $AgNO_3$. The resultant product, D_{230}–MMT, was dried at 60°C to give 13 g. The same procedure was followed for the polymers with different molecular masses (Table I). The samples were placed in a vacuum oven at 80°C for 24 h and were then cooled in a desiccator and immediately weighed in sintered glass to the nearest 0.001 g to get the initial mass (m_0). Then, the samples were immersed in a buffer solution for 72 h. The sintered glasses were centrifuged and weighed to obtain the final mass (m_1). The swelling percentage was calculated with the following formula: $(m_1 - m_0)/m_0 \times 100$. The swellability at pH 7.8 was found to be 233% for Na-MMT, 262% for D230–MMT, 24% for D_{400}–MMT, and 1.5% for D_{2000}–MMT.

Intercalation of drugs into the polyoxypropylene–MMT nanocomposites

In a 100-mL conical flask, 1 g of D_{230}–MMT was first swollen for 48 h at room temperature in DMF, and then, 0.3 mmol of ibuprofen dissolved in 10 mL of DMF was added. The reaction mixture was stirred further for 24 h more at 40°C. The product was collected by filtration, washed with ethanol (three times) to remove the excess unreacted drug, and dried *in vacuo* at 40°C overnight. The same procedure was followed for the other molecular mass polymers and drugs (Table II).

Preparation of Na-MMT/ibuprofen

In a 100-mL conical flask, 1 g of the Na-MMT was swelled in 30 mL of water for 3 h at 60°C; this was

TABLE II
Composition Data of Polyoxypropylene–MMT/Drugs

Code	Support/ weight (g)	Drug/ weight (mg)	Yield (wt %)
D_{230}–MMT/ ibuprofen	D_{230}–MMT/1	Ibuprofen/61.8	82
D_{400}–MMT/ ibuprofen	D_{400}–MMT/1	Ibuprofen/61.8	83
D_{2000}–MMT/ ibuprofen	D_{2000}–MMT/1	Ibuprofen/61.8	85
D_{230}–MMT/ theophylline	D_{230}–MMT/1	Theophylline/54	92
Na-MMT/ ibuprofen	Na-MMT/1	Ibuprofen/61.8	90

followed by stirring for several hours at room temperature. After complete swelling, 10 mL of DMF was added, and then, 0.3 mmol of ibuprofen dissolved in 10 mL of DMF was added. The reaction mixture was stirred further for 24 h more at 40°C. The product was collected by filtration, washed with ethanol (three times) to remove the excess unreacted drug, and dried *in vacuo* at 40°C.

Preparation of phosphate buffer (PB) solution

The PB solution was prepared by the dissolution of 21.7 g of dibasic sodium phosphate (Na_2HPO4) and 2.6 g of monobasic potassium phosphate (KH_2PO4) in 1 L of deionized water, and the pH was adjusted to 7.8 or 5.4 with a 0.1*N* NaOH or 0.1*N* HCl solution, respectively.

Calcination measurements

A certain amount of the sample was introduced into a porcelain crucible after drying in an electric oven overnight and then introduced into an ignition oven at 1000°C for 8 h. The crucibles were then left in a desiccator overnight to determine their weight. The polymer loading of each sample was expressed as the weight loss per 100 g of the dry sample. The total amount of ibuprofen and theophylline intercalated into polyoxypropylene–MMT was calculated (Table III) by subtraction of the weight loss of polyoxypropylene–MMT from the weight loss of polyoxypropylene–MMT/drug.

TABLE III
Loading Amounts of Drugs Calculated from the Weight Loss from Calcination Measurements

Code	Weight loss (%)	Code	Weight loss (%)	Drug (wt %)
D_{230}–MMT	7.1	D_{230}–MMT/ibuprofen	16.69	9.59
		D_{230}–MT/theophylline	18.56	11.46
D_{400}–MMT	16.8	D_{400}–MMT/ibuprofen	24.53	7.73
D_{2000}–MMT	40.3	D_{2000}–MMT/ibuprofen	41.98	1.68
Na-MMT	11.0	Na-MMT/ibuprofen	16.51	5.5

In vitro drug release

A suspension of 10 mg of sample in 50 mL of an aqueous buffer solution (pH 5.4, 7.8) was kept at 37°C. The amount of drug released at different intervals was evaluated by measurement of the UV absorbance of the supernatant solutions. The release of theophylline and ibuprofen was followed with a Shimadzu UV-2101 PC spectrophotometer (Tanta, Egypt) at $\lambda_{max} = 332.5$ nm for ibuprofen and $\lambda_{max} = 270$ nm for theophylline as a function of time.

At specific intervals, 3 mL of the buffer was collected for analysis. Each experiment was carried out three times, and the average was calculated.

Characterization

Infrared absorption spectra were obtained on a PerkinElmer 1420 spectrophotometer (Tanta, Egypt) with the KBr disc technique in the wavelength range 4000–400 cm^{-1}. Wide-angle X-ray diffraction (XRD) measurements were recorded with a Phillips powder diffractometer equipped with Ni-filtered Cu Kα ($\lambda = 1.5418$ Å) at a scanning speed of 2°/s. The samples were dried in a vacuum oven at 80°C for 12 h and then mounted on a sample holder with a large cavity. We obtained a smooth surface by pressing the powder samples with a glass plate. Bragg's law ($n\lambda = 2d \sin\theta$; where n is an integer, λ is the wavelength of incident wave, d is the spacing between the planes in the atomic lattice and θ is the angle between the incident ray and the scattering planes) was used to compute the crystallographic spacing. Thermogravimetric analysis (TGA) was carried out with a PerkinElmer thermal analyzer system at a heating rate of 10°C/min from 30 to 800°C under a nitrogen flow (20 mL/min). Transmission electron microscopy (TEM) specimens were cut from nanocomposite samples embedded in epoxy resin with an ultramicrotome (LKB 8800 ultramicrotome III (Cairo, Egypt) equipped with a glass knife). We cut the ultrathin films by moving the sample across a knife edge of glass. The ultrathin flakes floated onto a trough filled with water, from where they were collected on 200-mesh copper grids and dried at room temperature. In addition, 0.1 g of the sample was dispersed in 10 mL of water, and a drop of the suspension was placed on the copper grid for TEM examination. TEM (Cairo, Egypt) micrographs were taken with a JEOL JEM-1230 electron microscope at an accelerating voltage of 100KV. The absorption spectra were recorded with a Shimadzu UV-2101 direct-current spectrophotometer.

RESULTS AND DISCUSSION

Nanostructure and morphology

Clay minerals are generally highly hydrophilic species and, therefore, naturally incompatible with a wide range of nonpolar systems. Organoclay can be obtained by a simple ion-exchange reaction of a hydrophilic clay mineral with an organic cation, such as an alkyl ammonium or phosphonium ion. This ion-exchange reaction has two consequences; first, the gap between the single sheets is widened, which enables organic cation chains to move between them, and second, the surface properties of each single sheet are changed from being hydrophilic to being organophilic. The hydrophilic nature of Na-MMT allows the polymer molecules to migrate between the layers. The high surface energy of the clay mineral attracts polar species molecules so that they diffuse between the layers during the cation-exchange process. In this work, the role of polyoxypropylene hydrochloride was to lower the surface energy of the inorganic host and improve the wetting characteristics with the drug. Additionally, the polyoxypropylene amine could provide functional groups that could react with the drug to improve the strength of the interface between the inorganic and the drug.

The XRD pattern displayed in Figure 2(a–e) indicates regular lattice spacings of 14.7 Å for D_{230}–MMT, 16.3 Å for D_{400}–MMT, and 18.4 Å for D_{2000}–MMT with an expansion of the clay galleries by 5.4, 7, and 9.1 Å, respectively. Subtraction of the thickness of the silicate layer (9.3 Å) from the observed d_{001} spacing produced the amount of polymer within the interlamellar span. XRD showed the characteristic crystalline peaks of ibuprofen around $2\theta = 12.5$, 14, 16.5, 18, 18.5, 19.5, 22.5, and 23.5° and theophylline at 5, 11, 13, 17, and 20–24°. After D_{230}–MMT was incorporated with ibuprofen, the basal spacing characteristic of D_{230}–MMT was substituted by a broader peak. However, D_{400}–MMT/ibuprofen exhibited a diffraction shoulder. This indicated that a substantial part of the clay mineral was only exfoliated. In the case of D_{2000}–MMT/ibuprofen, the peak characteristic of D_{2000}–MMT virtually disappeared with the appearance of two broad peaks at $2\theta = 2.8$, 6°; this indicated the formation of an order-intercalated structure. However, in D_{230}–MMT/theophylline, a sharp peak was obtained. The high relative intensity of the 001 plane peak was due to a more narrow distribution of the interlamellar spacing. It is worth noting that the basal spacing of Na-MMT was expanded from 9.6 to 13.6 Å in Na-MMT/ibuprofen; this indicated the intercalation of ibuprofen between the layers of Na-MMT.

It is difficult for XRD to give definitive conclusions about the defined structure. Thus, the TEM technique is necessary to characterize the morphology of the nanocomposites.

TEM of ultramicrotome sections prepared from D_{230}–MMT/ibuprofen [Fig. 3(a)], D_{400}–MMT/ibuprofen [Fig. 3(b)], and D_{2000}–MMT/ibuprofen [Fig. 3(c)]

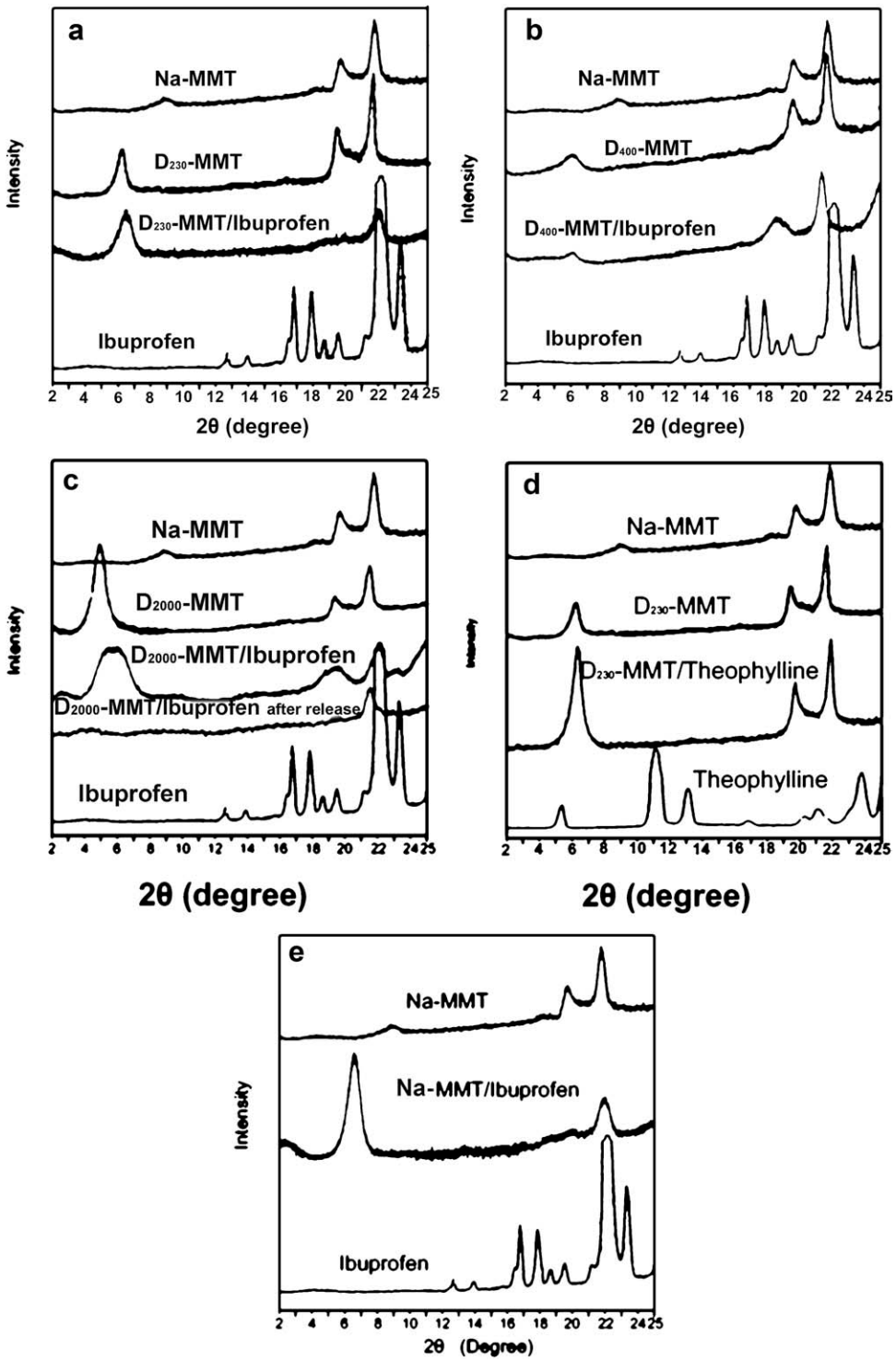

Figure 2 XRD patterns of (a) Na-MMT, D_{230}–MMT, ibuprofen, and D_{230}–MMT/ibuprofen; (b) Na-MMT, D_{400}–MMT, ibuprofen, and D_{400}–MMT/ibuprofen; (c) Na-MMT, D_{2000}–MMT, ibuprofen, D_{2000}–MMT/ibuprofen, and D_{2000}–MMT/ibuprofen after drug release; (d) Na-MMT, D_{230}–MMT, theophylline, and D_{230}–MMT/theophylline; and (e) Na-MMT, ibuprofen, and Na-MMT/ibuprofen.

specimens embedded in epoxy resin displayed typical portraits of the nanomineral domains. D_{230}–MMT/ibuprofen showed the existence of an intercalated structure. In D_{400}–MMT/ibuprofen, the domains appeared to be flocculated. However, in D_{2000}–MMT/ibuprofen, TEM revealed the presence of ordered multiplets with an average size of 50 nm.

Figure 4(a) illustrates the IR spectra from Na-MMT, D_{230}–MMT, and D_{230}–MMT/ibuprofen. In the

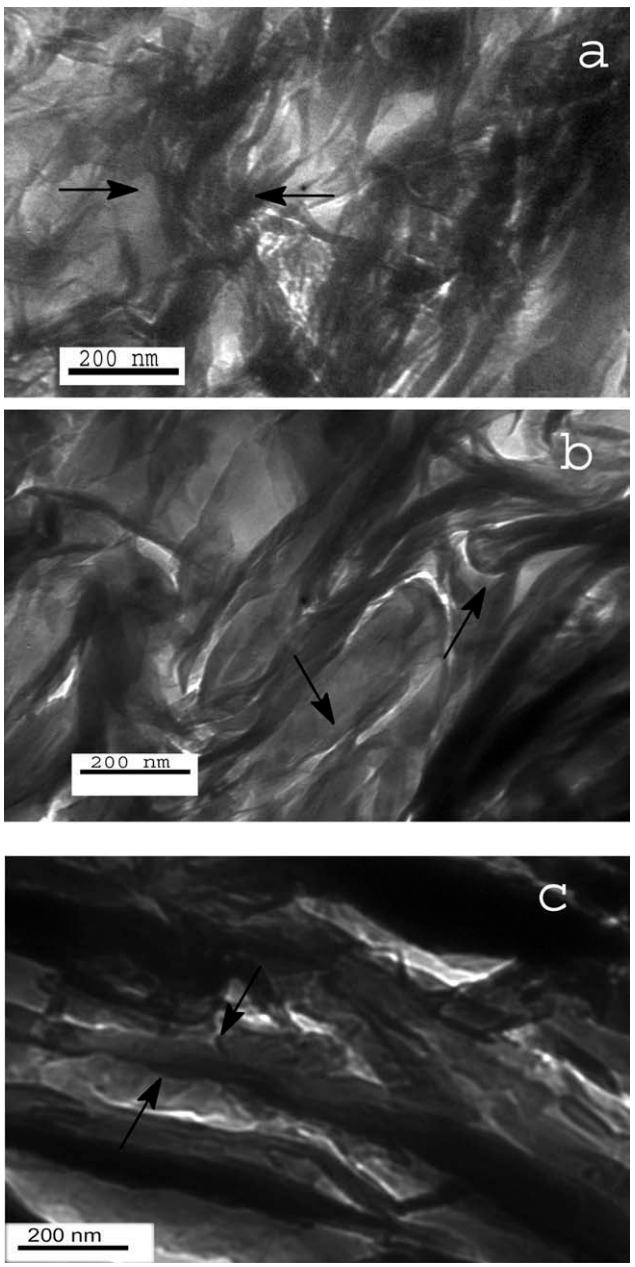

Figure 3 TEM micrographs of (a) D_{230}–MMT/ibuprofen, (b) D_{400}–MMT/ibuprofen, and (c) D_{2000}–MMT/ibuprofen at different magnifications.

spectrum of pure Na-MMT, the absorption band at 3627 cm^{-1} [υ (OH)] was assigned to the stretching vibration of Al—OH. The symmetrical Si—O—Si band [υ (Si—O—Si)] was characterized by the stretching band at 1045 cm^{-1}. Other characteristic bands of pure clay were observed at 921 cm^{-1} [δ (Al—Al—O)] and 523 cm^{-1} [δ (Si—O—Al)], whereas the spectrum of ibuprofen showed the absorption band at 3116 cm^{-1} [υ (OH)] corresponding to the stretching vibration of OH. The bands at 1443 and 1314 cm^{-1} [δ (OH)] were assigned to the bending of O—H. The absorption band at 1713 cm^{-1} [υ (C=O)] was assigned to C=O. The bands between 3000 and 2800 cm^{-1} were related to the alkyl stretching vibrations of ibuprofen.

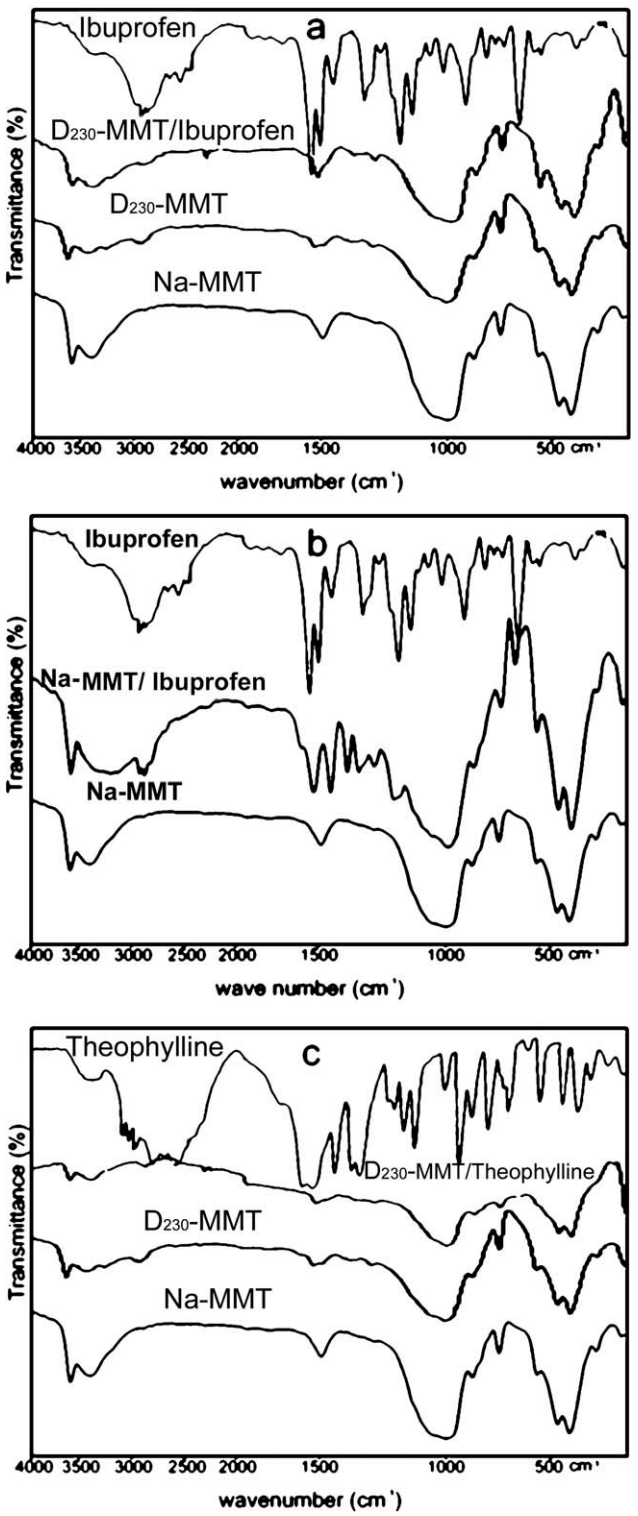

Figure 4 IR spectra of (a) Na-MMT, D_{230}–MMT, ibuprofen, and D_{230}–MMT/ibuprofen; (b) Na-MMT, ibuprofen, and Na-MMT/ibuprofen; and (c) Na-MMT, D_{230}–MMT, theophylline, and D_{230}–MMT/theophylline in the region 4000–400 cm^{-1}.

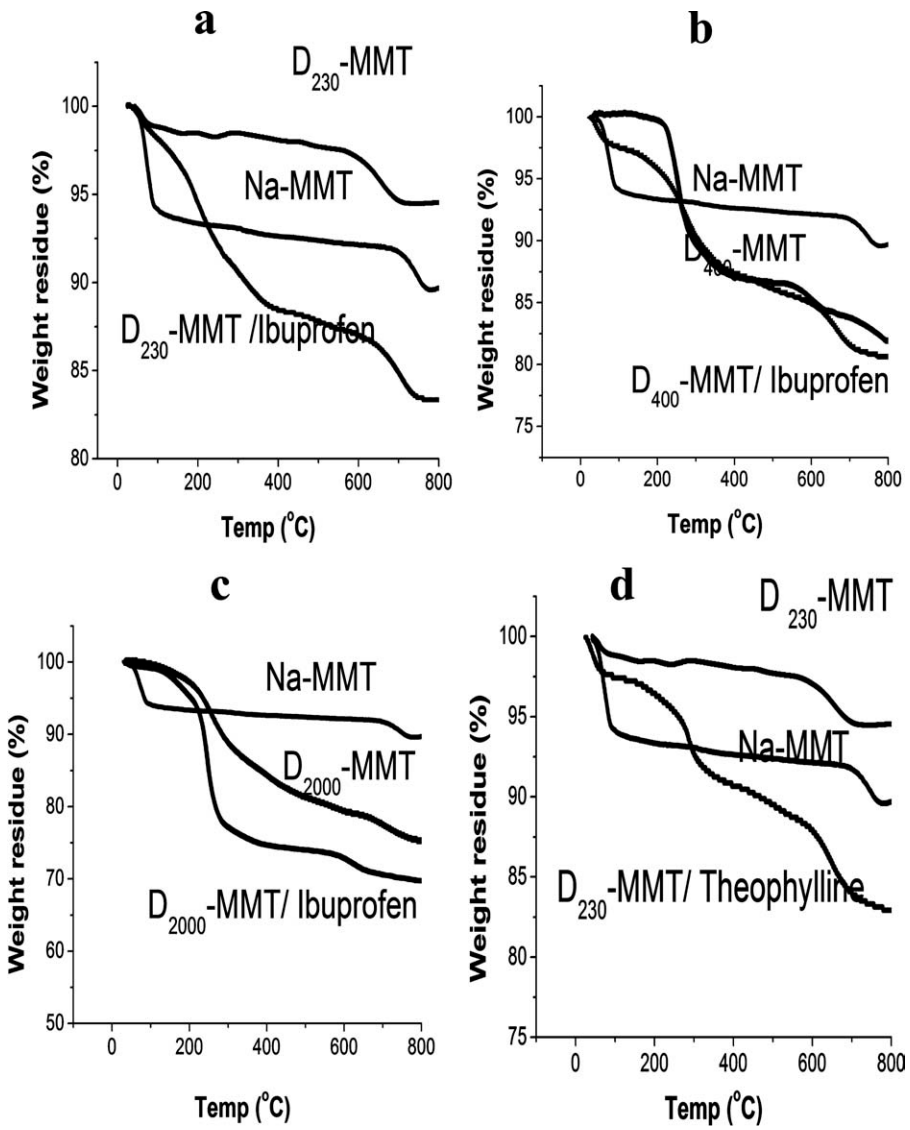

Figure 5 TGA of (a) Na-MMT, D_{230}–MMT, ibuprofen, and D_{230}–MMT/ibuprofen; (b) Na-MMT, D_{400}–MMT, ibuprofen, and D_{400}–MMT/ibuprofen; (c) Na-MMT, D_{2000}–MMT, ibuprofen, and D_{2000}–MMT/ibuprofen; and (d) Na-MMT, D_{230}–MMT, theophylline, and D_{230}–MMT/theophylline.

The IR spectrum of D_{230}–MMT showed bands at 3261 cm^{-1} [υ (NH_3^+)] corresponding to the asymmetrical vibrations of N—H in NH_3^+; this confirmed the electrostatic attraction between the polymer and layered silicate. The absorption bands at 1658 and 1485 cm^{-1} [δ (N—H)] were assigned to the asymmetrical and symmetrical bending of N—H in NH_3^+.[24] For D_{230}–MMT/ibuprofen, the characteristic absorption bands of D_{230}–MMT and ibuprofen were observed; this confirmed the successful loading of the ibuprofen on D_{230}–MMT. IR spectroscopy is an appropriate technique for studying D_{230}–MMT/drug interaction. In this regard, a band at 1713 cm^{-1} corresponding to C=O in ibuprofen disappeared, and a band at 1659 cm^{-1} corresponding to amide group formation was observed; this interfered with the asymmetrical bending of N—H in NH_3^+. The same results were observed for D_{400}–MMT/ibuprofen and D_{2000}–MMT/ibuprofen (not shown).

Not only did the characteristic bands belonging to Na-MMT and ibuprofen appear in the spectrum of Na-MMT/ibuprofen [Fig. 4(b)], but it was recognized that the characteristic absorption band of Si—O was shifted to 1043 cm^{-1}. This confirmed the formation of H bonding between the drug and Na-MMT.

The IR spectrum [Fig. 4(c)] for pure theophylline showed bands at 1653 cm^{-1}, corresponding to the stretching vibrations of C=O, and 1587 cm^{-1}, that is typical of NH. Comparing the spectrum of theophylline with theophylline/D_{230}–MMT, the 1587-cm^{-1} band assigned to N—H bending was shifted to 1531 cm^{-1}.

Thermal properties

Figure 5(a–d) depicts the TGA thermograms of Na-MMT, D_{230}–MMT, D_{400}–MMT, D_{2000}–MMT, D_{230}–MMT/ibuprofen, D_{400}–MMT/ibuprofen, D_{2000}–MMT/ibuprofen, and D_{230}–MMT/theophylline. The TGA profile for pure MMT showed two steps for weight loss at temperatures around 120–140 and 510–700°C. The first weight loss was due to free water evaporation. The second was due to OH group release from different positions of the MMT structure (structural dehydration).[25] There were three major stages of weight loss for D_{230}–MMT, D_{400}–MMT, and D_{2000}–MMT. The first weight loss below 100°C was a result of the release of free water. The second, in the temperature range 200–600°C, was associated with the decomposition of the polymer. In the last stage of weight loss, in the temperature range 510–780°C, the structural water that was bound as hydroxyl groups started to decompose and be released.

TGA of D_{230}–MMT/ibuprofen, D_{400}–MMT/ibuprofen, and D_{2000}–MMT/ibuprofen showed an obvious weight loss at the temperature around 200–470°C, corresponding to drug removal.

In vitro drug release

We examined the capability for drug release by heating the samples in PB at pH 7.8 and 5.4 for 6 h at 60°C. Then, the solution was filtered, and the concentrations of ibuprofen and theophylline were determined by UV absorption.

An interesting observation was that no release was observed at pH 5.4. This study suggested that the carrier would not release the drug in gastrointestinal fluid after oral administration. This would be expected because of the low solubility of the drug and the poor swellability of the carrier. It was reported that ibuprofen could be embedded into Na-MMT at pH 11.[26] The *in vitro* release of ibuprofen from Na-MMT was noticed in gastric acid fluid (pH 1.2) and simulated intestinal fluid (pH 7.4). This may have been due to the intercalation of ibuprofen in the form of sodium salt; this favored the solubility and release of the drug in gastric acid fluid. It is worth mentioning that our studies demonstrated the intercalation of drugs into MMT modified by polyoxypropylene. The intercalation of the polymer into the clay built a strong crosslinking structure because of the negatively charged clay and positively charged NH_3^+ group of the polymer. This influenced the swelling behavior of the support and, consequently, the diffusion of the drug through the bulk entity. With increasing molecular mass, a significant decrease in the swellability of the carrier led to a decrease in the burst release of the drug. In alkaline medium, the hydrolysis of the amide linkages took place through the attack of the nucleophile on the electron-deficient carbonyl carbon, and the high solubility of the drug in the alkaline medium led to their release.

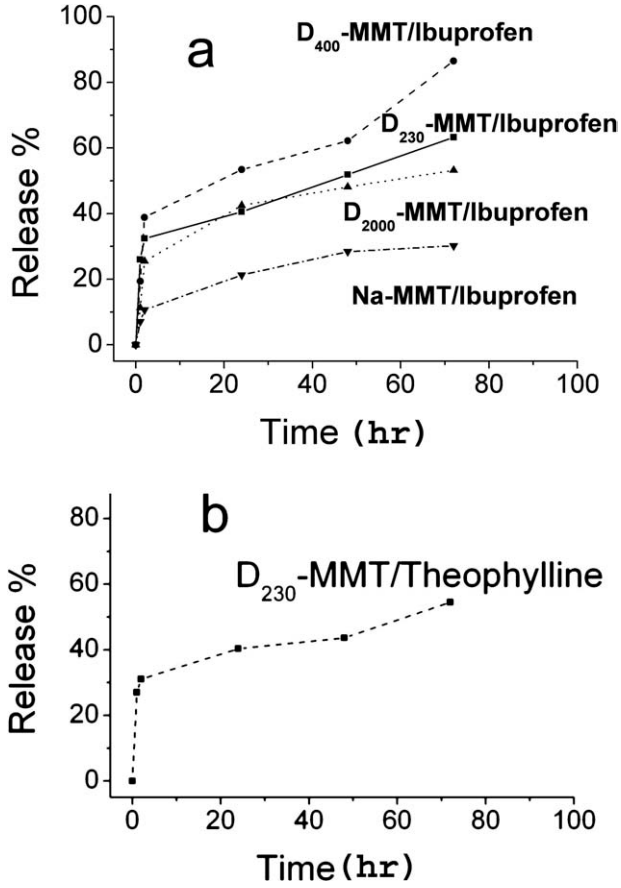

Figure 6 *In vitro* release of (a) ibuprofen from Na-MMT/ibuprofen, D_{230}–MMT/ibuprofen, D_{400}–MMT/ibuprofen, and D_{2000}–MMT/ibuprofen at pH 7.4 and (b) theophylline from D_{230}–MMT/theophylline at pH 7.4.

The release profile in Figure 6(a,b) shows a high drug-release rate in the initial 5 min, and the amount of drug released increased linearly after this initial period. The initial burst release was attributed to the diffusion of the drug due to rapid swelling. The maximum amount of ibuprofen released was almost 63% of the total from D_{230}–MMT, 86% from D_{400}–MMT, 53% from D_{2000}–MMT, and 30% from Na-MMT. However, the maximum amount of theophylline released was 55%. It is worth mentioning that the release rates of ibuprofen from D_{2300}–MMT, D_{400}–MMT, and D_{2000}–MMT (drug content percentage) indicated that the release from a partially flocculated structure with a low loading of drug (D_{400}–MMT) was higher than that from intercalated structures with a high loading of drug (D_{230}–MMT). However, the D_{2000}–MMT ordered structure showed the lowest release rate [Fig. 3(a–c)]. The amount released of ibuprofen (drug content percentage) was

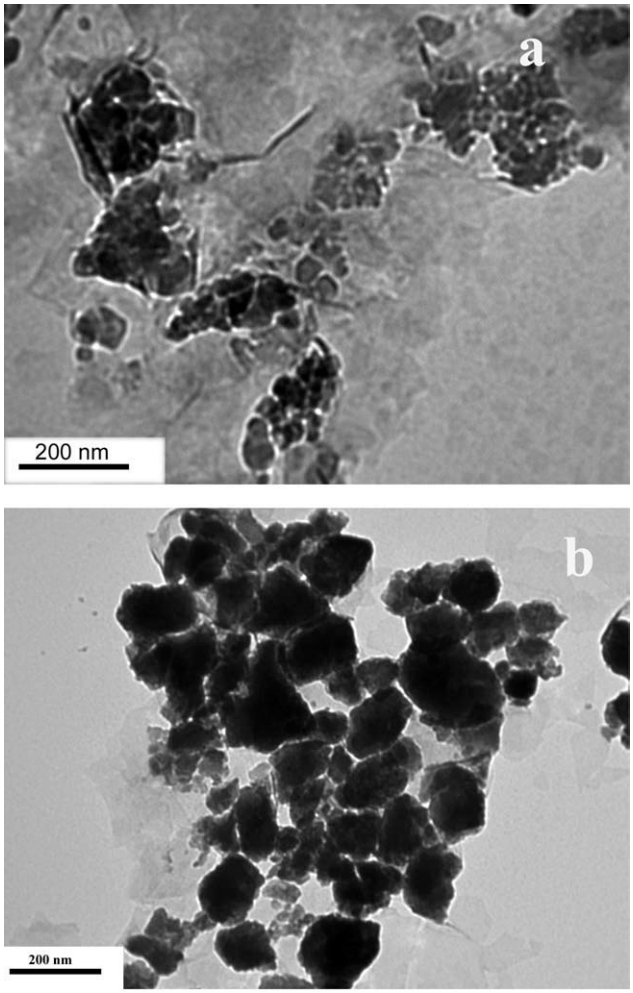

Figure 7 TEM micrographs of (a) D_{2000}–MMT/ibuprofen before drug release and (b) D_{2000}–MMT/ibuprofen after drug release.

higher than amount of theophylline (drug content percentage) released from the same support. These results indicate that the morphology of the support, the type of interaction between the drugs, and the support affected the rate of release.

It was reported that the rate of drug diffusion out of a matrix was hindered by the three-dimensional network formed by clay mineral particles via edge-face interactions and controlled by the rigidity of the layers and the diffusion path length.[27] In addition, the interactions between the drug and MMT should successfully prolong the action of drug.[28] In contrast to the release of other drugs from intercalated layered double hydroxide (LDH) materials reported in the literature,[29] the release of drugs from organoclay was not complete within 80 h. The cause of the partial release was attributed to the possibility that the drug molecules were deeply embedded in the organoclay, and complete release was very slow. The same result was observed in the release of thiamine hydrochloride from MMT.[30]

Morphology of the support after release

It is important to examine the morphology of a drug carrier before and after drug release because any dimensional change may provide a basis for understanding the mechanism of drug release. It is worth noting that a broad peak [Fig. 2(c)] was observed for D_{2000}–MMT/ibuprofen after drug release at lower *d*-spacing ($2\theta = 4^\circ$) due to the release of the drug. TEM micrographs of D_{2000}–MMT/ibuprofen at identical magnifications before and after drug release at the selected pH of 7.4 are presented in Figure 7(a,b). A monodispersion with an average size of 20 nm is shown in Figure 7(a), whereas Figure 7(b) implies that the size of the nanodomains after drug release was significantly increased to 70 nm. The reason for the increase in size after drug release is believed to be a consequence of the detachment or separation of drug, which led to the aggregation of the clay.

CONCLUSIONS

New systems for the delivery of ibuprofen and theophylline drugs based on the intercalation of drugs in polymer-layered silicate nanocomposites were developed. Herein, three polyoxypropylene–MMT intercalated nanocomposites with different polymer molecular masses were prepared and characterized as part of a new approach for drug delivery. The results obtained from the release experiments show that no release was observed at pH 5.4. Generally, the interaction between the drugs and carriers, nanocomposite morphology, and swelling behavior played important roles in the rate of release at pH 7.4.

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