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International Journal of Pharmaceutics 287 (2004) 89–95
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Enteric-coated layered double hydroxides as a controlled release drug delivery system

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Received 3 March 2004; received in revised form 26 August 2004; accepted 27 August 2004
Available online 18 October 2004

Abstract

Layered double hydroxides (LDHs) or so-called anionic clays consist of cationic brucite-like layers and exchangeable interlayer anions. Because of their biocompatibility, these layered inorganic solids can be used as host materials to create drug–LDH host–guest supramolecular structures. Because of the basicity of LDHs however, LDHs as drug delivery system will be limited for use in the stomach where pH is 1.2. A core-shell material has been prepared therefore in this work. A non-steroidal anti-inflammatory drug, Fenbufen-intercalated LDHs as the core was coated with enteric polymers, Eudragit® S 100 or Eudragit® L 100 as a shell, giving a composite material which shows controlled release of the drug under in vitro conditions which model the passage of a material through the gastrointestinal tract.

Keywords: Layered double hydroxide; Drug delivery system; Coated

1. Introduction

Site-specific drug delivery to the colon is attracting increasing attention, both for effective therapy of colon-related diseases such as irritable bowel syndrome as well as systemic drug delivery, taking advantage of the long transit time in the colon (up to 78 h) which increase the time available for drug absorption using controlled release formulations (Yang et al., 2002). Colonic delivery is of additional value when a delay in drug absorption is therapeutically desirable e.g. in treatment of angina and nocturnal asthma which are affected by circadian rhythms (Sinha and Kumria, 2002).

Most techniques used to achieve specific colonic drug delivery rely on the variation in pH values through the gastrointestinal (GI) tract, although enzymatic degradation by colonic bacteria has been increasingly investigated in recent years (Yang et al., 2002). The normal transit time (Sinha and Kumria, 2002) in the stomach (pH 1–2) is 2 h (although this may vary) and the transit time in the small intestine is 2–3 h. Absorption

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doi:10.1016/j.ijpharm.2004.08.016

of a drug in the stomach may be prevented by means of an enteric coating, which is insoluble in the acidic conditions in the stomach but dissolves at neutral pH. In the duodenum (the upper part of the small intestine) the pH is 4.5 ± 0.5 so that the enteric coating remains intact, but in the lower part of the small intestine (jejunum and ileum) the pH rises to 7.5 ± 0.4 before dropping to 6.4 ± 0.6 in the ascending colon and rising again to pH 7.0 ± 0.7 in the distal colon (Shimono et al., 2002). It is therefore necessary to incorporate the drug in a controlled release formulation that will both minimize premature release in the ileum and optimize the subsequent rate of release in the colon.

Most traditional controlled release formulations are polymer-based but alternative inorganic matrices, particularly layered double hydroxides (LDHs) (Cavani et al., 1991; Khan and O'Hare, 2002), have attracted considerable recent attention. The chemical composition of LDHs can be represented by the general formula $\left[M^{II}_{(1-x)}M^{III}_{x}(OH)_2\right]^{x+}A^{z-}_{x/z} \cdot yH_2O$ where M^{II} and M^{III} are divalent and trivalent metal cations respectively, occupying octahedral positions in the hydroxide layers and A^{z-} is a charge-compensating interlayer anion. O'Hare and co-workers (Khan et al., 2001) have reported the intercalation of drugs such as diclofenac sodium, gemfibrozil, ibuprofen, naproxen and tolfenamic acid in LDHs and demonstrated their potential as tuneable drug delivery systems. The intercalation of ibuprofen (Ambrogi et al., 2001), diclofenac (Ambrogi et al., 2002) and other non-steroidal anti-inflammatory drugs (Ambrogi et al., 2003) has also been investigated and the intercalation of a cisplatin derivative, *cis*-$[Pt(NH_3)_2(5'\text{-GMP})_2]$ (5′-GMP = guanidine 5′-monophosphate) has been recently reported (Yang and Guo, 2003). LDHs are basic compounds however, and will dissolve rapidly in gastric acid, with complete liberation of the intercalated drug in the stomach. In this paper, we demonstrate how the drug release may be controlled by a composite structure, in which an enteric coating is formed on the surface of LDH–drug intercalate.

As the pharmaceutically active component, we choose fenbufen, (γ-oxo-[1,1′-biphenyl]-4-butanoic acid, $C_6H_5C_6H_4C(O)CH_2CH_2COOH$) which is a non-steroidal anti-inflammatory drug used for the relief of symptoms of rheumatoid arthritis and osteoarthritis (Hawkey, 1990). Its use is often limited, however, by the frequent side effects that affect both the GI tract (Rodriguez and Hernandez-Diaz, 2001) and the cardiovascular system (Rodriguez and Hernandez-Diaz, 2003). Controlled release of the drug can be expected to significantly mitigate these harmful systemic effects. The presence of the carboxylate group should facilitate intercalation of fenbufen in LDHs.

As the enteric coating we select Eudragit® L 100 and S 100, which have been widely used in this area (Rodriguez et al., 1998; Lorenzo-Lamosa et al., 1998; Lamprecht et al., 2003). Those anionic copolymers of methacrylic acid and methyl methacrylate have a molecular weight of approximately 135,000 with a ratio of acid to ester of approximately 1:1 in Eudragit® L 100 and 1:2 in Eudragit® S 100. Both polymers are insoluble in aqueous acid solution but Eudragit® L 100 dissolves at pH 6 and above and Eudragit® L 100 at pH 7 and above. The presence of the carboxylate groups should facilitate a strong interaction of a monolayer of the polymer with the LDH layers, either through their hydrogen bonding with the surface hydroxyl groups or grafting to the layers. Such interactions have been observed between polystyrene sulfonate and LDH surfaces (Moujahid et al., 2003) and between Eudragit® L 100 and S 100 and the amine groups of chitosan (Lorenzo-Lamosa et al., 1998).

2. Experimental

2.1. Materials

The inorganic materials were all analytical reagent grade and used without further purification. Fenbufen was purchased from the Zhejiang Juhuan Pharmacy Co. Ltd. Deionized water from which carbon dioxide was removed by boiling under nitrogen was used in all preparations.

2.2. Preparation of fenbufen intercalate

A solution containing $Mg(NO_3)_2 \cdot 6H_2O$ (5.12 g, 0.020 mol) and $Al(NO_3)_3 \cdot 9H_2O$ (3.75 g, 0.010 mol) in deionized water (35 ml) was added over 1 h to a vigorously stirred solution (140 ml) containing NaOH (3.00 g, 0.075 mol) and fenbufen (2.54 g, 0.01 mol,

molar ratio FBF/Al, 1:1). The resulting gel was aged under a nitrogen atmosphere at 80 °C for 6 h. The product mixture was filtered and the resulting white solid fenbufen-intercalated Mg/Al–LDH (I) was extensively washed with deionized water and stored moistly. The content of water in the product was 71.0%. A small portion of (I) was dried for elemental analysis. The chemical composition is found to be %: Mg 10.58; Al 5.71; C 38.38; H 4.83, similar to that calculated for $Mg_{0.67}Al_{0.33}(OH)_2(C_{16}H_{13}O_3)_{0.33}\cdot H_2O$ which is %: Mg 10.02; Al 5.55; C 39.32; H 5.17.

2.3. Polymer coating process

As-prepared (I) (4 g) was vigorously stirred in a solution of Eudragit® S 100 (4 g) in ethanol (70 ml) at 70 °C for 2 h. The homogeneous suspension was poured into vigorously stirred water (400 ml) and the resulting product filtered and dried at 80 °C. The whole coating process was subsequently repeated once.

The coated fenbufen sodium samples were obtained by the same method as described above. The content of fenbufen in coated fenbufen-intercalated Mg/Al–LDH was equivalent to that in coated fenbufen sodium.

2.4. Characterization

Powder X-ray diffraction (XRD) data were collected on a Shimadzu XRD-6000 diffractometer using Cu Kα source, with a scan step of 0.02° and a scan range between 2 and 70°.

TEM micrographs were taken on a HITACHI H-800 transmission electron micrograph.

The XPS spectra were obtained using a VG ESCALAB MKII spectrograph with Mg Kα radiation (1253.6 eV, 150 W).

2.5. Drug release measurements

A sample of Eudragit® coated-(I) (1 g) was suspended in 0.1 M HCl (200 ml) and stirred for 2 h. KH_2PO_4 (0.76 g) and $NaH_2PO_4\cdot 12H_2O$ (1.53 g) were then added, followed by sufficient 1.2 M NaOH to bring the pH to 6.8. The mixture was stirred for a further 2 h, after which the pH was raised to 7.4 and the mixture was stirred for a further 5 h. Aliquots were removed from the mixture at regular intervals and diluted to fixed volumes using a buffer solution of pH 7.8. The amount of liberated fenbufen was determined from its UV-absorption at 284 nm.

3. Results and discussion

3.1. (I) coated with polymer

(I) was prepared by a coprecipitation method, typically employed for the preparation of LDHs. As shown in Fig. 1a, (I) has the XRD pattern characteristic of an LDH with a basal reflection at low angle and higher order reflections. The basal spacing is 2.35 nm. Given (Cavani et al., 1991) that the thickness of the brucite-like layer of LDH is 0.48 nm, the gallery height is 1.87 nm. This is consistent with that reported for the intercalation of organic anions of similar size within the gallery spaces of LDH. Elemental analysis of (I) is consistent with the formulation $Mg_{0.67}Al_{0.33}(OH)_2(C_{16}H_{13}O_3)_{0.33}\cdot H_2O$.

When (I) was separately treated with an ethanolic solution of Eudragit® S 100 and L 100, the XRD patterns of the resulting materials (Fig. 1d and e) are a superposition of those of (I) and the free polymers (Fig. 1b and c), showing that the integrity of the two phases has been achieved during the mixing process.

Fig. 2 shows the FT–IR spectra of (I) coated with Eudragit® S 100 and L 100. The FT–IR spectra of the materials show intense peaks from the polymer corresponding to the C=O vibrations of the ester (at 1730 cm^{-1}) and carboxylic acid (1705 cm^{-1}) moieties as well as further ester vibrations around 1265, 1195 and 1160 cm^{-1}. The asymmetric stretch of the carboxylate group of the intercalated fenbufen can be seen at 1561 cm^{-1}, but its other expected bands are obscured by those of the polymer.

The ^{13}C MAS NMR chemical shifts of the Eudragit® carbons in (I) coated with S 100 are essentially identical to those in the free polymer, showing that the local structure and crystallinity of the bulk polymer are not altered by incorporation of (I) (Vachon and Nairn, 1998). Determination of the composition of (I) by ESCA (electron spectroscopy for chemical analysis) gives a C/Mg ratio of 8.4 (similar to the ratio in the bulk material, 7.9, as determined by ICP). After reaction of (I) with Eudragit® L 100 or S 100, the resulting (I)-L 100 and (I)-S 100 have C/Mg ratios of 16.8 and

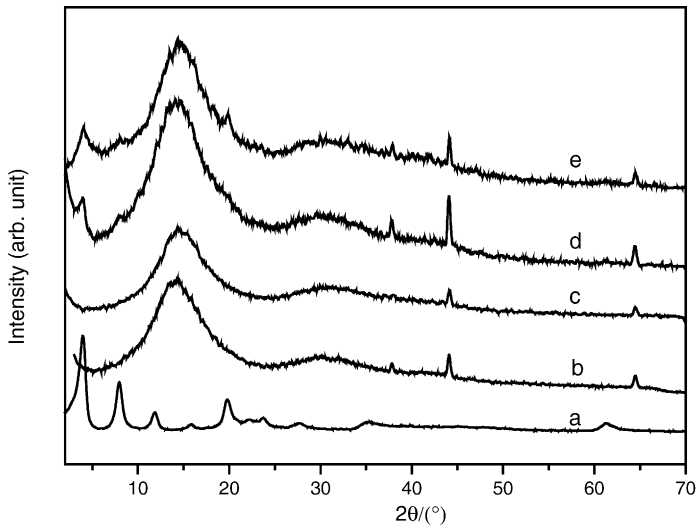

Fig. 1. Powder XRD patterns of (a) fenbufen-intercalated LDH (I); (b) Eudragit® S 100; (c) Eudragit® L 100; (d) (I) coated with Eudragit® S 100 and (e) (I) coated with Eudragit® L 100.

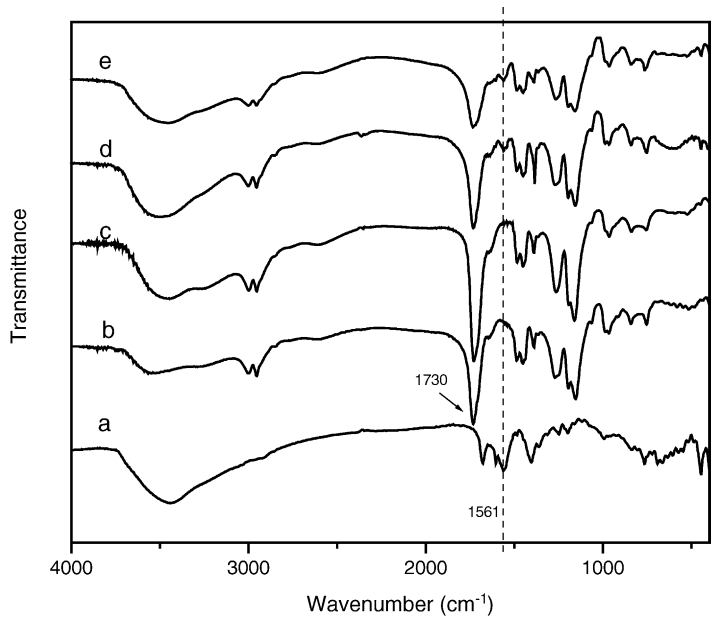

Fig. 2. FT-IR spectra for (a) fenbufen-intercalated LDH (I); (b) Eudragit® S 100; (c) Eudragit® L 100; (d) (I) coated with Eudragit® S 100 and (e) (I) coated with Eudragit® L 100.

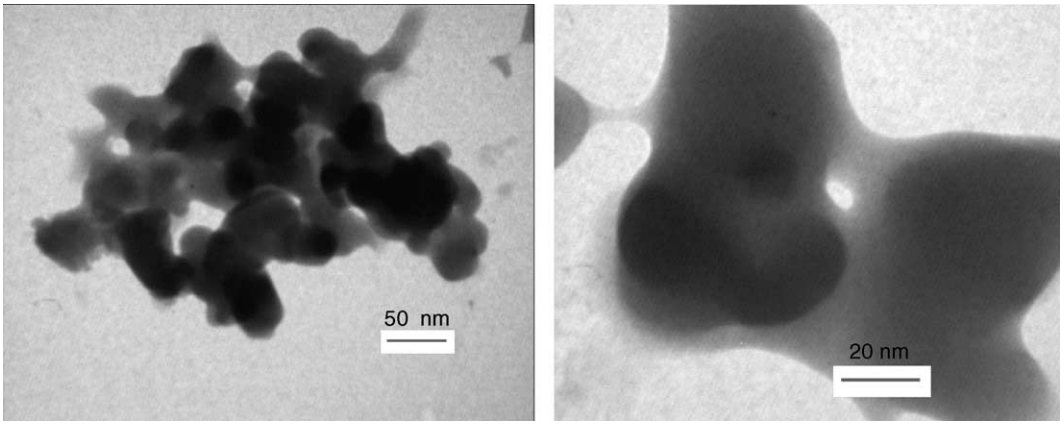

Fig. 3. TEM micrographs of fenbufen-intercalated LDH (I) coated with Eudragit® S 100.

18.5, respectively, confirming that the polymer forms a coating on the surface of (I).

Fig. 3 illustrates the TEM micrograph of (I) coated with a polymer shell. A composite structure in which (I) exists as the dark center surrounded by a lighter polymer shell can be clearly observed.

Table 1 shows the XPS result of (I) coated with an ethanolic solution of Eudragit® L 100 and S 100. After (I) is coated by enteric polymer, the binding energy of Mg 2p increases from 55.6 eV to 56.8–58.4 eV, and that of Al 2p increases from 77.8 eV to 78.6–79.8 eV. This shift to high energy may result from the interaction between the surface of LDH and enteric polymer. The surface composition given in Table 1 shows that the surface content of Mg decreases, while the surface contents of C and O increase after coating, further confirming that (I) has been coated with enteric polymer successfully.

3.2. Drug release property

Drug release profiles were determined at constant temperature (37 ± 0.5 °C). The solid was suspended in a stirred aqueous medium, the pH of which was initially kept at 1.2 for 2 h, and then at 6.8 (2 h) and finally 7.4 (5 h) in order to simulate passage through the GI tract. The results for (I)-S 100 and (I)-L 100 are shown in Fig. 4 along with those of (I), and fenbufen (as the sodium salt) coated with S 100 and L 100 for comparison. Dissolution of (I) accompanied by complete release of fenbufen is observed within a very short time (Fig. 3a), confirming that unmodified layered double hydroxides are unsuitable as a controlled release matrix under realistic conditions. When coated with Eudragit® L 100, both fenbufen and (I) are stable in acid conditions but the coating dissolves at pH 6.8. Under these conditions, deintercalation of fenbufen from the LDH is rapid, so that the release profile of (I)-L 100 (Fig. 3c) is comparable with that of fenbufen coated with Eudragit® L 100 (Fig. 3b).

When coated with Eudragit® S 100, both fenbufen and (I) are stable at pH 6.8. In the case of fenbufen, dissolution of the polymer at higher pH is accompanied by rapid dissolution of the drug (Fig. 3d) and release is essentially complete after 3 h at pH 7.4. In the case of (I)-S 100 however, dissolution of the polymer

Table 1
XPS results of fenbufen-intercalated LDH (I) coated with Eudragit® S 100 and Eudragit® L 100

Samples	Mg 2p BE (eV)	Al 2p BE (eV)	Surface content (mol%)		
			Mg	C	O
Fenbufen-intercalated LDH (I)	55.6	77.8	11.38	47.23	22.65
(I) coated with Eudragit® S 100	58.4	79.6	7.39	61.37	26.21
(I) coated with Eudragit® L 100	56.8	78.6	7.14	65.26	22.00

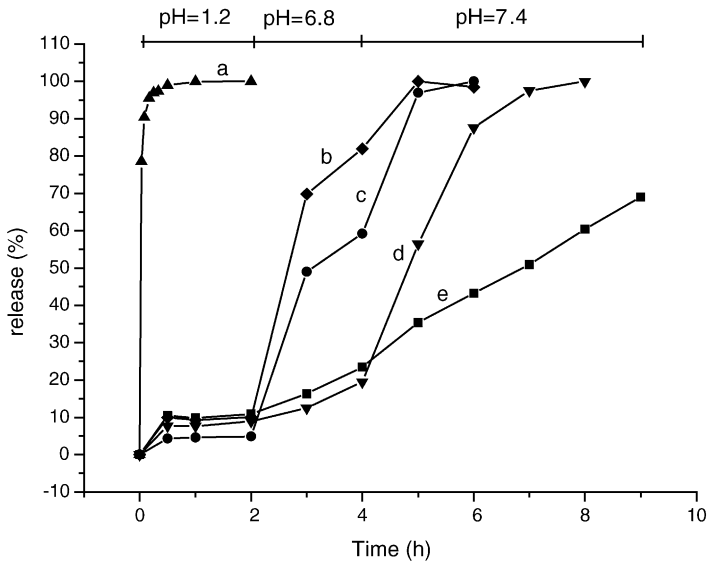

Fig. 4. Release profiles for (a) fenbufen-intercalated LDH (I); (b) fenbufen coated with Eudragit® L 100; (c) (I) coated with Eudragit® L 100; (d) fenbufen coated with Eudragit® S 100; (e) (I) coated with Eudragit® S 100.

is followed by slow release of the intercalated drug in a linear fashion and only 67% of the drug was liberated after 5 h at pH 7.4. In previous reports (Khan et al., 2001; Ambrogi et al., 2001) of controlled release of similar pharmaceutically active components from layered double hydroxides, dissolution was reported to be complete after a few minutes at pH 4 and complete release of the active component was observed within 2 h when the material was directly exchanged at pH 7. This suggests that complete dissolution of the polymer and deintercalation of fenbufen from the LDH may be inhibited by an interaction between the carboxylate groups of the polymer and the surface of the LDH.

4. Conclusions

In summary, we have shown that intercalation of fenbufen in a layered double hydroxide followed by coating with Eudragit® S 100 gives a composite material which shows controlled release of the drug under in vitro conditions which model the passage of a material through the gastrointestinal tract. Work is underway in our laboratory to explore how the drug release characteristics may be modified by variation of the physicochemical properties of both the layered double hydroxide and the polymer coating.

Acknowledgments

We thank Degussa-Hüls Pacific Ltd., Shanghai for a gift of Eudragit® polymers.

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