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Controlled release of donepezil intercalated in smectite clays

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ABSTRACT

The inorganic–organic hybrid for a drug delivery system was successfully realized by intercalating donepezil molecules into smectite clays (laponite XLG, saponite, and montmorillonite). According to the powder XRD patterns, TG profiles, and FT-IR spectra, it was confirmed that donepezil molecules were well stabilized in the interlayer space of clay via mono or double layer stacking. The adsorption amount and molecular structure of donepezil appeared to depend on the cation exchange capacity of the clay, which in turn, tailored the drug release patterns. Especially in the presence of a bulky cationic polymer (Eudragit® E-100) in the release media, the release rate was found to be improved due to its effective replacement with intercalated donepezil molecules. Therefore, to formulate a complete drug delivery system, the hybrids were coated with Eudragit® E-100 using a spray dryer, which also showed great enhancement in the release rate during a short period of time (180 min).

1. Introduction

Drug delivery systems have been of great interest for the past few decades to realize the effective and targeted drug delivery and minimize the side effects in the field of pharmaceutics (Chandrasekar et al., 2007; Allen and Cullis, 2004; Sinha and Trehan, 2003). Nowadays, various synthetic polymers have been intensively studied as a delivery carrier due to their well-known therapeutic benefits, such as biocompatibility, biodegradability, and long-term safety of drugs. However, the polymers, such as polylactide (PLA) and polylactide-co-glycolide (PLGA), are known to have some drawbacks resulting from their hydrophobic nature. For example, due to the accumulation of hydrophilic drugs near the surface of polymer based carriers, a high burst effect was often observed (Sinha and Trehan, 2003). Moreover, because of their hydrolysis to lactic and glycolic acid monomers, the acidic environment was formed at the inside of the polymer-based carriers, which could cause undesirable drug degradation (Sinha and Trehan, 2003; Soppimath et al., 2001). Thus, new effective delivery systems for hydrophilic drug have been needed to resolve the problems stated above.

The smectite clay, a kind of layered aluminosilicates, is composed with tetrahedral sheets of SiO_4 unit and octahedral sheets of Al^{3+} ions. The isomorphous substitution of Al^{3+} with Mg^{2+} or Fe^{2+} on octahedral sheets or that of Si^{4+} with Al^{3+} on tetrahedral ones can generate negative surface charge (Swartzen Allen and Martijevic, 1974; Thomas et al., 1999). The former two are considered as montmorillonite (MMT) and laponite (LA), respectively and the latter as saponite (SA) (Chattopadhyay and Traina, 1999; Liu and Kerry Thomas, 1991). In order to compensate the excessive negative layer charges, the interlayer cations, which are in general solvated, are stabilized between the layers. As a result, the smectite clay possesses hydrophilicity, high dispersibility in water, and most importantly, cation exchange capacity (CEC) (Lin et al., 2002). With CEC and swelling property along the (0 0 *l*) axis of these layered minerals, smectite clays can encapsulate various protonated and hydrophilic organic molecules into the interlayer space of the (0 0 *l*) plane, which can be released in controlled manners by replacement with other kinds of cations in the release media (Dong and Feng, 2005; Yang and Hu, 2006). Therefore, the smectite clays are suggested to be good delivery carriers of hydrophilic drugs.

The smectite clay and donepezil were employed as inorganic matrices and organic guest molecules, respectively. The donepezil, chemically (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one, is a well-known drug for Alzheimer's disease. This disease is related to the cognitive dysfunction and progressive deterioration of memory due to the cholinergic deficit. The donepezil, an acetylcholine-blocking agent, is known to prevent the rapid hydrolysis of acetylcholine in synapses of central and peripheral nervous system, and hence a potent drug for Alzheimer' disease. However, the adverse effects have been still reported due to the increase in gastric acid secretion caused by enhanced cholinergic activity through the gastrointestine (Contreras et al., 2001; da Silva et al., 2006).

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In this study, donepezil-nanoclay hybrids were successfully synthesized employing three different clay materials, which were MMT, LA, and SA. They could be expected to enhance the encapsulation efficiency of drugs and reduce the adverse effect of donepezil because the clay used in this study is able to reduce the acidity by absorbing proton and control the drug release behavior (Chattopadhyay and Traina, 1999; Liu and Kerry Thomas, 1991). The donepezil-nanoclay hybrids were characterized via powder XRD, FT-IR, thermogravimetry (TG), zetasizer, and scanning electron microscopy (SEM). The release profiles of donepezil were also studied with UV–vis spectrometry and HPLC.

2. Experimentals

2.1. Materials

The donepezil and clay materials were used without any purification. Na^+-MMT (Kunipia-F, Kunimine Corp.), Na^+-SA (Sumecton SA, Kunimine Industries), and Na^+-LA (Laponite XLG, Rockwood Additives Ltd.) were used as the host materials. The chemical formulas of MMT, SA, and LA are $Na_{0.7}K_{0.02}Ca_{0.04}(Si_{7.78}Al_{0.22})(Al_{3.20}Mg_{0.64}Fe_{0.16})O_{20}(OH)_4$, $Na_{0.35}Mg_{0.14}(Si_{7.20}Al_{0.80})(Al_{0.03}Mg_{5.97})O_{20}(OH)_4$, and $Na_{0.70}Si_{8.00}(Mg_{3.50}Li_{0.30})O_{20}(OH)_4$, and the CECs were 100, 71, and 63 mequiv./100 g, respectively (Kakegawa et al., 2003). All other reagents were analytical grades.

2.2. Hybrid sample preparation

One gram of each kind of smectite clay was dispersed in deionized water of 100 ml for 3 h to obtain a 1 wt% suspension. Then, the donepezil hydrochloride with the amount twice as much as the CEC of each clay material was dissolved in the mixture of 30 ml of methylene chloride (MC) and 30 ml of ethanol (EtOH). The donepezil solution was added dropwisely into three different 1 wt% clay suspensions with vigorous stirring for 3 h at an ambient temperature. The mixed solutions were centrifuged and washed 3 times with 50 ml of MC and 50 ml of EtOH to eliminate the excessive drug. Finally, the products were freeze-dried for 1 day and ground with mortar and pestle to obtain fine powder.

2.3. The sample preparation of polymer coated hybrids

To prepare donepezil-nanoclay coated with Eudragit® E-100, which contained multiple amine sites (Sparnacci et al., 2002), the hybrids prepared as described above were dispersed again in a mixed solvent of MC and EtOH, where Eudragit® E-100 was dissolved. The weight fraction of hybrids and Eudragit® E-100 was 1:0.6. Thus prepared suspensions were spray-dried with an EYLA spray dryer SD-1000 under the following condition: atomizing pressure, 130 kPa; blower speed, 0.63 m^3/min; and inlet temperature, 85 °C.

2.4. Sample characterization

Powder XRD patterns were measured by a Philips PW1830 diffractrometer with Ni-filtered Cu Kα radiation (λ = 1.5418 Å). The patterns were recorded at 40 kV and 20 mA. TG analyses were performed using a pyris diamond TG-DTA of PerkinElmer with a heating rate of 5 °C/min under an ambient atmosphere to determine the total amount of donepezil in the hybrid. The CHNS and HPLC analyses have been also carried out to quantitatively determine the amount of drug and confirm the result from TG analysis. FT-IR spectra were obtained with a JASCO FT/IR-660 plus spectrometer by the standard KBr disk method. The surface charge and particle size of intact clay materials, hybrids and Eudragit® E-100 coated hybrids were examined using a Malvern Zetasizer (Nano ZA). Samples were suspended in DI water at room temperature and diluted to 0.1 wt%. The resulting suspension was measured 4 times. The images of Eudragit® E-100 coated hybrids were obtained with field emission SEM (JSM-35CF, Jeol, Japan). The samples were mounted on a double-faced adhesive carbon tape and sputter coated with platinum before imaging.

2.5. Release test

Release profiles of donepezil from the hybrids were measured via the peddle stirring method with a dissolution tester DST-810 of LABFINE, Inc. One hundred milligrams of each sample was weighed and dissolved in 1 l of the simulated human gastric (SHG) media, which were aqueous HCl solutions of pH 1.2. To enhance the drug release rate, 270 mg of Eudragit® E-100 was added into each batch for non-coated hybrid samples. The impeller equipped in the dissolution tester was set at 50 rpm and the bath temperature was maintained at 36.5 °C to mimic the movement of human's gastric cavity. Aliquots of the solutions were collected at the scheduled intervals and filtered with 0.45 μm-pore nylon filters. The drug concentrations of aliquots were estimated with an UV/vis lambda 35 spectrometer of PerkinElmer at 271 nm.

2.6. HPLC experiment

The HPLC analyses were performed using HPLC-UV equipment (Hewlett-Packard 1100, USA) with a column, ZORBAX Eclipse XDB-C18 (4.6 mm × 150 mm, 3.5 μm). The mobile phase of acetonitrile and a pH 3 buffer solution (30:70, v/v) prepared with trimethylamine and phosphoric acid, was filtered by a nylon membrane with the pore size of 0.45 μm. The flow-rate and injection volume per min were 1 ml/min and 10 μl, respectively. Column temperature was adjusted to 40 °C. The UV absorbance was measured at 271 nm.

2.7. Determination of drug content

In order to accurately determine the encapsulated amount of drug, the drug needed to be extracted completely from the clay lattice. For such a purpose, the solution was prepared by adding trimethylamine in deionized water, titrating with phosphoric acid to obtain pH 2, and then being mixed with acetonitrile. In 100 ml of the resulting solution, 10 mg of hybrids or Eudragit® E-100 coated ones were dispersed, stirred for 20 min and sonicated for another 20 min to extract the drug molecules.

3. Results and discussion

3.1. Powder X-ray diffraction analysis

Fig. 1 shows the XRD patterns of donepezil only and donepezil-nanoclay hybrids. All characteristic crystalline peaks ($18^\circ < 2\theta < 40^\circ$) of the pristine clays (Fig. 1(b)–(d)) were seen in the XRD patterns for all the hybrids (Fig. 1(e)–(g)) prepared in the present study. For the hybrids, the shift of (0 0 *l*) peaks to a lower 2θ angle was clearly observed, which indicated that drug molecules were successfully intercalated into the interlayer space of clay. Notably, no XRD peaks, corresponding to donepezil crystalline itself, could be seen after intercalation (Fig. 1(e)–(g)), suggesting that donepezil molecules were distributed in the interlayer of clay with a molecular level as previously reported with other various organic-nanoclay hybrid systems (Dong and Feng, 2005; Yang and Hu, 2006; Choy et al., 1997, 2002). The clay lattice is expanded upon intercalation with the basal increments from 12.6 to 22.1 Å for donepezil-MMT (Fig. 1(e)), from

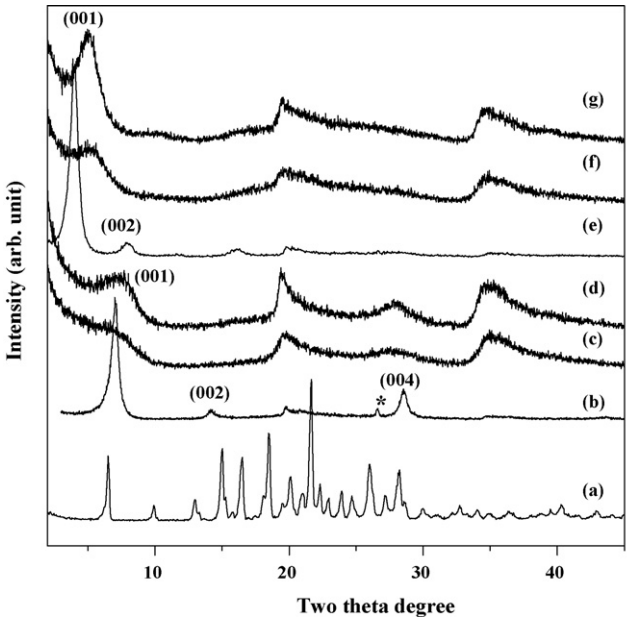

Fig. 1. Powder XRD patterns of (a) pure donepezil hydrochloride, (b) pristine Na^+-MMT, (c) pristine Na^+-laponite, (d) pristine Na^+-saponite, (e) donepezil-MMT hybrid, (f) donepezil-laponite hybrid, and (g) donepezil-saponite hybrid (*: quartz).

12.6 to 16.3 Å for donepezil-LA (Fig. 1(f)), and from 11.5 to 17.6 Å for donepezil-SA (Fig. 1(g)), respectively.

Based on these XRD patterns, the spatial arrangement of donepezil molecules in the interlayer of clay could be described as shown in Fig. 2. Subtracting the layer thickness of clay (9.3 Å) from the basal spacing of the hybrid, the gallery heights could be estimated to be 12.8 Å for donepezil-MMT, 7.0 Å for donepezil-LA, and 8.3 Å for donepezil-SA, respectively. Thus, considering the molecular dimension of donepezil, it became evident that donepezil molecules in the MMT interlayer were stabilized in a double layer arrangement (Fig. 2(a)) while those in LA and SA were in a monolayer arrangement (Fig. 2(b)). This is surely due to the difference in the CEC of clay materials (Choy et al., 1998; Endo et al., 1989; Chattopadhyay and Traina, 1999) since the larger the CEC was, the more probable the multiple layer arrangement of the donepezil molecules would become. The CEC of MMT (100 mequiv./100 g) was fairly larger than those of LA (63 mequiv./100 g) and SA (71 mequiv./100 g), but the latter two exhibited similar CEC values. It is, therefore, not surprising that the (0 0 1) peak position of donepezil-MMT was remarkably different from those of donepezil-LA and donepezil-SA.

3.2. Thermogravimetric analysis

Fig. 3 shows the TG profiles of the hybrids, which provides the information on the molecular arrangement and organic content in the clay lattices. Two major weight losses could be seen around at 55 and 250 °C. The first step around at 55 °C represented the desorption of approximately 3% of the solvent, MC. Because the latter region at 250 °C was not associated with the weight loss of clay (Lin et al., 2002; Endo et al., 1989; del Hoyo et al., 1996), such thermal change was clearly related to the oxidative decomposition or graphitization of intercalated donepezil (Fig. 3(b)–(d)). Importantly, the temperatures of oxidative decomposition of the hybrids (Fig. 3(a)) were about 30 °C higher than that of the donepezil hydrochloride, indicating that the thermal stability of donepezil was improved through hybridization.

Based on those oxidative decompositions, the total amounts of donepezil in the hybrids were found to be about 33% for MMT (Fig. 3(b)), 22% for SA (Fig. 3(c)), and 17% for LA (Fig. 3(d)), respectively, which could be also confirmed by CHNS analysis (Table 1). The larger encapsulation amount in the MMT could be explained by the molecular arrangement of the donepezil in the interlayer space. As shown in the powder XRD patterns (Fig. 1(e)), the double layer arrangement was highly probable with donepezil-MMT hybrid, which suggested that the drug could be encased more than those in the donepezil-LA and -SA hybrids. Consequently, the drug content also appeared to depend on the CEC of the clay.

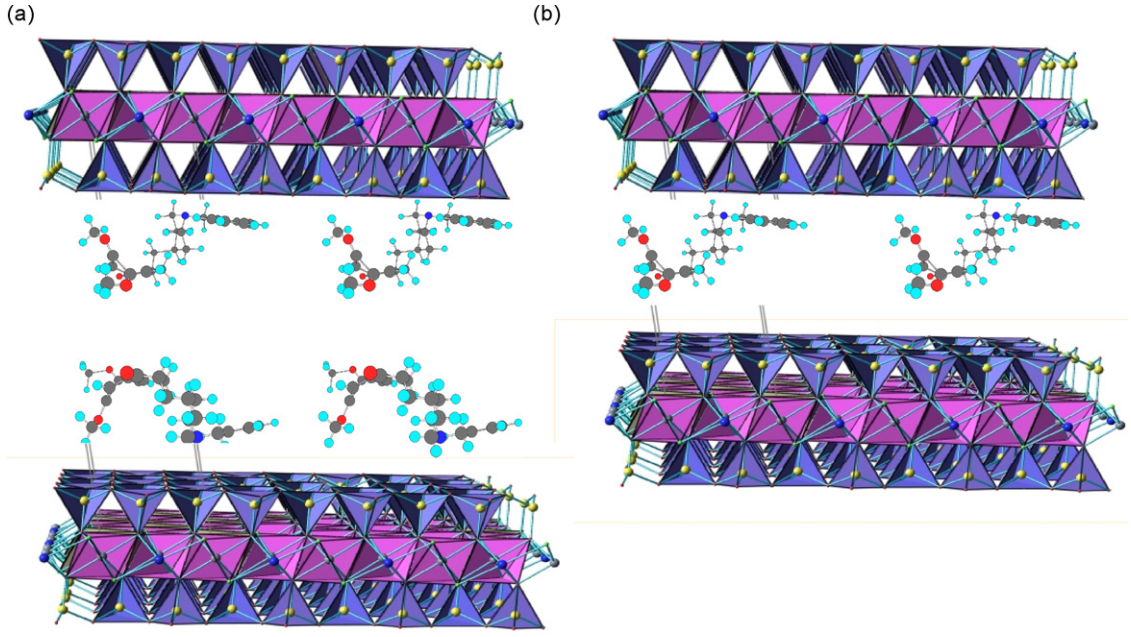

Fig. 2. Schematic diagrams of the arrangement of the intercalated donepezil in nanoclay materials: (a) double layer arrangement in donepezil-MMT and (b) mono layer arrangement in donepezil-SA or donepezil-LA.

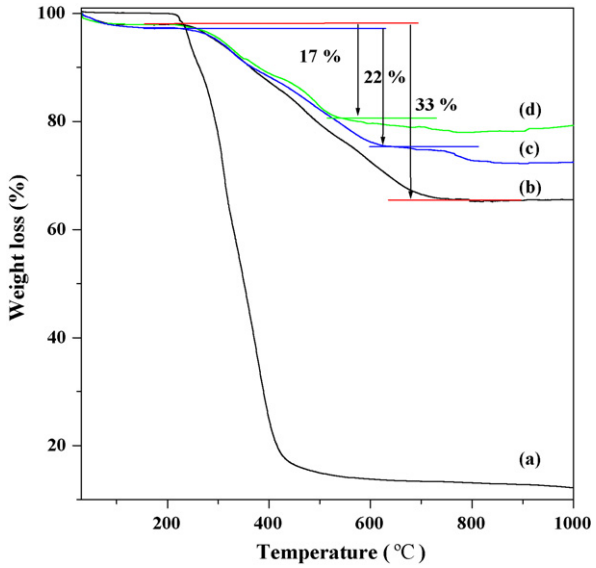

Fig. 3. Thermogravimetric analyses of (a) donepezil, (b) donepezil-MMT, (c) donepezil-SA, and (d) donepezil-LA.

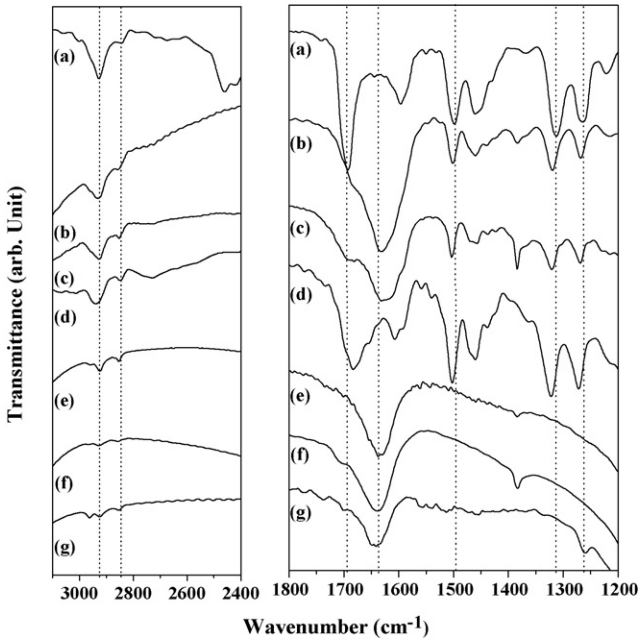

Fig. 4. FT-IR spectra of (a) pure donepezil hydrochloride, (b) donepezil-LA, (c) donepezil-SA, (d) donepezil-MMT, (e) pristine Na^+-LA, (f) pristine Na^+-SA, and (g) pristine Na^+-MMT from 2200 to 3100 cm^{-1} and from 1200 to 1800 cm^{-1}.

3.3. FT-IR analysis

Fig. 4 illustrates the FT-IR spectra of the donepezil hydrochloride, three different types of the pristine clay materials, and donepezil-nanoclay hybrids. For the donepezil hydrochloride, a sharp peak corresponding to the C=O stretching, C–H wagging, and C–N–C stretching bands were observed at 1697, 1313, and 1498 cm^{-1}, respectively as shown in Fig. 4(a). The stretching vibrations of sp^3 C–H were also seen at 2926 and 2856 cm^{-1} (Pavia et al., 1996; Singh et al., 2002). All these characteristic bands were also clearly shown in the spectra of the hybrids (Fig. 4(b)–(d)), indicating that donepezil molecules were well stabilized in the interlayer space of clay without any chemical deterioration of functional groups.

It should also be noted that the band shifts of C=O stretching could be seen upon intercalation of donepezil into clay. The ν(C=O) stretching bands of donepezil in LA and MMT were shifted from 1697 to 1683 cm^{-1} and that in SA to 1690 cm^{-1} as shown in Fig. 4(c) and (d), which were due to the fact that the intermolecular interaction between crystallized drug molecules was absent upon hybridization. This result proved that donepezil molecules intercalated in the interlayer space were not crystallized but resided in the molecular form (White and Hem, 1983).

3.4. Zeta potential and size analysis

Table 2 shows the size and zeta potentials of the intact clay materials, hybrids and Eudragit® E-100 coated hybrids dispersed in DI water. The particle sizes of all clay materials increased after hybridization with donepezil and spray drying with Eudragit® E-100. The increase in particle size of the hybrids could be attributed to their agglomeration, which appeared to be elevated while being dry as shown in Fig. 5(a)–(c). The particle size and morphology of all polymer coated hybrids became similar since polymeric microparticles embedded with nano-sized hybrids were formed by spray drying with a single fixed condition. Therefore, although the initial particle sizes of hybrids were very different for SA, LA, and MMT, the coated particle sizes were in a narrow size range of 1200–1450 nm. After hybridization and Eudragit® E-100 coating, zeta potentials also increased with all clay materials.

3.5. Release behavior

According to the donepezil release profiles as shown in Fig. 6, the release fraction during the first 180 min increased in the order of donepezil-MMT (Fig. 6(a)), -SA (Fig. 6(c)), and -LA (Fig. 6(e)), indicating that the CEC of the clay was a critical factor on the drug release (MMT > SA > LA) (Jacobs and Schoonheydt, 2001). Hence, the larger the CEC was, the stronger the ionic attraction between drug molecules and clay would become, and eventually the smaller release fraction could be expected. For donepezil-LA and -SA, the release was continous during the first 180 min and the total amount of release was 37% and 15%, respectively. Due to the higher CEC of SA than that of LA, the donepezil release was found to be more sustained with the SA. However, donepezil-MMT exhibited a most retarded release as expected, because of the strongest electrostactic interaction between drug molecules and MMT. The release of about 7% was observed during the first 10 min and became minimal afterwards.

Although the drug release could be controlled depending on the types of clay used in this study, the properties required for the drug delivery system, such as the total amount of release and the release

Table 1
Amount of donepezil in hybrids and Eudragit® E-100 coated hybrids obtained by the HPLC and CHNS analyses

	MMT-donepezil (%)	SA-donepezil (%)	LA-donepezil (%)	Coated MMT-donepezil (%)	Coated SA-donepezil (%)	Coated LA-donepezil (%)
HPLC	33.31	22.04	17.27	18.46	12.51	9.41
Theoretical value	–	–	–	17.70	12.70	9.70
CHNS	34.34	23.31	17.21	–	–	–

Theoretical values were calculated based on the weight fraction of hybrids and polymer (1:0.6) used for spray drying.

Table 2
Particle sizes and zeta potentials of intact clay materials, clay-donepezil hybrids and Eudragit® E-100 coated hybrids

	MMT	SA	LA	MMT-donepezil	SA-donepezil	LA-donepezil	Coated MMT-donepezil	Coated SA-donepezil	Coated LA-donepezil
Size (nm)	387.7	99.1	42.4	1133.3	244	172.7	1440	1420	1193
Potential (mV)	−41.7	−37.8	−28.3	16.7	−20.9	−22.8	43.6	31.7	15.9

rate were not desirable as yet. As stated above, the total amount of release was only about 37% during the first 180 min with donepezil-LA, the hybrid with the lowest CEC. In the present study, a bulky cationic molecule, Eudragit® E-100, was added to easily replace donepezil molecules by ion exchange reaction and also facilitate the swelling of the clay, hence enhancement in drug release rate (Sparnacci et al., 2002). As shown in Fig. 6(b), (d), and (f), with the presence of Eudragit® E-100, the total release amount and the release rate could be improved for all hybrids. The total release amount increased from 7% to 12% for donepezil-MMT (Fig. 6(b)), from 15% to 23% for donepezil-SA (Fig. 6(d)), and from 37% to 61% for donepezil-LA (Fig. 6(f)), respectively. Due to the stronger electrostatic interaction with the clay, Eudragit® E-100 could replace the intercalated donepezil molecules, which in turn, facilitated the drug release rate. Moreover, many hydrophilic chemical groups such as NH_4^+ of Eudragit® E-100 could improve the hydration of the hybrids. It should be also noted that even after the addition of Eudragit® E-100, the release rate still depended on the CEC of the clay. Since the CEC of MMT was the highest among the clay materials used in this study, the release was still the lowest (∼12%) and became in steady state after 120 min for donepezil-MMT hybrid.

It was, therefore, required to examine the release profiles for a longer period of time (>180 min) with donepezil-SA and -LA. To study the effect of cations, two distinct release media were utilized with NaCl and Eudragit® E-100, respectively. For all hybrids, the release was faster in the presence of Eudragit® E-100 than NaCl. The donepezil-LA exhibited 100% drug release after 72 h with Eudragit® E-100 while it took 96 h with NaCl (Fig. 7(c) and (d)). For donepezil-SA, about 96% of donepezil was released with Eudragit® E-100 during the first 120 h but 90% was released with NaCl (Fig. 7(a) and (b)). It seemed that unlike a small cation such as Na^+ and a proton, a bulk cationic polymer, Eudragit® E-100, when replaced with donepezil molecules, expanded the lattice spacing along the (0 0 *l*) direction, thus facilitating the out-diffusion of drug molecules.

Since the Eudragit® E-100 was utilized as an additive to improve the drug release rate, the encapsulation efficiency of all formulations decreased after polymer coating as shown in Table 1. To improve the release behavior of the hybrids without too much loss of encapsulation efficiency, one may be able to optimize several parameters. The particle size of polymer coated hybrids can be controlled not only to utilize less amount of polymer used for coating but also to enhance the drug release rate from the hybrids. The polymer solution, where the hybrids are suspended before spray drying, may also contain the drug, so that both polymer and clay can function as a drug carrier.

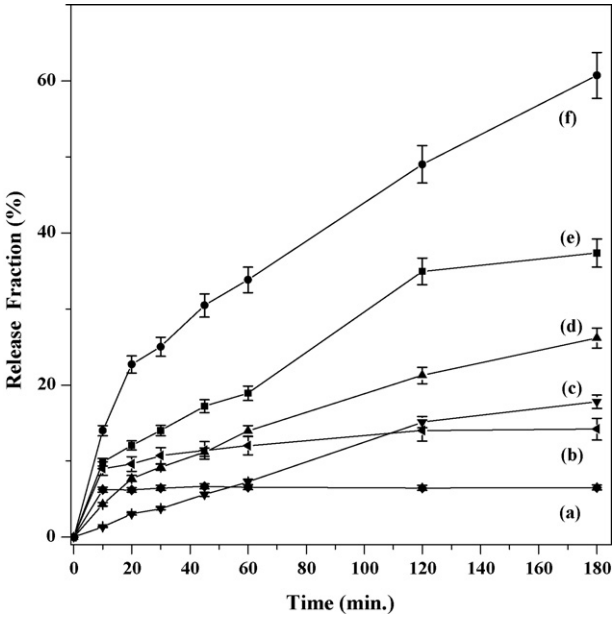

Fig. 6. Release profiles of donepezil from (a) donepezil-MMT in pH 1.2 HCl (aq), (b) donepezil-MMT with Eudragit® E-100 in pH 1.2 HCl (aq), (c) donepezil-SA in pH 1.2 HCl (aq), (d) donepezil-SA with Eudragit® E-100 in pH 1.2 HCl (aq), (e) donepezil-LA in a pH 1.2 HCl (aq), and (f) donepezil-LA with Eudragit® E-100 in pH 1.2 HCl (aq).

We also examined the release mechanisms of donepezil from the hybrids based on the data plotted in Fig. 7. In general, four kinetic diffusion models have been suggested to describe the desorption behaviors of cations from clay materials, which were parabolic diffusion, elovich, two-constant rate and first-order kinetic models. Among them, the parabolic diffusion was often considered as a model to explain the desorption of anions such as NH_4^+ from clay minerals (Lombardi et al., 2003; Li et al., 2001). As shown in Table 3, the release profiles of donepezil by the ion-exchange reaction were in good agreement with the parabolic diffusion model ($R^2 > 0.99$), indicating that the donepezil release

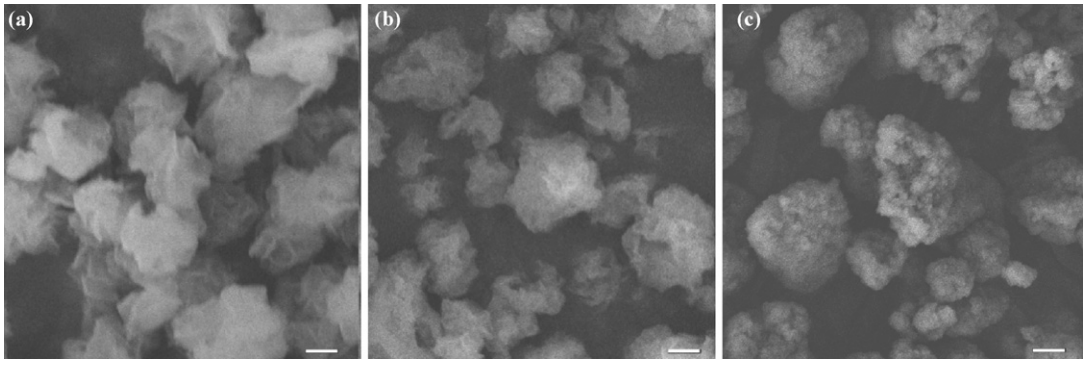

Fig. 5. SEM images of Eudragit® E-100 coated hybrids. The clay materials used are (a) MMT, (b) SA and (c) LA. The scale bar = 1 μm.

Table 3
The regression equations and R^2 values from the parabolic diffusion model

	Donepezil-LA	Donepezil-SA
pH 1.2 aqueous solution	$Mt/Mo = -0.01887 + 0.03003t^{1/2}$, $R^2 = 0.9933$	$Mt/Mo = -0.04376 + 0.01601t^{1/2}$, $R^2 = 0.9926$
pH 1.2 aqueous solution with Eudragit	$Mt/Mo = 0.03592 + 0.04002t^{1/2}$, $R^2 = 0.9906$	$Mt/Mo = -0.02064 + 0.02077t^{1/2}$, $R^2 = 0.9984$

from the clay materials used in this study was mediated by diffusion.

In general, the hybrids after freeze drying are not well dispersed in the release media because of agglomeration. In order to improve dispersibility and formulate a donepezil delivery system with an improved release rate, the hybrids were coated with Eudragit® E-100 through spray drying. The resulting particles would form Eudragit® E-100 microparticles containing nano-sized hybrids as shown in Fig. 5. Since Eudragit® E-100 would dissolve in an acidic SHG solution, the hybrids could be redispersed in nano-sizes. The encapsulation efficiencies obtained by HPLC and theoretical calculation for the coated hybrids agreed well as shown in Table 1, which indicated that there was almost no loss of donepezil during polymer coating.

Fig. 8 shows the release patterns from Eudragit® E-100 coated hybrids. When compared with the results shown in Fig. 6, the total release amount during the first 180 min was greatly enhanced by Eudragit® E-100 coating. The release increased from 12% to 43% for donepezil-MMT (Fig. 8(a)), from 23% to 83% for donepezil-SA (Fig. 8(b)), and from 61% to 83% for donepezil-LA (Fig. 8(c)), respectively. It is worthy to note here that the release rate is still determined by the CEC of the clay even after Eudragit® E-100 coating. As shown in Fig. 8, the release fraction was about 83% with donepezil-SA and -LA while the donepezil-MMT exhibited only 43% release. Therefore, the formulation suggested in this study would not only enhance the release rate but also provide the controlled release property depending on the kinds of clay used as a delivery vehicle.

However, the release patterns with Eudragit® E-100 coated hybrids were different from those with intact hybrids. Instead of sustained release, the coated hybrids showed a distinctive biphasic release pattern, being consisted of a burst and slow release. It seemed that some donepezil molecules encased in clay materials were already replaced by Eudragit® E-100 while the hybrids were spray-dried. Therefore, for donepezil-SA and -LA, the hybrids with smaller particle size and lower CEC, more of free drug molecules could be replaced rapidly during the spray drying process, resulting in a larger burst release than donepezil-MMT.

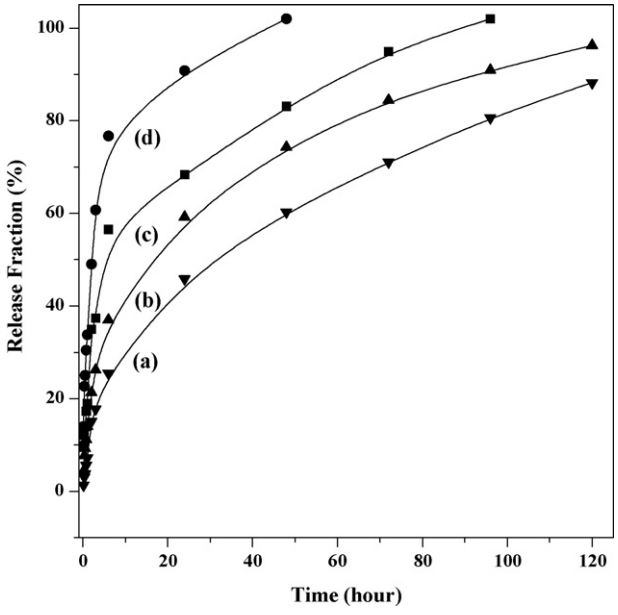

Fig. 7. Release profiles of donepezil from (a) donepezil-SA and (c) donepezil-LA in a pH 1.2 aqueous HCl solution containing 0.05 M NaCl, and (b) donepezil-SA and (d) donepezil-LA in a pH 1.2 aqueous HCl solution containing Eudragit® E-100.

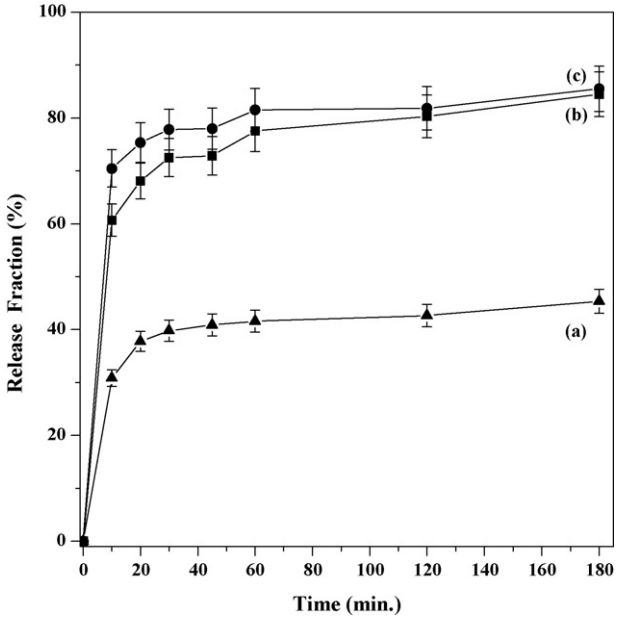

Fig. 8. Release profiles of donepezil in pH 1.2 HCl (aq) from the Eudragit® E-100 coated hybrids. The hybrids are (a) donepezil-MMT, (b) donepezil-SA, and (c) donepezil-LA.

4. Conclusion

In this study, donepezil molecules were successfully intercalated by cation exchange reaction without any deterioration of their functional groups. The thermal stability of drug molecules was also improved after the hybridization. We found that the CEC of the clay could determine the absorption amount and molecular arrangement of the drug molecules in the interlayers, as well as the release patterns of donepezil. The release rate could be easily enhanced utilizing a bulky cationic polymer, Eudragit® E-100. The hybrids coated with such polymer showed a faster drug release during a short time period. Therefore, the smectite clay materials could be suggested as an advanced drug delivery carrier with controlled release characteristics.

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