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Inorganic-polymer nanohybrid carrier for delivery of a poorly-soluble drug, ursodeoxycholic acid

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ABSTRACT

Delivery of poorly soluble drugs has been problematic due to its low absorption profile and bioavailability. In this work, ursodeoxycholic acid (UDCA), a poorly-soluble drug, was intercalated into inorganic nanovehicle, layered double hydroxides (LDHs), with a molecular level to enhance its solubility in biological fluid. The UDCA-loaded nanovehicle (i.e., UDCA-LDHs) was also coated with an anionic polymer, Eudragit® S100, to increase the dissolution rate of UDCA. According to the powder X-ray diffraction (PXRD) patterns of UDCA-LDHs, the gallery height of LDHs was expanded from 3.6 Å to 28.3 Å, indicating that the UDCA molecules were successfully intercalated into the interlayer space of LDHs. Fourier transform infrared (FT-IR) spectra also revealed that the UDCA molecules were well stabilized in the LDHs through electrostatic interaction. The in vitro dissolution test in a simulated biological fluid (pH = 6.8) showed that the total dissolved fraction of UDCA for the first 2 h was about 60.2% for the Eudragit® S100 coated UDCA-LDHs, which was a dramatic increase as compared with 19.0% dissolution from intact UDCA. It is, therefore, concluded that LDHs nanovehicle coated with an anionic polymer is a promising delivery system for improving aqueous solubility of poorly soluble drugs.

1. Introduction

Poorly soluble drugs have suffered from low bioavailability and inefficacy in therapy due to their low dissolution profile in biological fluid. Without a proper level of drug concentration in the gastrointestinal (GI) fluid, the drugs may not be effectively transported via the epithelia present through the GI tract, resulting in low systemic absorption (Khan et al., 2001; Porter et al., 2008; Yasuji et al., 2008). Therefore, numerous approaches have been made to improve aqueous solubility of poorly soluble drugs in pharmaceutical industry and science. Most of strategies are based on particulating the drugs in small scale (nano- or micro-scale) through milling (Remenar et al., 2003; Choi et al., 2004; Hu et al., 2004), spray drying (Hu et al., 2004; Kondo et al., 2009) and nanoemulsification (Shakeel and Faisal, 2009) to increase the surface area-to-volume ratio of drug particles themselves, hence better interaction with the surrounding aqueous media. Many different types of delivery vehicles were also introduced to improve drug solubility, the approach of which was basically similar as distributing drug particles of small size inside of delivery vehicles (Chung et al., 2003; Denga et al., 2008).

Although those methods proved to increase the drug solubility to some extent, the achievable drug solubility is still limited as the decrease of drug-particle size is restricted with those conventional approaches. To further improve drug solubility, the dissolution aids, such as surfactants, were often incorporated in drug delivery vehicles or formulations (Fini et al., 1995; Orienti et al., 1999), which, however, is not yet practical since the use of such additives is limited in their allowable amount. Therefore, the desirable approach should be to formulate the poorly soluble drugs to the smallest size possible, i.e., the size of molecule, with decreasing/minimizing the use of dissolution aids.

In this sense, bio-inorganic nanohybrid is advantageous since the drug of interest can be encased into the layered structures of inorganic materials with a molecular level, greatly enhancing the active area of drug particles interacted with surrounding aqueous media (Lin et al., 2002; Aguzzi et al., 2007; Choy et al., 2007). Previously, we have successfully intercalated poorly soluble drugs, such as itraconazole, donepezil and indole-3-acetic acid into the inorganic nanovehicles and showed great enhancement in drug

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solubility in simulated biological fluid (Yang et al., 2007; Jung et al., 2008b; Park et al., 2008). Some other groups also reported that the solubility of poorly soluble drugs, such as ibuprofen, indomethacin, tiaprofenic acid, ketoprofen and fenbufen, could be improved by encasing the drugs in inorganic nanovehicle with a molecular-level distribution (Ambrogi et al., 2001, 2003; Li et al., 2004a,b).

Ursodeoxycholic acid (UDCA; 3α,7β-dihydroxy-5β-cholan-24-oic acid (R)-4((3R,5S,7S,8R,9S,10S,13R,14S,17R)-3,7-dihydroxy-10,13-dimethylhexadecahydro-1H cyclopenta[a]phenanthren-17-yl) pentanoic acid) is a cholagogue, cholelitholytic and hepatic protector agent and exhibits low bioavailability for oral delivery due to its poor water solubility (Ventura et al., 1997). Therefore, in this work, we utilized layered double hydroxides (LDHs) as inorganic nanovehicle of UDCA to improve its aqueous solubility. The LDHs, an anionic clay is represented by the general formula $[M^{II}_{1-x}M^{III}_{x}(OH)_2]^{x+}(A^{n-})_{x/n}\cdot yH_2O$, where M^{II}, M^{III}, and A^{n-} are di-, tri-valent metal cations and interlayer anions, respectively (Choy et al., 1999; Kwak et al., 2004). Thus, UDCA, an anionic drug can be intercalated and stabilized in the interlayer space of LDHs, consisting of the positively charged metal hydroxide, to form a bio-nanohybrid (i.e., UDCA-LDHs).

In this study, the UDCA-LDHs was also coated with anionic polymer, Eudragit® S100 to further increase the dissolution rate of poorly soluble UDCA. We previously reported that the presence of macromolecules, possessing the same polarity as the intercalated compounds, facilitated the out-diffusion of intercalated compounds by enlarging the lattice spacing of nanohybrids (Jung et al., 2008b; Park et al., 2008). The UDCA-LDHs was characterized with the powder XRD and the FT-IR analyses to examine the property of UDCA intercalated in the LDHs. The dissolution profiles of UDCA with both non-coated and coated nanohybrids were also studied in the simulated biological fluids and measured quantitatively with the HPLC.

2. Materials and methods

2.1. Materials

UDCA ($C_{24}H_{40}O_4$, purity > 99.9%) was supplied by Daewoong Pharmaceutical (Korea) and was used as obtained. Magnesium chloride hexahydrate ($MgCl_2\cdot6H_2O$, purity > 98.0%) and aluminum chloride hexahydrate ($AlCl_3\cdot6H_2O$, purity > 99.0%) of pharmacopoeia grade were purchased from Dae Jung Chemical and Metals (Korea) and Aldrich (Korea), respectively. Eudragit® S100 (MW 1,35,000 g/mol) of pharmacopoeia grade was purchased from Degussa (Germany). All other reagents of high purity were purchased from Mallinckrodt Baker (USA) and used without further purification.

2.2. Preparation of nanohybrids

The UDCA-LDHs nanohybrid was prepared by the direct co-precipitation method. Briefly, UDCA was dispersed in deionized water and titrated with a 1.0 M NaOH solution to give a 0.12 M solution of UDCA at pH 10.0 ± 0.2. Then, an aqueous solution of $MgCl_2\cdot6H_2O$ (0.24 M) and $AlCl_3\cdot6H_2O$ (0.12 M) was added dropwisely to the UDCA solution, where the pH was maintained at 10.0 ± 0.2 by adding a 1.0 M NaOH solution dropwisely at the same time. Thus-produced slurry was further aged for 20 h in order to reach equilibrium. The whole process was performed under a nitrogen atmosphere at 60 °C. The resulting precipitate was collected by filtration and washed with deionized water, 50% ethanol solution and pure ethanol (>99.9%), respectively. To prepare the non-coated nanohybrids, the resulting precipitate (20.0 g) was dispersed in a mixture of methylene chloride and ethanol (150 ml:150 ml, v/v) and spray dried (EYLA spray dryer SD-1000, Tokyo, Japan) under the following condition: atomizing pressure, 130 kPa; blower speed, 0.30 m^3/min; inlet temperature, 80 °C; and outlet temperature, 40–50 °C. To prepare the Eudragit® S100 coated nanohybrid, the hybrid (5.0 g) was dispersed in a mixture of methylene chloride and ethanol (150 ml:150 ml, v/v), where Eudragit® S100 (7.5 g) was dissolved, and spray dried under the same condition described above.

2.3. Sample characterization

For structural analysis, the powder X-ray diffraction (PXRD) patterns were obtained using a diffractometer (Rigaku D/MAX RINT 2200-Ultima+, Japan) with monochromatized and Ni-filtered Cu K_α radiation (λ = 1.5418 Å). The diffractometer was operated at 40 kV and 30 mA. Fourier transform infrared (FT-IR) spectra were collected from a JASCO FT-IR-6100 spectrometer (Tokyo, Japan) by the standard KBr disk method. To determine the chemical composition of the hybrids, three different analyses were performed: the elemental CHNS analysis (EA1112, CE instrument, Italy), the inductive coupled plasma (ICP) analysis (ICPS-1000IV, Shimadzu, Japan) and the thermogravimetric (TG) analysis (pyris diamond TG-DTA, PerkinElmer, Japan).

2.4. Determination of UDCA content

To measure the encased amount of UDCA, the solution was first prepared with a mixture of acetonitrile, distilled water and phosphoric acid (60:40:0.5, v/v/v). Then, a known amount of the samples (25 mg of non-coated UDCA-LDHs, 50 mg of coated UDCA-LDHs) was dispersed in a mixture of 5 ml methanol and 20 ml of the resulting solution and sonicated for 40 min to completely extract UDCA from the LDHs lattice. The suspension was then filtered by a polypropylene membrane with a pore size of 0.45 μm (Pall, USA) and measured using the HPLC (Agilent 1100 series Instrument, USA) with a column, Agilent Zorbax Eclipse XDB-C18 (4.6 mm × 250 mm, 5 μm; USA). The mobile phase was prepared with acetonitrile and distilled water (55:45, v/v) and the pH was adjusted to 3.0 with phosphoric acid. The flow rate and injection volume was 1 ml/min and 50 μl, respectively. The column temperature was adjusted to 40 °C and the UV absorbance was measured at 210 nm.

2.5. In vitro dissolution test

The in vitro dissolution profiles of intact UDCA, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs were obtained via the paddle stirring method with a dissolution tester DST-810 of LABFINE (Korea). The impeller was set at 50 rpm and the bath temperature was maintained at 37 °C. The dissolution tests were performed at pHs = 1.2 and 6.8 to simulate human's gastrointestinal fluid (USP, 2002a, pp. 2011–2012) and also at pH = 8.0, following the protocol designed for the dissolution test of ursodiol tablets (USP, 2002b, p. 1788). Each of the samples with an equivalent amount of 150 mg UDCA was dispersed in 500 ml of the dissolution media, the aliquot of which was collected at scheduled intervals. The sampled aliquot was filtered with a 0.45 μm-pore polypropylene membrane filter (Pall, USA) and measured by the HPLC as described above.

2.6. Stability test

To assess the shelf life of UDCA, the accelerated stability test was performed with intact UDCA, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs (Kuu et al., 1998; Waterman and Adami, 2005). Each of the samples was put into a glass vial and sealed, which was then placed in a constant temperature and humidity chamber (LH-1000, New Power Engineering Company, Korea). The temperature and humidity of the chamber were maintained at 40 °C and 75%,

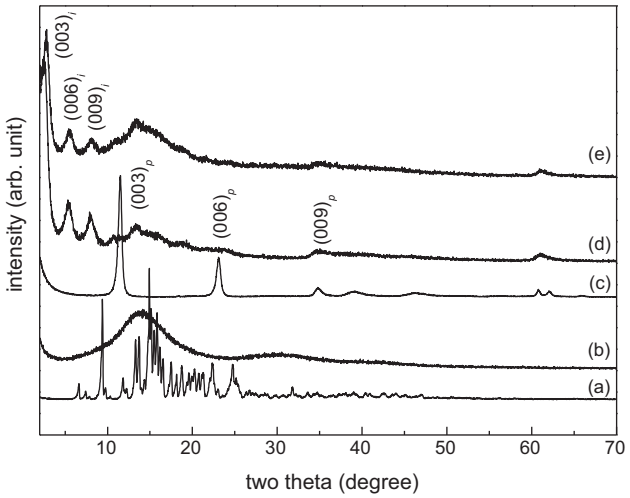

Fig. 1. Powder X-ray diffraction (PXRD) patterns of (a) intact UDCA, (b) Eudragit® S100, (c) pristine LDHs(Cl), (d) UDCA-LDHs and (e) Eudragit® S100 coated UDCA-LDHs. $(001)_i$ and $(001)_p$ indicate the (001) reflections for the intercalate(i) and pristine(p).

respectively. The samples were obtained after the incubation times of 0, 2, 4, 6 and 8 weeks, and 3 and 6 months, and the amount of non-degraded UDCA was determined as described in the Section 2.4. For each of the samples, the fraction of non-degraded UDCA amount was calculated in percentage, based on the UDCA content measured initially before the stability test.

3. Results and discussion

3.1. Powder X-ray diffraction analysis

Fig. 1 shows the PXRD patterns of intact UDCA, Eudragit® S100, pristine-LDHs, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs. The chemical compositions of LDHs of pristine form and UDCA-LDHs were $Mg_{0.667}Al_{0.333}(OH)_2Cl_{0.333}\cdot 0.52H_2O$ and $Mg_{0.670}Al_{0.330}(OH)_2[(UDCA)_{0.153}Cl_{0.177}]\cdot 0.12H_2O$ as shown in Table 1. The pristine-LDHs exhibited a series of well developed (001) reflections (Kloprogge and Frost, 1999), which were also clearly seen with both the coated and the non-coated UDCA-LDHs. The basal spacing of the pristine-LDHs was estimated to be 7.69 Å, which increased to 33.12 Å for both UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs, indicating successful intercalation of UDCA into the interlayer space of LDHs. The fact that there was no difference in the PXRD patterns between the non-coated and the coated UDCA-LDHs implied that UDCA still resided in the interlayer space of the LDHs even after the Eudragit® S100 coating. No PXRD peaks of intact UDCA crystalline was observed after hybridization, suggesting that UDCA molecules were distributed in the LDHs lattice with a molecular level as previously reported with the other nanohybrid systems (Jung et al., 2008b; Park et al., 2008).

With the layer thickness 4.8 Å of LDHs, the gallery height of the UDCA-LDHs could be estimated to be 28.32 Å. Therefore, considering that the longitudinal and lateral molecular dimensions of UDCA are 17.2 Å and 3.7 Å, respectively, it could be suggested that UDCA molecules be stabilized in a double layer arrangement with a tilting angle of about 55.5°, as shown in Fig. 2. To explain such configuration, we examined the steric limitations between the intercalated UDCA and charged sites of LDH layers. The steric limitation is generally imposed by the equivalent area (A_e) of lattices of layered materials and the area demand (A_c) of intercalated molecules. The LDHs prepared in this work (Mg:Al ratio of 2:1 (Table 1)) exhibited the equivalent area (A_e) of about 24.4 Å^2 per unit charge (Zhao and Nagy, 2004) while the area demand (A_c) of UDCA was 63.6 Å^2. Since A_c is larger than $2A_e$, the intercalated UDCA molecules, therefore, should have a tilted bilayer arrangement to avoid steric hindrance (Yang et al., 2007).

Table 1
Chemical composition of the pristine LDH and UDCA-LDH hybrids.

	Chemical composition[a]	Mg/Al molar ratio[b]
Pristine LDHs	$Mg_{0.667}Al_{0.333}(OH)_2Cl_{0.333}\cdot 0.52H_2O$	2.00
UDCA-LDHs	$Mg_{0.670}Al_{0.330}(OH)_2[(UDCA)_{0.153}Cl_{0.177}]\cdot 0.12H_2O$	2.03

[a] Calculated from elemental CHNS analysis, ICP, TGA data.
[b] Calculated from ICP data.

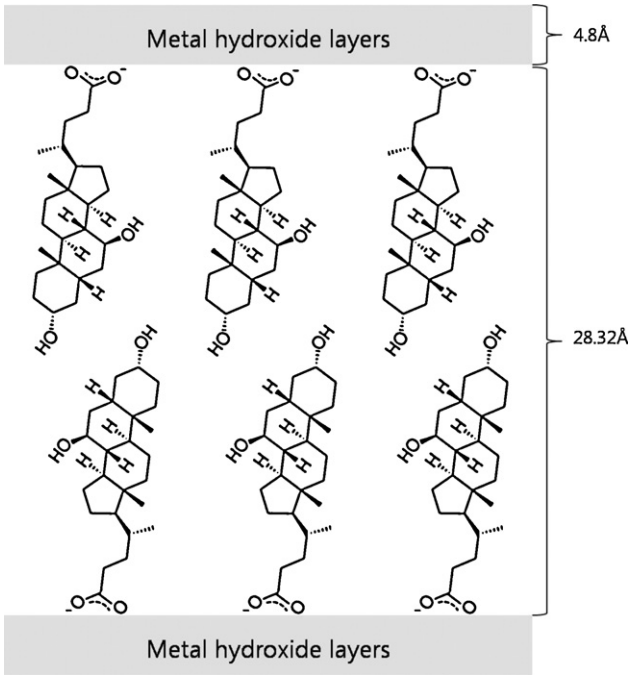

Fig. 2. Schematic diagram of the UDCA-LDHs structure.

3.2. FT-IR analysis

Fig. 3 exhibits the FT-IR spectra of intact UDCA, Eudragit® S100, pristine-LDHs, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs. The intact UDCA clearly shows broad absorption bands at 3300–3500 cm^{-1}, sharp ones at 2800–3000 cm^{-1} and 1715 cm^{-1} (circle), which can be assigned as (O–H) stretching vibrations, (C–H) and (C=O) ones (Pavia et al., 1996; Oguchi et al., 2003), respectively, as shown in Fig. 3(a). For Eudragit® S100, broad bands at 3300–3600 cm^{-1} and 2900–3000 cm^{-1} are also due to (O–H) and (C–H) groups, respectively (Fig. 3(b)). It is worthy to note here that a sharp band seen at 1730 cm^{-1} (arrow) is surely due to the esterified carboxyl groups, which explains why anionic UDCA could be intercalated into LDH lattice by ion exchange reaction. The peaks at 1450 cm^{-1} and 1385 cm^{-1}, and at 1250 cm^{-1} and 1150 cm^{-1} can be interpreted as (C–H) vibrations and ester group ones, respectively (Degussa AG, 2005). For pristine LDHs, broad bands around at 3400 cm^{-1} and those at 1635 and 1545 cm^{-1} are observed, which can be ascribed to (O–H) group vibrations owing to both the hydroxide layer and the interlayered water (Fig. 3(c)) (Choy et al., 2004). The peaks at low energy side, 850 cm^{-1}, 620 cm^{-1} and 454 cm^{-1} (dashed vertical lines) are due to the lattice vibrations resulting from (M–O) and (O–M–O), respectively (Pavia et al., 1996; Kloprogge and Frost, 1999; Aisawa et al., 2001; Choy et al., 2004).

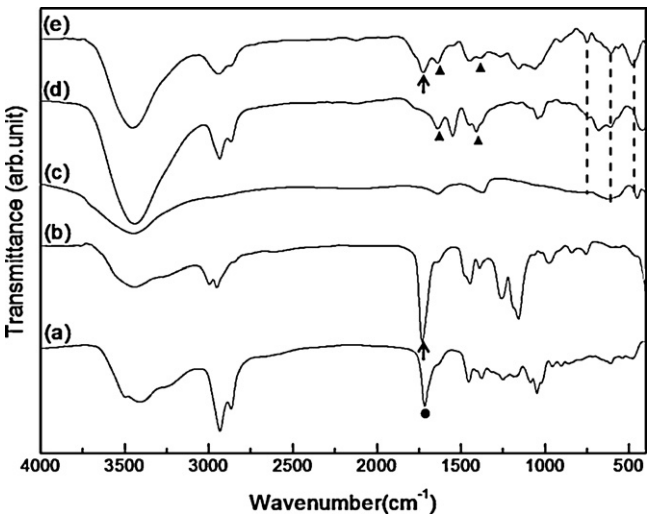

Fig. 3. FT-IR spectra of (a) intact UDCA, (b) Eudragit® S100, (c) pristine LDHs(Cl), (d) UDCA-LDHs and (e) Eudragit® S100 coated UDCA-LDHs. The circle (●), the arrows (↑), and the dashed vertical lines locate several characteristic peaks seen with intact UDCA, Eudragit® S100, and pristine LDHs, respectively. The triangles (▲) indicate the peaks by the stretching vibration of COO^-.

For UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs, new bands are seen at 1635 cm^{-1} and at 1380 cm^{-1} (triangles), which are due to the asymmetric vibration of ν_{as} (COO^-) and the symmetric vibration of ν_s (COO^-), respectively (Fig. 3(d) and (e)) (Jiao et al., 2009). All the characteristic bands from UDCA are found and overlapped in the spectrum of UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs, which indicated that UDCA molecules are stabilized in the interlayer space of LDHs through electrostatic interaction without any structural changes.

3.3. UDCA content analysis

The content of UDCA was measured with both non-coated UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs using the HPLC. The content of UDCA in UDCA-LDHs was 60.89 ± 0.06%, which decreased to 27.33 ± 0.03% for the coated UDCA-LDHs due to incorporation of Eudragit® S100 (mass fraction of nanohybrids and Eudragit, 1:1.5, w/w).

3.4. In vitro dissolution profiles

Fig. 4 shows the in vitro dissolution profiles of intact UDCA, UDCA-LDHs and Eudragit® coated UDCA-LDHs. At the simulated gastric solution (pH 1.2), almost no UDCA was dissolved from all samples due to very low solubility of UDCA at low pH (Fig. 4(a)) (Degussa AG, 2005). This could also explain almost no dissolution of UDCA from UDCA-LDHs even with its molecular level distribution in the LDHs lattice. The dissolution of UDCA was also much suppressed with the coated UDCA-LDHs since Eudrigit® S100 would function as a diffusion barrier without dissolution at low pH (Li et al., 2004a).

However, as the pH increased, the dissolution of UDCA became apparent. At pH 6.8, 19.0% of UDCA was dissolved for the first 2 h from intact UDCA due to increased solubility of UDCA at the higher pH (Fig. 4(b)). However, only a slight enhancement of UDCA dissolution was observed for the UDCA-LDHs nanohybrid (24.6%), surely due to the strong ionic interaction between UDCA and the LDHs. Notably, 60.2% of UDCA was dissolved from the coated UDCA-LDHs, which was a three-fold increase in dissolution rate as compared with intact UDCA. Eudragit® S100, an anionic polymer, would be dissolved in the neutral media and replace the intercalated UDCA

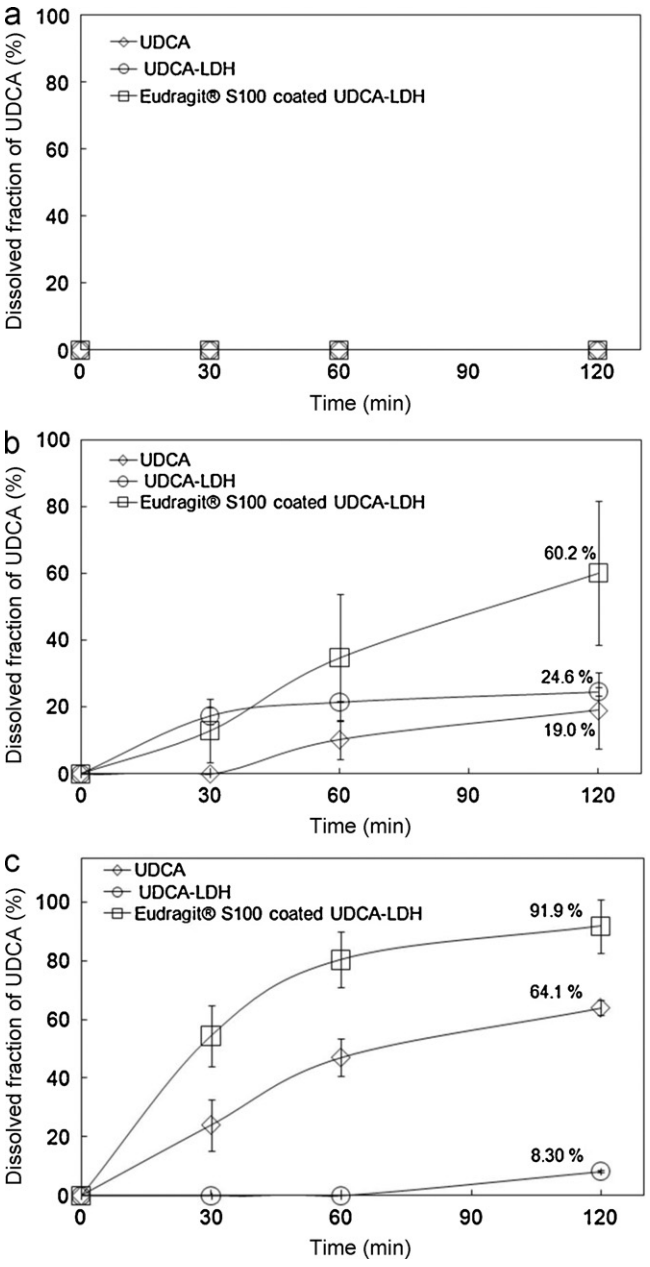

Fig. 4. In vitro dissolution profiles of intact UDCA, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs at (a) pH 1.2, (b) pH 6.8 and (c) pH 8.0.

efficiently because of its stronger electrostatic interaction with the LDHs. Moreover, due to the large molecular dimension of Eudragit® S100, it would expand the lattice spacing, further facilitating the out-diffusion of UDCA molecules (Park et al., 2008; Albertini et al., 2004; Li et al., 2004a).

We also tested the dissolution profiles of UDCA in the slightly basic media (pH 8.0), following the protocol designed for the dissolution test of ursodiol tablets (Fig. 4(c)) (USP, 2002b, p. 1788). Due to the increased solubility of UDCA at the basic pH, the increase of UDCA dissolution rate was more apparent. The intact UDCA exhibited 64.1% dissolution for the first 2 h, which increased to 91.9% for the Eudragit® S100 coated UDCA-LDHs. However, for the non-coated UDCA-LDHs, the dissolution of UDCA was only 8.3%, which was even lower than that observed at pH 1.2. The LDHs is known to be dissolved to some extent in the acidic media but not in the basic media (Prasanna and Kamath, 2009). Therefore, the LDHs could be better retained structurally at pH 8 and again, due to ionic interac-

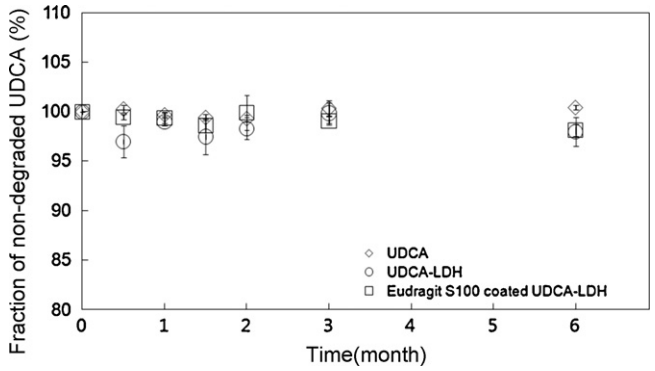

Fig. 5. Percentages of non-degraded UDCA in intact UDCA, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs placed under an accelerated stability test condition (temperature, 40 °C; humidity, 75%).

tion between UDCA and the LDH lattice, the drug release would be more impeded.

3.5. Stability of UDCA

The shelf life of drug is important especially with the nanohybrid systems since the drug molecules are distributed with a molecular level, giving a higher chance of interaction with the surrounding environment, hence higher sensitivity to degradation. Therefore, we examined the fraction of non-degraded UDCA amount in intact UDCA, UDCA-LDHs and Eudragit® S100 coated UDCA-LDHs placed under an accelerated stability test condition (temperature, 40 °C; humidity, 75%) (Kuu et al., 1998; Waterman and Adami, 2005). As shown in Fig. 5, almost no change in the amount of non-degraded UDCA was observed during the first 6 months for all samples (±3%). Even with a molecular-level distribution of UDCA, the UDCA molecules appeared to be well protected inside of the interlayer space of the LDHs via the strong ionic interaction. The maintained stability with intact UDCA may also partly explain the excellent stability profiles for both the non-coated and the coated UDCA-LDHs.

4. Discussion

In this work, our approach to improve the solubility of UDCA was focused on particulating the drug into the smallest size possible, i.e., the size of molecule, thereby maximizing the interaction of the drug with the surrounding aqueous environment. For this purpose, we utilized the LDHs, an inorganic carrier and employed its lattice space as the drug reservoir, where the drug could be intercalated and distributed with a molecular level, giving a nanohybrid, UDCA-LDHs. In addition, our nanohybrid formulation is advantageous for the following reasons: (1) the inorganic vehicle, LDHs with high biocompatibility was employed as a drug carrier (Choi et al., 2008) and (2) the carrier itself already showed fairly small particle sizes, i.e., the size in nanometer scale.

Therefore, our method was different from the conventional strategies mostly relying on the physical methods, such as milling of drug (Kipp, 2004), co-grinding of drug and water-soluble polymer (Sugimoto et al., 1998) and using biopolymers as drug carrier (Shah et al., 1995). Although the physical methods could decrease the drug-particle size and improve the drug solubility to some extent, the methods still posed the limitations in achievable size of drug-particles due to the inherent restrictions involved with the grinders (e.g., bluntness and uniformity of grinding blade) or physical/chemical properties of drug carriers. Some other approaches, such as corporation of dissolution aids (Fini et al., 1995; Orienti et al., 1999), complexation of drug and excipients, such as polyvinylpyrrolidone, hydroxypropylmethyl cellulose and sodium lauryl sulphate (Vogt et al., 2008), and preparation of prodrugs (Fleisher et al., 1996) have been suggested to improve the solubility of poorly soluble drugs. However, toxicity of excipients or prodrugs was still problematic, which unfortunately has not been fully resolved.

Although a molecular distribution of the drug was successfully formed with the nanohybrids in this work, the out-diffusion of the drug was still hindered due to the strong ionic interaction between the LDHs lattice and UDCA. In the biological fluid, the prevalent anions, such as Cl^-, may easily replace the anionic drug molecules in the lattice. However, due to its small size, this would cause the zipping effect, where the lattice spacing would become smaller than the size of drug molecules and in turn, would make the out-diffusion of the drug even more difficult (Jung et al., 2008a). To resolve this, we introduced an anionic macromolecule, Eudragit® S100, and coated the nanohybrid to facilitate the drug dissolution. Such anionic macromolecules, when dissolved and ionized, could replace the intercalated drug molecules and enlarge the lattice spacing, hence improvement of drug out-diffusion towards the release media. Therefore, our nanohybrid system (Eudragit® coated UDCA-LDHs), equipped with both molecular distribution of the drug (i.e., very large interfacing area of the drug) and macromolecule for enlargement of lattice-space, could achieve more than a three-fold increase in dissolution of UDCA as compared with intact UDCA itself (Fig. 4(b)).

5. Conclusion

In this study, UDCA, a poorly soluble drug, was intercalated into an inorganic nanovehicle, the LDHs to improve the stability and aqueous solubility of UDCA. After intercalation, the UDCA molecules were distributed in a molecular level and stabilized through electrostatic interaction without structural deformation and chemical decomposition of UDCA molecules. The UDCA-LDHs coated with an anionic polymer, Eudragit® S100 showed that the total fraction of dissolved UDCA during the first 2 h increased up to three-fold in a simulated biological fluid as compared with that of intact UDCA. The stability of UDCA was also well retained for 6 months under an accelerated stability test condition employed in this work. Therefore, Eudragit® S100 coated LDHs nanovehicle could be suggested as a promising delivery system for improvement of aqueous solubility and release rate of poorly soluble drugs.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2010.09.039.

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