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Synthesis of composites of sodium oleate/Mg–Al-ascorbic acid-layered double hydroxides for drug delivery applications

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ABSTRACT

Mg–Al-ascorbic acid (ASA)-layered double hydroxides (ASA-LDHs) with Mg/Al = 3 were synthesized by ion-exchange, coprecipitation and reconstruction methods. Composites with sodium oleate (SOA)/ASA-LDH were prepared by an ion-exchange method using various concentrations of SOA solutions. The (0 0 3) basal spacing of the ASA-LDHs changed from 0.76 nm in the CO_3-LDH to 0.78 and 0.86 nm after intercalation of the ASA ions and these basal spacings are in good agreement with models based on the assumption as mono layers and double layers of ASA ions in the LDH interlayers, respectively. The amounts of ASA in the LDHs prepared by the reconstruction method were higher than those by the ion-exchange and coprecipitation methods. In the preparation of composites of SOA/ASA-LDH, an ion-exchange method was more suitable than a reconstruction method to cause surface sorption of the SOA molecules with maintaining intercalated ASA ions in the LDH interlayers. The acid-resistant properties of the composites of SOA/ASA-LDH were found to be much higher than for the pure ASA-LDH and mixture of CO_3-LDH and ASA. The surfaces of the LDH particles in the composites are, thus, mostly covered with sorbed SOA molecules and they are good candidates as drug delivery materials for intestines through the stomach.

1. Introduction

Layered double hydroxides (LDHs) are represented by the chemical formula $M^{2+}_{1-x}M^{3+}_x(OH)_2A^{n-}_{x/n}\cdot mH_2O$ and are composed of octahedral $M^{2+}(OH)_6$ brucite-like layers, which are positively charged by the partial substitution of M^{3+} for M^{2+}, and anions are intercalated into the interlayers to achieve charge neutrality (Carrado et al., 1988). A large number of LDHs have been synthesized due to the wide variety of combinations of cations and anions possible, e.g. M^{2+} = Mg, Ni, Cu, Zn, Co, Fe, Cr, Mn, Cd and Ca, M^{3+} = Al, Ni, Co, Cr, Mn, Fe, Sc and In, and A^{n-} = F, Cl, Br, I, NO_3, SO_4 and CO_3 (Okada et al., 1997). Since LDHs are anion-exchangers, various anions such as metal complex ions (Okada et al., 1997; Miyata and Kumura, 1973), phosphate ions (Dutta and Puri, 1989), dodecyl sulfate ions (Sugahara et al., 1988), various harmful oxyanions (You et al., 2001; Das et al., 2004), etc. have been intercalated between their layers by ion-exchange. Various organic ions and molecules as well as inorganic ions can be intercalated into the layers using ion-exchange and reconstruction methods, for example, alkylsulfate (Chibwe and Jones, 1989), porphyrin (Ukrainczyk et al., 1995), ftalocyanine (Ukrainczyk et al., 1995), stearic acid (Kanoh et al., 1999), oleic acid (Inomata and Ogawa, 2006; Kameshima et al., 2006), amino acids (Aisawa et al., 2001), peptides (Nakayama et al., 2004), DNAs (Portier et al., 1998) and so on. Since organic ions and molecules mentioned above are much larger than inorganic ions, such an intercalation is preferably performed generally by reconstruction than ion-exchange method.

LDHs have been used as a pH controller of stomach because they dissolve easily in acid solution and increase the pH (Miyata, 1983). By contrast, LDH starts to be used as drug reservoir intercalating inflammatory agents of ibuprofen (Ambrogi et al., 2001), folate derivatives (Choy et al., 2004), indometasine (Mohanambe and Vasudevan, 2005), etc. Such a drug reservoir function is considered to be applied more widely by enhancing acid-resistant property of LDH, e.g. a drug working in the intestines. In order to enhance the chemical durability of LDH in acid solution, surface coating of LDH particles by acid-proof ions and molecules is thought to be effective. Saturated and unsaturated fatty acids are the candidate for surface coating ions because of the high acid-resistant properties. Since intercalation of saturated fatty acids of stearic acid ($CH_3(CH_2)_{16}COOH$) (Kanoh et al., 1999) and unsaturated fatty acids of oleic acid ($CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$) (Inomata and Ogawa, 2006) was reported, it may be possible to use these ions for the

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surface coating of LDH to enhance acid-resistance. We, therefore, synthesized sodium oleate (SOA)/LDH composites by ion-exchange and reconstruction methods using Mg–Al–CO_3 type LDHs with Mg/Al ratios ranging from 2 to 5 synthesized by coprecipitation method (Kameshima et al., 2006). As a result, the surfaces of the LDH composites can be covered by oleic acid as well as interlayers under certain synthetic conditions. Due to the surface coverage by long chain SOA molecules, they showed good acid-resistant properties because of their high stability in acid solution. It is therefore thought that such composites are candidates for drug delivery to the intestines, being unaffected by the strongly acidic gastric juices of the stomach.

For drug delivery to the intestines, the composites should have a structure as drug component in the interlayers of LDH with surface covering of acid-resistant fatty acid. In this work, composites of SOA/LDH with ascorbic acid (ASA) ions in the interlayers were synthesized by ion-exchange and reconstruction methods as a model case for drug delivery system. The reason to choose ASA is that L-ASA, vitamin C, is easily oxidized and also dissolved in acidic condition such as in stomach. If ASA is able to be supplied without decomposition to the intestines through the stomach, it is thought to be very effective for intake of vitamin C. The intercalation behavior of ASA in the LDHs was investigated by ion-exchange, coprecipitation and reconstruction methods and the surface covering of fatty acids and its effect on the interlayered ASA molecules was investigated by ion-exchange and reconstruction methods. The acid-resistant properties of the composites were also investigated, with a point of view to medical applications as possible enteric capsules.

2. Materials and methods

2.1. Synthesis of materials

The starting materials were reagent grade magnesium nitrate hexahydrate (MNH; $Mg(NO_3)_2{\cdot}6H_2O$), aluminum nitrate nonahydrate (ANN; $Al(NO_3)_3{\cdot}9H_2O$), sodium carbonate (Na_2CO_3), sodium hydroxide (NaOH), sodium ascorbate (ASA; $C_6H_7O_6Na$) and fatty acid of sodium oleate (SOA; $C_{17}H_{33}COONa$). All these chemicals were obtained from Wako Pure Chemical Industries and used without any purification.

ASA-LDH was synthesized by coprecipitation, ion-exchange and reconstruction methods. In the coprecipitation method, a precipitate was obtained by mixing of a solution dissolving MNH (0.66 M) and ANN (0.22 M) with a solution containing NaOH (1.5 M) and ASA (1 and 10 mM), with vigorous stirring at room temperature. After stirring for 24 h, the precipitate was separated by centrifugation and washed three times with deionized water. The resulting precipitate was dried at 60 °C overnight in an oven.

In ion-exchange method, CO_3-LDH was synthesized by coprecipitation method first as the host material. MNH (0.66 M) and ANH (0.22 M) were dissolved in 50 ml of deionized water. This solution was added to a solution (150 ml) dissolving NaOH (0.5 M) and Na_2CO_3 (0.33 M) and a precipitate was obtained. The precipitate was mildly stirred at room temperature for 24 h. After that, it was separated by centrifugation, washed three times with distilled water and dried at 60 °C overnight in an oven. A prescribed concentration of ASA (1 and 10 mM) was dissolved in 100 ml of deionized water and the CO_3-LDH (0.2 g) synthesized was added in it. This was reacted with stirring for 24 h to ion-exchange ASA ions for CO_3^{2-} in the interlayers. After this, same processes with the coprecipitation sample were adopted to obtain ion-exchange samples.

In reconstruction method, CO_3-LDH was first heated at 500 °C for 12 h to obtain thermally decomposed LDH. This was added to solutions (100 ml) dissolving different concentrations of ASA (1, 10 and 100 mM) and reacted with stirring for 4–72 h at room temperature. After this, same processes with the coprecipitation and ion-exchange samples were adopted to obtain reconstruction samples.

Previously, composite of SOA/Mg–Al–SO_4–LDH was synthesized by ion-exchange method (Obata et al., 2006). The adsorption and ion-exchange of SOA for the LDH was found to depend strongly on concentration of SOA. Adsorption of SOA on the surfaces of LDH was dominant in the SOA concentration $\leq$5 mM while ion-exchange for interlayer SO_4 ions was dominant in the SOA concentration $\geq$10 mM. Considering these results, the concentrations of SOA in the solutions were set at 1, 5, 10 and 100 mM. Composites of SOA/ASA-LDH were synthesized by reconstruction method. SOA was dissolved in NaOH solution (50 ml) as SOA/NaOH = 1/1 molar ratio with stirring for 1 h. Thermally decomposed LDH (0.1 g) was added to this solution with stirring for 24 h at room temperature and/or 70 °C. Same processes with the above-described samples were adopted to obtain composites of SOA/ASA-LDH after this.

Composites of SOA/ASA-LDH were synthesized by an ion-exchange method because these fatty acids have high solubility in water and easier to handle than other fatty acids. ASA-LDH (0.2 g) was added to SOA dissolved solution (5 mM and 100 ml) and reacted with stirring for 4–12 h. After this, the precipitates were treated as same with other samples to obtain the composite samples. These sample names are designated as composite (*n* h), where *n* denotes reaction time.

2.2. Characterization of materials

X-ray powder diffraction (XRD) patterns were obtained on a Shimadzu XRD-6100 diffractometer operated at 40 kV and 30 mA, using monochromatic Cu Kα radiation. Chemical compositions of the samples were analyzed for Mg^{2+} and Al^{3+} by ICP-OES (Prodigy, Leeman Labs, Inc.). Thermal analysis was performed using a DTA–TG instrument (TG-8120, Rigaku) at a heating rate of 10 °C/min. The infrared spectra of the samples were recorded on a Shimadzu FTIR 8600PC Fourier transform infrared spectrophotometer by the KBr disk method. The contents of carbon in the composites were analyzed on a Yakano Corder MT-6 CHN analyzer using antipyrine for the standard. The concentrations of ASA in the solutions were measured on a Japan Spectroscopy high performance liquid chromatography (HPLC).

2.3. Acid-resistance test

The acid-resistance test for medical applications was carried out under simulated stomach conditions. The sample powder (25 mg) was reacted with 25 ml of HCl solution (pH 2) at room temperature with stirring. After reaction, the sample powder was filtered. The concentrations of ASA ions in the separated solution after the acid-resistance test were measured using a Japan Spectroscopy HPLC.

Simulated gastric juice (SGJ) was prepared by dissolving HCl to be the pH at 1.2 and adding 2.0 g of NaCl and 3.2 g of pepsin with stirring to completely dissolving. The powders (25–50 mg) of the composite samples were uniaxially pressed at 98 MPa into a pellet (⌀5 mm). The pellet was added in a SGJ (40 ml) at 36.5 °C and incubated at 100 rpm for various times. The concentrations of ASA in the separated solution after the SGJ resistance test were analyzed using a HPLC liquid chromatography.

3. Results and discussion

3.1. ASA-LDH samples

The XRD patterns of the ASA-LDH samples synthesized by an ion-exchange method in 1 and 10 mM ASA solutions are shown in Fig. 1 together with CO_3-LDH and SA. The (0 0 *l*) basal reflec-

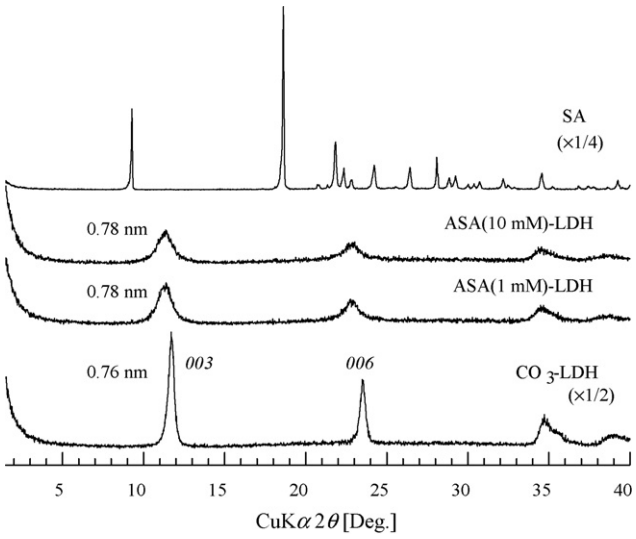

Fig. 1. XRD patterns of the synthesized CO_3-LDH, ASA-LDHs synthesized by an ion-exchange method using 1 and 10 mM ASA solutions and SA.

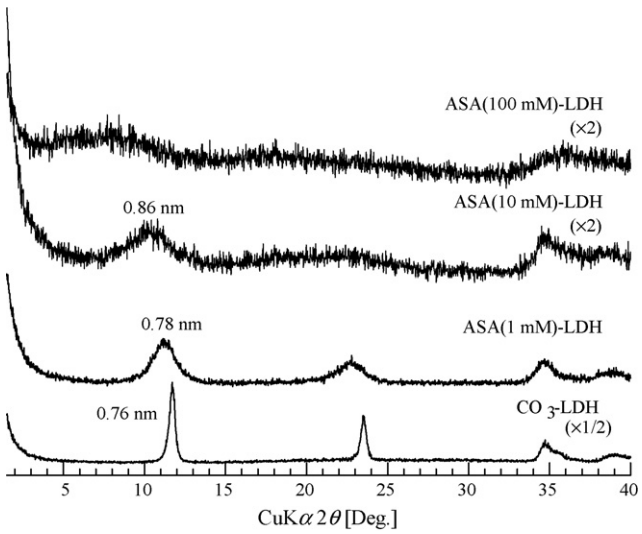

Fig. 3. XRD patterns of the samples synthesized by a reconstruction method using 1, 10 and 100 mM ASA solutions (duration = 72 h).

tions of the synthesized ASA-LDH samples were slightly shifted to lower angle side with broadening of the reflections, thus, the obtained *d*-spacings of (0 0 3) reflections were 0.78 nm and only slightly larger than 0.76 nm of CO_3-LDH peak. Since the change of interlayer distances is small, it is not clear from the XRD data whether ASA molecules intercalated into the interlayers or merely adsorbed on the surfaces of LDH particles. Assuming intercalation of ASA molecules, the intercalated ASA molecules should be lying almost parallel to the host layers from the size of ASA molecules. The resulting *d*-spacing of the present samples is smaller than that (0.86 nm) synthesized by a reconstruction method (Aisawa et al., 2007). This difference may be attributed to the difference of the amount of intercalated ASA molecules because configuration of ASA molecules is possible to lying to the host layers in the low amount of ASA in the interlayers but they have to have higher lift-off angle to the host layers with higher intercalated ASA amount, increasing the interlayer spacing. The FTIR spectra of the ASA-LDH samples are shown in Fig. 2 together with ASA and CO_3-LDH. With comparison of the reference samples and assignment of absorption bands by Aisawa et al. (2007), the weak band in the ASA-LDH samples

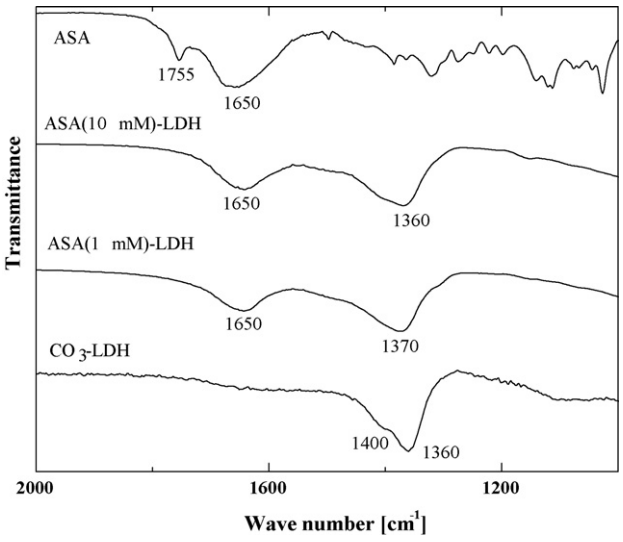

Fig. 2. FTIR spectra of the synthesized CO_3-LDH, ASA-LDHs synthesized by an ion-exchange method using 1 and 10 mM ASA solutions and ASA.

at ≈1650 cm^{-1} is assigned to the stretching of C=O and C—O—C bonds of ASA while the stronger band at ≈1375 cm^{-1} is that of C—O bonds of interlayered CO_3^{2-} ions. The ASA-LDH samples are indicated to maintain the original CO_3^{2-} ions in the interlayers largely and less amount of intercalated ASA molecules. This suggests that ion-exchange of ASA for CO_3^{2-} ions in the interlayers of LDHs is difficult to process by this method.

The ASA-LDH samples synthesized by a coprecipitation method were characterized similarly by XRD and FTIR. The obtained results are, however, very similar with those obtained in the samples synthesized by the ion-exchange method. Thus, this method is also concluded to be inadequate to synthesize the target ASA-LDH compound.

In the reconstruction method, the XRD patterns of the ASA-LDH samples synthesized in 1, 10 and 100 mM ASA solution are shown in Fig. 3. Although the (0 0 3) reflection of the sample in 1 mM was very similar with those of the ion-exchange method showing *d* = 0.78 nm, that in 10 mM shifted further lower angle and the *d*-spacing was 0.86 nm, being same value with Aisawa et al. (2007). This is because the amount of ASA in the 1 mM solution was only 15% of the stoichiometric amount for the interlayers while that in the 10 mM solution corresponded to 1.5 times. Increasing of amount of the intercalated ASA in the 10 mM sample is also confirmed from the FTIR spectra shown in Fig. 4. Compared with the spectrum of the 1 mM sample, the FTIR spectrum of the 10 mM sample shows lowering of absorption band at 1375 cm^{-1} assigned as interlayer CO_3^{2-} ions whereas strengthening of absorption band at 1600 cm^{-1} assigned as ASA. Thus, targeted ASA-LDH is considered to be synthesized by the reconstruction method. The XRD reflections are, however, considerably broadened by the intercalation and less ordered state. This becomes more evident with higher concentration of ASA in the solutions and almost no basal reflections are observed in the 100 mM sample.

The ASA contents in the samples analyzed by CHN method are listed in Table 1. Since the total amount of ASA in the 1 mM solution corresponds to be 8.2 mass% of the sample, all the ASA is thought to be taken into the sample. However, as mentioned above, the ASA in the 1 mM samples is not intercalated largely into the interlayers of LDH. Thus, larger extent of ASA in the samples is adsorbed on the surfaces of LDH particles. By contrast, the maximum amount of ASA possible to intercalate into the interlayers of LDH is 39 mass% when the concentration of ASA in the solution is higher than 6.7 mM. The content of ASA in the 10 mM samples was about 19 mass% and

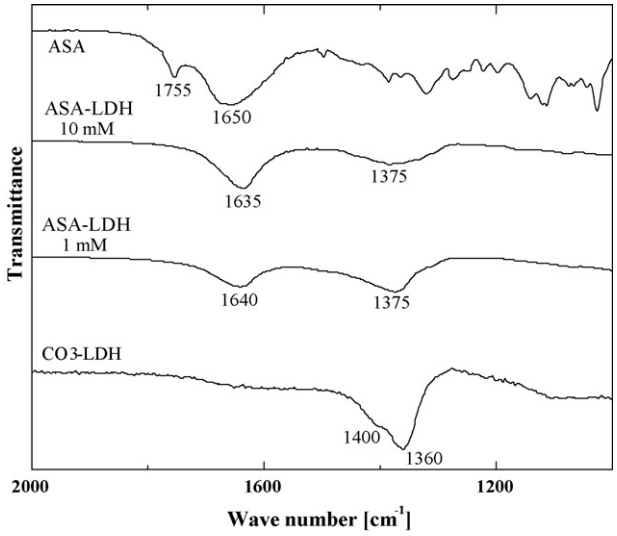

Fig. 4. FTIR spectra of the synthesized CO_3-LDH, ASA-LDHs synthesized by a reconstruction method using 1 and 10 mM ASA solutions (duration = 72 h) and ASA.

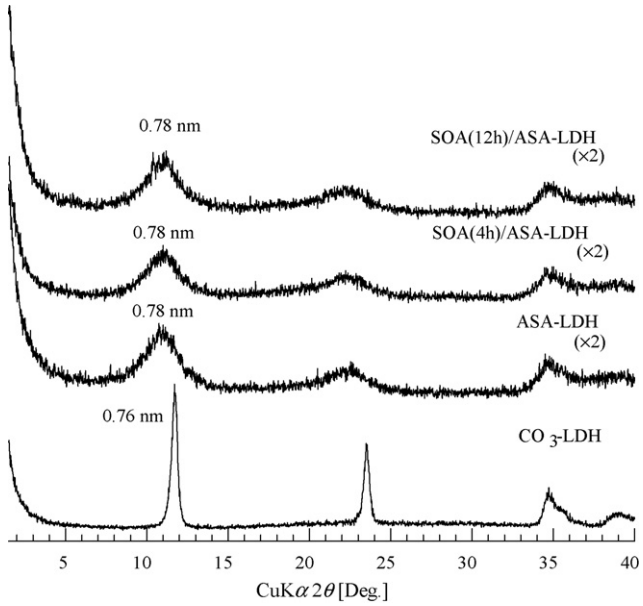

Fig. 5. XRD patterns of the synthesized CO_3-LDH, ASA-LDH, and SOA/ASA-LDH synthesized by ion-exchange for 4 h and 12 h.

this corresponds to about 50% of the stoichiometric amount of ASA in the interlayers. In the 100 mM samples, the saturated content of ASA was about 28 mass% and much higher than those in the 10 mM samples. The ASA contents in these samples are considered to be not all into the interlayers but also adsorbed on the surfaces of the LDH particles. It is, however, very difficult to evaluate their ratios properly. Since the resulting maximum content of ASA in the samples is considerably high, it is possible to intake necessary amount of vitamin C per day from a 350 mg pellet of the present sample.

3.2. SOA/ASA-LDH composites

The state of oleic acid (OA) after the preparation of composites was examined from their XRD patterns (Fig. 5) and FTIR spectra (Fig. 6). XRD patterns of CO_3-LDH, ASA-LDH and SOA/ASA-LDHs are shown in Fig. 5. No clear changes were observed between those of ASA-LDH (Fig. 5(b)) and SOA/ASA-LDHs (Fig. 5(c) and (d)). This is because the SOA molecules taken into the samples were adsorbed on the surfaces of LDH particles and not exchanged with the interlayer ASA. This was confirmed from the analysis of the concentration of ASA after the experiments because the ASA concentration in the solution was only 1% of the intercalated ASA. Presence of SOA in the samples was confirmed by the FTIR spectra shown in Fig. 6. No changes were observed in the absorption bands of ASA at 1635 cm^{-1} and CO_3^{2-} ion at 1375 cm^{-1} in the interlayers before and after the ion-exchange experiment as expected from the XRD patterns. By contrast, new bands assigned to SOA were observed at around 2900–3000 cm^{-1} and 1560 cm^{-1} in the SOA/ASA-LDH samples. Detection of absorption band at 1560 cm^{-1} assigned as —COONa and no band at 1730 cm^{-1} assigned as —COO— group reveals that the OA in the composites is suggested to adsorb on the surfaces of the Mg–Al–ASA-LDH particles as SOA and not OA molecules. The amounts of adsorbed SOA molecules increased as 26, 79 and 92 mol/mol-Al^{3+} of LDH with increasing SOA concentration in the solutions as 1, 5 and 10 mM, respectively. Since these adsorbed amounts are very high, they are suggested to form multilayers and/or micelles.

Table 1
ASA contents [mass%] in the samples.

ASA concentration [mM]	Reaction time [h]		
	4	24	48
1	5.4	0	5
10	5.4	27	31
100	3.6	17	58

3.3. Acid-resistant test

Releasing of ASA from the powder samples was investigated using HCl solution and the results are shown in Fig. 7 for mixed powder of LDH and ASA, ASA-LDH and SOA/ASA-LDH composites (4 and 12 h). The ASA in the mixed powder sample dissolved completely within 2 min and all the ASA was released into the solution. The ASA-LDH powder sample showed slightly slower the ASA releasing owing to the capsulating of ASA into the interlayers of the LDH structure. However, the retarding effect was very limited due to the poor chemical durability of the host LDH. By contrast, the composite samples showed an apparent retarding effect by the

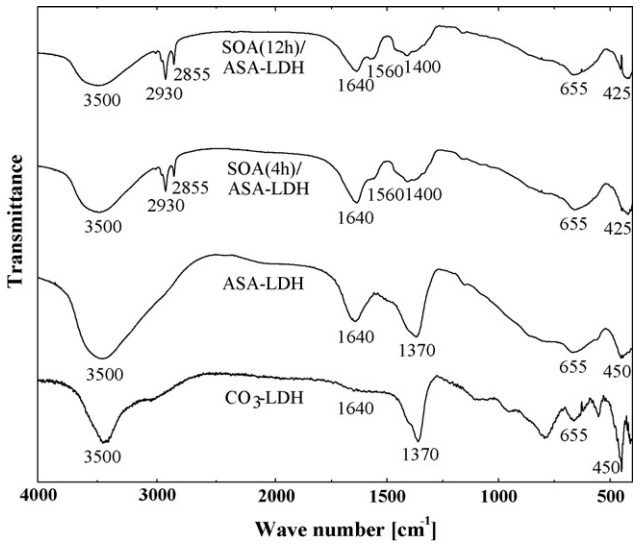

Fig. 6. FTIR spectra of the synthesized CO_3-LDH, ASA-LDH, and SOA/ASA-LDH synthesized by ion-exchange fro 4 h and 12 h.

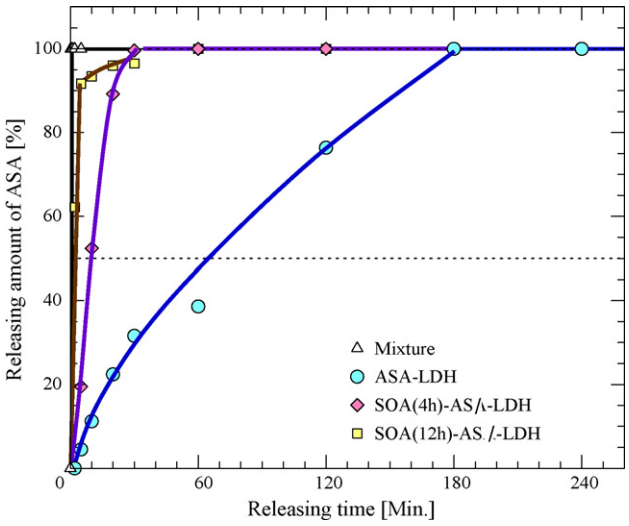

Fig. 7. Releasing of ASA from various powder samples in HCl solution.

surface coating of SOA molecules. Although the composite (4 h) released about 50% of ASA by 10 min of reaction time, the composite (12 h) showed higher retarding effect and released only about 40% of ASA by 60 min. This difference is attributed to the increase of adsorbed amount of OA molecules in this composite. Since necessary time for foods intake from the mouse pass through the stomach is generally about 3–4 h, the retarding effect of ASA releasing by the composite (12 h) powder is still insufficient to leach to the intestine, these composite powders have a role of controlled ASA release effect.

In order to enhance retarding effect of the composite sample (12 h), the powder was formed to pellets with different weights 20, 30 and 50 mg. Releasing of ASA from those pellet samples is shown in Fig. 8. Their releasing rates were almost same up to about 50% of the ASA release but differed above 50%. The releasing occurred linearly in the 20 mg pellet sample and the ASA was completely released after 210 min. The half life time of ASA releasing (120 min) is longer than the powder sample. The 30 and 50 mg pellet samples showed retarding of ASA releasing than the 20 mg sample and the life times for complete releasing became longer as 300 and 600 min, respectively. Thus, the palletized samples with weight ≥30 mg have suitable ASA releasing property for drug delivery to the intestines.

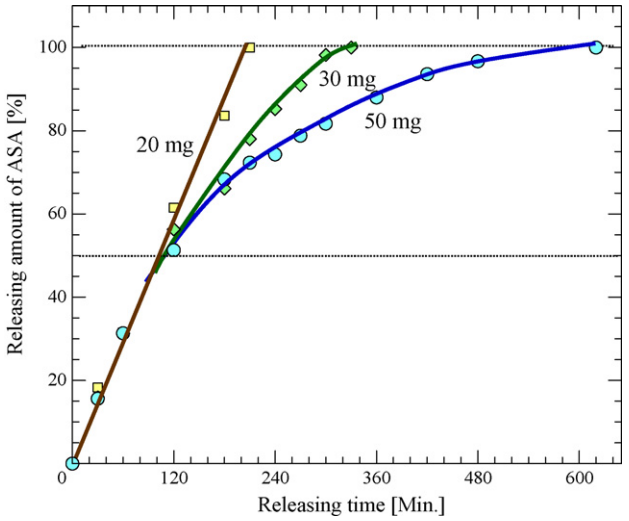

Fig. 8. Releasing of ASA from pellet samples in simulated gastric juice (SGJ).

4. Conclusion

Composites with sodium oleate (SOA) surface coated Mg–Al-ascorbic acid (ASA)-layered double hydroxides (ASA-LDHs) with Mg/Al = 3 were prepared by an ion-exchange method. The following results were obtained.

(1) Mg–Al-ascorbic acid (ASA)-layered double hydroxides (ASA-LDHs) with Mg/Al = 3 were synthesized by ion-exchange, coprecipitation and reconstruction methods. The basal spacings were 0.78 and 0.86 nm, corresponding to mono and double layers of ASA in the LDH interlayers, respectively. The amounts of ASA in the LDHs were higher in the reconstruction method than those in the ion-exchange and coprecipitation methods. The maximum amount of sorbed ASA ions was about 30 mass% and this corresponds to the amount necessary for intake of vitamin C (100 mg/day) from an ASA-LDH pellet in the weight 350 mg.
(2) In the preparation of composites of SOA/ASA-LDH, an ion-exchange method was more suitable than a reconstruction method to form surface coating of the SOA molecules with maintaining intercalated ASA ions in the LDH interlayers.
(3) The acid-resistant properties of the composites of SOA/ASA-LDH were found to be much higher than for the pure ASA-LDH and mixture of CO_3-LDH and ASA. The palletized samples with weight ≥30 mg have more suitable ASA releasing property for drug delivery to the intestines than powder samples.

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