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Synthesis and Controlled Release of Vitamin C Intercalated Zn/Al Layered Double Hydroxide

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A drug-inorganic composite involving vitamin C intercalated in Zn-Al layered double hydroxides has been synthesized by a coprecipitation method. Powder X-ray diffraction, fourier transform infrared, elemental analysis, thermogravimetric analysis and UV-visible absorption spectroscopy indicate a successful intercalation of vitamin C into the interlayer galleries of the layered double hydroxides host and the loading of vitamin C in the layered double hydroxides is 84 %. Studies of vitamin C release from the layered double hydroxides in deionized water and in aqueous CO_3^{2-} solutions imply that Zn_2Al-vitamin-C layered double hydroxides is a better controlled release system. Analysis of the release profiles using a number of kinetic models suggests a solution-dependent release mechanism and a combination process of diffusion-controlled and ion exchange deintercalation mechanisms in deionised water, but an ion exchange process in CO_3^{2-} solution.

Keywords: Layered double hydroxide, Controlled release, Vitamin C, Coprecipitation.

INTRODUCTION

Layered double hydroxides (LDHs) are a family of natural and synthetic compounds having a general formula of $[M_{1-x}M'_x(OH)_2](A^{n-})_{x/n}\cdot mH_2O$ (abbreviated as $M_{1-x}M'_x$-A), where M and M' represent divalent and trivalent metal ions, respectively and A^{n-} is the anion between the layers. They consist positively charged hydrotalcite-like layers of metal hydroxide and the interlayer region typically occupied by anionic species and water molecules. Layered double hydroxides can be prepared in laboratory using a range of different techniques, for example coprecipitation[1], anion exchange[2] and reconstruction[3]. Layered double hydroxides are well known for their anionic exchange properties and their stable structure, so have been extensively studied in many fields[4-7].

Recently, layered double hydroxides as biocompatible inorganic materials, are being concentrated on the intercalation of some drugs[8-11] anions into layered double hydroxides interlayer space. These guest species are stablized with respect to heat and light upon intercalation. Furthermore, the resultant nanocomposites can act as reservoirs for the biomolecules, releasing them in a controlled manner under approperiate conditions and have potential pharmaceutical applications.

L-Ascorbic acid (vitamin C), a water soluble vitamin, has a variety of biological, pharmaceutical and dermatological functions[12,13]. Vitamin C, however, is very unstable to air, moisture, light, heat, metal ions and base, resulting in decomposition to biologically inactive compounds[14]. To prevent the decomposition of vitamin C, delivering it to a specific location is very important. On the other hand, human body requires only a very small amount of vitamin C for physiological functions. Both insufficient and excessive supplies of vitamins cause harmful effects on human body[15]. Therefore, a drug delivery and controlled release system is a more sophisticated drug administration method designed to overcome such problems. layered double hydroxides are such kind of materials to store drugs and then slowly release them in order to maintain drug concentrations at the desired levels for a longer period of time.

Several studies describing the synthesis and controlled release of vitamin C in a few layered double hydroxides have been reported[16-18]. However, the amounts of vitamin C intercalated and then subsequently released are still not high enough. Moreover, the release mechanism of vitamin C from layered double hydroxides host was not described carefully. In this paper, we report the synthesis of a layered double hydroxide material, ZnAl-vitamin-C layered double hydroxides, using the coprecipitation method. Furthermore, the release kinetics of vitamin C was investigated.

EXPERIMENTAL

The ascorbic acid, sodium ascorbate and other inorganic reagents were purchased from Sigma-Aldrich and used without further purification.

Preparation of NO_3-LDH host: The NO_3-LDH (Zn_2Al-NO_3) was synthesized by a standard coprecipitation method for comparing with vitamin-C-layered double hydroxide product. A base solution was prepared by dissolving 9.6 g of NaOH and $NaNO_3$ in 150 mL of deionized water. This solution was then added dropwise to 200 mL of a mixed salt solution prepared by dissolving 23.8 g of $Zn(NO_3)_2{\cdot}6H_2O$ and 15 g of $Al(NO_3)_3{\cdot}9H_2O$ under flowing N_2 (to prevent the formation of the carbonate intercalation). A suspension was formed and stirred vigorously at 80 ºC for 24 h. The product was filtered, washed with deionised water to remove any precursor impurities and with a small amount of acetone to facilitate drying and then dried at 60 ºC for 24h.

Preparation of vitamin-C-layered double hydroxide intercalation compound: Analogously, the vitamin C intercalation product (Zn_2Al-vitamin-C LDH) was prepared by the coprecipitation method. A base solution was prepared by dissolving 0.72 g of NaOH and 2.38 g of $C_6H_7O_6Na$ (containing a fourfold excess of the vitamin C anion) in 100 mL of deionized water. This solution was then added dropwise to 100 mL of a mixed salt solution prepared by dissolving 1.79 g of $Zn(NO_3)_2{\cdot}6H_2O$ and 1.13 g of $Al(NO_3)_3{\cdot}9H_2O$ under flowing N_2. Again, aluminium foil was used to limit the photo-degradation of the vitamin C solution. The solution was stirred vigorously at room temperature (about 15 ºC) for 120 h, then filtered, washed and dried as described above. The product Zn_2Al-vitamin-C LDH is pale yellow solid.

***in vitro* Release studies:** 0.1 g of the vitamin-C-LDH composite was added to 50 mL of either deionised water, or the carbonate solutions with different concentration (0.1 M and 0.01 M) and stirred at room temperature (about 15 ºC). After the appropriate time, the suspension was filtered and the concentration of released vitamin C in the filtrate quantified using the UV-visible spectrophotometer at 265 nm, corresponding to the typical absorption peak of vitamin C and the solid product after releasing of vitamin C from vitamin-C-LDH was collected for further analysis of structure and composition.

Characterization: Carbon, hydrogen and nitrogen analyses were carried out by a Carlo Erba EA1108 Elemental Analyzer and metals analysis by Fisons Horizon Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES). X-ray powder diffraction (XRD) patterns were recorded using a PA Nalytical X'pert Pro diffractometer, fitted with a solid state X'Celerator detector. All the FTIR spectra were recorded on a Bio-Rad FTS 6000 FTIR Spectrometer equipped with a DuraSamplIR II diamond accessory in the range of 700-4000 cm^{-1}. The absorption in the range 2300-1850 cm^{-1} is from the DuraSamplIR II diamond surface. Thermogravimetric analysis was carried out using a Rhoemetric Scientific STA-1500H between room temperature and 800 ºC at a rate of 10 ºC min^{-1} under a flowing stream of argon. UV-visible absorption spectroscopy was used to determine the concentration of vitamin C on a T60U PG Instruments UV-visible spectrophotometer using wavelength scan mode and quartz cuvettes. The wavelength range used was from 190 to 400 nm.

RESULTS AND DISCUSSION

The XRD patterns of Zn_2Al-NO_3 and Zn_2Al-vitamin-C LDHs are shown in Fig. 1a. The NO_3-LDH exhibits a series of obvious Bragg reflections (00l; l = 3, 6) and the basal spacing is 8.8 Å, which is in good agreement with that of hydrotalcite[19]. In the pattern of the intercalation compound vitamin-C-LDH, it is found that the (003) and (006) Bragg reflection shift to lower angles and become a little broader and weaker, implying that the intercalation vitamin C decreases the crystallinity of layered double hydroxides. The XRD patterns of solid products after releasing of vitamin C from Zn_2Al-vitamin-C LDH in 0.01 M and 0.1 M sodium carbonate are shown in Fig. 1b. The typical CO_3-LDH characteristic diffraction peaks are present and the basal spacing is 7.6 Å, which proves that a large amount of vitamin C anions between the layers have been exchanged by CO_3^{2-} anions.

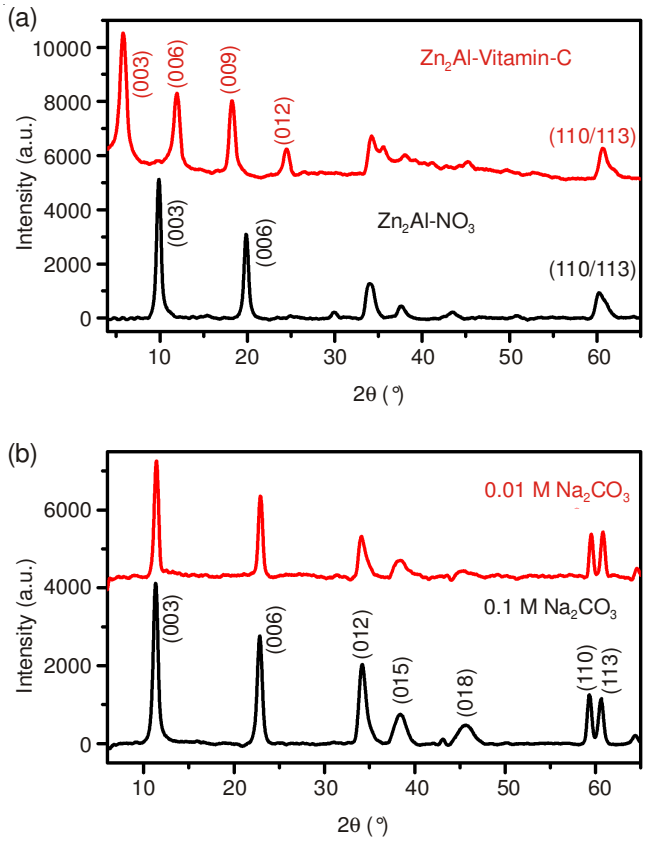

Fig. 1. XRD patterns of (a) Zn_2Al-NO_3 and Zn_2Al-vitamin-C and (b) solid products after releasing of vitamin C from Zn_2Al-vitamin-C in 0.01 M and 0.1 M sodium carbonate, respectively

The basal spacing of Zn_2Al-vitamin-C LDH is calculated to be 15 Å from the d_{003}-spacing, subtracting the inorganic layer thickness (4.8 Å)[20], the interlayer distance is 10.2 Å. The length and cross-sectional area of the ascorbate anion have been determined to be 4.9 Å and 21.6 $Å^2$, respectively[21]. We speculated that for Zn_2Al-vitamin-C, an interdigitated bilayer of anion vitamin C perpendicular to the metal hydroxide layers is adopted (the terminal hydroxyl group hydrogen bonded to the basal layer); meanwhile, some water molecules are also present between the layers. The schemes of NO_3-LDH and vitamin-C-LDH are shown in Fig. 2.

The vitamin C contents in the Zn_2Al-vitamin-C and solid products after releasing vitamin C in 0.1 M and 0.01 M Na_2CO_3 solutions were tested by ICP and CHN elemental analysis

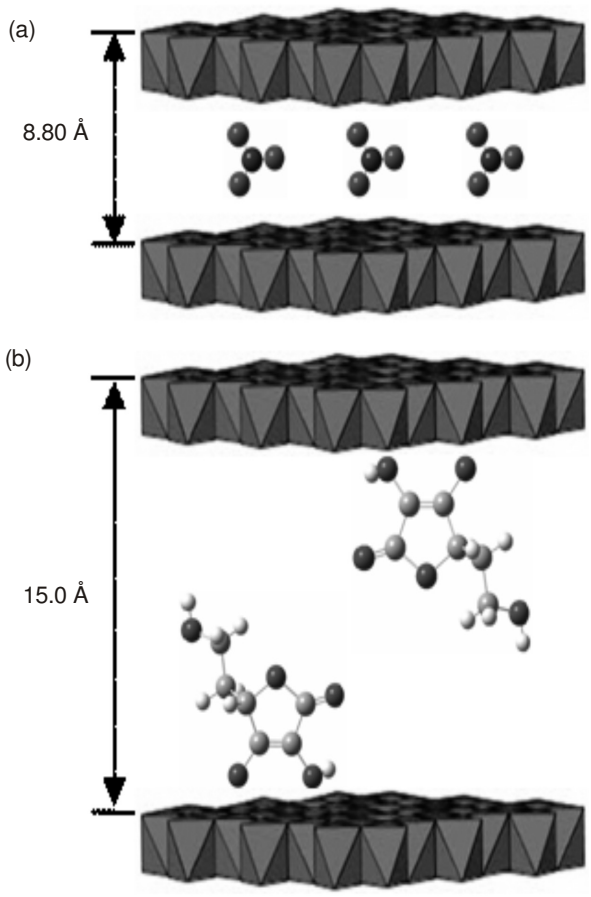

Fig. 2. Schematic illustrations of Zn_2Al-NO_3 (a) and Zn_2Al-vitamin-C (b)

(Table-1). The loading of vitamin C intercalated in the interlayer of layered double hydroxides is 84 % for Zn_2Al-vitamin-C, which is higher than those in previous reports[16,18]. It is found that in the two solid products obtained after releasing vitamin C, a large amounts of vitamin C anions have been deintercalated by CO_3^{2-} anions, but a small amount of vitamin C anions are still present.

Fourier transform infrared: Fig. 3 shows the FTIR spectra used to verify the intercalation of the vitamin C anion into the layered double hydroxides host. The vitamin-C-LDH spectrum is compared with that of sodium ascorbate. The broad peak centered at about 3400 cm^{-1} is characteristic of all layered double hydroxides and arises from the ν_{OH} absorptions of the co-intercalated water molecules. Absorptions occurring below 1000 cm^{-1} are associated with metal-oxygen vibrations within the hydroxide layers. In the spectrum of solid sodium ascorbate (Fig. 3a), the peaks relating to O-H and C-O bonds stretches are found in the expected regions. The absorption at about 1380 cm^{-1} can be assigned to the stretching vibration of NO_3^- as shown in Fig. 3b. For vitamin-C-LDH spectrum, considering that ν(C=O) for sodium ascorbate appears at 1704 cm^{-1} (Fig. 3a), 1717 cm^{-1} absorbance peak in Fig. 3c shows very weak absorption. The 1614 cm^{-1} band seems to comprise overlapping water bending and ν(C=C) modes (based on ν(C=C) for sodium ascorbate at 1579 cm^{-1} in Fig. 3a). The absorptions occurring at 1388 cm^{-1} corresponds to vibrations within the lactone linkage (C-O-C)[18], which shifted to slightly higher wavenumbers (in contrast to the absorption at 1347 cm^{-1} in Fig. 3a) possibly due to weakening of intramolecular H-bonds upon intercalation, are present in Zn_2Al-vitamin-C. Meanwhile, the absorptions around 1185-1000 cm^{-1} corresponding to the C-O stretch vibrations are also present in Fig. 3c. The FTIR data likewise confirm the vitamin C anion has been intercalated in the interlayer.

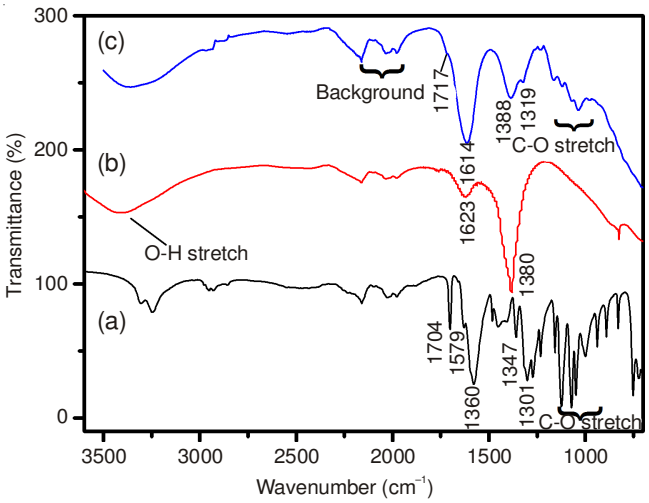

Fig. 3. FTIR spectra of sodium ascorbate (a) Zn_2Al-NO_3 (b) and Zn_2Al-vitamin-C (c)

Thermogravimetric analysis: The intercalation product and sodium ascorbate were analyzed by TGA and DTG to determine the intercalated water content and the decomposition temperature of vitamin C. The TGA straight lines, for the Zn_2Al-vitamin-C (a) and sodium ascorbate (b), are shown in Fig. 4. The intercalation compound decomposes by the well-established route observed for most layered double hydroxides intercalated with organic molecules. In the first step, the cointercalated water is lost at temperatures up to 120 °C, leaving a dehydrated layered double hydroxides (calculated loss 6.88 %, observed loss 7.10 %). This is then followed by the loss of water from the hydroxide layers (calculated loss 13.4 %, observed loss 13.9 %) and the decomposition of the vitamin C anion in consecutive steps from around 346 °C onwards, is a combination of the further decomposition of the guest including vitamin C and NO_3^-, resulting in a final product that is a mixture of zinc and aluminium oxide[22] and carbon soot (calcd. 32.7, obsvd. 32.3 %).

TABLE-1
COMPOSITION AND CHEMICAL FORMULAS OF Zn_2Al-VITAMIN-C LDH (A), SOLID PRODUCTS AFTER RELEASING VITAMIN-C FROM Zn_2Al-VITAMIN-C LDH IN 0.1 M (B) AND 0.01 M (C) Na_2CO_3 SOLUTIONS

Solid product	Solid chemical formula	Elemental analysis, wt (%)				
		Zn	Al	C	H	N
A	$Zn_{2.08}Al(OH)_{6.16}[(C_6H_7O_6)_{0.84}(NO_3)_{0.16}]\cdot 1.74H_2O$	29.6	5.90	13.5	3.44	0.500
B	$Zn_{2.08}Al(OH)_{6.16}[(C_6H_7O_6)_{0.12}(NO_3)_{0.08}(CO_3)_{0.40}]\cdot 1.65H_2O$	39.1	7.80	3.88	2.95	0.321
C	$Zn_{2.08}Al(OH)_{6.16}[(C_6H_7O_6)_{0.18}(NO_3)_{0.08}(CO_3)_{0.37}]\cdot 1.62H_2O$	38.2	7.60	4.92	3.00	0.314

In addition, from the DTG data (dash lines in Fig. 4a and b), the decomposition of intercalated vitamin C occurs at elevated temperatures. The strong decomposition temperatures correspond to 232 °C and 440 °C for sodium ascorbate and Zn_2Al-vitamin-C, respectively. It implies that intercalating vitamin C in the layered double hydroxides can improve the thermal stability of vitamin C.

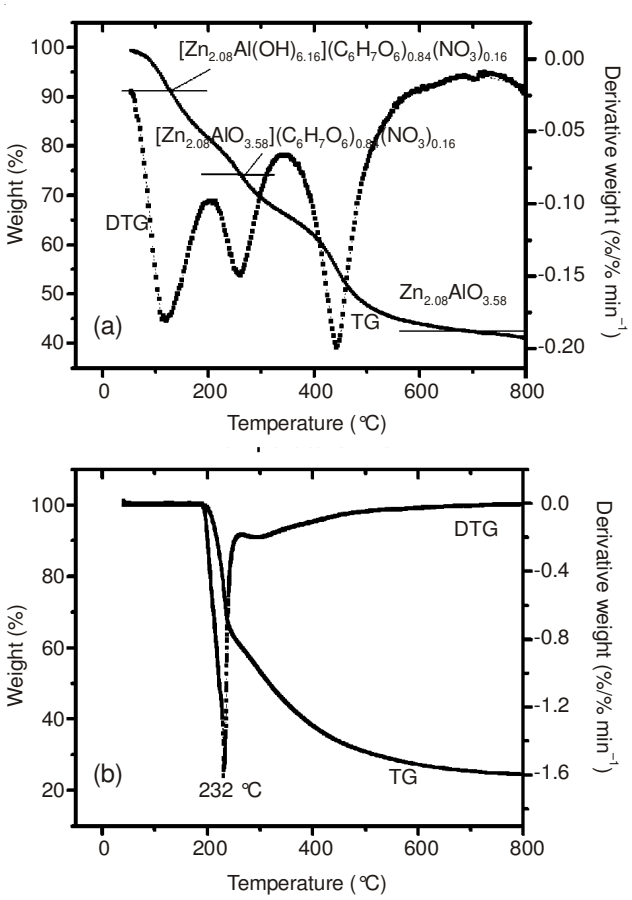

Fig. 4. TG-DTG plots of Zn_2Al-vitamin-C (a) and sodium ascorbate (b)

Controlled release data: Deintercalation of the vitamin-C-LDH hybrid was carried out in deionised water and Na_2CO_3 aqueous solutions at two different concentrations (0.1 M and 0.01 M) for time intervals of up to 420 min. After the required time interval, the products were filtered. Then, the UV-visible absorption spectra of the filtrates collected were tested. The concentrations (wt %) of deintercalated vitamin C were estimated by the characteristic absorption peaks at 265 nm in the UV-visible spectra of vitamin C, respectively. The amount of deintercalated vitamin C plotted with reaction time is depicted in Fig. 5.

Similar to the release of other drugs from pillared layered double hydroxides[8], the rapid release of the intercalated material during the initial stage is followed by a slow release of some or all of remaining drug. But for the different deinter-calation medium, the rate and amount of vitamin C released are different. The release processes in CO_3^{2-} solutions are uniformly found to lead to greater release after 420 min than the corresponding reactions in deionised water, which is consistent with previously observed data on the release of some drugs from a hydrotalcite-like compound[23]. The maximum amounts of released

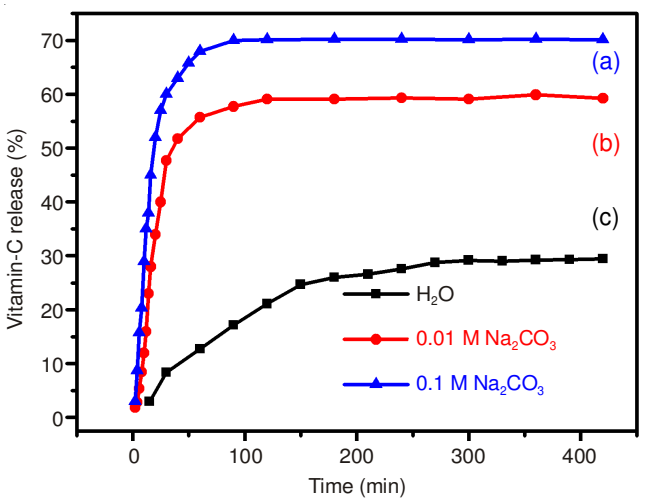

Fig. 5. Release profiles between 0 and 420 min of Zn_2Al-vitamin-C in (a) 0.1 M CO_3^{2-} solution (b) 0.01 M CO_3^{2-} solution (c) deionized water

vitamin C in 0.1 M, 0.01 M Na_2CO_3 solutions and deionized water are 70.5, 59.5 and 29.8 % of the total when the release time attains 90, 120 and 300 min, respectively. Combining with above vitamin C intercalation amount of 84 % in Zn_2Al-vitamin-C, the amount of vitamin C released for Zn_2Al-vitamin-C is nearly 60 % compared to the theoretical value (100 %), which is higher than the previously published data[16-18]. The rate of drug diffusion out of the matrix is controlled by the rigidity of the layers and the diffusion path length[8]. The cause of the partial release of vitamin C from layered double hydroxides may be attributed to the possibility that the drug molecules are deeply embedded in the layered double hydroxides host and complete release is difficult.

Kinetic analysis: In order to gain more insight into the kinetics of the release, we applied five commonly used models to the release curves. Models used are the Avrami-Erofe'ev equation, Elovich model, modified Freundlich equation, first order model and parabolic diffusion model[24-28]. Their mathematical forms are given in Table-2. In each model, Fits of the models to the experimental release data in initial release stage (within 16 min in sodium carbonate and 150 min in deionized water, respectively) are shown in Fig. 6.

TABLE 2
KINETIC MODELS USED TO ANALYSE VITAMIN C RELEASE*

Model	Equation
Avrami–Erofe'ev	$\ln(-\ln(C_t/C_0)) = n\ln(k_d) + n\ln(t-t_0)$
Elovich	$1-C_t/C_0 = a\ln(t-t_0) + b$
Freundlich	$\ln(1-C_t/C_0) = \ln(k_d) + a\ln(t-t_0)$
First-order	$\ln(C_t/C_0) = -k_d(t-t_0)$
Parabolic diffusion	$(1-C_t/C_0)/t = k_d(t-t_0)^{(-0.5)} + a$

*C_0 is the amount of guest vitamin C in the vitamin-C–LDH at t = 0, C_t is the amount of guest vitamin C in the vitamin-C–LDH at time t, and k_d is the rate of release. a, b and n are constants

It can be seen from Fig. 6 that all models can be used to describe the kinetic of release of vitamin C except for the parabolic diffusion model. In these models, according to the R^2 values and visual inspection of these "linear" plots, it appears that the first-order rate model and Avrami-Erofe'ev model are the more appropriate for describing release of vitamin C. The

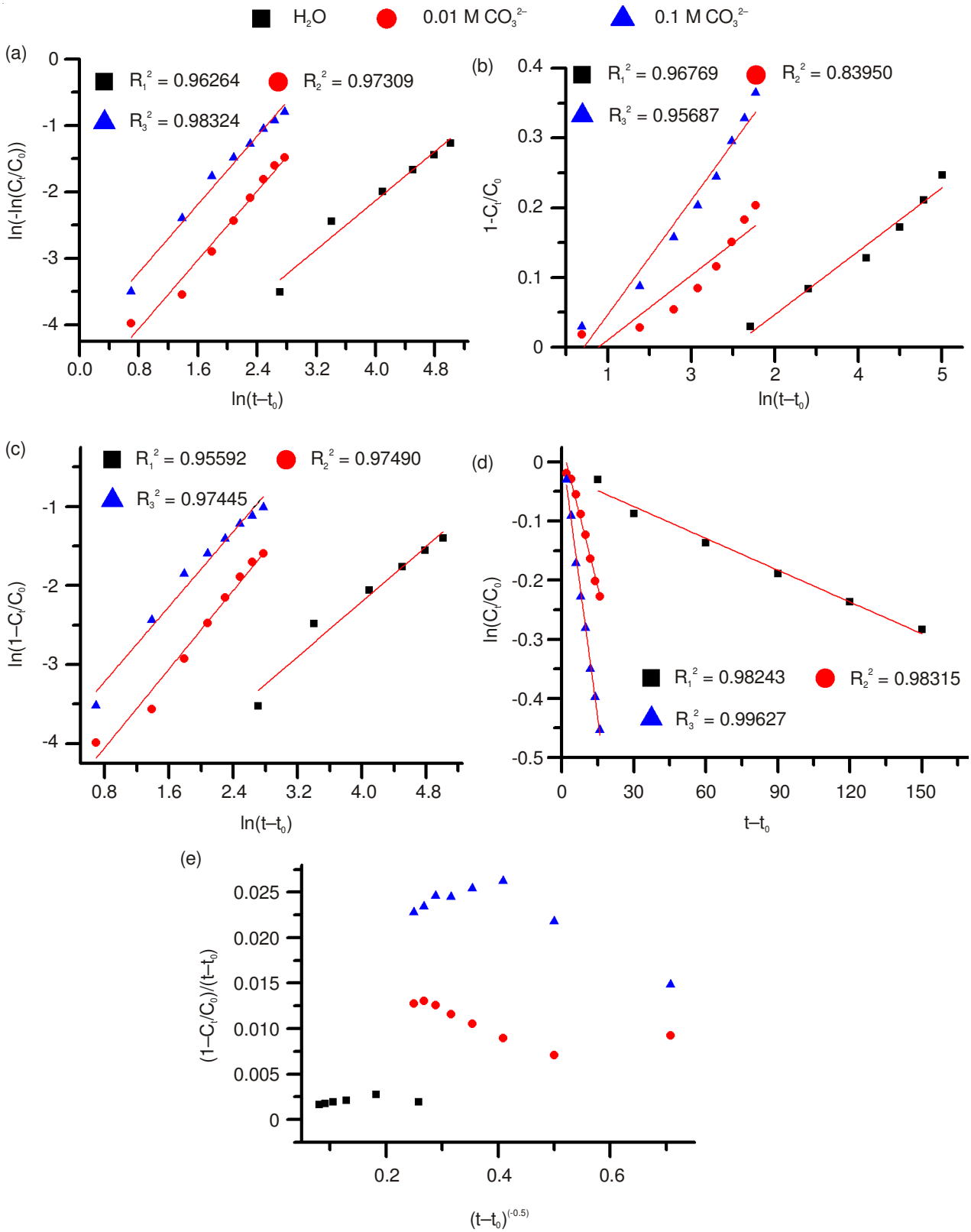

Fig. 6. Linear fitting of various models to the release of vitamin C from Zn_2Al-vitamin-C in 0.1 M sodium carbonate, 0.01 M sodium carbonate and deionized water. Fits for (a) the Avrami-Erofe'ev model, (b) the Elovich model, (c) the freundlich model, (d) the First-Order model and (e) the parabolic diffusion model, are shown

first order model describes a system where release is dependent on the dissolution of the host material and the Avrami-Erofe'ev model describes release in terms of the formation and expansion of nucleation sites. In order to gain more insight into the mechanisms involved in guest release, the reaction exponent (n) from the Avrami-Erofe'ev data is possibly valuable. In the Avrami-Erofe'ev model, the values of n may be determined from the slope of the fitted plots. Usually, n is close to zero or

one, with zero representing instantaneous nucleation. However, the final value may also represent more than one possible mechanism, the identity of which may not be easily determined.

The values of n in deionised water for Zn_2Al-vitamin-C is 0.9, which corresponds to the combination of diffusion control and ion exchange with residual CO_3^{2-} ions in the water, or simultaneous leaching of the guest anions and cations from the layered double hydroxides matrix. In contrast, the process in sodium carbonate seems to be dominated by a direct ion-exchange route because the values of n are 1.29 and 1.28, respectively. It is likely that the presence of significant amounts of replacement anions in the carbonate solution lead to ion exchange being the predominant release mechanism. For the functional guests to be released *via* this mechanism requires the replacement anions to move to the edges of the layers and then force the functional guests out (hence, nucleation control). This release route is barely available in deionized water and release will occur by slow leaching of anions and cations from the layered double hydroxides lattice. The rate of this leaching will be determined by the speed at which the ions diffuse out of the layered double hydroxides matrix, giving diffusion control.

Conclusion

Vitamin C anions can be intercalated successfully in the interlayer of Zn-Al LDH, which has no effect on the hydroxide lattice of layered double hydroxides. Both of the loading and release amount of vitamin C are higher than those previous results. The first-order rate and Avrami-Erofe'ev models provide the better fit for the release results. The diffusion-controlled and ion exchange deintercalation mechanisms in deionized water, changes to an ion exchange process in CO_3^{2-} solution. Zn-Al LDH can not only protect vitamin C against decomposition, but release of intercalated vitamin C can be intentionally triggered and so, they have potential applications as pharmaceutical materials.

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REFERENCES

1. X.R. Gao, L.X. Lei, C.G. Lv, Y.M. Sun, H.G. Zheng and Y.P. Cui, *J. Solid State Chem.*, **181**, 1776 (2008).
2. X.R. Gao, M. Hu, L.X. Lei, D. O'Hare, C. Markland, Y.M. Sun and S. Faulkner, *Chem. Commun.*, **47**, 2104 (2011).
3. R.J. Lu, X. Xu, J.P. Chang, Y. Zhu, S.L. Xu and F.Z. Zhang, *Appl. Catal. B*, **111**, 389 (2012).
4. C.X. Chen, Y.C. Hou, B. Li and W.Z. Yi, *Asian J. Chem.*, **25**, 3167 (2013).
5. X.L. Liu, Q. Wang, D.G. Geng, M. Wei and X. Duan, *Asian J. Chem.*, **24**, 101 (2012).
6. H. Saikia and J.N. Ganguli, *Asian J. Chem.*, **24**, 5909 (2012).
7. Y. Yasin, N.M. Ismail and F. Ahmad, *Asian J. Chem.*, **25**, 3328 (2013).
8. V. Ambrogi, G. Fardella, G. Grandolini and L. Perioli, *Int. J. Pharm.*, **220**, 23 (2001).
9. M. del Arco, A. Fernandez, C. Martin and V. Rives, *J. Solid State Chem.*, **183**, 3002 (2010).
10. L. Dong, L. Yan, W.-G. Hou and S.-J. Liu, *J. Solid State Chem.*, **183**, 1811 (2010).
11. F. Kovanda, Z. Maryskova and P. Kovar, *J. Solid State Chem.*, **184**, 3329 (2011).
12. J. Aguilera, M.V. de Galvez, C. Sanchez and E. Herrera-Ceballos, *J. Dermatol. Sci.*, **66**, 216 (2012).
13. E. Chikvaidze and I. Khachatryan, *Int. J. Cosmet. Sci.*, **33**, 322 (2011).
14. E. Shimoni, *J. Food Sci.*, **69**, R160 (2004).
15. K. Bangash, F. Shigri, A. Jamal and K. Anwar, *Int. J. Pathol.*, **9**, 63 (2011).
16. J.H. Choy and Y.H. Son, *Bull. Korean Chem. Soc.*, **25**, 122 (2004).
17. M.S. Gasser, *Colloids Surf. B*, **73**, 103 (2009).
18. Y. Kameshima, H. Sasaki, T. Isobe, A. Nakajima and K. Okada, *Int. J. Pharm.*, **381**, 34 (2009).
19. E. Kanezaki, *J. Incl. Phenom. Macrocycl. Chem.*, **36**, 447 (2000).
20. F. Cavani, F. Trifiro and A. Vaccari, *Catal. Today*, **11**, 173 (1991).
21. S. Aisawa, N. Higashiyama, S. Takahashi, H. Hirahara, D. Ikematsu, H. Kondo, H. Nakayama and E. Narita, *Appl. Clay Sci.*, **35**, 146 (2007).
22. V. Rives, *Mater. Chem. Phys.*, **75**, 19 (2002).
23. C. Markland, G.R. Williams and D. O'Hare, *J. Mater. Chem.*, **21**, 17896 (2011).
24. J.H. Yang, Y.S. Han, M. Park, T. Park, S.J. Hwang and J.H. Choy, *Chem. Mater.*, **19**, 2679 (2007).
25. Z.H. Li, *Langmuir*, **15**, 6438 (1999).
26. T. Kodama, Y. Harada, M. Ueda, K. Shimizu, K. Shuto and S. Komarneni, *Langmuir*, **17**, 4881 (2001).
27. J.D. Hancock and J.H. Sharp, *J. Am. Ceram. Soc.*, **55**, 74 (1972).
28. M. Avrami, *J. Chem. Phys.*, **8**, 212 (1940).