

DEVELOPMENT OF CONTROLLED DRUG RELEASE FORMULATION BASED ON PAMOATE-ZINC-ALUMINIUM-LAYERED DOUBLE HYDROXIDE NANOCOMPOSITE

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Abstract

Controlled drug release formulation of pamoate was developed by the intercalation of pamoate anion into Zn-Al-layered double hydroxide (LDH). The resulting layered organic-inorganic hybrid nanocomposite material was formed using pamoate as guest anion intercalated into the Zn-Al layered double hydroxide inorganic host by direct co-precipitation method. As a result of successful intercalation of pamoate ion into the interlayer structure of Zn-Al-LDH, an expansion of the interlayer spacing, from 8.9 Å in the layered double hydroxide to 18.1 Å in the nanocomposite (ZAP) could be observed in the powder X-ray diffractogram. The reverse process, i.e., the deintercalation or release of the guest, pamoate was found to be rapid initially, followed by a more sustained release thereafter and this behavior was dependent on the pH of the release medium, the aqueous solution. The mechanism of release has been interpreted on the basis of the ion-exchange process between the pamoate anion intercalated in the lamella host and nitrate, or hydroxyl anions in the aqueous solution. This study suggest that layered double hydroxide can be used as a carrier for drugs that allow safe and controlled delivery of various bioagents into target with high efficiency.

Keywords: controlled release, pamoate anion, layered double hydroxide, organic-inorganic hybrid

Introduction

Recently, there has been rapid expansion of the development of bioinorganic hybrid systems for safe drug delivery. Bioinorganic systems can allow safe and controlled delivery of various bioagents into targets with high efficiency. Hybrid systems for drug delivery require biocompatible inorganic matrices that permit safe retention as well as controlled delivery of drugs [1]. Among a variety of inorganic materials, layered double hydroxides (LDHs) are amongst attractive materials for the preparation of a controlled drug release formulation.

Layered double hydroxides (LDHs) commonly known as hydrotalcite-like materials or anionic clays are a family of natural and synthetic materials with general formula $[M^{2+}_{1-x}M^{3+}_x(OH)_2]^{x+}[(A^n)_{x/n}H_2O]^{x-}$ where M^{2+} is a divalent cation and M^{3+} is a trivalent cation. A^n is an interlayer anion such as CO_3^{2-} , NO_3^- , SO_4^{2-} or Cl^- . The value of mole fraction, x ($x = M^{3+}/(M^{2+} + M^{3+})$) generally lies between 0.20 and 0.33 [2]. LDHs consist of layers of M^{2+} and M^{3+} cations which are octahedrally co-ordinated by six oxygen anions, as hydroxides. These layers exist with a similar layered structure to that exhibited by natural $Mg(OH)_2$, also known as brucite. The substitution of M^{3+} cations into brucite-like hydroxide layer imparts an overall positive charge on the octahedral layer. Overall electrical neutrality is maintained by the presence of anions, which are typically CO_3^{2-} or NO_3^- , in the interlayer region between the metal hydroxide layers [3].

A variety of anionic species could be intercalated for the formation of LDH-intercalated or the so-called the host-guest type materials. The guest species enhance the interlayer distance in the LDH compounds and the thickness of the layer is determined by the ionic radius of the anion. If the anion is of a beneficial agents such as drugs or herbicides and by virtue of the ion-exchange properties of LDH, then this type of materials can be exploited as controlled release formulation. For example, intercalation of an anti-inflammatory drug such as ibuprofen [4] between LDHs is aimed to give a formulation with controlled release capability. Previous study done on the intercalation of herbicides such as 4-chlorophenoxyacetate and α -naphthaleneacetate into the interlayer structure of LDH can be used as a controlled release formulation [5,6] in agricultural industry.

In the present study, we report and discuss the formation of a new layered organic-inorganic nanohybrid material by intercalation of pamoate anion (PA), anion of imipramine, which is belong to a general class of

drugs called tricyclic antidepressants [7] into the Zn-Al-LDH by self assembly technique. Following the successful intercalation of the PA moiety into the Zn-Al-LDH inorganic lamella, we subsequently study the controlled drug release property of the resulting intercalated PA from the material into the aqueous solution at various pH values.

Experimental

All chemicals used in this synthesis were obtained from various chemical suppliers and used without any further purification. All solutions were prepared using deionized water.

The synthesis of the intercalated compound, ZAP was done by the spontaneous self-assembly method. A mother liquor containing Zn^{2+} and Al^{3+} cations with Zn/Al initial ratio ($R_i = 4$) and pamoate anion (PA) was prepared and the pH was adjusted to about pH 7. The concentration of PA was fixed at 0.02 M and the reaction was carried out with stirring under nitrogen atmosphere. The solution was aged for 18 h in an oil bath shaker at 70 °C. The resulting precipitate was centrifuged, thoroughly washed and dried in an oven at 70 °C for 3 days and kept in a sample bottle for further use and characterizations. A similar method was adopted for the preparation of Zn-Al-LDH with nitrate as the intergallery anion (ZAL) by omitting the addition of PA solution in the mother liquor.

Powder x-ray diffraction (PXRD) patterns of the samples were obtained by a Shimadzu Diffractometer XRD-6000, using filtered CuK_{α} radiation. FTIR spectra were recorded by a Perkin-Elmer 1750 Spectrophotometer. KBr pellet containing 1 % sample was used to obtain the FTIR spectra. CHNS analyser, model EA 1108 of Finons Instruments was used for CHNS analyses. The Zn/Al ratio of the resulting ZAP was determined by an inductively coupled plasma emission spectrometry (ICP-ES), using a Labtest Equipment Model 710 Plasmascan sequential emission spectrometer.

The buffering effect of ZAP was studied by adding about 0.05 g of the materials into 250 mL aqueous solutions at various pH values, controlled by using 1 M HNO_3 or 1 M NaOH. The mixture was stirred using a magnetic stirrer. The pH values were recorded on a HANNA instrument H1931400 microprocessor bench pH meter, connected to a personal computer assisted with HILOG software. The pH values were recorded every 30 s. The release of pamoate from the interlayer of ZAP into the release media, the aqueous solutions at various pH values was done by adding 0.4 g of ZAP into a 200 mL of the aqueous solution. The accumulated amount of pamoate released into the solution was measured at $\lambda_{max} = 364.9$ nm using a Perkin Elmer UV-visible Spectrophotometer model Lambda 20. The samples recovered from the aqueous solutions at various contact times were also subjected to PXRD analysis. In addition, the pH profile of the aqueous solutions was also monitored.

Results and Discussion

Powder X-Ray Diffraction and FTIR Study

Figure 1(a) shows PXRD patterns of the layered double hydroxide (LDH), ZAL and its pamoate-intercalated compounds, ZAP. The PXRD patterns show a sharp, intense and symmetry peak indicating a well ordered nanolayered structure was formed in the resulting materials. As shown in the figure, pamoate anion was successfully intercalated inside the interlayer of Zn-Al layered double hydroxide with the increase of the basal spacing from 8.9 Å in ZAL to 18.1 Å in the nanocomposite, ZAP. The expansion is attributed to spatial orientation of the pamoate anion together with its size, which is bigger than nitrate.

Figure 1(b) shows the FTIR spectra for pamoate (PA), layered double hydroxide (ZAL) and its nanocomposite (ZAP). The FTIR spectrum for ZAL shows a broad absorption band centred at around 3438 cm^{-1} which is due to the presence of OH stretching of the hydroxyl group of LDH and/or physically adsorbed water molecule. The band at 1629 cm^{-1} is due to ν_{H-O-H} bending vibrations. A sharp and very intense band located at approximately 1386 cm^{-1} is attributed to the $\nu_3(NO_3^-)$ vibration [8]. Another two bands at 604 cm^{-1} and 432 cm^{-1} can be attributed to the Al-OH and Zn-Al-OH bending vibrations respectively [9].

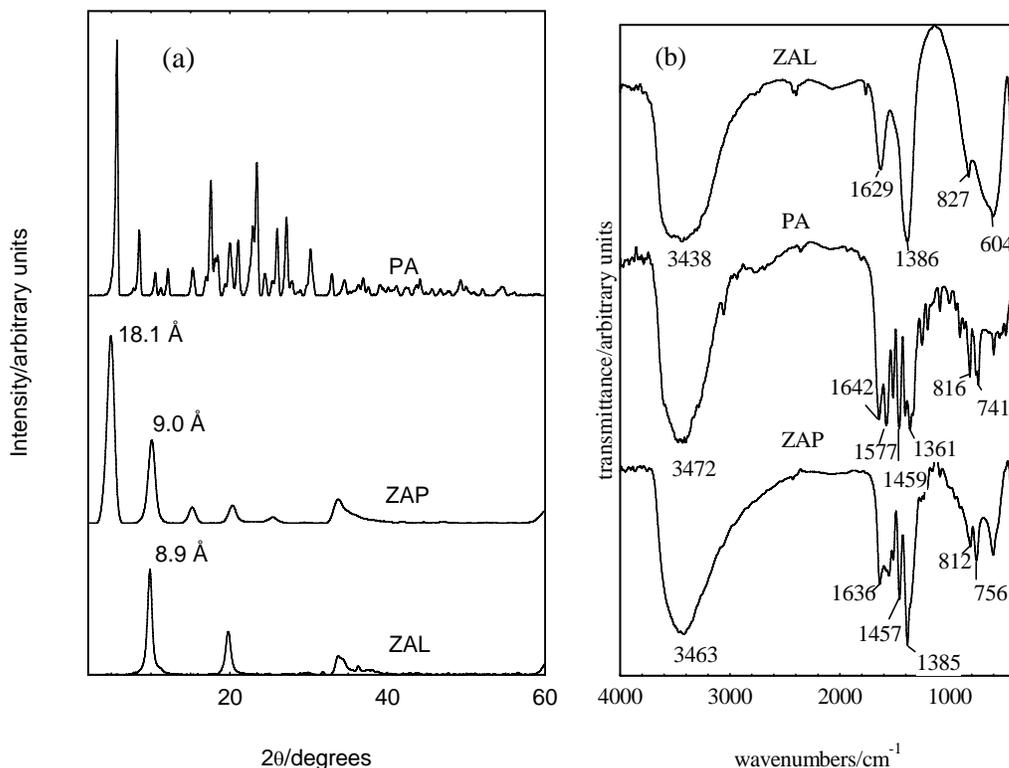


Fig. 1: PXRD patterns of ZAL and ZAP (a) and their corresponding FTIR spectra together with PA (b)

The FTIR spectrum of PA showing a broad band at 3472 cm^{-1} , which is attributed to the OH stretching. Strong bands at 1577 and 1361 cm^{-1} are due to the antisymmetric and symmetric stretching of $-\text{COO}$, respectively [10]. The bands at 1516 and 1642 cm^{-1} are attributed to the stretching of aromatic rings, $\text{C}=\text{C}$ and another sharp intense band at 1459 cm^{-1} is due to CH_2 scissoring. Strong bands near $741\text{--}816\text{ cm}^{-1}$ can be attributed to the presence of phenyl ring substitution [11]. As expected, the FTIR spectrum of ZAP resembles a mixture of both the spectra of PA and ZAL. This indicates that both functional groups of PA and ZAL are simultaneously present in ZAP and confirmed the intercalation of PA in the interlamella of ZAL.

Buffering effect

One of the interesting features of ZAP is the ability to neutralize both acidic and alkaline aqueous solutions. In this study, ZAP was added into the an aqueous solution with initial pH values (1-11), and the pH of the solution was monitored up to 300 min. The pH profiles of the aqueous are shown in Figure 2(a). As shown in the figure, the nanocomposite, ZAP has the capacity to neutralize aqueous solutions at different initial pH values, 3-10. Equilibrium was achieved at pH 6.5 – 7.5 after 100 min. This shows that ZAP exhibited buffering effect within this pH range. However, ZAP was unable to neutralize the aqueous solution with initial pH 1, 2 and 11, effectively. In the earlier study, Zn-Al-LDH (ZAL) also shows an efficient neutralizing power in the range of initial pH values (1-13) [6]. Ion exchange property of ZAL and ZAP is expected to contribute to this property and this will be discussed further in the deintercalation section.

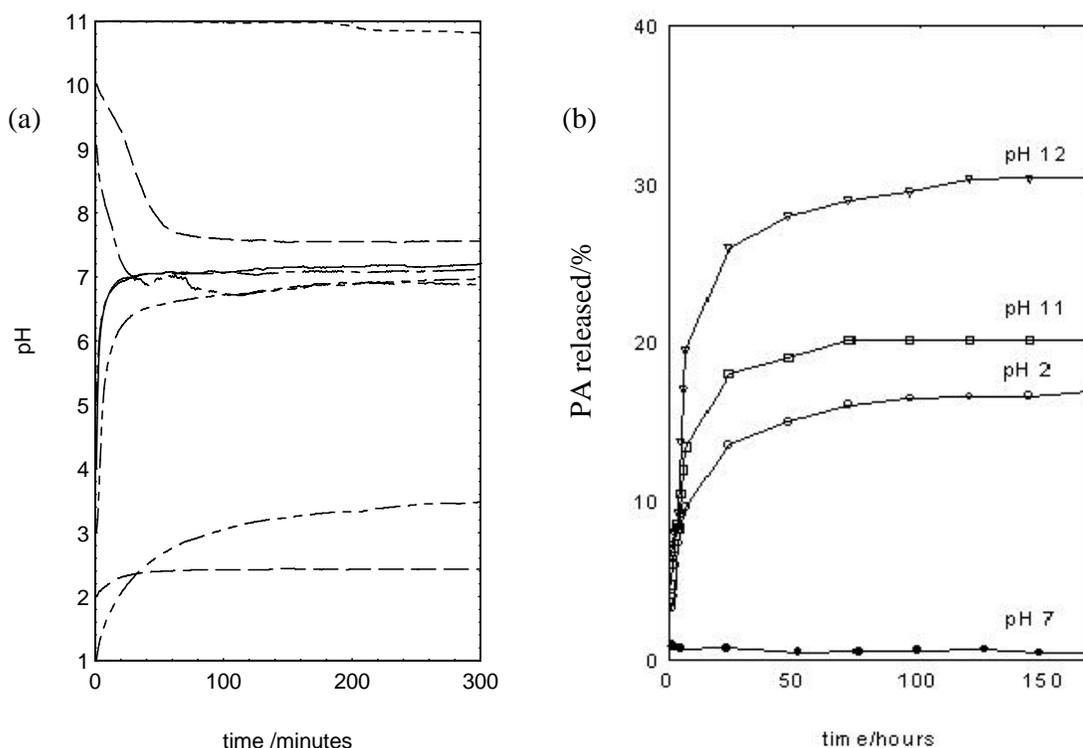


Fig. 2: pH profile of the release media, the aqueous solutions at various initial pH values (a), percentage release of PA from Zn-Al-PA nanocomposite (ZAP) lamella into the aqueous solutions at various initial pH values (b).

Controlled release of pamoate into aqueous solution

About 0.40 g of ZAP was added to a 200 mL aqueous solutions with various pHs, controlled by using HNO₃ or NaOH. The PA concentrations released into the aqueous solution from the interlamellae of the nanocomposite was determined by UV-visible spectrophotometer at 364.9 nm.

Figure 2(b) shows the release profile of PA from the interlamellae of ZAP into the aqueous solution at various initial pH values. The accumulated PA released into the aqueous solution increased with contact time when ZAP was put in contact with the aqueous solutions. The release rate was found to be faster in the first 20 hours from the initial time of the experiment and the rate became slower thereafter. The PA anion was released slowly from ZAP and equilibrium was achieved after 3 days for the aqueous solution with initial pH 2 and pH 11. For the aqueous solution of pH 12, the equilibrium was achieved after 5 days.

The percentage of PA released from the interlayer of ZAP into the aqueous solutions at initial pH 2 was found to be the lowest as shown in Figure 2(b). It was observed that at the end of rapid release rate, the amount of PA released into the aqueous solution at various initial pH values were 16% (pH 2); 20% (pH 11) and 30% (pH 12). The highest percentage of PA released was achieved in highly alkaline aqueous solution. The most possible reason might be because of the affinity to replace the PA anion as the result the ion-exchange phenomena in ZAP was higher for OH⁻ than NO₃⁻ ions.

In aqueous solution at low initial pH (set by adding HNO₃) and high initial pH (set by adding NaOH), the high concentration of NO₃⁻ and OH⁻ ions in the solutions resulted in NO₃⁻ or OH⁻ being exchanged with PA ion. As a result, NO₃⁻ or OH⁻ will be incorporated into the interlayer of ZAP and at the same time PA ion would then be released into the solution, i.e., the formation of LDH. The amount of PA released at equilibrium is higher at pH

11 and 12 than at pH 2. Several factors such as the extent of the dissolution of the inorganic LDH with the collapse of the nanolayered structure and the actual composition of the controlled release formulation

As shown in Figure 2(b), the release of PA from the nanocomposite into the aqueous solution with initial pH 7 is less than 3 % or considered as no release of PA in this aqueous solution. At pH 7, the amount of H⁺ and OH⁻ is low. As a result, the extent of dissolution of the inorganic LDH structure or the collapse of the nanolayered structure of ZAP is also less. This in turn will reduce the amount of PA released into the aqueous solution. On the other hand, higher concentration of OH⁻ at pH 12 resulted in higher amount of PA released. This presumably due to the ion-exchange of the OH⁻ from the aqueous solution with the PA in the inorganic interlayer of ZAP.

Release kinetics

Release kinetics of organic moieties has been evaluated with various models such as zero order, first order, Baker-Lonsdale, Bhaskar *et al.* etc. It was suggested that drug release based on drug-LDHs system could be controlled either by dissolution of LDH or by diffusion through the LDH [5].

The PA release profiles suggested that the zero and first order kinetic equation given in Equation 1 and 2 could be used to describe the release behavior, which normally used to describe dissolution phenomena.

$$(M_i/M_f) = t + C \quad (1)$$

$$\ln [1 - (M_i/M_f)] = t + C \quad (2)$$

in which M_i and M_f are the initial and final concentrations of PA, respectively. Attempt has been made to fit the data obtained from the PA released into the aqueous solution to the zero and first order kinetic and the results obtained are shown in Figure 3. As shown in the figure, the release of PA nicely followed the zero and first order kinetic up to 7 hours for pH 2 and pH 11, with the regression value (r²) of 0.99 and 0.98, respectively. The release of PA in the solution of pH 12 does not really followed the zero and first order kinetics, with the regression value (r²) of 0.92.

In addition to the first order kinetics, the release of PA can be due to diffusion mechanism. The data obtained from the release of PA into the aqueous solution can be fitted to the model developed by Baker and Lonsdale, a straight line is expected for a plot of PA release using equation 3 in which Q is the percentage release of PA at time. t and C is a constant.

$$3/2 [1-(1-Q)^{2/3}] - Q = t + C \quad (3)$$

After 7 hours of PA release process, a straight line was obtained for 9, 14 and 20 % of PA released from ZAP into the aqueous solutions with initial pH 2, 11 and 12, respectively. As shown in Figure 3 of Baker-Lonsdale equation, the regression values of 0.99 (pH 2), 0.98 (pH 11) and 0.92 (pH 12) were obtained. This indicated that the released of PA in these solutions were consistent with a diffusion mechanism at least at the beginning of the process [12].

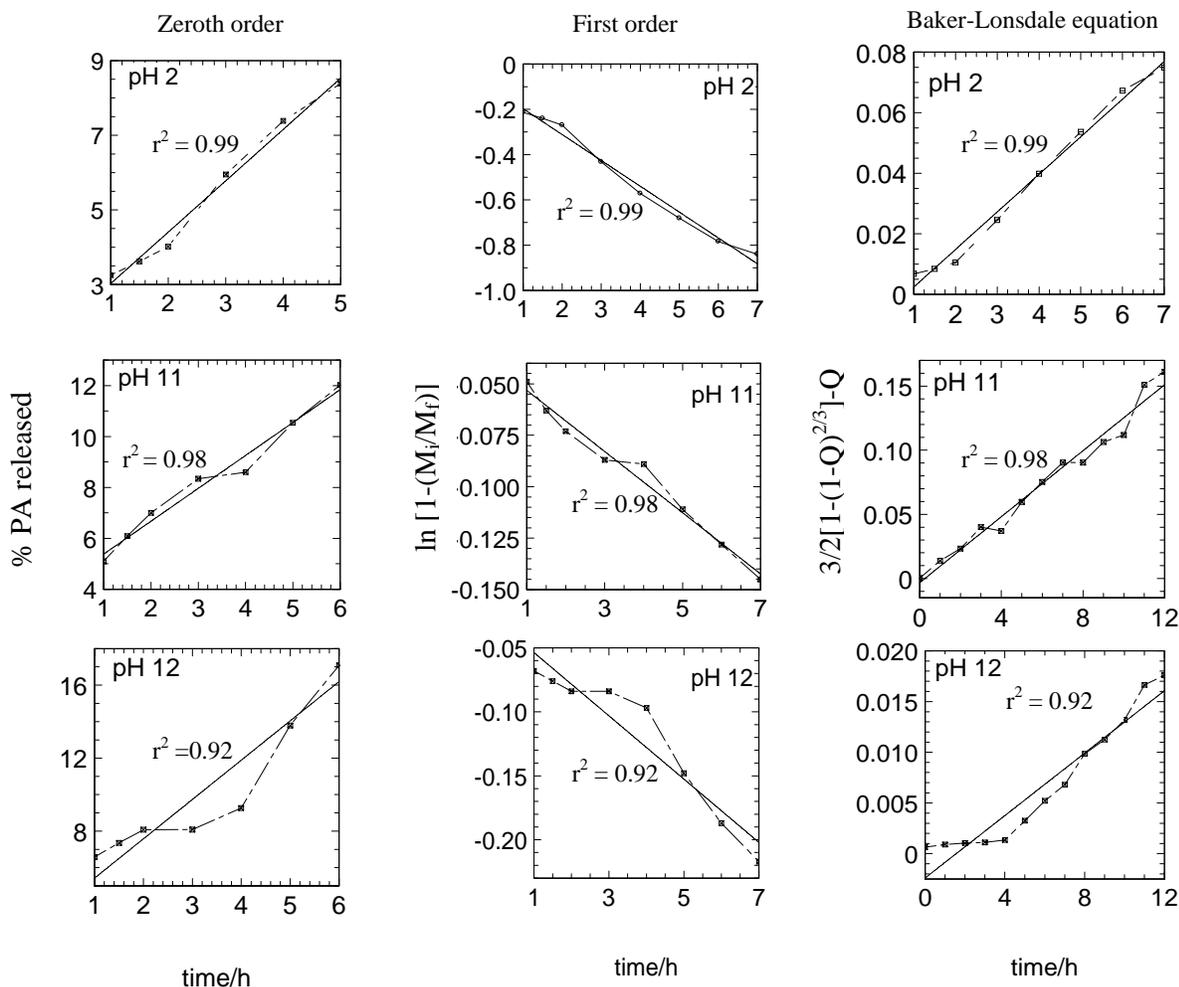


Fig. 3: Fitting of the data to the zeroth, first order kinetics and Baker-Lonsdale equation for PA released into the aqueous solutions.

Powder X-Ray Diffraction

In order to obtain some information on the ion-exchange phenomena, the resulting samples were recovered from the aqueous solutions after the PA release experiment. The recovered samples were dried and characterized by PXRD and FTIR techniques. The PXRD patterns of the recovered samples, PA and ZAP are shown in Figures 4(a)-(c). PXRD patterns in Figure 4(a) shows that the intensity of the 003 reflection peak and other associated peaks decreased, indicating lower crystallinity of the resulting material compared to the starting material, ZAP. Since the percent released of PA into the aqueous solutions with initial pH 2 is only 16 % so the layered structure is still not collapse with interlayer spacing of about 18.1 Å. The PXRD patterns also show a number of peaks which are characteristic of PA phase. This might be due to the PA released from the layered structure of ZAP into the aqueous solution and was adsorbed onto the surface of the recovered sample.

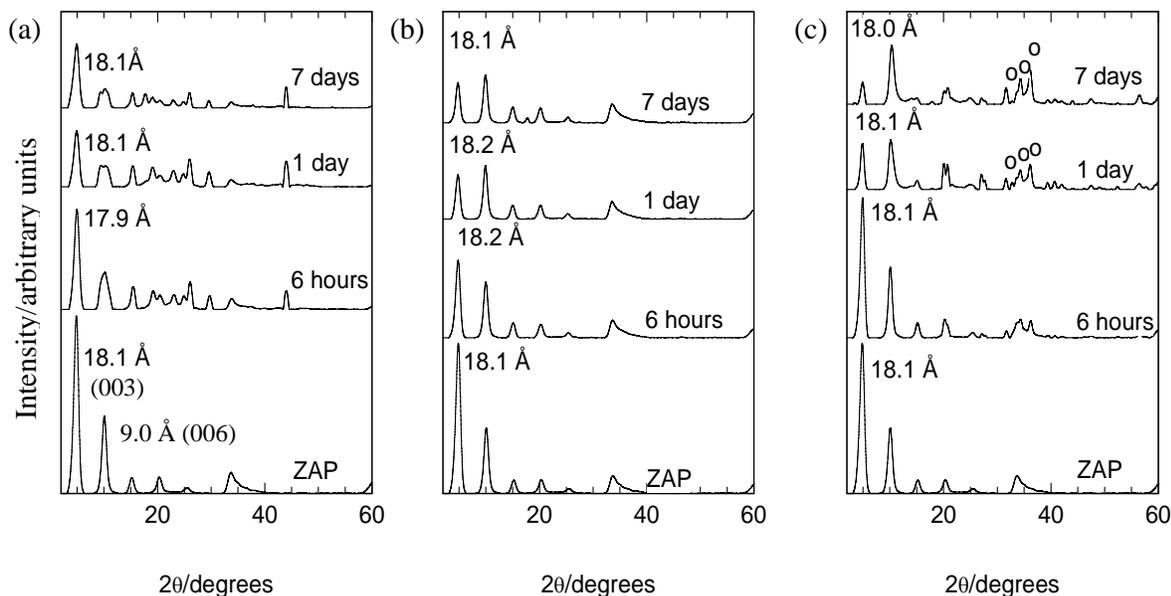


Fig. 4: PXRD patterns for samples recovered from the aqueous solutions with initial pH 2 (a), pH 11 (b) and pH 12 (c).

Figures 4(b) and (c) show that as the time for the release of PA was increased to 6 hours, the intensity of 003 peaks was decreased, indicating the change in the crystallinity of the sample as the result of the release of PA into the aqueous solution. With further increase in the release time from 6 hours to 1 day the 003 peaks further decreased and its intensity became slightly lower than the peak at $d = 006$. Further increase in the contact time (7 days) resulted in the $d = 006$ peak higher than 003.

The d -spacing for the 006 peak for the recovered samples in Figures 4(b) and (c) is 8.9 Å, which is also similar to the d -spacing for the 003 peak of LDH with nitrate as the counter ion. These indicated the 006 peak for the recovered sample was superimposed with the 003 peak of LDH. The release of PA anion from the interlayer of ZAP probably occurred via ion-exchange mechanism, in which the PA anions were exchanged with NO_3^- or OH^- ions and were released into the aqueous solution from the interlayer spacing of Zn-Al-LDH into the aqueous solution of initial pH 11 and 12 with amount of PA release was 20% and 30%, respectively.

Figure 4(c) also shows that as the release time was increased from 1 to 7 days, the nanocomposite phase is almost disappeared, due to the formation of the LDH phase and three new peaks were observed, which is due to the ZnO phase. The decrease in the intensity of these peaks shows that the release of PA lowered the degree of order and the crystallinity of the nanohybrid and at the same time the reorientation of the PA moiety between the inorganic LDH interlayer took place, resulting in reduced basal spacing. In addition, the formation of LDH occurred as a result of ion-exchange with NO_3^- and the slow collapses of the layered structure is due to the dissolution phenomenon [6].

Fourier transform-infrared (FTIR) spectroscopy

Figure 5(a) shows the FTIR spectra of the samples recovered from the aqueous solution with initial pH of 2. As shown in the figure, after 6 hours of the PA release time, the intensity of 1656 and 1456 cm^{-1} bands increased slightly. The band at 1656 cm^{-1} is attributed to the stretching vibrations of aromatic rings, C=C and the other sharp intense band at 1456 cm^{-1} is due to the CH_2 scissoring mode. Similarly, the same bands were also observed for ZAP. This showed that the recovered samples contain the PA moiety and the nanocomposite phase still remained in the interlayer of the recovered samples. The intensity of band located at 1388 cm^{-1} , which is attributed to NO_3^- vibration decreased slightly as the release time increased to more than 6 hours. This showed that not only PA anions released from the interlayer spacing of nanocomposite but the remained nitrate anions left in the nanocomposite also released to the aqueous solution.

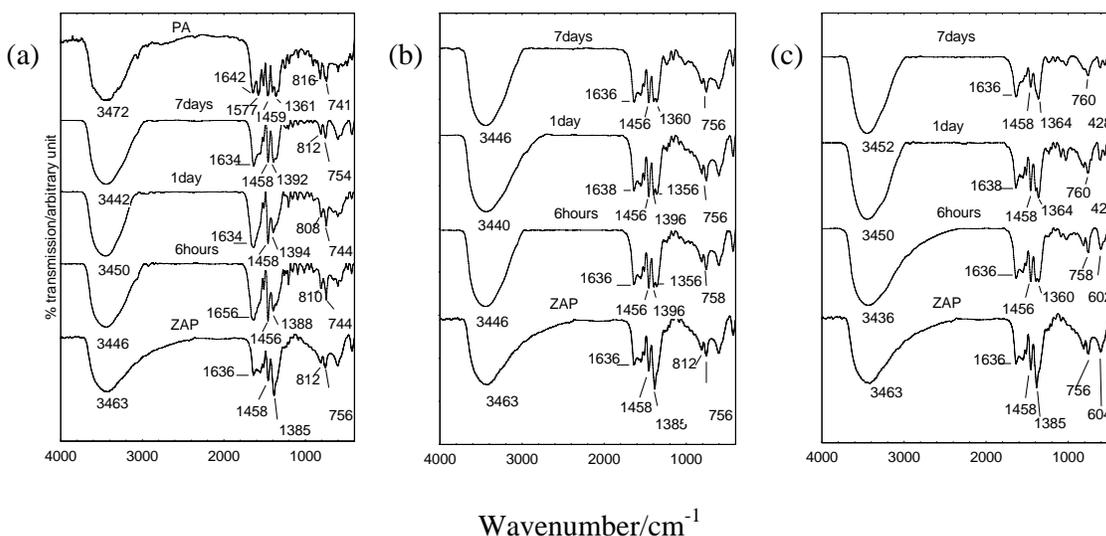


Fig. 5: FTIR spectra of samples recovered from the aqueous solutions with initial pH 2(a), pH 11(b) and pH 12 (c).

The FTIR spectra of samples recovered from the aqueous solutions with initial pH 11 shown in Figure 5(b) is similar to the FTIR spectra in Figure 5(a). The presence of bands belongs to Zn-Al-pamoate nanocomposite, as shown in the figure, indicated that the pamoate anions are still intercalated inside the interlamellae of the Zn-Al-LDH. As discussed earlier only 20 % of the pamoate anions were released into the aqueous solution with initial pH 11 after 7 days.

The pattern of the FTIR spectra of the samples recovered from aqueous solution with initial pH values, 2, 11 and 12 at various release times are essentially similar, except for the bands' intensity. Figure 5(c) shows that the intensity of bands belongs to pamoate anions decreased after 1 and 7 days of the release time. This showed that the pamoate anions were released into the aqueous solution with initial pH value of 12. The intensity of band located at 428 cm^{-1} increases, indicating the presence of metal-oxide group, which is in agreement with the detection of ZnO phase in the XRD pattern [6].

Conclusion

A new layered organic-inorganic hybrid nanocomposite was prepared using pamoate anion (PA) as the organic guest intercalated into the interlamella of inorganic host of Zn-Al-layered double hydroxide. The resulting nanocomposite material can be used as a controlled drug release formulation and by adjusting the pH of the release medium, the aqueous solution, could control the release of PA from the lamella of Zn-Al-LDH. It was also found that the release of PA anions from the interlamellae of ZAP was controlled by the first order kinetic at least at the beginning of the reaction up to 7 hours, depending on the initial pH values of the release media, the aqueous solutions. The highest percentage of PA released was achieved in highly alkaline aqueous solution. The most possible reason might be because of the affinity to replace the PA anion as the result of the ion-exchange phenomenon of ZAP is higher for OH^- than NO_3^- ions. The atmospheric CO_2 gas has a greater tendency to dissolve in the highly alkaline solution, which will form carbonate ion in the aqueous solution. Carbonate ion also has greater affinity to replace the PA anion through the ion-exchange process. This study suggests that layered double hydroxide can be used as a controlled release formulation for slow drug release in pharmaceutical industry.

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