

Controlled release formulation of an anti-depression drug based on a L-phenylalanate-zinc layered hydroxide intercalation compound

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ABSTRACT

The intercalation of L-phenylalanate (LP) into the interlayer gallery of zinc layered hydroxide (ZLH) has been successfully executed using a simple direct reaction method. The synthesised intercalation compound, zinc layered hydroxide-L-phenylalanate (ZLH-LP), was characterised using PXRD, FTIR, CHNS, ICP-OES, TGA/DTG, FESEM and TEM. The PXRD patterns of the intercalation compound demonstrate an intense and symmetrical peak, indicating a well-ordered crystalline layered structure. The appearance of an intercalation peak at a low angle of 2θ with a basal spacing of 16.3 Å, signifies the successful intercalation of the L-phenylalanate anion into the interlayer gallery of the host. The intercalation is also validated by FTIR spectroscopy and CHNS elemental analysis. Thermogravimetric analysis confirms that the ZLH-LP intercalation compound has higher thermal stability than the pristine L-phenylalanine. The observed percentage of L-phenylalanate accumulated release varies in each release media, with 84.5%, 79.8%, 63.8% and 61.8% release in phosphate buffer saline (PBS) solution at pH 4.8, deionised water, PBS solution at pH 7.4 and NaCl solution, respectively. The release behaviour of LP from its intercalation compounds in deionised water and PBS solution at pH 4.8 follows pseudo second order, whereas in NaCl solution and PBS solution at pH 7.4, it follows the parabolic diffusion model. This study shows that the synthesised ZLH-LP intercalation compound can be used for the formation of a new generation of materials for targeted drug release with controlled release properties.

1. Introduction

Layered hydroxide salts (LHSs) are compounds originating from brucite-like structure and can be represented using the general formula $M^{2+}(\text{OH})_{2-x}(\text{A}^{m-})_{x/m} \cdot n\text{H}_2\text{O}$, where M^{2+} refers to the metal cation and A^{m-} is the counter ion [1]. LHSs can form when some of the hydroxide groups in the structure are compensated by water molecules and guest anions [2]. One example of a LHS that has been frequently reported in previous studies is zinc layered hydroxide (ZLH) [3–7]. In the structure of ZLH, one quarter of the octahedral coordinated zinc cations are displaced from the main layer to tetrahedral sites located above and below each empty octahedron [8].

ZLH has attracted extensive worldwide attention due to its versatility for incorporation of various inorganic and organic guest anions, such as anionic orange azo dyes [9], p-aminobenzoic acid [7] and low-density polyethylene [10]. Various methods have been adopted in

synthesising ZLH and its intercalation compounds, including anion exchange [11], co-precipitation [12] and pulsed-laser ablation in a liquid medium [13]. Direct reaction using ZnO as a precursor is a facile method to prepare ZLH intercalation compounds, which can be easily carried out for either aqueous or non-aqueous systems [14]. This method is also economic and more environmentally friendly as it involves fewer steps and chemicals. Hence, due to their versatility and easy fabrication, ZLH intercalation compounds have generated significant opportunities in various fields, including agricultural [3], pharmaceutical [11], and cosmetic industries [15]. For instance, the ZLH intercalation compounds were used as catalyst [16], sensor [17] bactericide [18] and also herbicide [19].

Owing to its great anion exchange properties and low toxicity, ZLH has demonstrated its potential to be exploited as a host for targeted delivery of various drugs, such as diclofenac [20], ciprofloxacin [21], para-amino salicylic acid [5], indole-3-acetic acid [22] and ellagic

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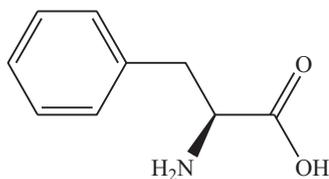


Fig. 1. Chemical structure of L-phenylalanine.

acid [14]. Targeted drug delivery has been proven to enhance the delivery of poorly water-soluble drugs, boost the drug efficiency against various diseases, reduce the possible cytotoxic effect of the active agents and help to optimise the drug release rate [23]. Great biocompatibility, easy degradation without accumulation in the body and controlled release behaviour of drugs are some of the important properties possessed by ZLH, which makes it an excellent host for use in drug delivery systems [5]. The controlled release formulation has been proven in increasing the prolonged hour of the release of the active ingredient in the drugs [20], provide better protection of the drugs against physio-chemical degradation and lessening the dosing frequency, hence helping to reduce the treatment duration [5].

L-phenylalanine (LP) is a type of aromatic amino acid that has been used in the pharmaceutical field to help people deal with depression [24]. The chemical structure of LP is shown in Fig. 1. LP is also widely used to treat people with attention deficit-hyperactivity disorder (ADHD), Parkinson's disease, chronic pain, osteoarthritis, rheumatoid, alcohol withdrawal symptoms and vitiligo [25]. In the present study, LP have been intercalated into the interlayer gallery of ZLH via a direct reaction method, using ZnO as a precursor. The controlled release behaviour of the synthesised intercalation compound, zinc layered hydroxide intercalated with L-phenylalanate (ZLH-LP), has been studied in deionised water, sodium chloride (NaCl) solution and phosphate buffer saline (PBS) solution at pH values of 4.8 and 7.4. Based on the results obtained in the controlled release study, the kinetic behaviour of the intercalation compound has been determined.

2. Experimental

2.1. Synthesis of intercalation compound

All the reagents used in this study were provided by various suppliers and were used as received. Deionised water was used as a solvent to prepare all solutions. The ZLH-LP intercalation compound was prepared by the direct reaction of ZnO with the LP guest anions. First, 0.5g of ZnO (6.144 mmol) (Acros Organics) was dispersed into 50 mL of deionised water. LP (Sigma-Aldrich) was dissolved in deionised water to prepare LP solutions with three different concentrations, ranging from 0.015 to 0.05 mol L⁻¹ (0.75–2.5 mmol). The prepared solutions were mixed with the dispersed ZnO and the mixtures were stirred for 2 h. Then, the mixtures were aged at 70 °C in an oil bath shaker for 24 h. The resulting slurry was centrifuged at 40 rpm for 5 min, washed with deionised water and dried at 60 °C. The samples were ground and stored in a sample bottle for further characterisation and the controlled release study.

2.2. Characterisation

Powder X-ray diffraction patterns (PXRD) of ZLH, LP and the differently concentrated ZLH-LP intercalation compounds were recorded on a Shimadzu XRD-6000 X-ray diffractometer in the 2θ range of 2–60° using filtered Cu-K_α radiation (λ=0.1540562 nm) at 40 kV and 20 mA with 2° min⁻¹. The Fourier transform infrared (FTIR) spectra of the materials were recorded using a Perkin-Elmer model 1725X over the range of 400–4000 cm⁻¹. Finely ground 1% samples in the KBr powder were compressed to form a pallet, which were used in the FTIR analysis. The elemental analysis of the samples was con-

ducted using a CHNS-932 LECO and an inductively coupled plasma optical emission spectrometry (ICP-OES), model Perkin-Elmer Plasma 1000. A Perkin-Elmer thermogravimetric and differential thermogravimetric (TGA/DTG) 700 thermal analyser was used to determine the thermal stability of the intercalation compounds. The TGA/DTG analysis was performed in the temperature range of 35–1000 °C, with heating rate of 10 °C min⁻¹ and under a constant flow of nitrogen gas. The surface morphology of the samples was studied using high resolution field emission scanning electron microscopy (FESEM) and transmission electron microscopy (TEM) with a Hitachi SU 8020 UHR instrument.

2.3. Release of intercalation compound

The release behaviour of LP anions from the interlayer gallery of ZLH into the release media was performed on different human body simulated environments, using deionised water, a 0.1 mol L⁻¹ aqueous solution of NaCl and a 0.1 mol L⁻¹ PBS solution, at room temperature. The release behaviour of the ZLH-LP intercalation compound was also studied at two different pH values, using a PBS solution of pH 4.8 and 7.4. These pH values were selected due to the fact that human blood has a very constant reading at pH 7.4 and different parts of the body may also have different pH values [26]. The PBS powder was dissolved and diluted to form 1 L of PBS solution containing 2.7 mmol L⁻¹ potassium chloride, 137 mmol L⁻¹ sodium chloride and 1.76 mmol L⁻¹ potassium phosphate. About 0.6 g of the intercalation compounds was added into 3.5 mL of the aqueous solutions. The accumulated amount of LP released into each release media was measured in situ using a Perkin-Elmer ultraviolet visible (UV/Vis) spectrometer. All release data were obtained using similar experimental conditions of UV/vis measurements (λ_{max}=257 nm, time interval=60 s, slit width=1.0 nm, lamp change=326.0 nm, ordinate max=1.0 and ordinate min=0.0). The data obtained is fitted to zeroth order, first order and pseudo second order kinetics as well as the parabolic diffusion and Fickian diffusion models.

3. Results and discussion

3.1. Powder X-ray diffraction

The PXRD patterns of ZnO and the ZLH-LP intercalation compound with various concentrations of LP (0.015, 0.025 and 0.05 mol L⁻¹) are presented in Fig. 2. Based on the PXRD pattern of ZnO (Fig. 2(a)), a typical ZnO peak pattern can be observed, which indicates that the pristine ZnO used is a pure phase material with high crystallinity. In the PXRD pattern of the ZLH-LP intercalation compound, a new peak appeared at a lower angle of 2θ in the range of 15.9–16.3 Å (Fig. 2(c–e)). These basal spacing were obtained from the analysis of PXRD pattern using PXRD software, MDI Jade 6.5. The enlargement of the basal spacing signifies that the LP anions were successfully intercalated into the interlayer gallery of ZLH, thus forming a novel ZLH-LP intercalation compound. The occurrence of the intercalation is due to the electrostatic attraction between the negatively charged anion LP and the positively charged ZLH [5]. This result is also consistent with a recent study that reported the intercalation of LP into LDH [27]. The resulting intercalation compounds obtained show symmetrical, sharp and intense reflections, which showed the formation of well-ordered layered structures.

The formation of the ZLH-LP intercalation compound occurred in three steps through a dissociation-deposition mechanism [14]. In the first step, a thin layer of Zn(OH)₂ was formed on the surface of the organic particle due to the hydrolysis of ZnO (Eq. (1)). The Zn(OH)₂ was then dissociated under acidic conditions, thus forming Zn²⁺ and OH⁻ ions in the second step (Eq. (2)). In the third step, the Zn²⁺ cation reacts with the hydroxyl ions, LP anions and the water molecules, thus forming a layered intercalation compound (Eq. (3)). The mechanisms are given as follows:

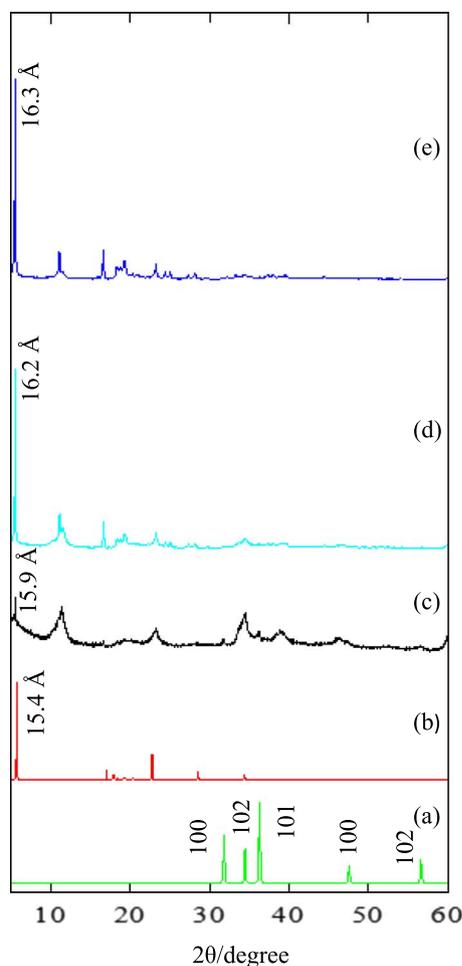


Fig. 2. Powder X-ray diffraction patterns of (a) ZnO, (b) LP and the intercalation compounds prepared using (c) 0.015, (d) 0.025 and (e) 0.05 M LP.



It also can be seen from the PXRD pattern that the ZLH-LP intercalation compound synthesised using 0.05 mol L⁻¹ of LP exhibited a higher crystallinity compared to the other intercalation compounds. No ZnO phase was observed for the intercalation compound prepared at 0.05 mol L⁻¹ LP, indicating that a complete reaction had occurred between the pristine ZnO and LP anions. These intercalation compounds were used for further characterisation and the controlled release study.

3.2. FTIR spectroscopic analysis

In order to identify the functional group changes before and after the occurrence of the intercalation, FTIR analysis was conducted. The FTIR spectra of the pristine ZnO, LP and the ZLH-LP intercalation compounds obtained are compared and several differences were observed (Fig. 3). The FTIR spectrum of ZnO shows a broad peak around 600 cm⁻¹, which represent the vibration of zinc and oxygen sublattice [28].

For LP, broad peaks appeared at 3121 and 3458 cm⁻¹ which are attributed to the O-H stretching vibration of the carboxylic group and N-H stretching vibration, respectively. A sharp peak was also observed

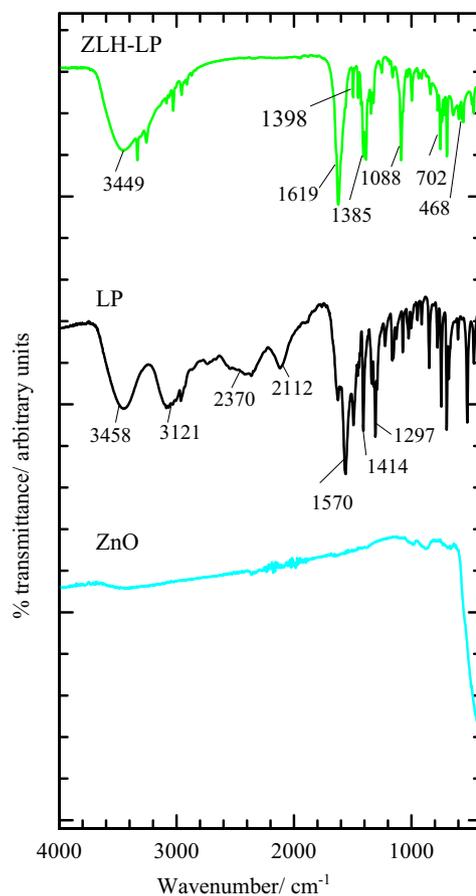


Fig. 3. FTIR spectra of ZnO, LP and the ZLH-LP intercalation compound.

in the FTIR spectrum of LP, at 1297 cm⁻¹, resulting from the C-OH vibration. This peak, however, seems to disappear in the ZLH-LP intercalation compound. The disappearance of the C-OH vibration peak indicates that the carboxylic acid group in LP has been deprotonated into a carboxylate ion during the intercalation process [5]. Owing to the deprotonation of the carboxylic group, the vibrational mode of C=O becomes coupled to the other oxygen, therefore lead to the formation of COO⁻ symmetric and asymmetric vibration peaks, represented by the 1385 and 1398 cm⁻¹ peaks, respectively [29]. These peaks indicates that the species that were intercalated into the interlayer gallery are in the anionic form of L-phenylalanine, i.e. L-phenylalaninate. The difference of asymmetric and symmetric stretching bands (Δ_{a-s}) enable the coordination mode of the carboxylate to be deduced, which may be in unidentate, bidentate or bridging modes [30]. The Δ_{a-s} values for unidentate, bridging, bidentate and ionic species are in the following order:

$$\Delta_{a-s} \text{ unidentate} > \Delta_{a-s} \text{ ionic} > \Delta_{a-s} \text{ bridging} > \Delta_{a-s} \text{ bidentate}$$

where Δ_{a-s} (ionic) is approximately 160–170 cm⁻¹ [31]. Based on the FTIR spectra of ZLH-LP, the Δ_{a-s} obtained is very small (13 cm⁻¹). Hence, it is very much possible that the coordination mode of the carboxylate ion is bidentate. Δ_{a-s} bidentate < Δ_{a-s} bridging was founded on the theory that the O-C-O angle is smaller in bidentate than in bridging modes, and on calculations, showing that decreasing the O-C-O angle decreases Δ_{a-s} [30]. A more pronounced broad peak is also observed at 3449 cm⁻¹, attributable to the O-H stretching of hydroxyl group from the hydroxide layer and a strong peak at 1619 cm⁻¹ which represent the interlayer water molecule in the ZLH-LP intercalation compound [12].

All the characteristic bands of pristine LP are also present in the FTIR spectrum of ZLH-LP intercalation compound, hence confirm the presence of LP in its anionic form. The positions of certain peaks were,

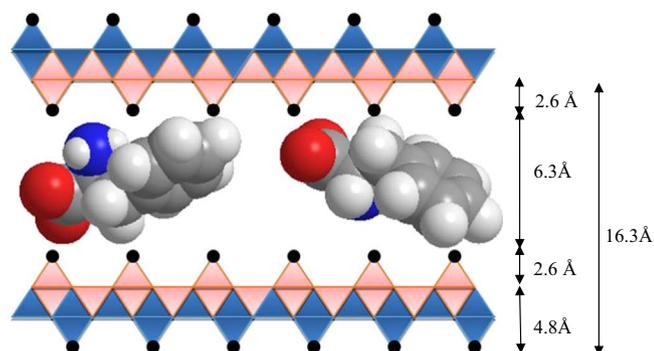


Fig. 4. Proposed spatial orientation of LP in the ZLH inorganic interlayer.

nevertheless, slightly shifted due to the interaction between the LP anion and ZLH due to intercalation [32].

3.3. Spatial orientation of LP anions in the ZLH interlayer gallery

Based on the PXRD pattern of the ZLH-LP intercalation compound (0.05 mol L^{-1}), the basal spacing of the intercalation peak is 16.3 \AA , whereas the thickness of the ZLH and the thickness of each zinc tetrahedron layer are 4.8 and 2.6 \AA , respectively [33]. Referring to these values, the gallery height of the ZLH after the occurrence of LP intercalation is calculated as 6.3 \AA . The intercalated anion is believed to possess a monolayer arrangement and interact with the ZLH via electrostatic interactions [6,34]. Fig. 4 illustrates the orientation of LP in the interlayer gallery ZLH, meanwhile Fig. 5 demonstrates the three-dimensional molecular size of LP as proposed using Chemoffice software 2008 (Cambridge, MA). The x, y and z axes of LP were calculated and determined to be 10.8 , 6.3 and 6.6 \AA , respectively.

3.4. Thermal analysis

The thermal decomposition behaviour of ZnO, LP and ZLH-LP were studied using TGA/DTG. The data obtained were shown in Fig. 6(a) and summarise into Table 1. As can be seen from the TGA/DTG result, a very low decomposition percentage of pristine ZnO (less than 0.5% weight loss) was observed at temperatures below $100 \text{ }^\circ\text{C}$ due to the elimination of sorbed species which exist on the external surface of ZnO [28]. No maximum decomposition temperature recorded when the TGA/DTG analysis was performed in the temperature range of 35 – $1000 \text{ }^\circ\text{C}$, hence proving the good thermal stabilities own by the pristine ZnO. The TGA/DTG curves of the LP shows that the weight loss of LP occurred at two stages, due to the combustion of the organic molecule [35]. The first stage of the LP decomposition occurred at a temperature of $324.1 \text{ }^\circ\text{C}$ with an abrupt weight loss of 56.3%, meanwhile the second stage shows a maximum temperature of weight loss of LP at $356.2 \text{ }^\circ\text{C}$ with a 31.7% weight loss. Fig. 6(c) shows that the thermal decomposition of the ZLH-LP intercalation compound occurred in four major stage of weight loss. The first stage of weight loss was attributed to the weight loss of 6.1% at $76.8 \text{ }^\circ\text{C}$, which resulting from the removal of surface physisorbed water molecules. The weight loss of 7.2% at $170.6 \text{ }^\circ\text{C}$ was attributed to the removal of interlayer

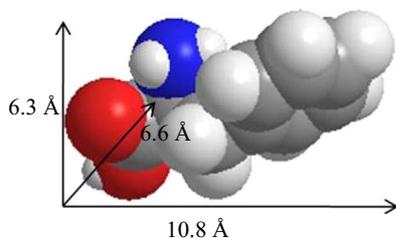


Fig. 5. Three-dimensional molecular size of the LP anion.

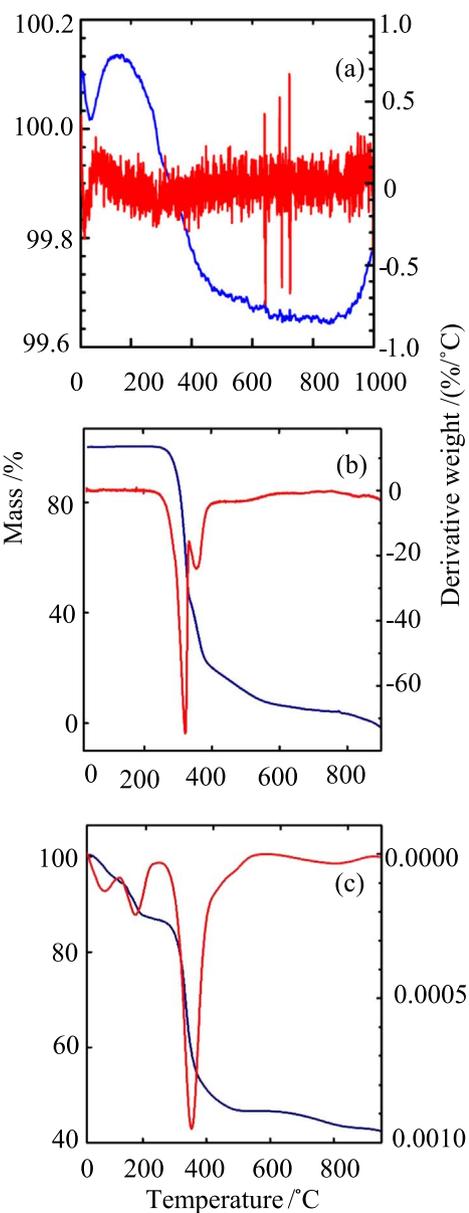


Fig. 6. TGA/DTG curves of (a) ZnO, (b) LP and (c) ZLH-LP intercalation compounds.

anions and dehydroxylation of the hydroxyl layer [32]. The highest percentage of weight loss occurred at decomposition temperature of $372.6 \text{ }^\circ\text{C}$, with 45.2% of abrupt weight loss owing to the decomposition of the organic moiety of the intercalation compounds [21,36]. The fourth stage of decomposition occurred at temperature $767 \text{ }^\circ\text{C}$, with minor weight loss of 8.1%, due to the collapse of the layered structure of ZLH-LP.

The maximum decomposition temperature of the ZLH-LP intercalation compound ($372.6 \text{ }^\circ\text{C}$) is higher than the pristine LP ($324.1 \text{ }^\circ\text{C}$), hence proving that the intercalation of LP into the interlayer gallery of ZLH could enhance the thermal stability of the intercalation compound.

3.5. Elemental analysis

The elemental compositions of ZnO and the ZLH-LP intercalation compounds are listed in Table 2. Based on the CHNS results, neither hydrogen, nitrogen nor carbon were detected in ZnO. Whereas for the ZLH-LP intercalation compounds, all three elements were present, hence confirming the presence of LP anions in the intercalation

Table 1
TGA/DTG data for ZnO and ZLH-LP intercalation compound.

	Stage 1		Stage 2		Stage 3		Stage 4		Total weight loss (%)
	Weight loss (%)	Temp. (°C)							
ZnO	< 0.5	52.2	–	–	–	–	–	–	< 0.5
LP	56.3	324.1	31.7	356.2	–	–	–	–	88.0
ZLH-LP	6.1	76.8	7.2	170.6	40.2	336.9	8.1	767.0	61.6

Table 2
Elemental chemical composition of ZLH-LP intercalation compound.

Sample	Weight percent (%)				^a Percentage loading of LP (% w/w)	^b Formula
	C	H	N	Zn		
ZnO	–	–	–	81.47	–	ZnO
ZLH-LP	41.11	4.81	5.86	53.18	62.38	Zn ²⁺ (OH) _{1.53} (C ₆ H ₅ CH ₂ CH(NH ₂)COO [–]) _{0.47} ·0.73H ₂ O

^a Estimated from CHNS analysis.

^b Estimated from ICP-OES, CHNS and TGA/DTG analysis.

compounds. The percentages of carbon, hydrogen and nitrogen elements determined in the ZLH-LP intercalation compounds are 41.11%, 4.82% and 5.86%, respectively. The percentage loading of LP in ZLH-LP intercalation compounds can be calculated using the CHNS data, which is approximately 62.38% (w/w). The percentage loading may be influenced by several factors, including the polarity of the guest anions, the surface charge density and unoccupied interlayer space [12]. The ICP-OES analysis shows that the percentage of Zn in the ZLH-LP is 53.18%, which is lower than the percentage of Zn in the pristine ZnO (81.47%). The presence of carbon, hydrogen and nitrogen in the ZLH-LP change the overall elemental composition of the intercalation compounds, hence lowering the percentage of Zn. Based on the data obtained from the CHNS and ICP-OES analyses, the formula of the ZLH-LP intercalation compound is proposed as Zn²⁺(OH)_{1.53}(C₆H₅CH₂CH(NH₂)COO[–])_{0.47}·0.73H₂O. So as to support the chemical formula proposed, a comparison between ashes theoretically obtained with the proposed formula and the ashes obtained from the TGA/DTG curve was also executed. The percentage of ash content in ZLH-LP, having 100% of bound water (as calculated based on the proposed formula), is 37.43%, whereas the percentage of ash content for ZLH-LP obtained from the TGA/DTG result is 38.49%. Based on the comparison, it can be seen that the percentage of ash content obtained from both proposed formula and TGA/DTG result are not much differ (1.06%). Hence, it can be concluded that the proposed formula, Zn²⁺(OH)_{1.53}(C₆H₅CH₂CH(NH₂)COO[–])_{0.47}·0.73H₂O, is therefore supported by the comparison between ashes theoretically obtained with the proposed formula and the ashes obtained from the TGA/DTG curve.

3.6. Surface morphology

The scanning electron micrographs of ZnO and the ZLH-LP intercalation compound are shown in Fig. 7(a) and (b). The surface morphologies of ZnO show very fine particles with non-uniform sizes and shapes of granular structure [37]. The intercalation of LP into the interlayer gallery of ZLH via the direct reaction method seems to transform the irregular granular structure into a thin, sheet-like structure. Hence, the intercalation of LP was proven to change the surface morphology of the intercalation compound. Similar transformation was also reported in a recent study [32]. Fig. 7(c) shows the TEM image of the ZLH-LP intercalation compound. Based on the TEM image, a thin-like structure for the intercalation compound with various lateral sizes can be seen clearly.

3.7. Controlled release study of LP from ZLH-LP intercalation compound

The release profile for the controlled release study of LP from the ZLH-LP intercalation compounds in deionised water, NaCl solution and PBS solution at pH 4.8 and pH 7.4 as the release media are displayed in Fig. 8. The values presented are means of three replicates performed for each test and standard deviations are shown as error bars. Due to the anion exchange ability possessed by the ZLH host, the intercalated LP anions can be released and exchanged with the anions present in the release media [38]. Recent studies have shown that the occurrence of the anion exchange is because of the higher affinity, smaller size and higher charge density own by the phosphate, chloride and hydroxide anions compared to the anions intercalated into the host layered material hydroxide [29,39,40].

The results show that the accumulated release of LP from the interlayer gallery of ZLH-LP for all solutions begins rapidly, followed by slower release before saturated release is achieved. The percentage release of ZLH-LP does, however, vary in each solution. For the release of ZLH-LP in PBS solution at pH 4.8, a rapid release is found within 90 min, before reaching equilibrium at 120 min with 84.5% release. For the release of ZLH-LP in deionised water, the accumulated release is around 79.8%, with rapid release occurring until 150 min. Meanwhile, for the release of ZLH-LP in the other two release media, PBS solution at pH 7.4 and NaCl solution, the accumulated release in both solutions were recorded to be 63.8% and 61.8%, respectively.

Based on the release behaviour of LP from the ZLH-LP interlayer in PBS solution, it was obvious that the pH of the release media plays a very significant role in the accumulated release of the LP anion. The release of LP from ZLH-LP interlayer is faster in the PBS solution at pH 4.8 compared to pH 7.4, which may occur due to the different release mechanism [41]. This is because the ZLH layer is less stable due to the acidic environment at pH 4.8 [5], hence, enabling the release of LP anions from the ZLH-LP interlayer to occur through both the dissolution of the ZLH-LP layer as well as anion exchange (governed by a pseudo second order model, as proven in the next section). Meanwhile, in neutral conditions at pH 7.4, the ZLH-LP intercalation compound is more stable, thus resulting in the ZLH-LP intercalation compound only undergoing a surface diffusion mechanism (governed by the parabolic diffusion model, as proven in the next section). Therefore, this leads to a slower release rate, compared to the release at pH 4.8.

3.8. Kinetic study of ZLH-LP intercalation compound

In order to study the release kinetics of the LP anion, the data obtained from the release profile were fitted into several kinetic models, including zeroth order (Eq. (4)), first order (Eq. (5)) [42], pseudo second order (Eq. (6)) [43], parabolic diffusion (Eq. (7)) [44] and Fickian diffusion models (Eq. (8)) [45]. The equations are given as follows:

$$x=t+c \quad (4)$$

$$-\log(1-M_i/M_f) = t+c \quad (5)$$

$$t/M_i = 1/M_f^2+t/M_f \quad (6)$$

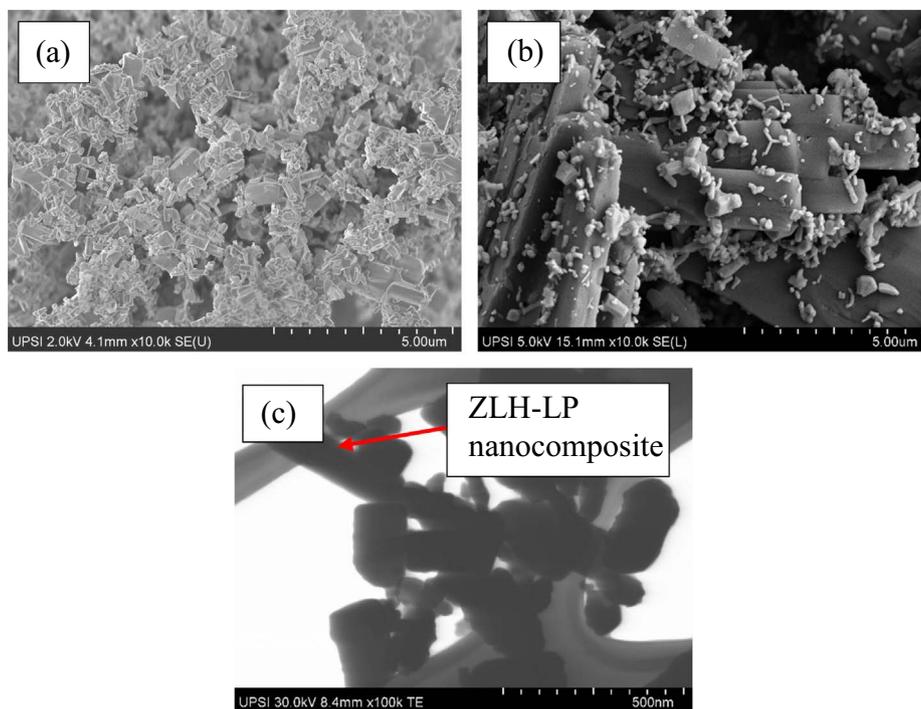


Fig. 7. (a) SEM images of ZnO, (b) SEM images of ZLH-LP intercalation compound (c) TEM image of ZLH-LP intercalation compound.

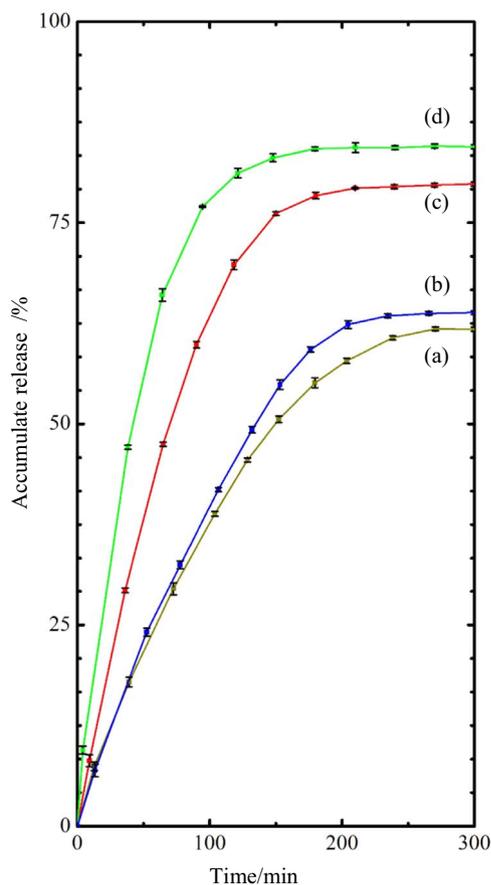


Fig. 8. Release profiles of LP anion from ZLH-LP intercalation compound into (a) sodium chloride solution, (b) PBS solution at pH 7.4, (c) deionised water and (d) PBS solution at pH 4.8.

$$M_i/M_f = kt^{0.5} + c \tag{7}$$

$$M_i/M_f = kt^n \tag{8}$$

where x is the percentage release of the intercalated LP anions at time t , c is a constant, M_i represents the initial concentration of the LP and M_f is the final concentration of the LP.

The zeroth, first and pseudo second order models can be used to determine the variable or concentration that affects the dissolution rate of the release, whereas the parabolic diffusion model is applicable in determining the diffusion-controlled release of the intercalated anions into the release media [46]. The Fickian model, on the other hand, can be applied to determine the rate of the respective release profile, where $n < 0.43$ (Fickian diffusion) is a slow release, $0.43 < n < 0.85$ (non-Fickian) is comparable diffusion and relaxation rates and $n > 0.85$ is a faster release [45]. The fitting of the LP anion release data to the zeroth order, first order, pseudo second order, parabolic diffusion and Fickian diffusion models into each release media (deionised water, NaCl solution, PBS solution at pH 4.8 and PBS solution at pH 7.4) are shown in Fig. 9. The corresponding rate constant, k , and regression values, r^2 , obtained from the fitting are summarised in Table 3. The regression values which are closest to 1 were taken as the best fit for the release.

Generally, the release of LP from the ZLH-LP intercalation compound in deionised water and PBS solution at pH 4.8 follow pseudo second order with regression values of 0.945 and 0.991, respectively. This result indicates that the release of LP from the ZLH-LP intercalation compound in both release media occurred via dissolution of the intercalation compound as well as anion exchange between the intercalated LP and the anions present in the release media. This result also corresponds to the result obtained in a recent study [47]. Meanwhile, for the release of LP in the other two media, NaCl solution and PBS solution at pH 7.4, the regression value obtained for parabolic diffusion model are acceptable and better than those obtained from the other models. The regression values for both NaCl solution and PBS solutions at pH 7.4 are 0.978 and 0.965, respectively. Generally, the parabolic diffusion model describes that the occurrence of the release process is controlled by intra particle diffusion or surface diffusion [47]. This result indicates that the release of LP from the interlayer gallery of

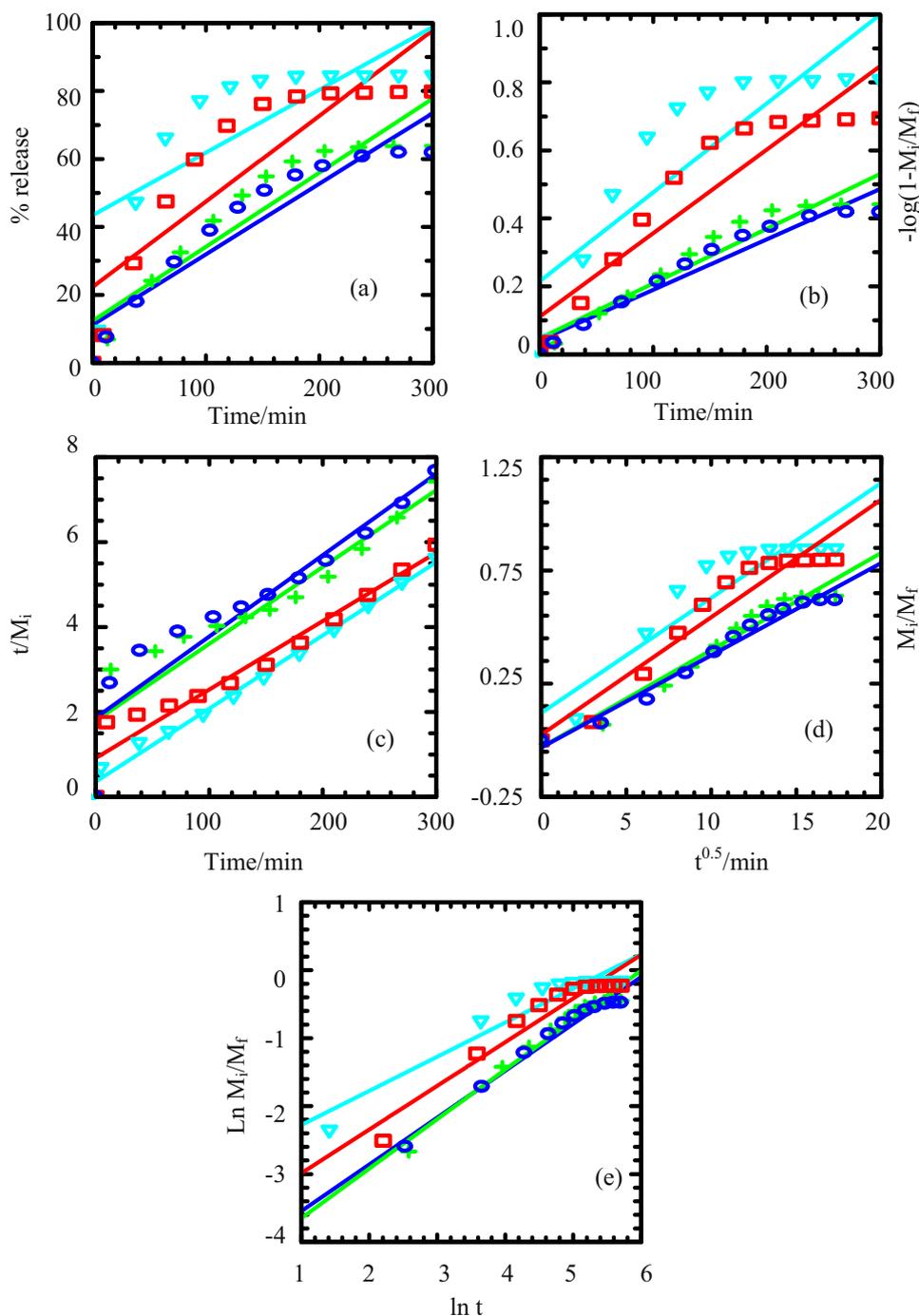


Fig. 9. Fitting of the LP anion release data to the (a) zeroth, (b) first, (c) pseudo second order, (d) parabolic diffusion and (e) Fickian diffusion models into (□) deionised water, (○) aqueous sodium chloride solution, (▽) aqueous PBS solution at pH 4.8 and (✚) aqueous PBS solution at pH 7.4.

Table 3
Comparison of rate constants, k , and regression values, r^2 , obtained from the fitting of the release data of LP in deionised water, NaCl solution and PBS solutions at pH 4.8 and pH 7.4.

Media	Zeroth Order	First Order	Parabolic Diffusion	Fickian Diffusion	Pseudo Second Order		
	r^2				r^2	$k (\times 10^{-2})$	$t_{1/2} (\text{min})$
Deionised water	0.766	0.865	0.927	0.924	0.945	1.61	52.68
PBS solution (pH 4.8)	0.579	0.760	0.861	0.903	0.991	1.72	33.66
Media	Zeroth Order	First Order	Pseudo Second Order	Fickian Diffusion	Parabolic Diffusion		
			r^2		r^2	$k (\times 10^{-2})$	$t_{1/2} (\text{min})$
NaCl solution	0.892	0.947	0.899	0.977	0.978	2.81	77.25
PBS solution (pH 7.4)	0.867	0.922	0.865	0.964	0.965	4.29	75.21

ZLH-LP intercalation compounds was governed by intra particle diffusion or surface diffusion via ion exchange, and is the rate-determining step in the release process.

Based on the fitting, the time taken required for the concentration of the LP to be half of the accumulate release, $t_{1/2}$, was calculated (Table 3). The results obtained show that the value of $t_{1/2}$ increases in the order of PBS solution at pH 4.8 < deionised water < PBS solution at pH 7.4 < NaCl solution. Higher $t_{1/2}$ values signify slower release behaviour possessed by the ZLP-LP in the particular release media. The release behaviour of the ion exchange process between the intercalated anions and the incoming anions in the release media is commonly influenced by the charge, charge density and hydrogen bonding own by each anions [48]. Even though the order of preference of anion during ion exchange process is $\text{Cl}^- < \text{OH}^- < \text{HPO}_4^{2-}$, the result obtained shows that the release of LP in PBS solution at pH 7.4 is slower compared to the release in the deionised media. This is due to the composition of the PBS solution used in the study are dominantly composed of Cl^- (98.75%) with a very small portion of H_2PO_4^- and $\text{H}_2\text{PO}_4^{2-}$ (1.24%). The very small portion of H_2PO_4^- and $\text{H}_2\text{PO}_4^{2-}$ present in the media during the release makes the presence of these phosphate anions less significant, compared to Cl^- . Hence, this results in the occurrence of slower release of LP in the PBS solutions, compared to deionised water. The results obtained in this study indicate that ZLH can be used to host a model anion guest, LP, for its controlled release properties.

3.9. PXRD studies of the recovered sample

So as to obtain some insight on the ion exchange phenomena of ZLH-LP in each release media, the sample remains after the ZLH-LP release study was recovered and PXRD analysis was then performed towards the samples. Based on the PXRD pattern of the recovered samples (Fig. 10), a reduction of interlayer basal spacing can be observed after the release experiment of ZLH-LP. In each PXRD pattern, the peaks of intercalated LP (16.3 Å) were diminished, and new peaks with smaller interlayer basal spacing, 9.2 Å and 7.8 Å appeared, which representing NO_3^- (in PBS at pH 4.8) and Cl^- (in PBS at pH 7.4 and NaCl solution), respectively [49]. The reduction of the interlayer basal spacing of the PXRD pattern is, therefore, indicates the occurrence of ion exchange process between the ZLH-LP and the ions present in the release media. The PXRD pattern of the recovered sample (9.2 Å for NO_3^- and 7.8 Å for Cl^-) is in agreement with ZLH- NO_3^- (JCPDS No. 01-072-0627)[34] and ZLH- Cl^- (JCPDS 01-077-2311)[50].

According to the release profile provided earlier, around 62% and 80% of ZLH-LP has been released in the PBS solution at pH 4.8 and pH 7.4, respectively. Hence, supposedly there were remaining LP still intercalated in the interlayer gallery of ZLH. The LP peak, however, was barely seen in the PXRD pattern of recovered sample released in both PBS at pH 4.8 and pH 7.4. This is due to the remaining 38% and 20% of LP inside the interlayer could not provide a significant presence of LP in the interlayer gallery of ZLH. Therefore, the higher percentage of NO_3^- and Cl^- in the recovered sample will make it more dominant than LP as the interlayer anion. The PXRD pattern of the recovered sample also revealed that even though a similar PBS solution were used in the release study of ZLH-LP in PBS solution at pH 4.8 and PBS solution at pH 7.4, the presence of NO_3^- , (originating from nitric acid added during pH alteration) lead to the selection of different anion during the anion exchange process.

3.10. FTIR studies of the recovered sample

FTIR spectra of the recovered samples from the release media were shown in Fig. 11. As can be seen from the FTIR spectra, certain peaks were disappeared and other peaks were emerging at the end of the release experiment. The changes observed from the FTIR spectra indicates that certain functional group found in the ZLH-LP nanocom-

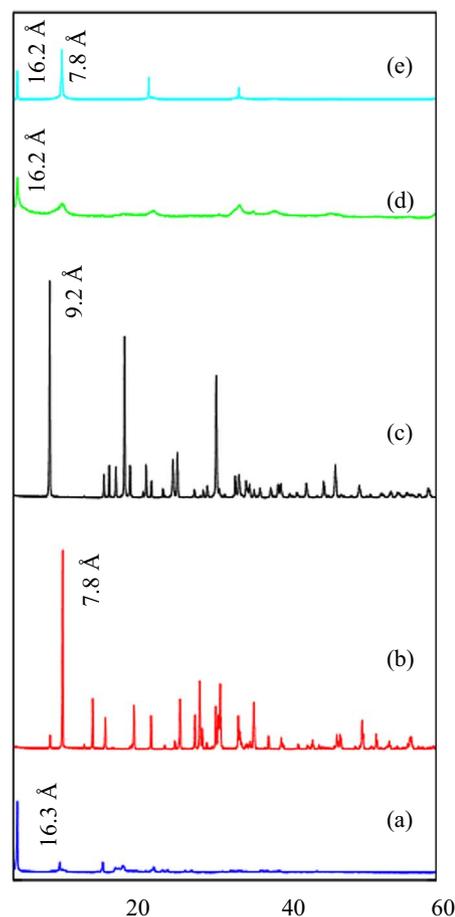


Fig. 10. The PXRD pattern of (a) ZLH-LP intercalation compound and recovered samples from (b) PBS solution at pH 7.4, (c) PBS solution at pH 4.8, (d) deionised water and (e) NaCl solution.

posite were no longer exist in the recovered sample, and were replaced with a new functional group that were resulting from the ion exchange between ZLH-LP nanocomposite and anion present in the release media.

In the FTIR spectra of recovered samples from PBS solution at pH 7.4, a strong peak appeared at 1018 cm^{-1} , which is associated with the Cl^- vibration. Even though there are other anions present in the PBS solution, the dominance of Cl^- ions (98.75%) have resulted in the occurrence of ion exchange between Cl^- ions and the LP ions via intra particle diffusion or surface diffusion (parabolic diffusion model). Similar peak was also observed in the FTIR spectra of the sample recovered from the release in the NaCl, which emerged at 1022 cm^{-1} . The peak appeared in the FTIR spectra of recovered samples from PBS solution at pH 7.4 and NaCl solution are parallel to their PXRD pattern (7.8 Å), which represents the presence of Cl^- [51]. The FTIR spectra of recovered samples from PBS solution at pH 4.8 reveal strong peak around 1374 cm^{-1} attributed to the antisymmetric stretching mode ν_3 of nitrate anion [52]. For the recovered samples from the deionised water, the pattern of the FTIR spectra is basically similar with the FTIR spectra of the ZLH-LP nanocomposite, except with lower intensity [53].

All of the FTIR spectra of the recovered samples consist of a peak in the range of $1600\text{--}1670\text{ cm}^{-1}$, which resembles the interlayer water molecule in the ZLH-LP intercalation compound. These peaks, however, appeared with lower intensity due to the ion occurrence of ion exchange with the ions in the release media. The existence of these peaks indicates that the recovered sample contains the LP moiety and the nanocomposite phase still remained in the interlayer of the recovered samples [53].

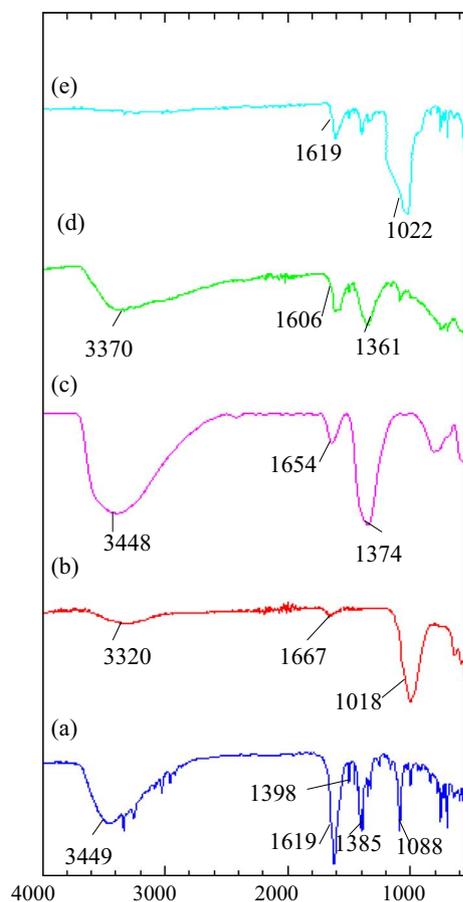


Fig. 11. The FTIR spectra of (a) ZLH-LP intercalation compound and recovered samples from (b) PBS solution at pH 7.4, (c) PBS solution at pH 4.8, (d) deionised water and (e) NaCl solution.

4. Conclusion

The intercalation of LP anions has been successfully achieved via a direct reaction method using ZnO as a precursor. The intercalation of LP into the interlayer gallery of ZLH was proven by the appearance of a new peak at a lower angle of 2θ with the basal spacing of 15.9–16.3 Å. The success of the intercalation process was supported by FTIR and elemental analysis. The percentages of the accumulated release of LP from the ZLH-LP intercalation compound is studied in four different release media, PBS solution at pH 4.8 and pH 7.4, deionised water, and NaCl solution, and were determined to be 84.5%, 63.8%, 79.8% and 61.8%, respectively. Based on the controlled release profile, the release behaviour of LP from its intercalation compound in all release media was determined. It was observed that the release of LP from the ZLH-LP intercalation compound in deionised water and PBS solution at pH 4.8 followed pseudo second order, meanwhile, the release of LP from the ZLH-LP intercalation compound in NaCl solution and PBS solution at pH 7.4 were governed by a parabolic diffusion model. The PXRD and FTIR studies performed on the recovered sample provide some understanding on the ion exchange phenomena of ZLH-LP in each release media. Due to the anion exchange ability possessed by the ZLH host, the intercalated LP anions can be released and exchanged with the anions present in the release media. Based on this result, it can be suggested that the novel synthesised ZLH-LP intercalation compound has potential to be used as a new generation material for controlled drug release.

Conflict of interest

None declared.

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