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Research Article

Design and evaluation of zinc-aluminium layered double hydroxide-palmitic acid nanocomposites: Synthesis, characterization and antimicrobial properties

Alsya Haneeza Mohd Shah[1,2], Sheikh Ahmad Izaddin Sheikh Ghazali[1*], Nurul Elysha Md Norizan[1], Nursyafiqah Jori Roslan[1], Nur Nadia Dzulkifli[1], Hamizah Mohd Zaki[3], Sandeep Poddar[4], Hari Shankar Biswas[5], Is Fatimah[6], and Vadym Kovalenko[7]

[1]Material, Inorganic and Oleochemistry (MaterInoleo) Research Group, School of Chemistry and Environment, Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), 72000 Kuala Pilah, Negeri sembilan, Malaysia
[2] Department of Chemistry Malaysia, Jalan Sultan, 46661 Petaling Jaya, Selangor, Malaysia
[3]Faculty of Applied Sciences, Universiti Teknologi MARA, 40450, Shah Alam, Selangor, Malaysia
[4]Lincoln University, Research and Innovation Division, WismaLincoln, 12-18, Jalan SS 6/12 Petaling Jaya, Selangor, 47301, Malaysia
[5]Department of Chemistry,Surrendranath College, 24/2, M.G. Road, Kolkata-09, India
[6]Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Kampus Terpadu UII, Yogyakarta 55584, Indonesia
[7]Department of Analytical Chemistry and Chemical Technologies of Food Additives and Cosmetics, Faculty of Chemical Technologies and Ecology, Ukrainian State University of Chemical Technology, Dnipro 749005, Ukraine

[*]Corresponding author: sheikhahmadizaddin@uitm.edu.my

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Abstract
An efficient drug delivery system lies in its bioavailability to improve therapeutic effects. Incomplete administration of drugs may lead to reduced drug efficacy, requiring patients to take higher doses or take the drugs more frequently. Therefore, this study aims to synthesize a nanocomposite that utilizes the layered double hydroxide as a carrier and improves its bioavailability. Zinc-aluminium layered double hydroxide (ZnAl-LDH) was synthesized using the co-precipitation method, and palmitic acid (PA) was intercalated into this carrier by anion exchange technique, resulting in a layered double hydroxide-palmitic acid (LDH-PA) nanocomposite. The successful intercalation process is confirmed by powder x-ray diffraction (PXRD) analysis, with an increased interlayer spacing from 8.6 Å to 14.5 Å due to including a larger anion in the interlayer. The absence of a nitrate peak at 1396 cm^{-1} and the presence of a newly formed COO^- peak at 1596 cm^{-1} in fourier transform infrared (FTIR) spectroscopy analysis also confirmed the presence of PA in the host layer. Energy dispersive x-ray (EDX) analysis showed that no nitrogen element could be detected in the nanocomposite. Instead, carbon dominated the distribution of the sample by 71.90%. The Brunauer, Emmett, and Teller (BET) surface area increased from 4.82 m^2/g for the ZnAl-LDH host layer to 21.35 m^2/g for LDH-PA, indicating that the nesting process had occurred. Antimicrobial activity tests showed that the synthesized nanocomposite could retain activity against *Escherichia coli* and *Klebsiella pneumoniae*, highlighting the potential of ZnAl-LDH as a vehicle for enhanced drug delivery systems. By uncovering its synthesis, characterization, and potential applications, this research contributes valuable insights to the pharmaceutical industry. Further exploration of its applications and optimization strategies holds promise for addressing current challenges in drug delivery and infectious disease management.

Keywords: drug delivery system, anion exchange technique, *Escherichia coli*

Introduction

Nanocomposites have become a revolutionary field of research in materials science as they offer advantages and alternatives to overcome the obstacles of today's engineering materials. A nanocomposite is a multiphase composite material in which one of the phases has a nanoscale morphology or dimensions of 10-100 nm [1]. Nanocomposites have many advantages. The most significant advantage is their excellent mechanical properties, as they have improved strength, toughness, and ductility compared to conventional composites due to a high surface-to-

volume ratio [2]. In addition, the nanocomposite is considered a versatile and flexible material, as the nanoparticles' size, shape, and composition can be customised and designed by researchers to exhibit a wide range of properties. This expands the application potential of nanocomposites, which range from electronics to medicine.

In the medical field, nanocomposites such as layered double hydroxide (LDH) show great potential due to their advantages, such as biocompatibility, antigenicity, acceleration of tissue regeneration, biodegradability, bioactive interface, and controlled release of drugs, especially in drug delivery studies [3]. LDHs are an example of a two-dimensional (2D) nanocomposite and have been described as an anionic clay that exhibits similar properties to naturally occurring brucite ($Mg(OH)_2$). This compound comprises a positively charged host layer formed by partially substituting divalent (M^{2+}), such as Zn^{2+} cations, by trivalent (M^{3+}), such as Al^{3+} cations. This positive charge deficit is compensated by anions located in the interlayer space and bound to water molecules [4]. The easily accessible interlayer allows them to exchange anion and organic-inorganic intercalation. These properties can potentially be great carriers for drug delivery systems where the drug can be intercalated and deintercalated into the interlayer of the LDH host.

PA also known as hexadecenoic acid, exhibits diverse applications owing to its notable advantages. Above all, its high stability, oxidation resistance, and ability to prevent rancidity make it an effective preservative in the food industry. In addition, PA is primarily used in the production of soaps, cosmetics, and pharmaceutical products. Furthermore, PA was claimed to be an effective antibacterial agent as it inhibits gram-negative and gram-positive bacteria [5]. However, the research on PA as an antibacterial drug and its bioavailability is still limited. An efficient drug delivery system depends on the bioavailability of the drug to improve its therapeutic effect. Incomplete administration of drugs may lead to reduced efficacy, requiring patients to take higher doses or more frequently [6]. Therefore, this research aims to develop a drug delivery system using the LDH nanocomposite as a carrier to protect the drug and improve its bioavailability while reducing the negative effects on the biological process.

In this study, zinc-aluminium-layered double hydroxide (ZnAl-LDH) hosts were synthesised using co-precipitation methods, and different concentrations of PA were intercalated into the interlayer of the host as the guest anion through anion exchange method. Then, the synthesised LDH-PA nanocomposites were characterised in terms of its physicochemical properties using different instrumentations such as Fourier Transform Infrared with Attenuated Total Reflectance (FTIR-ATR), Powder X-ray Diffraction (PXRD), Field Emission Scanning Electron Microscope with Energy Dispersive X-ray (FESEM-EDX), Brunauer, Emmett, and Teller (BET) analysis and Thermogravimetric Analysis-Derivative Thermogravimetric (TGA-DTG).

Materials and Methods

Chemicals

The chemicals that were used for synthesising the nanocomposite are aluminium nitrate nonahydrate, $Al(NO_3)_3 \cdot 9H_2O$ (R&M Chemicals), zinc nitrate hexahydrate $Zn(NO_3)_2 \cdot 6H_2O$ (R&M Chemicals) and palmitic acid (Sigma Aldrich). *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), and *Klebsiella pneumoniae* (ATCC 700603) are the bacteria that were used in the antibacterial activity studies and ciprofloxacin (Sigma Aldrich) as the positive control. The other chemicals that were used are hydrochloric acid, HCl (Merck), sodium hydroxide, NaOH (R&M Chemicals), dimethyl sulfoxide, DMSO (Sigma Aldrich), Mueller Hinton Agar (MHA), Mueller Hinton Broth (MHB) deionized water along and nitrogen gas.

Preparation of nanocomposite

A direct co-precipitation method was used to synthesise the ZnAl-LDH host in a nitrate form. A 1:4 ratio of $Al(NO_3)_3 \cdot 9H_2O$ and $Zn(NO_3)_2 \cdot 6H_2O$ were mixed in a conical flask, agitated with a magnetic stirrer, and under a setting where nitrogen gas was continuously purged into the mixture to prevent the dissolution of ambient carbon dioxide. The pH was adjusted to pH 7.5 [7] with NaOH. The solution was then aged at 70°C for 18 hours in an oil bath shaker. Then, it was left to cool at room temperature before centrifugation and filtration processes were performed to reclaim the precipitate. The precipitate was dried in an oven at 70°C for 72 hours [8], and the resulting product was characterised using FTIR and PXRD for ZnAL-LDH confirmation. Next, the anion exchange method was used to synthesize the LDH-PA nanocomposite. First, 1:9 deionized water and methanol were used to dissolve palmitic acid. Then, 0.35 g of previously synthesized ZnAL-LDH host was added into 25mL of 0.05 to 0.2 M of PA and stirred for 7 hours. It was aged at 70°C for 18 hours, and the final product of LDH-PA was reclaimed in the same step as previous [8].

Characterization

Perkin Elmer Spectrum 100 spectrometer was used to record the FTIR absorption spectra of the samples, and the wavelength was set from 4000 to 650 cm^{-1}. PXRD analysis was done using the PANalytical X'pert Pro

model operating under Cu Kα radiation at 40 mA and 45 kV (λ = 1.5418 Å). The data was gathered in the range of 2θ = 2°-70°. FESEM-EDX spectroscopy was used to determine the surface morphology and elemental composition. TGA-DTG with a TA Q500 (Manual sampler) model was used, with a heating rate of 10 min^{-1}. Micrometric ASAP 2060 with nitrogen gas adsorption-desorption at 77 K was used to acquire the surface area and pore size distribution.

Antimicrobial study

The disc diffusion method was used to test the bactericidal activity of PA, ZnAl-LDH, host, and 0.2M LDH-PA nanocomposite on sterile Mueller Hinton Agar (MHA). Three species of pathogenic bacteria were tested: *Escherichia coli, Staphylococcus aureus,* and *Klebsiella pneumoniae*. A blank sterile paper disc with a diameter of 6 mm was impregnated with 30 µL working concentration of the samples together with 5% dimethyl sulfoxide (DMSO) as negative control and positive control (ciprofloxacin), placed onto the prepared agar. The plates were then incubated at 35°C for 16-18 hours. The inhibition zone of the pathogens against the sample disc was measured using a ruler [9].

Results and Discussion

X-ray diffraction analysis

The PXRD pattern of PA, ZnAl-LDH host, and LDH-PA nanocomposite synthesized at different concentrations of PA ranging from 0.05 to 0.2 M were shown in **Figure 1**. The diffractogram pattern for the ZnAl-LDH host shows an intense line located at lower 2θ, conforming to a high crystallinity of the synthesized compound. The well-identifiable peak is located at 10.31° with a basal spacing of 8.6Å, indicating the typical basal spacing of LDH with nitrate as counter anion [8]. The resulting nanocomposite of 0.05 M LDH-PA and 0.1 M LDH-PA have expanded from 8.6 Å to 14.3 Å, indicating the successful intercalation of PA into the host interlayer. However, the existing nitrate anion did not fully replace the PA compared to 0.2 M LDH-PA, which has a broad reflection peak with a basal spacing of 14.5 Å. The diffraction peaks for both 0.05 M and 0.1 M nanocomposites are sharp and slightly shifted to a lower 2θ angle = 6.16°, indicating that the gallery height has slightly increased. The small extension of gallery height could be attributed to the orientation of the nitrate anion, which is slightly inclined to the surface layers and held in place by electrostatic forces [10]. When the electrostatic interaction between the counter anion and the surface layer grows, the basal spacing value decreases due to stronger electrostatic attraction [11]. Moreover, a small fraction of carbonate contamination can be observed around 2θ angle = 20-30° for all nanocomposites and the LDH host, which is caused by the interference of atmospheric carbon dioxide [12]. As the molarity increased to 0.2 M, the diffraction peaks nanocomposite portrayed that the diffraction peak was shifted to a lower 2θ angle = 6.07° and it might potentially be attributed to polymorphic change as the nitrate anion was removed from the interlayer area. The significant increase in basal spacing and shifted peak to a lower 2θ angle indicates successful intercalation of bigger anions in the interlayer space. Thus, it is notable that the palmitic acid anion can be intercalated in the interspacing at a higher concentration of 0.2 M.

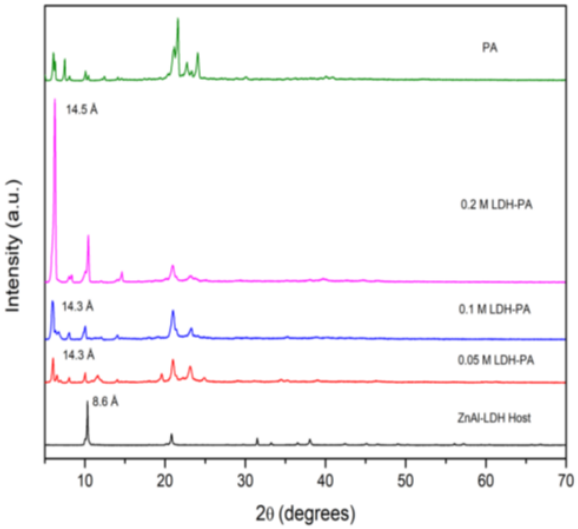

Figure 1. PXRD study for PA, ZnAl-LDH host, and various concentrations of LDH-PA

Infrared study

FTIR spectra of PA, ZnAl-LDH, and different concentrations of LDH-PA were displayed in **Figure 2**. The absorption band for the host was dominated by a high-intensity nitrate (NO_3^-) ion stretching band at 1369 cm^{-1}. Furthermore, the broad absorption band observed at 3474 cm^{-1} showed the presence of O-H stretching vibration of the hydroxyl groups of inorganic layers and water molecules in the interlayer. The presence of a weak band at a lower wavenumber of 607.66 cm^{-1} indicates the bending vibrations of metal-OH. Based on the FTIR spectra of PA, a band at 1635 cm^{-1} confirms the visibility of the carbonyl (C=O) of the carboxylic compound, and the emergence of a medium peak at 1280 cm^{-1} indicates C-O stretching frequency of the COOH functional group. Moreover, strong stretching bands at 2917 cm^{-1} and 2849 cm^{-1} indicate the occurrence of antisymmetrical and symmetrical stretching vibration of the $-CH_2$ group of PA, respectively. A peak at 3431 cm^{-1} is associated with the stretching vibration of the O-H groups from COOH.

The LDH-PA spectral pattern that assembles the host and PA mixture suggests successful intercalation of PA inside the host. A broad absorption band of the O-H hydroxyl group and interlayer water molecule belonging to the host was visible at 3410 cm^{-1} to 3439 cm^{-1} for all LDH-PA. In addition, the C-H band of the alkane group of PA is spotted at each concentration, implying that this compound is present in the layer of the LDH host. The presence of a COO^- peak at 1557 cm^{-1} and 1596 cm^{-1} region of all LDH-PA spectra signifies that the drug was integrated into the interlayer. The absence of the nitrate peak at 0.05, 0.1 M, and 0.2 M implies that these concentrations successfully accommodated the palmitic acid in the LDH layer. In distinction, no carboxylic component is detected in the FTIR spectra of the ZnAl-LDH host. Table 1 shows the main peaks and functional groups for the LDH host and the nanocomposites.

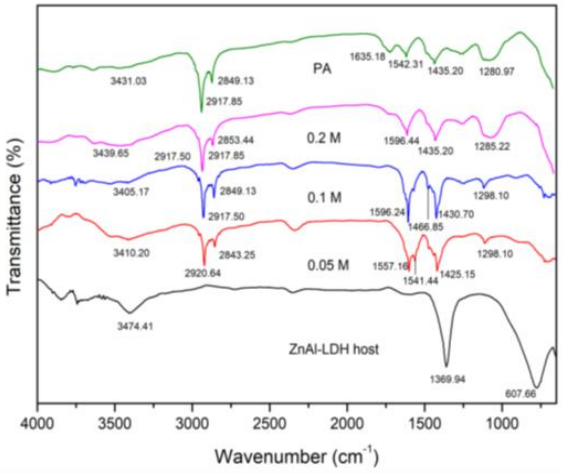

Figure 2. FTIR spectra of PA, ZnAl-LDH host, and various LDH-PA concentrations

Table 1. Peaks observed in IR spectra for the host and its nanocomposites

Sample	Functional Group	Observe Peaks (wavenumber, cm^{-1})
PA	O-H stretch (hydroxyl)	3431
	C=O stretch (carboxyl)	1635
	C-O stretch (carboxyl)	1280
	C-H stretch	2917, 2849
ZnAl-LDH host	O-H stretch, bend (water molecules)	3474
	NO_3^- ion	1369
LDH-PA (0.05 M)	O-H stretch (hydroxyl)	3410
	COO- ion	1557
	C-H stretch	2920, 2843
LDH-PA (0.1 M)	O-H stretch (hydroxyl)	3405
	COO- ion	1596
	C-H stretch	2917, 2849
LDH-PA (0.2 M)	O-H stretch (hydroxyl)	3439
	COO- ion	1596
	C-H stretch	2917, 2849

Microscopic morphology study

From the EDX pattern of the host in **Figure 3(a)**, the percentage of zinc (Zn) has a value of 13.7%, while the percentage of nitrogen (N) has a value of 1.7%. This composition reflects the structure of the ZnAl-LDH host, which is mainly composed of the nitrate anion and the main divalent cation, Zn. Next, based on **Figure 3(b)**, the percentage of carbon (C) of LDH-PA is increased to 71.9%, and the absence of nitrogen (N) indicates that the PA compound was intercalated into the host and replaced the host's existing nitrate anions.

Figures 4(a) and (b) show the FESEM image of the ZnAl-LDH host and LDH-PA nanocomposite. For the ZnAl-LDH host, the typical morphology of layered material, which displays aggregated plate-like with non-uniform particles of different sizes and shapes as described in the previous study, namely a highly aggregated, irregular plate assembled layer by layer [9]. After the PA had intercalated into the interlayer region of ZnAl-LDH host, the structure changed into a smaller size, which appeared as non-uniform, aggregated hexagonal and small-edged particles combined with flaky plate shape materials and more compact with higher surface area.

Thermogravimetric study

The thermal behaviour of the PA, ZnAl-LDH host, and LDH-PA was examined using differential thermogravimetric analysis, as shown in **Figures 5 (a), (b),** and **(c)**. The thermal degradation of pure PA at 243 ºC resulted in 76.3% weight loss through evaporation [12]. PA's longer carbon skeleton ($C_{16}H_{32}O_2$) requires a greater breakdown temperature due to the increased force. Figure 5(b) shows the thermal degradation of the ZnAl-LDH host that undergoes two exothermic processes. The first decomposition happens at 158.8ºC with 14.4% weight loss due to the removal of the physisorbed water from the internal and external LDH structures. The second exothermic reaction shows that the host's weight was reduced by 13.0% at 439°C due to the loss of water molecules between layers, creating metal oxides [8,13]. The intercalated compounds were observed, as shown in **Figure 5(c)**.

The DTG results revealed an endothermic event in the first thermal degrading phase in which phase change begins to occur and accelerate the melting process to break the crystallinity of the brucite-like layers. It also increases the enthalpy of the thermal event, which linearly increases the endothermic value [13]. Interestingly, during the degradation step of the DTG curve, an elevated endothermic peak develops at 186°C due to the formation decomposition of the hydroxide layers and interlayer species. The TGA-DTG data, corresponding to the FTIR data, show that nanocomposites are formed by strong interactions (electrostatic attractions between opposite charges, H-bond, and Van der Waals force) between the guest anion and host layers.

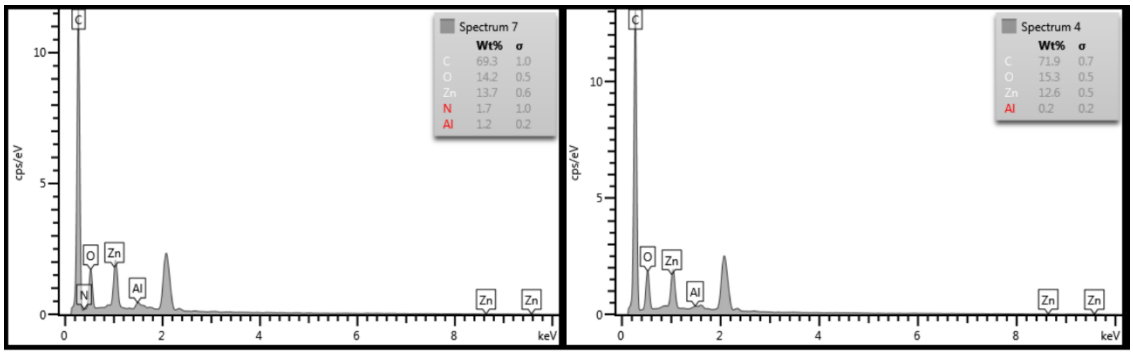

Figure 3. EDX pattern for (a) ZnAl-LDH host, (b) 0.2 M of ZnAl-LDH-PA

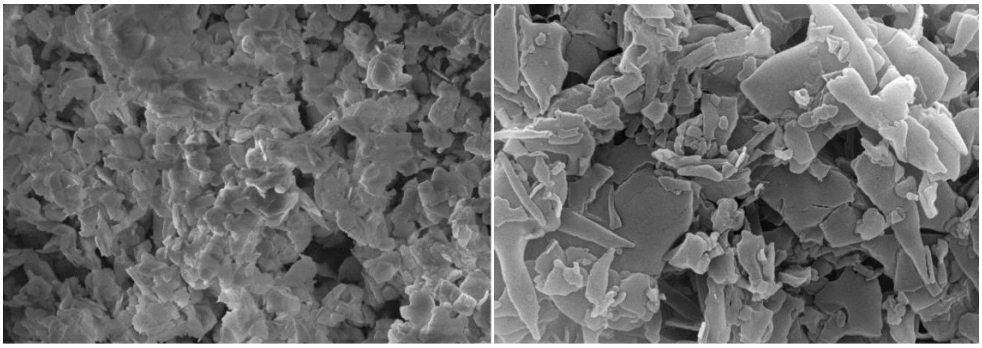

Figure 4. FESEM images of (a) ZnAl-LDH host at 15,000× magnification, (b) LDH-PA at 10,000× magnification

Surface area and porosity study

The nitrogen adsorption-desorption isotherms and pore size distribution for the ZnAl-LDH host and LDH-PA are all portrayed in **Figures 6** and **7**. Both nanocomposite and host demonstrated the Type IV isotherm with the H3 hysteresis loop of the International Union of Pure and Applied Chemistry (IUPAC) standard, demonstrating that the materials were mesoporous. This sort of H3 hysteresis loop was caused by the non-rigid aggregates of plate-like particles, which gave rise to slit-like pores [14]. BET measurements demonstrate the total pore volume increased from 4.0 to 50.0 cm^3/g before PA was intercalated into the host. It has also been found that the loss of NO_3^- ions increases the total pore volume of mesoporous LDH. However, the intercalated compound exhibited fast adsorbate uptake of nitrogen at pore volumes ranging from 0.07 to 10.0 cm^3/g and a relative pressure of 1.0. Furthermore, the variability in pore shape and distribution for both hosts and guests is due to the creation of interstitial pores between particle and crystallite sizes during the interleaving process.

The BET and Barrett, Joyner, and H"lenda (BJH) methodologies describe the surface area and porosity of ZnAl-LDH and LDH-PA. The BET surface area increased from 4.82 m^2/g for the ZnAl-LDH host to 21.35 m^2/g for LDH-PA. The increased surface area of the nanocomposite implies that the interleaving process has occurred, which is consistent with the expansion in basal spacing seen in **Figure 1**. In addition, including bigger nanocomposite anions creates more pores in the crystallites, increasing the surface area for the intercalated compound.

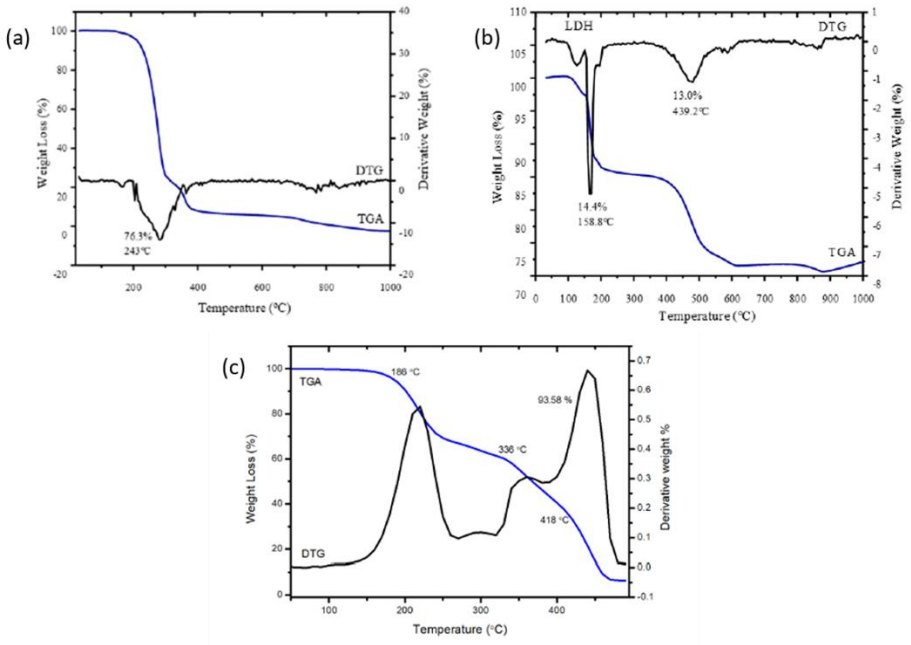

Figure 5. Thermogram of (a) Palmitic acid, (b) ZnAl-LDH host, and (c) LDH-PA

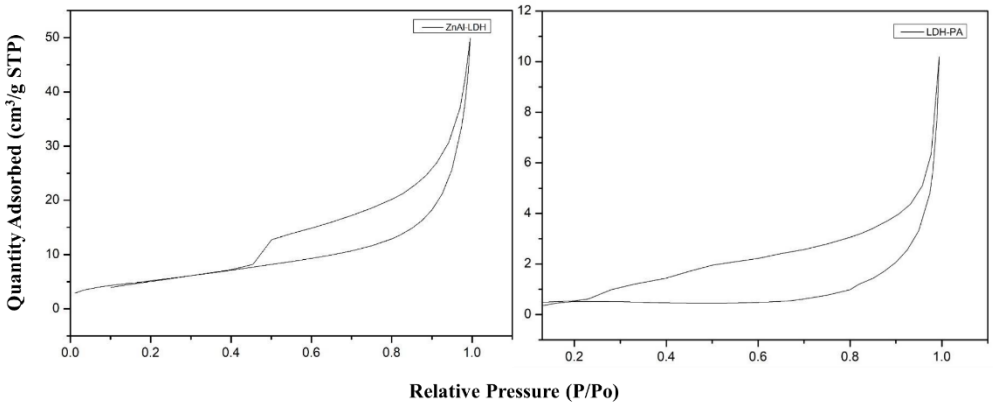

Figure 6. Adsorption-desorption isotherm of ZnAL-LDH (left) and LDH-PA (right)

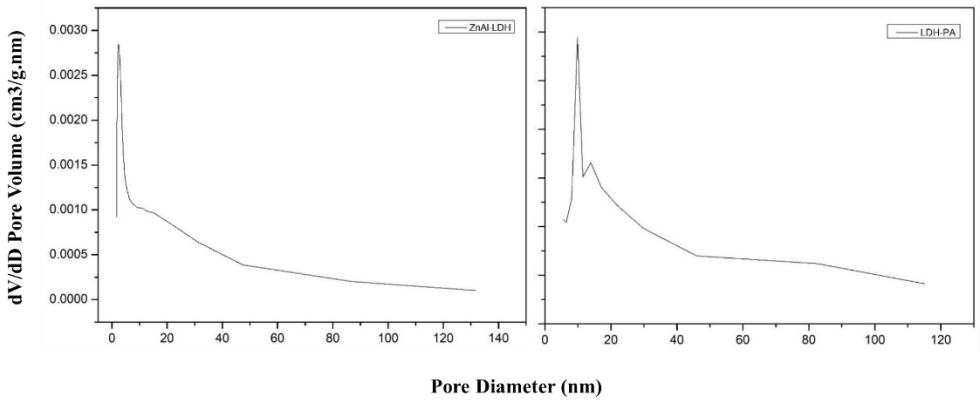

Figure 7. Pore size distribution of ZnAl-LDH (left) and LDH-PA (right)

Antimicrobial study

The results of the antimicrobial susceptibility test against bacteria for PA, ZnAl-LDH, and LDH-PA nanocomposites are shown in **Figure 8**. Based on the recorded inhibition zone, it can be observed that the LDH-PA inhibits *K. pneumoniae* more efficiently than *E. coli* and *S. aureus,* with an inhibition zone diameter of 1.0 cm. The zone of the ZnAl-LDH host against those bacteria has a constant value of 0.7 cm, which is considered smaller, followed by the drug (PA). Gram-negative bacteria, such as *E. coli* and *K. pneumoniae,* have a negatively charged outer membrane due to the presence of lipopolysaccharide. The electrostatic attraction of positively charged LDH to the negatively charged surface of gram-negative bacteria promotes contact and, perhaps, membrane rupture. This finding demonstrates that the drug is loaded into the host and that the host can transport the drug without altering its antibacterial capabilities. LDH-PA nanocomposite results show an inhibitory zone occurred on *K. pneumonia* and *E. coli* but not on *S. aureus*. This can be explained by the bacteria's varying susceptibility to the antibacterial actions of LDH. Previous studies reveal that zinc-based LDH's antibacterial mechanism involves direct surface contacts, which can impede bacterial growth. The specific ability of zinc in LDH to interact with bacterial cells may vary between various bacterial strains, resulting in varied amounts of inhibition [15]. As a result, the absence of an inhibitory zone for *S. aureus* could be due to its lesser susceptibility to the antibacterial activities of ZnAl-LDH. However, assessing the antimicrobial activity of the layered double hydroxide (LDH) host, PA, and its nanocomposites revealed a less successful outcome, as evidenced by the observation of smaller inhibition zones compared to the desired outcome.

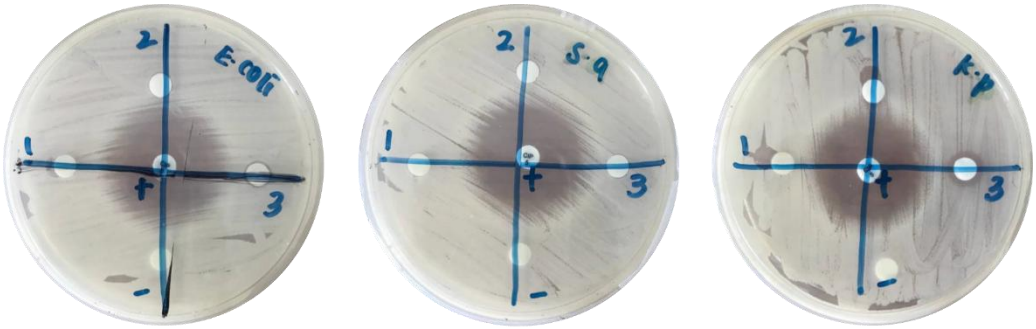

Figure 8. Inhibition zone diameter of (1) PA, (2) ZnAL-LDH host, and (3) 0.2 M ZnAl-LDH-PA on (a) *E.Coli,* (b) *S. aureus* and (c) *K. pneumoniae*

Conclusion

The ZnAl-LDH host was successfully synthesised via the co-precipitation method, and PA was intercalated at 0.2 M concentration via the anion-exchange method. The absence of the NO_3^- peak at 1369 cm^{-1} and the appearance of the COO^- ion band at 1596 cm^{-1} in the FTIR spectrum for LDH-PA nanocomposite proved that the compound was incorporated into the host in a palmitate form. Moreover, PXRD analysis revealed that the basal spacing of 0.2 M of LDH-PA increased from 8.6Å to 14.5Å, indicating that NO_3^- was replaced by the larger palmitate anion. This is supported by EDX analysis, which shows that no nitrogen element was detected in 0.2 M LDH-PA. Instead, carbon elements dominated the distribution of the sample about 71.9%. The BET surface area increased from 4.82 m^2/g for the ZnAl-LDH host to 21.35 m^2/g for LDH-PA. Incorporating the drug into the host enhanced the thermal stability, as evidenced by the weight loss of palmitic acid at a higher temperature upon integration into the host. Lastly, the antimicrobial studies show that 0.2 M of LDH-PA nanocomposite was effective against *K. pneumoniae* and *E. coli* but not against *S. aureus*. The antimicrobial activity appears less successful, as indicated by the smaller inhibition zone observed. However, it could be said that LDH-PA acts as a potential drug carrier because it tends to inhibit bacteria. To conclude, this study highlights the ability of ZnAl-LDH to be a potential vehicle for PA drug delivery systems and contribute valuable insights to the pharmaceutical industry.

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