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Vitamin B_3 Intercalated in Layered Double Hydroxides: A Drug Delivery System for Metabolic Regulation

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Cite This: *ACS Omega* 2024, 9, 32962−32968

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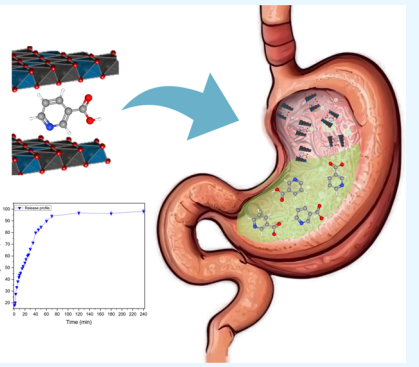
ABSTRACT: The organic compound niacin or nicotinic acid, also known as vitamin B_3 ($VitB_3$), is essential for human nutrition and metabolic regulation. However, in high doses, it can provoke side effects, such as hyperglycemia, liver damage, and flushing. Development of a controlled release system that slowly releases $VitB_3$ into the organism would avoid high dosing peaks, thus contributing to decrease the occurrence of side effects in nutritional supplementation. Here, we show that the slow and controlled release of $VitB_3$ in an acid environment can be achieved via its intercalation in layered double hydroxides (LDHs). The synthesis of a ZnAl-$VitB_3$ system is shown, in which $VitB_3$ is intercalated in a ZnAl LDH. The presence of $VitB_3$ in the ZnAl-$VitB_3$ system was confirmed by elemental analysis, infrared (FTIR) and NMR spectroscopy, while successful intercalation in the LDHs was revealed by powder X-ray diffraction (PXRD). In vitro release tests were carried out in a concentrated HCl solution of pH 1.5, a pH similar to the human stomach environment. The results showed a steady release of $VitB_3$ from the LDH host, with 90% of the vitamin liberated in the first 60 min after the suspension of the LDH in the acidic solution.



1. INTRODUCTION

Vitamins are organic compounds needed by humans in small amounts for metabolic and physiological functions. As many of them are not synthesized by the human body, they must be obtained from external sources, e.g., from nutrition and/or supplementation. Vitamins can be classified based on their absorption process as fat-soluble vitamins (e.g., Vitamins A, D, E, and K) and water-soluble vitamins (e.g., Vitamin C and all of the B vitamins).[1−3] Vitamin B_3, also known as nicotinic acid or niacin, has a molecular formula of $C_6H_5NO_2$ (Figure 1) and is a water-soluble vitamin, absorbed in the stomach and small intestine. It is naturally found in foods of animal and vegetable origin. Since 1950, it has been used in high doses to treat dyslipidemias (high levels of lipids), and due to its high absorption in the organism, the patient may experience side effects such as hyperglycemia, liver damage, and flushing.[4−6] These side effects can be avoided if vitamin B_3 is slowly released into the organism after intake, with the additional benefit of decreasing the necessity of frequent intake by the patient. One way to optimize drug action and minimize side effects is to store the vitamin in a delivery host system that slowly releases it when in contact with the acid solution of the human stomach.[7−9] In this regard, layered double hydroxides could be used as host systems.

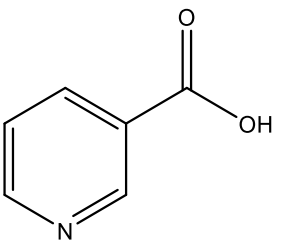
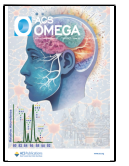


Figure 1. Structural formula of vitamin B_3 (niacin or pyridine-3-carboxylic acid, pK_a = 4.85).

Layered double hydroxides (LDHs) are clay-like layered materials with the general formula $[M^{II}_{1-x}\ M^{III}_{x}\ (OH)_2](A^{n-})_{x/n}\cdot mH_2O$ that can incorporate anionic species (A^{n-}) in their interlayer space. They are formed by the stacking of $M^{II}_{1-x}M^{III}_{x}(OH)_2$ double hydroxide layers in which the divalent (M^{II}) and trivalent (M^{III}) metal cations can be wisely chosen to maintain the biocompatibility of the system. Based on this flexibility in composition, LDHs have been used as delivery systems for anti-inflammatory medication,[10−12] antibiotics,[13] vitamins,[14] and anticancer drugs.[15]

Received: April 24, 2024
Revised: June 12, 2024
Accepted: July 9, 2024
Published: July 17, 2024



LDHs are easy to prepare via green and biocompatible synthetic routes.[16] LDHs containing M^{II} = Zn^{2+} or Mg^{2+} and M^{III} = Al^{3+} have already been demonstrated to be biocompatible.[17−20] LDHs decompose at acid pH, releasing the interlayer anions as the consequence of a controlled dissolution process due to acid attack.[21] Based on these properties, here we propose the synthesis of a $VitB_3$-intercalated LDH composed of Zn^{2+} and Al^{3+} (here, named ZnAl-$VitB_3$) and investigate its in vitro controlled release properties in an acidic condition mimicking the pH of the human stomach. The successful uptake of $VitB_3$ by the ZnAl-$VitB_3$ during synthesis was confirmed by elemental analysis, Fourier transform infrared (FTIR) and NMR spectroscopy, while successful intercalation in the LDH was revealed by powder X-ray diffraction (PXRD) measurements. The $VitB_3$ release properties of the system were tested in a concentrated HCl solution of pH 1.5, showing that 90% of the $VitB_3$ in the host system is liberated within the first 60 min of contact with the acidic solution.

2. MATERIALS AND METHODS

2.1. Materials. All chemicals were purchased and used without further purification, including the metal precursor salts $Zn(NO_3)_2{\cdot}6H_2O$ (98% mol, Vetec) and Al $(NO_3)_3{\cdot}9H_2O$ (98% mol, LabSynth), nicotinic acid ($VitB_3$, 97% mol, Vetec), and chloridric acid (HCl, 37% vol, Sigma-Aldrich).

2.2. Synthesis. Intercalation of $VitB_3$ in the LDHs was achieved by coprecipitation of Zn^{2+} and Al^{3+} at constant pH in a solution containing dissolved $VitB_3$.[22] A 0.7 mol·L^{-1} solution of $VitB_3$ was prepared by dissolving $VitB_3$ in 200 mL of deionized water and adjusting the pH to pH 8 to deprotonate its acid group. The LDHs intercalated with $VitB_3$ were prepared by dosing into the $VitB_3$ solution 10 mL of a metal solution containing 0.333 mol·L^{-1} of $Al(NO_3)_3{\cdot}9H_2O$ and 0.666 mol·L^{-1} of $Zn(NO_3)_2{\cdot}6H_2O$. During dosing, the pH of the $VitB_3$ solution was stated to pH 8 by an automatic titrator (Titrino 702 SM, Metrohm, Switzerland) that controlled the dosing of a 1 mol·L^{-1} NaOH solution in the synthesis pot. The solution was stirred at a constant stirring of around 100 rpm during the synthesis. After the dosing of the metals was finished, the produced slurry was stored in an oven at 60 °C for 2 days to optimize crystallization. After that, the solid phase was recovered by centrifugation and washed with deionized water several times to dilutions of more than 100 times to remove residual ions. The solid was subsequently dried at 60 °C for 4 days in an oven.

2.3. Characterization. XRD measurements were performed in the Bragg−Brentano geometry on a D8 Discover diffractometer (Bruker) equipped with a Cu Kα radiation source (λ = 1.5418 Å, 40 kV and 30 mA) and a Lynxeye detector. The 2θ angle between the incidence and the detection directions ranged from 4 to 70° in steps of 0.05° using an integration time of 1.5 s while the sample was rotated perpendicularly to the incident beam at a rate of 20 rpm. CHN elemental analysis was performed in a PerkinElmer 2400 series ii Elementary Analyzer to determine the concentration of carbon, hydrogen, and nitrogen (CHN) through the Pregl-Dumas method. Inductively coupled plasma optical emission spectrometry (ICP-OES) was performed in a Spectro Arcos analyzer (SPECTRO Analytical Instruments GmbH, Germany) to analyze the Zn and Al contents of the LDH sample. Thermogravimetric analysis was carried out using a Thermogravimetric analysis (TGA) Q500 (TA Instruments) from room temperature up to 800 °C at a heating rate of 5 °C min^{-1} using an airflow of 60 mL min^{-1}. The Fourier transform infrared (FTIR) spectrum shown was recorded in the range 400 to 4000 cm^{-1} in a PerkinElmer Frontier FTIR spectrometer using sample-embedded KBr pellets. Nuclear magnetic resonance spectroscopy was performed in a Bruker Avance II+ 400 MHz spectrometer equipped with a 4 mm triple resonance solid-state magic angle spinning (MAS) probe. ^1H direct excitation and $^1H-^{13}C$ CPMAS spectra were acquired at 22 °C at a MAS rate of 15 kHz. For the measurement, the sample was packed in a 4 mm ZrO_2 rotor. Mass spectrometry (MS) experiments were performed using a linear quadrupole ion trap MS (LTQ XL, Thermo Scientific, San Jose, CA) equipped with a heated electrospray source (HESI) using N_2 as nebulizer, sheath, and dry gas (Peak Scientific, NM32LA model). The mass spectrometry data was obtained by direct infusion of the samples solubilized and diluted in acetonitrile at a final concentration of vitamin B_3 of 10^{-5} mol L^{-1} at a flow rate of 3 μL min^{-1}. The solutions containing LDH were filtered (0.45 μm PTFE filter) before analysis. The MS spectra were acquired in positive mode with a mass scan range of m/z 60−140, a maximum inject time of 10 ms, and averaging 5 spectra. The spray voltage was 4.0 kV, the temperature was set at 275 °C, and the dry gas (N_2) flow rate was 15 arb.

2.4. In Vitro Drug Release. The drug release profile was determined in an in vitro assay. The experiment was performed using an HCl aqueous solution of pH 1.5 at 37 °C and with magnetic stirring at 100 rpm. 200 mg of ZnAl-$VitB_3$ were dissolved in 200 mL of this HCl solution, and, at different time intervals, 2 mL aliquots were removed, and the same volume of the original HCl solution was replenished. This procedure was repeated until the maximum time of 240 min was reached. The concentration of vitamin B_3 in the aliquots was determined by ultraviolet−visible (UV−vis) spectrophotometry using a double beam UV-2700i (Shimadzu) equipped with a double monochromator previously calibrated for $VitB_3$ determination using standard $VitB_3$ solutions of known concentrations. The spectra were analyzed in the range of 260 to 400 nm.

3. RESULTS AND DISCUSSION

The intercalation of $VitB_3$ within the hydroxide layers of LDHs was achieved here (sample dubbed ZnAl-$VitB_3$) by a coprecipitation procedure in which nitrate salt precursors of Zn^{2+} and Al^{3+} were dropwise added to a solution containing $VitB_3$ deprotonated by stating the pH of this solution to pH 8. To achieve high $VitB_3$ loading in the solid, a high Al/(Al+Zn) ratio of 0.33 was used in the composition of the solids, this ratio representing the maximum M^{III} loading that can be obtained using ambient conditions. More details on the experimental procedure are available in Section 2.

The presence of $VitB_3$ in the ZnAl-$VitB_3$ solid after washing to remove unbound and unreacted salts was examined via $^1H-^{13}C$ CPMAS NMR (Figure 2) and FTIR (Figure 3). The $^1H-^{13}C$ CPMAS NMR spectrum confirms the presence of $VitB_3$ in the sample, with the presence of the typical ^{13}C NMR resonances of $VitB_3$ appearing at chemical shifts δ_C(400 MHz) 121, 130, 135, 148, and 170 ppm (lit., 123.71, 126.66, 136.90, 150.21, and 166.23 ppm[23]). The resonance observed at 170 ppm can be attributed to the carbonyl (C═O) group, whereas the remaining resonances are associated with carbon atoms within the aromatic ring structure.

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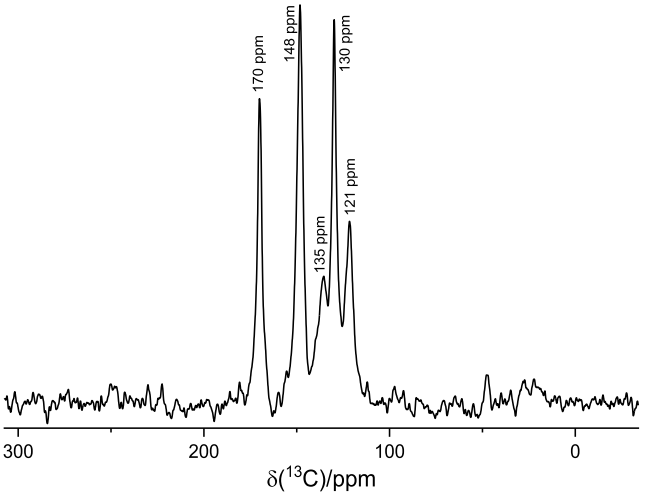

Figure 2. ^{1}H decoupled $^{1}H-^{13}C$ CPMAS NMR spectrum of the ZnAl-VitB$_3$ solid acquired at 22 °C under an MAS rate of 15 kHz. Magnetic field: 9.4 T (^{1}H frequency: 400 MHz).

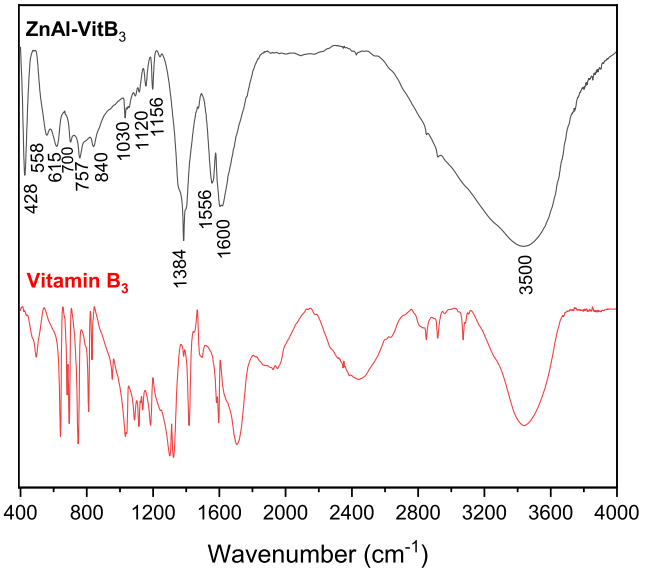

Figure 3. FTIR spectrum of as-purchased Vitamin B$_3$ and ZnAl-VitB$_3$. The numbers represent the center (in cm^{-1}) of the major absorption bands observed in the spectrum of ZnAl-VitB$_3$.

The FTIR spectrum of ZnAl-VitB$_3$ (Figure 3) exhibits prominent peaks and well-defined absorption bands corresponding to the functional groups present in the LDH solid, also confirming the presence of VitB$_3$ in the sample. The broad band observed at approximately 3500 cm^{-1} corresponds to the stretching mode of the hydroxyl (O−H) groups and water (H_2O) molecules. The peak centered around 1600 cm^{-1} corresponds to the stretching mode of C═C bonds of VitB$_3$, while the peak at 1556 cm^{-1} arises from N−O stretching bonds of the nitrate anions co-intercalated in the LDH. The peak at 1384 cm^{-1} corresponds to the antisymmetric stretching mode (ν_3) of the nitrate anion, and the peak at 1197 cm^{-1} is associated with C−O stretching of carboxylate from VitB$_3$. The band ranging from 1156 to 1030 cm^{-1} is attributed to in-plane C−H vibrations, while the band spanning from 700 to 615 cm^{-1} is ascribed to out-of-plane C−H vibrations, both ascribed to the pyridine ring of VitB$_3$. Furthermore, the peaks observed at 840 cm^{-1}, 750 cm^{-1}, and 558 cm^{-1} can be attributed to the weak out-of-plane symmetric deformation mode (ν_2) of nitrate, the Al−OH deformation, and the Zn/Al−OH translation, respectively.[24−]

The elemental composition of ZnAl-VitB$_3$ was examined by using ICP-OES and CHN analysis. The empirical formula of the precipitate was derived based on specific assumptions: first, that carbon solely originates from vitamin B$_3$; and second, that nitrogen is sourced from nitrate ions within the samples. The resulting empirical formula is: **ZnAl-VitB$_3$**. Anal. Calcd for $[Zn_2Al_{0.95}(OH)_{5.9}][(NO_3^-)_{0.24}(VitB_3^-)_{0.71}]\cdot 2.0\ H_2O$ wt % Calc.: Zn, 33.17; Al, 6.50; C, 12.96; H, 3.23; N, 3.37. wt % Found: Zn, 34.23; Al, 6.71; C, 12.8; H, 3.3; N, 3.1. Based on this data, the total amount of VitB3 on LDHs corresponds to 22.2 wt %.

As suggested by the experimental formula, most of the layer charge of the LDHs is compensated by intercalation of VitB$_3$ in the LDHs, while nitrate is still present in a considerable amount. The M^{II}/M^{III} metal fraction for ZnAl-VitB$_3$ (2.1) is in accordance with the nominal value (2.0) expected from the Zn and Al stoichiometries initially added during synthesis.

The crystalline structure of ZnAl-VitB$_3$ was examined using PXRD, as depicted in Figure 4. A comparison was made

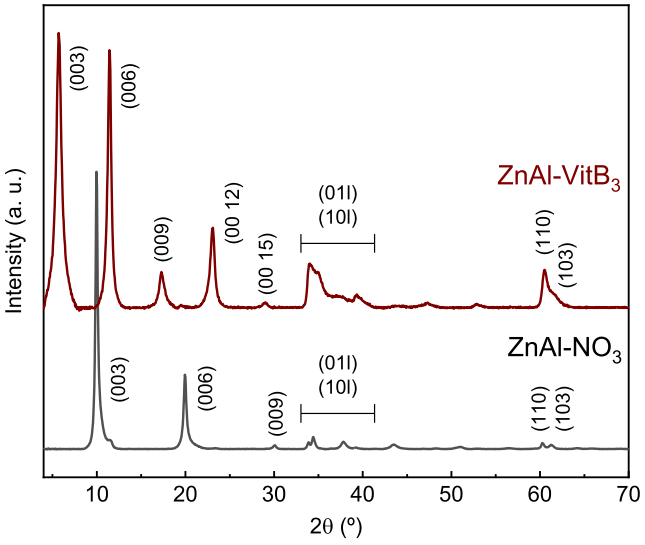

Figure 4. PXRD patterns for a nitrate-intercalated (ZnAl-NO$_3$) and Vitamin B$_3$-intercalated ZnAl-VitB$_3$ LDH sample. Data were measured using Cu Kα radiation with λ = 1.5418 Å. The diffraction patterns have been indexed based on a 3-layer hexagonal unit cell.

between the PXRD diffractogram of ZnAl-VitB$_3$ and a purely nitrate-intercalated Zn^{2+}/Al^{3+} LDH sample investigated by us in a previous study (here, dubbed ZnAl-NO$_3$).[28] For LDHs, the interlayer distance calculated from the main Bragg reflection at low 2θ can be used to assess the successful interaction of the desired anion. Nitrate-intercalated LDHs exhibit an intense Bragg reflection at 9.97° 2θ, corresponding to the (003) crystalline plane, with a basal spacing of 8.905 Å, characteristic of nitrate-intercalated LDH materials.[29] In the case of ZnAl-VitB$_3$, the Bragg reflection corresponding to this same crystalline plane appears at 5.70° 2θ, accompanied by an increased basal spacing of 15.5 Å, along with broadening of the peak. These observations indicate the intercalation of vitamin B$_3$ within the LDH structure.[29] Accounting for the thickness of a hydroxide layer (~4.8 Å[30]), the interlayer distance matches with the longitudinal dimensions of VitB$_3$. This implies a

https://doi.org/10.1021/acsomega.4c03934
ACS Omega 2024, 9, 32962−32968

perpendicular positioning of this interlayer anion relative to the hydroxide layers of the LDHs. From the (110) reflection at 60.45° 2θ, the metal−metal distance within the hydroxide layers can be calculated: "$a = 2d_{(110)} = 3.06$ Å".

The thermal stability of the new ZnAl-VitB_3 solid was investigated using thermogravimetry, and the intensity of the observed mass loss events in the TGA curve was compared against the proposed chemical formula derived from elemental analysis. The TGA curve (Figure 5) shows a 10.5% decrease in

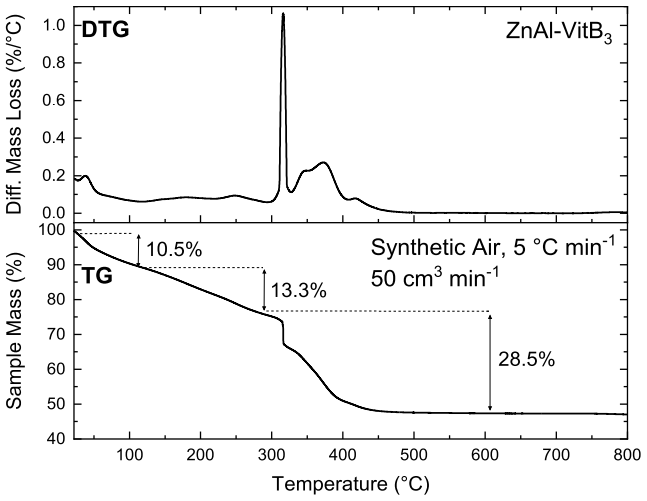

Figure 5. Thermogravimetric analysis of ZnAl-VitB_3 showing the thermal stability of the material and its decomposition events at temperatures of up to 800 °C.

the weight of the sample when the temperature is ramped up to 120 °C, which is attributed to the removal of superficial and coordination water intercalated in the interlayers of the LDHs (Calc. 9.1%). The continued mass loss from 120 to 290 °C is mainly attributed to the dehydroxilation of the hydroxide layers, with the formation of mixed oxyhydroxides and the release of water vapor (Exp. 13.3%, Calc. 13.4%).[31] The decomposition process of vitamin B_3 and nitrate intercalated in the LDHs mainly occurs between 290 and 490 °C, observed in the derivative thermogravimetric (DTG) curve as two intense mass loss events (Exp. 28.5%, Calc. 25.8%).[32,33]

To investigate the in vitro release of vitamin B_3 in a condition mimicking the pH of the human stomach, the ZnAl-VitB_3 solid was dispersed in an HCl solution of pH 1.5 under continuous stirring. The decomposition of the LDH host under acidic conditions leads to the release of interlayer contents. During the experiment, aliquots of 2 mL were collected at various time intervals until a maximum duration of 240 min. Following calibration, the release profile (Figure 6) was determined by measuring the absorbance of vitamin B_3 (see also Figure S1). The release kinetics demonstrate an initially rapid process, with 50% of the Vitamin B3 loaded in the LDH being released at $T_{50} \sim 20$ min. Subsequently, the release rate gradually decreases, with 75 and 90% of the intercalated vitamin B_3 being released after $T_{75} \sim 40$ min and $T_{90} \sim 65$ min, respectively.

Finding a suitable mathematical model to describe a set of experimental drug release data is crucial in pharmaceutical research. Such a model not only grants an understanding of drug behavior upon release from diverse delivery systems but also enables predictions. By effectively characterizing drug

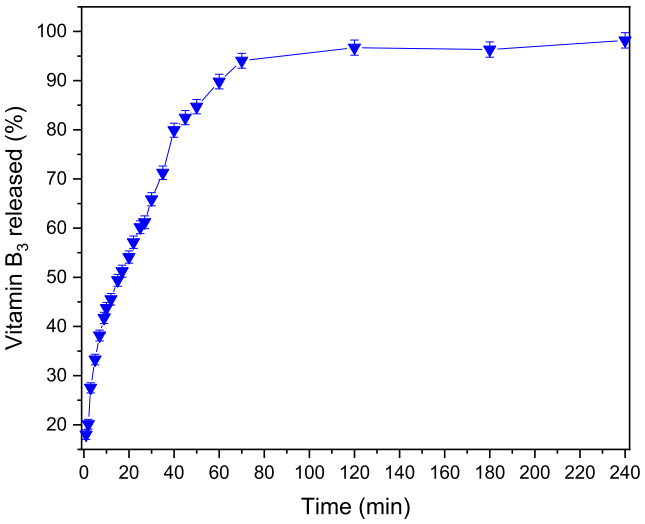

Figure 6. Drug release profile measured as the amount of Vitamin B_3 released from the solid ZnAl-VitB_3 phase when this sample is suspended and stirred in an aqueous HCl solution of pH = 1.5.

release kinetics, drug formulations, dosage regimens, and delivery mechanisms can be optimized, ultimately leading to enhanced therapeutic outcomes. Among the different models available, the zero-order and first-order fits (see also Figure S2), and the widely used Higuchi and Korsmeyer−Peppas models were considered.[34] For the release until 70 min, the Higuchi and Korsmeyer−Peppas models emerge as the best fits for the release data of VitB_3 in the LDH system (Figure 7). The Higuchi model can be expressed by the equation

$$C_t = K\sqrt{t} \quad (1)$$

where C_t represents the drug concentration at a given time t and K is the release constant. The release constant K, influenced by factors such as the drug's diffusivity, matrix membrane thickness, and others, provides insights into the underlying diffusion-driven drug release process. Higher K values indicate a faster drug release; lower K values suggest a slower drug release. For our specific case, the fitted value of K for the Higuchi model is 10.8 ± 0.2 $min^{-0.5}$, in the range usually referred to as a slow-release profile.[34]

The Korsmeyer−Peppas model is described by

$$C_t/C_\infty = K_{KP}t^n \quad (2)$$

where C_t represents the drug concentration at a given time t, C_∞ represents the total amount of the drug in the equilibrium, K_{KP} is the Korsmeyer−Peppas constant, and n is the release exponent, which is used to characterize the different release mechanisms. If $n \leq 0.45$, the release mechanism is predominantly Fickian diffusion; for $0.45 < n < 0.89$, it is non-Fickian diffusion; $n = 0.89$ is a Case II transport and $n > 0.89$ a super Case II transport.[35] Fickian diffusion refers to the molecular process where the mass transfer rate is proportional to the concentration gradient (Fick's laws). This type of diffusion is characteristic of systems in which particle movement occurs in a relatively slow and predictable manner, typical in solids and low-concentration liquids. Case II transport, otherwise, does not follow Fick's law and usually occurs on polymers where the diffusion is also dependent on the polymer relaxation dynamics. By fitting the data with the

https://doi.org/10.1021/acsomega.4c03934
ACS Omega 2024, 9, 32962−32968

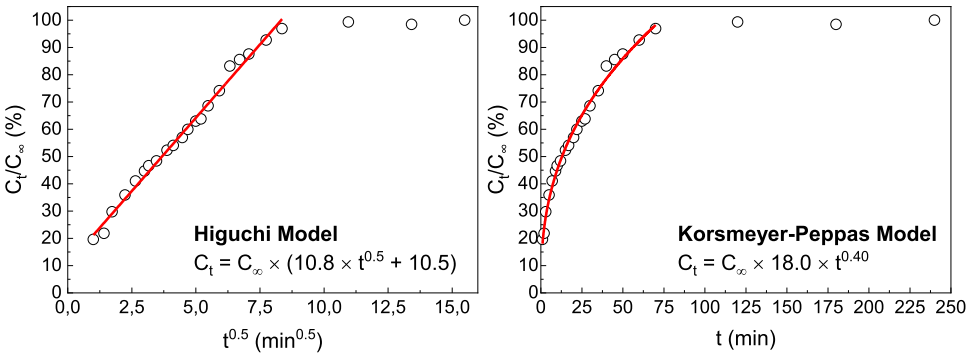

Figure 7. Fittings of the drug release profile using (left) the Korsmeyer-Peppas model and (right) the Higuchi model.

Korsmeyer−Peppas model, $n = 0.399 \pm 0.010$ is obtained, which indicates a predominantly Fickian diffusion.[36]

To further verify the integrity of Vitamin B_3 under the conditions applied during the synthesis of LDH and during the release experiment, mass spectrometry was employed to analyze the presence of Vitamin B_3 in the solution obtained after the release experiment. Figure S3a shows the mass spectrum of as-purchased Vitamin B_3 in water before any kind of treatment. The protonated species $[VitB_3 + H]^+$ appears at m/z 124. Figure S3b shows the mass spectrum of the solution containing Vitamin B_3-intercalated LDH after filtering the solution with a 0.45 μm PTFE filter. No relevant signals were observed in the same intensity range as that in Figure S3a, thus showing the immobilization of Vitamin B_3 in the LDH phase. Figure S3c shows the mass spectrum of the solution resulting from the acid treatment of the ZnAl-$VitB_3$ LDH sample. Vitamin B_3 is again observed in a relative intensity similar to what was observed in Figure S3a. This shows not only that Vitamin B_3 is still present in solution after acid treatment but also that it has not degraded.

4. CONCLUSIONS

In summary, the controlled release of vitamin B_3 in in vitro conditions mimicking the human stomach can be achieved by intercalating vitamin B_3 in layered double hydroxides. Intercalation can be achieved by coprecipitation of the drug in the presence of Zn^{2+} and Al^{3+}. When dispersed in concentrated HCl solution with pH 1.5, the LDH host is decomposed and 90% of the vitamin is liberated to the solution within a timelapse of 60 min. These findings turn ZnAl-$VitB_3$ into a potential $VitB_3$ delivery system. Further investigations will explore its performance in different physiological environments and its potential applications in pharmaceutical formulations, as well as explore other anion combinations to harness the potentially harmful effect of nitrate in the intestine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c03934.

Calibration curve for the drug release test; zero-order and first-order model fittings for the release profile; and mass spectrometry for the $VitB_3$ and ZnAl-$VitB_3$ before and after the acid treatment (PDF)

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Author Contributions

conceptualization, I.G.N.S. and D.M.; methodology, A.F.M., I.G.N.S., and D.M.; validation, C.I.L., N.F.A., and A.C.T.; formal analysis, A.F.M., C.I.L., N.F.A., and A.C.T..; investigation, C.I.L., N.F.A., A.C.T., A.F.M., and I.G.N.S.; resources, D.M.; data curation, C.I.L., A.C.T., F.W.R.M., T.C.C., A.F.M., I.G.N.S., and D.M.; writing—original draft preparation, C.I.L., I.G.N.S., and D.M.; writing—review and editing, C.I.L., A.F.M., and D.M.; visualization, D.M., A.F.M. and C.I.L.; supervision, D.M. and I.G.N.S.; project administration, D.M.; funding acquisition, D.M., I.G.N.S., and A.F.M.

Funding

This research was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, 2015/19210−0; 2015/08539−1; 2018/13837−0; 2021/06726−0; 2022/01314−8; 2022/00498−8 and 2023/01180−4) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES,

1723707, Finance Code 001). A.F.M. acknowledges support from the European Union's Horizon Europe program through a Marie Skłodowska-Curie postdoctoral fellowship (No. 101063656, H2E).

Funding

The Article Processing Charge for the publication of this research was funded by the Coordination for the Improvement of Higher Education Personnel - CAPES (ROR identifier: 00x0ma614).

Notes

The authors declare the following competing financial interest(s): The data included in the figures are available free of charge at https://doi.org/10.48804/WWLYSD.

■ ACKNOWLEDGMENTS

The authors acknowledge the Laboratory of Crystallography (IFUSP, São Paulo) for assistance with the PXRD measurements.

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https://doi.org/10.1021/acsomega.4c03934
ACS Omega 2024, 9, 32962−32968