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Progress in the removal of pharmaceutical compounds from aqueous solution using layered double hydroxides as adsorbents: a review

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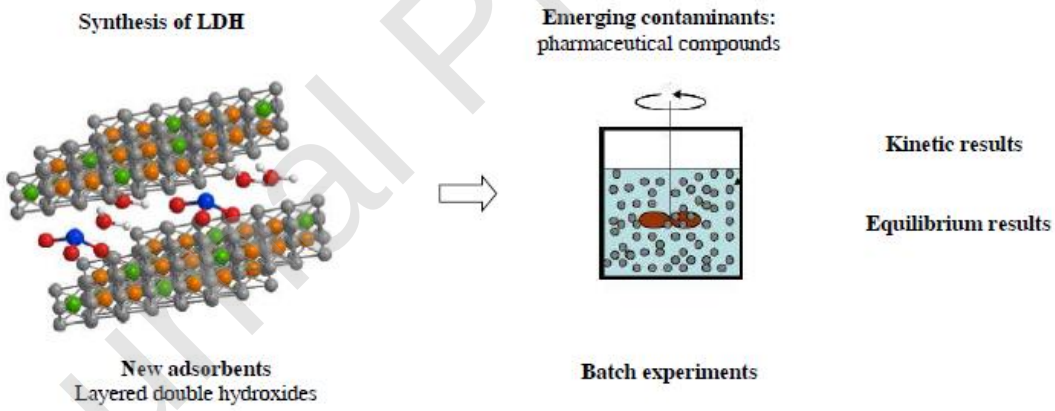
Graphical_Abstract



Highlights

- ► Layered double hydroxides as efficient systems to clean water from emerging contaminants.
- ► Layered double hydroxides as adsorbents of antibiotics and non-steroidal anti-inflammatory drugs.
- ► Various factors such as the synthesis proportions of Me^{2+}:Me^{3+}, the memory effect, and the use of support or foreign substances have been described and analyzed
- ► Several strategies to recover the adsorbents in a simple yet effective way have also been described and analyzed.

Abstract

Emerging contaminants and, among them, pharmaceutical compounds, have a significant impact on water ecosystems. Layered Double Hydroxides (LDH), being easy to synthesize and cheap materials, have recently gained attention as adsorbents in aqueous solutions. This work describes the latest research performed in the adsorption capacity of LDH towards both antibiotics and Non-Steroidal Anti-Inflammatory Drugs (NSAID) describing and analyzing the synthesis conditions (Me^{2+}:Me^{3+} molar ratio, calcination temperature, choice of metals for the memory effect), kinetics and isotherm models used, use of support (more practical in a 3D over a 2D form), temperature effect and several techniques for the recovery of the adsorbents. LDH exhibited great performance and potential as clean adsorbents for these emerging contaminants.

Keywords: layered double hydroxides, adsorption, emerging contaminants, pharmaceutical compounds.

1. Introduction

A wide range of emerging contaminants is being currently detected in worldwide aqueous environments. These include pesticides, industrial additives, pharmaceutical compounds, caffeine and nicotine metabolites, flame retardants, surfactants, hormones, personal care products and fragrances [1,2]. These pollutants are not appropriately regulated by law although they have been detected in both surface and groundwater. Although it is clear that they are a risk to water and soil environments, they are not presently being monitored because of a lack of information regarding their effects [3]. Thus, more research has to be performed on the prevalence, fate and treatments of emerging contaminants and human originated metabolites to try to develop risk based screening models and an appropriate framework [4]. Among the wide range of emerging contaminants, the most commonly detected are pharmaceuticals like carbamazepine, ibuprofen or diclofenac [3,5,6].

Several treatment processes like membrane bioreactors [7], microfiltration – reverse osmosis [8], ozonation – photocatalysis [9,10] or adsorption can be selected for the removal of emerging contaminants. Each of them has a number of advantages and disadvantages well described by *Patel et al.* [11]. In general the main problems of these techniques involve their high operational/energy costs, their difficulty to be applied in a large scale or their low removal rates. Adsorption technology has none of these issues as it is capable of obtaining a high percentage removal, needs low energy and mild operation conditions, and no byproducts are added to the system. There are, however, several concerns with adsorption that need to be tackled: mainly the regeneration and sludge management and the selection of an efficient adsorbent.

Layered Double Hydroxides (LDH), also called hydrotalcites or anionic clays, are a family of layered materials with hydrotalcite structure, derived from that of brucite ($Mg(OH)_2$), in which a partial substitution of Mg^{2+} by Al^{3+} takes place and the electric charge is balanced by anions in the interlayer space. Their general formula is $Mg_6Al_2(OH)_{16}CO_3{\cdot}4H_2O$, water being located with the anions in the interlayer. These materials are usually easy to prepare, not expensive and offer a wide range of variants within the family. Their divalent and trivalent cations choice is almost entirely restrained only by their charge and size and a combination of more than one divalent or trivalent cation can be also made. The interlayer anion choice has nearly no limits: simple or complex, organic or inorganic, anions can be selected.

These features are responsible for the selection of LDH as adsorbents in recent studies. Although they have been largely studied as adsorbents for the release of drugs in animals and humans [12], the recent discoveries highlighting the need for an effective emerging contaminant collector have increased the interest of these compounds as adsorbents [13,14]. In this review work, a compilation of the recent studies that use LDH as adsorbents of pharmaceutical compounds, an important group of emerging contaminants, taking into account several factors such as kinetic and isotherm studies, the use of support, synthesis strategies and recovery techniques has been carried out. At the end of the review, the main conclusions and perspectives regarding some of the main scientific challenges remaining in this field are also summarized.

2. Pharmaceutical compounds

Among the adsorbates studied (described in **Table 1**), there are two main groups of compounds: antibiotics and Non-Steroidal Anti-Inflammatory Drugs (NSAID). Both cause great concern due to their environmental impact. Although caffeine is considered a central

nervous system drug, it was also considered in this work, as it is commonly added to over-the-counter medications. At present, there is a general rise in the production and consumption of pharmaceutical compounds all over the world. Several factors are responsible: the increase of the worldwide population and life expectancy, the great prevalence of chronic diseases or a steady input of new compounds entering the market every year [11]. *Van Boeckel et al.* [15] analyzed the global antibiotic consumption from 2000 to 2010 (see **Figure 1**); in this decade, global antibiotic sales raised by 35%, such an increase was mainly due to developing countries such as Brazil, India, China and Russia. An increment in the antibiotic consumption has a synergic effect, as is a major driver for antibiotic resistance. The prevailing pathway of pharmaceuticals into the environment starts with their excretion by humans or animals, the release into raw sewage and the management in a WasteWater Treatment Plant (WWTP) followed by a discharge into water environment. However WWTP procedures are usually not effective for pharmaceutical compounds, with very different removal rates [16,17]. As an example, *He et al.* [18] reviewed the potential adverse effect of NSAID residues on terrestrial and aquatic ecosystems and showed that concentrations as low as 1 μg/dm^3 of diclofenac can cause tubular necrosis in the kidneys and histological changes in the liver and gills of the rainbow trout. Diclofenac has been detected in groundwater, surface water or drinking water in 50 countries and concentrations higher than 1 μg/dm^3 usually occur downstream of sewage-treatment plants in densely populated areas [5]. Antibiotic sulfamethoxazole was found in the surface water of 47 countries and had an average concentration of 2.53 μg/dm^3 in African countries [5] (see **Figure 2**). Its risk quotient values indicated that this antibiotic has a high ecological risk in soils of Kenya [19].

3. Synthesis conditions, ratios and components

The synthesis of LDH can be performed using various metals, the most used for the preparation of LDH destined to the adsorption of pharmaceutical compounds are Mg^{2+} and Zn^{2+} as divalent cations, and Al^{3+} as the trivalent one. These metals can be combined in several molar ratios and the resulting LDH can also be calcined at different temperatures, usually between 573 and 883 K. A calcination step is essential; its purpose is the elimination of the anions, usually carbonates, from the interlayer. When the calcined LDH is placed in an aqueous environment, it can recover its original structure, thanks to the memory effect, and "trap" the adsorbate in its interlayer. In the case of MgAl LDH, a calcination process above 653 K guarantees the formation of the metal oxide but a calcination above 1073 K leads to the formation of stable MgO and spinel phases, thus preventing the memory effect from occurring [20].

Xu et al. [21] synthesized MgAl LDH with 2:1, 3:1 and 4:1 Me^{2+}:Me^{3+} molar ratios via the hydrothermal method, and their tetracycline (TCY) adsorption capacity was investigated. The reconstruction of the LDH in water by the memory effect was only partial. Calcined LDH had a better performance than the non-calcined counterpart. These authors concluded that the adsorption of aqueous TCY by calcined LDH could occur by (i) adsorption in the interlayers of structurally restored LDH, (ii) adsorption on the external surfaces of structurally restored LDH, and (iii) adsorption on MgO surfaces as not all the LDH was restored. When comparing the samples prepared with various ratios, all of them showed similar performances at low TCY concentrations and TCY was mostly adsorbed in the interlayer of the LDH. With greater drug concentration, the adsorption capacity of the 4:1 sample was the best one. In the 3:1 ratio sample the adsorption process followed a crystal-growth model, suggesting that the drug adsorption was controlled by the

reconstruction of the LDH. TCY adsorption by the calcined LDH fitted better a pseudo-second-order kinetics model and the isotherm was adjusted to the Langmuir model.

The removal capacity of, in this case, ZnAl LDH synthesized with various ratios (1:1, 3:1 and 5:1) and calcined at four temperatures (573, 673, 773, and 883 K) over salicylic acid (SLC) as a model of pharmaceutical pollutants was studied by *Elhalil et al.* [22]. Both molar ratios and calcination temperature were proven to have a great effect over the adsorption capacity of the adsorbent. The LDH with 3:1 Zn:Al ratio calcined at 573 K gave the best results. The adsorption process took place in two steps: first, a rapid process due to the adsorption on the external surface of the crystallites, followed by a slower process when the reconstruction of the LDH took place (see **Figure 3**).

Not all the LDH show the memory effect; as seen above, it greatly depends on the calcination temperature and the molar ratio used in the synthesis process. The divalent metal chosen is also of great importance, Mg^{2+} and Zn^{2+} LDH can recover their structure when placed in water if they had been calcined at the correct temperature, however metals like Co^{2+} or Ni^{2+} do not show the memory effect under normal circumstances, cobalt forms a highly stable Co_3O_4 spinel even when the calcination has been performed at low temperatures [23], while nickel would need both high pressure and temperature to recover its original structure [24]. This was verified by *Rosset et al.* [25] by synthesizing LDH with Mg, Ni or Zn as Me^{2+} and Al as Me^{3+} (2:1 ratio, continuous co-precipitation method) as adsorbents for the removal of sodium diclofenac (DCF). The structure of the LDH was regenerated, due to the "memory effect of the LDH", in the case of ZnAl and MgAl LDH but not in the case of the sample with NiAl, which gave the poorest results (see **Figure 4**). *Santamaria et al.* [26] also studied the adsorption performances of various LDH synthesized with different Me^{2+} (Co, Mg, Ni and Zn) and Al^{3+} (extracted from saline slag waste) and a 3:1 molar ratio by the co-precipitation method. Batch experiments were

performed to analyze the adsorption capacity of the LDH on DCF and SLC, as example of emergent pollutants. The solids showed different behaviors and the equilibrium was reached at different times, MgAl and ZnAl had higher adsorption capacity, as they showed interlayer adsorption, but longer equilibrium times. This could be due to: a) the time taken by both LDH to recover their structure when dispersed in water and/or b) the time taken by the drugs to enter the interlayer in those two samples. CoAl and NiAl reached the equilibrium faster as the drug adsorption happened only in the external surface of the adsorbents.

Although usually carbonates are the interlayer anions in the synthesis of LDH, other anions can be present. Carbonates are the most common because the synthesis process is easier as it does not require an inert atmosphere to prevent the influence of atmospheric CO_2 and they are going to disappear anyway in the calcination process. However, the use of different interlayer anions can greatly influence the interlayer distance [27] and, thus, change the adsorption capacity of the LDH. *Sui et al.* [28] synthesized MgAl LDH and studied their capacity to adsorb the antibiotic norfloxacin (NFX) in aqueous solution. MgAl LDH were prepared with three Mg^{2+}/Al^{3+} molar ratios (2:1, 3:1 and 4:1) and with two anions in the interlayer (CO_3^{2-} and Cl^-) (see **Figure 5**). The samples with greater Al^{3+} content showed a better performance and Cl^- as interlayer anion increased the adsorption capacity of the LDH. In the case of Cl^-–LDH both the anion exchange process and the electrostatic attraction contributed to the adsorption of the antibiotic while only the electrostatic attraction was responsible for the adsorption in CO_3^{2-}–LDH. The pseudo-second rate model fitted well the kinetic data and the Freundlich model fitted better the equilibrium data than the Langmuir model. The initial pH value (3.0 to 11.0) did not significantly influence the adsorption, proving the pH buffering ability of the LDH. In the same work, the change in the adsorption capacity of the samples with the incorporation of

various cations in the structure of the LDH was also studied. The authors incorporated Sn^{4+} in an attempt to increase the charge density; however this only resulted in a reduction of the adsorption capacity of the LDH.

The incorporation of various cations was also studied by *Santamaría et al.* [29][30]. They synthesized Zinc-Titanium-Aluminum (ZnTiAl) LDH with various proportions of Al-Ti and a Zn/(Al-Ti) molar ratio of 3:1 by the co-precipitation method. The adsorption capacity of DCF and SLC, as examples of emergent pollutants, by the different LDH on batch and fixed-bed column experiments was analyzed. Two series, made with commercial aluminum and aluminum extracted from saline slags, were characterized and compared. The incorporation of Ti^{3+} did not improve the adsorption capacity of the LDH although it was useful when the LDH were used as catalysts in an advanced oxidation process [30].

4. Combined adsorption and effect of foreign substances

Studies that involve the adsorption of various substances at the same time, or in real effluents with the presence of several substances, have also been performed. The simultaneous adsorption of two substances can lead to different results than when these substances are studied individually [31,32].

Chen et al. [33] studied the combined adsorption of TCY and Cd^{2+} on MgMn LDH. The adsorbents were synthesized by the hydrothermal method at a 2:1 ratio and activated with persulfates. The presence of TCY increased the adsorption of cadmium and the presence of cadmium sharply increased TCY adsorption. The authors credited the synergistic effect to the strong complex formation between the adsorbates as both the oxygen atoms and naphthamide group on the tetracene structure could bind to Cd^{2+}. They also compared the results between a calcined and non-calcined MgMn LDH. The kinetic

experiments showed a better adjustment to the pseudo-second-order model in TCY adsorption and the isotherm data fitted better the Langmuir than the Freundlich model.

Real water samples coming from a dam, a river, three lakes and a wastewater plant were used by *Panplado et al.* [34] when studying the adsorption capacity of calcined MgAl LDH, synthetized by the co-precipitation method with a 3:1 mole ratio, over TCY. The removal capacity of TCY was superior to 90% in all cases. The process involved the utilization of the LDH components to initiate the precipitation of mixed metal hydroxides to act as sorbents. Hydrogen bonding and electrostatically induced attraction were responsible for a removal accomplished within 4 min. The recovery of TCY was tested by dispersing the adsorbents with the antibiotic in several solutions with common anions PO_4^{3-}, CO_3^{2-}, SO_4^{2-}, NO_3^-, CH_3COO^-, and Cl^-, phosphates giving a 98% recovery due to their high charge density.

Boukhalfa et al. [35] concluded that the adsorption capacity of both ZnAl LDH and a K10 montmorillonite on DCF decreased when background electrolytes were present, while pH did not have a significant effect. LDH was synthesized with a 2:1 ratio and the co-precipitation method. Kinetic studies revealed that a pseudo-second-order model fitted better the experimental results and isotherm experiments fitted better with the Langmuir over the Freundlich model. Maximum adsorption capacities were 55.46 mg/g for the montmorillonite and 737.02 mg/g for the LDH with equilibrium achieved after 5 and 20 min, respectively.

The effect of foreign ions such as nitrate, sulfate, carbonate and a hardness agent greatly affected drug adsorption in the experiments performed by *Sepehr et al*. [36] (see **Figure 6**). They synthesized MgAl LDH by the urea method (ratio 2:1) and used them to remove metronidazole (MTD) from water. Sulfate, nitrate and the hardness agent decreased the removal efficiency of the LDH. This may be due to the competing effect that

they had with the MTD molecules for adsorption. In the case of carbonate-LDH, the opposite effect was observed; the removal efficiency was decreased at lower concentration of carbonate, and increased with the increment of carbonate concentration. This could be due to the buffering effect of carbonate anions in solution. A higher final pH gave better removal results. The adsorption isotherm was described with Langmuir, Freundlich, Redlich-Peterson and Sips equation, the latter giving the best fit. The maximum adsorption capacity was of 62.8 mg/g.

Rosset et al. [37] studied the adsorption capacity of ZnAl LDH (ratio 2:1, coprecipitation method) over acetylsalicylic acid. The effect of excipient present in two commercial aspirins was tested suggesting that a probable competition existed between the SLC and the other components. SLC removal was lower for both samples (62 and 73%) than for pure SLC sample (92% removal). The first sample had the lowest removal, which was probably related to the presence of sodium carbonate, since this compound effortlessly occupied the interlayer spacing facilitating the LDH reconstruction and thus decreasing the acetylsalicylic acid removal. The adsorption kinetics were better adjusted to the pseudo-second order model and the Sips equation was more precise in describing the isotherms' behavior showing that the adsorption occurs mainly by chemisorption in a monolayer (maximum adsorption capacity 198 mg/g).

5. Use of supports

Much effort has been put in the development of a composite LDH + support when trying to improve the adsorption capacity of the LDH. Immobilizing the adsorbent into a 2D or 3D structure aims at reducing the aggregation of the LDH. Their characteristics, adsorption conditions and performances are summarized in **Table 2**.

Wu et al. [38] prepared MgFe LDH (ratio 3:1, co-precipitation method) supported on chitosan to study its removal capacity of both TCY and methyl orange from water. Various calcination temperatures were considered (573, 673 and 773 K) and 673 K gave the best results, with a maximum adsorption capacity of TCY 195.31 mg/g. The pH change did not greatly affect the adsorption processes; the results from initial pH 5 to 9 were similar. The presence of different anions in the water sample was studied and the monovalent anions had almost no effect while divalent and trivalent anions had a great effect in the adsorption capacity of chitosan-LDH against TCY. The kinetics of both adsorbates showed a better fit with the pseudo-second order model and TCY isotherm experiments fitted better the Langmuir than the Freundlich model.

The adsorption capacity of the LDH and the support separately and together has been compared by *Xiong et al.* [39]. They synthesized MgAl LDH (ratio 2:1, urea method synthesis) along with poly(m-phenylenediamine) (PmPD) to remove DCF from actual medical wastewater. The composites were prepared via a chemical oxidation polymerization method. The composite had a maximum adsorption capacity of 588.9 mg/g, while PmPD and LDH on their own had 272 and 104 mg/g, respectively. PmPD particles tend to aggregate and a combination with LDH weakened the accumulating density of PmPD and increased the specific surface area, which favored diclofenac adsorption on LDH-PmPD surface. Its removal efficiency in medical wastewater was almost 100% in only 2 minutes with 0.125 g/dm^3 of adsorbent. The presence of electrostatic attraction, π-π electron-donor-acceptor interaction and N···HO hydrogen bonding between diclofenac and LDH-PmPD were responsible for the good adsorbent performance. The adsorption kinetics was described with the pseudo-second-order model and the isotherm data fitted better the Langmuir model than the Freundlich one. Humic acids present in water decreased the adsorption capacity of the samples.

Eniola et al. [40] studied the separated and combined adsorption performances of a modified copper ferrite/NiMgAl LDH composite over oxytetracycline hydrochloride. The adsorption capacities went from 106 mg/g ($CuFe_2O_4$) and 116 mg/g (NiMgAlLDH), to 192 mg/g for the composite. Anionic exchange, electrostatic attraction and hydrogen bonding were responsible for the adsorption process. The kinetics and isotherm data followed a pseudo-second-order and Langmuir models. Three temperatures were tested (303, 313, 323 K) with the last one giving the best results, that is, the process was endothermic and spontaneous. In all the cases, adsorption performance was better at an acidic pH. The co-adsorption results with various salts showed synergistic ($CuSO_4$), neutral ($NaHCO_3$) and antagonistic (NaCl) effects on the antibiotic adsorption.

Zhou et al. [41] considered various methods to immobilize the LDH into different surfaces such as polypropylene chips, glass slides and metal coins (see **Figure 7**). Although methods like colloid deposition, sol-gel spin coating and solvent evaporation have been previously used, they often suffer from an uncontrollable formation of multiple layers due to strong aggregation. For this reason, they used the in situ growing strategy to immobilize a LDH film in one step. NiAl, ZnAl, CuFe and MgFe LDH (ratio 2:1, urea method) were prepared, and polydopamine was used to immobilize the LDH film and study the adsorption capacity of the samples over both pharmaceutical compounds and organic dyes. NiAl LDH showed the best adsorption capacity for rhodamine B. Further adsorption experiments were performed with NiAl LDH. The LDH were immobilized onto the inner wall of the 1.5 mL polypropylene centrifuge tube and a dense and homogeneous LDH film with a thickness of 400 nm formed onto the tube's surface. The aqueous solutions containing pharmaceuticals (ketoprofen, flurbiprofen) or acid organic dyes (rhodamine B or Congo Red) were put into the tube, obtaining a good adsorbance performance of the immobilized LDH.

Yang et al. [42] also used an in-situ method to synthesize MgAl LDH/cellulose nanocomposite beads and study their amoxicillin adsorption capacity. Cellulose beads were produced with an optimal extrusion dropping technology. The synthesis of MgAl LDH/cellulose was carried out by the co-precipitation method using urea with no calcination afterwards. The maximum adsorption capacity of the composite was of 138.3 mg/g. The kinetics of the adsorption process followed better a pseudo-second-order than a pseudo-first-order model. The isotherms fitted better the Freundlich than the Langmuir model which suggested that the antibiotic removal process was mainly controlled by chemical adsorption and involved a multiple surfaces system. The adsorption mechanism suggested by the authors was an electrostatic interaction that drove the combination of anionic amoxicilin groups and the positively charged LDH particles.

Chen et al. [43] fabricated 3D hierarchical MgAl LDH on the surface of SiO_2 spheres and studied the LDH adsorption capacity with and without support. A good dispersion of the adsorbent particles maximized the contact between the solid surface and water, as shown in a previous study were LDH nanosheets were synthesized on a 2D structure [44]. This planar structure would however encounter difficulties in practical operations such as high pressure drop when filled in a column for continuous adsorption or inefficient separation from water due to small particle sizes. That is why LDH mobilized into SiO_2 spheres were more attractive for practical operations. The spheres were synthesized with a modified Stöber method and the dispersed SiO_2-LDH composite was fabricated by a slow co-precipitation method. An ultrasound treatment during growth and aging of the LDH and the removal of free electrolytes after precipitation were the two main factors that influenced the formation of well dispersed spheres. The adsorption capacity of SiO_2-LDH spheres could reach 758 mg/g for DCF compared to 489 mg/g for the LDH without support

and the same drug. The adsorption capacity of SiO_2-LDH spheres onto ibuprofen and folic acid was also tested and found to be around 400 mg/g and 332 mg/g, respectively.

Li et al. [45] also used the 3D support strategy to synthesize a structure composed of stacks of MgAl LDH with different Mg/Al ratios (3, 2 and 1) arranged directionally over γ-AlO(OH) nanowires and amorphous carbon by a biotemplate method (see **Figure 8**). Carbon was removed through hydrothermal treatment followed by calcination. Both the molar ratio and the pH during the hydrothermal process had an important role in the formation of the 3D structures. They studied the composite adsorption capacity over minocycline and Congo Red with maximum values of 302 and 447 mg/g, respectively. The isotherms were best described by the Langmuir model and the kinetics by the pseudo-second-order model. The main adsorption mechanisms were ion exchange, electrostatic adsorption and π−π interaction. A change in pH did not have a significant effect on the adsorption capacity of the composite, due to the amphoteric nature of minocycline.

Hossein Beyki et al. [46] synthetized a polymeric ionomer together with a CaAl LDH (2:1 ratio) by means of the urea method. The magnetic polymer ionomer was prepared in several steps that involved the addition of iron, pyridine and epichlorohydrin to the cellulose. The magnetite cellulose – LDH (MCL) and the ionomer were used for efficient adsorption of diclofenac sodium. The equilibrium time of the magnetic ionomer was only of 2 min with an uptake of up to 268 mg/g. The kinetic models showed a better pseudo-second order fit. In the isotherm studies, the Freundlich model was better at a high concentration of diclofenac. The study of the pH effect on the removal efficiency showed that the adsorption capacity of the adsorbates went up progressively from 3 reaching a maximum removal capacity at 9.

The use of environmental friendly materials such as biochar or cotton fiber as supports has also been studied. *de Souza dos Santos et al.* [47] fabricated a composite with

a MgAl LDH supported on *Syagrus Coronata* biochar that achieved a great efficiency in DCF adsorption (see **Figure 9**). The biochar was produced by pyrolysis of the endocarp of the palm tree at 673 K. The LDH was synthesized with a 2:1 ratio by the co-precipitation method and the biochar was added after the dissolution of the salts. The kinetic studies showed that different mechanisms worked depending on the adsorbate initial concentration. Low concentrations favored physisorption, equilibrium time was reached in less than 1 h and data were better fitted to the pseudo-first order model. At greater concentrations equilibrium time took up to 6 h as the adsorption was more complex with chemisorption also taking place, and data were better fitted to the pseudo-second order model. Several isothermal models were used; Sips model gave the best results. The effect of the initial pH was also tested with maximum removal efficiency at a pH between 6 and 12.

dos Santos Lins et al. [48] synthesized a MgAl LDH (3:1 ratio, coprecipitation method) with bovine bone biochar as support for the LDH. The composite was used as adsorbent for caffeine removal from water. Kinetic studies showed that the adsorption mechanism better fitted the pseudo-first-order model suggesting a physical adsorption. The equilibrium was reached in 20 min achieving a 26.22 mg/g adsorption capacity. The isotherm models that better adjusted the experimental data were Redlich–Peterson and Sips.

Wang et al. [49] immobilized NiAl LDH onto cotton fiber via a polydopamine functionalization procedure, thus upgrading the adsorption performance of free-standing LDH. Its performance on the adsorption of ketoprofen and Congo Red (in addition to flurbiprofen, ciprofloxacin, enrofloxacin and bromophenol blue) was tested. Several ratios (3:1, 2:1, 1:1, 1:2 and 1:3) were considered, finally choosing 2:1 due to its better effectiveness. The kinetics was studied with the pseudo-second order model and the

isotherms were better fitted to the Langmuir model *vs* the Freundlich one. The maximum adsorption capacities of the composite were 625 and 714 mg/g for ketoprofen and Congo Red, respectively. The authors also adjusted the adsorbent into different devices such as micropipettes, a precolumn or a syringe-driven filter, obtaining good results in all cases.

6. Kinetic and isotherm studies

The 82% of the works reviewed in this study used kinetics and isotherm studies to describe the adsorption processes. The most common expressions used to try to adjust the experimental data are shown in **Table 3**.

Kinetic experimental results are in all the cases fitted to pseudo-first and pseudo-second order models. When only these models were used, the 83% of the studies were better adjusted to the pseudo-second order model and only one work [47] changed the best fit model depending on the adsorbate concentration, the authors suggested that a better fit to the pseudo-first order model was due to physisorption, and the pseudo-second order model fitted better when chemisorption also took place. The fact that the pseudo-second-order model is usually seen as the best fit model can be however due to the introduction of an excess of data close to, or at, equilibrium. This creates a methodological bias which has promoted it as the number one model [50].

The results in the isotherm studies show that 63% of the works analyzed fit the experimental results to only the Langmuir and Freundlich models. Among them, 67% of the works considered that their data fitted better the Langmuir model. One of the studies that considered that the Freundlich model gave a better fit of the results was that from *Mourid et al.* [51]. They investigated the removal of sulfamethoxazole by a ZnAl LDH with a Zn^{2+}/Al^{3+} ratio of 1:1, prepared by the co-precipitation method and calcined at 773 K. The kinetic results fitted better the pseudo-second-order model and the thermodynamic

parameters (298, 318 and 333 K) showed that the adsorption was governed by physisorption; the process was spontaneous and exothermic. The LDH adsorption capacity for the drug reached 4314 mg/g. The recovery of the adsorbents with Na_2CO_3 solution, selected because of the high affinity of carbonate for LDH, meant a decrease in their adsorption capacity from 93% to 71% after six cycles. When studying the effect of the pH, the low retention values observed in acidic solutions may be explained by partial dissolution of the solid by hydrolysis. The maximum retention was obtained for a pH value between 7 and 8. The low retention capacity of the calcined LDH at higher pH values may result from the competition with the carbonate anions, for which the LDH matrix has a very high affinity.

Studies that used three and even four parameter models to fit their isotherm experimental data almost always preferred their adjustments to those given by the Langmuir and Freundlich two parameter models. One of the works that more isotherm models used was that from *Younes et al*. [52] (see **Figure 10**). They synthesized ZnFe LDH with a 4:1 molar ratio by the co-precipitation method and studied its efficiency as adsorbent for the removal of DCF. The equilibrium was achieved in 30 min with an adsorption capacity of 74.5 mg/g, a pseudo-second order kinetic model gave the best adjustment results and the best-fitted isothermal models were those with three and four parameters (Sips, Langmuir-Freundlich and Baudu). They also studied the adsorption mechanism between DCF and the LDH with molecular dynamic simulations, suggesting both physisorption, due to the formation of H-bonds between the diclofenac and the hydroxyl groups of the LDH, and chemisorption, due to the presence of free-bond metal atoms in the LDH surface. In addition, a LDH toxicity study was performed in mice showing no toxic symptoms or mortality, thus, concluding that these LDH could be used on different body organs safely.

7. Adsorption thermodynamics

Several works have collected the thermodynamic data for adsorption systems of LDH over pharmaceutical compounds. In order to do so, they have performed a series of experiments at various temperatures. Most used thermodynamic equations involving enthalpy (ΔH), entropy (ΔS) and Gibbs free energy (ΔG), shown in **Table 3**. Thermodynamic results for various drugs and LDH are shown in **Table 4**.

Boukhalfa et al. [35] studied the adsorption of diclofenac on ZnAl LDH. The adsorption process was spontaneous and inversely proportional to the temperature as ΔG° values at various temperatures were negative and decreased with an increase of temperature. The negative value of ΔS° implied that an associative mechanism was involved in the adsorption process and that the adsorbent did not have significant changes in its internal structure. The process was exothermic as revealed by the negative values of ΔH°. *Wu et al*. [38] also found the process of TCY adsorption over MgFe LDH to be spontaneous; however, the nature of the adsorption process was endothermic as it implied positive enthalpy changes. Positive entropy values showed an increase in randomness of the irreversible adsorption process and, thus, a good adsorbate-adsorbent affinity. *Sepehr et al.* [36] found the metrodinazole adsorption over MgAl LDH to be non-spontaneous in nature as indicated by the positive values of free energy (ΔG°, temperatures from 283 to 303 K). The process was exothermic; ΔG° values went up with increasing temperature and the negative values of ΔS° showed that during the adsorption process a decrease in the randomness at the solid/liquid interface occurred.

Xiong et al. [39] used the Hill model to estimate the number of bonded molecules and the adsorption energy at various temperatures to study diclofenac adsorption over MgAl LDH. The number of molecules linked per adsorbent site was inferior to one

indicating a parallel adsorbate position. At higher temperature this number was above one showing a change in the diclofenac adsorption geometries, possibly due to the thermal agitation effect. The adsorption energy decreased with an increase of temperature, which may be associated with a decrease of the adsorbed quantity.

8. Recovery of the adsorbent

One of the main problems of adsorption technology, due to its difficulty and cost, is the regeneration of the adsorbents. It may account for more than 70% of the total operating and maintenance cost of an adsorption system [53]. A regeneration process is successful if it restores the adsorbent to performances similar to the initial ones for effective reuse. Several strategies can be followed when trying to regenerate the adsorbate, like an oxidation method, washing with an organic solvent or a basic solution or a thermal treatment. **Table 5** describes several adsorbent reuse strategies followed when adsorbing pharmaceutical compounds.

Thermal decomposition (773 K for 12 h) was used by *Rosset et al.* [25] in the regeneration of three different samples synthesized: NiAl, MgAl and ZnAl. This strategy did not work for neither NiAl nor MgAl samples, were the loss in their DCF removal capacity was important in the third and fourth cycle, respectively. ZnAl removal capacity, however, did not significantly lower until the eighth cycle. After characterizing the samples by XRD and FTIR techniques, the authors associated NiAl and MgAl problem to both the progressive loss of crystallinity of the samples during the reconstruction process of the material (memory effect) and the incorporation of organic species [54]. *Chen et al.* [43] used an advanced oxidation method [55] to decompose the adsorbed drugs using oxone as oxidant and Co^{2+} as catalyst. Their results were excellent as DCF was eliminated by the oxidation process in less than 1 min and the LDH efficiency did not suffer any

apparent loss of removal capacity for four consequent cycles (above 90% in the four cases). The use of organic solvents like methanol or salts such as NaCl as desorption agents was tried by *dos Santos Lins et al.* [48]. After 6 cycles, their results showed no loss in the adsorption capacity when methanol was employed and a 35% loss with the use of NaCl. The latter lower efficiency could be due to the loss of solubility that caffeine suffers when NaCl is present in the solution, which hinders its desorption form the adsorbent. The drug is better extracted with methanol because its affinity to the solvent is higher than to the adsorbent phase. *Wang et al.* [49] tested the use of an alkaline solution (NaOH 1 M) in cotton supported LDH. The theory supporting this method is the strong affinity that OH^- has towards the highly positive layers of the LDH. The pipette tip packed with the ketoprofen-cotton-LDH was rinsed with the NaOH solution and deionized with water. There was no apparent loss on the removal capacity of the cotton supported LDH after 8 cycles. The authors found no differences in the morphology or crystal structure of the immobilized LDH in the SEM and XRD analysis made after regeneration.

9. Conclusions and future perspectives

In the last years, LDH have been investigated as successful adsorbents for a range of organic compounds as dyes, pesticides, and herbicides, among others. These materials have demonstrated to be promising adsorbents, and their great potential is mostly due to their properties, including the porous structure and surface basicity. This review work aims to collect recent studies of LDH adsorption over pharmaceutical compounds as the need for an efficient system to clean water from emerging contaminants is of considerable importance. Several antibiotics (tetracycline, metrodinazole, amoxicillin, norfloxacin, sulfamethoxazole) and NSAID (diclofenac, salicylic acid, ibuprofen, ketoprofen, flurbiprofen) have been reviewed. Various factors such as the synthesis proportions, the

memory effect, and the use of support or foreign substances have been described and analyzed. Kinetics and isotherm models highlighted the prevalence of pseudo-first and pseudo-second-order models and Langmuir and Freundlich models, respectively. Temperature seems to have a greater effect than initial pH, with the majority of the processes being exothermic and spontaneous. As is one of the main drawbacks of the adsorption technique, different strategies to recover the adsorbents in a simple yet effective way have also been described.

Even though much effort has been put into the study of LDH as adsorbents for pharmaceutical compounds over the last years, there are several factors that need to be further studied and implemented, such as the further study of green supports, the use of real water effluents containing more than one contaminant, the adsorption in continuous mode (fixed-bed experiments) or the search for low cost and environmentally friendly regeneration methods. Thus, the removal process should be studied using larger-scale processes to check its feasibility in full-scale installations at an industrial level.

There are still many interesting areas to explore for LDH applications. The particular structure of these materials can be designed, controlled and adapted to the desired purpose, such as the immobilization of enzymes and microorganisms and their possible applications as biocatalysts. The synthesis of LDH from industrial metal wastes [26,29,30] may be of relevant interest because this method achieves the loop closure of a circular economy system.

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CAPTIONS

Figure 1. Consumption of antibiotics in 2010. Expressed as pill, capsule or ampoule per person (A), and compound annual growth rate of antibiotic drug consumption between 2000 and 2010 (B). (Reproduced with permission from [15]).

Figure 2. Regional patterns of pharmaceutical therapeutic groups analyzed in each United Nations region. MEC = measured environmental concentration; WEOG, Western Europe and Others Group; EEG = Eastern Europe Group; GRULAC = Latin American and Caribbean States. (Reproduced with permission from [5]).

Figure 3. Schematic illustration of the adsorption phenomenon of salicylic acid (SLC) onto LDH structure. (Reproduced with permission from [22]).

Figure 4. XRD patterns of the solids before and after the calcination and after the adsorption of diclofenac sodium (DCF). Samples based on Mg (a), Zn (b) and Ni (c). (Reproduced with permission from [25]).

Figure 5. Adsorption kinetics of NOR on: (a) CO_3-LDH and CO_3-MAS-LDH, (b) Cl-LDH and Cl-MAS-LDH. Experimental conditions: initial concentration of NOR: 20 mg/L, dose of LDH: 2 g/L, initial pH: 6.7, and T: 298 K. (Reproduced with permission from [28]).

Figure 6. Effect of increasing concentration of nitrate, sulfate, carbonate and hardness on metronidazole (MN) removal efficiency (pH = 9; LDH dose = 6 g/L; MN conc. = 40 mg/L; contact time = 2 h). (Reproduced with permission from [36]).

Figure 7. Photographs and SEM images of the bare and modified polypropylene chip, (A) Bare chip, (B) polydopamine (PD) modified chip, (C) NiAl-LDH modified chip, (D) SEM

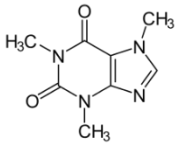
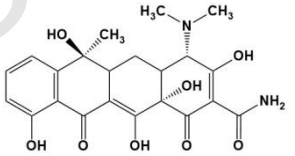
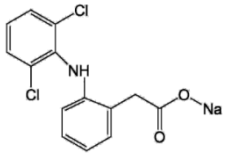
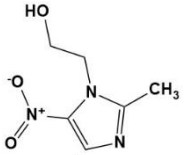
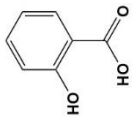
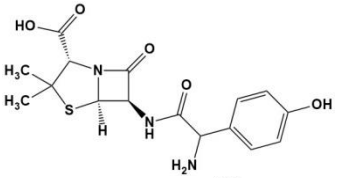
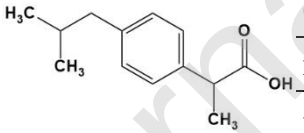
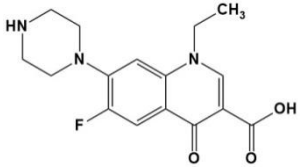
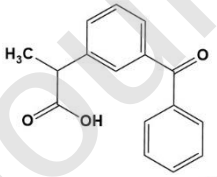
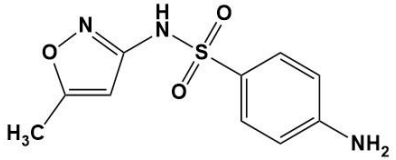
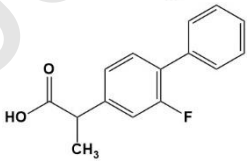
cross-sectional view of PD layer, and (E) SEM cross-sectional view of NiAl-LDH film. (Reproduced with permission from [41]).

Figure 8. Schematic representation of the formation process of MgAl LDH arranged over γ-AlO(OH) nanowires. (Reproduced with permission from [45]).

Figure 9. MgAl LDH supported on biochar as adsorbent of diclofenac sodium (DCF). (Reproduced with permission from [47]).

Figure 10. Equilibrium adsorbed amount of diclofenac sodium (DCF) on Zn–Fe LDH. (Reproduced with permission from [52]).

Table 1. Antibiotics and non-steroidal anti-inflammatory drugs (NSAID) molecules studied as adsorbates.

Name	Structure and characteristics		Name	Structure and characteristics	
Caffeine (CAF)		$C_8H_{10}N_4O_2$ m=194.19 pk_a=10.4	Tetracycline (TCY)		$C_{22}H_{24}N_2O_8$ m=444.15 pk_a=7.38*
Diclofenac sodium (DCF)		$C_{14}H_{10}Cl_2NNaO_2$ m=296.15 pk_a=4.15	Metrodinazole (MTD)		$C_6H_9N_3O_3$ m=171.06 pk_a=13.41
Salicylic acid (SLC)		$C_7H_6O_3$ m=138.03 pk_a=2.98, 13.04	Amoxicillin (AMX)		$C_{16}H_{19}N_3O_5S$ m=365.10 pk_a=6.52*
Ibuprofen (IBP)		$C_{13}H_{18}O_2$ m=206.13 pk_a=4.37	Norfloxacin (NFX)		$C_{16}H_{18}FN_3O_3$ m=319.13 pk_a=8.39, 2.63
Ketoprofen (KTP)		$C_{16}H_{14}O_3$ m=254.09 pk_a=4.13	Sulfamethoxazole (SFM)		$C_{10}H_{11}N_3O_3S$ m=253.05 pk_a=--
Flurbiprofen (FBP)		$C_{15}H_{13}FO_2$ m=244.09 pk_a=4.15			

m=molecular mass
*molecule with more than 2 pk_a

Table 2. Adsorption conditions of supported LDH.

LDH	Support	Adsorbate	Adsorption conditions	q_{max}	Adsorbent concentration	Reference
MgAl	*Syagrus Coronata* biochar	DCF	50-1000 mg/L, 333 K, pH 5.65, 6 h	168 mg/g	4g/dm^3	[47]
CaAl	Polymer ionomer	DCF	0.5-200 mg/L, pH=9, 2 min, room temperature	268 mg/g	1g/dm^3	[46]
MgAl	Poly(m-Phenylenediamine)	DCF	50-400 mg/L, 313 K, pH=7, 2 min	589 mg/g	0.125 g/dm^3	[39]
MgAl	Bovine bone biochar	CAF	5-200mg/L, 313 K, pH=12, 30 min	26 mg/g	4g/dm^3	[48]
NiAl	Cotton fiber	KTP	200 mg/L, 30 min, room temperature,	714 mg/g	3g/dm^3	[49]
NiMgAl	Copper ferrite	TCY	250 mg/L, 303 K, pH =4, 6 h	192 mg/g	1 g/dm^3	[40]
NiAl, ZnAl, CuFe MgFe	Polypropylene chip	KTP, FBP	1mg/L, 303 K, 20 min			[41]
MgAl	SiO_2 spheres	DCF, IBP	10 mg/L, room temperature, 5 min	758 mg/g, 400 mg/g	0.11g/dm^3	[43]
MgAl	cellulose	AMX	60 mg/L, 318 K, natural pH, 24 h	138 mg/g	0.1g/dm^3	[42]
MgAl	γ-AlO(OH) nanowires	TCY	200 mg/L, pH=7	302 mg/g	0.5g/dm^3	[45]

Table 3. Most used isotherm equations, kinetic models and thermodynamic equations.

Isotherm model	Expression	Kinetic model	Expression
Two parameter isotherm			
Langmuir	$q_e = \frac{k_L \cdot q_L \cdot C_e}{1 + k_L \cdot C_e}$	**Pseudo-first order**	$\frac{dq}{dt} = k_1 (q_e - q_t)$
Freundlich	$q_e = k_F \cdot C_e^{1/m_F}$	**Pseudo-second order**	$\frac{dq}{dt} = k_2 (q_e - q_t)^2$
		Intraparticule diffusion	$\frac{dq}{dt} = k_3 t^{1/2} + C$
Three parameter isotherm		**Thermodynamic equations**	
Toth	$q_e = \frac{k_T \cdot q_T \cdot C_e}{[1 + (k_T \cdot C_e)^{m_T}]^{1/m_T}}$	**Van't Hoff**	$\ln\left(\frac{q_e}{C_e}\right) = \frac{\Delta S^\circ}{R} - \frac{\Delta H^\circ}{RT}$
Sips	$q_e = \frac{q_s (K_S C_e)^{1/m}}{1 + K_S C_e^{1/m}}$	**Gibbs**	$\Delta G^\circ = -RT \ln(K_d)$
Langmuir-Freundlich	$q_e = \frac{q_{max} (K_{LF} C_e)^{\beta}}{1 + (K_{LF} C_e)^{\beta}}$	q_e: equilibrium capacity, C_e: equilibrium conc.	
		q_L: Langmuir capacity K_L:Langmuir constant, K_F, n: Freundlich constants.	
Redlich-Petersson	$q_e = \frac{C_e K_{rp}}{(1 + a_{rp} C_e^{b_{rp}})}$	q_T, K_T, m_T : Toth constants, q_S: Sips capacity, K_S, m: Sips constants; K_{LF}, β, qmax: Lanmguir-Freundlich constants; a_{rp}, K_{rp}, b_{rp}: Redlich-Petersson constants	
		qt: capacity at t, K1: adsorption rate constant, t: adsorption time, K_2: adsorption rate constant, K_3: diffusion rate constant, C: indicates thickness of the boundary layer	
		R: gas constant, T: temperature, ΔG: change in free energy, ΔH: enthalpy, ΔS: entropy	

Table 4. Thermodynamic parameters of NSAID/antibiotic adsorption onto LDH.

LDH	adsorbate	ΔH° (J/mol)	ΔS° (J/mol·K)	−ΔG° (J/mol)			Adsorption nature	Reference
				303 K	313 K	323 K		
MgAl on tree biochar	DCF	−111.61	−0.271	−29.6	−28.57	−20.09	Spontaneous, exothermic	[47]
MgAl on bovine bone biochar	CAF	−10.37	−0.0195		−16.93	−15.74	Spontaneous, exothermic	[48]
MgAl	MTD	−4.36	−34.669	6073			Non spontaneous, exothermic	[36]
NiMgAl on copper ferrite	TCY	21.48	5.8	−2.089	−2.818	−2.978	Spontaneous, endothermic	[40]
				298 K	308 K	318 K		
ZnAl	DCF	−13.11	−23.25	11.13	9.42	9.00	Non spontaneous, exothermic	[35]
MgAl CO_3	NFX	−3.03	45.87	−16.70	−17.16	−17.61	Spontaneous, exothermic	[28]
MgAl Cl	NFX	−27.65	−22.21	−21.03	−20.80	−20.50	Spontaneous, exothermic	[28]
MgFe	TCY	1.493	6.13	−0.334	−0.395	−0.456	Spontaneous, endothermic	[38]
ZnAl	SLC	−33.76	103.17	−29.68	−30.71	−31.74	Spontaneous, exothermic	[37]
ZnAl	SFM	−15.586	−30.827	−3.962		−3.381	Spontaneous, exothermic	[51]

Table 5. LDH regeneration strategies and performance.

LDH	Adsorbate	Regeneration conditions	Regeneration performance	Reference
CaAl on Polymer ionomer	DCF	Basic solutions and organic solvents	Reduction of 11% after 3 cycles	[46]
MgAl on a biochar	CAF	NaCl or methanol	6 cycles	[48]
NiAl on cotton fiber	KTP	NaOH 1 M rinse	Close to 100% after 8 cycles	[49]
NiMgAl on copper ferrite	TCY	NaOH, acetone and ethanol	42.5% reduction after 3 cycles	[40]
MgAl on SiO_2 spheres	DCF, IBP	Oxidation method	Above 90% in four cycles	[43]
MgAl on γ-AlO(OH) nanowires	TCY	Thermal decomposition at 823 K for 3 hours	Adsorption capacity of 88% after 3 cycles	[45]
ZnAl	SLC	Thermal regeneration at 573 K	Second adsorption lowered adsorption by 16.7%	[22]
ZnAl	DCF	Ethanol	4 cycles reduction less 10%	[35]
ZnAl, MgAl, NiAl	DCF	Thermal treatment at 773 K for 12 hours	8 cycles, ZnAl stable for 7 cycles	[25]
MgFe on chitosan	TCY	$NaCO_3$ solution + thermal treatment 673 K for 2 hours	Good results	[38]
ZnAl	SLC	Thermal regeneration at 673 K	In 5 cycles, reduction of 22%	[37]
ZnAl	SFM	Na_2CO_3	Reduction from 93 to 71% in 6 cycles	[51]

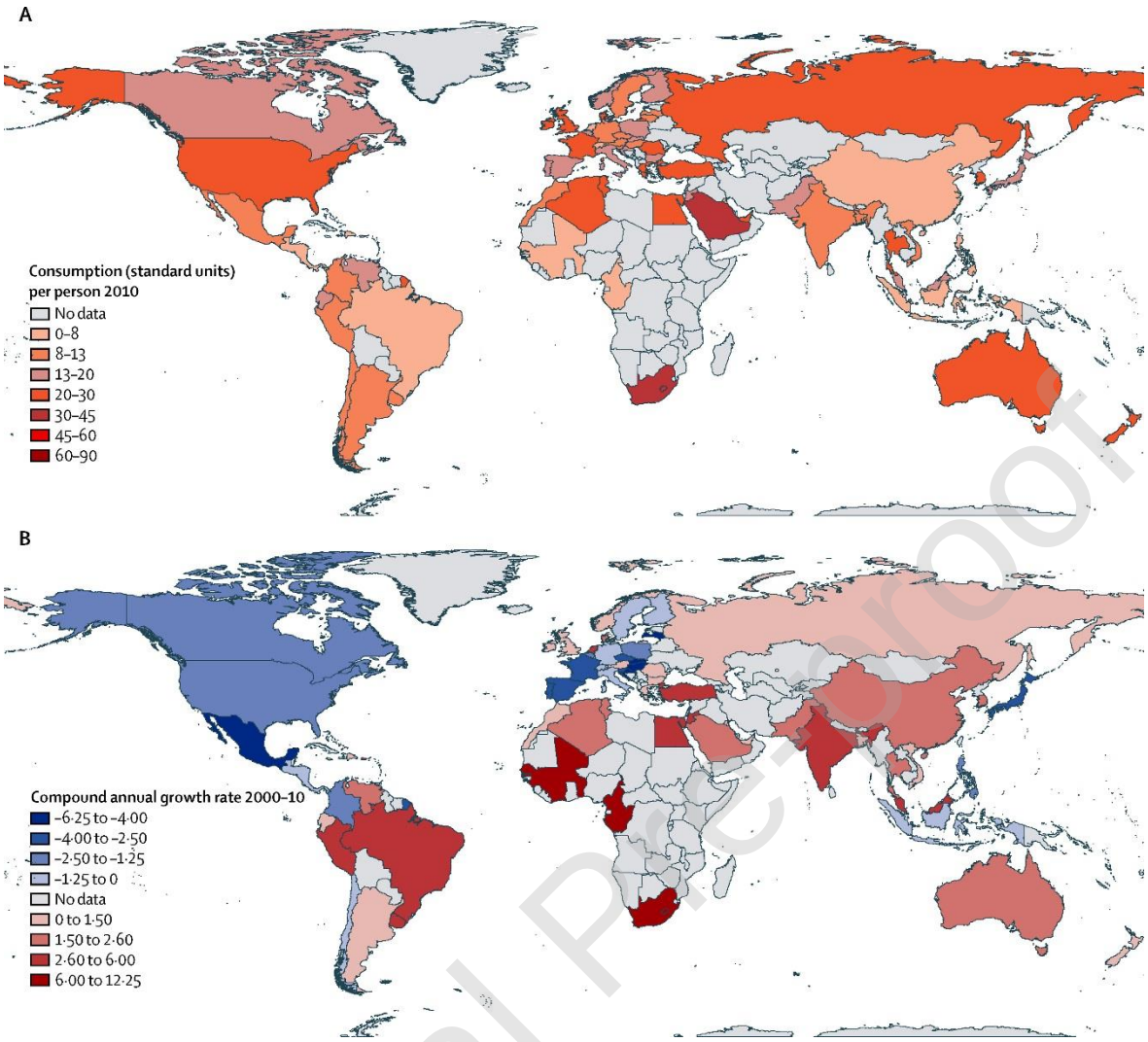


Figure 1. Consumption of antibiotics in 2010. Expressed as pill, capsule or ampoule per person (A), and compound annual growth rate of antibiotic drug consumption between 2000 and 2010 (B). (Reproduced with permission from [15]).

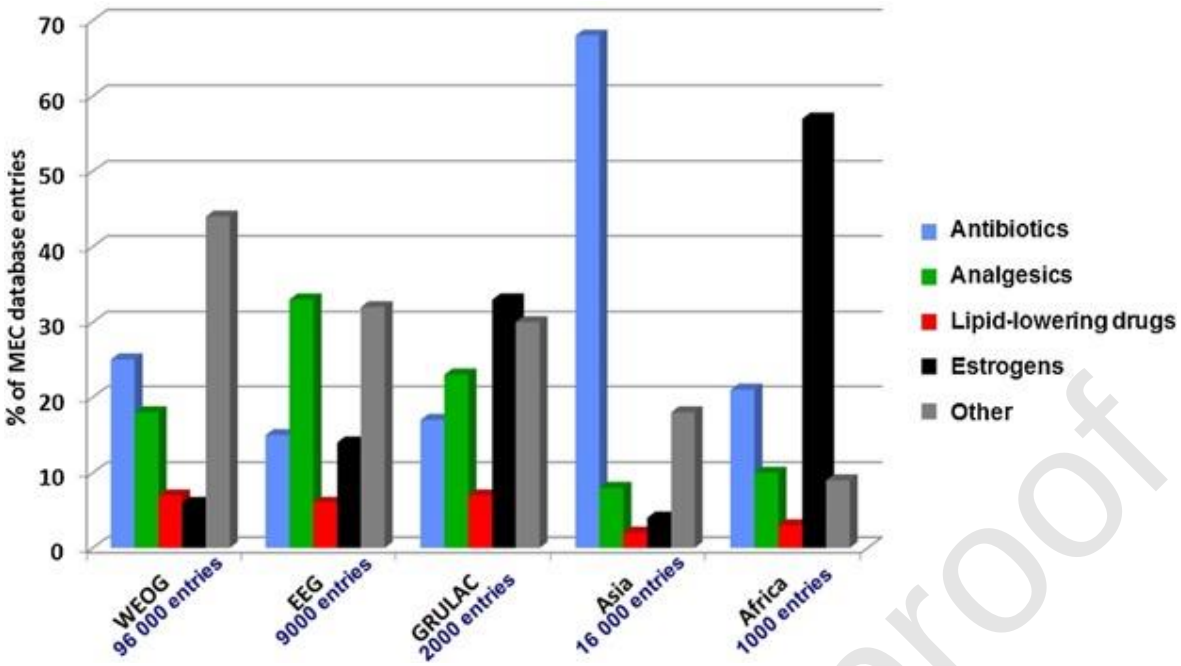


Figure 2. Regional patterns of pharmaceutical therapeutic groups analyzed in each United Nations region. MEC = measured environmental concentration; WEOG = Western Europe and Others Group; EEG = Eastern Europe Group; GRULAC = Latin American and Caribbean States. (Reproduced with permission from [5]).

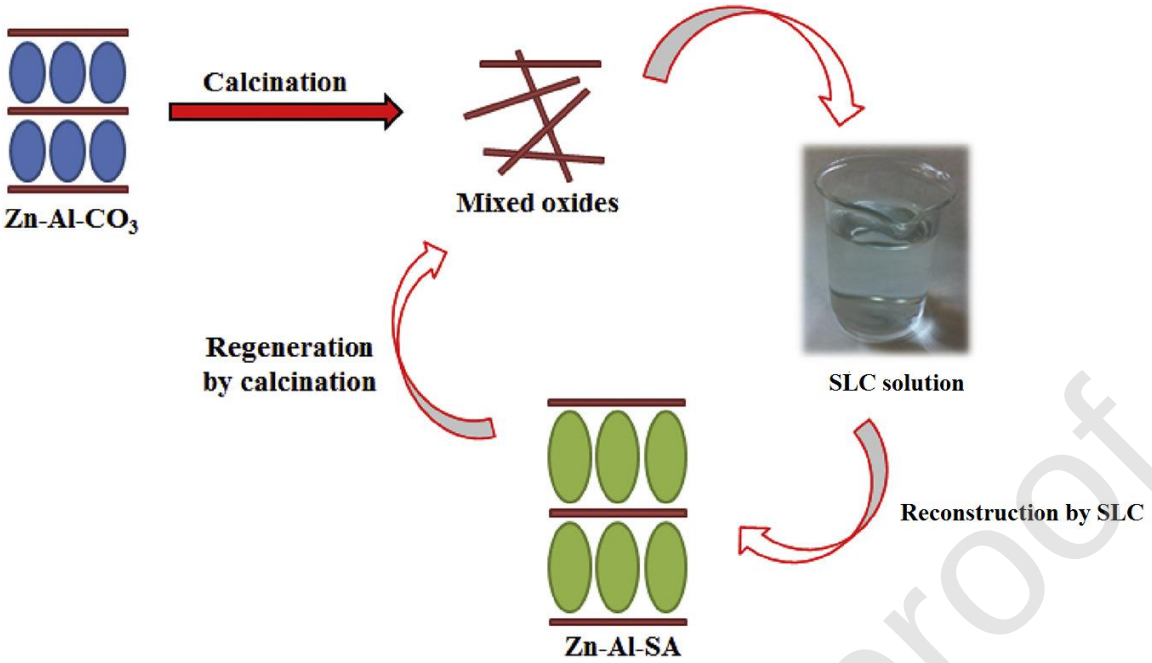


Figure 3. Schematic illustration of the adsorption phenomenon of salicylic acid (SLC) onto LDH structure. (Reproduced with permission from [22]).

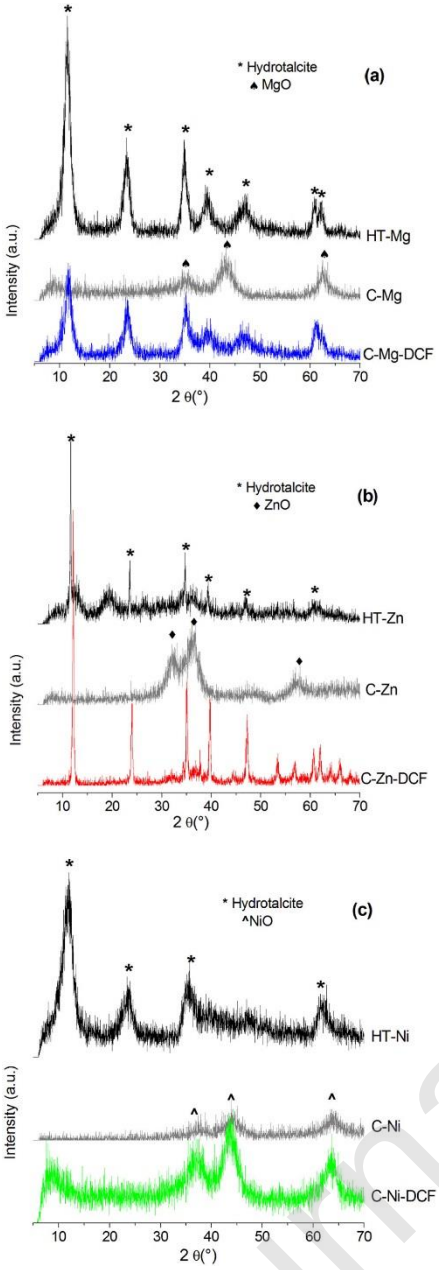


Figure 4. XRD patterns of the solids before and after the calcination and after the adsorption of diclofenac sodium (DCF). Samples based on Mg (a), Zn (b) and Ni (c). (Reproduced with permission from [25]).

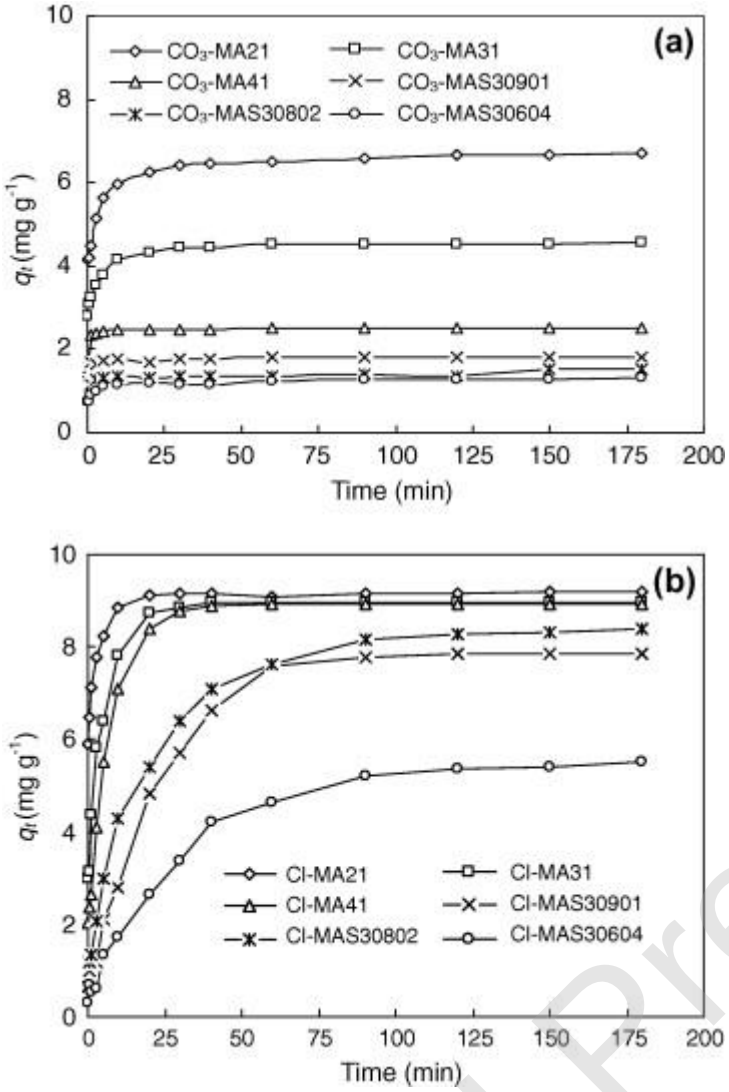


Figure 5. Adsorption kinetics of NOR on: (a) CO_3-MA-LDH and CO_3-MAS-LDH, (b) Cl-MA-LDH and Cl-MAS-LDH (MAS denotes Mg, Al and Sn, respectively). Experimental conditions: initial concentration of NOR: 20 mg/L, dose of LDH: 2 g/L, initial pH: 6.7, and T: 298 K. (Reproduced with permission from [28]).

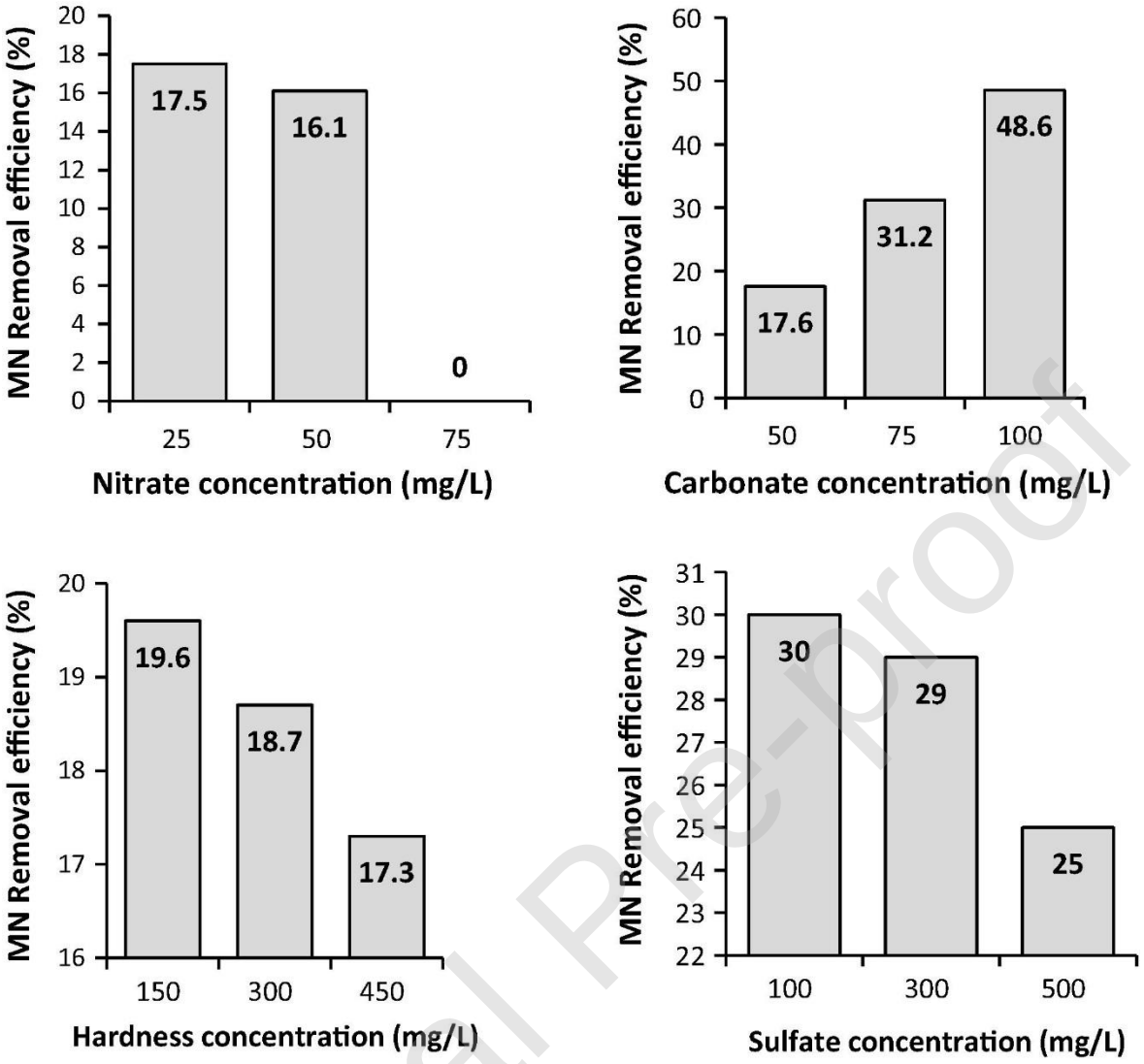


Figure 6. Effect of increasing concentration of nitrate, sulfate, carbonate and hardness on metronidazole (MN) removal efficiency (pH = 9; LDH dose = 6 g/L; MN conc. = 40 mg/L; contact time = 2 h). (Reproduced with permission from [36]).

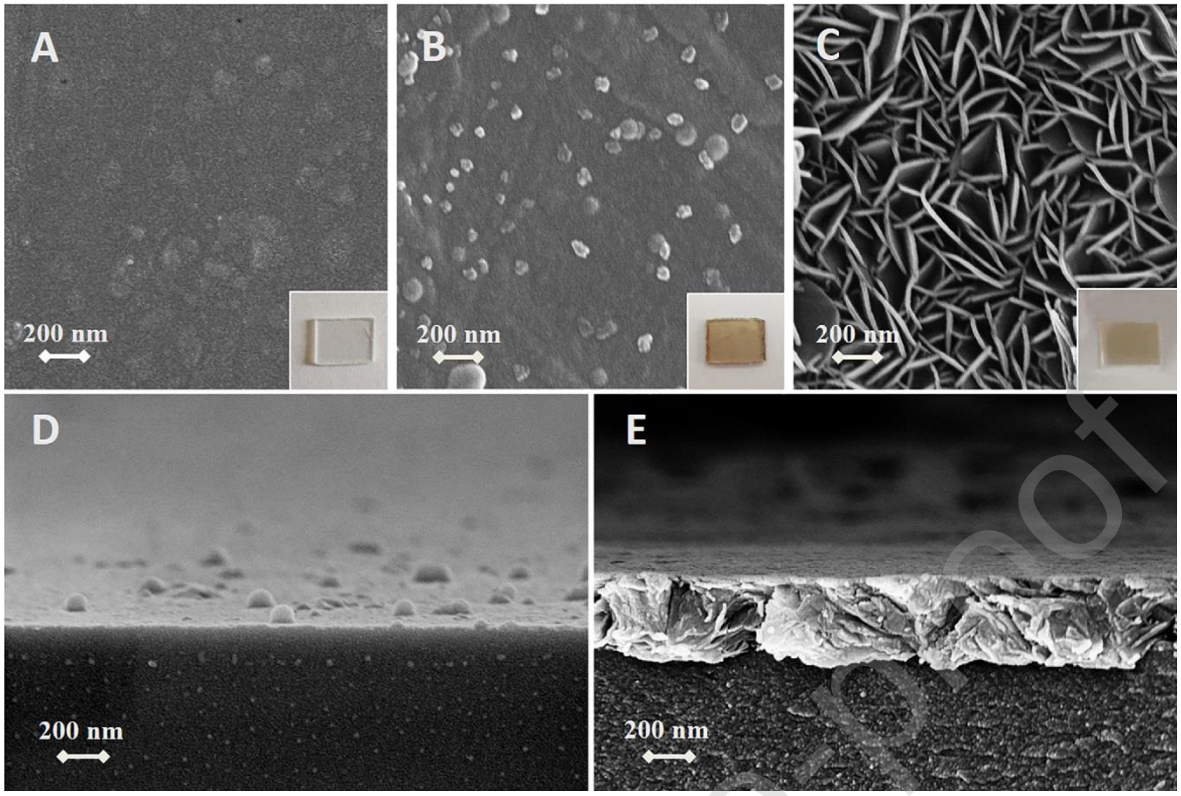


Figure 7. Photographs and SEM images of the bare and modified polypropylene chip, (A) Bare chip, (B) polydopamine (PD) modified chip, (C) NiAl-LDH modified chip, (D) SEM cross-sectional view of PD layer, and (E) SEM cross-sectional view of NiAl-LDH film. (Reproduced with permission from [41]).

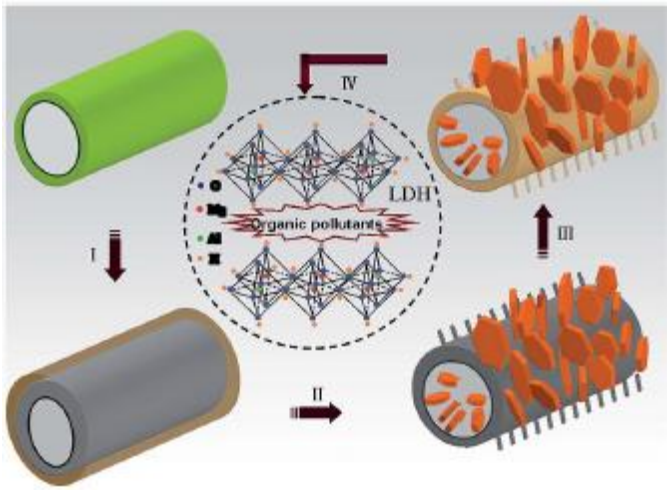


Figure 8. Schematic representation of the formation process of MgAl LDH arranged over γ-AlO(OH) nanowires. (Reproduced with permission from [45]).

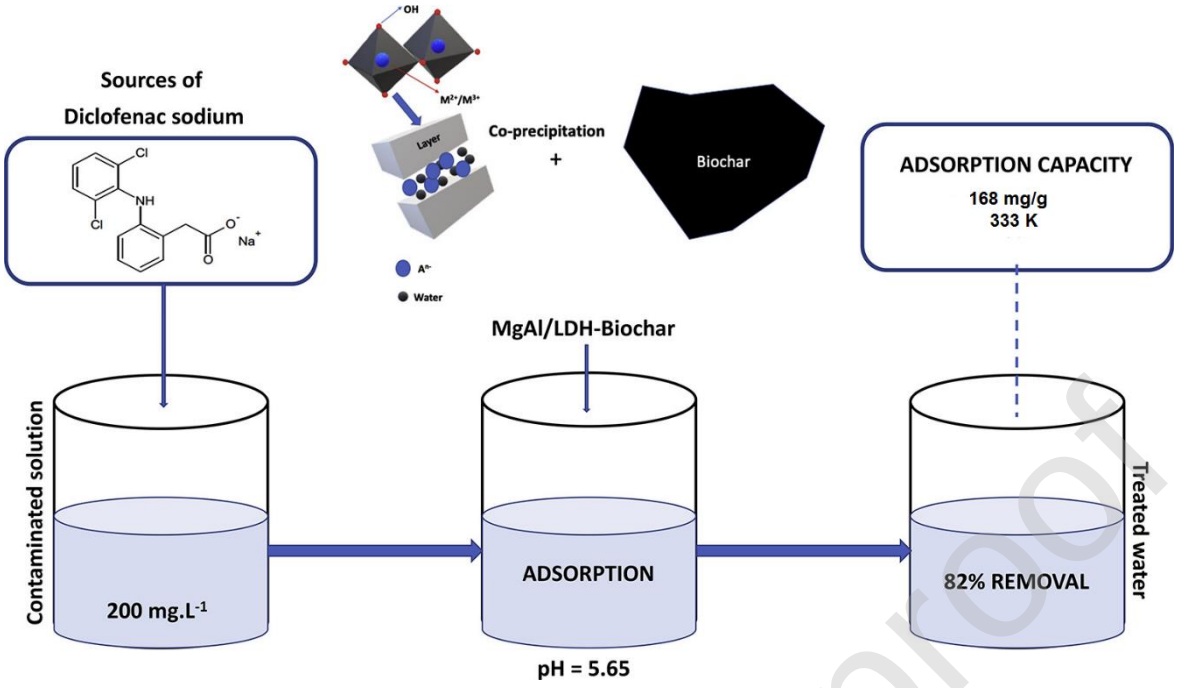


Figure 9. MgAl LDH supported on biochar as adsorbent of diclofenac sodium (DCF). (Reproduced with permission from [47]).

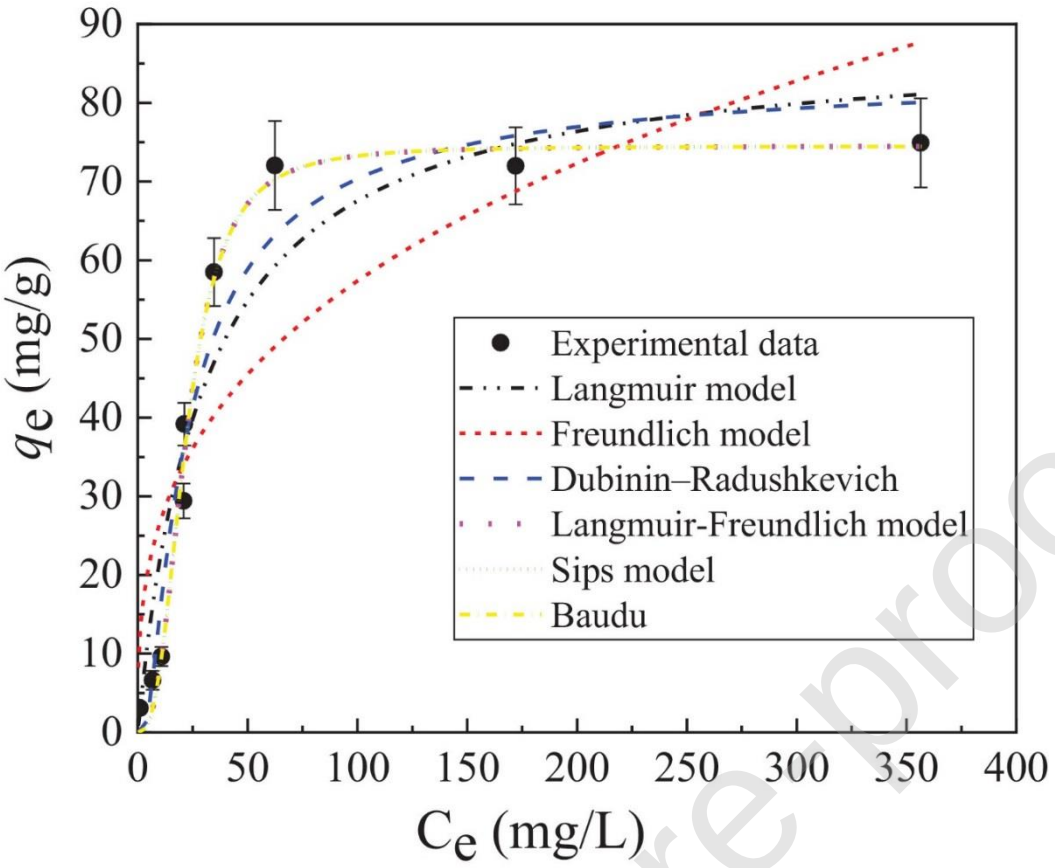


Figure 10. Equilibrium adsorbed amount of diclofenac sodium (DCF) on ZnFe LDH. (Reproduced with permission from [52]).