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Design of Selective Nanoparticles of Layered Double Hydroxide (Mg/Al-LDH) for the Analysis of Anti-Inflammatory Non-Steroidal Agents in Environmental Samples, Coupled with Solid-Phase Extraction and Capillary Electrophoresis

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Abstract: A simple, fast, and low-cost pre-concentration methodology based on the application of solid-phase extraction coupled to layered double hydroxides (LDHs) and capillary electrophoresis was developed for the determination of naproxen (NPX), diclofenac (DFC), and ibuprofen (IBP) in environmental sample waters. A systematic study of the LDH composition was designed, including the effects of interlayer anions (NO_3^-, Cl^-, CO_3^{2-}, $BenO^-$, and SDS^-) and the effect of molar ratio (Mg:Al). The optimal composition of MgAl/Cl^--LDH (Mg:Al; 1.5:1.0) was coupled to an SPE system: pH (neutral pH), LDH amount (15 mg), and extraction capacity ranged from 79.71 to 83.11% for the three anti-inflammatory non-steroidal agents analyzed. A recovery rate of up to 80.87% was obtained when 0.01 M chloride acid in methanol was used as the eluent and 50 mL of sample was used. Under optimal conditions, the linear range of the calibration curve ranges from 18.02 to 200 μg L^{-1}, with limits of detection ranging from 6.03 to 18.02 μg L^{-1} for the three NSAIDs. The precision of the methodology was evaluated in terms of inter- and intra-day repeatability, with %RSD < 10% in all cases. The proposed method was applied to analyze environmental water samples (bottle, tap, cistern, well, and river water samples). The developed method is a robust technique capable of combining with other analytical methods to quantitatively determine anti-inflammatory non-steroidal agents.

Keywords: layered double hydroxides; solid-phase extraction; NSAIDs; capillary electrophoresis

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1. Introduction

Emerging contaminants (ECs) are defined as chemical compounds without regulatory status from an international organization. However, the impact of these contaminants on the environment and human health is poorly understood. These contaminants have been the main focus of research, and the principal reason is their widespread use in daily life; the most common ECs are pesticides, food additives and pharmaceuticals [1,2]. Pharmaceutical products are formulations that may contain one or more active ingredients; these products are widely used in human and veterinary medicine and include antibiotics, antidepressants, contraceptives and non-steroidal anti-inflammatory drugs (NSAIDs), among others [3].

NSAIDs have anti-inflammatory, analgesic, and antipyretic properties; the pharmacological action of NSAIDs is related to the inhibition of cyclooxygenase (COX), a key enzyme of prostaglandin biosynthesis at the inflammation site [4]. In Mexico, NSAIDs such as naproxen (NPX), diclofenac (DFC), and ibuprofen (IBP) are over-the-counter medications that do not require a prescription for sale to the public. This practice, easy access, and

low cost have led to excessive consumption of self-medication and medical applications. Their release into the environment occurs through human excretion, improper treatment of unused medications, and hospital and private household effluents, contaminating the ground, surface, and drinking water [5]. NPX, DCF, and IBP are among the top 10 persistent pollutants, accounting for more than 15% of all pharmaceuticals detected in aquatic environments [6]. NSAIDs are toxic for aquatic flora and fauna, particularly fish, gastropods, bivalves, and crustaceans, which are critical links in the trophic chain [7]. Even though NSAIDs are considered safe drugs, acute overdose or chronic abuse is associated with renal disorder, nephrotoxicity, and gastrointestinal and cardiovascular complications [8,9].

Electrochemical methods [10,11], gas chromatography (CG) [12,13], and high-performance liquid chromatography (HPLC) [14,15] have been applied in the analysis of NSAIDs in food, biological, and environmental samples. Despite the benefits offered by these instrumental techniques, some are inconvenient in NSAID determination, such as mono-analyte analysis, highly time-consuming derivatization procedures, high consumption of organic solvents, and the use of complex and expensive instrumentation [10,12,15]. On the other hand, capillary electrophoresis (CE) provides some advantages, such as multi-analyte analysis, high-resolution separations, short-time analysis, and low solvent and sample consumption, which has led to its application in NSAID analysis [16,17]. In the NSAID analysis, the main problems are the low concentration of analytes in the sample and the complexity of the analytical matrix. These problems have been overcome by the implementation of sample treatment procedures to clean-up and pre-concentrate the analytes [18].

Among several sample treatments, the solid-phase extraction process (SPE) is the most common pre-concentration technique, with its main advantage being the use of large sample volumes, consisting of four main steps: (1) conditioning; (2) sample loading; (3) interference removal; and (4) the elution process [18]. The SPE technique employs a variety of adsorbents, including commercial polymeric materials (C8, C18), carbonaceous materials, functional and imprinted polymers, and metal–organic frameworks, and in recent years, researchers have explored the use of layered double hydroxides [19–22].

LDHs are represented by the general formula $[M^{2+}_{1-x}M^{3+}_{x}\ (OH)_2]^{x+}[A^{n-}_{x/n}\cdot yH_2O]$, where M^{2+} and M^{3+} are divalent and trivalent metal cations, respectively, and A^{n-} is an n-valent anion. These compounds have a layered crystal structure with wide variations depending upon the nature of metal cations and the molar ratio (M^{2+}:M^{3+}) with a molar ratio of $0.07 < x < 0.5$. The versatility of LDHs is due to the wide combination of metal cations and anions that can be used in their synthesis [23,24]. LDHs have proven to be highly suitable for pre-concentration systems of phenolic acids [25], polycyclic aromatic hydrocarbons [26], pesticides [27], and antibiotics [28] because of their numerous physicochemical properties, straightforward synthesis process, structural arrangement, adjustable nature, ability to exchange anions, capacity to swell, and chemical and thermal stability [24].

This research details the development, synthesis, and application of MgAl-LDH selective adsorbents in the analysis of ibuprofen, diclofenac, and naproxen in environmental and potable water samples using a solid-phase extraction (SPE) pre-concentration technique and capillary electrophoresis. The univariable method optimized the LDH composition (interlayer anion and molar ratio) and the critical factors of the SPE system. The physical–chemical properties of the LDH were characterized by infrared spectroscopy (IR), scanning electron microscopy (SEM), thermogravimetric analysis (TGA), and isotherm models (Langmuir and Dubinin–Radushkevich).

2. Materials and Methods

2.1. Reagents and Materials

Sodium tetraborate, sodium hydroxide, and hydrochloric acid were provided from J.T. Baker (Phillipsburg, NJ, USA). Diclofenac, ibuprofen, naproxen and the α-naphthaleneacetic acid used as the internal standard (IS) were obtained from Sigma-Aldrich (St, Louis, MO, USA). The solutions were obtained by dilution from the respective analytical-grade reagent in deionized water, provided by a Milli-Q system, with a resistivity of less than 18.0 MΩ

cm (Millipore, Bedford, MA, USA). The background electrolyte (BGE) consisted of 30 mM sodium tetraborate and 2 mM β-ciclodextrind adjusted at pH 10.0.

Magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$), aluminum chloride nonahydrate ($AlCl_3 \cdot 9H_2O$), sodium nitrate ($NaNO_3$), sodium chloride (NaCl), sodium carbonate (Na_2CO_3), sodium dodecyl sulfate (SDS^-), and sodium benzoate ($BenO^-$), all with a purity of 98.0%, were obtained from Sigma-Aldrich (St. Louis, MO, USA), used in the LDH synthesis. HPLC-grade methanol from Sigma-Aldrich (St. Louis, MO, USA) was used in the elution process.

2.2. LDH Synthesis

LDHs were synthesized by the coprecipitation method. To obtain Mg-Al LDHs with molar ratios of 4.5–1.0, 3.0–1.0, and 1.5–1.0, different amounts of the metal cation precursors $MgCl_2 \cdot 6H_2O$ and $AlCl_3 \cdot 9H_2O$ (1.84 g and 0.49 g, 1.22 g and 0.49 g, and 0.61 and 0.49 g, respectively) were dissolved in 40 mL of deionized water. Subsequently, 3 mL of a 6M NaOH solution was added dropwise to maintain a constant pH (~11), stirred at 80 °C for 1 h under an inert atmosphere [29]. The obtained LDHs were stored for 3 days and washed five times with 10 mL of deionized water and dried at 80 °C for 24 h. The SDS^--LDH and $BenO^-$-LDH were synthesized by the anion exchange method employing 200 mg of $MgAl/NO_3{}^-$-LDH dispersed in 10 mL of deionized water containing 80 mg of SDS^- or $BenO^-$, dispersed for 15 min by vortexing. After the dispersion, the LDHs were washed five times with 5 mL of deionized water and dried at 80 °C for 24 h.

2.3. Instrumental

The characterization of the optimal LDH was conducted using a Perkin Elmer Fourier infrared spectrophotometer (FITR) with a Pike Gladi ATR. The morphology was evaluated using a JEOL JSM-820 scanning electron microscope (SEM). The molar ratio of the optimal adsorbent was assessed by flame atomic absorption (FAAS) using a Varian SpectrAA 880 spectrometer (Varian, Inc., Mulgrave, Australia) and 10 mg of the optimal adsorbent. The particle size was determined using a Beckman Coulter LS I3 320 Laser Diffraction Particle Size Analyzer. The thermal stability of the adsorbent was assessed using a TGA Analyzer 200 with Universal V4.7A software in the temperature range of 35 to 600 °C (10 °C min^{-1}). The pH value was adjusted with a pH/ion analyzer (model 450; Corning Science Products, New York, NY, USA).

Electrophoretic separation was performed using a Beckman Coulter P/ACE 5500-UV (Fullerton, CA, USA), employing a fused silica capillary (41.7 cm × 75 μm ID). The data were collected and analyzed with a Beckman P/ACE system with MDQ version 2.3 software.

2.4. Capillary Electrophoresis Analysis

The capillary was activated with 1.0 M NaOH for 15 min, 0.1 M NaOH for 10 min, deionized water for 10 min, and BGE for 10 min. The capillary was sequentially cleaned between each analysis with 1.0 M NaOH for 4 min, 0.1 M NaOH for 2 min, deionized water for 2 min, and BGE for 4 min. The injection was performed in a hydrodynamic way (0.5 psi, 10 s), and a voltage of 18 kV was applied to separate the analytes.

2.5. Adsorption Experiments

Adsorption experiments were carried out under ambient conditions using a batch technique; 10 mg of the LDH and 1 mL of NSAID solution (10 mg L^{-1}) adjusted to pH 10 were added to an Eppendorf tube (1.5 mL) and dispersed for 5 min by vortexing. After that, the mixture was centrifugated (3 min, 5000 rpm); the remaining solution was spiked with IS (1.0 mg L^{-1}) and analyzed by CE.

The amount of NSAIDs adsorbed per gram of adsorbent (q_e) was calculated from the difference between the initial concentration (C_0) and the equilibrium concentration (C_e).

$$q_e = \frac{(C_0 - C_e)v}{m} \quad (1)$$

2.6. Sample Treatment

In total, 15 mg of MgAl/Cl^--LDH was packed in an SPE cartridge and conditioned with 5 mL of deionized water (1mL min^{-1}). Subsequently, 50 mL of a water sample was passed through the SPE cartridge (1mL min^{-1}); after the sample loading, the adsorbent was washed with 5 mL of deionized water. Finally, elution was carried out with 1 mL of methanol/HCl (0.01 M); the eluate was evaporated to dryness and reconstituted in 1 mL of a solution containing the IS in 0.5 mg L^{-1} for its CE analysis.

3. Results and Discussion

3.1. Characterization of the Optimal Adsorbent (MgAl/Cl^--LDH)

The FTIR spectra of MgAl/Cl^--LDH are shown in Figure 1a. The peak at 3450 cm^{-1} is due to the stretching vibrations of O-H groups of both hydroxide layers and interlayer water in LDH. The weak peak around 1635 cm^{-1} is associated with the bending vibration of interlayer water molecules. The band observed around 1370 cm^{-1} is due to the asymmetric stretching of the CO_3^{2-}, which is introduced to the interlayer by CO_2 adsorption during the synthesis. The peaks in the region between 1000 cm^{-1} and 641 cm^{-1} are assigned to the lattice vibrations of metal hydroxide sheets [30–32].

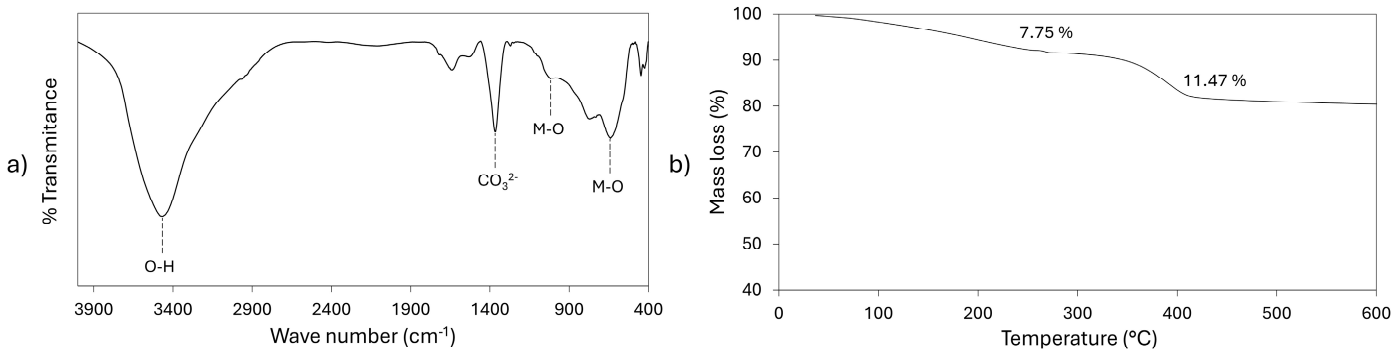

Figure 1. (**a**) FTIR spectra of the MgAl/Cl^--LDH and (**b**) TGA curve MgAl/Cl^--LDH.

Figure 1b presents the TGA of the optimal adsorbent. We observed two main stages in the MgAl/Cl^--LDH degradation process. The first stage occurred from 70 °C to 302 °C, where the adsorbed surface and interlayer water molecules contributed 7.75% of the mass loss. Finally, the second degradation stage, from 320 to 450 °C, accounted for 11.47% of the total mass and was attributed to the dihydroxylation of the laminar LDH structure and the loss of interlayer anions [33].

The overall shape of the optimal adsorbent (MgAl/Cl^--LDH) was examined using SEM. Figure 2 shows that despite the high aluminum content of the optimal adsorbent, the morphology surface obtained by SEM shows only the characteristic hexagonal plates of LDH, discarding the presence of impurity phases of aluminum hydroxides [34–36]. The particle size distribution was determined within the range of 85 to 100 nm by measuring the diameters of particles from a uniform sample of the adsorbent. On the other hand, the metal content was determined to corroborate the molar ratio of the optimal adsorbent by EDS and FAAS. The EDS method found 23.95% of Mg and 14.59% of Al, with a molar ratio of 1.6:1.0 and a %RSD of 5.79. The FAAS method found 22.76% of Mg and 13.28% of Al, with a molar ratio of 1.7:1.0 and a %RSD of 6.91. A *t*-test was conducted to verify significant differences between EDS and FAAS; there is no evidence of significant differences ($t_{crit} > t_{exp(95\%)}$).

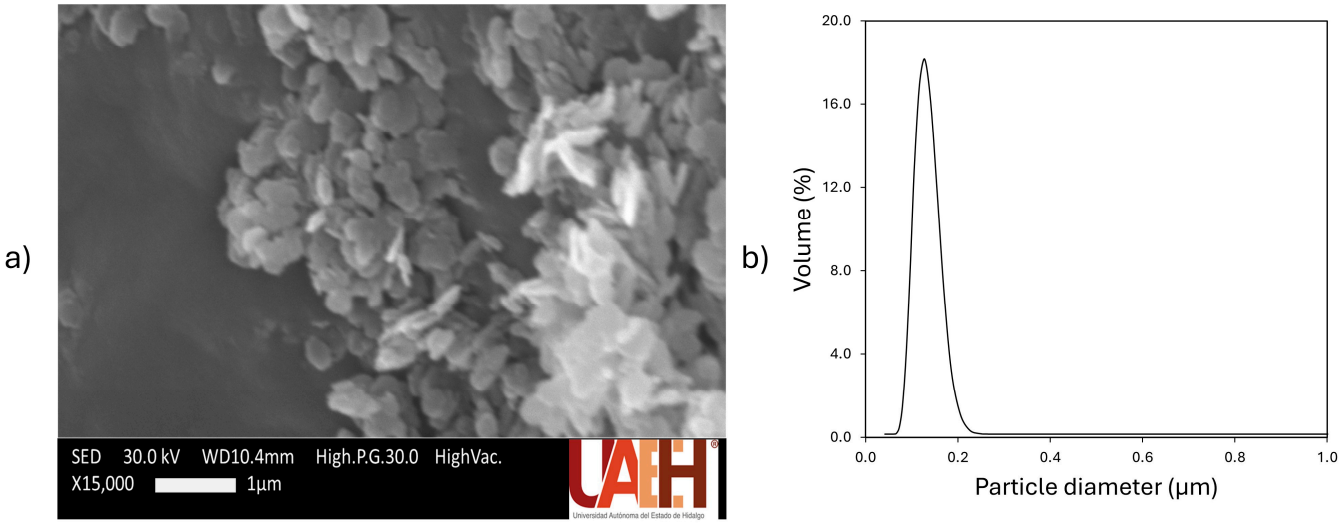

Figure 2. (**a**) Scanning electron microscope image and (**b**) particle size distribution of the MgAl/Cl^--LDH.

The particle size of the MgAl/Cl^--LDH in the aqueous suspension, presented in Figure 2b, indicates that the optimal adsorbent exhibits a uniform particle size, with a mean size of 135 nm. Finally, according to previous reports of LDH-based adsorbents, the optimal adsorbent's expected surface area is between 95.44 and 137.45 $m^2\ g^{-1}$ [37].

The Langmuir model (Equations (2) and (3)) assumes that the active centers on the adsorbent surfaces are identical; adsorbed molecules have no effect on the active sites that have not been occupied, and there is no interaction between adsorbed molecules. The Langmuir model was employed to determine the theoretical saturation capacity (Q_{max}) and the feasibility of the adsorption process [36].

$$\frac{1}{Q_e} = \frac{1}{Q_{max} K_L C_e} + \frac{1}{Q_{max}} \tag{2}$$

$$R_L = \frac{1}{1 + K_L C_0} \tag{3}$$

The Dubinin–Radushkevich model (Equations (4)–(6)) allows us to determine the adsorption mechanism on homogeneous and heterogeneous surfaces. Physical adsorption occurs when E < 8 kJ/mol, while chemical adsorption occurs when E is 8 kJ/mol < E < 16 kJ/mol [36].

$$LnQ_e = LnQ_m - \beta\varepsilon^2 \tag{4}$$

$$\epsilon = RTln\left(1 + \frac{1}{C_e}\right) \tag{5}$$

$$E = \frac{1}{\sqrt{2\beta}} \tag{6}$$

Table 1 shows the obtained results; the theoretical saturation capacity was between 6.29 and 16.22 mg g^{-1}, and the R_L values from 0.274 to 0.597 demonstrate the feasibility of the adsorption process. Finally, according to the Dubinin–Radushkevich model, the adsorption process corresponds to a chemical adsorption process, based on the obtained energy values (9.053 to 10.541 kJ mol^{-1}).

Table 1. Adsorption parameters for IBP, NPX and DCF.

	Langmuir			Dubinin–Radushkevich	
	Q_{max} (mg g^{-1})	R_L	r^2	E (kJ mol^{-1})	r^2
IBP	16.216	0.597	0.985	9.053	0.979
NPX	6.297	0.274	0.997	10.541	0.989
DCF	8.554	0.336	0.992	9.535	0.965

3.2. Composition Effect of the LDH on IBP, NPX and DCF Extraction

The interlayer anions and the molar ratio M^{2+}-M^{3+} are the critical factors that determine the extraction efficiency of organic pollutants; therefore, a systematic study of both factors was performed to find the optimal composition of the LDH [37].

3.2.1. Effect of Interlayer Anions on IBP, NPX and DCF Extraction

In order to investigate the effect of the interlayer anions on the extraction performance, MgAl-LDHs with a molar ratio of 3.0–1.0 were synthetized using NO_3^-, Cl^-, CO_3^{2-}, $BenO^-$ and SDS^-. The results are shown in Figure 3a. The results show that the charge density and size of the employed anion influence the extraction efficiency for the inorganic interlayers (NO_3^-, Cl^-, and CO_3^{2-}) [37]. This effect could be explained by the strong interactions between the analytes and the positively charged sheets in LDH, which decrease the anion exchange process [37]. However, despite the fact that Cl^- anions have a higher charge density than NO_3^- anions, the size of the Cl^- anions provides a higher extraction percentage (36.01 to 53.19%, %RSD < 10%), allowing for better mobility in the system [38].

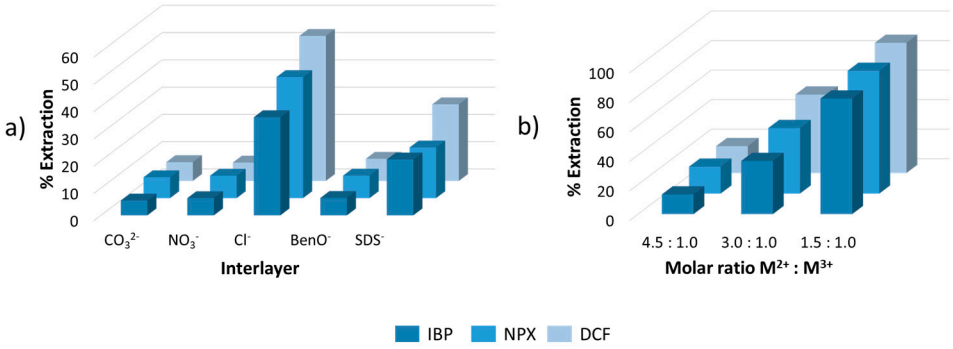

Figure 3. Effect of the LDH composition on the NSAID extraction performance. (**a**) Anion interlayer effect and (**b**) molar ratio M^{2+}:M^{3+} effect.

On the other hand, the incorporation of organic anions in the interlayer space promotes hydrophobic interactions; therefore, the effect of $BenO^-$ and SDS^- anions on the extraction performance was evaluated [39]. The results are shown in Figure 3a. It was observed that the incorporation of $BenO^-$ anions does not improve the extraction performance, despite the expected π–π interactions between the aromatic rings in analytes and the interlayer [40]. The use of SDS^- as an interlayer improves the extraction performance, with extraction percentages ranging from 18.60 to 28.12% through σ–π interactions between the aliphatic chain in the interlayer and the aromatic rings in the analytes [39]. However, based on the obtained results, MgAl/Cl^--LDH was selected as optimal for subsequent analysis.

3.2.2. Effect of Molar Ratio on IBP, NPX and DCF Extraction

In order to investigate the effect of the molar ratio Mg:Al on the extraction performance, MgAl/Cl^--LDHs with molar ratios of 4.5:1.0, 3.0:1.0 and 1.5:1.0 were synthetized. The results are shown in Figure 3b.

It was observed that the extraction performance improves as the Al content in the LDH increases. According to the literature, this behavior can be explained as a function

of two principal mechanisms: the anion exchange process and the possibility of promoting electrostatic interactions between the positively charged sheets due to the higher Al content and the conjugate base of the analytes, based on their pKa values (4.2, 4.3 and 4.15 for DCF, IBP and NPX, respectively [34,37,41]). As a consequence, the $MgAl/Cl^{-}$-LDH with a molar ratio of 1.5:1.0 was selected as the optimal composition with extraction percentages $\geq$ 83.18% (%RSD < 10%).

3.3. Optimization of the SPE Process

3.3.1. pH Effect

The pH is a critical factor during the extraction process as it determines the net charge of the adsorbent and the analytes, which is a determinant of their interaction modes. The pH effect on the extraction performance was evaluated from 4 to 12. Figure 4a shows the obtained results. It was observed that the extraction efficiency is homogeneous in the pH range from 4 to 10 with extraction percentages from 79.71 to 83.95%; this effect is attributed to a synergistic effect of electrostatic interactions and anion exchange mechanisms [42]. On the other hand, the extraction performance decrease drastically (7.99% to 15.84%) when pH = 12, due to the saturation of the active sites because of the higher presence of hydroxyl groups [43]. As a result, a neutral pH was selected as optimal for subsequent studies.

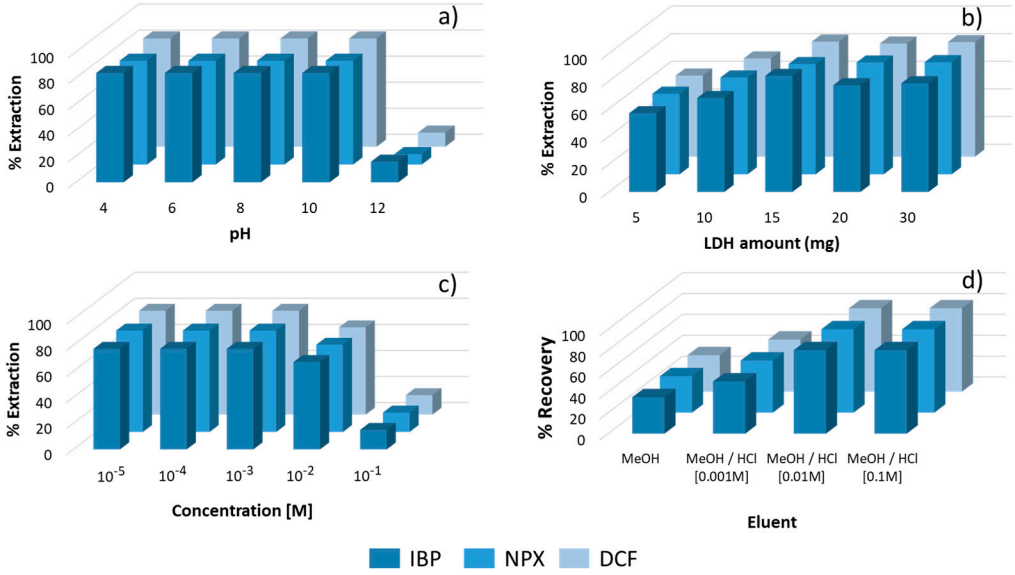

Figure 4. Univariate optimization of the SPE process. (**a**) pH effect, (**b**) LDH amount effect, (**c**) concentration effect (salting-out effect) and (**d**) elution.

3.3.2. LDH Amount Effect

In order to improve the analytical sensitivity, the LDH amount was evaluated in the range of 5 to 30 mg. Figure 4b presents the obtained results. The obtained results indicate no significant differences between the extraction percentages from 15 mg with extraction percentages from 79.71 to 83.11%. On the other hand, at lower mass amounts (5 and 10 mg), the active sites could be saturated, affecting the extraction process with values from 56.95 to 71.18%. Therefore, 15 mg of LDH was selected as the optimal amount.

3.3.3. Salting-Out Effect

The simplest way to decrease the solubility of the analytes in solution and improve extraction efficiency is through the salting-out effect, which is achieved through increases in ionic strength [41]. Therefore, the ionic strength was evaluated as a NaCl concentration in the range of 10^{-5} M to 10^{-1} M. The results are shown in Figure 4c. According to the results, no positive effect on the extraction performance was obtained with 15.45% when

the NaCl concentration was higher than 10^{-1} M, attributed to the competence of the active sites between the Cl^- anions and the analytes [44].

3.3.4. Elution

Finally, elution tests were conducted in order to optimize the analytical response; we evaluated the use of methanol, ethanol, acetone and acetonitrile. According to the results obtained, methanol was the only solvent that allowed the elution of the analytes (35%, %RSD < 10%). In order to improve the elution performance, different acidic methanol levels were evaluated. The results show a recovery percentage of up to 80.87% when a methanolic acid solution with HCl [0.01 M] was used; therefore, this eluent was selected as optimal for the SPE process.

As a result of this stage, it was found that the optimal SPE conditions are neutral pH and 15 mg of adsorbent, and the optimal eluent is MeOH/HCl [0.01 M].

3.4. Selectivity Analysis

The extraction performance of IBP, NPX and DCF was evaluated in the presence of three organic pollutants (phenol (PHEN), saccharine (SAC) and aspartame (ASP)) as interferents that may coexist with NSAIDs in environmental water samples. The experiments were carried out at three concentration levels (10, 20 and 30 mg L^{-1}). Figure 5 shows the obtained results. Under the optimal conditions of the proposal SPE method, MgAl/Cl^--LDH exhibits high affinity toward the NSAIDs, even in conditions of high concentrations of interferents, providing extraction percentages around 80% (%RSD < 10%) in all cases.

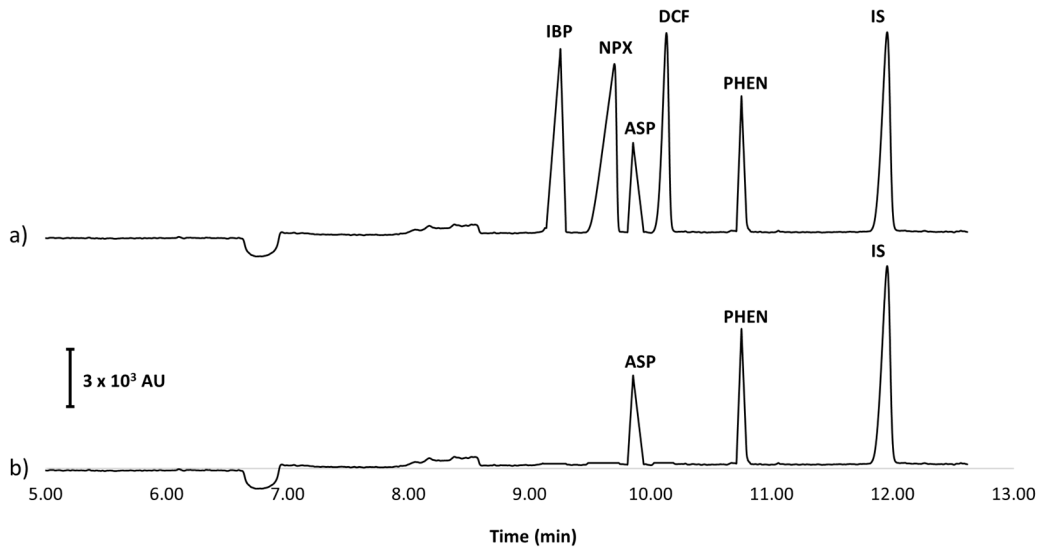

Figure 5. Electropherograms obtained in the analysis of NSAIDs and interferents. (**a**) Solution standard containing NSAIDs, IS, ASP, PHEN and SAC [10 mg L^{-1}] and (**b**) solution standard containing NSAIDs, IS, ASP, PHEN and SAC [10 mg L^{-1}] and treated by the optimal conditions of the SPE methodology.

3.5. Reusability and Long-Term Stability

Reusability is one of the boundaries offered by LDH adsorbents, with benefits in terms of costs and environmental concerns. In order to evaluate the reusability of the packed adsorbent, the extraction was performed under the optimal conditions obtained in previous stages; subsequently, the elution was carried out employing 1 mL of MeOH/HCl [0.1 M]. Finally, the column was washed with 10 mL of deionized water. The cycle loading–elution of the sample was performed five times with three replicates (n = 3) with extraction performance > 80.07% (%RSD < 5%) in all cases.

To evaluate the long-term stability of the MgAl/Cl^--LDH, the extraction performance was evaluated 30 days after LDH synthesis. According to the results, there is no evidence of

significant differences between the results obtained 30 days after synthesis and the obtained results using LDH immediately after the synthesis process ($p < 0.05$). These results exhibit MgAl/Cl^--LDH's reusability and long-term stability using just 15 mg of the adsorbent. The NSAID analysis can be performed at least five times under acidic conditions, and the extraction performance was the same 30 days after the synthesis.

3.6. Comparison of the Developed Adsorbent

The developed adsorbent was compared with previous reports in the literature; the information is summarized in Table 2. The main advantage of the developed adsorbent over previous reports is found in its simplicity; the adsorbent can be successfully synthesized in just 1 h, in one stage, which represents some benefits in terms of adsorbent synthesis reproducibility without requiring the use of specific instrumentation, toxic organic solvents, or expensive reagents. Lastly, the adsorbent exhibits high stability, making it suitable for use in multianalyte analyses of the most common NSAIDs.

Table 2. Adsorbents applied in the NSAID analysis.

Adsorbent	Synthesis	Interaction Modes	Pros	Cons	Ref
MICOF	A total of 83.98 mg of TFB was dissolved in 13 mL of a suspension (NH_2-SiO_2/Dioxane 100 g L^{-1}) and the mixture was stirred for 1h. Then, 193.70 mg of BD and 200 µL of acetic acid (3 mol L^{-1}) were added, and the mixture was stirred for 10 min; subsequently, 210. 6 of TFB and 484.3 mg of BD were added. Finally, 1.17 mL of acetic acid and 268.2 mg of the template (IBP) were added; the reaction mixture was refluxed at 120 °C for 3 h.	Hydrophobic interactions and π–π interactions.	Structural homogeneity, porosity, high surface area and high extraction capacity.	Selectivity and high consumption of time and reagents during synthesis stage.	[45]
PANI/Pan NFsM	A solution containing 15% (*w*/*v*) of PAN was prepared by dissolving PAN in DMF with constant stirring at room temperature for 24 h. The nanofibers were prepared by the electrospinning method (V = 10 kV, solution feed rate: 1.0 mL h^{-1}); the spinneret diameter was 0.5 mm at 15 cm distance. Subsequently, the nanofibers were functionalized with amino groups; 100 mL of hydrazine and 0.2 g of PAN nanofibers were mixed and heated at 363 K for 2.5 h.	Electrostatic interactions, hydrogen bonding and π–π interactions.	High stability, high reusability and high surface area.	Low extraction capacity and tedious synthesis stage.	[46]
PMIP	A total of 0.320 g of DCF and 0.5 mL of 4-VP were dissolved in 50 mL of ACN and stirred for 15 min; then, 0.05 g of AIBN and 5 mL of EGDMA were added to the mixture. Subsequently, the reaction mixture was purged with nitrogen. Finally, 1 g of PSSs was added to the solution and stirred at 60 °C for 10 h.	Electrostatic interactions, hydrogen bonding and π–π interactions.	High reusability, high stability and selectivity.	Mono-analyte analysis, highly time- and reagent-consuming during synthesis and low adsorption capacity.	[47]

Table 2. *Cont.*

Adsorbent	Synthesis	Interaction Modes	Pros	Cons	Ref
Starch-MgAl-LDH	In total, 0.03 and 0.17 mol of $Al(NO_3)_3 9H_2O$ and $Mg(NO_3)$ $6H_2O$ were dissolved in 50 mL of TWD and stirred at room temperature for 30 min; subsequently, 0.12 mol of starch was dissolved in 100 mL of TD and added to the solution containing the cationic metals. The mixture was stirred at 90 °C for 30 min. Finally, the pH solution was adjusted to 9.5–10.5, employing a 1 M NaOH solution; the mixture was refluxed at 90 °C for 24 h.	Hydrophobic interactions and hydrogen bonding.	Swelling capacity, porosity, multianalyte analysis, high stability and reusability.	Low adsorption capacity, low surface area, selectivity.	[48]
MgAl/Cl^--LDH	Described in Section 2.2	Anion exchange, electrostatic interactions and hydrogen bonding.	Swelling capacity, porosity, multianalyte analysis, thermal stability, long-term stability and high reusability.	Low adsorption capacity and selectivity.	This work

MICOF: molecularly imprinted covalent organic framework; TFB: 1,3,5-triformylbenzene; BD: 4,4′-diaminobiphenyl; PAMNI/Pan NFsM: polyan line/polyacrylonitrile nanofiber; PAN: polyacrylonitrile; PMIP: porous molecularly imprinted polymer; DCF: diclofenac; AIBN: 2,2-azobisisobutyronitrile; EGDMA: ethylene glycol dimethacrylate; PSSs: porous silica shells; MOFs: metal–organic frameworks, TDW: triple-distillated water.

3.7. Analytical Parameters

Under the optimal conditions concerning the LDH composition and the SPE process, 50 mL water samples were treated and the analytical parameters were determined. The analytical parameters of the LDH-SPE-CE method are shown in Table 3. The linearity range was from 18.08 to 200.00 μg L^{-1} with an adequate correlation coefficient (>0.99) for IBP, NPX and DCF. The detection limits (S/N = 3.29) were from 6.00 to 18.02 for the analytes. Finally, the precision was evaluated in terms of the intra- and inter-day repeatability of the peak area ratio (analyte/IS) at two concentration levels (75 y 150 μg L^{-1}); in all cases, %RSDs less than 10% were obtained.

Table 3. Analytical parameters of the proposal method.

		IBP	NPX	DCF
Correlation coefficient, r^2		0.998	0.999	0.999
Intercept				
$b_0 \pm ts(b_0)$		-0.0051 ± 0.0232	0.0187 ± 0.0250	-0.0006 ± 0.0141
Slope				
$b_1 \pm ts(b_1)$		2.2109 ± 0.1795	5.9527 ± 0.2184	6.6438 ± 0.1399
Repeatability (intra-day) (RSD %, n=3)	75.00 μg L^{-1}	4.24	4.56	4.15
	150.00 μg L^{-1}	3.62	3.68	4.06
Repeatability (inter-day) (RSD %, n=3)	75.00 μg L^{-1}	6.67	5.89	6.17
	150.00 μg L^{-1}	5.84	5.36	5.49
Linearity range (μg L^{-1})		54.06–200.00	30.21–200.00	18.09–200.00
Limit of detection (μg L^{-1})		18.02	10.07	6.03
Limit of quantification (μg L^{-1})		54.06	30.21	18.09

3.8. Application in Real Water Samples

The proposal method was applied in NSAID determination in ten water samples, including bottle, tap, cistern, well, and river, collected around the state of Hidalgo, México.

Among the analyzed samples, a cistern water sample was positive for NPX with a concentration of 32.76 ± 2.83 μg L^{-1}; the obtained electropherograms are shown in Figure 6.

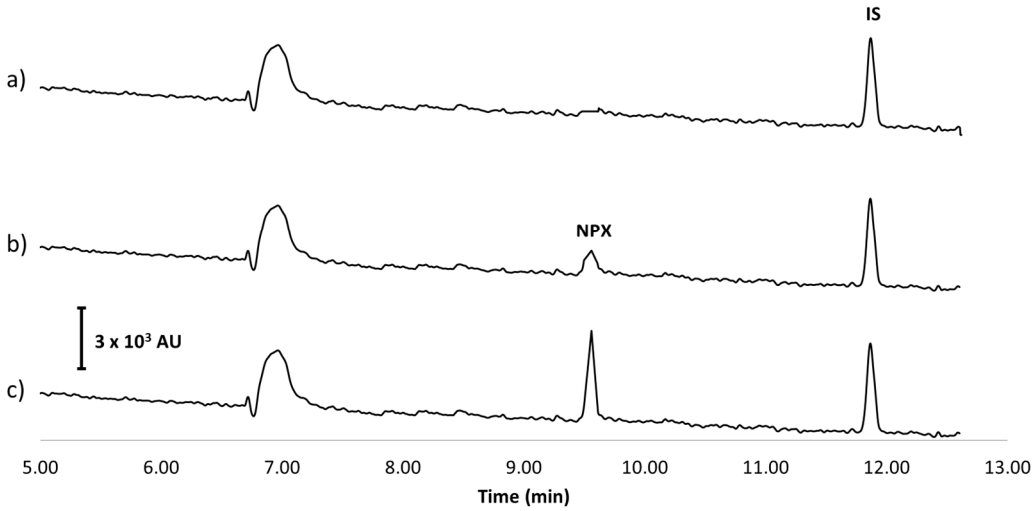

Figure 6. Electropherograms obtained in the analysis of real water samples. (**a**) Cistern water sample spiked with internal standard (0.5 mg L^{-1}) and analyzed by the SPE-CE-UV. (**b**) NPX-positive cistern water sample, with internal standard (0.5 mg L^{-1}) and analyzed by SPE-CE-UV. (**c**) Positive sample spiked with NPX 100 μg L^{-1} with internal standard (0.5 mg L^{-1}) analyzed by SPE-CE-UV.

3.9. Comparison of the Proposed SPE Method

The proposed method was compared with previous pre-concentration methods reported in the literature. Table 4 summarizes the information. The developed pre-concentration SPE-CE method based on the application of MgAl/Cl^{-}-LDH provides competitive LODs; among the main advantages over previous reports, we can mention the multianalyte analysis with the same methodology, the lack of time-consuming derivatization steps, the easy, fast, and low-cost synthesis of the adsorbent (which can be reused), and finally, the low organic solvent consumption during the pre-concentration and CE analysis.

Table 4. Comparison of the proposed method.

Methods	Analytes	Detection	Matrix	LOD (μg L^{-1})	Ref
LLE	NPX	CG-MS	Human plasma	30	[7]
SBSE	NPX, KEP and FBF	HPLC-UV	Water	0.23–0.31	[49]
SPME	NPX	HPLC-UV	Urine	30	[50]
SDME	KEP, DCF, IBP and NPX	CE-UV	Urine	1000–2000	[51]
SPE	IBP, NPX and DCF	CE-UV	Water	6.03–18.02	This work

LLE: liquid–liquid extraction; SBSE: stir-bar sorptive extraction; SPME: solid-phase microextraction; SDME: single-drop microextraction; KEP: ketoprofen; FBF: Fenbufen.

4. Conclusions

The present work describes the development of a pre-concentration system based on the application of LDH. The composition of the LDH in relation to the anion interlayer and the molar ratio Mg:Al determines the extraction performance. The experiments carried out herein revealed that the electrostatic interactions between the adsorbent and the analytes predominantly control IBP, NPX, and DCF extraction. The main advantages of the adsorbent $Mg_{1.5}Al_1$/Cl^{-}-LDH are its high and long-term stability, reusability, and simplicity in the synthesis stage, which does not require specific instrumentation, toxic organic solvents, or expensive reagents. Under the optimal conditions, the adsorbent $Mg_{1.5}Al_1$/Cl^{-}-LDH can be successfully applied in the pre-concentration of IBP, NPX and DCF. Under the optimal conditions, the methodology provides LODs from 6.03 to 18.02 μg L^{-1} and can be

successfully applied in real water samples, while the repeatability indicates that the results are accurate.

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