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Spectrophotometric Determination of Mefenamic Acid in Biological Samples Using Magnetic Iron Oxide Nanoparticles as a Sorbent for Solid Phase Extraction

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Abstract

This work investigates the potential of magnetic Fe_3O_4 nanoparticles as an adsorbent for separation and preconcentration of trace amounts of mefenamic acid in aquatic and biological samples, prior to spectrophotometric determination. The magnetic iron oxide nanoparticles (MIONs) were synthesized by mixing of ferrous and ferric chlorides. The possible parameters affecting the enrichment were optimized. It is shown that the novel magnetic nano-adsorbent is quite efficient for fast adsorption of mefenamic acid in pH =7.0. Various parameters affecting the adsorption of mefenamic acid on MIONs, such as pH of solution, desorbing reagent, adsorption isotherms, sample volume, amount of adsorbent and matrix effects, have been investigated. The calibration graph for the determination of mefenamic acid was linear in the range of 1.25-7.25 ng mL^{-1}. The limit of detection, defined as LOD= $3S_b/m$ was 0.5 ng mL^{-1} (n=3) of mefenamic acid and the relative standard deviation was 3.6%. The preconcentration factor of 150 was achieved in this method. The proposed procedure has been successfully applied to the determination of mefenamic acid in biological samples such as human plasma and dextrose saline.

Keywords: Mefenamic acid, Magnetic nanoparticles, Solid phase extraction, Spectrophotometric, Biological sample

1. Introduction

With the advent of improved technology in the recent years, nanostructures have attracted a great deal of interests in the research community due to their unique size and physical properties. These materials have been used in various fields such as biotechnology, biomedical, environmental, and material science [1-4]. Because of the importance and very wide application of magnetic nanoparticles (MNPs), some researcher groups recently published good reviews about their synthesis methods and applications in

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various scientific fields [5-7]. Magnetic Iron Oxide Nanoparticles (MIONs) have a paramagnetic behavior under certain particle sizes, which can be magnetized with an external magnetic field, once the magnetic field is removed [8]. In addition, dispersed adsorbents avoid problems such as occluding in filtration and fouling in packed columns and membranes.

Pertinent sample preparation is crucial for obtaining meaningful results from the analysis of real samples, since it is the most tedious and time-consuming step and a possible source of imprecision and inaccuracy of the overall analysis. Solid-phase extraction (SPE) is widely used for the extraction and preconcentration of analytes in various environmental, food and biological samples. It is the most popular clean-up technique due to factors such as convenience, cost, time saving and simplicity and it is the most accepted sample pretreatment method today [9, 10]. At present, there are several types of sorbents for SPE, including normal-phase, reversed-phase and other special sorbents. However, due to their unsatisfactory selectivity, these sorbents usually cannot separate analytes efficiently in complex biological [11]. A great preference of using MIONs is the possibility of the collection of MIONs by application of a magnetic field in a system. This makes magnetic nanoparticles excellent candidates for combining adsorption properties with ease of phase separation [12]. The adsorbent needs not be packed into the cartridge when using dynamic extraction mode, and no centrifugation or filtration of sample is needed after extraction when static batch mode is applied. Their separation and concentration are easier, more convenient and faster than other SPE methods. In addition, high surface area and surface charge density, depend on the pH, are some of the advantages [13-19].

Mefenamic acid, *N*-(2, 3-xylyl) anthranilic acid is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties (Figure 1). It is used to relieve the symptoms of many diseases such as rheumatoid arthritis, osteoarthritis, nonarticular rheumatism, and sport injuries [20, 21]. Overdoses of mefenamic acid produce toxic metabolite accumulation that causes acute hepatic necrosis, inducing mortality in humans.

Owing to the vital importance of the assay of mefenamic acid for pharmaceutical formulations and biological fluids, several analytical methods have been developed for the quantitative determination of this drug in both pharmaceutical and biological samples. These methods include high-performance liquid chromatography (HPLC) [22-25], gas chromatography–mass spectrometry (GC–MS) [26, 27], spectrophotometric method [28], micellar electrokinetic capillary chromatography, and capillary electrochromatography [29, 30]. It was emphasized that a high consumption of reagents and a long time for analysis are inherent to most of the reported procedures. Magnetic iron oxide nanoparticles were applied in analytical science as a new effective adsorbent in solid-phase extraction method for separation and determination of chemical species [31–33]. In this study, the MIONs were synthesized by mixing of ferrous and ferric chlorides with a molar ratio of 1:2 in an ammonium hydroxide solution with constant stirring [34, 35].

In this present work, an efficient and economic method is developed for the preconcentration of trace amount of mefenamic acid in aquatic and biological samples using this novel magnetic solid phase. Extraction of mefenamic acid is based on adsorption of Fe (III)–mefenamic acid complex on MIONs. Desorption of analyte is done by NaOH solution and the absorption of the pre-concentrated solution of mefenamic acid was determined spectrophotometrically at 281 nm. The proposed procedure has been successfully applied to the determination of mefenamic acid in human plasma. The method needs no expensive instrument, consumes no organic solvent, and shows shorter analysis time [22-35].

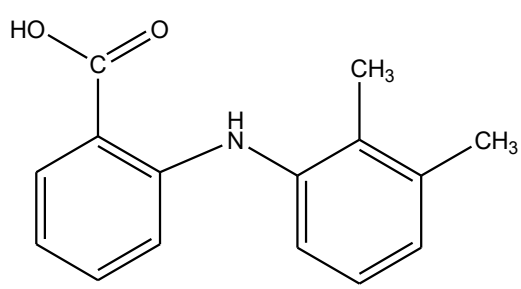

Figure 1. Chemical structure of Mefenamic acid.

2. Experimental

2.1. Material and apparatus

All reagents were of analytical-grade and they were used without further purification. Ammonia solution, hydrochloric acid, acetic acid, $FeCl_3$ and $FeCl_2{\cdot}4H_2O$ were purchased from Merck (Germany). A 1000 μg mL^{-1} stock solution of mefenamic acid was prepared. The pH adjustments are performed with HCl and NaOH (0.01-1.00 mol L^{-1}) solutions by a model 780 Metrohm pH-meter with combined glass-calomel electrode. A Universal buffer (pH=7) was prepared using acetic acid, boric acid, phosphoric acid (0.04 mol L^{-1}) solution. Some samples were prepared with diluted blank plasma (100 μL plasma is diluted to 300 mL) and stored at -8 °C after preparation. A Hewlett-Packard 8453 diode array spectrometer controlled by a Hewlett-Packard computer and equipped with a 1 cm quartz cell was used for recording the spectra. SEM image of the Fe_3O_4 NPs was prepared by a KYKY-EM3200 instrument.

2.2. Synthesis of magnetite nanoparticle

Preparation of magnetic iron oxide nanoparticles was based on alkaline hydrolysis of concentrated mixed solutions of ferrous and ferric chlorides [36]. This is an easy method for preparing a ferrofluid. The synthesis is based on reacting iron (II) and iron (III) ions in an aqueous ammonia solution to form magnetite, Fe_3O_4, as shown in Equation 1.

$$2FeCl_3 + FeCl_2 + 8NH_3 + 4H_2O \rightarrow Fe_3O_4 + 8NH_4Cl \qquad (1)$$

To obtain maximum yield for magnetite nanoparticles during co-precipitation, the ideal ratio of Fe^{2+}/Fe^{3+} is about 0.5. Combine 1.0 mL of stock $FeCl_2$ solution and 4.0 mL of stock $FeCl_3$ solution. Place a magnetic stirring bar in the flask and begin stirring vigorously. Add dropwise by burette 50 mL of 0.7 mol L^{-1} aqueous NH_3 solution into the flask. Magnetite, a black precipitate, will form immediately. Stir throughout the addition of the ammonia solution. Stirring is ceased and allowed the precipitate to settle (5–10 min), then decant and dispose of most of the liquid. The remaining solution is centrifuged the solution for 1 min at 1000 rpm. The supernatant is decanted after centrifugation. The dark, sludge like solid at the bottom of the tube is magnetite. The nanoparticles were collected by the magnet and thoroughly washed with distilled water to remove excess amounts of ammonium hydroxide. The size of nanoparticles can impressible by experimental conditions such as temperature, rate of ammonia addition and stirring rate.

2.3. Extraction studies

For the extraction and preconcentration of analyte in aqueous sample, A 300 mL solution containing 100 ng mL^{-1} of mefenamic acid was transferred to a 500 mL beaker. Batch adsorption experiments were carried out at ambient temperature, after that 0.75 mL of $FeCl_3$ (0.1 mol L^{-1}) and 0.5 mL of universal buffer solutions were stirred with 0.15 g of wet MIONs for 2 min in a beaker. Then the magnetic adsorbent was collected at the bottom of beaker by the application of an external field on the outside of the beaker via a piece of permanent magnet, and the supernatant was decanted directly. The magnet was removed, nanoparticles washed with 2 mL of NaOH (0.1 mol L^{-1}) solution by stirring for 3 min in order to desorb the adsorbed mefenamic acid. The absorption of the solution was measured spectrophotometrically at 281 nm. The procedure for the magnetic extraction is presented in Figure 2. The percent adsorption, i.e., the drug removal efficiency, was determined using the following equation:

$$\%R = \left[\frac{(C_0 - C_t)}{C_0}\right] \times 100 \qquad (2)$$

where C_0 and C_t represent the initial and final (after adsorption) concentrations of the drug in mg L^{-1}, respectively. All the experiments were performed at room temperature.

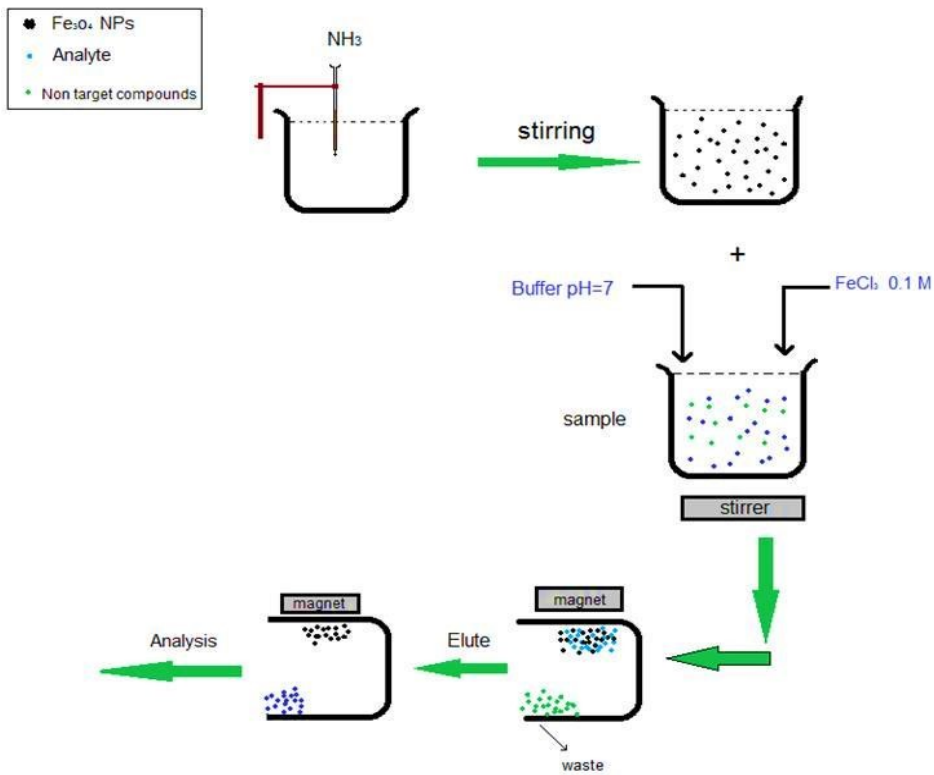

Figure 2. Procedure for magnetic solid-phase extraction of mefenamic acid.

2.4. Characterization of prepared nano-solid phase

The particle size and morphological characteristics of the magnetite nanoparticles was investigated by using SEM (Figure 3). As can be seen from Figure 3, the bare magnetic nanoparticles show a roughened, porous structure and spherical shape with some aggregates due to the lack of any repulsive force between the magnetite nanoparticles. This is mainly due to the nano-size of the Fe_3O_4, which is about 63 nm (averaging of 50 particles). According to the literature [36] and also Figure 3, spherical structure is obvious, although, in this study, the goal is the application of Fe_3O_4 as nanoparticle for preconcentration and determination of mefenamic acid.

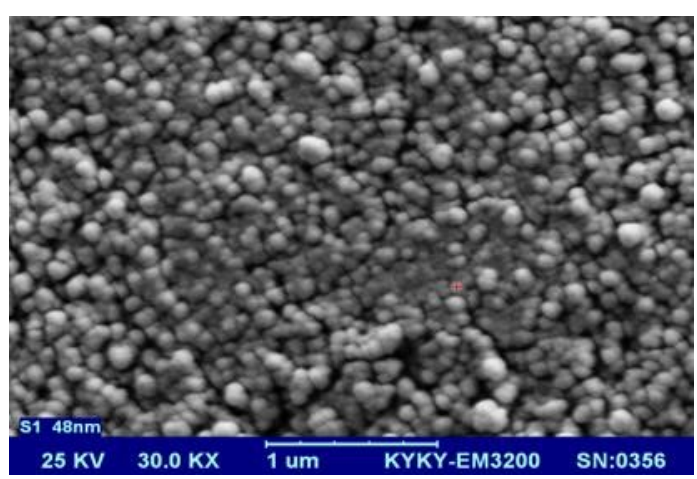

Figure 3. SEM image of magnetic iron oxide nanoparticles.

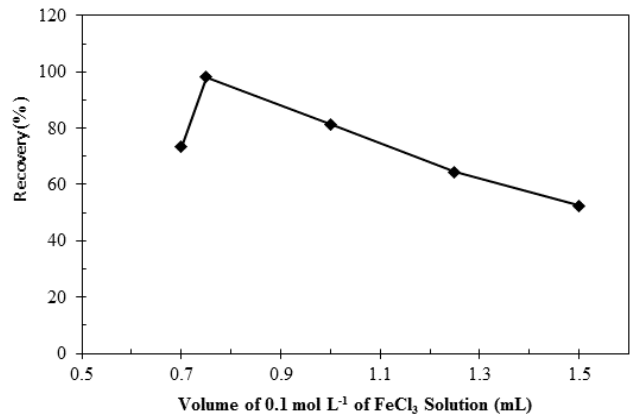

Figure 4. The effect of Fe(III) concentration in Fe(III)–mefenamic acid complex formation and its sorption on MIONs (conditions-pH = 7; sample volume: 300 mL; amount of adsorbent: 0.15 g).

3. Results and Discussion

Various parameters affecting the adsorption of analyte on MIONs, such as pH of solution, desorbing reagent, adsorption isotherms, sample volume, amount of adsorbent and matrix effects, have been investigated. These parameters were chosen to optimize the extraction efficiency via a univariate optimization approach. Each experiment was performed in triplicates. All the experiments carried out on the solution containing 100 ng mL^{-1} of Mefenamic acid.

3.1. Effect of Fe (III) concentration on the adsorption of mefenamic acid on MIONs

Preliminary experiments revealed that the magnetic precipitation of the prepared magnetic adsorbent was non-efficient and time-consuming, when using the adsorbent individually. This was attributed to the weak magnetic properties of the MIONs. An efficient strategy was used to overcome this problem. The strategy was addition of Fe^{3+} ions in the sample solution to formation Fe (III)–mefenamic acid complex during the extraction. In this stage investigate the optimum concentration of Fe (III), so using different volumes of $FeCl_3$ solution (0.1 mol L^{-1}). The obtained results are displayed in Figure 4.

3.2. Effect of solution's pH

It is known that pH of sample solution could affect the physical adsorption of analyte on the MNPs. The adsorption of mefenamic acid by MIONs was studied at various pH values. The pH of each solution was adjusted to values ranging from 3 to 10. HCl and NaOH 0.1 mol L^{-1} solutions were used for pH adjustment. The results are shown in Figure 5.

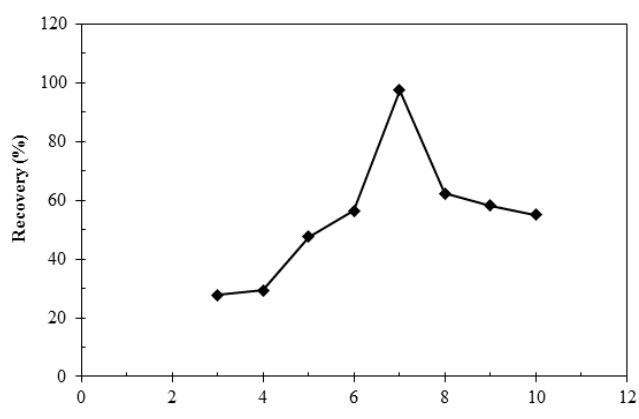

Figure 5. The effect of pH on the recovery percentage of 100 ng mL^{-1} of mefenamic acid conditions-volume of 0.1 mol L^{-1} of $FeCl_3$ solution: 0.75 mL; sample volume: 300 mL; amount of adsorbent: 0.15 g).

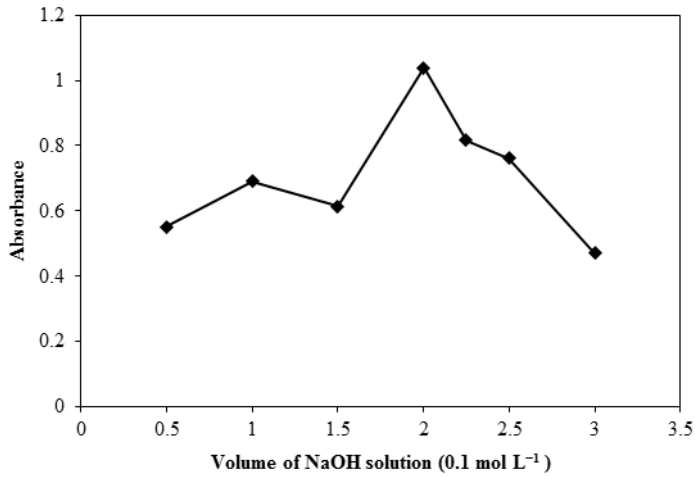

Figure 6. The effect of volume of NaOH as desorbing solution on the recovery percentage of 100 ng mL^{-1} of mefenamic acid (conditions-pH = 7; volume of 0.1 mol L^{-1} of $FeCl_3$ solution: 0.75 mL; sample volume: 300 mL; amount of adsorbent: 0.15 g).

With increasing pH from 3 to 7 slight changes were observed. The probable reason may be that the target compounds are neutral. At pH values lower than 7, the magnetic iron oxide nanoparticles dissolve in the acidic solution and no adsorption takes place; on the other hand, in higher pHs, the MIONPs are converted to colloids (due to adsorption of hydroxide ions on the particles surfaces), which decrease the active surface area of the adsorbent resulting in lower sensitivity to the magnetic field. Additional experiments on the volume of the suitable buffer 0.5 mL of universal solution (pH=7) give the best results. Therefore, 0.5 mL of universal buffer solution was used in all subsequent experiment.

3.3. Effect of the desorbing solution

To achieve satisfactory extraction performance, type and volume of the desorbing solution were studied. Different solutions for desorbing analyte from MIONs were tested. The experimental results indicated that NaOH solution was best solution. Effects of NaOH concentrations (0.1-1 mol L^{-1}) were investigated. It was found that 0.1 mol L^{-1} was adequate and selected as optimum. Ulteriorly, the effect of volume of NaOH was evaluated over the range of 0.5-3.0 mL. As shown in Figure 6, with the increasing volume up to 2 mL a significant increase of the recovery percentage was observed, therefore 2 mL of NaOH (0.1 mol L^{-1}) solution was selected for desorption. It must be mentioned that larger volume of solution causes lower recovery, because of dilution of analyte.

3.4. Adsorption isotherms

An adsorption isotherm describes a relationship between the concentration in the solution and the amount of dye adsorbed when the two phases are at equilibrium. Several isotherm models are often used to interpret the equilibrium data. Batch adsorption studies were carried out at a concentration range of 10.0-300.0 mg L^{-1}. In our study, Langmuir [37] and Freundlich [38] models were used to explain the experimental results. The Langmuir isotherm is represented by the following equations:

$$\frac{q_e a_L}{K_L} = \frac{K_L C_e}{1 + K_L C_e} \qquad (3)$$

where C_e is the equilibrium concentration of the Mefenamic acid in the solution (mg L^{-1}), q_e is the monolayer adsorption capacity (mg g^{-1}), at equilibrium concentration, C_e, a_L (Lmg^{-1}) and K_L (L g^{-1}) are the Langmuir constants with a_L related to the free adsorption energy and $q_m=[K_L/a_L]$ signifies the maximum adsorption capacity (mg g^{-1}), which depends on the number of adsorption sites. By linearization of the Langmuir isotherm we obtain:

$$\frac{C_e}{q_e} = C_e\left(\frac{a_L}{K_L}\right) + \left(\frac{1}{K_L}\right) \quad (4)$$

The values of a_L and K_L are calculated from the slope and intercept of the plot of C_e/q_e vs. C_e. The amount of Mefenamic acid adsorbed (mg g^{-1}) was calculated based on a mass balance equation as given below:

$$q_e = \frac{V\left(C_0 - C_e\right)}{m} \quad (5)$$

where C_0 is the initial concentration of Mefenamic acid in mg L^{-1}, V is the volume of experimental solution in L, and m is the dry weight of nanoparticles in g. The parameters of the Langmuir equation were calculated and are given in Table 1. Table 1 indicates that the maximum adsorption capacity of nanoparticles, q_m, is 18.509 mg g^{-1}. The essential feature of the Langmuir isotherm can be expressed in terms of a dimensionless constant separation factor (R_L) given by the following equation:

$$R_L = \frac{1}{1 + a_L C_0} \quad (6)$$

R_L values within the range $0 < R_L < 1$ indicate favorable adsorption [39]. In this study, The R_L values of magnetic nanoparticles for the initial Mefenamic acid concentrations 200 mg L^{-1}, obtained as 0.236, indicate favorable adsorption of Mefenamic acid onto them. The Freundlich Models proposes a monolayer sorption with heterogeneous energetic distribution of active sites and with interaction between adsorbed molecules. It can be expressed as follows:

$$q_e = K_F C_e^{1/n} \quad (7)$$

The equation can be written as a linearized form:

$$\ln q_e = \ln K_F + \left(\frac{1}{n}\right)\ln C_e \quad (8)$$

where q_e is the amount adsorbed at equilibrium (mg g^{-1}), K_F (mg$^{1-1/n}$ $L^{1/n}$ g^{-1}) and n are the Freundlich constants, n gives an indication of how favorable the adsorption is, and K_F is the adsorption capacity of the adsorbent. The values of K_F and 1/n (Freundlich coefficients) calculated from the intercept and slope of the plot of ln q_e vs. ln C_e are listed in Table 1. The Freundlich constants should have value lying in the range of 1 to 10 for classification as favorable adsorption. Table 1 show that the values of correlation coefficient, r, for the fit of experimental isotherm data to Langmuir equation are more close to 1.0000 than that for Freundlich equation. Therefore, the Langmuir model represents the experimental data better on the basis of values of regression coefficients.

3.5. Effect of the adsorbent amount

In order to study the effect of the adsorbent, 0.06–0.35 g of the Fe_3O_4 NPs was added to the sample solution. Based on Figure 7, by increasing the adsorbent amounts from 0.06 up to 0.10 g, recovery percentage was increased.

Table 1. Parameters of Langmuir and Freundlich isotherm equations, regression coefficients(r) for the adsorption of mefenamic acid on MIONs.

Langmuir isotherm					Freundlich		
a_L(L mg^{-1})	K_L (Lg^{-1})	$[K_L/a_L]=q_m$ (mg g^{-1})	R_L[a]	r	K_F(mg$^{1-1/n}$ $L^{1/n}$ g^{-1})	1/n	R
0.0161	0.298	18.509	0.237	0.9902	5.751	1.338	0.9816

[a] for Mefenamic acid concentration 200.0 mg L^{-1}.

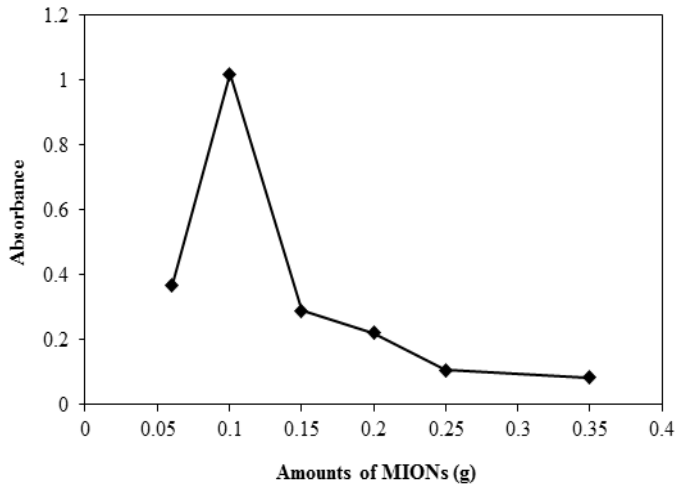

Figure 7. The effect of the magnetic iron oxide nanoparticles (MIONs) adsorbent amount on the recovery percentage of 100 ng mL^{-1} of mefenamic acid (conditions—pH = 7; volume of 0.1 mol L^{-1} of $FeCl_3$ solution: 0.75 mL; sample volume: 300 mL).

3.6. Effect of sample volume

In view to obtain a higher enrichment factor, a larger volume of sample solution is required. Fortunately, due to the magnetically assisted separation of the adsorbent (Fe_3O_4 NPs), it is possible to collect the adsorbent from larger volumes of the sample solution. Thus the extraction of 100 ng mL^{-1} of mefenamic acid from different volumes of the samples ranging from 50 to 300 mL was investigated. It was found that the best result was obtained when the sample volumes were less than 300 mL. However, the extraction efficiency would slightly decrease when the sample volumes were more than 300 mL.

3.7. Analytical figure of merit

Once the proposed SPE method based on Fe_3O_4 NPs sorbent was optimized, different quality parameters were evaluated to assess the method performance. Calibration graph was constructed from spectrophotometric measurement of the desorbed mefenamic acid. The spectrophotometric method was validated according to the definition of IUPAC. Linear dynamic range was obtained for the analyte in the concentrations ranged from 1.25-7.25 ng mL^{-1} with good determination coefficients (R^2=0.9973). The limit of detection, defined as LOD = $3S_b/m$, (where LOD, S_b and m are the limit of detection, standard deviation of the blank and the slope of the calibration graph, respectively), was 0.5 ng mL^{-1} of Mefenamic acid. In order to study the precision of the develop method, three replicate extraction of solutions containing 5 ng mL^{-1} of Mefenamic acid were performed and the relative standard deviation (RSD) was obtained 3.6%. As mentioned previously, the amount of target analyte in 300 mL was measured after elution of adsorbed analyte by 2.0 mL of NaOH, therefore the maximum preconcentration factors for this method is 150. Other analytical characteristics of the optimized method are summarized in Table 2. Figure 8 shows the residuals in absorbance of calibration graph and according to the resulted normal distribution, the systematic errors in proposed method do not exist [40].

Table 2. Analytical characteristics of proposed method for determination of mefenamic acid.

Parameters	Values
Slope	16.153
Intercept	0.099
Standard deviation of slope	0.394
Standard deviation of intercept	0.154
Residual standard deviation	2.462×10^{-3}
Method standard deviation	1.524×10^{-4}

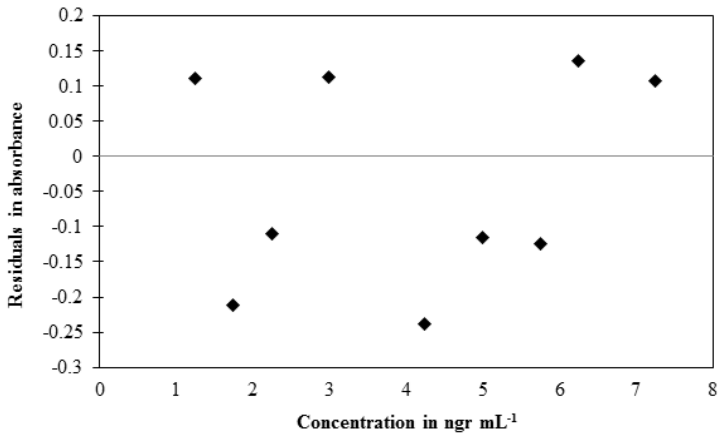

Figure 8. Residuals of the calibration equation.

3.8. Application of the proposed method to real samples

In order to demonstrate the applicability and reliability of the proposed method for real samples, it was successfully applied to some real samples including blood serum matrices (Obtained from the blood bank of the Arak Hospital) and dextrose saline under the optimum conditions. Human plasma samples (fresh frozen plasma) were kept in the freezer at −8 °C. It must be mentioned that the serum samples were diluted to 300 mL with water and then the extraction procedure was carried out. The dilution of the serum could suppress the matrix effect and prevent contamination of the sorbent. Relative recovery tests were also performed by standard addition of the analyte to the real blood serum samples and dextrose saline to verify the accuracy. The results obtained are shown in Table 3.

The obtained results clearly revealed that relative recoveries of the proposed method (expressed as the mean percentage between the amounts found and the ones spiked) for analysis the mefenamic acid in the real matrix samples were in the range of 92.2-104.5% with the RSDs (n = 3) ranging from 3.07% to 7.32%, which showed the ability of the presented method to determine Mefenamic acid levels in the real matrices.

3.9. Interference study

The effect of interfering ions and pharmaceutical compounds at different concentrations on the extraction and determination of mefenamic acid sample containing 2 ng mL^{-1} was studied. Ions or pharmaceuticals were considered as interference when its presence produced a variation in the absorbance of sample (at considered wavelength) greater than 3%. The results indicate that most of the ions and pharmaceuticals did not show any significant spectral interference at concentrations 500-times greater than those of the analyte. The cations such as Cr^{3+}, Cd^{2+}, Cu^{2+}, Bi^{3+}, Ni^{2+}, Mg^{2+}, Zn^{2+}, Al^{3+}, Sn^{2+}, Pb^{2+}, Ba^{2+}, Ag^{+}, K^{+}, Na^{+}, Co^{2+} and pharmaceuticals such as ascorbic acid, thiamin, pyridoxal, riboflavin, acetaminophen, ibuprofen, nicotinic acid, captopril, tetracycline, codeine, did not have any interfering effect. Although Fe^{3+} could cause interference Fe^{3+} plays an important role in extraction step. Finally, this proposed method is very selective for extraction and determination of mefenamic acid.

Table 3. Removal of mefenamic acid from blood serum and dextrose saline samples using MIONs.

Sample	Founded [c] (ng mL^{-1})	R.R.(%) [a] Spiked (ng mL^{-1})			R.S.D. (%) [b] Spiked (ng mL^{-1})		
		4.0	5.5	7.0	4.0	5.5	7.0
Blood serum [d]	N.D. [e]	92.2	98.4	102.1	7.32	5.23	4.14
Dextrose saline	N.D.	96.0	104.5	98.9	3.88	3.07	4.91

[a] Relative recovery.
[b] Relative standard deviation based on three replicates of each real sample.
[c] Initial concentration of mefenamic acid in non-spiked samples that found by proposed method.
[d] Obtained from the blood bank of the Arak Hospital, Markazi, Iran.
[e] Not detected.

Table 4. Comparison of the proposed method with other reported method.

Method	Recovery (%)	LOD (ng mL^{-1})	LDR (ng mL^{-1})	R.S.D. (%)	Reference
SPE-SUPRASF/HPLC-UV [a]	95.2-97.0	0.1	2.0-200.0	6.7	[41]
CPE/Spectrophotometry [b]	95.0-97.0	45.0	200.0-5000.0	1.5	[42]
CPE/Spectrofluorimetry [c]	105.0-107.0	6.0	50.0-5000.0	2.5	[43]
SPE/Spectrophotometry	92.2-104.5	0.5	1.25-2.75	3.6	this study

[a] Solid-phase extraction- Supramolecular solvent
[b] Cloud point extraction / Spectrophotometry
[c] Cloud point extraction / Spectrofluorimetry

4. Conclusions

In this paper, the results obtained demonstrate the applicability of the procedure for preconcentration and determination of Mefenamic acid in aquatic and biologic samples based on the use of Fe_3O_4 NPs. The performance of the developed this method in comparison with some other methods reported in the literatures [41-43] for extraction and determination of mefenamic acid is given in Table 4.
The advantages of the method include rather easy, simple, fast, and inexpensive synthesis method; rapid and convenient extraction operation, feasibility for large-volume samples, low detection limits, high recovery, and precision and accuracy in preconcentration and determination of mefenamic acid in comparison with the other methods.

5. Acknowledgements

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