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Solid phase extraction–spectrophotometric determination of salicylic acid using magnetic iron oxide nanoparticles as extractor

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ABSTRACT

This method shows a novel, fast and simple solid phase extraction–spectrophotometric procedure for preconcentration and determination of salicylic acid (SA) in blood serum using magnetic iron oxide nanoparticles (MIONs) as extractor. It is shown that the novel magnetic nano-adsorbent is quite efficient for fast adsorption of SA at 25 °C. Various parameters affecting the adsorption of SA on MIONs, such as pH of solution, type, volume and concentration of desorbing reagent and amount of adsorbent and matrix effects, have been investigated. The calibration graph for the determination of SA was linear in the range of 0.025–1.250 μg mL^{-1}. The limit of detection (LOD) based on three times the standard deviation of the blank ($3S_b$) was 5.5×10^{-3} μg mL^{-1} ($n = 10$) for SA. The intra-day precision (R.S.D.) was below 10.1% and inter-day R.S.D. was less than 17.5%, while accuracy (relative error R.E.) was within ±3.6 determined from quality control samples for salicylic acid (SA) which corresponded to requirement of the guidance of Food and Drug Administration (FDA). The preconcentration factor of 100 was achieved in this method. The proposed procedure has been successfully applied to the determination of SA in blood serum.

1. Introduction

Nanotechnology has recently become one of the most exiting forefront fields in analytical chemistry. The unique properties of nanoscale materials offer excellent prospects for designing new methods and instrumentation for chemical analysis [1–2]. Homogeneous distribution of dispersed nanoparticles in solution cause favorable mass transport to surfaces and can permit magnetic capture of depleted materials. In addition, dispersed adsorbents avoid problems such as occluding in filtration and fouling in packed columns and membranes.

Magnetic iron oxide nanoparticles (MIONs) have been studied extensively due to their wide range of applications in ferrofluids, high-density information storage, magnetic resonance imaging (MRI), biological cell labeling, sorting and separation of biochemicals, targeting, drug delivery and the treatment of waste waters [3–16].

A major advantage of using MIONs as solid phase extractor is the possibility of collection of the particles by application of a magnetic field in a batch system. This makes magnetic nanoparticles excellent candidates for combining adsorption properties with ease of phase separation [17].

The sensitivity and selectivity of analytical methods for testing of drugs in body fluids have increased markedly with the modification of instrumental methods. However, with instrumental screening methods, these advantages have been offset to some extent by a significant reduction of the volume of biological fluid taken for analysis, particularly if extraction methods such as liquid–liquid extraction (LLE), solid phase extraction (SPE) and cloud point extraction (CPE) are to be used. Among these techniques, SPE is one of the most important preconcentration methods because of its simplicity, flexibility to choose the solid phase, high preconcentration factor, low consumption of the organic solvents, low cost and short extraction time for sample preparation [18].

Since salicylic acid is too irritating to be taken orally, salicylate (as its sodium and aluminum salts), which is the main metabolite of aspirin or acetylsalicylic acid (ASA), is most widely used in the world as a painkiller and anti-inflammatory drug. In the human blood (pH = ~7.4), it is present as the deprotonated form, salicylate ion. Besides, SA is also used in ointments for their analgesic and antiseptic effects. The biological half-life of SA, between 3 and 19 h, is much greater to ASA half-life, between 15 and 20 min. Healthy volunteers, who have taken a dose of 500 mg of ASA, have presented a maximum concentration of 30 μg mL^{-1} of SA in the first 3–4 h [19]. Salicylic acid is absorbed percutaneously and distributed in the extracellular space, with maximum plasma level occurring 6–12 h after application. Since 50–80% of the salicylate is bound to albumin, transiently increased serum levels of free salicylates are found in patients with hypoalbuminemia. Salicylate is highly toxic

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when taken in overdose and the amounts which produce toxicity may be only twice the daily dose taken for chronic pain. Measurement of this compound in plasma gives a useful clinical index of the severity of poisoning, an indication of prognosis and the need for additional therapy.

The most frequently used method for the clinical analysis of SA [20] is "Trinder test" which is based on the formation of purple–violet complex of SA–Fe (III) ions that can be monitored spectrophotometrically. This complex is strongly affected by interference from substances bearing enol and phenol groups. For this reason, several other instrumental methods have been developed based on chromatography [21–29], spectrofluorometry [30–33], spectrophotometry [34], potentiometry with ion selective electrodes [35], capillary electrophoresis [36–37], and voltammetry [38] for the determination of SA. Some of quantitative pharmaceutical determination methods such as HPLC suffer from long time of analysis, large solvent consumption and also require more expensive instrumentation.

In this investigation, we present a novel, fast and simple method for extraction and determination of trace amounts of SA using MIONs as solid phase extractor. Extraction of SA is based on adsorption of Fe (III)–salicylate complex on MIONs. Desorption of analyte is done by NaOH solution and the absorption of the preconcentrated solution of SA was determined spectrophotometrically at 298 nm. The proposed procedure has been successfully applied to the determination of SA in blood serum. In comparison with other reported methods [21–29], the proposed method shows a faster analysis procedure for SA (total time of analysis is about 10 min) without serious spectral interferences from pharmaceuticals such as aspirin, paracetamol and bilirubin. The method needs no expensive instrument, consumes no organic solvent, and shows shorter analysis time and lower LOD in comparison to most of the other reported methods [21–29,34–38].

2. Experimental

2.1. Chemicals and reagents

All chemicals and reagents were of analytical grade. Salicylic acid, ammonia solution (25%, m/m), hydrochloric acid (37%, m/m), acetic acid (99.9%, m/m), $FeCl_3$ (96%, m/m) and $FeCl_2{\cdot}4H_2O$ (99.9%, m/m) were purchased from Merck (Darmstadt, Germany). A 1000 μg mL^{-1} stock solution of SA was prepared. pH adjustments were performed with HCl and NaOH (0.01–1.0 mol L^{-1}) solutions. A formate buffer (pH 2.5) was prepared using formic acid (1.0 mol L^{-1}) and NaOH (1.0 mol L^{-1}) solutions. Some quality control (QC) samples were prepared with diluted blank plasma (100 μL plasma is diluted to 200 mL) at different concentrations of 0.025, 0.250, 0.500 and 0.750 μg mL^{-1} and stored at −8 °C after preparation.

2.2. Apparatus

The spectrophotometric measurements were carried out with a Cintra 101 spectrophotometer (GBC Scientific Equipment, Australia). A transmission electron microscope (906E, LEO, Germany), pH-meter (632 Metrohm, Herisau, Switzerland) and a super magnet (1.2 T, 10 cm × 5 cm × 2 cm) were used.

2.3. Preparation of MIONs

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 [39]. To obtain maximum yield for magnetite nanoparticles during co-precipitation, the ideal ratio of Fe^{2+}/Fe^{3+} is about 0.5. The nanoparticles were collected by the magnet and thoroughly washed with distilled water to remove excess amounts of ammonium hydroxide. Experimental conditions such as temperature, rate of ammonia addition and stirring rate are of critical parameters that can affect the size of nanoparticles. As shown in the transmission electron micrograph (TEM), image of MIONs (Fig. 1), the average size of these nanoparticles was about 50 nm.

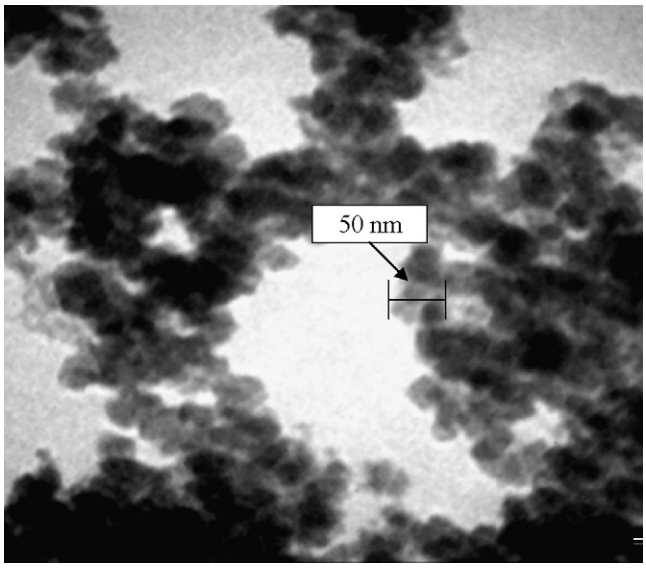

Fig. 1. TEM image of MIONs.

2.4. Extraction and desorption procedure

A batch procedure was applied for the extraction process. A 200 mL solution containing 25–1250 ng mL^{-1} of SA, 0.75 mL of $FeCl_3$ (0.1 mol L^{-1}) and 0.5 mL of formate buffer solutions were stirred with 0.25 g of wet MIONs for 2 min in a beaker. Nanoparticles were collected by the magnet and washed with 2 mL of NaOH (1.0 mol L^{-1}) solution by stirring for 3 min in order to desorb the adsorbed SA. The beaker was placed on the magnet and the mixture was decanted. The absorption of the solution was measured spectrophotometrically at 298 nm. A blank solution was also run under the same conditions without adding the analyte.

In order to show the performance of the proposed method, samples of real blood serum (100 μL) were analyzed under optimum conditions. It must be mentioned that the serum samples were diluted to 200 mL. Recovery tests were also performed by standard addition of the analyte to the real blood serum samples. Preconcentration and extraction of SA by MIONs and also desorption process were performed using recommended procedure.

2.5. Method validation

The method was validated for linearity, precision, accuracy, extract recovery and selectivity according to the FDA guideline for validation of bioanalytical methods [40]. Validation runs were conducted on 4 consecutive days. The absorbance measurements of desorbing solution containing the preconcentrated SA amounts of quality control (QC) samples were interpolated from the calibration curve on the same day to give concentrations of the analyte. The results from QC samples in three runs were used to evaluate the precision and accuracy of the method developed.

The calibration curve of SA was constructed using standard desorbing sample solutions at eight concentrations in the range of 0.025–1.25 μg mL^{-1} with least squares linear regression method. The lowest limit of quantification (LLOQ) is defined as the lowest concentration on the calibration curve at which an acceptable accu-

racy (R.E.) within ±20% and a precision (R.S.D.) below 20% can be obtained.

In order to test the reproducibility and repeatability of the proposed method, the intra-day precision and accuracy were evaluated by determining a replicate analysis of QC samples of SA on the same day. The run consisted of a calibration curve and five replicates of each low, mid, and high concentration quality control samples. For determining the inter-day accuracy and precision, analysis of three batches of QC samples was performed on different days.

The solid phase extraction efficiency of SA was determined by analyzing five replicates of plasma sample solutions at four QC concentration levels of SA. The recovery was calculated by comparing the absorbance of the preconcentrated SA (spiked into blank plasma, extracted and 100-fold preconcentrated) in the desorbing solution (2 mL of 1.0 mol L^{-1} NaOH solution) with those obtained from SA standard solutions in 1.0 mol L^{-1} NaOH solution.

The selectivity was evaluated by comparing the absorbance changes for extracted SA by MIONs from different batches of diluted blank plasma containing different interfering species.

3. Results and discussion

Fe (III)–salicylate complex has been known for a long time and used for identification of SA [41]. Primary experiments showed that adsorption of SA on MIONs took place as Fe (III)–salicylate complex in acidic solutions. The uptake of this complex by MIONs can take place via the surface complexation mechanism due to the adsorption affinity of hydrated surface of ferric oxides at low pHs [15]. The optimum conditions for extraction and determination of trace amounts of SA adsorbed on magnetite nanoparticles were investigated.

3.1. Effect of pH

The influence of pH on the adsorption of SA was studied by applying the proposed extraction and desorption procedure to the sample solutions. The pH of each solution was adjusted to values ranging from 1 to 4 with HCl solution. According to the obtained results (Fig. 2), maximum recovery for the analyte was at pH 2.5. Additional experiments on type and volume of the suitable buffer showed that 0.5 mL of formate buffer solution (pH 2.5) gives the best results. Therefore, pH adjustment in each sample was carried out by adding 0.5 mL of formate buffer. However, at pH values higher than 2.5, adsorption of SA was diminished owing to decrease of the hydrated surface of ferric oxides and formation of colloidal particles; on the other hand, in lower pHs, the amount of MIONs was decreased because of high solubility of nanoparticles in stronger acidic solutions.

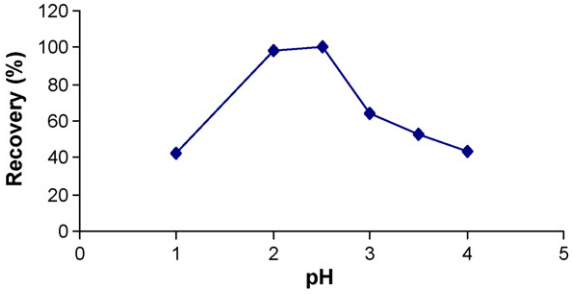

Fig. 2. Effect of pH on the recovery of SA [conditions: 200 mL solution containing fixed amount (125 μg) of SA; 0.250 g of damped MIONs; 0.75 mL of 0.1 mol L^{-1} Fe (III) solution; 2.0 mL of desobent solution (NaOH 1 mol L^{-1})].

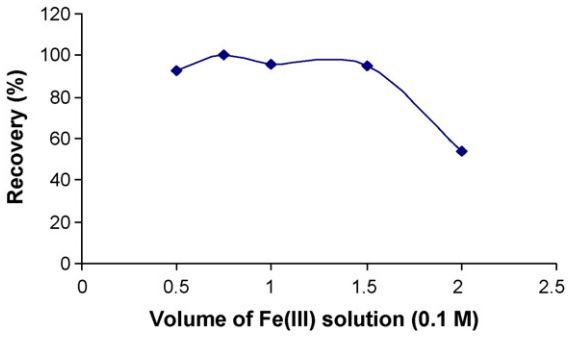

Fig. 3. Effect of Fe (III) concentration in Fe–SA complex formation [conditions: 200 mL solution containing a fixed amount (125 μg) of SA; pH 2.5; 2.0 mL of desobent solution (NaOH 1 mol L^{-1})].

3.2. Effect of Fe (III) concentration on the adsorption of SA on MIONs

The adsorption of SA is not quantitative without addition of Fe^{3+} ions. It seems that SA adsorption on nanoparticles occurs via Fe (III)–SA complex. In order to determine the optimum concentration of Fe (III) for quantitative recovery of SA, the proposed method was applied using different volumes of $FeCl_3$ solution (0.1 mol L^{-1}). The obtained results are shown in Fig. 3. Therefore, 0.75 mL of Fe (III) solution was chosen as optimum reagent value for quantitative recovery of SA. It seems that this amount of Fe (III) is enough for complete complexation and adsorption of SA on MIONs.

3.3. Effect of the adsorbent amount

The required amount of MIONs for the complete separation and recovery of SA in 200 mL solution (containing 125 μg of SA) at pH 2.5 was investigated and optimized. Maximum recovery was obtained when the amount of MIONs was 0.250 g (Fig. 4). Greater amounts of MIONs cause a decrease in the recovery percentage of SA as a result of higher surface area of nanoparticles and also small volume of desorbing solvent.

3.4. Effect of the type, concentration and volume of the desorbing solution

Various desorbing reagents were used to find the best desorbing solution for the adsorbed SA. Among different solutions used, NaOH solution provided higher recovery. The concentration of the NaOH solution was optimized. The results indicated that highest recovery is obtained at 1 mol L^{-1} NaOH solution. Since the desorbing NaOH solution contains high concentration of hydroxyl ions,

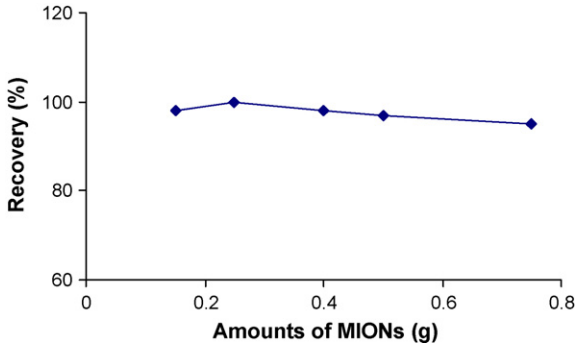

Fig. 4. Effect of the amount of the adsorbent [conditions: 200 mL solution containing a fixed amount (125 μg) of SA; pH 2.5; 2.0 mL of desobent solution (NaOH 1 mol L^{-1}); 0.75 mL of Fe (III) solution (0.1 mol L^{-1})].

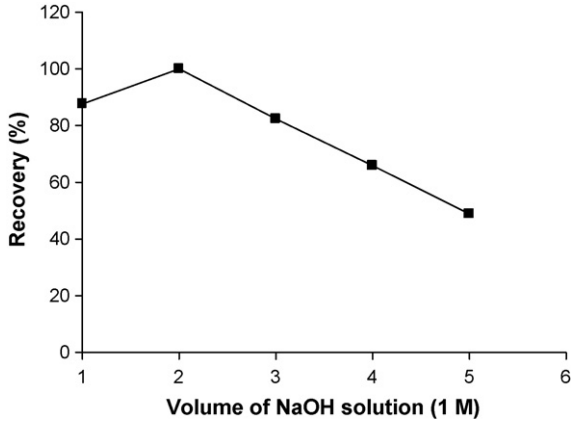

Fig. 5. Effect of volume of 1 mol L^{-1} NaOH solution as desorbing reagent [conditions: 200 mL solution containing a fixed amount (125 μg) of SA; 0.250 g damped of MIONs; pH 2.5; 0.75 mL of 0.1 mol L^{-1} Fe (III) solution].

we propose that OH^- ions can exchange the salicylate ions from Fe (III)–SA complex to form iron hydroxide precipitate and desorb the analyte from the nanoparticles. Subsequent experiments showed that 2 mL of 1 mol L^{-1} solution of NaOH was the optimum volume for desorbing of SA from MIONs (Fig. 5). It must be noted that higher amounts of NaOH solution cause lower desorption and recovery of SA which may be due to formation of colloidal particles of iron oxides and entrapment of SA between the particles.

3.5. Enrichment factor

The maximum applicable sample volume was determined by increasing the dilution of SA solution. Different feed volumes in range of 25–300 mL were tested, while keeping the total amount of loaded SA fixed at 125 μg. As can be seen in Fig. 6, the recoveries of SA were quantitative up to 200 mL of the sample volume. Higher solution volumes of the analyte (SA) will decrease the adsorption and recovery of SA which may be due to washing characteristics of water solvent. The preconcentration factor of the method was calculated to be 100.

3.6. Effect of interfering ions and compounds

For application of recommended solid phase extraction to real samples, effects of some interfering ions and compounds on the recovery of SA were investigated. The tolerance limit was defined as the amount of the foreign ion causing a change of ±5% in the absorbance reading. The tolerable limits of interfering ions are given in Table 1. The results showed that the presence of 50-fold increase in concentration of HPO_4^{2-} and PO_4^{3-} with respect to SA would

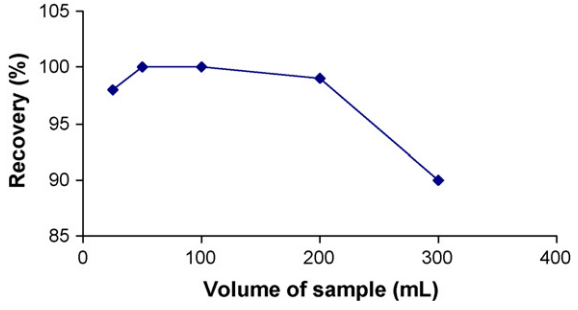

Fig. 6. Effect of analyte sample volume on the recovery of SA [conditions: 25–300 mL solution containing a fixed amount (125 μg) of SA; 0.250 g damped of MIONs; 0.75 mL of 0.1 mol L^{-1} Fe (III) solution; pH 2.5; 2.0 mL of desobent solution (NaOH 1 mol L^{-1})].

Table 1
The effect of foreign ions and compounds on adsorption and desorption of SA by MIONs.

Ion	Tolerance limit (w/w)
Na^+, K^+	1000
Ca^{2+}	100
Mg^{2+}	100
NO_3^-	200
SO_4^{2-}	100
CO_3^{2-}	100
Aspirin, paracetamol, bilirubin	100
HPO_4^{2-}, PO_4^{3-}	50

cause a decrease in the adsorption of SA on the MIONs. The results also showed that pharmaceuticals such as aspirin and paracetamol which show spectral interference with SA [34] do not interfere in adsorption and desorption of analyte when their concentrations are 100-fold more than SA. The presence of 100-fold of bilirubin is also tolerable. However, in most articles the drug determination was carried out only after a dilution step (500–2000 times). Simply diluting the sample can sometimes minimize analyte matrix interference if the interferent produces no significant interference effect below a certain concentration level [42].

3.7. Loading capacity

The loading capacity of MIONs was determined by batch method. The adsorbent (0.250 g) was added to a 50 mL solution containing 10 μg mL^{-1} SA and stirred on a stirrer for 1 h. After removing supernatant, nanoparticles were washed by 8 mL of 1 mol L^{-1} of NaOH solution and the amount of the SA was determined. The loading capacity was 1.152 mg g^{-1}.

3.8. Analytical performance and method validation

In order to show the validation of the proposed method, the analytical features of the method such as linear range of the calibration curve, limit of detection (LOD), lowest limit of quantification (LLOQ), accuracy and precision were examined. Under the optimum conditions, the calibration graph for the determination of SA is obtained in the concentration range of 0.025–1.25 μg mL^{-1} with a correlation coefficient of 0.9975. The regression equation for the line was $A = 1.0262C_{SA} + 0.0529$ ($n = 8$), where C_{SA} is the concentration of SA in μg mL^{-1} and A is the absorbance. The slope of the line $b = 1.0262 \pm 0.0528$ which shows a R.S.D. = 3.0% and the intercept of the line $a = 0.0529 \pm 0.002$ with a R.S.D. = 3.9% were also obtained. Under optimum experimental conditions, the limit of detection (LOD) of the proposed method based on three times the standard deviation of the blank ($3S_b$), [43] were 5.5×10^{-3} μg mL^{-1} for SA ($n = 10$). The lowest limit of quantification (LLOQ) of the proposed method is 0.025 μg mL^{-1}.

Intra- and inter-day precision and accuracy data (showing reproducibility and repeatability terms) for SPE of SA by MIONs from QC samples are summarized in Table 2. The precision and accuracy of the present method conform to the criteria for the analysis of biological samples according to the guidance of FDA where the R.S.D.

Table 2
Precision and accuracy data for SPE of SA from plasma solution by using MIONs (intra-day: $n = 12$; inter-day: $n = 12$ runs per day, 4 days).

Concentration (μg mL^{-1})		R.S.D. (%)		R.E. (%)
Added	Found (mean ± S.D.)	Intra-day	Inter-day	
0.025	0.029 ± 0.003	10.1	17.5	1.1
0.250	0.241 ± 0.007	7.5	9.2	−3.6
0.500	0.515 ± 0.014	4.7	5.6	+3.0
0.750	0.731 ± 0.042	3.8	6.4	−2.6

Table 3
Validation results of SA analysis in the blood serums (A and B) by HPLC-UV method compared with the proposed method under the optimum conditions.

Serum samples	Added SA ($\mu g\,mL^{-1}$)	Concentration found SA[a] ($\mu g\,mL^{-1}$)	
		HPLC-UV method (mean ± S.D.) (R.E. %)	Proposed method (mean ± S.D.) (R.E. %)
1A[b]	–	0.550 ± 0.011	0.555 ± 0.012
2A	0.250	(0.801 ± 0.009) (+0.4)	(0.802 ± 0.011) (−1.5)
3A	0.300	(0.845 ± 0.010) (−1.7)	(0.841 ± 0.013) (−4.7)
4A	0.400	(0.942 ± 0.011) (−2.0)	(0.968 ± 0.010) (+3.2)
5A	0.550	(1.105 ± 0.012) (+1.0)	(1.109 ± 0.012) (+1.8)
1B[c]	–	ND[d]	ND
2B	0.250	(0.247 ± 0.013) (−1.2)	(0.257 ± 0.011) (+2.8)
3B	0.400	(0.390 ± 0.011) (−2.5)	(0.388 ± 0.015) (−3.0)
4B	0.500	(0.522 ± 0.015) (+4.4)	(0.524 ± 0.017) (+4.8)
5B	0.750	(0.765 ± 0.015) (+2.2)	(0.784 ± 0.017) (+4.3)

[a] $x \pm s$ ($n = 3$).
[b] Main components of serum A: albumin, 5.5 gm/dL; globulins, 3.1 gm/dL; fibrinogen, 0.4 gm/dL; urea, 18 mg/dL; uric acid, 6.5 mg/dL.
[c] Main components of serum B: albumin, 4.7 gm/dL; globulins: 2.9 gm/dL; fibrinogen, 0.3 gm/dL; urea, 11 mg/dL; uric acid, 4.6 mg/dL.
[d] Not detected.

determined at each concentration level is required not exceeding 15% (20% for LLOQ) and R.E. within ±15% (±20% for LLOQ) of the actual value [40].

The extraction recoveries from QC samples of plasma solutions containing low, middle and high concentrations of SA (0.10, 0.50 and 1.00 $\mu g\,mL^{-1}$) were 98.9 ± 3.3%, 96.6 ± 2.6% and 95.9 ± 2.9%, respectively. No significant matrix effect for SPE of SA by MIONs was observed indicating that no co-adsorbing substance could influence the separation and determination of the analyte. Compounds such as aspirin, paracetamol and bilirubin do not interfere when their concentrations are 100-fold more than SA.

3.9. Application to real sample

In order to test the validity of the proposed SPE method, the optimum procedure was applied to determine SA concentration in real blood serum of two volunteers (serum A was taken from a 43 years old patient man with hypoalbuminemia and serum B was obtained from a healthy 25 years old man). Human plasma samples (fresh frozen plasma) were obtained at the Hemocentro of Jundi-Shapor Medical Science University and were kept in the freezer at −8 °C. The validity of the above mentioned model was checked by predicting the concentration of the spiked SA to the real samples to obtain the standard deviation (S.D.) and percent relative error (R.E.%) values. Blood serum samples (100 μL) were diluted to 200 mL and then the preconcentration procedure was performed by MIONs under optimum conditions. There was no available certified reference material (CRM) of SA to test the validity of the proposed method but the results of the method were compared with the results of a high-performance liquid chromatography with UV spectrophotometric detection (HPLC-UV) method [27] (Table 3). The recoveries of analyte were evaluated and the results showed the capability and validity of the method to the real sample analysis. However, in most articles the drug determination was carried out only after a dilution step (500–2000 times).

4. Conclusion

The proposed methodology possessed several advantages like simplicity, high preconcentration factor and low cost, especially if more sophisticated techniques such as spectrofluorometry or HPLC are not available. In addition, it is notable that both the adsorption and desorption of SA are fast and could be completed within 5 min and because of dilution of samples according to the procedure, there was not particular interference to the method, especially by the compounds such as aspirin and paracetamol [34]. The R.S.D. and LOD of the method are comparable or better than some of the previously reported methods [21–37]. The method was successfully applied to determine SA in blood serum.

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