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Trace Analysis of Niflumic Acid in Milk and Human Plasma by Ion-pair-based Vortex Assisted Dispersive Liquid-liquid Microextraction Combined with UV-Vis Spectrophotometry

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A simple, accurate and fast vortex-assisted dispersive liquid-liquid microextraction procedure has been developed for the extractive spectrophotometric determination of niflumic acid in biological samples. The method is based on the formation of an ion association complex between niflumic acid and methylene blue. The resulting ion-pair was extracted into dichloromethane and its absorbance was measured at 655 nm. All experimental parameters affecting the analytical performance of the method such as pH, type and volume of buffer and extraction solvent, dye concentration, extraction time, ionic strength and interfering species were investigated. The calibration curve was linear in the range of 5-70 ng ml^{-1} and the limit of detection (LOD) was found to be 2.8 ng ml^{-1}. The procedure was successfully applied for the determination of niflumic acid in human plasma and goat's milk samples. The main advantages of the proposed method are rapidity, little solvent consumption, low cost and providing low LOD by the simple UV-Vis spectrophotometer.

Keywords: Niflumic acid, Vortex-assisted dispersive liquid-liquid microextraction, UV-Vis spectrophotometry, Methylene blue, Milk, Human plasma

INTRODUCTION

Sample preparation is a critical step in the chemical and biological analysis. The main aims of sample preparation are the analyte preconcentration, removal of interferences and converting (if needed) the analyte into a suitable form for detection [1]. Classical liquid-liquid extraction (LLE) is a time-consuming and multi-step sample preparation technique that uses large amounts of organic solvents which are usually hazardous and expensive [2].

To overcome these drawbacks, miniaturized techniques derived from conventional LLE including single-drop microextraction (SDME) [3], hollow-fiber liquid-phase microextraction (HF-LPME) [4] and dispersive liquid-liquid microextraction (DLLME) [5] have been developed in recent years. Dispersive liquid-liquid microextraction is a high performance and powerful extraction method which has been introduced by Assadi and co-workers in 2006. In recent years, much attention has been paid to DLLME, because of its rapidity, simplicity of operation, little solvent consumption, low cost, high recovery and enrichment factor [6]. Despite the mentioned advantages, the conventional DLLME needs to the relatively high amounts of disperser solvent which is toxic and decreases efficiency of extraction [7]. To resolve these problems, various methods have been introduced to remove or decrease the disperser solvent such as air-assisted liquid-liquid microextraction (AALLME) [8], ultrasound assisted dispersive liquid-liquid microextraction (UA-DLLME) [9], surfactant assisted dispersive liquid-liquid microextraction (SA-DLLME) [10] and vortex- assisted dispersive liquid-liquid microextraction (VA-DLLME) [11,12].

Vortex-assisted liquid-liquid microextraction was introduced by Yiantzi *et al.* in 2010. This method is a mild

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emulsification procedure that dispersion of the extractant solvent into the aqueous phase is achieved using vortex mixer [13]. The use of vortex mixing can accelerate the mass transfer to organic phase and reduce the volume of required organic solvent [14].

Ion-pair extractive spectrophotometry is a popular and attractive method because of simplicity, low cost, sensitivity and rapidity for determination of many pharmaceutical compounds [15-17]. The method is based on the formation of an ion-pair complex between a drug and a dye which is extracted into an organic solvent and then its concentration is determined spectrophotometrically [18,19]. Methylene blue (MB) is a cationic dye mainly used as a medication for treatment of methemoglobinemia [20]. MB has also wide applications as an ion-pairing reagent to form water immiscible ion-pair complex with some species such as anionic surfactants [21-24], large inorganic anions [25-27] and pharmaceutical compounds [28-30].

Niflumic acid (NFA), 2-([3-(trifluoromethyl)phenyl] amino) nicotinic acid, is one of the non-steroidal anti-inflammatory drugs (NSAIDs) which acts as an inhibitor of cyclooxygenase [31]. It is a potent analgesic drug widely used for treatment of rheumatoid diseases such as osteoarthritis and rheumatoid arthritis [32]. NFA is rapidly absorbed and followed by extensive metabolization basically hydroxylation and glucuroconjugation [33]. Peak-plasma levels of NFA are obtained within 2-3 h after oral administration [34]. The main undesired side effects of NFA are dizziness, nausea and vomiting [35]. The necessity of sensitive and reliable analytical methods for determination of NFA in biological and pharmaceutical samples have been led to the introduction of a variety of determination methods such as HPLC [32,33,36-39], liquid chromatography-mass spectrometry (LC-MS) [40], liquid chromatography-tandem mass spectrometry (LC/MS/MS) [41], gas chromatography mass spectrometry (GC-MS) [42-44], capillary isotachophoresis [45], luminescence [46], ATR/FTIR spectroscopy [47] and kinetic spectrophotometry [48]. To the best of our knowledge, there is no report on the microextraction methods for the determination of NFA. Thus, in this work, a rapid and sensitive vortex-assisted dispersive liquid-liquid microextraction method combined with spectrophotometric technique was developed for determination of NFA. The method is based on the formation of ion-pair complex between NFA and MB. It was successfully applied for the determination of NFA in real samples such as human plasma and goat's milk.

EXPERIMENTAL

Reagents and Solutions

Methylene blue, acetic acid, hydrochloric acid, sodium hydroxide, sodium chloride, acetonitrile, chloroform, dichloromethane, carbon tetrachloride, 1-octanol and 2-octanol were purchased from Merck (Darmstadt, Germany). Niflumic acid was obtained from Sigma-Aldrich (Steinheim, Germany). Raw goat's milk sample was obtained from a local farm. Drug-free human plasma was provided by Iranian Blood Transfusion Organization (IBTO), Center of Damghan (Damghan, Iran). Milk and plasma samples were kept at -20 ºC. Double distilled water was used throughout the experiments.

A 100 μg ml^{-1} stock solution of NFA was prepared by dissolving 10.0 mg of NFA in 10 ml NaOH 0.1 M and making up to 100 ml with double distilled water in a volumetric flask. A stock solution of MB was prepared by dissolving 10.0 mg of MB in 100 ml double distilled water. Working solutions were prepared by appropriate serial dilution of the stock solutions. Acetate buffer solution (0.05 M) was prepared by the addition of 0.1 M sodium hydroxide to 50 ml of acetic acid (0.1 M) to adjust the pH at 6.0 and the mixture is brought up to 100 ml with double distilled water.

Apparatus

Absorbance measurements were made by an Analytik Jena Specord 205 UV-Vis spectrophotometer (Jena, Germany) using 700 μl quartz microcells. The spectra were automatically obtained and processed by WinAspect software. All of pH measurements were carried out by a Metrohm 780 digital pH meter (Switzerland) with a combined glass electrode. An IKA genius 3 vortex mixer (Staufen, Germany) was employed in extraction procedure. A Hermle Z-300 centrifuge (Wehingen, Germany) was used to separate the organic from aqueous phase.

VA-DLLME Procedure

For the sample extraction process, 10 ml of a solution (containing 5-70 ng ml^{-1} of NFA, 2.6 mg l^{-1} of MB and 0.5 ml of acetate buffer pH = 6.0) was transferred to a 15 ml glass centrifuge tube. A volume of 400 µl dichloromethane was rapidly injected into the sample solution. The tube was vigorously shaken with the vortex mixer at maximum shaking speed for 3 min. Fine droplets of organic phase were formed through the solution and the NF^--MB^+ ion-pair complex was extracted into the fine droplets of the organic phase. The resulting solution was centrifuged for 3 min at 4000 rpm to separate two phases. The sedimented dichloromethane phase at the bottom of the tube was removed using a syringe and placed in a microcell. The same procedure was applied to the blank solution. The absorbance of the dichloromethane layer was measured in absorbance unit (AU) against a reagent blank at 655 nm ($\Delta A = A_{Sample} - A_{Blank}$). The proposed procedure is illustrated in Fig. 1.

RESULTS AND DISCUSSION

It is well known that an ion-pair complex can be formed between anionic form of drugs and cationic MB. At appropriate conditions NFA is deprotonated and produces niflumate anion (NF^-) which can react with cationic dye (MB^+) to form an intense blue-colored ion-pair complex (NF^--MB^+). This complex is quantitatively extracted into dichloromethane and measured spectrophotometrically. The formation of the ion-pair complex is shown in Scheme 1 and the absorption spectra (against blank) of the NF^--MB^+ ion-pair complex extracted into dichloromethane with different initial concentrations of NFA are shown in Fig. 2.

Optimization of VA-DLLME Procedure

In order to obtain the best conditions for preconcentration and determination of NFA, various experimental parameters such as pH, type and volume of buffer, microextraction solvent, concentration of MB, etc. were optimized.

Effect of extraction solvent type. The selection of a suitable extraction solvent is an important parameter to achieve efficient liquid-liquid microextraction procedure. The extraction solvent should have low solubility in water and high extraction capability for the analytes. For this purpose, several organic solvents including chloroform ($CHCl_3$), dichloromethane (CH_2Cl_2), carbon tetrachloride (CCl_4), 1-octanol ($C_8H_{17}OH$) and 2-octanol ($C_8H_{17}OH$) were examined. The experiments were performed using 500 µL of each solvent. According to the results shown in Fig. 3, dichloromethane was chosen as the most suitable solvent for extraction of NF^--MB^+ ion-pair complex.

Effect of pH. The pH of the sample solution has an important role in the procedure because of the formation of NF^--MB^+ ion-pair complex is dependent on the pH, therefore, it must be controlled to achieve the maximum complex formation and sensitivity of the method. The influence of pH on the extraction of NFA was studied over the pH range of 2.0-10.0. The pH values were adjusted by addition of adequate amounts of either HCl or NaOH solution. According to the results (Fig. 4), the optimum pH value obtained was 6.0.

At the optimum pH value, NFA (pK_a = 4.31) [45] is deprotonated and comprises a negative charge. In addition, in this pH, MB has a positive charge and, as a result of the electrostatic attraction, the NF^--MB^+ ion-pair complex is formed. At lower pH values, the analyte is protonated and the ion-pair formation is disturbed. At pH values higher than 6.0, MB^+-OH^- ion-pair complex can be formed because of increasing hydroxide ion concentration and extracted into organic phase. Thus, the blank absorbance is increased and ΔA decreased [49].

Effect of buffer type and volume. The effect of buffer type on the efficiency of extraction procedure was studied by the use of different kinds of buffer at pH = 6.0. Based on the results shown in Fig. 5, acetate buffer was selected as the best to obtain maximum effectiveness. The optimum volume of acetate buffer at pH = 6.0 was also investigated .It was concluded that 0.5 ml of acetate buffer solution gives the best results. Therefore, in the subsequent studies, pH adjustment in each sample was carried out using 0.5 ml of the acetate buffer.

Effect of the extraction solvent volume. The influence of the extraction solvent volume on the efficiency of proposed method was also investigated. Different volumes of dichloromethane in the range of 300-900 µl were subjected to the VA-DLLME procedure. Based on the results, volume of 400 µl was selected as the optimum

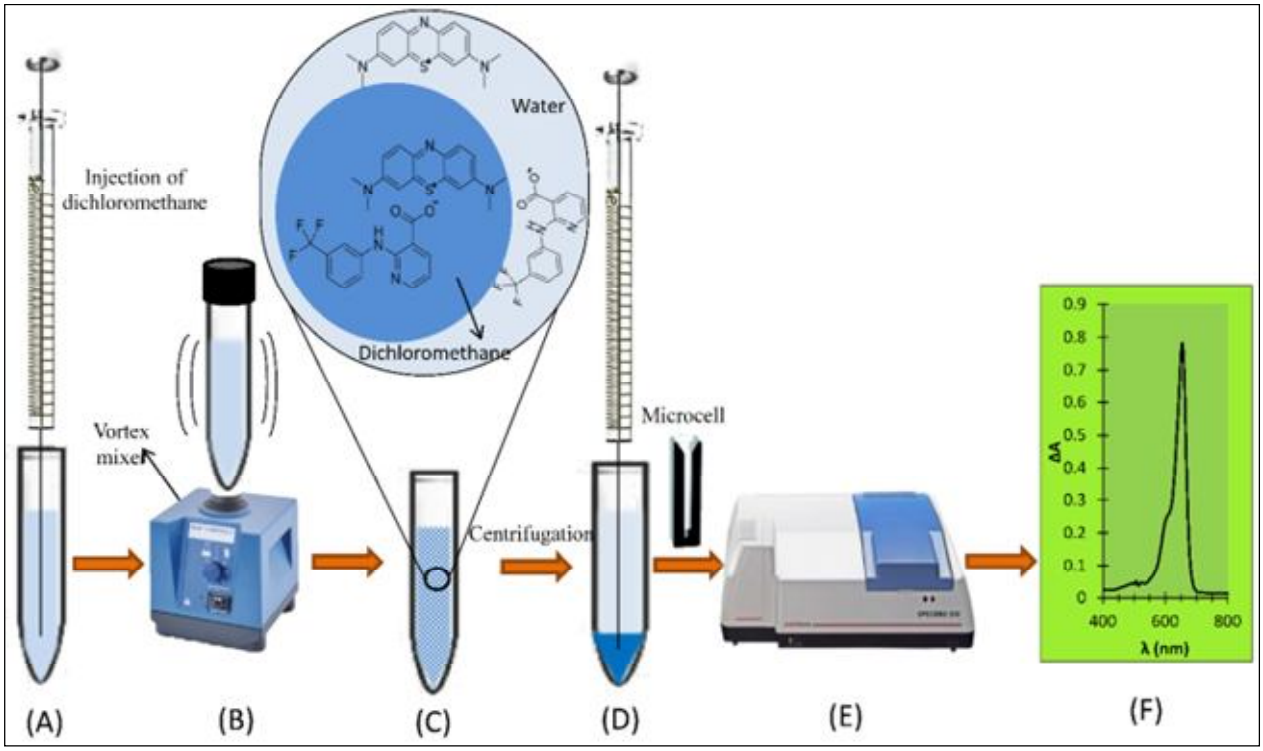
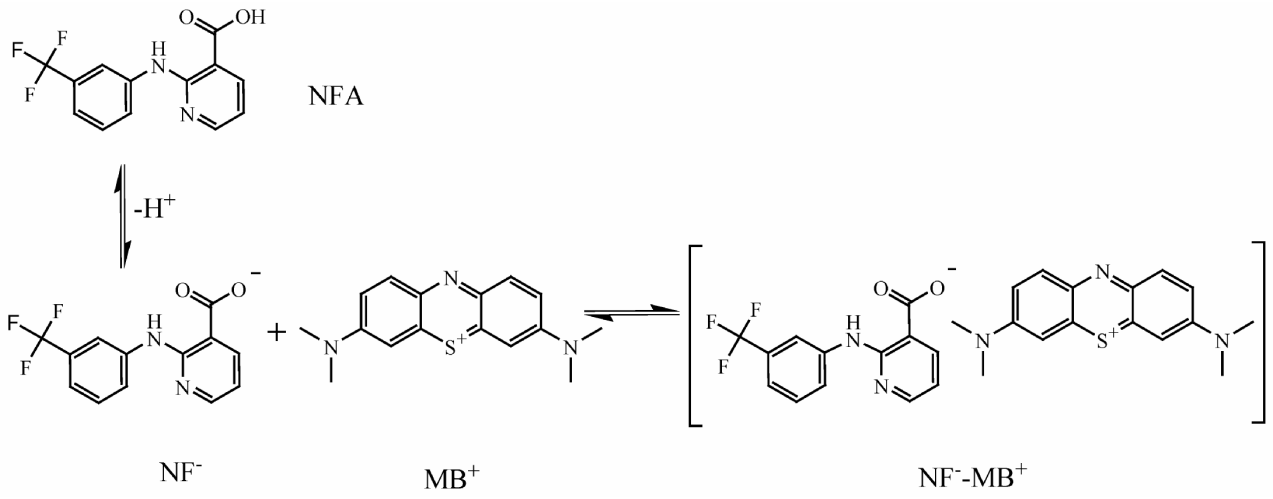


Fig. 1. Schematic diagram of ion-pair based VA-DLLME procedure. (A) injection of extraction solvent (dichloromethane) into aqueous sample solution containing NFA and MB (B) vortex agitation of the sample solution, (C) ion-pair complex formation and extraction into the fine droplets of dichloromethane, (D) phase separation after centrifugation and collection of organic solvent, (E) spectrophotometric analysis of organic phase, (F) absorption spectrum of organic phase containing the analyte.



Scheme 1. The reaction of NF^--MB^+ ion-pair complex formation.

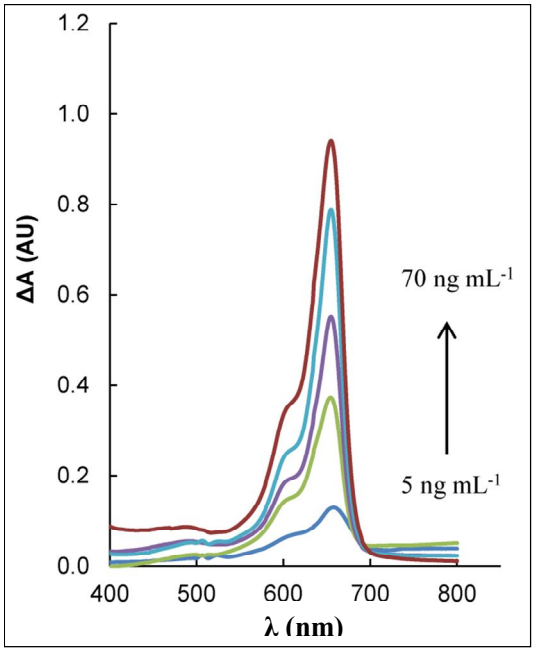


Fig. 2. Absorption spectra (against blank) of the sedimented phase after VA-DLLME of aqueous sample with different concentrations of NFA.

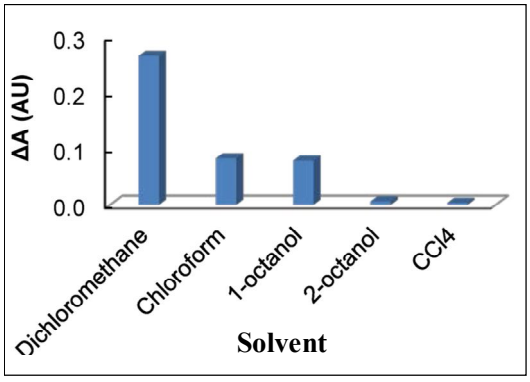


Fig. 3. Effect of extraction solvent on the extraction efficiency. Conditions: 10 ml solution containing NFA (50 ng ml^{-1}) and MB (0.2 mg l^{-1}), extraction time = 2 min and 500 µl of extraction solvent.

volume of extraction solvent. It was observed that a portion of the injected extraction solvent was dissolved in the aqueous phase, because of its solubility in water, and the sedimented organic phase had a smaller volume than the injected solvent. Hence, for the volumes less than 400 µl, the collected organic phase was not enough for spectrophotometric measurements. On the other hand, at higher volumes, the efficiency of the method was decreased as a result of an increase in the volume of sedimented phase and dilution effect.

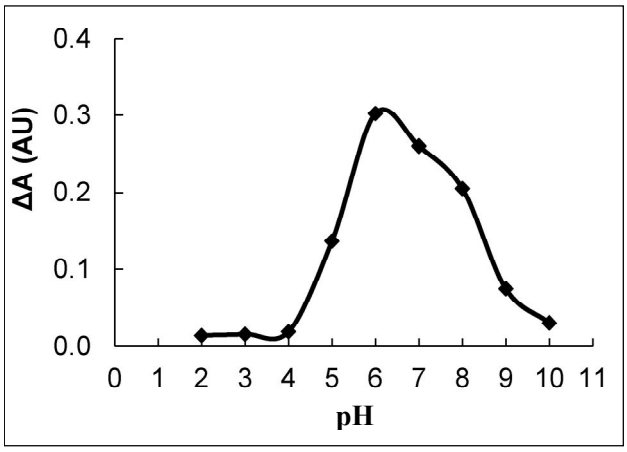


Fig. 4. Effect of pH on the extraction efficiency. Conditions: 10 ml solution containing NFA (50 ng ml^{-1}) and MB (0.2 mg l^{-1}), extraction time = 2 min and 500 µl of dichloromethane as extraction solvent.

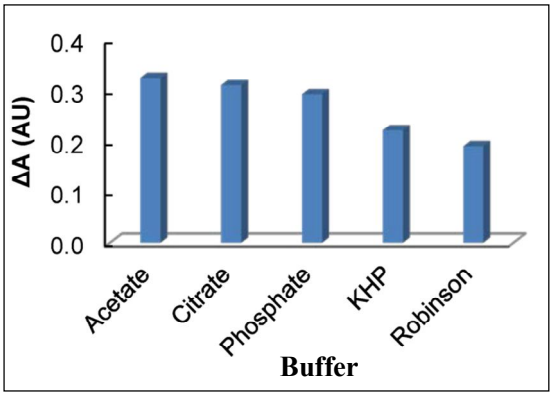


Fig. 5. Effect of buffer type on the extraction efficiency. Conditions: 10 ml solution containing NFA (50 ng ml^{-1}) and MB (0.2 mg l^{-1}), extraction time = 2 min and 500 µl of dichloromethane as extraction solvent.

Effect of dye concentration. In order to investigate the effect of dye concentration on the extraction efficiency, the MB concentration was varied between 0.03 and 3.8 mg l^{-1}. As can be seen in Fig. 6, ion-pair complex extraction increased up to 1.6 mg l^{-1} of MB and remained almost constant in the concentration range of 1.6 to 3.8 mg l^{-1}. Therefore, a concentration of 2.6 mg l^{-1} was used as the optimum dye concentration.

Effect of extraction time. The extraction time can play an important role in ion-pair based VA-DLLME because an enough time is necessary to disperse the organic solvent into the aqueous solution and also extraction of drug-dye ion-pair complex to the organic phase. The influence of vortex time on the extraction efficiency was evaluated over the range of 0.25-7 min. As shown in Fig. 7, extraction efficiency remains constant in the range of 2-7 min. Hence, vortex treatment for 3 min was selected as the optimum extraction time.

Effect of ionic strength. The effect of the ionic strength on the extraction efficiency was investigated by the addition of different sodium chloride amounts in the range of 0.01-0.2 M in the sample solutions while the other

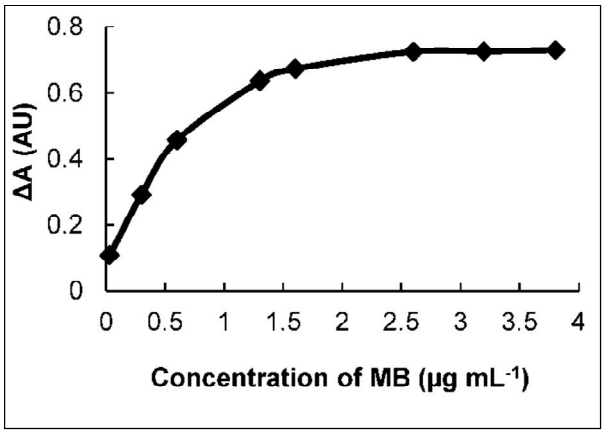


Fig. 6. Effect of dye concentration on the extraction efficiency. Conditions: 10 ml solution containing NFA (50 ng ml^{-1}) and 0.5 ml acetate buffer pH = 6, extraction time = 2 min and 400 µl dichloromethane as extraction solvent.

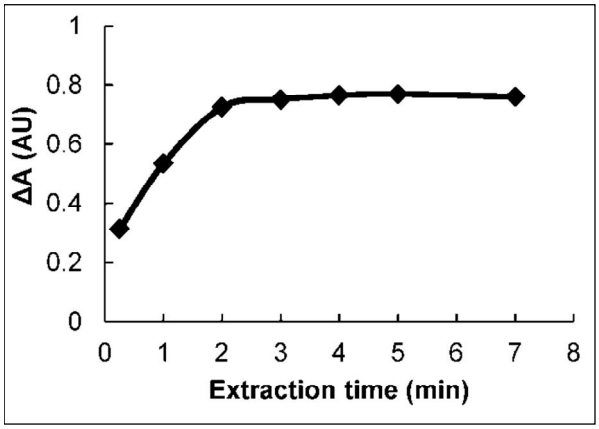


Fig. 7. Effect of extraction time on the extraction efficiency. Conditions: 10 ml solution containing NFA (50 ng ml^{-1}), MB (2.6 mg l^{-1}) and 0.5 ml acetate buffer pH = 6 and 400 µl dichlomethane as extraction solvent.

parameters were kept constant. The results showed that, by increasing the concentration of NaCl in the sample solutions, the extraction efficiency was decreased. This is probably because of the decrease in the solubility of extractant in the presence of salt which leds to increase in the volume of sedimented phase [50]. Further experiments were carried out without salt addition.

Enrichment Factor and Consumptive Index

The enrichment factor (EF) is the ratio of the analyte concentration in sedimented phase (C_{sed}) to the analyte concentration in the sample (C_0), EF = C_{sed}/C_0 [51]. Base on this concept, the enrichment factor of 36 was obtained for the proposed method.

The consumptive index (CI) is another factor that

Table 1. Analytical Features of the VA-DLLME Method for Spectrophotometric Determination of NFA

Analytical parameters	Obtained results
λ_{max}	655 nm
Calibration curve equation	$\Delta A = 0.0151 \times C_{NFA} + 0.0335$
Linear dynamic range (ng ml^{-1})	5-70
Correlation coefficient (r)	0.9997
Limit of detection (LOD) (ng ml^{-1})	2.8
RSD% (10 and 50 ng ml^{-1})	4.8% and 2.5%
Enrichment factor (EF)	36
Consumptive index (CI) (ml)	0.28

Table 2. Effect of Interfering Species on VA-DLLME of NFA

Foreign species	Tolerance ratio
Na^+, K^+, Mg^{2+}, Fe^{3+}, Fe^{2+}, Cr^{3+}, Ag^+, Cu^{2+}, Cd^{2+}, Zn^{2+}, Pb^{2+}, Ba^{2+}, Sn^{2+}, Ni^{2+}, F^-, Cl^-, Br^-, I^-, CO_3^{2-}, $H_2PO_4^-$, $C_2O_4^{2-}$, CN^-, S^{2-}, NO_3^-, CH_3COO^-, Citrate, Glucose, Urea, Glycine, Bromhexine hydrochloride, Fluvoxamine maleate, Isosorbide dinitrate, Ethambutol	1000
Ca^{2+}, Al^{3+}, Hg^{2+}, SCN^-, SO_4^{2-}, EDTA, Theophylline	750
Ceftizoxime	250

characterizes the preconcentration systems. CI is defined as the sample volume (ml) which is consumed to reach a unit of enrichment factor (EF) and is calculated by $CI = V_s/EF$, where V_s is the sample volume (ml) and EF is the enrichment factor of the method [52]. Based on this definition, the consumptive index of 0.28 was obtained for the method.

Analytical Features

The Analytical characteristics of the proposed method obtained under the optimum conditions are summarized in Table 1. The calibration curve was obtained by plotting the ΔA against the corresponding NFA concentration. The calibration curve was linear in the range of 5-70 ng ml^{-1} and the correlation coefficient was 0.9997 demonstrating an

excellent linearity for the proposed method. The linear regression equation was found to be $\Delta A = 0.0151 \times C_{NFA} + 0.0335$, where ΔA is the absorbance difference between sample and blank at λ_{max} (AU), and C_{NFA} is the concentration of NFA (ng ml^{-1}). Limit of detection (LOD) was set to the lowest concentration where the signal of the analyte was three fold higher than background noise and determined by analyzing the blank solutions (n = 8). Based on the results, the LOD of 2.8 ng ml^{-1} was achieved.

Repeatability of the analytical procedure was assessed by the determination of relative standard deviation (RSD). Intra-assay (within-day) variability was evaluated by analyzing eight replicates of NFA solutions at two different concentrations (10 and 50 ng ml^{-1}). RSDs were obtained equal to 4.8% and 2.5% for 10 and 50 ng ml^{-1} of NFA, respectively.

Effect of Interfering Ions and Compounds

In order to apply the proposed ion-pair-based VA-DLLME procedure to real samples, the effect of different ions and compounds on the preconcentration and determination of NFA was studied. For this purpose, 10 ml solution containing 35 ng ml^{-1} of NFA, 0.5 ml of acetate buffer (pH = 6.0) and different foreign species at various concentrations was prepared and the optimum VA-DLLME procedure was applied. The maximum acceptable error for determination of NFA in the presence of foreign species was ± 5%. The obtained results are given in Table 2. As can be seen, most species showe low interference effect on the determination of NFA.

Analysis of Real Samples

In order to show the performance and applicability of the proposed method in real samples, the procedure was applied to the determination of NFA in human plasma and goat's milk samples.

Human plasma. 0.5 ml of human plasma was spiked with different amounts of NFA (final concentration 0, 30, 50 and 70 ng ml^{-1}) and then was deproteinized by the addition of 1 ml acetonitrile. After centrifugation, the supernatant along with 4 ml of MB (6.5 mg l^{-1}) and 0.5 ml of acetate buffer (pH = 6.0) was transferred to a 10 ml volumetric flask and made up to volume with double-distilled water. Concentration of NFA in plasma was obtained by applying the proposed VA-DLLME procedure and spectrophotometric measurment.

Goat's milk. 30 ml of raw goat's milk was transferred into a tube and centrifuged at 3500 rpm for 7 min to get skimmed milk. 0.5 ml of skimmed milk was spiked with different amounts of NFA (final concentration 0, 30, 40 and 50 ng ml^{-1}). For deproteinization, 1 ml of acetonitrile was added to the drug-supplemented skimmed milk and the resulting mixture was centrifuged. The supernatant was transferred to a 10 ml volumetric flask and made up to volume with 4 ml of MB (6.5 mg l^{-1}), 0.5 ml of acetate buffer (pH = 6.0) and double-distilled water. Optimum VA-DLLME procedure was performed on the milk solutions to obtain the concentration of NFA in the milk.

The obtained results for both real samples are demonstrated in Table 3. The range of recovery values are between 99.2% and 101.3% indicating that the matrix has not considerable effect on the VA-DLLME procedure for the spectrophotometric determination of NFA.

Comparison with other Methods

The analytical performance of the suggested ion-pair-based VA-DLLME procedure for preconcentration and spectrophotometric determination of NFA was compared with some previously reported determination methods, and the results are summarized in Table 4. As it can be seen, the suggested VA-DLLME is comparable to (or even better than) most other given methods regarding to the lowest determinable concentration, RSD or recovery.

CONCLUSIONS

A simple and accurate ion-pair-based VA-DLLME technique combined with UV-Vis spectrophotometry is proposed for the determination of NFA. The method is based on the formation and extraction of an intense blue-colored ion-pair complex of NF^--MB^+. The main advantages of the proposed method are rapidity, little solvent consumption, low cost and providing low LOD by the simple UV-Vis spectrophotometer. Good precision and sensitivity were achieved as demonstrated by obtained RSD and LOD. The proposed VA-DLLME was successfully applied for the extraction and quantitative determination of NFA in human plasma and goat's milk samples. With

Table 3. Determination of NFA in real Samples

Real sample	Concentration of niflumic acid ($ng\ ml^{-1}$)		Recovery (%)
	Added	Found[a]	
Human plasma	0.0	N.D[b]	-
	30.0	30.2 ± 1.4	100.7
	50.0	49.6 ± 1.5	99.2
	70.0	70.3 ± 1.7	100.4
Goat's milk	0.0	N.D	-
	30.0	30.4 ± 0.8	101.3
	40.0	39.7 ± 1.5	99.2
	50.0	50.3 ± 1.8	100.6

[a]Average of three measurements ± Standard deviation. [b]Not Detected.

Table 4. Comparison of Ion-pair-based VA-DLLME Method and Previously Published Liquid-liquid Extraction Methods for the Determination of NFA

Method (Solvent)	Real sample	Detection	Linear range ($ng\ ml^{-1}$)	RSD (%)	Recovery (%)	Ref.
LLE (Et_2O)	Human plasma	GC-NPD	100-20000	5.3	97.9-119.0	[53]
LLE (Et_2O)	Urine	GC/NCI MS[a]	500-50000	4.1	98.26	[44]
LLE (Et_2O)	Human plasma	HPLC-UV	500-50000	1.44-7.28	91.85	[54]
VA-DLLME (CH_2Cl_2)	Human plasma, goat's milk	UV-Vis	5 -70	3.4-4.6[b] 2.6-3.8[c]	99.2-100.7[b] 99.2-101.3[c]	*This work*

[a]Gas chromatography/negative chemical ionization mass spectrometry. [b]For plasma sample. [c]For milk sample.

respect to the negligible effect of interferences on the present method, the proposed procedure is potentially applicable for the determination of NFA in other matrices.

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