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Electromembrane-microextraction of bismuth in pharmaceutical and human plasma samples: optimization using response surface methodology

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ABSTRACT

An electromembrane-microextraction (EME) followed by microcell UV–Vis spectrophotometeric detection was developed for fast and sensitive determination of bismuth in bismuth subcitrate tablets and human plasma samples. To achieve the best extraction conditions, the organic membrane composition and stirring rate were optimized separately by one-variable-at-a-time (OVAT) methodology, and the other effective parameters, including extraction time, applied voltage and composition of acceptor/donor phases, were studied by application of response surface methodology (RSM). The working range was 2.1–800 ng mL^{-1}, with detection limit of 0.64–1.47 ng mL^{-1} of bismuth ions. The enrichment factor was in the range 151–187. Intra- and inter-day relative standard deviations were <6.0%. The developed method was successfully applied for the determination of bismuth in real samples.

1. Introduction

Bismuth has been associated with medicine for more than two centuries in the treatment of gastrointestinal disorders [1]. Some of its colloidal salts, including subcitrate and subgallate, have important applications in pharmaceutical and employed as anti-ulcer, antibacterial, anti-HIV and radiotherapeutic agents [2]. Besides, it is used in cosmetics, semiconductors, fuel carriers, metallurgical additives and the fabrication of catalysts, as well as in the preparation and recycling of uranium nuclear fuels. As the use of bismuth and its compounds in different areas has increased, toxicity of this element started to be considered for humans, animals and plants [3–5].

Although the absorption of Bi(III) in the human organism is usually low, several cases of toxic effects in human beings such as nephrotoxicity, neurotoxicity, gingivitis, rheumatic pain, kidney damage and fever have been reported for the use of bismuth (III)-containing pharmaceutical formulations [6]. Despite the medicinal interest, the metabolism of bismuth drugs is still not well understood. This is partially due to the lack of suitable techniques to detect bismuth at trace or ultra-trace levels [7]. Therefore, due to the presence of bismuth in environmental and biological samples at low concentration levels, the request for sensitive, low cost and rapid analytical techniques for the preconcentration-determination of this element has increased.

A variety of analytical and sophisticated techniques have been developed for the determination of bismuth in various matrices such as alloy, water, rock, and biological samples. Among these techniques are spectrophotometry [8], flame atomic absorption spectrometry (FAAS) [5,9], electrothermal atomic absorption spectrometry [10], hydride generation atomic absorption spectrometry [3,11], inductively coupled plasma atomic emission spectrometry (ICP-AES) [12] and voltammetry [13]. UV-–Vis spectrophotometry is, undoubtedly, the simplest and most cost-effective technique for routine analysis and is also accessible in many laboratories. Nevertheless, direct determination of trace amount of bismuth by UV–Vis spectrophotometry is seldom accomplished. However, due to the presence of Bi in environmental and biological samples at low concentration levels and its separation from other elements present, a simple and efficient preconcentration step before to its determination is often essential.

In recent years, different microscale sample preparation techniques such as cloud point microextraction (CPE) [7] and dispersive liquid-liquid microextraction (DLLME) [4] have been reported for analysis of Bi in biological samples. Recently, hollow fiber-liquid phase microextraction (HF-LPME), as a microscale sample preparation technique, has been used for the extraction and preconcentration of a wide variety of analytes, including metal ions [14,15]. Application of hollow fibers is one of the most promising developments in preconcentration, separation, and clean up purposes. This microextraction technique provides low consumption of hazardous organic solvents, efficient clean-up, good preconcentration factor and

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reduced analysis costs for analysis of complex matrices [16]. Since HF-LPME is based on diffusive transport of analytes across the supported liquid membrane (SLM), stirring or agitation of the sample solution is critical. However, in general and even by applying an efficient stirring of sample solution in HFLPME experiments, extraction time is relatively long and is ranged between 10 and 60 min [17,18].

In order to increase the extraction speed, an electrical potential as the driving force, has been applied across the SLM. Application of the voltage across a SLM results in very fast extraction of an analyt from small sample volumes. This system as a relatively new concept is termed as electromembrane-microextraction (EME), and has been conducted with exactly the same setup used for HF-LPME assisted by a DC power supply and two electrodes to maintain the voltage across the SLM [19].

In this specific microextraction technique, charged analytes were extracted by electrokinetic migration from a sample solution (donor phase), through a SLM impregnated the wall of a hollow fiber, and further extraction into an acceptor solution inside the lumen of the hollow fiber. Therefore, the use of an electrical potential difference as the driving force shortens the extraction time to approximately 5–15 min [20]. In addition to rapid extraction, EME also provides high preconcentration factor, excellent clean-up and selective extraction of analytes from complex matrices such as biological samples [21,22]. This technique has been successfully applied for the preextraction-determination of a variety of heavy metals in various real samples [23–29].

The aim of this work was to develop a new method for the determination of bismuth using EME in combination with microcell UV–Vis spectrophotometry. The performance of the method was evaluated and applied for preconcentration-determination of bismuth in pharmaceutical and human plasma samples.

2. Experimental

2.1. Chemicals and materials

O-Nitrophenyloctyl ether (NPOE), 1-hexanol, 1-heptanol and 1-octanol used for EME experiments were obtained from Fluka (Buchs, Switzerland). Examined carriers bis(2-ethylhexyl) phosphate (DEHP) and tris(2-ethylhexyl) phosphate (TEHP) were purchased from Sigma (Munich, Germany). Metal chlorides, metal nitrates, bismuth(III) nitrate pentahydrate, xylenol orange tetrasodium salt (as indicator), sulfuric acid and nitric acid, were from Merck chemical company (Darmstadt, Germany). All the chemicals used were of analytical reagent grade. The porous hollow fibers used for the immobilization of the SLM and housing the acceptor solution were PPQ3/2 polypropylene hollow fibers from Membrana (Wuppertal, Germany) with an inner diameter of 0.6 mm, a wall thickness of 200 μm, and a pore size of 0.2 μm. A Milli-Q water purification system from Millipore (Madrid, Spain) was used for preparing ultrapure water.

2.2. Preparation of standard solutions and real samples

A stock solution of 100 μg mL^{-1} bismuth(III) was prepared by dissolving 0.0232 g of bismuth nitrate pentahydrate in 5 mL of concentrated sulfuric acid and diluting to 100 mL in a volumetric flask with ultrapure water. Working standard solutions were prepared daily by successive dilutions of this stock solution with diluted sulfuric acid solution. Sulfuric acid solutions were prepared from its concentrated solution (98 w/w%, d = 1.84 g mL^{-1}) in ultrapure water. Xylenol orange as the indicator and chelating agent for spectrophotometric determination of bismuth was prepared by dissolving the reagent in sulfuric acid solution (0.05 mol L^{-1}). For the preparation of pharmaceutical samples [4,6], a bismuth subcitrate tablet containing 120 mg Bi_2O_3 was powdered and dissolved in 5 mL of concentrated nitric acid. The mixture was heated on a water bath (80–90 °C) to dryness. Three consecutive additions of 10 mL ultrapure water were then made and each time the solution was evaporated almost to dryness to eliminate the excess acid. The residue was dissolved in water and filtered using filter paper. The filtrate solution was diluted to 100 mL with water in a volumetric flask. An aliquot of this solution were diluted with 5 mmol L^{-1} sulfuric acid and analyzed for determination of bismuth using the EME procedure. The human plasma samples (blood group A^+) were collected from the Iranian Blood Transfusion Organization (Qazvin, Iran). The plasma samples were stored at −4 °C, thawed and shaken before extraction. The human plasma sample was spiked with certain amount of standard solution (μL) to achieve the desired concentration and diluted 1:5 with ultrapure water. Then, a solution of H_2SO_4 (2 mol L^{-1}) was dropwise added into the sample. The final H_2SO_4 concentration in the sample was adjusted at 5 mmol L^{-1}. This sample was then introduced into EME cell without any other pre-treatment procedure.

2.3. Equipment

The equipment used for EME is shown in Fig. 1. The electrodes used were platinum wires (0.25 mm diameter) obtained from Pars Pelatine (Tehran, Iran). These electrodes were connected to a DC power supply (Paya Pajoohesh Pars, Tehran-Iran) with a programmable voltage in the range of 0–600 V and provided currents in the range 0–500 mA. During the extraction experiments, the EME unit was stirred with a stirring rate in the range 250–1000 rpm, by a heater-magnetic stirrer (Heidolph model 301) using a magnetic bar. The spectrophotometric measurements were carried out with a UV–Vis spectrophotometer HACH (model DR 5000, Ontario, Canada) by monitoring the absorbance of bismuth/xylenol orange complex at maximum absorbance (540 nm) using quartz microcells with 100 μL capacities. Maximum absorbance for xylenol orange (sulfuric acid solution as blank) was at 440 nm.

2.4. EME procedure

Five mL of the donor phase containing analyte in 5 mmol L^{-1} sulfuric acid was transferred into a glass vial. To impregnate the SLM in the pores of hollow fiber wall, 3.5 cm piece of hollow fiber was cut out and immersed into the organic solvent for 10 s and then the excess amount of solution was gently removed away by blowing with a medical syringe. Then, 10.0 μL of 300 mmol L^{-1} of sulfuric acid as acceptor solution was introduced into the lumen of the hollow fiber, in which the bismuth ions were trapped as Bi^{3+} ions [4]. The lower end of the hollow fiber was closed by heat. The upper end of the hollow fiber was connected to a medical needle tip as a guiding tube which was inserted through the rubber cap of the vial. One of the electrodes, the cathode (negative electrode), was placed into lumen of the fiber. The fiber containing the cathode and the acceptor solution was subsequently directed into the sample solution. The other electrode, the anode (positive electrode), was located directly into the sample solution. The electrodes were subsequently coupled to the power supply and the extraction cell was placed on a stirrer with stirring speed of 700 rpm. The predetermined voltage was turned on and the extraction process was performed for 10 min. After the extraction was completed, the acceptor solution was collected by a microsyringe and transferred directly to a microvial for further analysis by microcell UV–Vis spectrophotometric determination.

2.5. Spectrophotometric determination procedure

Bismuth(III) was determined by the bismuth/xylenol orange complex spectrophotometric method. In acidic medium, the reaction between xylenol orange and bismuth ions results in the formation of a water soluble pink complex. The developed color is the basis for determining bismuth in the samples. It is noteworthy that the maximum color intensity of the complex can be developed in 0.05–0.1 mol L^{-1} solution of sulfuric acid [30]. The method was optimized with respect to the concentration of sulfuric acid and the complexing reagent