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Cloud point extraction of vanadium in pharmaceutical formulations, dialysate and parenteral solutions using 8-hydroxyquinoline and nonionic surfactant

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ABSTRACT

A cloud point extraction (CPE) method has been developed for the determination of trace quantity of vanadium ions in pharmaceutical formulations (PF), dialysate (DS) and parenteral solutions (PS). The CPE of vanadium (V) using 8-hydroxyquinoline (oxine) as complexing reagent and mediated by nonionic surfactant (Triton X-114) was investigated. The parameters that affect the extraction efficiency of CPE, such as pH of sample solution, concentration of oxine and Triton X-114, equilibration temperature and time period for shaking were investigated in detail. The validity of CPE of V was checked by standard addition method in real samples. The extracted surfactant-rich phase was diluted with nitric acid in ethanol, prior to subjecting electrothermal atomic absorption spectrometry. Under these conditions, the preconcentration of 50 mL sample solutions, allowed raising an enrichment factor of 125-fold. The lower limit of detection obtained under the optimal conditions was 42 ng/L. The proposed method has been successfully applied to the determination of trace quantity of V in various pharmaceutical preparations with satisfactory results. The concentration ranges of V in PF, DS and PS samples were found in the range of 10.5–15.2, 0.65–1.32 and 1.76–6.93 μg/L, respectively.

1. Introduction

Vanadium (V) compounds can be highly toxic to humans and their presence in the atmosphere is mainly due to the combustion of fossil fuels. V is normally found in ultra trace amounts in different food [1]. V and its compounds are toxic in high concentrations or after long periods of exposure [2,3]. However, in trace levels, V is an essential element and its compounds exhibiting chemotherapeutic effects in the treatment of leukemia and recent studies showed promising application in the management of diabetes [4,5]. The estimated daily intake of V ranges from 10 to 60 mg [6]. Too much intake of V may be harmful to humans, the symptoms of V poisoning being nervous depression, coughing, vomiting, diarrhea, and anemia [7,8]. In addition to the "normal" routes of intake of V via the gastrointestinal and respiratory tract, a third mechanism must be taken into account, namely the inadvertent administration of V through intravenously applied solutions containing high amounts of V as an impurity [9].

Parenteral nutrition (PN) consists of administering intravenously all nutrients necessary to patients who cannot receive normal alimentation due to various pathologies [10,11]. The importance of trace elements in the nutritional management of patients receiving total parenteral nutrition (TPN) is now widely recognized [12,13] and patients that are subject to long-term TPN can inadvertently receive significant amounts of V, present as contaminant in the PS.

The contamination levels of V depend strongly on the quality of water and of the dialysis concentrates that are used [14]. Sabbioni et al., found that, salts used for the preparation of dialysate are the main source of metal contamination [15]. Consequently, it is of great importance and significance for environmental science and life science to determine traces of V in different pharmaceutical formulations.

Since V concentrations in non-polluted PF, DS and PS are very low, powerful techniques are required and only neutron activation analysis (NAA) [16] and inductively coupled plasma mass spectrometry [17,18] show sufficient sensitivity. However, these methods require more sophisticated instrumentation, which may not be available in most analytical laboratories. Moreover, inductively coupled plasma–mass spectrometry is very sensitive to matrix effects [19]. Electrothermal atomic absorption spectrometry

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has been demonstrated to be an effective method for the determination of V in the presence of matrix modifier [20–23]. To determine the trace concentrations of V, a preconcentration technique is frequently required before the use of spectroscopic methods. Many such techniques have been proposed, including solvent extraction [24], co-precipitation [25], solid phase [26] and cloud point extraction CPE [27,28]. Solvent extraction and co-precipitations have been commonly used for the pretreatment of V, but they are laborious and kept to carry a risk of contamination and possibility of interference effects. The CPE is an impressive alternative to conventional solvent extraction because it produces high extraction efficiencies and enrichment factors, where as for CPE inexpensive and non-toxic reagents are required. The use of CPE process for extraction of metal chelates, biological and clinical samples and environmental clean-up procedure have been reported [29–31].

The V forms complexes with many chelating reagents, include 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino)-phenol (5-Br-PAPS) [32], hydrogen peroxide-2-(5-bromo-2-pyridylazo)-5-diethylaminophenol (5-Br-PADAP), bis(acetylpivalylmethane) ethylenediimine [33], 2-(2-thiazolylazo)-5-diethylaminophenol (TA-DAP) [34], and 2-(5-nitro-2-pyridylazo)-5-[N-n-propyl-N-(3-sulfopropyl) amino]phenol (nitro-PAPS) [35].

In different oxidation states, V also forms complexes with 8-hydroxyquinoline (8-quinolinol/oxine) [36,37]. Oxine and its derivatives have been widely used as complexing agents for the recovery of metal ions by solvent extraction [28,38]. However, most of the research on V complexes with oxine ligands or its derivatives was done on V^{5+} which forms stable complex with oxine [39,40]. Oxine was applied for selective determination of aluminum in environmental and pharmacological samples, using nonionic surfactant, Triton X-114 [41].

In the present work a CPE method using a complexing reagent, 8-hydroxyquinoline (oxine) has been developed for the determination of micrograms per liter level of V ions in PF, DS and PS samples. The preconcentration of V is based on the formation of a neutral, hydrophobic complex with oxine, which was subsequently trapped in the micellar phase of a nonionic surfactant (Triton X-114) at a temperature higher than the cloud point. Different variables, such as pH of sample solution, concentration of oxine and Triton X-114, equilibration temperature, and time period for shaking were investigated in detail. The analyte in surfactant-rich phase was determined by electrothermal atomic absorption spectrometry (ETAAS) with different modifiers, $Mg(NO_3)_2$, $Pd(NO_3)_2$, BaF_2 and mixture of two modifiers ($Pd(NO_3)_2 + BaF_2$).

2. Experimental

2.1. Reagents

Ultrapure water obtained form ELGA lab water system (Bucks, UK), was used throughout the work. The nonionic surfactant Triton X-114 was obtained from Sigma (St. Louis, MO, USA) and was used without further purification. The chemicals used were of analytical grade, and all solutions were prepared with ultrapure water. A 2% solution of oxine (Merck) was prepared by dissolving in 10 mL ethanol (Merck) and diluting to 100 mL with 0.01 mol/L acetic acid and was kept in refrigerator (4 °C) for one week. A solution of BaF_2 was used as chemical modifier by dissolving 1 g of the salt (99.99% purity, Aldrich, Milwaukee, WI, USA) in 100 mL of ultrapure water. The palladium nitrate solution of 1000 mg/L was prepared by dissolving 106.6 mg $Pd(NO_3)_2$ (Merck) in 50 mL of 0.1% (v/v) HNO_3. A 1.0 mol/L solution of $Mg(NO_3)_2$ (Merck) was prepared by dissolving 14.8 g $Mg(NO_3)_2$ in 100 mL of deionized water. The 0.01 mol/L acetate buffer was used to control the pH of the solutions. The pH of the samples was adjusted to the desired pH (3–8) by the addition of dilute HCl or NaOH solution in acetate buffer. All other chemicals were of analytical reagent grade and were used without further purification.

2.2. Instrumentation

A PerkinElmer model AAnalyst 300 atomic absorption spectrometer equipped with a deuterium background correction system and electrothermal atomizer, HGA-800. V was measured at 318.5 nm with a V hollow cathode lamp and a slit width of 0.7 nm. Pyrocoated graphite tubes with an integrated L'vov platform and peak area integration were used. The graphite furnace program for V determination was, temperature (°C)/ramp time (s)/hold time (s) for drying 100–150/1/10, ashing 1600/15/20 and atomization 2600/0/4, respectively, with Argon flow rate 200 mL/min.

2.3. Sample collection and conditioning

Total parenteral and pharmaceutical formulation solutions of four different batches packed on different four dates ($n = 16$) were purchased from pharmaceutical stores. The samples were taken directly from the packages. Five different dialysate solutions were also purchased from different pharmaceutical stores, batches packed on four different dates ($n = 20$). The sub-samples of each dialysate concentrate was prepared with ultrapure water. The same dialysate solutions prepared for dialysis were also collected from urological department of civil hospital Hyderabad Pakistan. The PF, DS and PS samples were filtered through 0.45 μm pore size membrane, immediately after sampling and were stored at −4 °C in the dark till further analysis.

2.4. Cloud point extraction

The standard solutions of V in the concentration range of 1–10 μg/L and triplicate of each PF, DS and PS samples (50 mL) were transferred into a centrifuge tubes with glass stopper (100 mL in capacity). Amounts of 0.2–1.0 mL of 0.1% oxine (6.9×10^{-2} mol/L), 0.1–0.5 mL of 1% Triton X-114 solution and 5 mL of acetate buffer were added and then the pH was adjusted in the range of 2–8 by using 0.1 mol/L of NaOH/HCl and pH were checked with a pH-meter. The solution was heated in an ultrasonic water bath for 10–60 min at 40–80 °C and centrifuged at 3500 rpm for 2–10 min. After cooling in an ice bath for 5 min, the surfactant-rich phase became viscous and was retained at the bottom of the tube. The supernatant aqueous phase was discarded, and the remaining micellar phase was diluted with 0.2 mL of HNO_3 in ethanol (1:10, v/v). The volume of the surfactant-rich phase after the phase separation was measured by using a graduated cylinder. 20 μL of the diluted extract was introduced into the electrothermal atomizer with 10 μL of standards and each three samples, and 10 μL of modifiers separately. A blank submitted to the same procedure was measured parallel to the samples and standard solutions.

3. Results and discussion

3.1. Optimization of cloud point extraction

The preconcentration of V is based on the formation of a neutral, hydrophobic complex with oxine, which is subsequently trapped in the micellar phase of a nonionic surfactant (Triton X-114). Utilizing the thermally induced phase extraction separation process known as CPE, the analyte is highly preconcentrated and free of interferences in a very small micellar phase. Several parameters play a significant role in the performance of the surfactant system that is used and its ability to aggregate, thus entrapping the

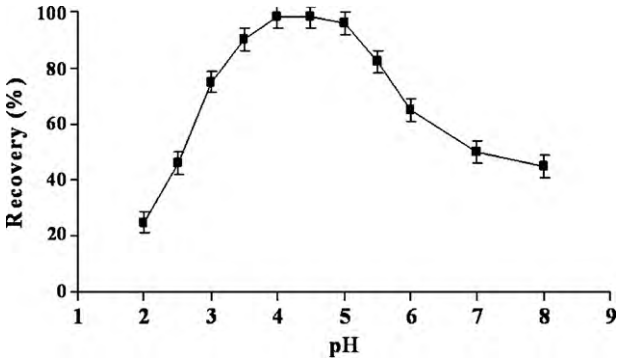

Fig. 1. Effect of pH on the recovery efficiency: 10 μg/L of V, 6.90×10^{-2} mol/L oxine, 0.3% (v/v) Triton X-114, temperature 45 °C, stirring time 20 min.

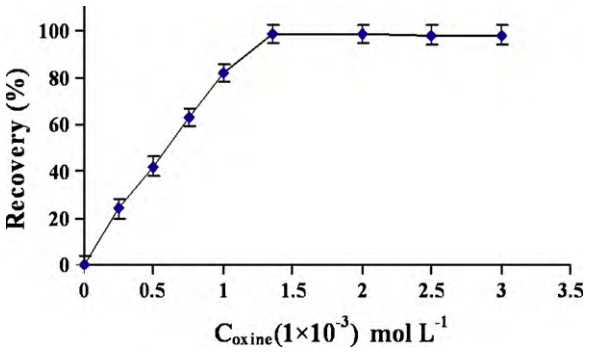

Fig. 3. Effect of oxine concentration on the recovery efficiency: 10 μg/L of V, 0.3% (v/v) Triton X-114, pH 4.0, temperature 45 °C, stirring time 20 min.

analyte species. The pH, complexing reagent and surfactant concentration, temperature and time were studied for optimum analytical signals.

3.1.1. Effect of pH

To study the effect of pH upon complex formation of V-oxine, six sub-samples of a DS and PS (50 mL) were spiked with 10 μg/L of V, the pH of solutions was adjusted with HCl/NaOH within the pH range from 2 to 8, then complexing reagent and surfactant were added. Fig. 1 shows the effect of pH on the extraction recovery of V. The complexation extraction begins at pH 3 and start to decrease at pH 5.5, quantitative extraction (>95%) being obtained in the pH range of 3–5 at which the V-oxine complex is neutral. Hence, pH 4 was chosen for optimum CPE of V. At higher pH values the complex is negatively charged, and cannot be entrapped in the nonionic micelles. This behavior is in agreement with the results of previous studies [42].

3.1.2. Effect of Triton X-114 concentration

The amount of Triton X-114 not only affected the extraction efficiency, but also the volume of surfactant-rich phase. Due to lower cloud point temperature of Triton X-114, back extraction of analyte during centrifugation is avoided. The variation of the analytical signal as a function of the concentration of Triton X-114 was investigated in the range of 0.1–0.5% (v/v). The results in Fig. 2 shows that the absorbance signal of V solutions is enhanced by increasing the Triton X-114 concentration from 0.1–0.3% (v/v). With further increase of Triton X-114 concentration, the signals decreased because of the increment in the overall analyte volumes and viscosity of the surfactant phase. Therefore, 0.3% (v/v) Triton X-114 was chosen as the optimum surfactant concentration in order to achieve the highest possible extraction recovery of V. This surfactant concentration permits to obtain a final volume of 200 μL of surfactant-rich phase.

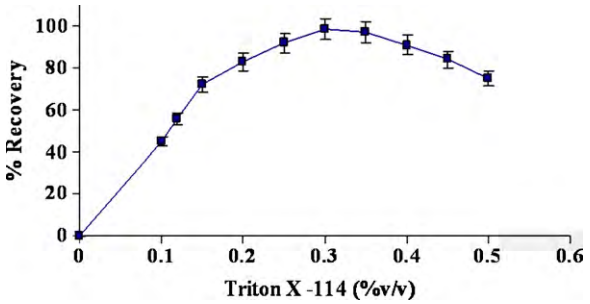

Fig. 2. Effect of Triton X-114 on the recovery efficiency: 10 μg/L of V, 6.90×10^{-2} mol/L oxine, pH 4.0, temperature 45 °C, stirring time 20 min.

3.1.3. Effect of oxine concentration

Different amounts (0.2–1.0 mL) of 6.9×10^{-2} mol/L oxine solution, corresponding to a concentration range from 0.552×10^{-3} to 2.76×10^{-3} mol/L, were added to replicate sub-samples of DS and PS, spiked with 10 μg/L of V solutions. The extraction procedure was carried out with a Triton X-114 concentration of 0.3% (v/v), at optimum pH value. As shown in Fig. 3, 0.5 mL of 6.9×10^{-2} mol/L oxine (corresponding to a concentration of 1.38×10^{-3} mol/L) was sufficient for complete extraction and the excess of oxine did not affected the extraction efficiency. The same procedure (with 0.5 mL of 6.9×10^{-2} mol/L oxine solution) was applied to 20, 50 and 100 μg/L of V solutions, diluted with acidic ethanolic solution 2, 5 and 10 times, respectively. The signals obtained were all identical with those of the 10 μg/L solution, showing that 0.5 mL (1.38×10^{-3} mol/L) of oxine solution is sufficient for the determination of V up to a concentrations at least 100 μg/L.

3.1.4. Effect of time and temperature

The reaction takes about 40 min to be completed at room temperature, but the rate can easily be increased by heating. While subjected to heating in ultrasonic bath. It was important to employ the shortest equilibration time and the lowest possible equilibration temperature, as a compromise between completion of extraction and efficient separation of phases. The dependence of extraction efficiency upon equilibration temperature and time was studied within the range of 25–60 °C and 5–30 min, respectively. It was found that and equilibration time of 20 min and temperature of 45 °C are the optimal conditions for achieving quantitative extraction.

3.1.5. Evaluation of centrifugation time

The effect of centrifugation time upon extraction efficiency was studied in the range 2–10 min. A centrifugation time of 6 min at 3500 rpm was selected as optimum; since complete phase separation occurred at the end of this period and no considerable enhancement was observed for longer times.

3.2. Interference

Experiments were performed to discover the degree to which the proposed method is affected by the presence of elements known to interfere with the formation of the V-oxine complex or with the determination of V by ETAAS, including those forming refractory compounds at high temperatures. The elements studied were Al, Ba, Ca, Fe, Mg, Cr and Mo. Interference was defined as being significant if a change of more than 10% in the measurements was observed. Experiment conducted using a 5 μg/L V solution met no interference from a 2000-fold excess of Ca^{2+}, $Mg^{2+}$and Ba^{2+}, a 400-fold excess of Zn^{2+}, Cd^{2+}, Ni^{+2}, Pb^{2+}, a 300-fold excess of $A1^{3+}$ and a 200-fold excess of Mo^{3+}, Cr^{3+} and Fe^{3+}. The levels of these

Table 1
Effect of the interferences ions on the recoveries of Vanadium ion in PS, DS and PF samples.

Ions	Tolerable value (μg/L)	%Recovery of V
Ca^{2+}, Mg^{2+}, Ba^{2+}	2000	98.6
Zn^{2+}, Cd^{2+}, Ni^{2+}, Pb^{2+}	400	98.5
Al^{3+}	300	98.4
Mo^{3+}, Cr^{3+}, Fe^{3+}	200	98.5
CO_3^{2-}, F^-, SO_4^{2-}, Cl^-, PO_4^{3}	500,000	98.8

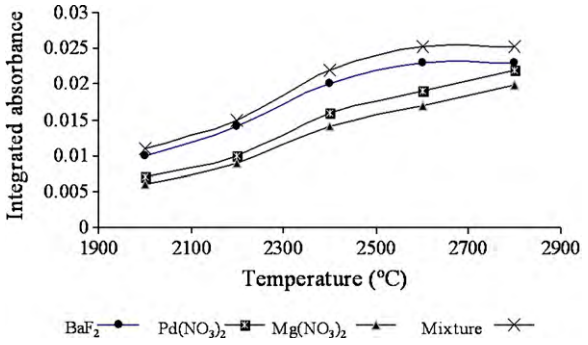

Fig. 4. Integrated absorbance values of standard solution of V (10 μg/L) after CPE with different chemical modifiers at various atomization temperature.

elements in the understudy pharmaceutical samples are less than those necessary to produce interference. On the other hand, anions such as CO_3^{2-}, F^-, SO_4^{2-}, Cl^- and PO_4^{3-} could be tolerated up to at least 500,000 μg/L (Table 1). The levels of these elements in the understudy pharmaceutical samples are less than those necessary to produce interference. As reported in our previous work the levels of Al in understudy pharmaceutical samples was found in the range of 0.65–43.3 μg/L [43–44]. Commonly encountered matrix components such as alkali and alkaline earth elements generally do not form stable complexes and are not extracted in the proposed system.

3.3. Matrix modifiers

Vanadium is a refractory element; meanwhile it is a carbide-forming element, and its atomization is carried out at very high temperatures in the graphite tube. The atomization efficiency could be obviously improved by increasing the atomization temperature, but at the same time, the deterioration of graphite tube occurred and frequently changes of graphite tubes were required. For improving of V signal, different modifiers, $Mg(NO_3)_2$, $Pd(NO_3)_2$, BaF_2 and mixtures of $Pd(NO_3)_2$ and BaF_2 (1:1) were tested. Fig. 4 shows that the use of BaF_2 as chemical modifier was more efficient than that of the other two modifiers. The positive effect on sensitivity is probably caused by the formation of volatile compounds between vanadium and fluoride [45]. The maximum experimental atomization temperature ensuring optimum sensitivity with BaF_2 was obtained at 2600 °C, and further increase of the temperature did not improve the absorbance values. In the other cases, the optimum signal was obtained at temperatures up to 2800 °C. The highest attainable temperature in the furnace is 3000 °C. Integrated absorbance values were enhanced with 5–10%, when mixture of $Pd(NO_3)_2$ and BaF_2 was injected with standards and samples into the furnace. The ashing step (1500–1600 °C) was not significantly influenced by the investigated modifiers, but the intensity of the signal clearly increased in the atomic curve, and an atomization temperature of 2800 °C was selected. For subsequent work, mixture of two modifiers ($Pd(NO_3)_2$ and BaF_2) was used.

3.4. Calibration and sensitivity

The calibration graph using the preconcentration system (CPE) for V was linear with a correlation coefficient of 0.998 at 2–50 μg/L. The slope value obtained by least-square regression analysis of calibration curves based on peak area measurements. The equation ($n = 5$) for the calibration curve was linear: $y = (0.013 \pm 0.0002[V] + (0.0026 \pm 0.0001)$. Where y is integrated absorbance, [V] is the V concentration in μg/L. The detection limit (DL), calculated as the amount of V required to yield a signal-to-noise ratio of (3σ)) was 42 ng/L. The proposed method was used for analyzing nine sub-samples of PF, DS and PS, the average quantity of V obtained being taken as a base value. Then standard additions method was applied by separately spiking the sub-samples of DS and PS with 2.0, 5.0 and 10 μg/L of V, prior to CPE (Table 2).

The enrichment factor of CPE was 125, as the original volume was 50 mL and the final volume was 0.4 mL. The relative standard deviation (%RSD) for nine replicates of a DS and PS samples spiked with 2–10 μg/L of V for CPE was found in the range of 4.39–5.95% and 4.41–7.75%, respectively.

3.5. Determination of vanadium in PF, DS and PS

To evaluate the analytical applicability of the method, the recommended procedure was used for the determination of V in pharmaceutical formulation (PF), dialysate solution (DS) and parenteral solution (PS). The standard additions method was used, and each sample was checked three times.

The concentration of V in PF, DS and PS was found in the range of 10.5–15.2, 0.65–1.32 and 1.76–6.93 μg/L, respectively (Table 3). The results obtained in PS are in good agreement with those reported by Pluhator-Murton et al. [12] and by Wuilloud et al. [27], the mean values of V concentration reported in parenteral solutions by these authors being 5.5 and 0.45–8.82 μg/L, respectively.

Table 2
Validation of cloud point extraction of vanadium by standard addition method in a dialysate and parenteral solutions samples using electrothermal atomic absorption spectrometry (ETAAS).

	Added (μg/L)	Found $x \mp s$	Paired t test[b] $t_{Experiment}$
Dialysate concentrate ($n = 6$)	0	1.21 ± 0.07	0.324
	2	3.16 ± 0.14 (98.6%)	0.368
	5	6.14 ± 0.23 (99.0%)	0.421
	10	11.07 ± 0.48 (98.8%)	0.415
Parenteral solution ($n = 6$)	0	2.41 ± 0.18	0.318
	2	4.34 ± 0.21 (98.5%)	0.278
	5	7.32 ± 0.28 (98.8%)	0.219
	10	12.23 ± 0.54 (98.6%)	0.272

Values in parenthesis ( ) are %Recovery.
[a] Mean ± standard deviation.
[b] $t_{certical} = 2.28$ at 95% confidence limit ($n = 6$).

Table 3
Determination of vanadium in parenteral solutions, dialysate solutions and Pharmaceutical formulations (μg/L).

Samples	Packing	Concentration of V (μg/L)
[a]Parenteral solutions		
PS1	Plastic	3.62 ± 0.38
PS2	Plastic	2.41 ± 0.25
PS3	Glass	1.76 ± 0.19
PS4	Plastic	9.12 ± 0.95
PS5	Plastic	5.89 ± 0.63
PS6	Plastic	4.87 ± 0.50
PS7	Glass	6.93 ± 0.72
[b]Dialysate solutions		
DS1	Plastic	0.82 ± 0.02
DS2	Plastic	1.32 ± 0.04
DS3	Plastic	1.21 ± 0.06
DS4	Plastic	0.65 ± 0.09
DS5	Plastic	0.84 ± 0.05
[c]Pharmaceutical formulations		
Sodium bicarbonate	Glass	12.8 ± 1.32
Sodium heparin	Glass	14.5 ± 1.56
Vitamin solution	Glass	10.5 ± 1.13
Human albumin	Glass	15.2 ± 1.53
Amino acid 10%	Glass	11.3 ± 1.14

[a] Matrixes composition: Na^+ 140–150 meq L^{-1}; K^+ 1.6–2.2 meq L^{-1}; Ca^{2+} 3–4.2 meq L^{-1}; Mg^{2+} 1.5–2.5; Cl^- 100–125 meq L^{-1}.
[b] Matrixes composition: Na^+ 145–172 meq L^{-1}; K^+ 1.3–1.8 meq L^{-1}; Ca^{2+} 2.7–3.4 meq L^{-1}; Cl^- 149.5–170 meq L^{-1}.
[c] Matrixes composition: Na^+ 142–146 meq L^{-1}; K^+ 1.4–1.56 meq L^{-1}; Ca^{2+} 3–4 meq L^{-1}; Cl^- 102–110 meq L^{-1}; Mg^{2+} 1.5–2 meq L^{-1}, acetate and citrate 35–55 meq L^{-1}.

The V compounds have been proven to be associated with various implications in the pathogenesis of some human diseases and also in maintaining normal body functions [46]. When V was administrated through parenteral route, 10% of the V was found in the feces of humans and rats [47,48]. The effects of V administration persist even after V has been withdrawn for several days [49]. Hoskawas et al., has been investigated the correlation of trace toxic elements in dialysate solution and complications in renal failure patients undergone more than two times hemodialysis in a week, which results to increased concentration of these elements in body fluids. They also recommended that the levels of non-essential elements must be low in dialysate solutions [50]. Based on data in the literature [51–53] and because in our study the preparation of the samples was carried out in the presence of air, we preliminary supposed V to exist almost exclusively in the +5 oxidation state (vanadate form).

4. Conclusion

CPE behavior of V was investigated, by using oxine and Triton X-114. The preconcentration method allows V determination in parenteral solutions, pharmaceutical formulation and dialysate samples at a concentration level as low as 42 ng/L, with good accuracy and reproducibility. The method was verified with real samples and it was proven satisfactory for the determination of trace levels of V in a variety of pharmaceutical samples matrixes. Also, it is possible to obtain a better limit of detection by extraction of V from large volumes of sample solution and diluting the surfactant-rich phase to a smaller volume, since the V-oxine complex was quantitativly extracted, and an enrichment factor of 125-fold was obtained. The great variability among the investigated samples, obtained from different manufacturers and different batches, suggests that the contamination takes place during manufacturing. Thus, the production of these medicines in pharmaceutical laboratories calls for very strict quality control, because they are injected directly into the blood stream at high volumes.

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