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Single-step procedure for trace element determination in synovial fluid by dynamic reaction cell-inductively coupled plasma mass spectrometry

Franco Moyano [a], Ernesto Verni [a], Héctor Tamashiro [b], Silvia Digenaro [b], Luis D. Martinez [a], Raúl A. Gil [a,*]

[a] Instituto de Química de San Luis (CCT-San Luis), Área de Química Analítica, Facultad de Química Bioquímica y Farmacia, Universidad Nacional de San Luis, Ejército de Los Andes 950, 3ª Bloque, San Luis, Argentina

[b] Laboratorio de inmunopatología del IMIBIO (CCT-San Luis), Facultad de Química Bioquímica y Farmacia, Universidad Nacional de San Luis, Ejército de Los Andes 950, 1ª Bloque, San Luis, Argentina

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ABSTRACT

A fast and single-step procedure for the dissolution of human synovial fluid in formic acid and further determination by dynamic reaction cell-inductively coupled plasma mass spectrometry (DRC-ICPMS) with a high-efficiency sample introduction system was developed. The samples were collected, treated and analyzed in the same screw-capped tubes. In order to overcome the effect of considerable carbon content, the sample introduction, nebulization and ICP operating conditions were carefully optimized. Furthermore, DRC technology with CH_4 as reaction gas was used for the elimination of spectral interferences due to polyatomic ions. The effect of the sample matrix was evaluated and mitigated through comparison of direct calibration against aqueous standards, direct calibration in formic acid media and analyte addition calibration. The recommended procedure involved low dilution and low detection limits (from 0.003 μg L^{-1} for U to 13.3 μg L^{-1} for Ti) with adequate precision (from 0.6% for Co to 6.6% for Ti). The proposed method was successfully applied to determine 16 trace elements in concentrations from 0.03 μg L^{-1} (Cd) to 88.2 μg L^{-1} (Cu) in human synovial fluid samples.

1. Introduction

Trace element determination in body fluids is a routine protocol in clinical laboratories specialized in nutritional diagnosis and toxicology of chemical elements. Atomic absorption spectrometry (AAS) is still the dominant analytical technique used for trace element analysis [1,2]. Inductively coupled plasma optical emission spectrometry (ICP-OES) has also been employed to analyze biological and clinical samples [3–5]. However, more and more clinical laboratories are transitioning away from flame (FAAS), and Electrothermal AAS (ETAAS) methods toward those based on inductively coupled plasma mass spectrometry (ICPMS) [6]. Moreover, ICPMS has some distinct advantages, including sequential multielement measurement capability with very low detection limits; thus, this technique is suitable for biomonitoring studies [7,8].

Some trace elements are cofactors of enzymes in the organism and despite the fact that they are found at trace levels in the body, deficiencies of them could cause serious problems. Two general types of abnormality associated with trace elements are encountered: one is a result of a specific deficiency from dietary inadequacies and the second is abnormality related to other diseases [9,10]. Both kinds of abnormality can be diagnosed by analyses of trace elements in plasma or other tissues. For instance, secondary changes of trace elements that occur in inflammatory and non-inflammatory arthritis were studied since the 1970s, but the causes are not known [9]. In recent years, a great number of studies have investigated the possible role of trace elements in the etiology and pathogenesis of rheumatoid arthritis (RA) [11]. As seen in the literature, the alterations in trace element concentrations in the synovial fluid of patients with RA are inconsistent and, to our knowledge, there are no available reports of the profile element in these patients.

Sample preparation is a critical step of any analytical procedure, and despite all recent advances, it still requires further improvement to reach the same high standards of the instrumental techniques required for accurate determination [12]. Wet decomposition is among the most used methodologies for biological sample treatment. However, it is time consuming, can require high amounts of corrosive and toxic reagents that increase the cost of the analyses, and can cause sample contamination [12]. Besides, the high temperature frequently reached during the procedures can cause losses of the most volatile elements. More recently, microwave-assisted sample dissolution has been employed extensively for shortening the time required for sample dissolution, as well as to avoid analyte losses and contamination. Although microwave ovens of different designs are widely used in the analytical laboratories throughout the world, some problems which are not commonly described have arisen, e.g. high instrumentation costs, short lifetime of the digestion vessels operated at high pressures, long time required for cooling the digestion, sample throughput is not very high and the constant supervision required, among others [13].

As an alternative to the decomposition process, the solubilization with organic reagents, such as primary amines and tetramethylammonium

* Corresponding author.
E-mail address: ragil@unsl.edu.ar (R.A. Gil).

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hydroxide (TMAH), has been proposed [14]. This treatment was applied with success to the determination of many elements in several samples by electrothermal atomic absorption spectrometry (ETAAS) [15–17], inductively coupled plasma optical emission spectrometry (ICPOES) [18], and inductively coupled plasma mass spectrometry (ICPMS) [12,19]. Recently, the use of formic acid (FA) as an alternative to TMAH has been suggested. However, it is not reliable introducing organic samples using the conventional cross-flow nebulizer and the double-pass Scott-type spray chamber, since the carbon loading may extinguish the plasma and/or may form carbon deposits on the cones and lenses [12]. Spectral interferences by carbon polyatomic ions are also a problem [20–22]. Some special sample introduction systems have been used to analyze organic samples, such as electrothermal vaporization (ETV), microconcentric nebulizers (MCN) [12,23–25], ultrasonic nebulization (USN) coupled to desolvation [26–28] and using oxygen as auxiliary gas [26,29]. New micromisting systems as used in this work are able to generate a stable fine mist spray allowing the formation of very low currents with a very good stability ICPMS.

In recent years, collision cells (CC) and dynamic reaction cells (DRC) have been increasingly used in ICPMS to reduce interferences in single-element, and multielemental analysis [30–32]. The DRC technology exploits ion–molecule reactions using a variety of reaction gasses. For instance, O_2 has been used to solve the interference of $^{40}Ar^{35}Cl^+$ over $^{75}As^+$ in high chlorine containing samples through the formation of $^{35}As^{16}O^+$ [33–35]. Other examples are the use of NH_3 for Fe determination in samples containing high Ca amounts [14,36,37], and the use of CH_4 to overcome the interference of the dimmer $^{40}Ar^{40}Ar^+$ over ^{80}Se [34,36,38].

In this work a fast and simple solubilization procedure with formic acid is proposed for the first time for the determination of 16 elements in synovial fluid samples in order to avoid issues related to sample preparation. The samples were treated with FA in the same tubes they were taken and analyzed by DRC-ICPMS with CH_4 as reaction gas. The goal of this method is offering a fast profiling tool to identify some marker trace elements associated with a specific physiological state by measuring Li, Mn, Co, Ni, Cu, Zn, Se, Sr, Cd, Ba, Tl, Pb, U, Ti, V and As and in human synovial fluid.

2. Material and methods

2.1. Instrumentation

An inductively coupled plasma mass spectrometer, PerkinElmer SCIEX, ELAN DRC-e (Thornhill, Canada) was used. The argon gas with minimum purity of 99.996% was supplied by Air Liquide (Córdoba, Argentina). An HF-resistant and high performance Teflon Nebulizer model PFA-ST, was coupled to a quartz cyclonic spray chamber with internal baffle and drain line cooled with the PC^3 system from ESI (Omaha, NE, USA) (Table 1).

Tygon black/black 0.76 mm i.d. and 40 cm length peristaltic pump tubing was used. The instrument conditions were: auto lens mode on, peak hopping measure mode, dwell time of 50 ms, 15 sweeps/reading, 1 reading/replicate, and 3 replicates. Nickel sampler and skimmer cones were used. Before changing to the microconcentric nebulizer, a performance check for sensitivity and oxide and doubly charged ion formation, using a conventional cross flow nebulizer and a Scott spray chamber was carried out (Table 1).

2.2. Reagents and samples

The used water was distilled and de-ionized, with a resistivity of 18.2 MΩ cm, produced by an Easy pure RF system from Barnstead (Dubuque, IA, USA). Concentrated nitric acid (65%v/v) from Sigma-Aldrich (Germany), tetramethylammonium hydroxide pentahydrate from Sigma-Aldrich (USA), dimethylformamide from Acros Organics (New Jersey, USA), and formic acid (98–100%v/v) from Fisher Scientific (Loughborough, Leicestershire, UK), were used. Multi-element calibration standard solution 1 containing 10 mg L^{-1} of Ag, Al, As, Ba, Be, Bi, Ca, Cd, Co, Cr, Cs, Cu, Fe, Ga, In, K, Li, Mg, Mn, Na, Ni, Pb, Rb, Se, Sr, Tl, U, V and Zn in 5% HNO_3, multi-element calibration standard solution 5 containing 10 mg L^{-1} of B, Ge, Mo, Nb, P, Re, S, Si, Ta, Ti, W and Zr in 5% HNO_3, Hg standard solution with 10 mg L^{-1} in 5% HNO_3, and setup/mascal solution from PerkinElmer Pure Plus, Atomic Spectroscopy Standard (Norwalk, USA), were used.

The analyzed sample was human synovial fluid taken previously from people with arthritis or evidence of disease by physician rheumatologists. The collected samples have been available after the relevant consents.

Table 1
Instrument settings and data acquisition parameters for DRC-ICP-MS.

Instrument	ELAN DRC-e (PerkinElmer SCIEX, Thornhill, Canada)
Sample uptake rate (μL min^{-1})	200
Sample introduction	Nebulizer model PFA-ST, coupled to a quartz cyclonic spray chamber with internal baffle and drain line, cooled with the PC^3 system from ESI (Omaha, NE, USA)
RF power (W)	1200
Gas flow rates (mL min^{-1})	Nebulizer, 0.77
Interface	Ni cones (sampler and skimmer)
DRC gas	Reaction gas CH_4
Standard mode	^{7}Li, ^{55}Mn, ^{59}Co, ^{60}Ni, ^{63}Cu, ^{66}Zn, ^{82}Se, ^{88}Sr, ^{111}Cd, ^{138}Ba, ^{205}Tl, ^{208}Pb, ^{238}U
DRC mode	^{47}Ti, ^{51}V, ^{75}As
Scanning mode	Peak hopping
Dwell time (ms)	50 in standard mode
Number of replicate	3

2.3. Analytical procedure

The samples (about 250 μL) collected in 15-mL polyethylene tubes from SARSTEDT AG & Co. (Nümbrecht, Germany) were added with 250 μL of the formic acid, and the mixture was hand shaken vigorously. In the sequence, the flask was kept at 90 °C in a water bath for 30 min. Then, the volume was completed to 2.5 mL with water and nitric acid to a final concentration of 1% v/v, obtaining transparent solutions. Spiked samples were also processed with this procedure to evaluate the recoveries. For the external calibration against aqueous standards, the standard solutions were prepared in 1%v/v nitric acid. For the calibration in the organic medium, the solutions were prepared in 10%v/v FA (discussed in Section 3.2) and 1%v/v nitric acid. The concentrations of the analytes were 5.0, 10, 20, 40, 80 and 100 μg L^{-1}. As internal standard, Rh was added to all solutions, including the samples, to a 20 μg L^{-1} final concentration.

3. Results and discussion

3.1. Effect of sample preparation and sample introduction conditions

Preliminary studies were performed to adequately dissolve HSF sample with low dilution factors and low sample handling in order to perform trace multielemental analysis. To these aims, different solubilization procedures were assayed involving formic acid, dimethylformamide and tetramethylammonium hydroxide, with and without heat.

The observation of the final solutions obtained enabled qualitative conclusions about the preferred reagent conditions. When the samples were added with TMAH (with and without heat) they remained as emulsions (turbid) and two phases appeared shortly. In the case of adding DMF (with heat), an homogeneous solution was observed, but it became turbid after several minutes. When using FA as dissolving agent, the HSF samples formed clear solutions, being clearer when heated

and remained stable for several days. Thus, the recommended procedure involved mixing the samples with small volumes of FA, requiring heating at 90 °C. Besides, since only a small amount of FA is used, this method needs relatively low sample dilution, resulting in high elemental concentrations in sample solutions for measurement. Finally, and with the aim to suit the samples with the sample introduction system (Section 2.1) of the ICPMS instrument, they were diluted 10-fold with HNO_3 solution. A clear sample of 2.5 mL was thus obtained.

3.2. Effect of formic acid on analyte sensitivity

A suitable calibration strategy must compensate the influence of the analytical sample matrix on the analyte signals for accurate analysis. Several authors [7,15] have observed that small amounts of organic compounds in the plasma can increase the nebulization and aerosol transport efficiencies. However, an increase of carbon content may cause plasma instability and carbon deposition on cones and lens [12].

A series of samples (pooled) were then prepared with the recommended procedure and the effect of carbon input on the analytes sensitivities was evaluated at different sample intake flow rates, and different desolvation temperatures, i.e. −5, 4 and 22 °C (Fig. 1). The outcome indicated that good sensitivities are obtained when the samples were introduced at 200 μL min^{-1} with the spray chamber cooled at −5 °C. The formic acid vapor pressures at −5, 4 and 22 °C were 9.6×10^{-3}, 1.7×10^{-2} and 4.4×10^{-2} atm respectively, which implies that there occurs a considerable reduction of solvent in the vapor phase at lower temperatures, allowing efficient solvent elimination in the spray chamber. The signal intensities of the analytes in terms of the formic acid content are shown Fig. 2.

3.3. Nebulizer gas flow rate and RF power optimization

The ICP operating conditions were optimized in the common way. Fig. 3 shows the analyte relative signal against the nebulizer gas flow rate for a standard aqueous solution containing the analytes with 10%v/v of formic acid. The signal intensities increased with the flow rate up to 0.77 L min^{-1}, but they declined at higher flow rates as it was expected. Consequently, a nebulizer gas flow rate of 0.77 L min^{-1} was

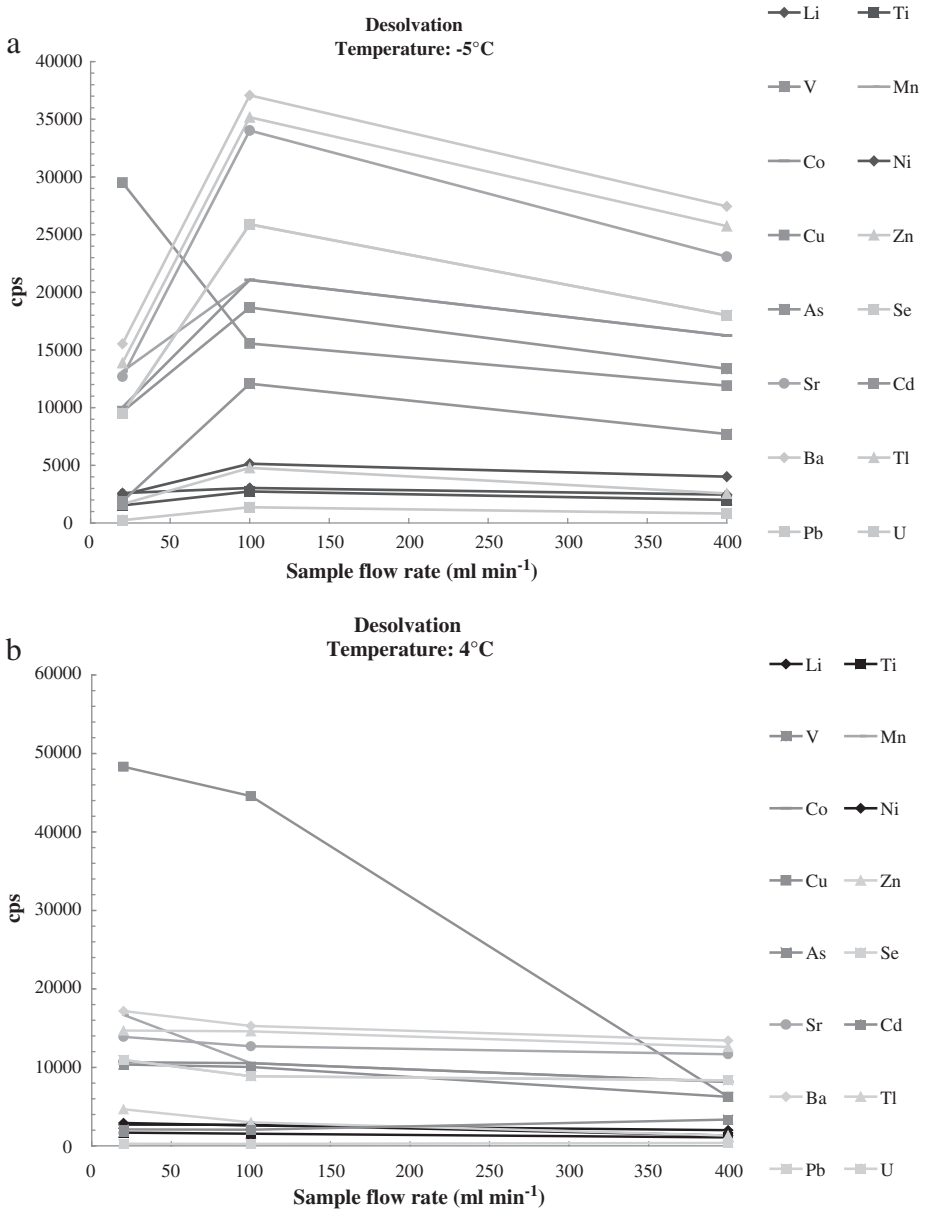

Fig. 1. Sample introduction comparing different temperatures, −5 °C (a), 4 °C (b) and 22 °C (c).

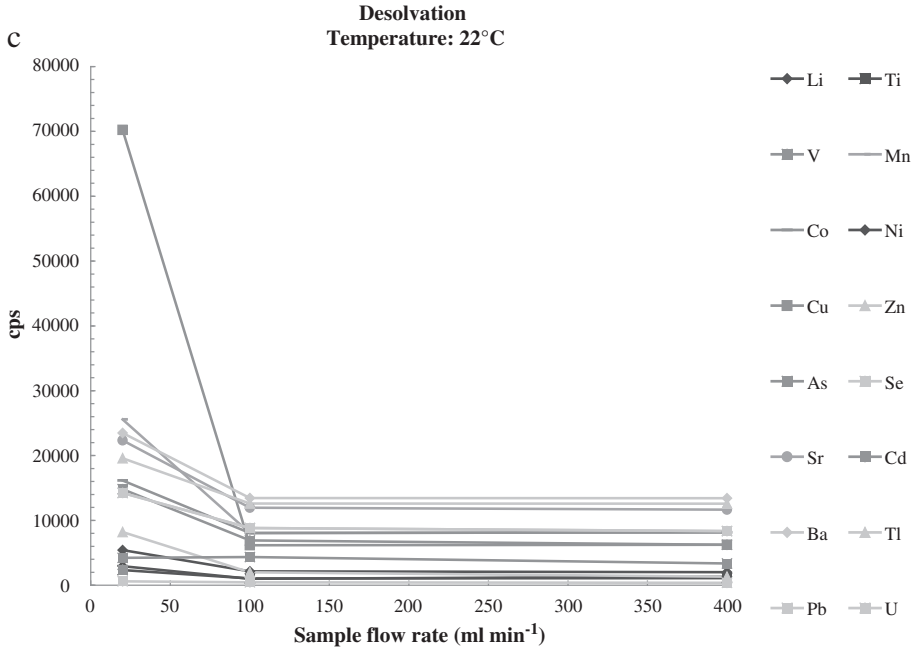

Fig. 1 (*continued*).

adopted for further experiments (Table 1). Undesirable background levels are observed for Ti and further optimization was mandatory (Section 3.4). The lesser viscosity and higher vapor pressure of the solutions (compared with pure water) may explain the lower flow rate required to reach the optimum sensitivity due to a more efficient nebulization and consequently, a more efficient analyte transport to the plasma.

On the other hand, the RF power was also evaluated, and although it was clear that powers higher than 800 W generate better sensitivities, at least 1200 W of RF power is needed in order to reach the best signals for the majority of the analytes in the standard solutions described above (Fig. 4). The decrease of the analyte signals for RF power above 1000 W is generally more intense for those elements with lower second ionization potential due to transfer effect provoked by C in the ICP.

The conditions established in this work, especially the RF power, are quite different from those indicated in other works [12] that employed conventional nebulizers to introduce organic solutions. The use of the PFA micronebulizer and the cooling system avoided undesirable effects in the ICP, and blockage of interface parts was not noticed. The use of this nebulizer allowed introducing sample solutions with a high content of organic compounds without affecting operation of the ICP-MS.

3.4. Optimization of DRC operating conditions for V, Ti and As

It is well recognized that the dynamic reaction cell can remove the argon related interferences such as Ar^+, ArH^+, CAr^+, ArO^+ and $ArAr^+$ completely, using pure CH_4 as a reaction gas [34,36,38]. Thus, CH_4 gas was investigated for the reduction of interferences on V ($^{35}Cl^{16}O^+$), Ti

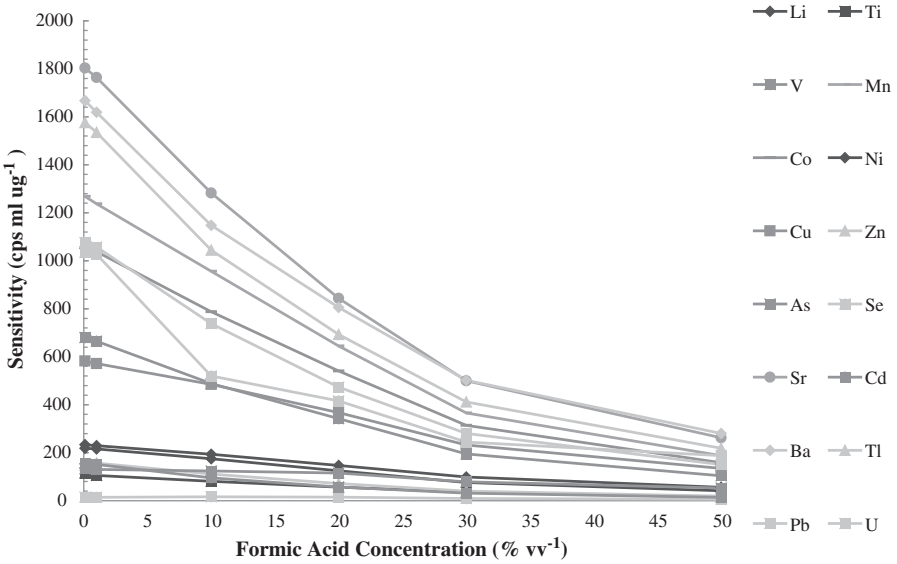

Fig. 2. Effect of formic acid content on the relative signal intensity of the analytes.

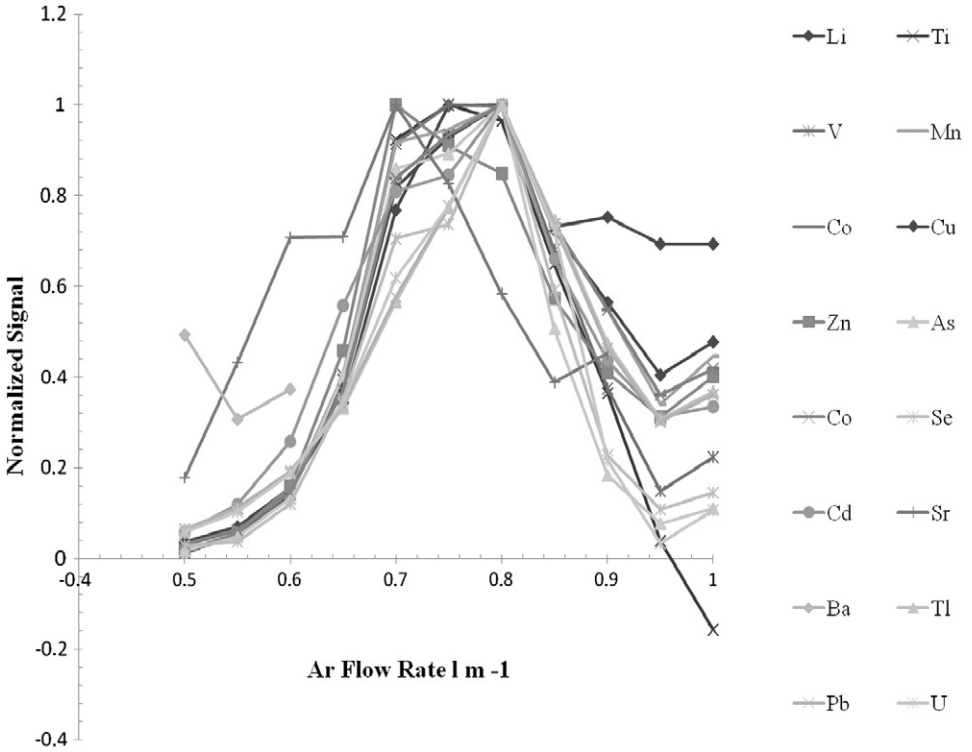

Fig. 3. Effect of the nebulizer gas flow rate on the relative signal intensity of the analytes.

($^{31}P^{16}O^+$,$^{14}N^{16}O_2H^+$, $^{32}S^{14}NH^+$) and As ($^{40}Ar^{35}Cl^+$, $^{23}Na^{12}C^{40}Ar^+$, $^{12}C^{31}P^{16}O_2^+$) generated in this particular situation.

To evaluate the DRC performance in HSF matrices for the determination of the trace elements, a series of solutions were prepared in 10%v/v FA and 1%v/v nitric acid with 50 μg L^{-1} of each element under study. The signals for the optimization solution were measured for various rejection parameter q (RPq) settings and increasing CH_4 flow rates. Since the objective was to maximize the analyte signal and suppress the background intensity, the data were evaluated as signal to background ratio (SBR) for the isotopes ^{47}Ti, ^{51}V, and ^{75}As. Fig. 5 shows the DRC optimization of CH_4 flow rate and RPq for elements in DRC mode. The outcome indicates that the best CH_4 gas flows were 0.75 mL min^{-1} for V and Ti; and 0.25 for As, as shown in Fig. 5a. The optimum bandpass of the DRC quadrupole was determined by measuring the SBR as a function of the rejection parameter q for the optimization solution. The higher value for the ratio indicates the optimum RPq that turned to be 0.8 for each element in study, as shown in Fig. 5b.

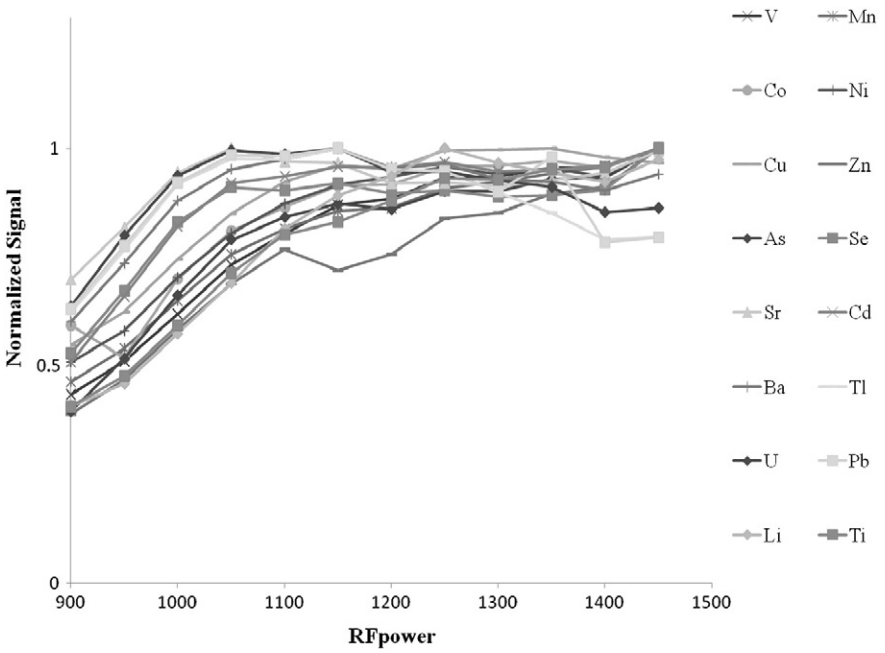

Fig. 4. Effect of the RF power on the relative signal intensity of the analytes.

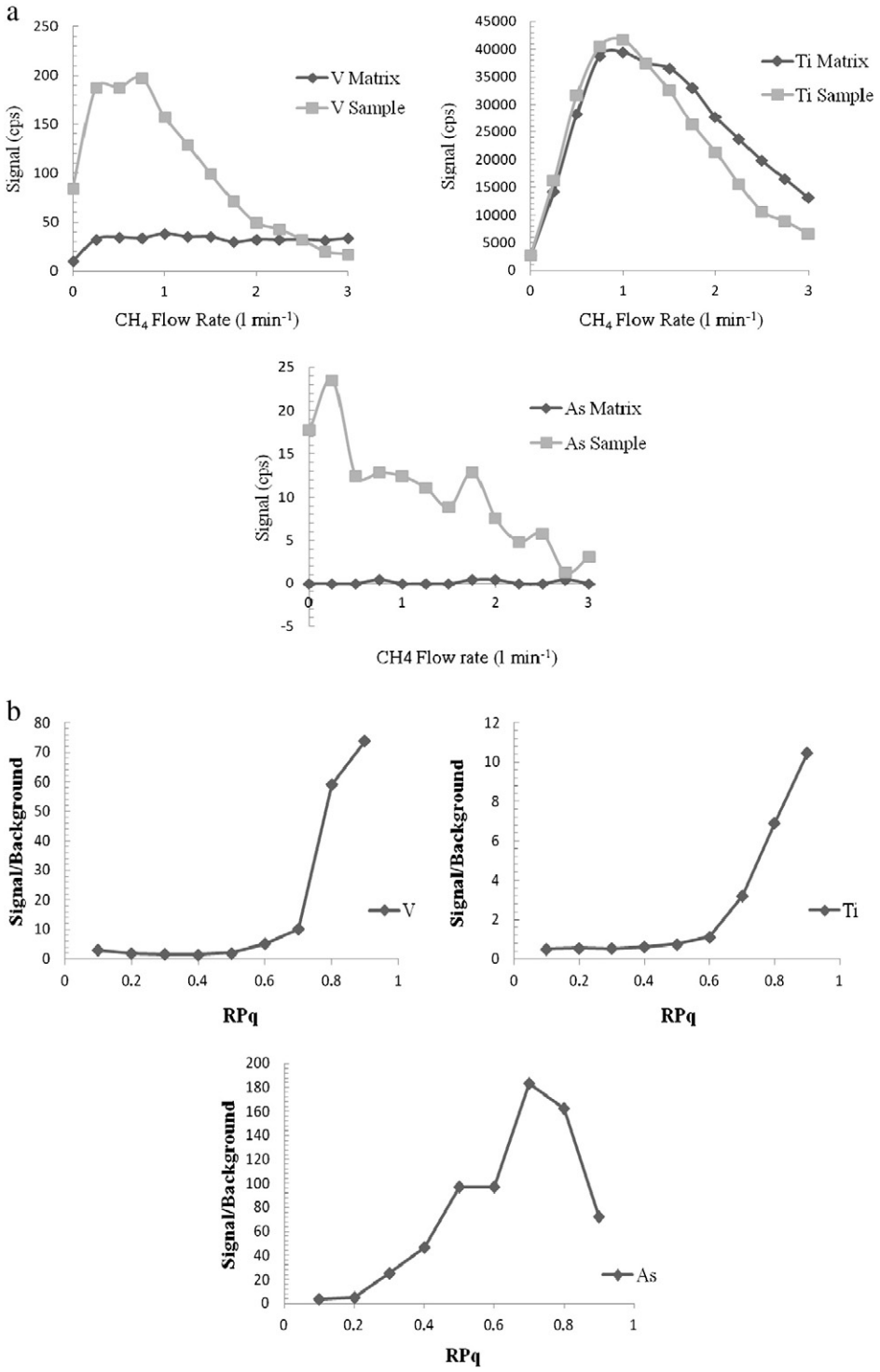

Fig. 5. DRC optimization of NH_3 flow rate (a) and RPq (b) for ^{31}P, ^{47}Ti, ^{51}V, ^{53}Cr, ^{54}Fe, ^{75}As and ^{118}Sn.

3.5. Calibration choice, analytical performance and application

As mentioned above, using a high performance introduction system with a cooled spray chamber enabled high solvent inputs to the ICP. However, it was demonstrated that the nebulization efficiency is strongly dependent on the sample composition (Section 3.2), and calibration against simple aqueous standards is not reliable. The accuracy of the results obtained with the optimized method and analyte addition calibration, was assessed through comparison (t-test, 95% confidence interval) with an independent sample treatment procedure such as microwave acid digestion in closed-vessels (Table 2).

This method involves low dilution allowing low detection limits for most analytes with adequate precision as relative standard deviation (from 0.6% for Co to 6.6% for Ti). Table 3 shows the figures of merit for the elemental determination in HSF samples treated with formic acid.

As seen in the literature, the alterations in trace element concentrations in the synovial fluid of patients with RA are inconsistent and, to our knowledge, there are no available reports of the element profile in

Table 2
Elemental profile of a pooled human synovial fluid treated with formic acid. Comparison with microwave assisted digestion approach.

Analyte	HSF treated with formic acid (μg L^{-1})[a]	HSF treated with microwave acid digestion (μg L^{-1})[a]
Li	2.8 ± 0.5	2.0 ± 0.5
Mn	0.53 ± 0.08	0.60 ± 0.01
Co	0.3 ± 0.1	0.4 ± 0.01
Ni	0.11 ± 0.02	0.10 ± 0.02
Cu	88.0 ± 1.9	90.5 ± 0.9
Zn	59.0 ± 1.1	62.0 ± 0.1
Se	4.30 ± 0.04	3.70 ± 0.04
Sr	4.5 ± 0.5	4.0 ± 0.01
Cd	0.03[b]	<LOD
Ba	5.5 ± 0.3	5.0 ± 0.5
Tl	0.10 ± 0.01	<LOD
Pb	0.20 ± 0.03	0.17 ± 0.03
U	0.04[b]	<LOD
Ti	<LOD[c]	<LOD
V	5.1 ± 0.9[c]	<LOD
As	0.7 ± 0.9[c]	0.3[b]

[a] Confidence intervals as 2 Standard Deviation (n = 3).
[b] Values between LOQ and LOD.
[c] Element in DRC mode.

these patients. Table 4 shows the element concentration assessed with this method and those reported in the work of Yazar et al. [9] where HSF was analyzed by electrothermal atomization atomic absorption spectrometry (ETAAS) after wet digestion to assess levels of Fe, Cu, Zn and Se. This new approach aims to get a multielemental mark. This allows a comprehensive study of HSF samples and to obtain better physiological outcomes.

The proposed method for solubilization with formic acid was applied to three samples collected from patients with rheumatoid arthritis (RA), and the elemental content obtained is shown in Table 5.

4. Conclusions

In this study, DRC-ICPMS was used to analyze human synovial fluid after formic acid dissolution. The use of a microconcentric nebulizer operated at low flow rate enables introducing sample solutions with high organic contents. This procedure gives a fast, precise, accurate, and less expensive sample preparation of complex matrices compared to other type of digestion, and allows high sample throughput. Furthermore, this entire procedure makes the method an attractive approach for routine analysis to identify the elemental profile of HSF generated in joint disorders. This last is of paramount importance since we are not only proposing a new strategy to analyze HSF, but also we are given new information of the global elemental composition of HSF. Future research in this field will focus to the characterization of elemental profiling in every joint disease process, thus providing biomarkers for clinical diagnosis and/or of disease evolution.

Table 3
Figures of merit for the trace element determination in HSF samples treated with formic acid.

Analyte	Mass (a.m.u.)	LOD[a] (μg L^{-1})	LOQ[b] (μg L^{-1})	RSD[c] (%)
Li	7	0.04	0.1	1.8
Mn	55	0.04	0.1	0.9
Co	59	0.1	0.05	0.6
Ni	60	0.1	0.4	0.9
Cu	63	0.1	0.4	1.3
Zn	66	0.03	0.1	1.6
Se	82	0.1	0.4	1.1
Sr	88	0.1	0.3	1.6
Cd	111	0.01	0.05	0.7
Ba	138	0.1	0.3	0.8
Tl	205	0.05	0.2	1.6
Pb	208	0.02	0.06	0.7
U	238	0.003	0.01	1.6
Ti[d]	47	13.3	44	6.6
V[d]	51	1	3	3.5
As[d]	75	0.3	0.8	4.4

[a] As three times the standard deviation of blank (n = 10).
[b] As ten times the standard deviation of the blank (n = 10).
[c] Relative standard deviation at 10 μg L^{-1} (n = 3).
[d] Measurements in DRC mode

Table 4
Comparison between pathological levels of elements in HSF and found in analyzed HSF samples (Ref. Yazar M. et al.).

Analyte	Mass	Previous data on elemental content of HSF[ra] (μg L^{-1}) [9]	Data on elemental content of HSF[ra] samples analyzed in this work (μg L^{-1})
Li	7	nd	53.4–82.1
Mn	55	nd	1.4–2.6
Co	59	nd	4.2–11.4
Ni	60	nd	10–18.2
Cu	63	5.6 ± 3.5	17.6–96.9
Zn	66	1.7 ± 0.8	47.2–66.4
Se	82	27.1 ± 11.8	3.73–5.82
Sr	88	nd	12.2–47.9
Cd	111	nd	0.38–2.95
Ba	138	nd	254.5–417.5
Tl	205	nd	0.41–0.99
Pb	208	nd	0.27–0.71
U	238	nd	0.31–0.96
Ti	47	nd	40.1–77.7[a]
V	51	nd	0.24–0.51[a]
As	75	nd	0.41–0.9[a]

[ra]Rheumatoid arthritic patients.
nd: not determined.
[a] Element in DRC mode.

Table 5
Application to real synovial fluid samples taken from patients with rheumatoid arthritis.

Analyte	HSF 1 (μg L^{-1})	HSF 2 (μg L^{-1})	HSF 3 (μg L^{-1})
Li	53.4 ± 2.5	60.5 ± 5.2	82.1 ± 2.0
Mn	1.6 ± 0.2	1.7 ± 0.1	2.4 ± 0.2
Co	4.4 ± 0.2	6.3 ± 0.3	11.2 ± 0.2
Ni	10.5 ± 0.5	13.1 ± 1.5	17.4 ± 0.8
Cu	88.4 ± 8.5	73.4 ± 5.0	27.7 ± 10.1
Zn	58.5 ± 3.5	64.9 ± 1.5	48.2 ± 1.0
Se	5.31 ± 0.51	4.33 ± 0.60	5.25 ± 0.22
Sr	46.4 ± 1.5	12.7 ± 0.5	28.8 ± 0.3
Cd	0.39 ± 0.01	2.92 ± 0.03	0.718 ± 0.08
Ba	412.48 ± 5.0	260.65 ± 5.5	275.58 ± 6.5
Tl	0.78 ± 0.06	0.45 ± 0.04	0.91 ± 0.08
Pb	0.42 ± 0.03	0.66 ± 0.05	0.28 ± 0.01
U	0.76 ± 0.02	0.36 ± 0.05	0.87 ± 0.09
Ti[a]	73.2 ± 4.5	40.1*	50.5 ± 3.5
V[a]	0.43 ± 0.02	0.25*	0.48 ± 0.03
As[a]	0.8 ± 0.1	0.4*	0.4*

* Concentration between LOQ and LOD.
[a] Elements determined in DRC mode

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