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Integrated pervaporation/detection for the determination of fluoride in pharmaceuticals

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Abstract

A selective dynamic method for the determination of fluoride in pharmaceuticals based on the integration of pervaporation and potentiometric detection in a laboratory-made module is proposed. The analyte was continuously converted into volatile trimetylfluorosilane by reaction with hexamethyldisilazane, injected into a donor stream and accepted in a basic buffer solution after pervaporation. The method thus developed has a determination range between 1.5 and 200 mg l^{-1}, precision (expressed as R.S.D.) of 3.4%, and has been applied to the determination of fluoride in different pharmaceutical products, with yields ranging between 90.6 and 100.3%. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Potentiometry; Pervaporation; Fluoride; Pharmaceuticals

1. Introduction

Miniaturisation is a subject of increasing development in analytical chemistry. At the laboratory scale, pervaporation is a microseparation technique as it involves the two general principles of miniaturisation: reduction of the equipment size and integration of different steps, as pervaporation combines both evaporation and gas diffusion in the same micromodule. A higher level of miniaturisation is involved in approaches in which detection is integrated with pervaporation [1]. When compared with gas diffusion for separation of volatile compounds, pervaporation presents as the most salient advantage the fact that the sample never enters into contact with the membrane, thus avoiding clogging or deterioration and making possible its use with solid and semisolid samples, membrane corrosive liquids and slurries [2,3].

Fluoride in pharmaceutical samples has been usually determined by ion chromatography [4–6], spectrophotometry [7–9], potentiometry [9–13] and, less frequently, by reverse phase liquid chromatography [14], thermometry [15], capillary electrophoresis [16], gas–liquid chromatography [17], and spectrofluorimetry [18]. Most of these methods involve a sample pretreatment or the use of organic solvents. Here we propose a continuous method for the determination of fluoride in phar-

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maceuticals that does not require any previous treatment of the sample. Separation and detection take place simultaneously in a pervaporation module in which a potentiometric sensor for fluoride has been placed, thus allowing monitoring of the kinetics of mass transfer through the membrane and determination of the analyte.

2. Experimental

2.1. Instruments and apparatus

One four-channel Gilson Minipuls-3 peristaltic pumps, two Rheodyne 5041 injection valve (one of them working as a selection valve) and poly(tetrafluoroethylene) (PTFE) tubing of 0.5 mm i.d. were used to build the manifold. The fluoride selective electrode (Metrohm, 6.0502.150) was fitted in the upper part of the pervaporation module faced to the acceptor side of the gas-diffusion membrane. A KCl reference electrode (Metrohm, 6.0233.100) was also used and located in a methacrylate flow-cell made in the laboratory. A PHM 64 potentiometer (Radiometer Copenhagen) coupled to a Knauer recorder was used for monitoring the potential.

A pervaporation cell designed in our laboratory [19] and PTFE membranes (47 mm diameter and 1.5 mm thickness) from Trace (Braunsweig, Germany) were used for constructing the overall dynamic manifold.

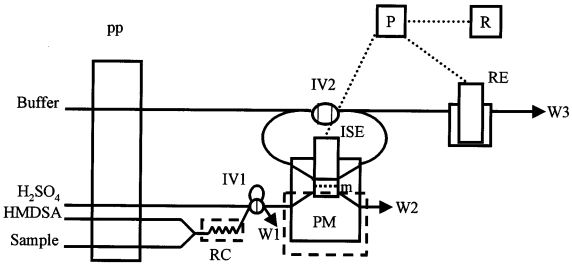

Fig. 1. Flow injection pervaporation/detection arrangement for the determination of fluoride. (pp: peristaltic pump; RC: reaction coil; IV1 and IV2: injection valves, PM: pervaporation module; m: membrane; ISE: ion-selective electrode; RE: reference electrode; P: potentiometer; R: recorder; W1, W2 and W3: waste. The dashed lines indicate thermostated zones).

2.2. Reagents

All materials and reagents were of analytical grade and ultrapure water obtained from a Millipore Milli-Q system was used throughout. Sodium fluoride (Merck) was dried at ca. 110°C for 4 h and a 10 g l^{-1} fluoride stock solution was prepared in water. Standards of different concentrations were prepared by appropriate dilution of the stock solution. The 1.5% (v/v) hexamethyldisilazane (HMDSA, Aldrich) solution was prepared daily by measuring out a volume of a 2 M H_2SO_4 solution into a flask, adding the appropriate volume of HMDSA and stirring for 5 min. After standing for 15 min, the upper organic layer was aspirated off. One and 2 M H_2SO_4 solutions were prepared by diluting the appropriate volume of concentrated acid (96%, Panreac) in water. The acceptor buffer (0.2 M Na_2HPO_4 (Merck)/0.1 M citric acid (Merck)/1 M KCl (Merck)) of pH 7.8 was prepared daily.

2.3. Sample preparation

Fluoride was determined in pharmaceuticals, namely: capsules, two toothpastes, a mouthwash and nutritional supplement. For capsules, 1 g was dissolved in 25 ml of water. In the case of the toothpaste, 0.5 or 1 g was dissolved in 25 ml of water, and 0.5 ml of ethanol was added in order to avoid foam formation. The mouthwash was 1:10 sample:water diluted, and the nutritional supplement was injected directly as such.

2.4. Manifold and procedure

Fig. 1 depicts the hydrodynamic system used. The sample or standard solution is mixed with HMDSA in acidic medium (H_2SO_4) to form the volatile derivative (trimethylfluorosilane, TMFS). The reaction takes place in a 300 cm coil thermostated at 80°C. This compound is injected through IV1 into a H_2SO_4 stream and lead to the lower part of the pervaporation cell, which is also thermostated at 80°C. During the evaporation and diffusion of the TMFS through the PTFE membrane, the acceptor buffer stream is halted for 5 min, by turning IV2 to the filling position,

Table 1
Optimisation of variables: range studied and optimum values found

Parameter	Range studied	Optimum value
KCl (in the acceptor stream, M)	1.0–3.0	1.0
HMDSA (%)	1.0–2.0	1.5
H_2SO_4 (derivatising medium, M)	1.0–4.0	2.0
H_2SO_4 (carrier, M)	0.5–2.0	1.0
Temperature[a] (°C)	60–90	80
Temperature[b] (°C)	40–80	80
Loop (ml)	100–1000	1000
Reaction coil length (cm)	100–560	300
Donor flow rate (ml min^{-1})	0.6–2.7	1.3
Acceptor flow rate (ml min^{-1})	0.6–2.4	1.3
Flow rate for the formation of TMFS (ml min^{-1})	0.5–1.8	0.5
pH of the acceptor stream	5.0–8.15	7.8
Waste length of the donor chamber (cm)	60–410	220
Waste length of the acceptor chamber (cm)	–	200

[a] Temperature for the formation of the volatile compound.
[b] Temperature for the pervaporation of the volatile compound.

and the increase of the potential due to the accumulation of fluoride in the upper part of the pervaporator, after hydrolysis of the volatile product, is monitored by the selective electrode whose active surface is faced to the acceptor side of the membrane.

3. Results and discussion

3.1. Fundamentals of the method

The analyte reacts in an acidic medium with HMDSA to yield the volatile product, according to the reaction:

$$2[(CH_3)_3Si]NH + 4HF + H_2SO_4 \rightarrow 4(CH_3)_3SiF + (NH_4)_2SO_4,$$

which evaporates and diffuses through the hydrophobic membrane to be accepted into a basic buffer solution, which allows the release of the analyte:

$$2(CH_3)_3SiF + 2OH^- \rightarrow [(CH_3)_3Si]_2O + 2F^- + H_2O$$

A fluoride-selective electrode monitors the released fluoride.

3.2. Optimisation of variables

A detailed study of variables affecting the system was performed by using the univariate method. The main variables have been studied in previous papers concerning the determination of fluoride performed in a flow-cell, integrating pervaporation and detection, as in the present work [19], or in-line with the acceptor chamber of the pervaporation unit [20]. All the variables studied and their optimum values are listed in Table 1.

3.2.1. Chemical variables

In order to choose the appropriate acceptor solution the following solutions 0.2 M Na_2HPO_4/0.1 M citric acid/1 M KCl, 0.2 M Na_2HPO_4/0.2 M NaH_2PO_4/1 M KCl, and 0.05 M $Na_2B_4O_7$/0.2 M H_3BO_3/1 M KCl, were checked. A higher analytical signal was obtained when the first buffer solution, adjusted to pH 7.8, was used, and so it was selected as optimum. Subsequently, the concentration of reagent used to form the volatile compound (HMDSA) and the acidic medium in which the reaction took place, were optimised. No increase in sensitivity was observed for concentrations of H_2SO_4 and HMDSA higher than 2.0 M and 1.5% (v/v), respectively. An increase in temperature had a positive effect on both the rate of volatile compound formation and the separation process as a consequence of a higher evaporation. A temperature of 80°C was selected for both.

3.2.2. FI variables

The injected volume had a marked influence on the analytical signal as it increased with increased volumes. One thousand μl was selected as a compromise between sensitivity and sampling frequency. The length of the reaction coil for the

Table 2
Figures of merit

Linear range (mg l^{-1})	1.5–200
Equation[a]	$Y = 10.95 + 79.58X$
r^2 (%)	99.67
Detection limit (mg l^{-1})[b]	1.1
Quantification limit (mg l^{-1})[c]	1.5
Precision (R.S.D., %)[d]	3.4

[a] Y is potential in mV; X is logarithm of fluoride concentration in mg l^{-1}.
[b] As three times S_{blank}.
[c] As ten times S_{blank}.
[d] At 50 mg l^{-1} ($n = 7$).

formation of the volatile compound affected the degree of development of the reaction. A 300-cm reaction coil was selected, as longer reactors did not improve the signal. As established in previous studies on pervaporation [1,2] the best performance of the separation unit is achieved when both the donor and acceptor streams circulate at the same flow rates. A donor to acceptor ratio equal to 1 and low flow rates provided the best results but also low sampling frequency. Both flow rates were set at 1.3 ml min^{-1}. A variable affecting the sensitivity was the length of the waste tubing of the donor chamber, as it affected the pressure in the module and therefore the free volume between the membrane and the surface of the liquid in the donor chamber. A 220 cm of waste tubing (0.5 mm i.d.) was selected as optimum, as longer lengths resulted in a loss of sensitivity, due, probably to the deterioration of the membrane by contact with the sulfuric mixture in the donor chamber. It was also necessary to place a long waste tubing in the acceptor chamber in order to increase the pressure and avoid bubbles formation that interfered in the potential measurements. A 200-cm length was sufficient (0.5 mm i.d.).

3.2.3. Pervaporation variables

After optimising the temperature and flow rates, the time necessary to obtain a stable potential measure was studied halting the flow of the acceptor stream, placing it in the loop of an injection valve. In the filling position, the flow through the system is continuous, except in the loop of the valve, where the upper chamber of the pervaporation cell is located; the flow through it is restored by switching the valve to the injection position. A 5-min stopped-flow time was enough to obtain the signal.

3.3. Features of the method

The calibration graph was obtained by triplicate injection of different concentrations of fluoride, ranging between 1 and 200 mg l^{-1}. The results obtained in terms of equation, linear range, correlation coefficient, detection and quantification limits, and precision, studied as repeatability and expressed as relative standard deviation, are listed in Table 2.

The sampling frequency was 6 h^{-1}.

3.4. Application of the method

To show the usefulness of the method, it was applied to the determination of fluoride in differ-

Table 3
Application of the method to pharmaceuticals and cosmetics

Sample	Nominal value	Found value ($n = 3$)	t[a]	Yield (%)
Capsules	0.2 mg/capsule (as F^-)	0.18 ± 0.01	3.46	90.6 ± 6.2
Mouthwash	0.05% (as NaF)	0.050 ± 0.002	0.29	100.3 ± 2.9
Toothpaste 1	0.33% (as NaF)	0.32 ± 0.02	0.96	97.1 ± 5.5
Toothpaste 2	0.8% (as Na_2PO_3F)	0.78 ± 0.04	0.79	97.5 ± 5.5
Nutritional supplement	200 μg 100 ml^{-1} (as F^-)	194.4 ± 11.5	0.84	97.2 ± 5.4

[a] t (0.05, two degrees of freedom) = 4.30.

ent pharmaceuticals, namely: capsules, a mouthwash, two different toothpaste and a nutritional supplement. Table 3 shows the nominal and found concentration values for each sample, analysed in triplicate. In order to compare both values, the t value was calculated, and no significant differences (significance level 0.05) were observed. The yields ranged between 90.6 and 100.3%.

4. Conclusions

A continuous method for the determination of fluoride in pharmaceutical samples is proposed, with results in agreement with the nominal values. Miniaturisation of the set-up for the determination of the analyte is achieved by integration of the separation and detection steps. Pervaporation avoids the pretreatment of the sample, contributing in this way to the automation of the method, which could be of great interest in the pharmaceutical industry. The potential of pervaporation for the determination of volatile compounds (either analytes or their reaction products) in the pharmaceutical field is thus demonstrated.

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References

[1] M.D. Luque de Castro, L. Gámiz-Gracia, Anal. Chim. Acta 351 (1997) 23–40.
[2] M.D. Luque de Castro, I. Papaefstathiou, Encyclopedia of Environmental Analysis and Remediation, Wiley, Chichester, UK, 1998, pp. 3462–3476.
[3] M.D. Luque de Castro, L. Gámiz-Gracia, Encyclopedia of Analytical Chemistry, Wiley, Chichester, UK, 2000.
[4] A. Tapparo, P. Pastore, G.G. Bombi, Analyst 123 (1998) 1771–1773.
[5] Y.J. Liu, G.X. Zhou, Fenxi Huaxue 21 (1993) 209–211.
[6] C. Wu, Z. Zhou, F. Luo, Q. Zhang, Yaowu Fenxi Zazhi 11 (1991) 202–206.
[7] R. Sandulescu, E. Florean, L. Roman, S. Mirel, R. Oprean, P. Suciu, J. Pharm. Biomed. Anal. 14 (1996) 951–958.
[8] P.N. Bhatt, Y.K. Agrawal, Int. J. Environ. Anal. Chem. 39 (1990) 411–415.
[9] M. Zancato, A. Pietrogrande, C. Macca, Ann. Chim. 85 (1995) 149–159.
[10] B.F. Avramovic, F.F. Gaal, Talanta 39 (1992) 511–515.
[11] J.C. Apostolakis, C.A. Georgiou, M.A. Koupparis, Analyst 116 (1991) 233–237.
[12] Q. Chen, Q. Zhang, X. Sun, R. Bai, G. Zhen, Yaowu Fenxi Zazhi 10 (1990) 217–219.
[13] A.C.C. Spadaro, D.N. Carlomagno, A.C.M. Polizello, Analyst 115 (1990) 1093–1095.
[14] S. Oszwaldowski, R. Lipka, T. Majewski, M. Jarosz, Analyst 123 (1998) 1529–1533.
[15] S. Salman, K. Haupt, K. Ramanathan, B. Danielson, Anal. Commun. 34 (1997) 329–332.
[16] K.D. Altria, D.M. Goodall, M.M. Rogan, Chromatographia 38 (1994) 637–642.
[17] A.M. Bouygues de Ferran, C. Pham Huy, M. Postaire, M. Hamon, J. Chromatogr. 585 (1991) 289–295.
[18] M.A. Raggi, Arch. Pharm. 324 (1991) 195–196.
[19] I. Papaefstathiou, M.D. Luque de Castro, Anal. Chem. 67 (1995) 3916–3921.
[20] I. Papaefstathiou, M.T. Tena, M.D. Luque de Castro, Anal. Chim. Acta 308 (1995) 246–252.