ION SELECTIVE ELECTRODE ARRAY FOR THE DETERMINATION OF BENZOATE IN THE PRESENCE OF IODIDE

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Abstract: The performance of an ion selective electrode array (ISEAR), designed for the determination of benzoate in the presence of iodide, constituted by all-solid-state electrodes with Aliquat 336 S or tetraoctylammonium salts immobilised in PVC membranes, is described. The response of the ISEAR to both ions was obtained by two treatments: (i) calculation by non-linear least squares (NLS) of the parameters of a model based on the Nikolskii-Eisenmann equation; and (ii) principal components regression (PCR). The results are compared and discussed. Results obtained in the determination of benzoate in pharmaceutical formulations containing iodide are included.

Key-words: All-solid-state ion selective electrode; ion selective electrode array (ESIAR); Benzoate; Iodide; Aliquat 336 S; Tetraoctylammonium; Nikolskii-Eisenmann equation; Principal components regression (PCR); Analysis of pharmaceutical formulations.

Introduction

Ion selective electrode arrays (ISEAR) [1], designed to compensate for the lack of selectivity of their component electrodes, are constituted by a set of ion selective electrodes (ISEs), usually in number larger than the number of species to be determined, which respond to the ions to be analysed with different selectivities. A ISEAR generates a large amount of information and there are several possibilities for processing its response, for instance, by fitting the experimental calibration data to models based upon the Nikolskii-Eisenmann equation [1,2], by treating the data by principal component regression (PCR) and partial least squares (PLS) [1], or by processing the response of the system with a neural network [3].

The applicability of direct potentiometry with ISEs to the determination of benzoate in pharmaceutical formulations is limited, because electrodes sensitive to benzoate also respond to other anions, for instance iodide, that are often also present in those formulations [4]. Effort to overcame the limitations of benzoate determination with ISEs has been oriented to the development of ISEs with more selective response [5], but using a ISEAR designed for the simultaneous determination of benzoate and iodide seems a more attractive alternative approach.

In this paper, we present preliminary results on the evaluation of the potentialities of ISEARs constituted by all-solid-state PVC membrane ISEs, with sensors based on Aliquat 336 S [6] or tetraoctylammonium (TOA) salts [4], for the determination of benzoate in the presence of iodide. The results of the ISEARs in response to both ions were obtained by two treatments: (i) calculation of the parameters of a model based on the Nikolskii-Eisenmann equation by non-linear least squares (NLS); and (ii) principal components regression (PCR). Results obtained in the evaluation of the arrays with the two data treatments as well as in their use for the determination of benzoate in pharmaceutical formulations containing iodide are presented.

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Experimental

Reagents and solutions

All the reagents for the preparation of solutions were of analytical grade (*p.a.* or equivalent). The solutions were prepared with deionised water of resistivity ≥ 4MΩ.cm.

All the reagents used for the preparation of the sensing membranes were from Fluka (Selectophore), except tetrahydrofuran (THF) wich was from Merck *p.a.*

Equipment

The calibrations were carried out with an automatic system controled by a personal computer, Prolinea 325 S. The values of potential difference were acquired with the AD converter of a Lab Master DMA (Scientific Solutions Inc.) card, through a high impedance circuit. An Orion 90.02 double junction reference electrode, with a 0.2 M sodium sulphate solution in the external compartment, was used. The electrodes were calibrated at 25 ± 0.2°C.

Construction and response characteristics of the ISEs

The all-solid-state ISEs, with PVC membranes of 6 mm diameter applied on a graphite/epoxy conductive support, were constructed by the procedure described previously [7 and references therein].

The membranes of the electrodes with the Aliquat 336 S were constituted by 33% of PVC, 7% of the ion exchanger and 60 % of dibutylsebacate. The membranes of the electrodes with TOA were constituted by 33 % of PVC, 9 % of the ion exchanger and 58 % of 2-nitrophenyl-*n*-octylether.

The electrodes were conditioned in a 0.1 M solution of sodium benzoate (benzoate ISEs), 0.1 M sodium iodide (iodide ISEs) or in a mixed solution of benzoate (0.05 M) and iodide (0.05 M) (mixed response ISEs).

Calibration curves of the ISE's in the range $2x10^{-5}$ to $2x10^{-2}$ M were obtained by titration of 20 mL of deionised water with a 0.1000 M standard solution of benzoate or iodide. Four units of each type were evaluated in paralell. The results obtained showed that ESIs with the two different ion exchangers showed similar characteristics of response in solutions whithout adjusted ionic strength: (i) the lower limit of linear response was $5x10^{-4}$ M and 10^{-4} M respectively for iodide and benzoate ESIs; (ii) the slope of response varied between -60 to -66 mV/decade for iodide and between -57 and -60 mV/decade for benzoate ISEs; (iii) the reprodutibility of the response potentials of the ISE's in consecutive calibrations in the same day was ±1 mV; and (iv) their life-time was larger than four months.

Constitution and multivariated calibration of the ISEARs

Two ISEARs were studied:

- Array 1: Three ISEs with Aliquat 336 responding respectively to benzoate, iodide and with a mixed response to both ions;
- Array 2: Similar to Array 1 but based on TOA.

For studying the performance of the ISEARs, a set of 36 solutions was used. The concentration levels of benzoate and iodide in these solutions were set accordingly to a full factorial design with six levels for each factor (benzoate and iodide) in the concentration range 1 mM to 50 mM. These solutions were prepared in a matrix of sodium sulphate 0.2 M. This set of 36 solutions was divided in two sets, each with 18 solutions, that were used for calibration (calibration set) and for testing the predictive ability of the calibration models (test set).

Calculations

The model based on Nikolskii-Eisenmann equation used Eq. 1, wich is expressed in concentrations instead of activities,

$$E_{ji} = E^{o}_{j} + s_{j} \log (C_{i}^{benz} + K_{j}C_{i}^{I}) \qquad \text{Eq.1}$$

where E_{ji} is the response potential of the ISE *j* to solution *i*, E^{o}_{j} is the reponse potential of the same ISE to a solution of benzoate 1 M, s_j is the slope of response of the ISE *j* (response potential *vs.* log of concetration of benzoate), K_j is an empirical selectivity coefficient of potentiometric response of the same ISE, and $C^{i benz}$ and C_i^{I} are respectively the concentrations of benzoate and of iodide in solution *i*. For the non-linear fitting of the data to this model [2], the Solver of Excel (version 3.0, from Microsoft) in a PC was used. Linear regression calculations for prediction of concentrations of benzoate and iodide in the samples [2] were made in a Worksheet of the same program.

For calculations by principal components regression (PCR) [8], the program Grams (Galactic) was used. The input concentration values were logarithmized.

The relative errors of prediction of the concentration values of iodide and benzoate in the test set samples were used to evaluate the predictive ability of the calibration models. They were calculated by,

$$\text{Error} = (|C_{pred} - C_{exp}| / C_{exp}) * 100 \qquad \text{Eq.2}$$

where C_{pred} is the concentration value predicted by the model and C_{exp} is the expected concentration in the test sample.

Results and discussion

Model based upon the Nikolskii-Eisenmann equation

The results obtained in the calculation of the model parameters for the ISE's (see Table 1) show that the slopes of response (s_j) of all of the ISEs are low, probably due to the high background concentration of sodium sulphate used. This is suggested by a decrease of slope when the electrodes were calibrated in 0.2 M sodium sulphate background. The values of the empirical selectivity coefficients (K_j) calculated show that ISEs based on TOA have a more selective response to benzoate than those based on Aliquat 336 S.

Table 1- Parameters of response of ISEs obtained by non-linear fitting of the data to Eq. 1[1].

ISE	R	K_j	s_j (mV/dec.)	E_j^{o}(mV)
Aliquat (Benzoate)	-0.969	22	-46.98	94.35
Aliquat (I^-)	-0.972	27	-47.59	-48.24
Aliquat (Benzoate/I^-)	-0.969	30	-46.34	-23.47
TOA (Benzoate)	-0.904	2	-40.41	-31.06
TOA (I^-)	-0.985	2	-46.26	80.39
TOA (Benzoate/I^-)	-0.852	1	-24.69	11.02

1) Model parameters of Eq 1; Correlation coefficient for 18 data points.

A comparative analysis of the ranges of the K_j values also shows that the Aliquat based ESIs have larger differences in their selectivity of response to benzoate, with K_j values in the range 22 to 30, than for TOA, with K_j values in the range 1 to 2. This information on the selectivity of response of the electrodes is crucial for the design of the ISEARs because the ideal component for electrode arrays is sensitive to only a few of the present analytes but in varying degrees [2]. As expected, Array 1, which is constituted by the three Aliquat electrodes, showed better predictive ability of the concentration of benzoate and iodide in the test set samples than Array 2. The relative errors of prediction of the concentrations by Array 1 are summarized in Table 2 and show that it is possible to determine benzoate in the 10 to 50 mM concentration range with relative errors lower than 10 %, provided that the concentration of benzoate in the samples is ten fold higher than the concentration of iodide (Table 2.A). Results in Table 2.B show that it is not possible to determine iodide without large relative errors.

Table 2 - Relative errors (%) of prediction[1] of concentration of benzoate (A) and iodide (B) in the test set samples by NLS (Eq. 1).

	A	Benzoate (mM)					B	Benzoate (mM)				
Iodide (mM)	1.0	2.0	5.0	10.0	20.0	50.0	1.0	2.0	5.0	10.0	20.0	50.0
1.0	-	117	-	7.3	-	3.3	-	33.8	-	38.2	-	21.3
2.0	227	-	20.9	-	4.8	-	8.5	-	2.1	-	5.0	-
5.0	-	47.1	-	20.7	-	2.1	-	21.2	-	28.1	-	26.9
10.0	2750	-	28.9	-	23.2	-	11.9	-	24.8	-	20.8	-
20.0	-	7879	-	313	-	56.4	-	188	-	46.2	-	51.4
50.0	32451	-	2415	-	198	-	29.3	-	24.8	-	27.1	-

1) Calculated by Eq. 2.

Results obtained in similar experiments with Array 2 showed that in this case the relative errors of prediction of benzoate and iodide concentrations were always large, in the range 10 to 60 %.

Principal component regression (PCR)

Calibration models based on PCR [8] are advantageous because they allow to minimize effects due to drift of response. One of the most difficult tasks in PCR is determining the correct number of factors in the calibration model. It is very important to define a model that contains enough factors to model the components of interest properly (benzoate and, if possible, iodide, in the present case), without adding too much contribution from noise. Based on this idea the function PRESS [8], (prediction residual error sum of squares) was used to determine the optimum number of factors. The representation of the PRESS function *vs.* the number of factors in the model for Array 1 is presented in Fig.1 and shows that the number of factors for the calibration model is 2.

The representation of predicted concentration values in the calibration set *vs.* input concentration values for Array 1 is in Fig.2 and shows some dispersion of the data. However, the results of prediction of concentration values in the test set (see Table 3) show that in the concentration ranges of 10 to 50 mM benzoate and 1 to 10 mM iodide, the relative errors are larger than those obtained with the previous model (Table 2), probably due to the logarithmic transformation of the concentration data.

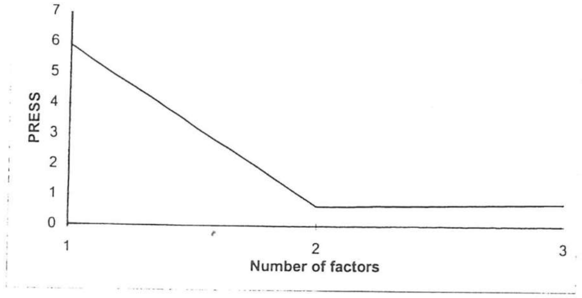

Fig.1 - PRESS function *vs.* the number of factors in the PCR calibration model for Array 1.

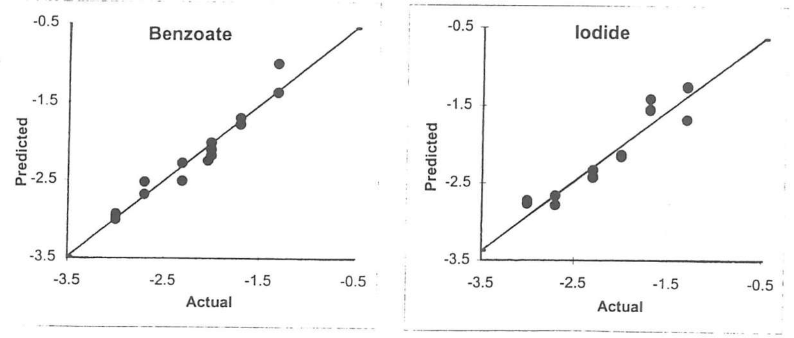

Fig.2 - Predicted concentration values in the calibration set *vs.* input concentration values for the calibration model of Array 1.

Table 3 - Relative errors (%) of prediction[1] of concentration of benzoate (A) and iodide (B) in the test set samples by PCR.

	A	Benzoate (mM)					B	Benzoate (mM)				
Iodide (mM)	1.0	2.0	5.0	10.0	20.0	50.0	1.0	2.0	5.0	10.0	20.0	50.0
1.0	-	8.5	-	39.0	-	18.8	-	37.9	-	59.0	-	182
2.0	2.0	-	19.2	-	35.2	-	1.9	-	1.0	-	33.8	-
5.0	-	55.8	-	3.5	-	20.7	-	25.9	-	27.6	-	3.9
10.0	26.9	-	6.5	-	19.6	-	26.4	-	28.0	-	16.7	-
20.0	-	9.0	-	17.7	-	1.0	-	151	-	36.7	-	59.5
50.0	12.6	-	17.3	-	20.3	-	1.8	-	12.9	-	22.1	-

1) See footnote on Table 2.

Determination of benzoate in pharmaceutical formulations containing iodide

Array 1 was used for the determination of benzoate in pharmaceutical formulations containing iodide. The results obtained in these determinations, based on the model based on Eq.1, are summarized in Table 4 and show that the relative errors of the determination are much lower than those reported by Lima *et.al.* [5] for the determination of benzoate by direct potentiometry, which fell in the range 50 to 300 %.

Table 4 - Determination of benzoate in pharmaceutical formulations containing iodide.

	Concentration (g/100 ml)		
	Nominal	Found [1]	Error (%)
Fluidin Adulto	1.0 [2]	0.93 ± 0.01	6.6
Fluidin Antiasmático	1.0 [3]	0.88 ± 0.03	12.1

1) Average of three determinations with standard deviation; 2) Iodide concentration in the syrup: 13 mM; 3) Idem: 6 mM.

Conclusions

The non linear fitting of the calibration data to a model based on Nikolskii-Eisenmann equation is simple and generates good results. With PCR for calibration of the arrays, no improvment of the predictive ability of the calibration models was obtained. Array 1, constituted by three ESIs based on Aliquat, showed the best performance.

The results obtained in the determination of benzoate in two pharmaceutical formulations containing iodide, with Array 1 and a calibration model based on the Nikolskii-Eisenmann equation, showed that the relative errors of the determination are much lower than those reported [5] for the determination of benzoate by direct potentiometry.

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