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ORIGINAL ARTICLE

ELECTROCHEMICAL SENSORS WITH PHARMACEUTICAL APPLICATIONS BASED ON POLYMER INCLUSION MEMBRANES CONTAINING PHOSPHOMOLYBDIC ACID COMPLEXES

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Abstract

The article presents the construction and characterization of selective membrane sensors based on electroactive material incorporated in PVC matrix for the determination of ranitidine, famotidine and nizatidine, which use their complexes with phosphomolybdic acid as their electroactive material. Ion-pair complexes have been synthesized and characterized in terms of structure, composition and solubility. The optimal proportion has been established in order to obtain homogeneous, thin, elastic, mechanically resistant membranes and to provide the best analytical response. Optimal operating conditions have been determined. The linear response, quantification limit, response time and selectivity were studied for each electrode. The electrodes have been used for the potentiometric determination of H_2 antihistamines from pharmaceutical products.

Rezumat

Lucrarea prezintă construcția și caracterizarea unor senzori cu membrană selectivă pe bază de material electroactiv încorporat în matrice PVC pentru determinarea ranitidinei, famotidinei și nizatidinei care folosesc ca material electroactiv complecșii acestora cu acidul fosfomolibdenic. Complecșii de tip perechi de ioni sintetizați au fost caracterizați din punct de vedere al structurii, compoziției și solubilității. A fost stabilită proporția optimă pentru obținerea unor membrane omogene, subțiri, elastice, cu rezistență mecanică și care să prezinte cel mai bun răspuns analitic. Au fost determinate condițiile de funcționare optimă. Pentru fiecare electrod a fost studiat domeniul de răspuns liniar, limita de cuantificare, timpul de răspuns și selectivitatea. Electrozii au fost utilizați pentru determinarea potențiometrică a antihistaminicelor H_2 studiate din forme farmaceutice.

Keywords: polymer membranes, electrochemical sensor, phosphomolybdic acid complexes, H_2 antihistamines

Introduction

Selective membrane sensors are a system in which a special membrane separates two electrolyte solutions containing the same chemical species in different concentrations, and between which there is a potential difference. As the potential changes because of the variation in concentration of one of the chemical species it comes into contact with, it is considered that such a membrane, specific to a certain chemical species, functions as a transducer whose potential is a measure of the activity of that particular chemical species [17].

The literature on the use of specific electrochemical sensors in the analysis of pharmaceutical products is very up-to-date [3, 7]. Selective membrane sensors based on electroactive material incorporated in vinyl polychloride (PVC) matrix have the advantage of design, long life and saves active material. They have been used to determine galantamine [1], umeclidinium [21], tetracaine [12], azithromycin [2], ranitidine [6], oxomemazine [22], phenobarbital [4], oxalate [13], heavy metals [5] and so on.

Heteropolyacids precipitate with some organic substances with basic groups, forming ion-pair complexes [8, 14, 19], that are crystallized substances, with a set composition, which can be used to obtain polyvinyl chloride (PVC) matrix membranes, used when constructing sensors for oseltamivir phosphate [11], promethazine [16], amitriptyline [15] or midodrine [9].

The present study describes the construction and characterization of ion selective membrane sensors (ion selective electrodes - ISE) with PVC matrix for the determination of ranitidine (ISE-R), famotidine (ISE-F), and nizatidine (ISE-N) using as electroactive material their respective complexes with phosphormolybdic acid.

Materials and Methods

Potentiometric measurements were carried out using a 301 digital Hanna pH/millivoltmeter. The ion-selective

membrane electrode was used as indicator electrode in conjunction with an OP-0830P Radelkis saturated calomel electrode (SCE) as reference electrode.

Reagents used while preparing the membranes were produced by Fluka or Aldrich: polyvinyl chloride (PVC), phosphomolybdic acid (PMA), o-nitro-phenyl-octyleter (o-NPOE), di(butyl)butylphosphonate (DBBP), dioctylphthalate (DOP), sodium tetraphenyl-borate (NaTPB) and tetrahydrofuran (THF). All chemicals were of analytical-reagent grade.

Synthesis of complexes

Ranitidine, famotidine and nizatidine produced during the reaction with phosphomolybdic acid, crystalline yellowish-green crystals.

Precipitation took place at pH 1.0 and ~50°C using 1% phosphomolybdic acid solution. After 60 minutes of rest at room temperature, the complexes were separated through filtration, washed with a saturated solution of the precipitate and then with distilled water and dried to constant weight at room temperature in a vacuum desiccator.

Complex characterisation

The insoluble complexes were characterized by UV spectra (*HP 8453 - diode-array spectrophotometer*), specific absorbance ($A_{cm}^{1\%}$), solubility (S), and melting points (*MEL-TEMP II - capillary melting point apparatus*) and elemental analysis (*CE* 440 Elemental Analyser).

Electrode construction

The selective membrane was obtained after evaporation of THF out of 2 mL solution that had been continuously poured as a thin layer inside a glass ring, 30 mm in diameter mounted, on a glass plate. The solution contained various proportions of an electroactive compound (ionophore), plasticizer, PVC powder, and additives.

Discs of suitable diameter had been cut from the membrane in order to be applied at the end of a PVC tube with 10 mm inner diameter using a PVC and THF mixture as a binder and it was allowed to dry for 24 hours. The body of the electrode that had the selective membrane attached to, was filled with the internal reference solution, within which the Ag/AgCl internal reference electrode was immersed. A solution of analyte salt that the electrode was selective to, was used as internal reference solution in a concentration of 10^{-3} M in AgCl saturated solution.

In order to obtain the Ag/AgCl electrode, a silver wire of 1 mm in diameter and 50 mm long was used after it had previously been cleaned with concentrated HNO_3 and then rinsed with distilled water. The silver wire constituted the anode of an electrolysis cell, while the cathode was a platinum plate. The electrode assembly was placed in an AgCl saturated solution and then it was connected to a 9 V battery with a 1 Mohm resistance to provide a 10 μA current. Thus a compact and uniform layer of AgCl was deposited on the surface of the silver wire.

Before the measurements, the selective electrode membrane had been conditioned by immersion in a 10^{-5} M analyte salt solution for 120 minutes after which it was rinsed thoroughly with distilled water.

Results and Discussion

Complex characterisation

The insoluble complexes specific absorbance ($A_{cm}^{1\%}$), solubility (S), and melting points are depicted in Table I. Elemental analysis confirmed the formation 3:1 complexes of R-PMA or F-PMA or N-PMA, respectively, as shown in Table II.

Table I

Specific absorbance, solubility and melting points of the complexes

Complex	$A_{cm}^{1\%}$	S (g/L)	Melting point
R-PMA (*ranitidine phosphomolybdate*)	136.11 (λ = 312 nm)	$5.3392 \cdot 10^{-3}$	> 350°C with decomposition
F-PMA (*famotidine phosphomolybdate*)	147.84 (λ = 209 nm)	$8.1495 \cdot 10^{-2}$	> 350°C with decomposition
N-PMA (*nizatidine phosphomolybdate*)	157.25 (λ = 309 nm)	$5.0999 \cdot 10^{-3}$	> 350°C with decomposition

Table II

Elemental analysis of complexes

Element %	R-PMA $[C_{13}H_{23}N_4O_3S]_3 \cdot [PMo_{12}O_{40}]$		F-PMA $[C_8H_{16}N_7O_2S_3]_3 \cdot [PMo_{12}O_{40}]$		N-PMA $[C_{12}H_{22}N_5O_2S_2]_3 \cdot [PMo_{12}O_{40}]$	
	Found	Calculated	Found	Calculated	Found	Calculated
C	16.88	16.92	10.19	10.16	15.41	15.33
H	2.54	2.51	1.73	1.70	2.39	2.36
N	6.12	6.07	10.30	10.37	7.62	7.45

Optimization of PVC membrane sensor composition

Various selective membrane compositions have been evaluated. According to literature, the plasticizer solubilizes the ion pairs complex, and its proportion regulates both membrane permeability and ions mobility to obtain the most selective and sensitive response [10, 23]. Table III shows the slope of the electrodes (mV/decade) depending on the plasticizer used and its proportion (weight percentage - %wt).

The optimal composition for obtaining homogeneous, thin, elastic, mechanically resistant and best-response membranes is shown in Table IV.

Table III

Optimization of membranes composition - slope (mV/decade)

Plasticizer	DOP			DBBF			o-NPOE		
(%wt)	ISE-R	ISE-F	ISE-N	ISE-R	ISE-F	ISE-N	ISE-R	ISE-F	ISE-N
63	53.81	50.14	49.77	52.88	49.89	48.65	47.70	44.02	42.66
64	54.90	51.30	50.82	53.01	50.77	49.13	48.55	44.81	43.55
65	55.30	52.40	51.80	54.85	51.69	50.01	49.12	46.21	44.87
66	55.01	52.00	51.23	54.17	51.01	49.72	48.70	45.78	44.11
67	54.11	51.68	50.71	53.69	50.13	49.00	48.11	45.00	43.17

Table IV

Composition of PVC matrix selective membranes (%wt)

Electrode	Ionophore (%wt)	Plasticizer (%wt)	Additive (%wt)	Matrix (%wt)
ISE-R	R-PMA (3)	DOP (65)	NaTPB (1)	PVC (31)
ISE-F	F-PMA (3)	DOP (65)	NaTPB (1)	PVC (31)
ISE-N	N-PMA (3)	DOP (65)	NaTPB (1)	PVC (31)

Effect of pH

The effect of pH on electrode response was examined by measuring the variation of the potential of the cell for three different concentration levels (10^{-4}, 10^{-3} and 10^{-2} M). Figure 1 shows the response of electrodes for 10^{-3}M concentration in the pH range 1.0 - 10.0.

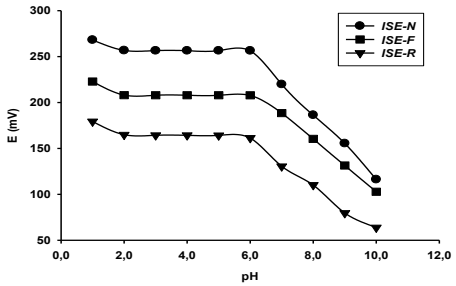

Figure 1.

Effect of pH on electrode response

The electrode response had the same profile for three concentration levels, and the optimal pH range was found to be between 2.0 and 6.0. At lower pH levels, there is a slight interference from the hydrogen ions, while in alkaline media, the membrane potential decreases due to the gradual precipitation of ranitidine, famotidine or nizatidine as free bases. The potential measurements were conducted at pH 4.0 maintained using acetate buffer solution.

Total ionic strength

Because the electrode response depended on ionic activity, it was important to keep the activity coefficient constant for all solutions. It was necessary to achieve a relatively constant concentration of a highly pure electrolyte to which the selective membrane did not respond. A 0.1 value for the ionic strength was found to be optimal for samples with the concentration below 10^{-2} M, and it was obtained using 1M KNO_3. The measured potential was uninfluenced by ionic strength for 10^{-2} and 10^{-1} M sample solutions.

Response time

The response time varied depending on the analyte concentration. For lower concentrations the response time was within 55 seconds while the electrodes response to higher concentrations was virtually instantaneous in all cases.

Experimental data obtained were subjected to statistical processing, establishing for each constructed electrode its linear response range, limit of quantification, precision, accuracy, selectivity, and robustness of the method.

Table V

Validation parameters of potentiometric determination methods

Electrode		ISE-R	ISE-F	ISE-N
Linearity range		10^{-1}-10^{-5} M	10^{-1}-10^{-5} M	10^{-1}-10^{-5} M
Regression		E = -55.3·pC + 321.7	E = -52.4·pC + 324.7	E = -51.8·pC + 382.2
Correlation coefficient (r^2)		0.9986	0.9981	0.9973
Slope		55.3 mV/decade	52.4 mV/decade	51.8 mV/decade
Standard deviation (σ)		0.6239	0.5300	0.4393
LOQ		$5.76 \cdot 10^{-6}$ M	$2.65 \cdot 10^{-6}$ M	$3.32 \cdot 10^{-6}$ M
Repeatability Ist Series	**SD**	2.04	1.71	1.05
	RSD	2.05%	1.75%	1.06%
Repeatability IInd Series	**SD**	2.07	1.57	0.76
	RSD	2.08%	1.60%	0.77%
Reproducibility	**SD**	2.00	1.62	0.90
	RSD	2.01%	1.66%	0.92%
Accuracy	$\overline{Xd}$	1.91%	2.17%	1.57%

Linearity

The response of the electrodes was studied in the 10^{-7} - 10^{-1} M concentration range at pH 4.0 and at 0.1 ionic strength. For each electrode the concentration range for linear response of the measured potential correlated to the concentration of the analysed ion was determined (Table V).

A graphical method was applied for calculating the limit of quantification (LOQ) defined as the intersection of the regression line for the linear domain with the range when the electrode response is relatively constant. An example is shown in Figure 2 for ISE-R (E = mV, C = mol/L, pC = - log C).

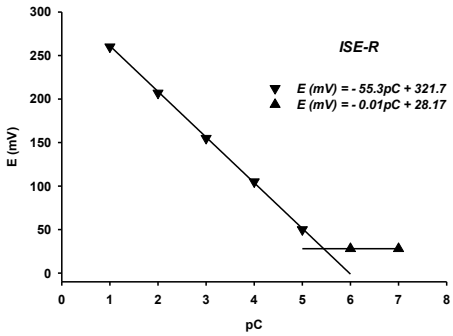

Figure 2.
LOQ and calibration curves for ISE-R

Precision

The precision of the method was studied in terms of repeatability and reproducibility. There have been two series of measurements in various days for three different concentrations of analyte 10^{-4}, 10^{-3} and 10^{-2} M. For each concentration level three determinations series were carried out (Table V).

Accuracy

The accuracy of the electrodes was assessed by analysing three standard solutions of 10^{-4}, 10^{-3} and 10^{-2} M respectively, following the correspondence between the real and the analytical result obtained from measurements by calculating the relative error, Xd (%), using the equation (1) [24]:

$$Xd(\%) = \frac{|Xr - Xa|}{Xa} \times 100 \ (1),$$

where Xr was the value calculated from the calibration curve for the theoretical value Xa (Table V).

Robustness

The robustness of the methods was assessed by comparison of the intraday and inter-days assay results measured by two analysts under a variety of conditions such as small changes of laboratory temperature and provenience of chemicals. The percent recoveries were good.

Electrode selectivity

The selectivity of electrodes (Table VI) was investigated by the separate solution method and the potentiometric selective coefficients (K) were calculated using equations (2) and (3) [18]:

$$logK = \frac{E_{(II)} - E_{(I)}}{P} + \log[A^{y+}] - \log[I^{z+}] \ (2),$$

$$K = 10^{\frac{\Delta E}{P}} \times \frac{[A^{y+}]}{[I^{z+}]} \ (3)$$

Two separate solutions of the same 10^{-3} M concentration were prepared for the primary ion (A^{y+}) and the interfering secondary ion (I^{z+}). Their potentials E_I (for A^{y+}) and E_{II} (for I^{z+}) were measured (P = slope of the calibration curve). The separate solution method is one of the methods recommended by IUPAC [20].

Table VI
Selectivity coefficient (K)

Interferer	ISE-R	ISE-F	ISE-N
NH_4^+	$1.27 \cdot 10^{-3}$	$5.30 \cdot 10^{-3}$	$1.12 \cdot 10^{-3}$
Na^+	$3.70 \cdot 10^{-3}$	$4.30 \cdot 10^{-3}$	$1.26 \cdot 10^{-3}$
Ca^{+2}	$1.90 \cdot 10^{-3}$	$3.44 \cdot 10^{-3}$	$4.19 \cdot 10^{-3}$
Mg^{+2}	$2.54 \cdot 10^{-3}$	$9.21 \cdot 10^{-4}$	$2.36 \cdot 10^{-4}$
Al^{+3}	$8.96 \cdot 10^{-4}$	$8.19 \cdot 10^{-4}$	$3.35 \cdot 10^{-4}$
Ranitidine	-	$1.11 \cdot 10^{-1}$	$1.60 \cdot 10^{-1}$
Famotidine	$1.23 \cdot 10^{-1}$	-	$1.32 \cdot 10^{-1}$
Nizatidine	$1.78 \cdot 10^{-1}$	$1.90 \cdot 10^{-1}$	-

Because of their similar structures, molecular weights and molecule dimensions, ranitidine, famotidine and nizatidine interfered with each other slightly as far as the response of electrodes. Since there are no pharmaceutical products containing any association of those three active ingredients, it is unlikely that these interferences will actually occur. The cations usually present in the excipients used in the formulation of tablets/capsules did not exhibit any interference.

Lifetime of electrodes

The electrodes used constantly during the experiment had an average lifetime of 4 - 5 weeks.

Analytical applications

The constructed and characterized electrodes have been used to quantify through direct potentiometry the analytes from some pharmaceutical products such as injectable solutions, tablets, and capsules. The results obtained were within the limits set by the Romanian Pharmacopoeia Xth edition (FRX) regarding the accepted variation of content for the active substance when compared to the labelled value (Table VII).

Table VII
Direct potentiometric quantitative determination

Active substance	Tablets/capsules			Injectable solution		
	Labelled	Quantified	FRX	Labelled	Quantified	FRX
Ranitidine (n = 6)	75 mg	74.70 ± 0.24 mg	75 ± 5.62 mg	50 mg/2 mL	49.79 ± 0.13 mg/2 mL	50 ± 2.50 mg
Famotidine (n = 6)	40 mg	39.52 ± 0.12 mg	40 ± 3.00 mg	20 mg/5 mL	19.56 ± 0.08 mg/5 mL	20 ± 1.00 mg
Nizatidine (n = 6)	300 mg	298.60 ± 0.27 mg	300 ± 15.0 mg	100 mg/4 mL	98.54 ± 0.17 mg/4 mL	100 ± 5.00 mg

Conclusions

A series of selective membrane potentiometric sensors have been constructed based on electro-active material embedded in the PVC matrix. The sensors were evaluated as far as their functional characteristics and then they were used for the quantitative determination of ranitidine, famotidine and nizatidine within 10^{-1} - 10^{-5} M concentration range.
Determinations are non-destructive, and they can be done even by direct analysis of turbid or viscous solutions with a sensitivity superior to classic titrimetric and spectrophotometric methods, but inferior to that of high performance liquid chromatography. The main disadvantages are the short life of the sensor membrane and the need for its periodic renewal. The proposed methods can be used for routine analysis in drug quality control laboratories providing a quick, simple, accurate and inexpensive solution considering the necessary equipment involved and the consumption of reagents.

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