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A cyproheptadine - membrane electrode and its use in pharmaceutical analysis

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SUMMARY

The construction and performance characteristics of ion-selective membrane electrode for cyproheptadine drugs on its ion-pair complex with dinonylnaphtalene sulphonate in a poly(vinyl chloride) matrix is described. The electrode shows a near- Nernstian response over the range 10^{-2}-10^{-4} M. The response is not affected by pH in the range 2-6. The selectivity relative to some inorganic ions, amino acids, drugs and various drug excipients are reported. The direct potentiometry and potentiometric titrations are used to determine the cyproheptadine drugs in pharmaceutical preparations with satisfactory results.

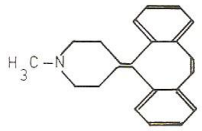
Key-words : Cyproheptadine hydrochloride hydrate. Cyproheptadine - membrane electrode. Direct potentiometry. Potentiometric titrations. Drugs analysis. Content uniformity assay.

The control of drug quality is a branch of analytical chemistry that has a wide impact on public health, so the development of reliable, quick and accurate methods for the determination of the active ingredient is welcomed.

In the recent years, ion-selective membrane electrodes are finding considerable use with many applications in pharmaceutical analysis [1-5], even though not all of them provided acceptable sensitivity and selectivity for the drug of interest. Much effort is required in the development of a rapid, simple and sensitive method for the determination of a certain drug, as it may be found also in complex pharmaceutical preparations or in human fluids, not only in pure forms. Usually, the potentiometric methods can be simple, fast for pharmaceutical analysis when a suitable sensor is available.

This paper describes the preparation and the characterization of a cyproheptadine-membrane electrode. The electrode uses dinonylnaphtalene sulphonic acid as the counter-ion in the electroactive material of the membrane and exhibits useful analytical characteristics for the potentiometric determination of cyproheptadine hydrochloride hydrate drugs (tablets and syrup).

Cyproheptadine hydrochloride hydrate [4-(5H-dibenzo [a, d] cyclohepten-5-ylidene)-1-methylpiperadine] (I) it is used in therapeutical practice for his appetite stimulant, anti-allergic and antihistaminic action.



HCl $1\frac{1}{2}$ H_2O

EXPERIMENTAL

Reagents and materials

All reagents were of analytical-reagent grade. Other materials were : sodium tetraphenylborate (III) (NaTPB), (Fluka) ; 2-nitrophenyloctylether (2-NPOE), (Fluka) ; dinonylnaphtalene sulphonic acid (DNNS), (Pfaltz and Bauer) and PVC of high relative molecular mass (Aldrich). Pharmaceutical preparations were obtained by one of us.

Apparatus

Direct potentiometric measurements were made at room temperature in mechanically stirred solutions, with a digital pH/mV-meter (Pracitrönic) and the cyproheptadine-membrane electrode in conjunction

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with a saturated calomel electrode (SCE), (type K4ol Radiometer). The pH measurements were made with a G 202 C glass electrode (Radiometer) and a SCE. The potentiometric curves were recorded with an automatic outfit composed of a TTT 2 titrator, ABU 12 autoburette and a SBR 2 c titrigraph recorder (Radiometer) with the cyproheptadine-membrane electrode and the SCE.

Construction of the Electrode

The basic principle of the cyproheptadine-selective membrane electrode has been described elsewhere [6-8] and the PVC-membrane composition was 4.0 % w/w dinonylnaphtalene sulphonic acid, 64.0 % w/w 2-nitrophenyloctylether and 32.0 % w/w PVC. The internal filling solution was 10^{-3} mol/l cyproheptadine hydrochloride hydrate of pH 5.0 (acetate buffer solution). The dinonylnaphtalene sulphonic acid in the PVC-membrane was converted to ion-pair complex by soaking the electrode in cyproheptadine hydrochloride hydrate solution (10^{-2} mol/l) for 24 h. When not in use the electrode was stored in the same solution as the internal one.

Recommended procedures

Direct potentiometry

Prepare 10^{-3}, 10^{-4}, 10^{-5} and 10^{-6} mol/l standards (I = const. ; pH 5.0) by serial dilution of cyproheptadine hydrochloride hydrate 10^{-2} mol/l solution. Place the cyproheptadine-membrane elecrode and the SCE in the stirred standards solutions in the order 10^{-6}-10^{-2} mol/l. Plot E against log concentration.

Potentiometric titration

Place the electrodes in a partially aqueous solution (2.0 % MeOH) , then titrate with 0.005 M sodium tetraphenylborate (III) solution. The end-point corresponds to the maximum slope on the E vs. volume titrant curve.

Content uniformity assay of cyproheptadine tablets

Ten individual tablets, accurately weighed, were transferred to separate 25-ml volumetric flasks and disolved in 10 ml partially aqueous solution (2.0 % MeOH) and then the suspension is diluted to volume with acetate buffer. Solution was titrated potentiometrically as described above for the drug substance.

RESULTS AND DISCUSSIONS

Membrane material

Cyproheptadine, in a protonated form, as well as other amines or quaternary ammonium compounds, reacts with dinonylnaphtalene sulphonic acid to form a stable complex. The ion-pair complex was obtained *in situ*, by soaking the dinonylnaphtalene sulphonic acid - PVC - membrane in a solution of 10^{-2} mol/l cyproheptadine hydrochloride hydrate. The composition of the membrane is given in the Experimental section.

The electrode function

The emf measurements were made with the electrochemical cell :

Cyproheptadine-membrane electrode	Cyproheptadine .HCl.$1\frac{1}{2}H_2O$ (C) I = const. ; pH 5.0	SCE	(I)

where C is the cyproheptadine concentration, ranging from 10^{-6} to 10^{-2} mol/l. The emf is given by :

$$E_I = E_o + 0.055 \log [\text{cyproheptadine}^+] \quad (1)$$

where the E_o value is the conditional standard potential for electrode under the conditions of use of cell (I).

Figure 1 shows the electrode function for the cyproheptadine-membrane electrode. The response is linear over the range 10^{-4}-10^{-2} mol/l with a near-Nernstian slope (55mV/decade). The slope of the curved part is only about 40 mV/decade.

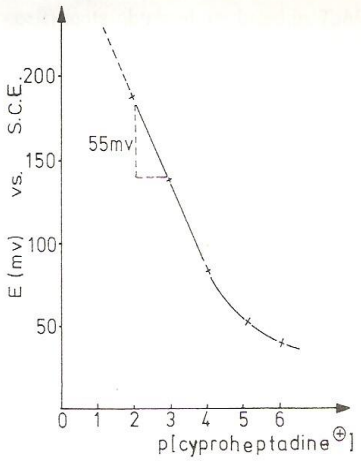

FIG. 1. — *Electrode function.*

Influence of pH

The effect of pH on the potential of the electrode was examined by measuring the emf of the cell (I) in cyproheptadine hydrochloride hydrate solutions in which the pH was varied by adding appropriate amounts of hydrochloric acid and/or sodium hydroxide solution. At pH values between 2.0 and 6.0, no signifi-

cant change in the membrane potential was observed (for different concentration of cyproheptadine hydrochloride hydrate). At pH values higher than 6.0-6.5, the cyproheptadine base in the aqueous test solutions precipitates, so the emf values are shifted toward more negative values *(fig. 2)*.

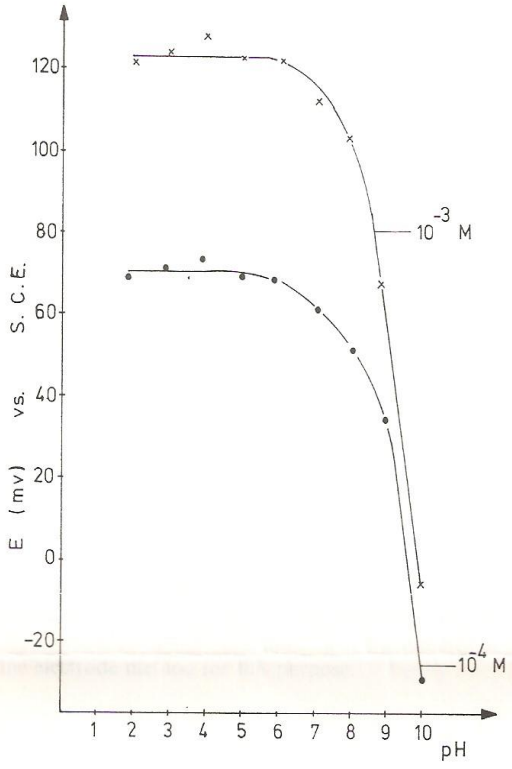

FIG. 2. — *Effect of pH on the electrode response.*

Response time

The electrode response times were measured for different concentrations of cyproheptadine hydrochloride hydrate solutions. The response times were about 2-3 minutes in the 10^{-4}-10^{-6} mol/l solutions. In more concentrated solutions the response times were of the order of a few seconds *(fig. 3)*.

Selectivity of the electrode

The interference of various substances on the electrode response was studied by the mixed solution method and the respective selectivity coefficients, $K^{pot}_{Cy,j}$, were calculated [9] from the equation :

$$K^{pot}_{Cy,j} = (10^{\Delta E/S} - 1)\,[Cy^+]/[j^{z+}]^{1/z}$$

where ΔE is the change in potential in the presence of interfering ion, j^{z+}, S is the slope of the calibration graph for the cyproheptadine primary ion, Cy^+, and

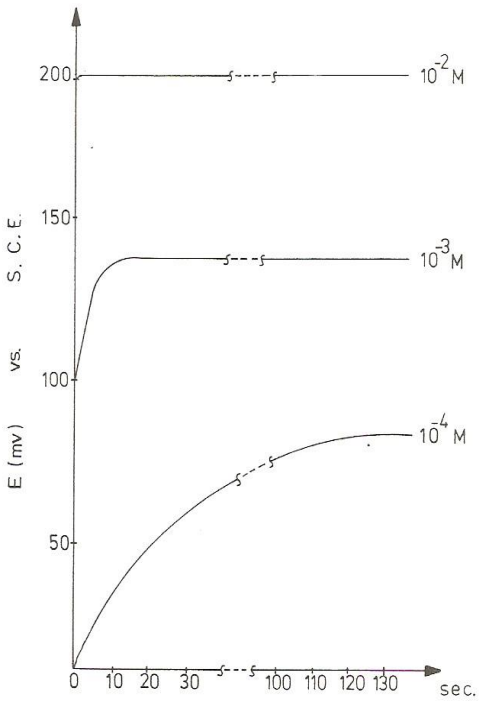

FIG. 3. — *The response time of the cyproheptadine-membrane electrode for 10^{-2}, 10^{-3}, 10^{-4} mol/l concentrations.*

$[Cy^+]$ and $[j^{z+}]$ are the concentrations of the primary and the interfering ions, respectively, at the same pH and ionic strength.

The coefficients obtained are listed in *Table 1.*

TABLE I. — *Selectivity coefficients for the cyproheptadine-membrane electrode.*

Interfering species j^{z+}	Selectivity coefficients $K^{pot}_{Cy,j}$
Na^+, K^+	5.6×10^{-4}
Mg^{2+}	1.8×10^{-5}
Glycine	1.8×10^{-4}
Atropine	1.8×10^{-4}
Scopolamine	1.8×10^{-4}
Phenylalanine	1.8×10^{-4}
Xiline	3.7×10^{-4}
Vitamin B_1	1.8×10^{-4}
Vitamin B_6	1.8×10^{-4}

Most excipients in pharmaceutical tablets (usually lactose or glucose as diluent and corn starch or gelatine as binder) do not interfere.

Analytical applications

The electrode proved useful in the potentiometric titration of cyproheptadine hydrochloride hydrate in the drug substance and in pharmaceutical preparations (tablets and syrup). The results of the assay of cyproheptadine hydrochloride hydrate in five samples of pharma-

ceutical preparations are given in *Table II* and show that good recovery was achieved, with a high precision in the case of the tablets.

TABLE II. — *Determination of cyproheptadine in tablets and syrup with a cyproheptadine-membrane electrode.*

Pharmaceutical preparation	Recovery % of nominal	Standard deviation (%)
Tablets (label amount : 0.0045 g/tablet)	99.90 100.00 101.30 100.20 100.40	0.56
Syrup (label amount : 0.045 g/bottle)	99.30 100.00 103.10 102.20 96.20	2.70

The electrode can also be used to determine the content uniformity of cyproheptadine tablets. In many cases the content uniformity test is preferred to the assay of a composite sample, as both preparation of the sample and measurement can be carried out more rapidly than that of the assay of a composite sample. If the accuracy of the assay is satisfactory, the mean value of the content uniformity test can be used as the assay result. *Table III* presents the results obtained for the determination of the content uniformity test of cyproheptadine tablets and indicate the suitability of the electrode method for this purpose.

TABLE III. — *Analytical results of content uniformity assay of cyproheptadine hydrochloride hydrate tablets with the cyproheptadine-membrane electrode* (label amount : 0.0045 g/tablet).

Tablet	Found	
	mg/tablet	% of nominal
1	4.70	104.40
2	4.28	95.10
3	4.63	102.90
4	4.59	102.00
5	4.47	99.30
6	4.61	102.40
7	4.47	99.30
8	4.52	100.40
9	4.40	97.80
10	4.45	98.90

CONCLUSIONS

The electrode-membrane ion-selective based on cyproheptadine- dinonylnaphtalene sulphonate ion-pair complex in PVC - matrix exhibits useful analytical characteristics for the determination of cyproheptadine hydrochloride hydrate based pharmaceutical preparations (tablets and syrup). Both direct potentiometry and potentiometric titrations can be applied succesfully for the determination of the drugs without prior treatment.

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