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PENBUTOLOL SELECTIVE MEMBRANE SENSOR

Keywords: Penbutolol plastic membrane sensor; drug analysis; content uniformity; dissolution release.

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ABSTRACT

The construction and performance characteristics of ion-selective PVC membrane electrode for penbutolol sulfate are described. The electrode, based on ion-pair complex with dinonylnaphthalenesulphonate anion, shows near-Nernstian response in the range 10^{-3} to 5×10^{-6} M drug concentration. Its selectivity relative to various cations is reported. Potentimetric methods are used to determine pure drug-substance and active principle in pharmaceutical preparation with good results. It was also applied to the determination of content uniformity and dissolution-rate of film-coated Betapresin® tablets.

INTRODUCTION

In recent years, ion-selective membrane electrodes have been used more and more in drug quality control [1-5], but no pharmacopoeia has yet introduced their use for assay, though this will probably be done in the next few years.

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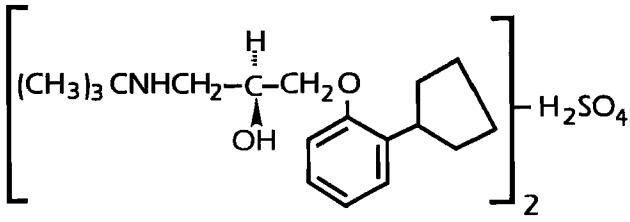
Penbutolol sulfate ((S)-1(tert-butylamino)-3-(o-cyclopentyl-phenoxy)-2-propanol sulfate (2:1)) salt) I is a non selective $beta_1$ - adrenergic receptor antagonist used as antihypertensive drug. It possesses intrinsic sympathomimetic activity which has been found to be intermediate between that of alprenolol and pindolol [6] Penbutolol is a lipophilic molecule approximately four times as potent as propranolol, and contains only the levorotary stereoisomer of the drug [7]



The official standard methods for the assay of penbutolol in pharmaceutical preparation are based on extraction of the drug followed by its determination by fluorimetric methods [8-11] or gas-chromatography [12] . In this paper, a method for the determination of penbutolol sulfate in pharmaceuticals is proposed. The method is rapid and shows good reproducibility.

EXPERIMENTAL

Apparatus

A Pracitronic digital pH/mV meter, model 870 MV was used for all direct potentiometric measurements. The electrode was used in conjunction with a Radiometer K401 calomel electrode. The titration curves were obtained by using an automatic titration assembly consisting of ABU 12 autoburette, a TTT 2 titrator and a SBR 2c recorder (Radiometer - Copenhagen, Denmark). The pH measurements were performed with a Radiometer G 202 B glass electrode in combination with a Radiometer K 401 calomel electrode. The dissolution test was performed in a basket-stirrer USP-type apparatus. The statistical approach and simulation of the experimental data were performed on a 80826 AT computer (IBM) - PC compatible).

Reagents and Materials

Pentutolol sulfate and the pharmaceutical preparation were supplied by Hoechst AG (Frankfurt, Germany) and other materials and reagents were: dinonylnaphtalenesulphonic acid (DNNS), dinonylphthalate (DNP), PVC of high relative molecular mass and tetrahydrofuran (THF) were of analytical-reagent grade. Solutions of penbutolol sulfate were prepared by serial dilution, while keeping pH constant (citrate buffer pH 5.5). A standard solution of sodium tetraphenylborate (NaTPB) ($5x10^{-2}$M) was prepared by dissolving 17.122 g of the compound in distilled water and dilution to 1 litre.

Construction of the electrode

The PVC membrane and the electrode, based on association of penbutolol ion-pair complex was constructed according to the method of Moody and Thomas [13]. The electrode body was filled with a 10^{-3} M penbutolol sulfate solution. The electrode was pre-conditioned for 1h by soaking it in a 10^{-2} M penbutolol sulfate solution. Penbutolol sulfate and other organic amines are well known for reacting with DNNS, to form stable ion-pair complex. The complex is obtained *in situ* by soaking the PVC membrane in 10^{-2} M penbutolol sulfate solution. The PVC membrane composition was: 4.0% w/w DNNS, 64.0% w/w DNP and 32.0% PVC.

Recommended Procedure

Direct potentiometry

Standard solutions (in 0.1 M HCl) of $1.5x10^{-4}$ M, $3x10^{-4}$ M, $7.5x10^{-4}$ M and $1.5x10^{-5}$ M concentrations were prepared by serial dilution of a 10^{-3} M penbutolol sulfate solution. The electrode was placed in the stirred standard solution in the order $1.5x10^{-4}$ M - $1.5x10^{-5}$ M, E(mV) versus log concentration is plotted. The unknown concentration is determined from the calibration graph.

Potentiometric titration

The electrodes were placed in the sample solution (30-40 ml, concentration approximately 10^{-2} M) and the solution is titrated with $5x10^{-2}$ M NaTPB). The

end-point corresponds to the maximum slope on the E(mV) versus volume of titrant curve (1 ml of $5x10^{-2}$ M NaTPB is equivalent to 34.048 mg of penbutolol sulfate).

Content uniformity assay of Betapresin® tablets

Ten individual tablets were placed in separate 100 ml beaker and dissolved by shaking with about 30-40 ml distilled water. The solutions were titrated potentiometrically, as described above.

Dissolution test

The test was carried out according to the USP XXII method[14] with the use of the equipment described elsewhere[15]. One film-coated tablet is placed in the basket, and the dissolution medium (250 ml of 0.1 M HCl) is maintained at 37 ± 0.5°C. The basket is rotated at 50 rpm. For the potentiometric determination, after an appropriate time interval (1 min), the potential values are recorded, and the amount of the penbutolol sulfate is calculated from the calibration graph. In order to investigate all the important physical processes during the dissolution period, the release profiles were numerically simulated by typical equations[16].

RESULTS AND DISCUSSION

Electrode response

Typical calibration curve for the penbutolol membrane sensor shows that the electrode response is linear in the range 10^{-3} - $5x10^{-6}$ M. The calibration curve is presented in Fig. 1.

The critical response characteristics of the electrode in the citrate buffer solutions are summarised in Table 1.

Effect of pH

The effect of pH on the potential readings of the penbutolol sensor was checked by recording the e.m.f. of a cell of type Ag-AgCl| 10^{-3} M penbutolol sulfate solution (inner solution) || plastic membrane || 10^{-4}M penbutolol sulfate solution (outer solution) SCE, and varying the acidity by the addition of very

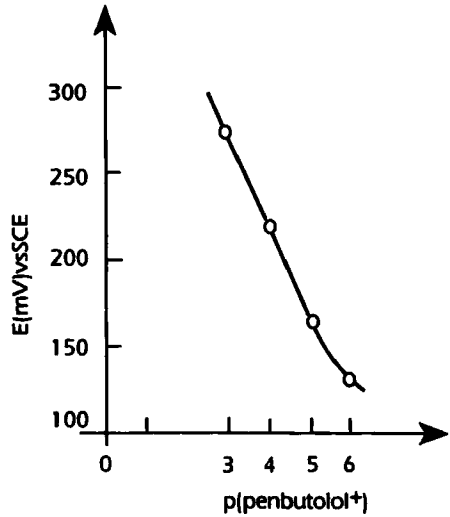


Figure 1. A typical calibration curve for the penbutolol membrane sensor.

Table 1. Response Characteristics for Penbutolol Sensor

Parameter	Response
Slope (mV per log a)*	55 ± 0.3
Intercept, E_o (mV)**	440.4 ± 0.5
Linear range (M)	10^{-3} -7.5 X 10^{-6}
Detection limit (M)	10^{-6}

*Standard deviation of average slope values for multiple calibrations.
**Standard deviation of values recorded over a period of two months (n=60)

small volumes of hydrochloric acid and/or sodium hydroxide solution (1.0 M of each). The graph presented in Fig. 2 shows the linearity in the range 3-8 of the potential E(mV) versus pH function. At higher pH values, free base precipitates in the test solutions, and consequently, the concentration of unprotonated species gradually increases. As a result, lower e.m.f. readings are recorded.

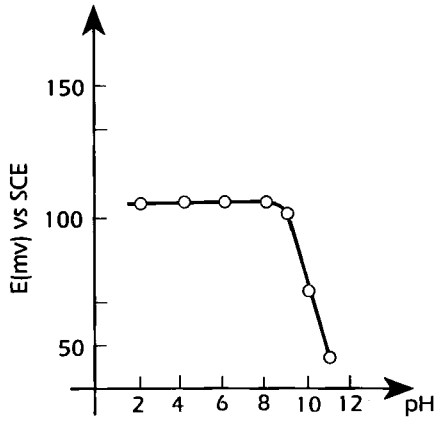


Figure 2. Effect of pH on the Response of the Penbutolol Sensor.

Table 2. Selectivity Coefficients for the Penbutolol Sensor
([Pen+]/[J^{z+}] = $10^{-4}/10^{-2}$)

Interfering species J^{z+}	$K^{pot}_{Pen,J}$
K^+, Mg^{2+}	$<10^{-4}$
Ephedrine HCl	2.1×10^{-3}
Glycine	1.6×10^{-3}
Timolol maleate	6.1×10^{-3}
Metoprolol tartrate	2.7×10^{-3}
Imipramine.HCl	3.87
Vitamin B_1	1.5×10^{-3}
Vitamin B_6	5.7×10^{-3}

Selectivity of the sensor

Penbutolol sulfate very often has to be determined in pharmaceuticals, which also contain various inorganic and organic substances. The effect of some of these matrices on the response of the sensor was studied by the mixed solution method [16]. The selectivity coefficients, presented in Table 2, indicate that

Table 3. Determination of Penbutolol Sulfate with a Penbutolol Sensor

Product	Sample	Recovery (% of nominal value)*	RSD (%)
Penbutolol sulfate raw-material	1	101.37	0.96
	2	100.97	
	3	100.76	
Betapresin® 40 mg tablets (Hoechst AG)	1	100.06	1.96
	2	99.45	
	3	99.06	

*All values are the average of four determinations

the response of the proposed sensor is not affected by the presence of the interfering ions studied. Excipients such as corn starch, gelatine, sugar and lactose also do not interfere.

Analytical Applications

The electrode proved useful for the assay of the penbutolol content in pharmaceuticals by using the potentiometric titration method. The results are given in Table 3.

As can be seen in Table 3 a high precision was attainable [RSD < 2%]. Usually the potentiometric assay could be accomplished within 10 min, in contrast to the 1 hr. required for the chromatographic determination.

Other immediate fields of application of the sensor would appear to be in the determination of tablet content uniformity and in dissolution profile studies.

In many cases the content uniformity test is preferred to the assay of a composite sample, as both preparation of the sample and measurements can be carried out more rapidly than those of the assay of a composite sample. If the accuracy of the assay is satisfactory, the mean value can be used as the assay result. Table 4 presents the results obtained for the determination of the content uniformity of film-coated penbutolol tablets (Betapresin®) and indicates the suitability of the electrode method for this purpose.

Table 4. Results of Content Uniformity Test of Penbutolol Sulfate Tablets with the Penbutolol-DNNS Sensor (label amount 40.0 mg/tablet).

Tablet	Found		RSD* (%)
	mg/tablet	%	
1	39.35	98.38	
2	40.29	100.72	
3	38.16	95.40	
4	40.81	102.02	
5	38.24	95.60	1.96
6	39.18	97.97	
7	39.35	98.38	
8	40.04	100.10	
9	39.02	98.00	
10	39.35	98.38	

*RSD (%) refers to all ten tablets.

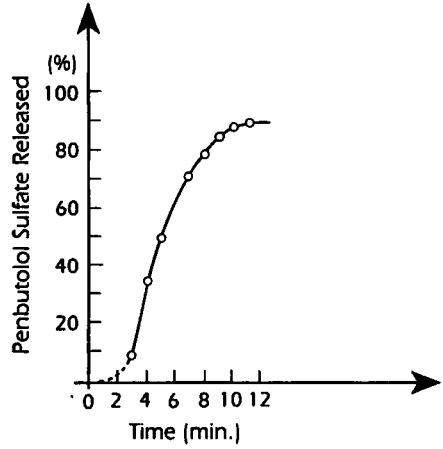


Figure 3. Dissolution profile of film-coated penbutolol sulfate tablets (Betapresin®).

The tested batch was considered acceptable as each of the individual units tested was found to be between 85 and 115% of the label amount and the RSD was less than 6.0%.

The desirability of an *in vitro* test that adequately reflects the physiological availability of solid dosage forms of drugs is now recognized. The measurement of a parameter that is related to the rate of dissolution of a solid has been suggested as a more realistic variable and this has led to numerous papers describing different methods and equipments for monitoring dissolution tests [17-20]. The advantage of the electrode technique for carrying out such a test is that the electrode can monitor continuously and selectively the concentration of the active ingredient in the standardized dissolution cells.

Fig. 3 shows the dissolution profile of film-coated penbutolol tablets (Betapresin®). Taking into account the S-shape of the curve, there are some possibilities for the simulation of physical processes involved in the dissolution steps. The method proved that the release of the active principle of the Betapresin® tablets in simulated gastric fluids follows the Wagner model [16] i.e. the dissolution process involves two main steps: an initial step, of about 2 min. while the film layer is removed, followed by a rapid process of active principle dissolution. All other simulation possibilities tested [16] were found to be inadequate for the film penbutolol tablets.

CONCLUSIONS

The penbutolol-selective plastic membrane sensor, based on penbutolol dinonylnaphthalenesulfonate ion-pair complex in a PVC matrix, exhibits useful analytical characteristics for the determination of penbutolol sulfate in pharmaceuticals. The sensor can be successfully used in establishing dissolution profiles for film-coated penbutolol tablets.

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