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MIANSERIN ION-SELECTIVE MEMBRANE ELECTRODE AND ITS PHARMACEUTICAL APPLICATIONS

Keywords: Mianserin hydrochloride; mianserin plastic membrane sensor; pharmaceutical analysis; potentiometric methods; content uniformity; dissolution release

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ABSTRACT

The construction and performance characteristics of ion-selective electrode for mianserin-drug cation, based on ion-pair complex with dinonylnaphthalenesulfphonate anion in a PVC matrix are described. The electrode shows a near-Nersntian response in the range 10^{-2} - 5 x 10^{-6} M drug concentration. Its selectivity relative to various cations is reported. The potentiometric methods are used to determine mianserin hydrochloride with good results. The electrode is also useful to the determination of content uniformity and dissolution-rate of uncoated mianserin tablets. The physical processes are numerically simulated by typical equations.

INTRODUCTION

Developments in pharmaceutical analysis with ion-selective membrane electrodes (ISMEs)[1-6] enable us to measure the activities of various drug directly and selectively from the formulation matrix. It is possible to develop methods for the determination of drug-substances in pharmaceutical preparations that would need only a pre-dilution step (e.g., injections solutions) or dissolution of tablets in the measuring solvent.

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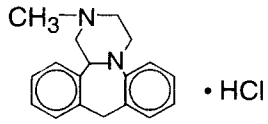
The paper describes the construction and performance characteristics of a new mianserin ion-selective electrode based on the complex mianserin-dinonylnapthalenesulfonate embedded in a polyvinyl chloride (PVC) matrix. The electrode has been used successfully for the assay of mianserin hydrochloride in pharmaceuticals. The measurements were performed by potentiometric titration method (content uniformity assay) and direct potentiometric method (dissolution studies), respectively. In order to investigate all the important physical processes during the dissolution period, the release profiles were numerical simulated by typical equations [7], and the most probable model was chosen.

Mianserin hydrochloride {1,2,3,4,10,14 b-hexahydro-2-methyldibenzo [c,f] pyrazino [1,2-a] azepine hydrochloride, I} is a tetracyclic compound that is widely used in the treatment of depression. Also. it display high affinities for histamine and serotonin receptors, and possess varying adrenergic and dopamine blocking properties.



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The official standard methods for the assay of mianserin hydrochloride are based on non-aqueous titration [8], gas chromatography [9], liquid chromatography [10-12], thin-layer chromatography [13], extractive colorimetric methods [14]. The present procedure allows the determination of mianserin hydrochloride in pharmaceuticals without any prior separation, with an average error of less than 1.0%

MATERIALS AND METHODS

Reagents and Materials

All reagents, except mianserin hydrochloride were of analytical-reagent grade. Mianserin hydrochloride drug-substance and uncoated tablets were synthesized in our laboratory. All solutions were prepared with distilled water. Solutions of mianserin hydrochloride were prepared by serial dilution, while keeping pH constant (pH 5.5; 0.1 M sodium citrate and 0.1 N NaOH). Standard solution of sodium tetraphenylborate (NaTPB) (5 x 10^{-2} M) was prepared by dissolving 17.122 g of the compound in distilled water and diluted to 1 litre.

Apparatus

A Pracitronic digital pH/mV meter, model 870 MV (± 0.1 mV precision) (Dresden,Germany) 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) and a Pye Unicam SP1800 spectrophotometer was used for the UV determinations. 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 I apparatus. The statistical approach and simulation of the experimental data were performed on a 80826 AT computer (IBM - PC compatible), using some proper programs (STATIS and ASPRODI 3.0, respectively).

Construction of the electrode

The basic principle of the mianserin-selective membrane electrode construction has been described elsewhere[15-17] and the PVC-membrane composition was 4.0% w/w DNNS (dinonylnapthalene sulphonic acid), 64.0% w/w DNP (dinonylphthalate) and 32.0% PVC. The electrode body was filled with a 10^{-3} M mianserin hydrochloride solution of pH 5.5 (citrate buffer solution). The electrode was pre-conditioned for 1 h by soaking it in a 10^{-2} M mianserin hydrochloride solution. Mianserin hydrochloride 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 mianserin hydrochloride solution.

Direct Potentiometry

Standard solutions (in 0.1 M HCL) of 1 x 10^{-4} M, 2 x 10^{-4} M, 4 x 10^{-4} M, 8 x 10^{-4} M and 1 x 10^{-5} M concentrations were prepared by serial dilution of a 10^{-2} M mianserin hydrochloride solution. The electrodes (mianserin-electrode and calomel electrode) were placed in the stirred standard solution in the order 10^{-5} - 10^{-4} 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 5 x 10^{-2} M NaTPB. The end-point corresponds to the

maximum slope on the E(mV) versus volume of titrant curve (1 ml of 5 x 10^{-2} M NaTPB is equivalent to 15.04 mg of mianserin hydrochloride).

Content uniformity assay

Ten individual tablets were placed in separate 50 ml beaker and dissolved by shaking with about 25 ml hydrochloric acid solution 0.1 M and then the solutions were titrated potentiometrically, as described above.

Dissolution test

The test was carried out according to the USP XXII method [8] with the use of the equipment shown in Fig. 1.

One 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 mianserin hydrochloride is calculated from the calibration graph. For the UV determination, after an appropriate time interval (2 min), 5 ml aliquots were withdrawn, filtered and diluted with the dissolution medium and the absorbance of the solution at 278 nm was measured against the dissolution medium and the amount of the mianserin hydrochloride is calculated from the calibraton graph. The withdrawn volumes were replaced with fresh dissolution medium kept at 37 ± 0.5°C.

RESULTS AND DISCUSSION

Electrode response

Typical calibration graph for the mianserin membrane sensor shows that the electrode response is linear in the range 10^{-2} - 5 x 10^{-6} M for citrate buffer solution. The critical response characteristics of the electrode in the citrate buffer solutions are summarized in Table 1.

Effect of pH

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

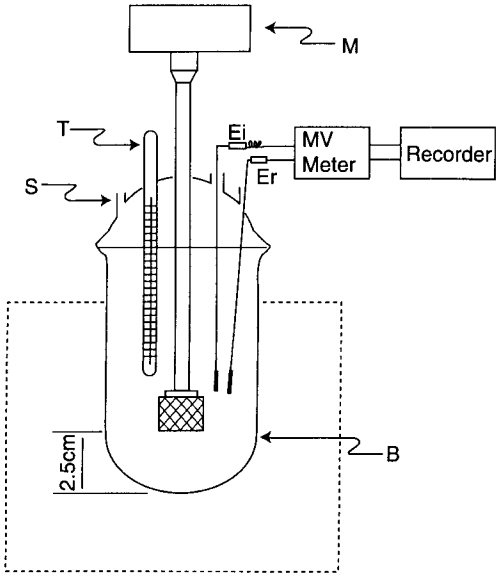

Figure 1. Modified USP basket stirrer dissolution apparatus
T - Thermometer; M-motor; B-basket-stirrer;
S - Sampling device; E_i -EMIS;
E_r - ESC (connected by a saturated KNO_3 agar-agar bridge)

Table 1. Response characteristics for Mianserin Sensor

Parameter	Response
Slope (mV per log a)*	56.5 ± 0.7
Intercept, E_o (mV)**	361 ± 0.5
Linear range (M)	10^{-2} - 5 x 10^{-6}
Detection limit (M)	1.5 x 10^{-6}

* Standard deviation of average slope values for multiple calibrations (n=45)

** Standard deviation of values recorded over a period of two month (n=60)

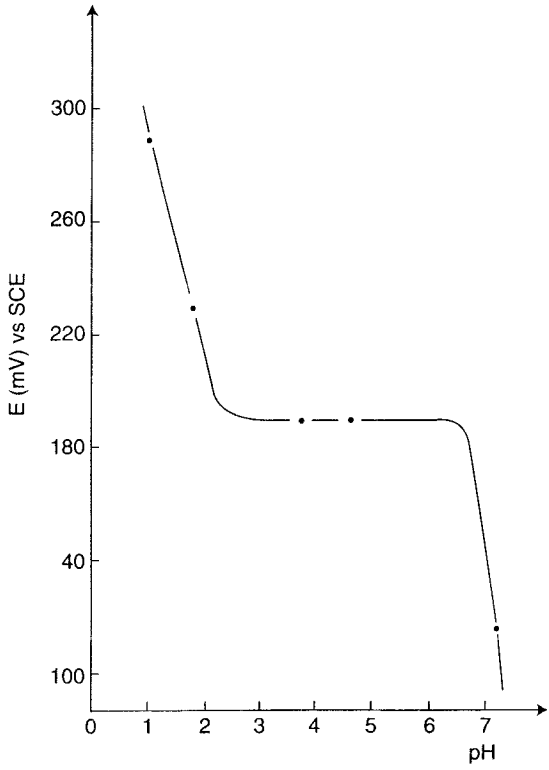

Figure 2. Effect of pH on the response of the mianserin sensor (10^{-3} mol/l mianserin hydrochloride solution)

varying the acidity by the addition of very 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 2 - 6.5 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.

Selectivity of the sensor

Mianserin hydrochloride very often has to be determined in pharmaceuticals, which also contains 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[19]. The selectivity coefficients, presented in Table 2, indicate that the response of the proposed sensor is not

TABLE 2. Selectivity coefficients for the mianserin sensor

($[Mianserin^+]/[J^{+2}] = 10^{-4}/10^{-2}$)

Interfering species J^{+2}	K^{pot} Mians, J
Ca^{2+}	1.2×10^{-2}
Ephedrine. HCl	2×10^{-4}
Glycine	$> 10^{-4}$
DL - Histidine	$> 10^{-4}$
Vitamin B_1	4×10^{-4}
Vitamin B_6	$> 10^{-4}$
Imipramine.HCl	5.1×10^{-1}

affected by the presence of the interfering ions studied except calcium. Excipients such as corn starch, gelatin, sugar and lactose also do not interfere.

Analytical applications

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

As can be seen in Table 3 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 official standard methods[8-9].

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 the mianserin tablets and indicates the suitability of the electrode method for this purpose.

TABLE 3. Determination of Mianserin Hydrochloride in Tablets with the Mianserin Sensor

Product	Sample	Recovery (% of nominal value)*	RSD (%)
MIANSERIN A 30 mg/tablet ICCF/Bucharest	1 2 3	95.57 94.52 95.80	1.52
MIANSERIN B 30 mg/tablet ICCF/Bucharest	1 2 3	100.32 99.54 100.73	0.98

* All values are the average of four determinations
Mianserin A represents a batch obtained without calcium hydrophosphate as excipient
Minaserin B represents a batch obtained with calcium hydrophosphate as excipient

TABLE 4. Results of Content Uniformity Test of Mianserin Tablets (Batch A) with the Mianserin-DNNS Sensor (label amount 30.0 mg/tablet)

Tablet	Found		RSD
	mg/tablet	%	(%)
1	28.98	96.60	
2	28.78	95.93	
3	28.59	95.40	
4	28.79	95.97	1.48
5	28.36	94.60	
6	27.62	92.10	
7	28.79	95.97	
8	28.69	95.66	
9	28.00	93.33	
10	28.77	95.90	

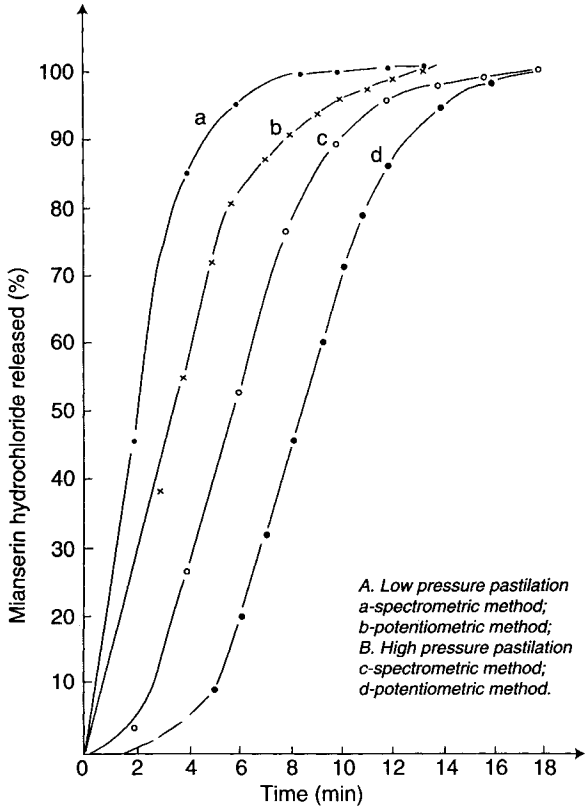

Figure 3. Dissolution profiles of uncoated mianserin tablets (average of six determinations)

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 equipment for monitoring dissolution tests [20-25].

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. The dissolution test was performed with the use of both potentiometric mianserin sensor method and a UV assay. For the former method, the potential value was recorded and the amount of mianserin hydrochloride released was determined from a re-calibration graph performed at 37 ± 0.5°C in the range 10^{-5} - 6 x 10^{-4} mol/l.

Fig. 3 shows the dissolution profile of uncoated mianserin tablets by both methods, at two different formulations. As can be seen, there are no significant differences between the two similar profiles.

Both methods proved that the release of the active principle of the uncoated tablets in simulated gastric fluids follows the Langenbucher model[20] (for high pressure pastilation, 6 kgf/cm^2): i.e. the dissolution process involves two main steps: an initial step, of about 4 min while there is a disintegration process, followed by a rapid process of active principle dissolution; and a Hixson-Crowell[25] (for low pressure pastilation, 3 kgf/cm^2): i.e. the dissolution process involves a rapid process of active principle. All other simulation possibilities tested[7] we found to be inadequate for the uncoated mianserin tablets.

CONCLUSIONS

The mianserin-selective plastic membrane sensor, based on mianserin hydrochloride-dinonylnaphthalenesulfonic acid ion-pair complex in a PVC matrix, exhibits useful analytical characteristics for the determination of mianserin hydrochloride in pharmaceuticals. The sensor can be successfully used in establishing dissolution profiles for uncoated mianserin tablets.

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