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SELECTIVE DETERMINATION OF VERAPAMIL IN SOME PHARMACEUTICAL PREPARATIONS USING SIMPLE POTENTIOMETRIC SENSOR

By

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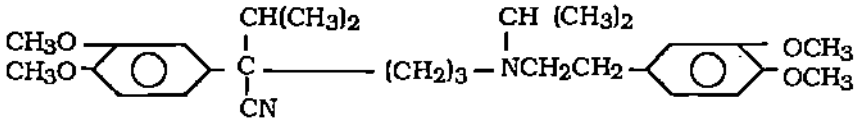
SUMMARY

A PVC membrane electrode for verapamil has been prepared for the direct potentiometric determination of verapamil in pharmaceutical preparations. It exhibits a near Nernstian response in the range $7x10^{-5}$-10^{-2}M verapamil hydrochloride with a slope of 55 mv per concentration decade. The electrode has a reasonably wide working pH range (2-7.6) in 0.1M NaCl, a fast response time (less than 60 S) and is stable for at least three months. It shows a good selectivity for verapamil in the presence of various excipients commonly present in a number of pharmaceutical preparations. The mean relative standard deviation for verapamil determination in 40 $\mu g\ ml^{-1}$-$1mgml^{-1}$ aqueous verapamil hydrochloride solutions is 1.2%.

INTRODUCTION

Verapamil 5-[3,4-dimethoxyphenethyl methyl-amino]-2-(3,4-dimethoxyphenyl)-2- isopropylvaleronitrile (I), is being intensively studied because of its ability to suppress inward calcium currents in cardiac and other excitable tissues.[1-3] Such "slow" calcium currents may be involved in fatal arrhythmias occurring during myocardial ischemia or infraction and associated with sudden

cardiac death[4]. The calcium antagonist verapamil reduces pathologically raised blood pressure by dilating the peripheral blood vessels peripheral resistance diminishes and the load on the heart is thus relieved.



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Verapamil hydrochloride in pharmaceutical preparations is extracted from powdered tablets and the supernatent solution is analysed by h.p.l.c.[5-8]. The high-performance liquid-chromatographic system is also recommended for the determination of the drug in blood corpuscles[9], blood plasma or serum[10], plasma[11-13], human serum[14] and in postmortem specimens[15]. Analysis of verapamil and its metabolites in human plasma[16], post mortem specimens[17], liver tissue or stomach content in fatal cases[18] and serum[19] has been performed by the gas-chromatography. Verapamil determination in biological material[20], stomach content and liver[21] were assigned by thin layer chromatography. Fluorometric determination of verapamil in blood, urine or tissue homogenates has been discribed[22]. Verapamil hydrochloride in pharmaceutical preparations was also determined spectrophotometrically[23].

The present study was made for preparing a PVC membrane electrode responsive for verapamil and using it for selective potentiometric measurments of verapamil in pharmaceutical preparations.

EXPERIMENTAL

Apparatus

The potentiometric measurments were made at 25±1°C using an Orion digital-pH-millivoltmeter (Model-720) with the PVC verapamil-TPB membrane electrode using an Orion (90-02) double junction Ag/AgCl reference electrode using 10% m/v potassium nitrate in the outer compartment and an Orion (90-00-02) solution in the inner compartment. pH measurments were made by an Orion combination glass electrode Model(91-01). Standardization of TPB was made by an Orion Ag-Ag_2S membrane elecrode (Model 94-02) versus the previously mentioned double junction reference electrode.

Reagents and Materials

Materials and reagents were obtained as follows:-

Sodium tetraphenyl borate from fluka, dioctylphthalate (DOP) and tetra hydrofuran from Aldrich, the PVC used was (Breon III Ep from UK). All other chemicals were of analytical reagent grade. A standard verapamil hydrochloride sample was a gift from Elnasr Pharm. Co, Egypt. Other verapamil drugs were obtained from local drug stores.

Solutions were prepared with deionized water. Sodium tetra phenyl borate (NaTPB) was prepared, filtered twice and standardized potentiometrically with standard 10^{-2} M $AgNO_3$ solution. 10^{-1}M verapamil hydrochloride standard was prepared by dissolving 4.91g of pure verapamil hydrochloride in 100 ml of 0.1M NaCl solution. A series of standard solutions were also prepared by appropriate dilution with NaCl solution from 10^{-1}-10^{-6} M.

Electrode Preparation

The sensor was prepared by mixing 100ml aliquot of 10^{-2} M aqueous verapamil solution and 100 ml aliquot of 10^{-2} M aqueous sodium tetraphenylborate solution. The white ion-pair precipitate was filtered off, washed several times with deionized water and dried at room temperature. The infrared spectrum of the complex displayed almost all absorption bands that present in the individual spectra of both verapamil HCl and NaTPB.

Master membranes were cast from PVC (190mg), plasticising solvent mediator (350mg) and sensor (10mg). The previous cocktail was dissolved in 5 ml of freshly distilled tetra hydrofuran (THF), then poured into a 5 cm diameter petri-dish. The solvent was allowed to evaporate slowly over a period of 48 h, whereby a transparent disc, approximately 0.2mm thick was formed, A disk was cut from the master membrane, and mounted in an electrode configuration according to the procedure of Moody et al[24].

The electrode internal solution was prepared from a mixture of equal volumes of $5x10^{-2}$ M of verapamil hydrochloride and $5x10^{-2}$ M of sodium chloride.

The membranes were stored at room temperature in closed containers. Before calibration, a fresh electrode was preconditioned in 10^{-2} M verapamil hydrochloride solution for at least 24h. The electrode was Kept in 10^{-2} M verapamil hydrochloride after each measurment . A steady state dynamic response was normally obtained in less than 60 S.

Electrode Calibration

Standard solutions of verapamil hydrochloride in the concentration range 10^{-1}-10^{-6} M were prepared. Aliquots of 10 ml of the standard solutions were transferred into 50-ml beakers and the PVC verapamil-TPB membrane electrode in conjunction with an Orion double-junction Ag-AgCl reference electrode (Model 90-02) was immersed in the solutions starting from 10^{-6} to 10^{-1}. The measured potentials were followed for a period of 15 min for each concentration, and plotted against the logarithm of the verapamil concentration. A steady state response has been reached in 90 S and the calibration curve show a slope of 55 mv/conc. decade Fig (1).

Determination of Verapamil

For direct potentiometric assay of verapamil in drugs, a 80 mg portion of the tablet was finelly powdered and transferred quantitatively with 0.1M NaCl solution into a 250ml calibration flask. The solution was then diluted to the mark with 0.1M NaCl solution and shaken for 5 min. Aliquots (10ml) of these drug solutions were transferred into 50 ml beakers, the PVC verapamil-TPB membrane electrode and Orion double junction Ag-AgCl reference electrode were immersed in the solutions. The electrode system was allowed to equilibrate with stirring and the e.m.f. was recorded and compared with the calibration graph. Alternatively, the standard addition (Spiking)[25] technique was used by recording the e.m.f. before and after the addition of 1.0 ml of standard 10^{-2} M verapamil hydrochloride solution to the obove solutions. The change in the potential readings was recorded and used to calculate the verapamil content in various pharmaceutical preparations.

Potentiometric Titration

Aliquots (10-30 ml) of verapamil hydrochloride test solutions (10^{-3}M) were pipetted into a 100-ml beaker. The verapamil selective electrode and the double junction reference electrode (Orion 92-02) were immersed into the solution and the stirred solution was titrated slowly with a standard $6.5x10^{-3}$ M sodium tetra phenylborate (NaTPB) solution. The inflection point of the titration curve corresponds to 1:1 verapamil: TPB reaction. 1.00 ml of $6.5x10^{-3}$ M NaTPB ≡ 3.195 mg of verapamil hydrochloride.

RESULTS AND DISCUSSION

Electrode Characteristics

The specific response characteristics of a PVC verapamil-TPB membrane electrode are shown in Table (1) and Fig (1). Calibration were made at a constant pH and ionic strength using 0.1 M NaCl solution. Table (1) shows that the electrode displays a linear response for aqeous verapamil hydrochloride solutions over the concentration range $7x10^{-5}$-10^{-2}M. The potential readings were stable and consistent to ± 2 mV day-to day for at least 4 weeks . The calibration slope is 55± 0.2 mV per concentration decade, the detection limit, as defined by an e.m.f. difference of 18 mV between the calibration graph and the extrapolated linear section, is better than $9x10^{-5}$ M (Ca 44.0 µg/ml). This indicates the feasibility of using this electrode to determine verapamil in pharmaceutical preparations.

Effect of pH and Time

The pH dependence of the electrode potential was measured as described previously[25]. Although the potential readings

displayed by the PVC verapamil-TPB membrane electrode are reasonably stable, measurments in NaCl solution provides stable potential readings for up to 10 min. The static response time of PVC verapamil-TPB membrane electrode is fast Ca 90S for 10^{-3} M verapamil, but the dynamic response is even better. All potentiometric measurments were made at 25± 1°C. The potential response of the electrode for 10^{-6}-10^{-1}M aqueous verapamil hydrochloride solutions was followed.

Effect of Interferents

The response of PVC verapamil TPB membrane electrode was checked in the presence of a number of organic and inorganic cations and other organic species. The resulting selectivity coefficients are shown in Table (2). The verapamil pharmaceutical drugs commonly contain excipients and diluents, such as talc powder, starch and lactose. None ef these diluents in concentration level as high as 100-fold excess affect the response of the electrode.

Determination of Verapamil

Results for measurments of pure aqueous verapamil hydrochloride solutions at concentrations of 44μg/ml-0.74μg/ml using the PVC verapamil -TPB membrane electrode (DOP plasticiser) and the standard addition spiking technique[25] are given in Table(3). The mean relative standard deviation is 1.2%. Potentiometric titration of 4.9-14.7 mg verapamil hydrochloride v.s standard $6.5x10^{-3}$M aqueous NaTPB solution using the PVC verapamil-TPB membrane electrode as an indicator electrode Fig.(2) shows potential break of Ca 100-150 mv at the stoicheiometric 1:1 molar reaction.

Determination of Verapamil in Pharmaceutical Preparations

Table (3) presents results obtained by direct potentiometry of verapamil in pharmaceutical tablets using th PVC matrix membrane electrode. Anaveragerecovery of 99.0% (SD 0.1% n=5) of the nominal values is obtained, for direct potentiometry and standard addition method.

In conclusion, the proposed membrane electrode system offers a simple, rapid and accurate, screening technique for the determination of verapamil in pharmaceuticals.

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Table (1)

Response characteristics of the PVC Verapamil-TPB membrane electrode with DOP plasticiser.

Parameter	DOP
Slope/mV decade-1	55.0
Intercept /mv	140 mV
Lower Limit of Linear ran ge/M	$7X10^{-5}$
Detection Limit/M	$9X10^{-6}$
Dynamic response time for 10^{-3}M Verapamil, s	60

Table (2)

Selectivity Coefficient of Some Organic and Inorganic Interferents

Interferent	$K^{pot}_{ver.\ B}$
Glutamic	$1.1x10^{-2}$
Urea	$7.3x10^{-3}$
K^+	$6.83x10^{-3}$
Mg^{++}	$6.72x10^{-3}$
Na^+	$6.66x10^{-3}$
Glucose	$1.4x10^{-2}$
Alanine	$3.99x10^{-3}$
Ca^{++}	$6.72x10^{-3}$
Maltose	$1.3x10^{-2}$
Amm. chloide	$7.5x10^{-3}$
m. aminophenol	$7.2x10^{-3}$
P-aminophnol	$9.9x10^{-3}$
Glycine	$1.42x10^{-3}$
ethylamine	$1.8x10^{-3}$
Butylamine	$1.2x10^{-4}$

Table (3)

Determination of Verapamil in Some Pharmaceutical Preparations

Pharmaccutical product and source	Recovery %	
	Direct Potentiometry	Standard addition
80 mg, Elnasr Pharm. Co, Egypt.	98.5%	99.2%
40 mg, Elnasr Pharm. Co, Egypt.	100%	98.5%

* Average of five measurments

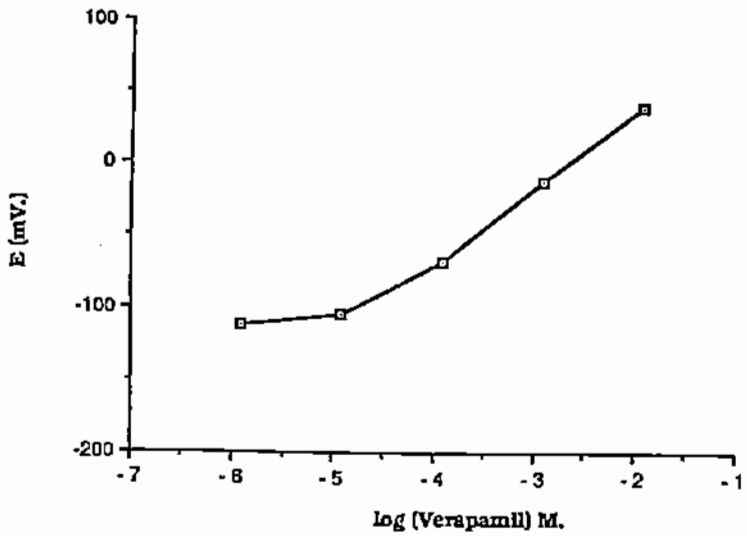

Fig (1) CALIBRATION CURVE

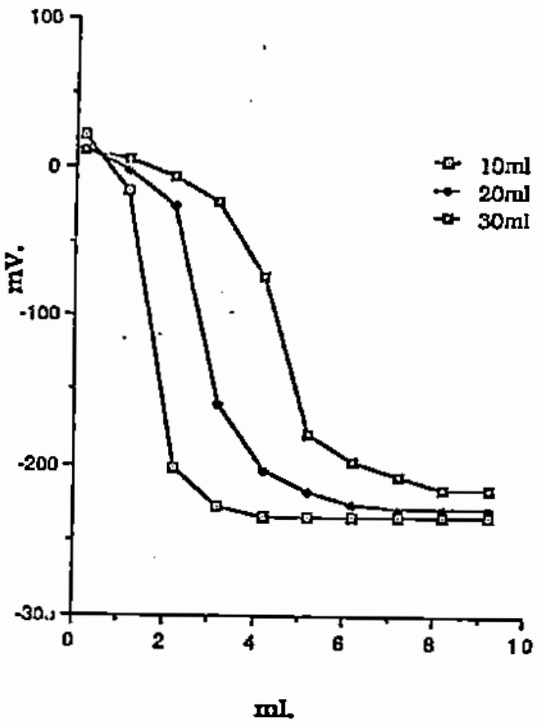

Fig (2) Potentiometric Titration of Verapamil 10^{-3} M v.s. Standard 6.5×10^{-3} M Na. TPB.

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التقدير المنتخب للفراباميل فى بعض المستحضرات الدوائية بأستخدام قطب بسيط نو غشاء من كلوريد البولى فينيل

منى عبد العزيز أحمد
قسم الكيمياء – كلية البنات – جامعه عين شمس
القاهرة – مصر

يتناول هذا البحث طريقة لتحضير قطب منتخب لمادة الفراباميل نو غشاء سائل محمل على مادة كلوريد البولى فينيل واستخدامه للقياس الجهدى المباشر للفراباميل فى بعض المستحضرات الدوائية . وقد دلت الدراسة على أن هذا القطب يستجيب استجابة تكاد تتطابق مع معادلة نرنست فى مدى تركيز من $١٠^{-٢}$–٧×١٠^{-٥} مولارى من الفراباميل مع ميل يقدر بـ ٥٥ ملى فولت لكل وحدة تركيز .

ولقد اظهر هذا القطب صلاحية للاستخدام فى مدى واسع من الأس الايدروچينى يتراوح بين ٢ و ٧.٦ فى محلول تركيزه ١٠ . مولارى من كلوريد الصوديوم حيث كان وقت الاستجابة سريع (أقل من ٦٠ ثانية) . ويعمل هذا القطب بكفاءة عالية على مدى ثلاثة اشهر على الأقل وهذا القطب له اختيارية عالية للفراباميل واظهرت النتائج دقة عالية تقدر بـ ٩٩٪ ، ومتوسط حيود ١.٢٪ عند تقدير كميات من الفراباميل تتراوح بين ٤٠ ميكروجرام و١ ملى جرام/ملى لتر .

وتم تقدير الفراباميل فى بعض المستحضرات الدوائية المستخدمة فى حالات ارتفاع ضغط الدم . حيث كانت النتائج مطابقة لتلك التى حصل عليها باستخدام الطرق المعتمدة فى دستور الأدوية الأمريكى .