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A review on the Pharmaceutical Compound Verapamil Hydrochloride

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Summary: A review for the analytical methods used for the determination of the pharmaceutical compound verapamil hydrochloride (VpCl) is presented. The different methods are classified and discussed. 27 references have been cited in this review.

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Chemically, verapamil hydrochloride (VpCl), is 5-[(3,4-Dimethoxyphenethyl) methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrilehydrochloride). It is a white, crystalline powder, soluble in water, freely soluble in methanol, sparingly soluble in alcohol, it melts at about 144^{o}C.[1]

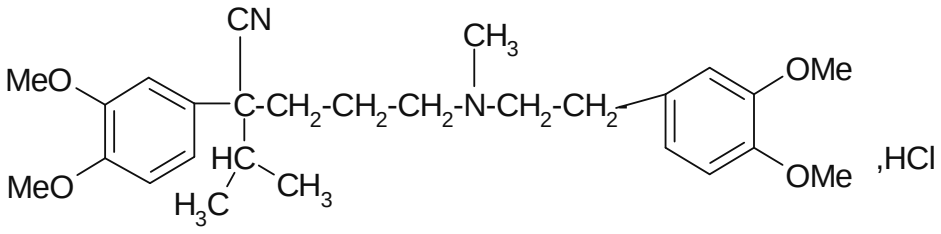

Figure 2. The chemical structure of verapamil hydrochloride

Chemical formula: $C_{27}H_{38}N_2O_4$ .HCl,

Molecular weight: 491.10

Verapamil hydrochloride inhibits the transmembrance influx of calcium ions into the heart and vascular smooth muscle cells. It improves the relation between oxygen supply and consumption in the myocardium because oxygen demand is lowered directly as a result of the effect on the energy consuming metabolic process of the myocardial cells and indirectly due to a reduction of the afterload. It also enhances myocardial blood flow due to the calcium antagonistic effect on the smooth vascular muscles of coronaries. Therefore, it contributes to the anti-ischemic and anti-anginal efficiency in all types of coronary artery diseases and is also used as anti-hypertensive and anti-arrhythmic. It is commonly formulated as tablets and injection as single component preparations.[(1)]

Methods of analysis of verapamil hydrochloride

Several methods have been reported in comprehensive reviews for the determination of verapamil hydrochloride. Most of these methods have been applied for its determination in pure state and in pharmaceutical preparations, some of which are listed in the following.

Spectrophotometric methods

Several spectrophotometric methods have been proposed for the determination of pharmaceutical compounds. Among of which are to be mentioned the direct measurement of the pharmaceutical compound at its maximum absorbance, derivative spectrometry methods were also used, other methods depend on oxidation of the pharmaceutical compound followed by measuring the absorbance at maximum absorbance of the oxidation product. Other methods may involve complexation with metal ions, or ion-pair formation with metal ion complexes. Charge transfer complex formation reaction is frequently used for spectrophotometric determination.

Rahman and Azmi described a rapid, simple, and sensitive validated visible spectrophotometric method for the assay of verapamil hydrochloride either in pure form or in pharmaceutical formulations. The method involves the oxidation of the verapamil hydrochloride with *N*-bromosuccinimide in perchloric acid medium at room temperature,

leading to the formation of a yellow colored product, which absorbs maximally at 415nm. Under the optimized experimental conditions, the color is stable up to 45 min and Beer's law is obeyed in the concentration range of 10.0–200.0 μg ml^{-1} with molar absorptivity and Sandell's sensitivity of 2.55 × 10^3 l mol^{-1} cm^{-1} and 0.192 μg cm^{-2} per 0.001 absorbance unit, respectively. The method has been successfully applied to the determination of the drug in commercial dosage forms. Statistical comparison of the results with those of a reference method by means of point and interval hypothesis shows excellent agreement and indicates no significant difference in accuracy and precision. Results of analyses were optimized and validated statistically and through recovery studies. The experimental true bias of all samples is smaller than ±2%.[(2)]

A spectrophotometric method was described for the determination of verapamil hydrochloride, based on its oxidation with chloramine-T in hydrochloric acid medium. A yellow-colored compound with maximum absorbance at 425 nm was produced. Beer's law was obeyed in the concentration range 0-340 μg mL^{-1} with molar absorptivity of 2x10^3 L mol^{-1} cm^{-1} and RSD 0.3-0.82%. All variables were studied to optimize the reaction conditions. No interferences were observed form the common excipients present in the formulations. The method has been applied successfully to the determination of the drug in pharmaceutical preparations. Statistical comparison of the results with those from the reference method reveals excellent agreement and confirms that accuracy and precision are not significantly different.[(3)]

According to Prabhakar et al., powdered tablets equivalent to 25 mg verapamil hydrochloride were accurately weighed and dissolved in water by shaking for 2-5 min. The volume was made up to 25 mL and the solution was filtered. After filtration, a 0.4 ml portion of the filtrate was transferred to a separating funnel and 5 ml of Alizarin red-S solution (0.1 g in 100 mL water) was added. The solution was mixed and successively extracted with $CHCl_3$. The combined extract was dried over anhydrous Na_2SO_4 and made up to 10 mL with $CHCl_3$. The absorbance of the resulting yellow-colored ion-pair complex was measured at 426 nm (ε= 4829). The color was stable for 25 min. Beer's law

was obeyed from 10-100 μg mL^{-1}. Student's tests and variance ratio F tests showed no significant differences between the results of the proposed method and those obtained using the USP method.[4]

Issa et al. proposed a new spectrophototometric method in which 0.1-1.0 mg verapamil hydrochloride were dissolved in 5 ml 1mN HCl and made up to 100 ml with the same acid. Portions (0.1-1.4 mL) of the solution were shaken for 5 min with 5 ml 1mM-Acid Red 29 or 10 ml Acid Red 176, 1.0.-2.0 mL 0 1 N HCl and 5 mL $CHCl_3$. A further 5 ml of $CHCl_3$ was added and the mixture was shaken again for 5 min. The combined $CHCl_3$ layers were centrifuged for 5 min at 2000 rpm and the absorbance was measured at 530 and 546 nm vs. $CHCl_3$ for Acid Red 29 and Acid Red 176, respectively. Calibration graphs were linear from 4.91-58.93 μg mL^{-1} of verapamil hydrochloride. RSD ranged from 1.07-3.85% and 1.09-4.1% for verapamil hydrochloride tablets using Acid Red 29 and Acid Red 176, respectively. The corresponding values for Isoptin tablets were 1.66-5.08% and 1.89-4.6%. Recoveries ranged from 98-108% and 101-109% for Acid Red 29 and Acid Red 176, respectively.[5]

El-Sayed and others determined chromonar hydrochloride, verapamil hydrochloride, acebutolol hydrochloride, carazolol and propranolol hydrochloride in extracts of their powder or powdered tablets by reaction with 0.2% chloranilic acid solution in 1,4-dioxan, 0.1% 2,6-dichlorophenolindophenol solution in $CHCl_3$ or 0.2% 2,3-dichloro-5,6-dicyano-p-benzoquinone solution in acetonitrile. The absorbance was measured at 540, 640 or 456 nm for the respective reagents. The results were comparable with those of UV spectrophotometry.[6]

Aqueous solution of verapamil hydrochloride or oxyfedrine hydrochloride were treated with acid dyes such as Sunset yellow (C. I. Food Yellow 3), erioglaucine (C. I. Acid Blue 9), Indigo carmine (C. I. Food Blue 1), or Carmosin-S (C. I. Acid Red 14), and the complexes were extracted into $CHCl_3$ for absorbance measurements. The optimum pH for complex formation was 3.0 for Food Yellow, and 1.0 for the other dyes. The wavelengths of maximum absorption were 483 nm (for verapamil hydrochloride with Food Yellow), 627 nm (verapamil hydrochloride with Acid Blue 9), 602 nm (verapamil

hydrochloride with Food Blue), 482 nm (oxyfedrine hydrochloride with Food Yellow), 627 nm (oxyfedrine hydrochloride with Acid Blue 9), 604 nm (oxyfedrine hydrochloride with Food Blue) and 520 nm (oxyfedrine hydrochloride with Acid Red 14). Beer's law was obeyed for concentration of verapamil hydrochloride in the ranges 1.3 to 5.3 μg ml^{-1} (with Acid Blue 9) and 33 to 130 μg mL^{-1} (with Food Blue 1) and for oxyfedrine hydrochloride in the ranges 1 to 4 μg mL^{-1} (with Acid Blue 9) and 40 to 105 μg mL^{-1} (with Food Blue 1). The method was sensitive, accurate and precise, and was suitable for application to the routine quality-control analysis for verapamil hydrochloride and oxyfedrine hydrochloride in tablets.[7]

Chromatographic methods

Many papers have been reported for the chromatographic determination of verapamil hydrochloride, some of which are listed in the following.

Ammonium hydrogen carbonate buffer has been found to be especially useful for high-pH HPLC analysis of samples from both combinatorial and medicinal chemistry sources. Satisfactory results were obtained by the standard diode array, evaporative light-scattering, and MS detection by using this buffer at a concentration of 10 mM. From a practical standpoint, ammonium hydrogen carbonate is an ideal buffer for chromatographers since it provides excellent chromatographic behavior and reproducible separation. In addition to this, its volatility makes it an essential tool for rapid liquid chromatography-mass spectrometry product identification. Ammonium hydrogen carbonate was tested for a number of drug-like compounds analyzed as mixtures, and data obtained were compared to those from the classical and mass spectrometry friendly buffers widely used by chromatographers: trifluoroacetic and formic acids. The results of this study revealed the suitability of this buffer for routine HPLC application in research laboratories.[8]

A high-performance liquid chromatographic procedure with two detectors is presented for the determination of verapamil in pharmaceutical dosage forms. The procedure is based on the use of reversed-phase high-performance liquid chromatography

with UV and fluorimetric detectors. Each analysis required no longer than 6 min for both detection procedures. Quantification was achieved by measurement of the ratio of the peak area of the drug to the internal standard (fluoxetine) and the detection limit was; 10 ng ml^{-1} for the UV detector, and 750 pg mL^{-1} for the fluorimetric detector. There was no significant difference between inter- and intra-day studies for verapamil determined for two different concentrations (0.05 and 1.00 μg mL^{-1}). This process could be used to determine verapamil concentrations in the range 0.025–50 and 0.0008–20 μg mL^{-1} for UV and fluorimetric detection, respectively. These methods were applied, without any interference from the excipients, for the determination of the drug in tablets and in drug dissolution studies. It is suggested that the proposed HPLC procedures could be used for routine quality control and dosage form assay of verapamil hydrochloride.[9]

Wang dissolved verapamil hydrochloride in and diluted with mobile phase to a concentration of 0.25 mg ml^{-1} for HPLC on a 10 μm Irregular-H C18 column (20 cm x 4.6 mm i.d.) operated at 40°C, with acetate buffer of pH 4/methanol/triethylamine (55:45:1) as mobile phase (1 mL/min) and detection at 278 nm. The calibration graph for verapamil hydrochloride was linear from 0.05-1.0 mg mL^{-1}, with a detection limit of 0.1 μg mL^{-1}. The method was also applied to verapamil hydrochloride pharmaceutical raw material, tablets and injection solutions. The recovery was 99.5-101.1% with RSD of 0.2-0.4%. Impurities and excipients did not interfere.[10]

Valvo et al. described the development of a reversed-phase liquid chromatographic method for the determination of related substances in verapamil hydrochloride. The method is based on the use of a simple mobile phase on a specialty base-deactivated reversed-phase column. It enables the resolution of 13 related compounds from the parent drug and from each other. Validation of the method showed it to be reproducible, selective, accurate and linear over the concentration range of analysis with a limit of detection of 0.5 μg mL^{-1}. The developed method proved to be a real improvement compared with the liquid chromatography test for chromatographic purity described in the USP monograph for verapamil hydrochloride. Verapamil hydrochloride (25 mg) was dissolved in 5 mL 0.04 M monobasic potassium phosphate

adjusted to pH 3 with H_3PO_4. A portion (10 µL) was analyzed by HPLC on a 5 µm Suplex pKb-100 column with gradient elution (1.5 mL/min) using 0.04 M dibasic potassium phosphate of pH 7.2/acetonitrile [63:37 for 22 min, then linear gradient to 1:1 (held for 8 min) in 5 min, then to 63:37 (held for 14 min) in 1 min] and detection at 278 nm. Separation of verapamil hydrochloride from 13 potential impurities was achieved. The calibration graphs were linear for 0.01-1.0% each potential impurity, the detection limits were ~0.5 µg/mL (0.01%) or lower and the quantitation limits were ~1 µg/mL (0.02%) or lower. Recoveries were 86-109%. Peak area RSD were <1.5% at 0.3-0.5% compound, <5% at 0.05-0.15% compound and <13% for 0.02% compound.[11]

Tablets containing about 25 mg verapamil hydrochloride, were dispersed in H_2O; the solution was filtered and diluted to 25 mL with more water. This solution was further diluted (2.5 ml to 100 mL). Ampoule formulations were also diluted (1 mL to 100 mL with water. HPTLC silica gel 60 F254 plates were washed with methanol, air-dried and heated at 120^oC for 30 min before use. Samples (10 µL) and standards (1-8 µL of a 25 µg ml^{-1} solution of verapamil hydrochloride) were applied as 4 mm long streaks, 3 mm apart along the origin line at 1 cm from the lower edge. The plates were developed for 8 cm (15 mL with water/methanol/ethyl acetate (10:13:10) and the spots were scanned in absorbance mode at 278 nm. The calibration graph was linear from 25-200 ng of verapamil hydrochloride /band. With pure verapamil hydrochloride samples (50-125 ng/band), the mean recovery was >99.9% and the intra- and inter-day RSD (n = 3 and 6, respectively), were 0.17-0.62 and 0.88-1%. Recovery of verapamil hydrochloride in three dosage forms agreed closely with the labeled values, with RSD (n = 6) of 1.51-3.52%. There was no interference from degradation products of verapamil hydrochloride or excipients.[12]

For determination of verapamil in rabbit plasma 0.1 ml of rabbit plasma, 375 µl acetonitrile and 25 µl 5,6-benzoquinoline (1 mg mL^{-1} in mobile phase; internal standard were mixed). After vortex-mixing for 13 min, the mixture was centrifuged at 5000 rpm for 5 min. A portion (5 µL) of the acetonitrile phase was analyzed by HPLC on a 5 µm Ultracarb C20 ODS column, acetonitrile/0.07% orthophosphoric acid (33:67) as mobile

phase (1 ml/min) and detection at 320 nm (excitation at 280 nm). The calibration graph was linear from 30-1000 ng mL^{-1} of verapamil and the detection limit was 3 ng mL^{-1}. Recoveries were 80-98%. RSD are not given. The method was applied to pharmacokinetic studies of verapamil after intravenous administration of verapamil hydrochloride to rabbits.[13]

Rutledge et al. mixed plasma (1 mL) with 50 µl of internal standard solution (5 µg mL^{-1} of verapamil hydrochloride in H_2O), 1 mL of borate buffer solution of pH 8.9 and 1 g of NaCl and the mixture was extracted with 6 mL of hexane/propan-2-ol (19:1). The organic layer was back-extracted with 200 µL of 5 mM H_2SO_4 and a 50 µL portion of the aquoues phase was analyzed on a SynChrom SCD 100 column with a mobile phase (1 mL/min) of 40 mM dibasic potassium phosphate/methanol (1:1) and detection at 237 nm. The calibration graphs were linear for 50-3000 µg mL^{-1} of celiprolol and 20-400 µg mL^{-1} of diltiazem, deacetyldiltiazem and desmethyldiltiazem; corresponding detection limits were 25.7, 4.8, 2.3 and 4.8 µg mL^{-1} from plasma. Within- and between-day RSD are tabulated and were 10%. A number of drugs commonly co-administered with either celiprolol or diltiazem were evaluated for possible interference effects; results are discussed.[14]

Fieger and Blaschke mixed plasma with 2 M NaOH and extracted with ethyl ether. After centrifugation, the organic phase was mixed with acetic anhydride solution and evaporated to dryness. The residue was dissolved in mobile phase [0.01 M phosphate buffer (pH 7.0)-acetonitrile (9:1)] and subjected to HPLC on a column of Chiral-AGP, with a mobile phase flow rate of 0.9 mL min^{-1} and detection at 223 nm. Alternatively, plasma was mixed with 0.9% NaCl and 2M NaOH and extracted with hexane. After centrifugation, the organic phase was evaporated to dryness and the residue was dissolved in propan-2-ol for HPLC analysis on a column of Chiralpak AD with a mobile phase (1 ml min-1) of hexane - propan-2-ol (9:1) and detection at 223 nm. The limit of determination on both columns was 20, 50 or 30 ng mL^{-1} for verapamil hydrochloride, norverapamil hydrochloride and gallopamil hydrochloride, respectively; corresponding recoveries after extraction with hexane were 65.5, 54.1 and 63.0%.[15]

Lacroix et al. made a modification of the USP HPLC method [USP XXII, pp. 1444–1446] for the assay of the purity of verapamil hydrochloride has been evaluated for the determination of the drug content and related compounds in drug raw material. The method enables the resolution of 16 related compounds from the parent drug and, in most cases, from each other. The minimum quantifiable amount for most related compounds is less than 0.05%. Six drug raw material samples are analyzed and the total impurities found to be 0.3% or less. All drug assay values were within the USP recommended limits of 99.0–100.5 %.[16]

Korponay et al. analyzed Gentamicin sulphate, verapamil hydrochloride, oxacillin sodium, ipriflavone and 3-(ethoxycarbonyl)-6,7,8,9-tetrahydro-6-methyl-4-oxo-4H-pyrido-[1,2a]-pyrimidin-9-ylacetic acid for solvent residues by GC with FID. Methanol, propan-2-ol, toluene, ethanol, acetone, ethyl methyl ketone and isobutyl methyl ketone were detected. Headspace analysis was more sensitive for verapamil hydrochloride, and prevented interference from decomposition products of the parent compound; 3-(ethoxycarbonyl)-6,7,8,9-tetrahydro-6-methyl-4-oxo-4H-pyrido-[1,2a]-pyrimidin-9-ylacetic acid could only be analyzed by headspace sampling.[17]

Solutions of verapamil hydrochloride and aqueous extracts of tablets with dextromethorphan hydrobromide as internal standard were mixed before h.p.l.c. analysis on a column (30 cm x 4 mm) of micro Bondapak Phenyl, with aqueous 0.02 M KH_2PO_4-acetonitrile (31:19) as mobile phase (2.4 ml min-1) and detection at 278 nm. For stability studies at a range of pH values for <=105 days at 50^o, the same conditions could be used or, alternatively, a column (30 cm x 4 mm) of micro Bondapak C18, with a mobile phase (2.0 ml min-1) of 49% (v/v) methanol-0.45% (v/v) anhydrous acetic acid-aqueous 36 mM ammonium format; no internal standard was used in this instance. Samples decomposed by heating in ~0.33 M NaOH for~50 min were also analyzed. The ratio of the peak heights of verapamil hydrochloride and the internal standard was rectilinearly related to the amount of verapamil hydrochloride from 2.5 to 7.0 μg. The coefficient of variation (n = 6) was 0.63%.[18]

Tsilifonis et al. extracted verapamil hydrochloride from powdered tablets with

0.05 N HCl; after centrifugation of the extract, the supernatant solution is analyzed by h.p.l.c. on a column (30 cm x 4 mm) of micro Bondapak C18 (10 μg m), with methanol-water-acetic acid-triethylamine (55:44:1:0.1) as mobile phase (1.2 mL min^{-1}) and detection at 280 nm. Calibration graphs are rectilinear up to 274 μg mL^{-1} of verapamil hydrochloride and average recoveries are >100%. The limit of detection is 2 μg mL^{-1}. The method was also applied to solution of verapamil hydrochloride diluted with the mobile phase.[19]

Atomic absorption methods

A flow injection analysis (FIA) method coupled to resonance Rayleigh scattering (RRS) detection for the determination of verapamil hydrochloride (VpCl) was proposed. In pH 1.0 acidic medium, 12-tungstophosphoric acid (TP) reacted with VP to form an ion-associate complex, which resulted in a significant enhancement of RRS intensity. The maximum scattering peak was located at 293 nm. RRS intensity was proportional to the concentration of VpCl in the range of 0.017–13.0 μg mL^{-1}, and the detection limit (3σ) was 5.1 μg mL^{-1}. The proposed method exhibited satisfactory reproducibility with a relative standard deviation (R.S.D.) of 2.1% for 11 successive determinations of 5.0 μg mL^{-1} VpCl. Therefore, a novel method for the determination of VpCl by FIA–RRS was developed. The optimum reaction conditions and the parameters of the FIA operation such as flow rate, injection volume, reactor length, and so on had been optimized. The method had been applied to the determination of VpCl in serum samples and pharmaceuticals with satisfactory results. The maximal sample throughput in the optimized system was 80 h^{-1}.[20]

Ion-associate complexes of verapamil hydrochloride with Cd(II), Mn(II) and Zn(II) thiocyanates, potassium ferricyanide and ammonium reineckate were precipitated, the solubility of the solid complexes at the recommended optimum conditions of pH and ionic strength values have been studied. Saturated solutions of each ion-associate at different temperatures under the optimum precipitation conditions were prepared and the

metal ion contents in the supernatant were determined. The solubility products were thus calculated at different temperatures and the thermodynamic parameters ΔH, ΔG and ΔS were calculated. A new accurate and precise method was reported based on the direct coupled plasma atomic-emission spectrometry for the determination of verapamil hydrochloride (1.96-62.86 μg ml^{-1}) in pure solutions and pharmaceutical preparations.[21]

Titrimetic methods

According to a Metrohm application note, the NIO electrode was applied to monitor the potentiometric titration of oleophilic compounds with sodium tetraphenylborate (NaTPB). The electrode was applied to determine pharmaceutical compounds in both raw materials and formulations (tablets, powders, gels, creams, syrups and drops). The titrations were performed in aqueous media using 0.01 M NaTPB as titrant and an Ag/AgCl reference electrode (3 M NaCl salt bridge). The method was applied to the determination of ambroxol hydrochloride, bamipine, benzalkonium chloride, bromhexine hydrochloride, chlorhexidine digluconate, chlorhexidine dihydrochloride, chlorphenoxamine hydrochloride, chloroquine phosphate, 8-chlorotheophylline dihydrochloride, clobutinol, clotrimazol, codeine phosphate, dihydrocodeine thiocyanate, ethacridine lactate, hexetidine, ipatropim bromide, lidocaine, metoclopramide hydrochloride, octenidine dihydrochloride, papaverine, phenyltoloxamine dihydrochloride, propafenone, salbutamol sulfate, verapamil hydrochloride and xylocaine.[22]

Potentiometric methods

According to a Metrohm application note, numerous surfactants and pharmaceutical compounds can be determined by potentiometric titration. Metrohm provides five different surfactant electrodes for the indication of the endpoint, namely the Ionic surfactant electrode, the High Sense surfactant electrode, the Surfactrode Resistant, the Surfactrode Refill and the NIO electrode. Anionic and cationic surfactants are determined using TEGO trant. A 100, and sodium dodecylsulfate (sodium lauryl sulfate),

respectively, as titrants. Titrants based on sodium tetraphenylborate are used for the determination of non-ionic surfactants and pharmaceutical compounds. The preparation of the titrants and the determination of their titer are described. A tabulated list of over 170 applications of potentiometric titrimetry to the determination of surfactants and pharmaceuticals is presented.[23]

Hassan et al. prepared membrane sensors using carboxylated-PVC and Nafion matrices supported on graphite. The electrodes were prepared by placing a spectrographic graphite rod in a polyethylene sleeve with about 3 mm protruding to serve as the measuring surface. This part was washed with acetone and dried for 3 hours. Two coating mixtures were prepared (a) carboxylated-PVC (100 mg), dioctyl phthalate (0.175 ml) and THF (6 mL) and (b) Nafion (5% in a mixture of lower aliphatic alcohol) and H_2. The dried rods were dipped into the coating mixture and solvent allowed to evaporate. This was repeated 5-7 times to produce a uniform membrane. Coated rods were soaked for 2 hours in 0.01 M verapamil hydrochloride before use. To ensure electrical contact with the connection cable a drop of Hg was added to the sleeve. Sensors were conditioned for 6 hours in 0.01 M- verapamil hydrochloride. Standard solutions of verapamil hydrochloride (4.9 µg mL^{-1}-4.9 mg mL^{-1}) were prepared. Standard 1 mL was added to a beaker containing 0.01 M NaCl solution (9 mL). Sensors were immersed in the stirred solution with a double junction Ag/AgCl reference electrode. Potentials measured were plotted against log. verapamil hydrochloride concentration to produce the calibration curve. Verapamil hydrochloride was determined in a pharmaceutical preparation. Sensors had a linear range from 10 µM to 0.01 M verapamil hydrochloride with a slope of 56-57 mV/decade of concentration, a response time <10 s, a working pH range 4.0-7.5, detection limit of 0.2 µg mL^{-1} for sensor carboxylated-PVC and 1.1 µg ml^{-1} for sensor Nafion and a lifetime >6 months. Determination of verapamil hydrochloride in pharmaceuticals gave recoveries of 102.7 ±0.3% to 98.7 ±0.8% (n=5).[24]

Zhonglin and Xinsheng prepared a verapamil-PVC membrane ion-selective electrode based on the verapamil-reineckate ion pair with dibutyl phthalate as a plasticizer. The electrode exhibited a linear response with a Nernstian slope (52.8 mV

decade^{-1} at 20^{o} C) for verapamil concentrations of 10^{-5}-10^{-2} M over the pH range 3.0-7.0. The electrode also exhibited very good selectivity for verapamil with respect to various inorganic and organic cations. Gran II linear and potentiometric titrations were used to determine verapamil in pure solution, with an average recovery of 99.3% and a relative standard deviation of 0.4%.[25]

Verapamil was automatically titrated in a non-aqueous medium with ethanolic 0.1 M KOH at 0.035 mL min^{-1} in an apparatus previously described, with use of a glass electrode versus a SCE. The end point was measured either from the change (~300 mV) of the potential, or conductmetrically. Starch, talc, sucrose and lactose did not interfere. Results obtained by both titration methods over a range of 5 to 20 mg are presented; they are equally accurate (standard deviation was 0.08 mg) and reproducible.[26]

Voltammetric methods

A sensitive reduction peak was obtained for verapamil by adsorptive stripping voltammetry in 0.01 M phosphate (pH 7.4) at an accumulation time of 30s. The peak potential is -1.81 V (vs. Ag/AgCl). The peak current is directly proportional to the concentration of verapamil ($1x10^{-8}$ -$1x10^{-6}$ M), with 3 sigma detection limit of $5x10^{-10}$ M (0.246 µg ml^{-1}). The RSD at the 1 x1o^{-7} M level is 1.8%. The interference of some metal ions, some amino acids, the application of the method to analysis of urine, and pharmaceutical formulations are described. The method is simple (no extraction, rapid (30 s accumulation time), sensitive (the detection limit of verapamil is 0.491 ng/ml), reproducible (within day RSD of 1.28-1.80%), and suitable for routine analysis of verapamil, urine, and pharmaceutical formulations.[27]

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