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Potentiometric Determination of Valsartan in a Pharmaceutical Preparation and Its Protonation Constants

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A potentiometric titration method for determination of valsartan in pharmaceutical dosage forms is developed and validated. From the titration data stochiometric protonation constants are also calculated and these constants are found to be 4.57 and 5.47. The investigations were carried out in ethanol solutions using NaOH as titrant, at constant temperature of 25.0 ± 0.1 °C and ionic strength of 0.10 M NaCl. The method was found to be reliable and precise, having a relative standard deviation of less than 1.0 % for valsartan. Commercial tablets containing 160 mg valsartan were successfully analyzed by the developed method. The validity of the method was tested by the recovery studies of standard addition to a pharmaceutical preparation and the results were found to be highly satisfactory. The proposed method is simple, rapid and sufficiently precise for quality control purposes of pharmaceuticals.

Key Words: Valsartan, Potentiometric titration, Assay.

INTRODUCTION

Valsartan, (N-valeryl-N[[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl]valine) (Fig. 1) is an antihypertensive drug belonging to the family of angiotensin II receptor antagonists acting at the ATI receptor which mediates all known effects of angiotension II on the cardiovascular system[1]. Hypertension is one of the main risk factor for the cardiovascular disease and still seems to be a major health problem in many countries. Valsartan is widely used in the treatment of hypertension[2].

When the literature on the determination of valsartan is examined, it can be seen that, several analytical methods such as high performance liquid chromatography[3-7], HPLC coupled with fluorescence detection[8,9], liquid chromatography and liquid chromatography-tandem mass spectrometry[10-12], spectrophotometry[13,14] and voltammetry[1,15] have been reported. So far there are no potentiometric titration methods for the determination of valsartan in ethanol-water mixture in pharmaceutical dosage forms have been reported.

The purpose of this work is to develop simple, accurate, reproducible and rapid potentiometric method for the determination of valsartan and applying it to the pharmaceutical dosage forms.

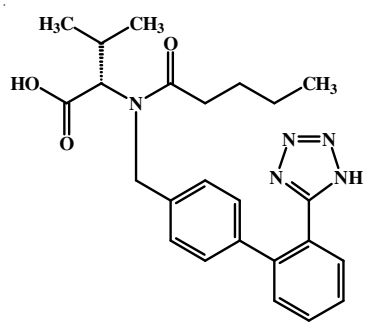

Fig. 1. N-valeryl-N [[2'-(1*H*-tetrazole-5-yl) biphenyl-4-yl] methyl] valine)

In this work the stochiometric protonation constants of valsartan were determined in ethanol:water (1:1) mixture. The stochiometric protonation constants (pK) of many compounds are reported in the literature[16]. The reason for the determination of such an enormous number of stochiometric protonation constants is the fact that many natural or artifically synthesized organic compounds include acidic and/or basic groups which affect the physical, biological and chemical properties of other compounds[17]. It is seen from the literature that most of the determinations are carried out in aqueous media. However, if we consider the fact that most of these compounds are either not soluble or are hydrolyzed in aqueous media, the determination of ionization constants in non-aqueous media has become increasingly important. The idea that biological media are very similar to non-aqueous media is another factor in the increased interest in such determinations[18-20].

EXPERIMENTAL

All potentiometric measurements were performed in an 80 mL jacketed titration cell thermostated at 25.0 ± 0.1 °C. An Orion (Beverly, MA, USA) 960 automatic titrator, equipped with a combined pH electrode (Ingold andover, MA, USA) containing a filling solution of 0.10 M NaCl, was used to measure the cell emf values. The potentiometric cell was calibrated before each experiment so that the hydrogen ion concentration rather than the activity was measured[21,22]. For ethanol-water (50:50 v/v) of the solvent mixture examined, reproducible values of the autoprotolysis constants K_w were calculated from several series of $[H^+]$ and $[OH^-]$ measurements at 0.10 M NaCl[19,23-25].

Valsartan, obtained from USP Reference Standard, was of chemically pure laboratory working standard having purity of 99.7 %. All other chemicals were of analytical grade quality (Merck) and used without further purifications. Water was deionized and purified on a Millipore water purification system and used throughout the experiments.

Valsartan stock solution was prepared by dissolving known amount of the product in 50 mL ethanol. The valsartan solution used in potentiometric titration was prepared by dilution of the stock solution with ethanol.

Stock solutions of acid and base were prepared using analytical reagent grade hydrochloric acid (Merck, Darmstadt, Germany) and sodium hydroxide (Merck), respectively.

Solution of standard base containing 0.10 M NaCl was prepared in 50 % aqueous ethanol solution (v/v) and was standardized potentiometrically against potassium phthalate (Merck) using Gran's plot techniques. Acid solution prepared in bidistilled low-conductivity water was standardized by titration against standardized sodium hydroxide solution. Primary standard sodium chloride (Merck) was used to keep the ionic strength constant.

Co-diovan (Novartis Co.) labelled to contain 160 mg valsartan per tablet.

Preparation of Co-diovan solution: Ten co-diovan tablets, which contain 160 mg valsartan/tablet, were weighed and their average weight was calculated. All the tablets were powdered in a mortar. The known amount of this powder dissolved in 100 mL ethanol and the mixture was sonicated for 5 min to have a completely dissolved co-diovan solution. The 4 mL of aliquots taken from the solutions of the pharmaceutical preparations was also titrated with standardized sodium hydroxide solution under the same conditions as valsartan.

Recovery experiments: To study the accuracy, reproducibility, precision and to check the interference from excipients used in the formulation of co-diovan, recovery experiments were carried out. In order to know whether the excipients show any interference with the analysis, known amount of the pure drug was added to pharmaceutical formulations of valsartan and the mixture was re-analyzed and recovery was calculated by the proposed method.

RESULTS AND DISCUSSION

This study is concerned with the determination of the stochiometric protonation constants of the valsartan in ethanol:water (1:1) mixture at 25.0 ± 0.1 °C. There is few study in the literature about the stochiometric protonation constants of valsartan[26]. Data on the ionization constants of similar compounds in the literature are also scarce[27-29]. The determination of the stochiometric protonation constants of valsartan is very important due to the fact that it has a wide range of practical uses. It is thought that the data obtained in 0.10 M NaCl, which simulates biological media, will be useful for determining the effective mechanisms of these compounds which has significant pharmaceutical potential.

Since the aim is to determine the stoichiometric protonation constants, the electrochemical cell used was calibrated for each medium to measure the hydrogen ion concentration and the calibration constants. These data are tabulated in Table-1. As seen from the table, the glass electrode has a slope of 59 mV, the same as the Nernstian value. It was therefore concluded that the electrode could be used to determine the stochiometric protonation constants for all this media. The electrode which exhibited Nernstian behaviour in acidic media was found to show the same behaviour in alkaline media.

TABLE-1
CALIBRATION CONSTANTS FOR THE POTENTIOMETRIC CELL AND pK_w VALUES FOR ETHANOL: WATER (1:1) MIXTURE

E^0	339.5 ± 1.90
k (slope)	59.14 ± 0.02
pK_w	14.43 ± 0.01

By using the same acid-base titrations, autopyrolytic constants (K_w) were determined for 50 % aqueous ethanol and are listed in Table-1. The value obtained was found to be in good agreement with those reported in the literature[23,24,30].

Valsartan was titrated potentiometrically with sodium hydroxide as titrant in 50 % aqueous ethanol at constant temperature of 25 ± 0.1 °C and ionic strength of 0.1 M NaCl. Although valsartan contains two acidic centers, the -COOH group and the tetrazole ring including nitrogen atoms, the titration curve of the valsartan gave one well-defined S-shaped stochiometric end-point (Fig. 2) corresponding two protons per molecule. This can be explained that the lipophilicity of valsartan displays the pattern typical of a molecule with two acidic centers with close pK values[27] and the protons of valsartan are titrated together instead of being titrated individually. The determination of equivalence points from the potentiometric data was carried using the Gran's method[31,32].

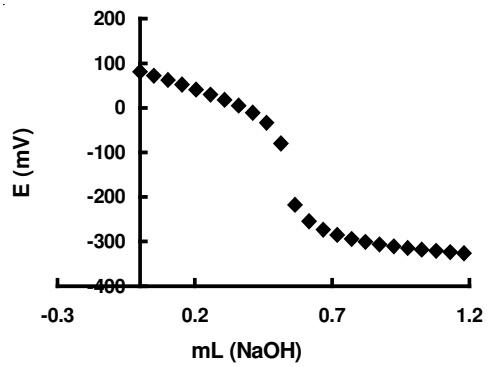

Fig. 2. Potentiometric titration curve for valsartan titrated with sodium hydroxide in ethanol-water mixture

From the potentiometric titration data, the stochiometric protonation constants of valsartan determined in ethanol:water (1:1) mixture at 25 ± 0.1 ºC are given in Table-2. The computation of the stochiometric protonation constants of valsartan from these data were done with BEST computer program. BEST software program was developed in recent years along with the potentiometric titration data. The fact that the fitted sigma (σ_{fit}) value was approximately 0.03 for the ionization constants computed using this software which show that the values were reasonable. σ_{fit} is a parameter that shows the fit between the experimental and theoretical values. The values given to the right of the ± symbols are the deviations from the mean values.

TABLE-2
IONIZATION CONSTANTS OF VALSARTAN AT 25.0 ± 0.1 ºC FOR ETHANOL:WATER (1:1) MIXTURE (μ = 0.1 M NaCl)

Experiment No.	pK_1	pK_2
1	4.61	5.49
2	4.57	5.47
3	4.55	5.47
4	4.57	5.47
5	4.57	5.45
Mean ± SD	4.57 ± 0.02	5.47 ± 0.01

$\sigma_{fit} \leq 0.01$; SD = Standard deviation.

Valsartan gave a sharp end-point (Fig. 2) when titrated with NaOH. It is thought that this end-point can be used for the quantitative determination of valsartan. Thus standard valsartan solutions were titrated with standard NaOH solution. In these titrations the consumption of NaOH at end point was used for the calculation of the % recoveries and recoveries were found about 100 %. When these results were evaluated, the proposed method was found to be suitable for the quantitative determination of valsartan.

In order to evaluate the applicability of the potentiometric titration method to pharmaceutical preparation, valsartan was determined in co-diovan under the same titration conditions as employed for the pure valsartan. The fact that the shapes of potentiometric titration curve of pure valsartan and its corresponding pharmaceutical is nearly the same proves that the excipients which might be present in the pharmaceutical preparations do not affect the titration curve (Fig. 3).

TABLE-3
ASSAY RESULTS FOR THE DETERMINATION OF VALSARTAN IN COMMERCIAL TABLET DOSAGE FORMS

Experiment No.	Theoretic value (mg)	Amount found (mg)	Recovery (%)
1	160	160.7	100.4
2	160	159.3	99.6
3	160	160.6	100.2
4	160	159.7	99.8
5	160	160.3	98.7
6	160	162.1	99.7
Average (mg ± SD)		160.5 ± 0.9	99.7 ± 0.6
% RSD		0.56	0.60

Table-3 summarizes the results obtained for valsartan in the co-diovan tablets, expressed as percentages of the nominal contents. The recovery is in good agreement with the nominal contents and the % RSD value is less than 1 %. Thus, the precision is very satisfactory for the analysis of pharmaceutical preparations as well as bulk drugs. These results show that proposed method was applied to the direct determination of valsartan in tablets without pretreatment.

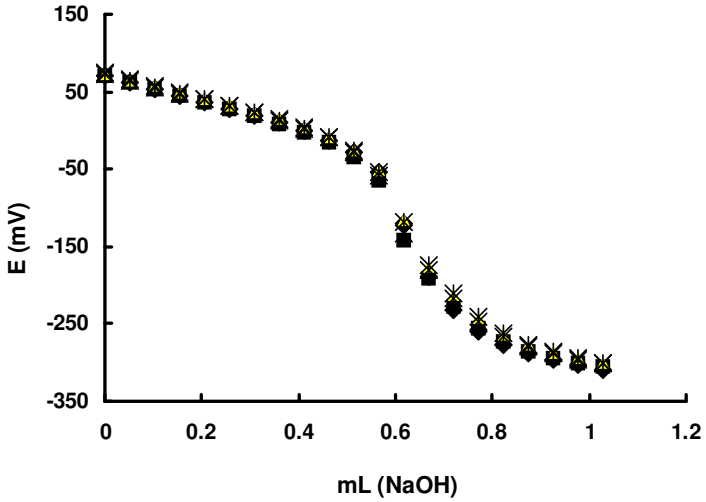

Fig. 3. Potentiometric titration curve for co-diovan and valsartan titrated with sodium hydroxide in ethanol-water mixture

The recovery studies of standard addition to commercial tablet (co-diovan) were also carried out in order to provide further evidence of the validity of the method. The results related to these studies are presented in Table-4. It can be seen from this table that the mean recovery value is 98.3 ± 1.5 % which is a good evidence of the validity of the method.

TABLE-4
RECOVERY STUDIES OF STANDARD ADDITIONS TO CO-DIOVAN TABLETS

Experiment No.	Added (valsartan) (mg)	Found (mg)	Recovery (%)
1	1.40	1.38	98.6
2	1.40	1.34	97.1
3	1.40	1.35	96.4
4	1.40	1.37	99.3
5	1.40	1.41	100.7
6	1.40	1.37	97.9
Mean: (mg ± SD)		1.38 ± 0.02	98.3 ± 1.5
% RSD		1.4	1.6

Conclusion

As a result of this work, valsartan can be determined potentiometrically in ethanol:water (1:1) mixture by the proposed method. This titration procedure was successfully applied to the determination of pure authentic samples and some of their pharmaceutical preparations. In conclusion, the proposed potentiometric method could be utilized readily for routine analysis for pharmaceuticals since it offers a simple system and with short analytical time coupled with good reproducibility and accuracy.

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