Bulgarian Chemical Communications, Volume 46, Number 3 (pp. 497 – 502) 2014

Development and validation of a potentiometric titration method for the determination of montelukast sodium in a pharmaceutical preparation and its protonation constant

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Received April 25, 20123 Revised February 14, 2014

In this study, a potentiometric titration method for the determination of montelukast sodium in pharmaceutical dosage forms was developed and validated. For this purpose, the potentiometric titration of the standard montelukast sodium was carried out using hydrochloric acid as titrant. The method was found to be highly accurate and precise, having a relative standard deviation of less than 1.0%. From the titration data the stoichiometric protonation constant was calculated in 40% ethanol–60% water and 60% ethanol–40% water (v/v) mixtures at constant temperature of 25.0 ± 0.1 °C and ionic strength of 1.0×10^{-1} M NaCl. The protonation constant was found to be 6.25 in 40% ethanol–60% (v/v) water mixture and 5.95 in 60% ethanol-40% (v/v) water mixture. Furthermore, it was shown that the method could be successfully applied to the assay of commercial pharmaceuticals containing 10.0 mg montelukast sodium. The validity of the method was tested by recovery studies of standard additions to a tablet solution and the results were found to be highly satisfactory. This titration method is simple, rapid, accurate, precise and low cost for quality controls of commercial pharmaceutical dosage forms.

Keywords: Montelukast sodium; potentiometric titration; pharmaceutical dosage, ethanol-water mixture.

INTRODUCTION

Montelukast is an oral selective leukotriene receptor antagonist [1,2] which is being used in the treatment of asthma. It belongs to a styryl-quinolines series with the chemical name {sodium salt of 2-[1-[[(1R)-1-[3-[2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl) phenyl] propyl] sulfanylmethyl] cyclopropyl] acetic acid} (Fig.1). It was developed by Merck as a therapeutic agent for the treatment of bronchial asthma [3] by means of once daily oral administration.

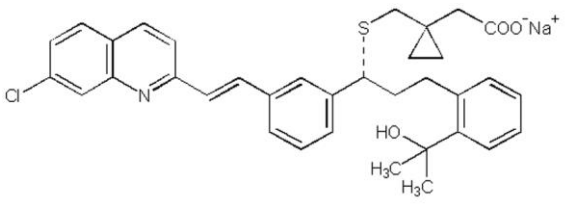

Fig.1. Chemical structure of montelukast sodium

The main objective of this paper is to propose a selective and validated potentiometric method for determining montelukast sodium and applying it to pharmaceutical dosage forms. A variety of analytical methods dedicated to the analysis of montelukast sodium have been previously reported. Most of them involve spectrophotometry [4], capillary electrophoresis [3], high performance liquid chromatography (HPLC) [5], high performance thin layer chromatography (HPTLC) [6], voltammetry [7]. Literature survey reveals that there are no potentiometric titration methods for the determination of montelukast sodium in ethanol-water mixture in pharmaceutical dosage forms. The analytical method reported here was validated considering linearity, accuracy and precision.

In this study, the stoichiometric protonation constants of montelukast sodium in 40% ethanol–%60 water (v/v) and 60% ethanol–%40 water (v/v) mixtures were determined. In pharmacology, ionization of a compound alters its physical behaviour and macro properties such as solubility and lipophilicity. For example, ionization of any compound will increase the solubility in water and decrease the lipophilicity. This is exploited in drug development to increase the concentration of a compound in the blood by adjusting the pK_a of an ionizable group [8]. The determination of the stoichiometric protonation constants of montelukast sodium is very important also from the point of absorption, distribution and elimination of the drug which is orally administered. The effective use of this compound depends greatly upon our knowledge of its ionization constants. There is only one study on the potentiometric determination of p*K*a constants of

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montelukast sodium, which was performed in the 40% dioxane – 60% water (v/v) solvent mixture [1]. This study is therefore expected to provide an important addition to the data that already exist in the literature. It is thought that the data obtained in 1.0×10^{-1} M NaCl, which simulates the ionic strength of biological media, will be very useful for determining the effective mechanism of this compound which has significant pharmaceutical potential. The data related to protonation constants in different organic-solvent mixtures will be valuable in the further understanding of biological systems.

There are various techniques such as potentiometry, conductometry and spectrophotometry used in the determination of protonation constants. In this study potentiometric technique was employed since it has the widest area of application and reliability [9-12].

EXPERIMENTAL

Chemicals and standard solutions

Montelukast sodium was purchased from Merck and it was used as a standard. Ethanol, hydrochloric acid, sodium hydroxide, potassium hydrogen phthalate and sodium chloride were of analytical grade (Merck) and were used without further purification.

Onceair: Tablet formulation containing montelukast sodium equivalent to montelukast 10 mg per tablet (Abdi İbrahim, Turkey) was procured from the local pharmacy.

Standard sodium hydroxide solution: Solution of standard base containing 1.0×10^{-1} M NaCl was prepared in the ethanol-water mixtures examined (v/v) and was standardized potentiometrically against potassium hydrogen phthalate (Merck) using Gran's plot techniques [13-14].

Standard hydrochloric acid solution: Acid solution prepared in redistilled low-conductivity water was standardized by titration against standardized sodium hydroxide solution.

Standard montelukast sodium solution: Standard stock solution of montelukast sodium was prepared at a concentration of 1.0×10^{-2} M in ethanol. The montelukast sodium solution used in potentiometric titration was prepared by dilution of the stock solution with ethanol. Montelukast sodium is a light-sensitive compound; therefore the stock solution was prepared daily and kept in amber glass volumetric flask to protect from light [3].

Tablet solution: Twenty eight Onceair tablets were weighed and their average weight was calculated. All tablets were finely powdered in a mortar and homogenized. The required amount of this powder was transferred to a 100.0 mL volumetric flask. 80.0 mL of ethanol was added to the same flask, sonicated for at least thirty minutes to ensure complete dissolution and diluted to 100.0 mL with ethanol.

Equipment

All potentiometric measurements were performed in an 80-mL jacketed titration cell thermostated at 25.0 ± 0.1°C. An Orion 940A Model pH-ion meter (Beverly, MA, USA) fitted with a combined pH electrode (Ingold) containing a filling solution of 1.0×10^{-1} M NaCl was used for measuring the cell emf values. The titrant, hydrochloric acid, was added by using Orion 960 Autochemistry system. The potentiometric cell was calibrated before each experiment so that the hydrogen ion concentration rather than the activity was measured [15-16]. For the ethanol-water solvent mixtures studied, reproducible values of autoprotolysis constants (K_{ap}) were calculated from several series of $[H^+]$ and $[OH^-]$ measurements at a constant ionic strength of 1.0×10^{-1} M NaCl [17-19].

The following solutions prepared in water and each of the solvent mixtures studied (total volume = 50.0 mL) were titrated potentiometrically with standard 5.0×10^{-2} M HCl dissolved in the corresponding solvents: (i) 5.0×10^{-2} M NaOH (for cell calibration); (ii) 1.0×10^{-3} M montelukast sodium. During each titration the ionic strength was maintained at 1.0×10^{-1} M NaCl and a potential reading was taken after a suitable time (normally 2-3 min) for equilibration.

The protonation constants of the montelukast sodium were determined by a method described by Irving and Rossotti [20]. The average of protons associated with the ligand (n_A) at different pH values was calculated by analyzing the titration data for 40% ethanol–%60 water and 60% ethanol–%40 water mixtures. The p*K*a values were calculated from the curve obtained by plotting n_A versus pH.

The content of montelukast sodium in the pharmaceutical preparations was estimated via potentiometric titration with standardized hydrochloric acid solution under the same conditions described for the standard montelukast sodium.

RESULTS AND DISCUSSION

Potentiometry

Method development

For potentiometric analysis, different organic solvents and organic solvent-water mixtures were

tried to obtain the best potentiometric titration curve. 40% ethanol–60% water (v/v) mixture was found to be an appropriate medium for the potentiometric titration of montelukast sodium.

In this study assay of tablets, recovery and precision studies were performed using the experimental conditions described. Protonation constant of montelukast sodium was determined in 40% and 60% ethanol–water (v/v) mixtures and the effect of solvent upon the protonation constant was investigated.

Protonation constants of montelukast sodium

The stoichiometric protonation constants were determined with an electrochemical cell calibrated in each medium to measure the hydrogen ion concentration. For this purpose, firstly, the hydrochloric acid solutions were titrated with the sodium hydroxide solutions prepared in each medium and the potential values were plotted against the logarithm of the hydrogen ion concentration to determine the calibration constants (E' and k). The calibration constants obtained from these curves are tabulated in Table 1, which shows that the glass electrode used in ethanol-water mixtures gave a Nernstian response with a slope of (59.1 ± 0.1) mV. Therefore, it was concluded that the electrode could be used to determine the stoichiometric protonation constant for all media.

Table 1. Calibration constants obtained in 40% ethanol–60% water (v/v) and 60% ethanol–40% water (v/v) mixtures with a combined glass pH electrode.

Medium	Calibration constant (n=3)	
	$E'_{(mean)}$ (mV)	k (mV-pH^{-1})
40% ethanol – 60% water	340.3 ± 1.9	59.1 ± 0.1
60% ethanol – 40% water	333.9 ± 1.2	59.0 ± 0.1

n, is number of analyses

The autoprotolysis constants (K_{ap}) for each medium were determined using the same acid-base titration data and are tabulated in Table 2. It was observed that the value obtained was found to be in good agreement with those reported in the literature [21-22].

Table 2. Autoprotolysis constants obtained in 40% ethanol–60% water (v/v) and 60% ethanol–40% water (v/v) mixtures.

Medium	pK_{ap}	pK_{ap} (in literature)
40% ethanol – 60% water	14.15 ± 0.01	14.24 [21]
60% ethanol – 40% water	14.32 ± 0.01	14.39 [21]

As there are a very limited number of studies related to the protonation constants of montelukast sodium, [1], the data obtained in this study will make an important contribution to the literature. Especially the protonation constants obtained in 1.0×10^{-1} M NaCl medium, which simulates biological systems, will shed light on the reaction mechanisms in biological reactions of montelukast sodium.

In the literature, two protonation constants of montelukast sodium are given [1]. However, in our study, we found one protonation constant for montelukast sodium. As can be seen from Fig. 4, the formation curve (n_A-pH) was found between 0 and 1. This indicates that the $\log_{10}K$ value of only one of the two protons could be determined for the ethanol-water mixtures studied.

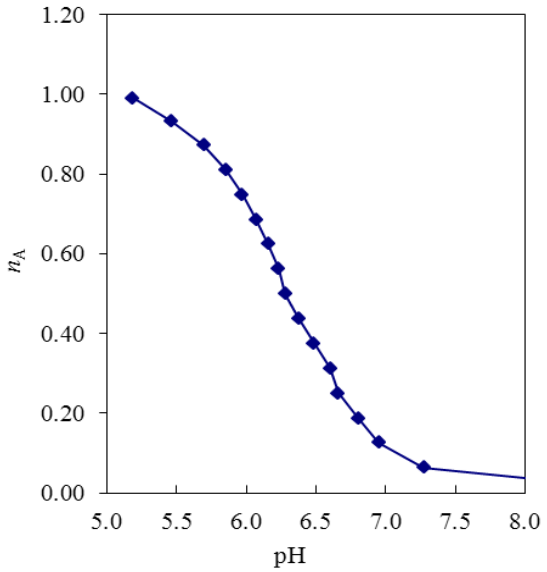

Fig. 4 nA-pH curves from the potentiometric titration of montelukast sodium standard in 40% ethanol-60% water (v/v) mixture. (I = 1.0×10^{-1} M NaCl; t = 25.0 ± 0.1 °C)

The numerical values of the protonation constant of montelukast sodium determined potentiometrically in 1.0×10^{-1} M NaCl at 25 °C are listed in Table 3.

Table 3. The stoichiometric protonation constants of montelukast sodium at 25.0 (±0.1) °C for different ethanol-water (v/v) mixtures (I = 1.0×10^{-1} M NaCl).

40% ethanol-60% water	60% ethanol-40% water
$\log_{10}K_1$ ± S.D.	$\log_{10}K_1$ ± S.D.
6.25 ± 0.03	5.95 ± 0.02

S.D. is standard deviation

The determinations were carried out in 40% and 60% ethanol–water (v/v) mixtures. The resulting stoichiometric protonation constants were calculated by the Irving-Rossotti method [20]. An example of the n_A – pH curve of montelukast

sodium obtained from the experimental data is given in Figure 4.

The protonation constants given in Table 3 are defined by Equation 1 where B^- represents the montelukast anion:

$$B^- + H^+ \leftrightarrows HB \quad K_1 = [HB]/[B^-][H^+] \qquad (1)$$

where $\log_{10}K_1$ values refer to the equilibria related to the attachment of H^+ to the oxygen atom in the acetate group.

As seen from Table 3, the $\log_{10}K_1$ values of montelukast sodium decrease with increasing ethanol percentage. The increase in the ethanol concentration decreases the dielectric constant of the medium. HB is better solvated than the B^- species in ethanol-rich media.

Potentiometric determination of standard montelukast sodium

In this study, montelukast sodium was titrated potentiometrically with hydrochloric acid as a titrant in 30%, 40%, 50%, 60%, 70% and 80% ethanol–water (v/v) mixtures at constant temperature of 25°C and ionic strength of 1.0×10^{-1} M NaCl. Since montelukast sodium behaves as a weak base in ethanol–water mixtures, its titration curve does not display a perceivable inflection for the second point of equivalence for all media studied. The best titration curve was obtained in 40% ethanol–60% water (v/v) mixture. Therefore, recovery, repeatability and assay studies were done in this medium. A typical potentiometric titration curve with only one inflection point is given in Figure 2. As seen from the figure, the changes at the titration end point were satisfactory enough for accurate and reproducible end point detection. The determination of equivalence points from the potentiometric data was carried using the Gran's method [13-14].

In order to assess the repeatability (precision) of the method, known amounts of chemically pure laboratory working standard solution were analyzed in three replicates. As seen from the data in Table 4, the values found by the proposed method are in good agreement with the taken value and furthermore the mean relative standard deviation is less than ± 3%. This indicates that the accuracy and precision of this method is quite satisfactory

Table 4. Titrimetric determination of chemically pure laboratory working standard of montelukast sodium.

40% ethanol – 60%water (v/v)				
Taken,mg	Found, mg (n = 3)	Bias, %	S.D.	RSD,%
30.0	31.2	4.0	0.26	0.83
50.0	52.8	4.2	0.47	0.90
75.0	73.6	1.5	0.20	0.27

S.D, is standard deviation and

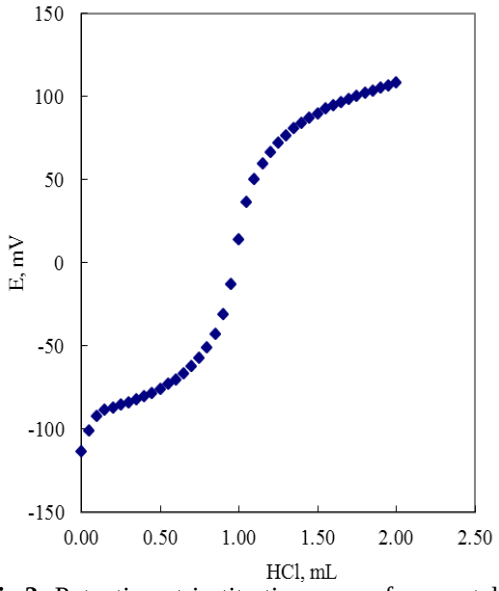

Fig.2. Potentiometric titration curve for montelukast sodium standard titrated with 5.0×10^{-2} M hydrochloric acid in 40% ethanol – 60% water (v/v) mixture.

Determination of the active component in pharmaceuticals

In order to evaluate the adequacy of the proposed method to be used for the analysis of pharmaceutical preparations, montelukast sodium was determined in 40% ethanol – 60% water (v/v) mixture in tablet formulations under the same conditions as for the pure montelukast sodium. The similarity of the shapes of potentiometric titration curve of pure montelukast sodium and its corresponding pharmaceutical proves that the excipients which might be present in the pharmaceutical preparations do not affect the titration curve (Fig. 3).

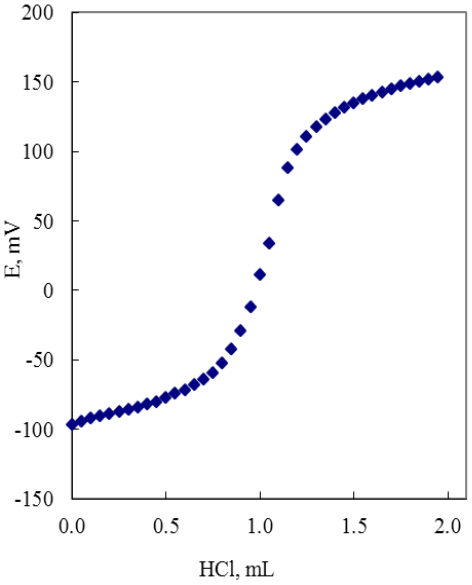

Fig.3 Potentiometric titration curve for pharmaceutical dosage form of montelukast sodium titrated with 5.0×10^{-2} M hydrochloric acid in a 40% ethanol – 60% water (v/v) mixture.

Table 5 summarizes the results obtained for the montelukast sodium in the corresponding pharmaceutical, expressed as labeled contents. The data given in Table 5 clearly indicate that the content of montelukast sodium in the pharmaceuticals can be safely determined using this method without interference from other substances in the preparations.

Table 5. Determination of montelukast sodium in pharmaceutical preparation.

Tablet (Batch Number)	Labeled (mg)	Found (mg)	Label % ± S.D (n = 3)
I	10.0	10.3	102.6 ± 0.43
II	10.0	9.8	98.3 ± 0.27

S.D, is standard deviation and n, is number of analysis

Recovery studies of standard additions to the commercial pharmaceuticals were carried out in order to provide further evidence of the validity of the proposed method. For this purpose, standard montelukast sodium solution was added to pharmaceutical formulation solutions at three different concentration levels. The results are tabulated in Table 6. It can be seen from this table that the mean recoveries and standard deviation values are in the range of 97.6–101.8% and 0.5–0.9, respectively, which is a good evidence of the validity of the method.

Comparing the obtained results with those of many of the already existing procedures for the determination of montelukast sodium, which require special instrumentation, reagents, precautions and experience, it is seen that the proposed potentiometric method exhibits the advantages of simple operation, reasonable selectivity, fast response, low-cost and sufficient accuracy in pharmaceutical formulations. Therefore this method can be used for routine analysis of montelukast sodium in combined tablet dosage forms without prior separation.

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Table 6. Recovery studies of standard additions to the pharmaceutical preparation.

Pharmaceutical	Active component	Taken, mg	Added, mg	Found, mg	% Mean recovery ± S.D. (n=3)
OnceAir	Montelukast sodium	25.0	25.0	48.8	97.6 ± 0.5
		25.0	30.0	54.9	99.9 ± 0.5
		25.0	35.0	61.1	101.8 ± 0.9

S.D, is standard deviation and n, is number of analyses

МЕТОД ЗА ПОТЕНЦИОМЕТРИЧНО ТИТРУВАНЕ ЗА ОПРЕДЕЛЯНЕ НА НАТРИЕВА СОЛ НА МОНТЕЛУКАСТ ВЪВ ФАРМАЦЕВТИЧНИ ПРЕПАРАТИ И НА КОНСТАНТАТА МУ НА ПРОТОНИРАНЕ

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Постъпила на 25 април, 2013 г.; коригирана на 14 февруари, 2014 г.

(Резюме)

Разработен е и е проверен метод за потенциометрично титруване и определяне на натриевата сол на монтелукаст във фармацевтични препарати. За тази цел са титрувани стандартни проби със солна киселина. Методът е много точен и надежден със стандартно отклонение под 1.0%. От тези данни е изчислена стехиометричната константа на протониране в среди от етанол/вода (40:60) и (60:40) обемни части при 25.0 ± 0.1ºC и йонна сила на 1.0×10^{-1} M NaCl. Константите на протониране са съответно 6.25 за средата етанол/вода (40:60) и 5.95 в среда (60:40). Показано е, че методът може да се използва успешно при анализа на търговски препарати, съдържащи 10,0 mg натриева сол на монтелукаст. Валидността на метода е изпитан чрез определяне на добива по метода на стандартната добавка към разтвори на таблетки, като резултатите са задоволителни. Методът е прост, бърз и евтин за качествен контрол на търговски фармацевтични форми.