

Original Article

## Spectrophotometric determination of pKa of Montelukast sodium

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### ABSTRACT

The value of the acid dissociation constant (pKa) is an important parameter that indicates the degree of ionization of molecules in solution at different pH values. The pKa of Montelukast Sodium were determined by spectrophotometrically by absorbance measurements at different pH values in the wavelength range between 200 and 400 nm. The pKa1 of Montelukast Sodium was found to be 3.3 and pKa2 of Montelukast Sodium was found to be 4.4. Two graphical methods were used to estimate the acid dissociation constant (pKa) using absorbance measurements. The equation for the dependence of the absorbance on pH at  $\lambda = 336\text{nm}$  and  $373\text{nm}$  was used for pKa1 determination and for pKa2 absorbance on pH at  $\lambda = 284\text{nm}$  and  $351\text{nm}$  was used for obtaining calibration curves. The literature contains no previous reports of the pKa by Spectrophotometric method. This spectroscopic method is simple, rapid, accurate, precise and low cost for quality controls of commercial pharmaceutical dosage forms.

## 1. INTRODUCTION

Montelukast sodium is a selective and orally active leukotriene receptor antagonist which is being used in the treatment of asthma. It belongs to a styrylquinolines series that inhibits the cysteinyl leukotriene CysLT1 receptor [1]. Montelukast sodium is described chemically as 2-[1-[[[(1R)-1-[3-[2-(7-chloroquinolin-2-yl)ethenyl]phenyl]-3-[2-(2-hydroxypropan-2-yl) acetic] cyclopropyl] sulfanylmethyl] propyl]phenyl acid} monosodium salt [2]. (Fig. 1)

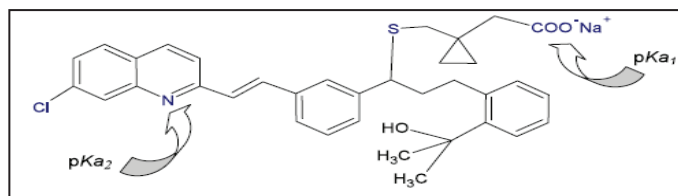


Fig. 1. Chemical structure of Montelukast Sodium [3].

Montelukast binds with high affinity and selectivity to the CysLT1 receptor. Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity. Literature survey reveals that Montelukast sodium is estimated individually by UV spectrometry, RP-UPLC, determination related substance by RP-HPLC, LC/MS/MS, UPLC-MS/MS, UV-HPLC and assay by HPLC [5].

Literature survey reveals that there are no spectrophotometry methods for the determination of montelukast sodium. For this reason, we have designed a practical way to determine the pKa, which requires only the use of a spectrophotometer. The main advantages of this technique are that it is sensitive, takes a short time, and the equipments are both inexpensive and user-friendly. An alternative to potentiometric titration is UV-VIS spectrophotometry because it can handle compounds with lower solubility and lower sample concentrations. The main advantage is higher sensitivity ( $>10^6$  M) to compounds with favorable molar absorption coefficients. The largest change in absorbance occurs at the pH corresponding to a pKa value. These changes are usually identified from the first derivative of the absorbance against time plot or from overlay plots of the different spectra. The determination of pKa values by UV-VIS assumes that the solute of interest is pure. Traditionally, spectral data at a single analytical wavelength are acquired from a sample in a series of buffer solutions with known pH values, after which the pKa is determined. To use this method, the absorption spectra of individual species must be characterized beforehand and the molar absorptivities of protonated and deprotonated species are thus required. These measurements are non-trivial if acid-base equilibria comprise more than two ionization steps or if reacting components are not stable within two pH units of the pKa value, so a multi-wavelength spectrophotometric approach has been

developed to determine acid dissociation. Target-factor analysis has been applied to deduce pKa values from the multi-wavelength UV absorption data recorded at different pH values.

### 1.1 pKa values determination (ACID DISSOCIATION CONSTANT)

The value of the acid dissociation constant (pKa) is an important parameter that indicates the degree of ionization of molecules in solution at different pH values. Many chemical, physical and biological properties of natural and synthetic compounds are governed by the interactions of acidic and basic groups [6]. Acid Dissociation constant, pKa, of a molecule decides its ionization state with respect to pH. pKa of drug directly affects pharmacokinetic properties like ADME, its absorption, distribution, metabolism and excretion (ADME) profile. Ionized form of a drug molecule is more aqueous soluble but less membrane permeable. The acid–base dissociation constant of substances (pKa value) is a very important parameter in drug design and optimization. The degree of ionization strongly affects solubility and permeability. The value of the acid dissociation constant (pKa) is an important parameter that indicates the degree of ionization of molecules in solution at different pH values [7].

## 2. MATERIALS AND METHODS

### 2.1 Materials

Montelukast Sodium was obtained as gift sample. Sodium hydroxide was procured from SD.Fine Chemicals limited (Mumbai, India). Isopropyl alcohol, Disodium hydrogen phosphate and ortho-phosphoric acid (85% pure) was received from Merck (Mumbai, India). Milli-pore water was used throughout the study.

### 2.2 Instrumentation

The pH of the buffer solutions were determined using digital pH meter (Metrohm, Model No 780). pH meter was calibrated using standard buffer solutions of pH 4.0, 7.0, 10.0 at room temperature. The spectra and absorbance readings (Spectrophotometric study) were conducted on UV Spectrophotometer (UV-1800 Shimadzu) operated at a wavelength range of 200–400 nm.

### 2.3 Experimental methodology for pKa estimation

The determination of pKa by spectrophotometric method is based on the principle that ionization of the acidic or basic compound is pH dependent. Hence with change in pH of the solution, the ratio of ionised form to the unionised form changes. At definite wavelength the ionised and unionised forms have different absorptions.

### 2.4 Preparation of buffer solutions at different pH

0.02M Disodium hydrogen phosphate buffer was prepared in water and series of buffers covering the pH range between 1.6 and 7.5 were prepared by adjusting pH with diluted ortho phosphoric acid. The pH values of all solutions were measured

on a Metrohm, Model No 780 pH meter equipped with combined glass electrode which was calibrated by using standard buffers at pH 4.0 and 7.0. Following series of buffers Solutions at different pH were prepared listed in Table 1.

**Table 1.** Series of buffers solutions at different pH i.e from 1.60 to 7.50 pH.

S. No.	pH of Buffer Solution	S. No.	pH of Buffer Solution
1	1.60	11	4.11
2	1.80	12	4.30
3	2.00	13	4.58
4	2.20	14	4.88
5	2.40	15	5.20
6	2.80	16	5.40
7	3.00	17	5.99
8	3.20	18	6.50
9	3.40	19	7.01
10	3.90	20	7.50

### 2.5 Sample stock solution preparation (5 mg/ml)

100 mg of Montelukast Sodium sample was weighed accurately and transferred into a 20 ml volumetric flask. To it was added about 3 ml of water and the solution sonicated to dissolve and then the volume made up to the mark with Isopropyl alcohol and mixed well. From this stock solution, samples were prepared in different series of buffers by adding 50 µL of stock sample solution, 5 mL of Isopropyl alcohol and 15 mL of respective buffer and scanned at 200 nm to 400 nm by using each of the twenty buffer solutions. These working solutions were then analyzed under UV Spectrophotometer to record their respective absorbance at 336 nm and 373 nm as depicted by (Table-1) (and UV spectra as depicted by (Fig. 1)

**NOTE:** All the solutions were kept in glass containers at 25 °C and protected from light.

**Table 2.** Absorbance value of Montelukast Sodium at 336 and 373 nm in respective buffer solutions of pH 1.6–7.5.

pH	Absorbance at wavelength (λ) 336nm	Absorbance at wavelength (λ) 373nm
1.60	0.206	0.683
1.80	0.282	0.865
2.00	0.260	0.727
2.20	0.275	0.644
2.40	0.316	0.611
2.80	0.373	0.473
3.00	0.391	0.437

pH	Absorbance at wavelength (λ) 336nm	Absorbance at wavelength (λ) 373nm
3.20	0.436	0.496
3.40	0.435	0.39
3.90	0.443	0.337
4.11	0.462	0.346
4.30	0.456	0.372
4.58	0.437	0.233
4.88	0.432	0.216
5.20	0.438	0.173
5.40	0.45	0.173
5.99	0.457	0.145
6.50	0.437	0.134
7.01	0.454	0.138
7.50	0.443	0.135

As illustrated in Figure 2, Overlaid spectra was observed for either appearance/ disappearance of absorbance peaks or increasing/decreasing of absorbance at particular wavelength at acidic and basic pH and on this basis four wavelengths were selected which were 284 nm, 351 nm, 336 nm and 373 nm.

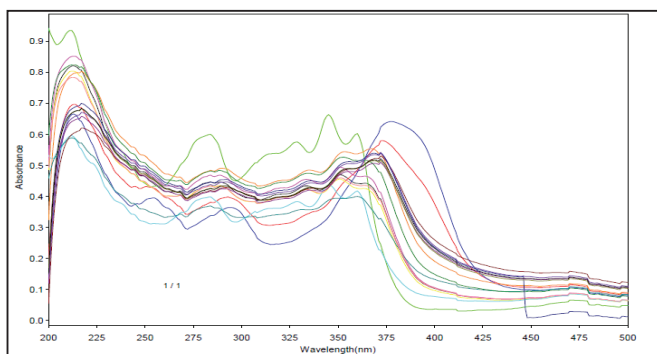


Fig. 2. Absorbance curves for the acidic, basic, and intermediate pH solutions

The plot of the absorbance vs. pH at these wavelengths is presented in Figure 2. The pKa was obtained by determining the pH of the point of intersection of the two linear curves as shown in Figure 3.

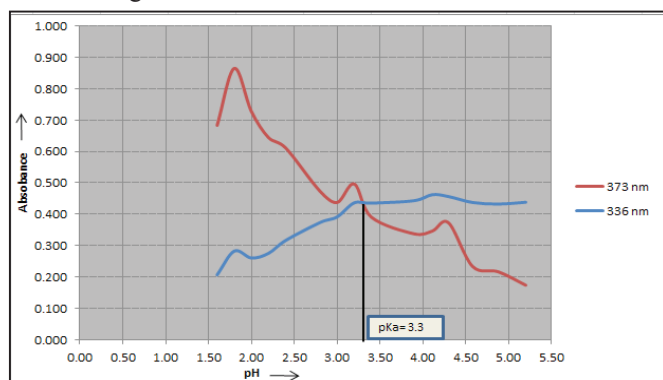


Fig. 3. Absorbance curve graph between pH and absorbance of Montelukast Sodium in buffer solutions of pH 1.60 to 7.50 at wavelength 373 nm and 336 nm. The point of intersection of graph depicted the pKa =3.3.

Table 3. Absorbance value of Montelukast Sodium at 284 and 351 nm in respective buffer solutions of pH 1.5–7.5.

pH	Absorbance at wavelength (λ) 284nm	Absorbance at wavelength (λ) 351nm
1.592	0.288	0.333
1.809	0.297	0.340
2.000	0.307	0.343
2.199	0.321	0.355
2.402	0.344	0.367
2.804	0.398	0.400
3.004	0.420	0.414
3.200	0.43	0.432
3.409	0.464	0.472
3.899	0.492	0.481
4.110	0.472	0.476
4.290	0.479	0.479
4.608	0.482	0.479
4.870	0.496	0.468
5.202	0.495	0.466
5.388	0.489	0.457
5.949	0.507	0.481
6.509	0.491	0.467
7.000	0.505	0.479
7.502	0.481	0.457

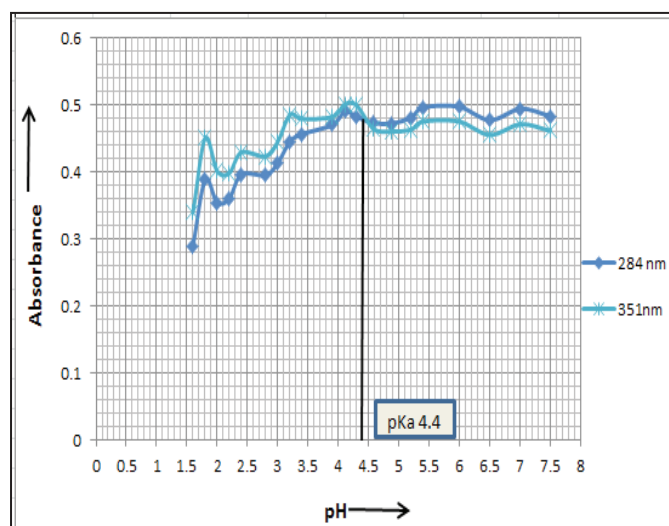


Fig. 4. Absorbance curve graph between pH and absorbance of Montelukast Sodium in buffer solutions of pH 1.60 to 7.50 at wavelength 284 nm and 351 nm. The point of intersection of graph depicted the pKa =4.4.

### 3. RESULTS AND DISCUSSION

The spectrophotometric and absorbance measurements were performed by using a UV-Vis spectrophotometer in the wavelength range between 200 and 400 nm. method for the pKa determination was opted by acknowledging the established fact that spectrophotometric determination of pKa produces most precise values. The pKa-1 of Montelukast Sodium was found to be 3.3 and pKa-2 of Montelukast Sodium was found to be 4.4. Two graphical methods were used to estimate the acid dissociation constant (pKa) using absorbance measurements. The equation for the dependence of the absorbance on pH at  $\lambda = 336$  nm and 373nm was obtained by using calibration curves.

### 4. CONCLUSION

Several advanced analytical methods have been used for the determination of dissociation constants of APIs. The spectrometric methodology gives the best accuracy and better precision than any of the methods mentioned. We performed this experiment in order to gain insights about the molecular behaviour of Montelukast Sodium. In the present study, pKa of Montelukast Sodium was calculated experimentally for the first time. pKa is important physicochemical parameter helpful in drug development. We conclude our study by inferring that Montelukast have two ionizable groups resulting two pKa values i.e pKa-1 = 3.3 and pKa-2 = 4.4, as calculated from our experiments.

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