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Spectrophotometric determination of montelukast sodium in bulk and pharmaceutical formulations

Shanmukha Kumar. J. V.[1*], Geeta Swarupa. P[1], Vardhan S. V. M[2] and Ramachandran. D[2]

[1]Dept.of.Chemistry, K L University, Green Fields, Guntur, A.P, India
[2]Dept of Chemistry, Acharya Nagarjuna University, Nuzvid, Campus, Nuzvid, Krishna District, A.P, India

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ABSTRACT

Two simple, sensitive and accurate spectrophotometric methods have been developed for the determination of montelukast sodium in pure and dosage forms. Both Method-A and B are based on the formation of ion association complex with acid dyes BTB and BCP which are extractable into chloroform from the aqueous phase. The colored chromogen for Method-A shows absorption maximum at 410 nm and linear within the limits 5.0-25.0 µg/mL. Method-B produced colored chromogen which is measured at 415nm. Beer's law is obeyed in the concentration range of 4.0-20.0 µg/mL for the developed method. Different experimental parameters affecting the color development and stability of colored product are carefully studied and optimized. The developed methods could be successfully applied to pharmaceutical formulations. The results obtained are in good agreement with those obtained using official methods.

Key Words: Motelukast Sodium (MTK), Spectrophotometry, Dosageforms, Bromothymol blue (BTB) Bromocresol purple (BCP).

INTRODUCTION

Motelukast sodium [1, 2] is [R-(E)]-1-[[[1-[3-[2-(7-chloro-2quinolinyl) ethenyl] phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, sodium salt (mono).which is a leukotriene receptor antagonist used as an alternative to anti-inflammatory medications in the management and chronic treatment of asthma and exercise-induced bronchospasm (EIB)drug that is marketed under trade names such as SingulairÃ‚Â® and Montair. It is usually administered orally. Montelukast blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor Cys LT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchi constriction otherwise caused by the leukotriene, receptor and results in less inflammation. Based on its mechanism of operation, it is not useful for the treatment of acute asthma attacks, as also because of its very specific locus of operation; it does not interact with other allergy medications such as theophylline. It is a oral Leucotriene receptor having wide biological and chemical functions. Acute asthma attack, hepatic impairment, phenylketonuria could be reduced by a steady dose of the drug.

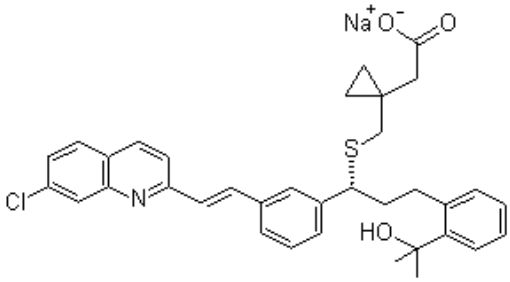


Fig: 1.1structure of Motelukast Sodium

It was however considered based on the structure the drug (Fig 1.1) that the analytically important functional groups were not fully exploited for designing suitable analytical methods as was quite evident from the literature, and, only a few methods viz, HPLC [3, 4, 6, 9, 11, 15] Spectrofluorimetry [5] electrophoresis [10] UV-visible spectrophotometry [7, 8], LC-ESI-MS [12] and Spectrophotometry [13, 14] appeared in the literature for the determination of MTK in bulk and pharmaceutical formulations.

There is a need for simple spectrophotometric method for the analysis of montelukast sodium in pharmaceutical formulations. No extractive spectrophotometric methods are reported in the literature for montelukast sodium analysis.

In this paper, simple and sensitive extractive spectrophotometric methods for the analysis of montelukast sodium were described. The methods are based on the formation of chloroform soluble ion-association complexes of montelukast sodium with bromothymol blue (BTB) and Bromocresol purple (BCP) in phthalate buffer at pH 3. No interference was observed in the analysis of montelukast sodium from common Excipients in levels found in pharmaceutical formulation. These proposed methods are not rapid but economic when compared with HPLC methods.

MATERIALS AND METHODS

Instrumentation:
After due calibration of the instrument, spectral and absorbance measurements are made using Genesys 10 UV Spectrophotometer procured from Thermo Scientific company marketed by Merck. All the chemicals used were of analytical grade. All the solutions were freshly prepared with double distilled water. Reagents were prepared a fresh for every method.

Preparation of Standard solution of drug
100mg of the MTK is accurately weighed and transferred into a 100mL standard flask and dissolved in 10.0mL of methanol and made up to 100mL with distilled water to get a clear solution with constant shaking and then 16mL and 20.0mL of this solution is accurately transferred into two 100mL standard flasks by means of a burette and made up to the mark with doubled distilled water to obtain 160µg/mL and 200µg/mL working standard solutions..

Preparation of Reagents
For Method – A: 0.1% solution of Bromothymol blue (BTB) was prepared by dissolving the 100mg dye (Rankem, India, 95% dye content) in water and filtered to remove the insoluble residue. Phthalate buffer (pH 3.0) was prepared by adjusting the pH(3.0) of 0.1 mol.L^{-1} Potassium hydrogen phthalate with 0.1 mol.L^{-1} hydrochloric acid and 0.1 mol.L^{-1} sodium hydroxide, respectively.

For Method – B: 0.1% solution of Bromocresol purple (BCP) was prepared by dissolving the 100mg BCP dye (Rankem, India) in 100mL double distilled water and filtering it to remove the insoluble residue. Buffer solution (pH 3.0) were prepared in the same way as the described in the **Method - A**.

Procedures
Method – A
Accurately measured portion (0.5-2.5mL, 200µg.mL^{-1}) of standard solutions of montelukast sodium [MTK] were taken into a series of 125mL separating funnels and the volume to 5.0mL with buffer solution (pH-3.0). To each of

the separating funnels BTB dye solution (5.0mL) and chloroform (10.0mL) were added and the separating funnels were shaken for 2min. The layers were allowed to separate. The separated layers were collected in dry test tubes containing anhydrous sodium sulphate. The absorbance of each organic layer was measured in 1.0 cm cell at 410nm against blank. The amount of the MTK was calculated from the calibration graph.

Method-B

Accurately measured portion (0.5-2.5mL, 160µg.mL^{-1}) of standard solutions of montelukast sodium [MTK] were taken into a series of 125mL separating funnels and the volume to 5.0mL with buffer solution (pH-3.0). To each of the separating funnels BCP dye solution (5.0mL) and chloroform (10.0mL) were added and the separating funnels were shaken for 2min. The absorbance of each organic layer was measured in 1.0 cm cell at 415nm against blank. The amount of the MTK was calculated from the calibration graph.

Analysis of tablets

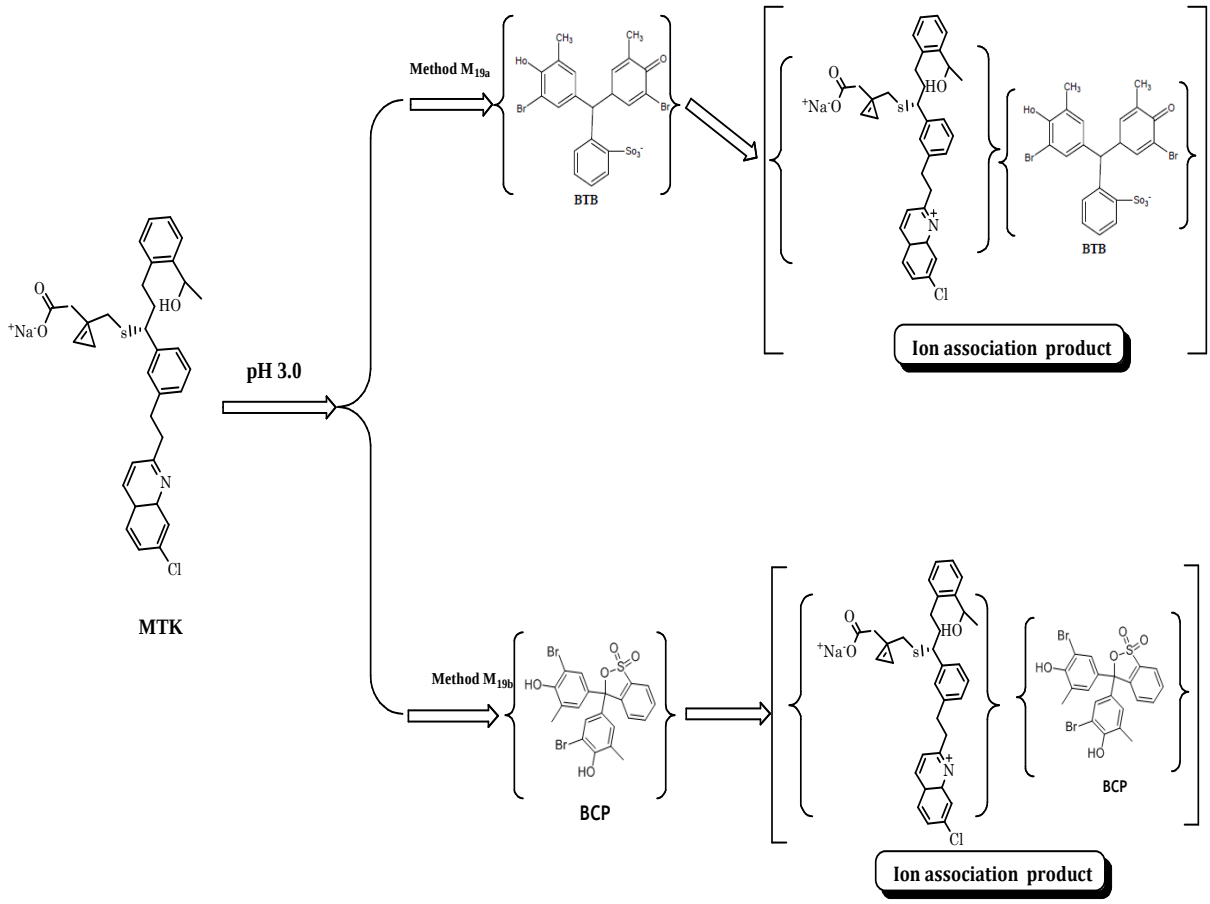
Five tablets were finely powdered. An amount equivalent to 50 mg of MTK was weighed accurately and transferred into a beaker. The powder was completely disintegrated in distilled ethanol using a mechanical stirrer, filtered and diluted up to 100 mL with distilled water. An aliquot was analyzed by the proposed procedure.

RESULTS AND DISCUSSION

Montelukast Sodium forms ion-association complexes in acidic buffers with bromothymol blue (BTB) and Bromocresol purple (BCP). The complexes were extracted quantitatively into chloroform and exhibiting absorption maxima at 410 nm and 415 nm with BTB and BCP respectively. Under the experimental conditions the reagent blank showed negligible absorbance because the blank contains the dye and buffer which are non-extractable in ionic form in non polar solvent (chloroform).The proposed reaction mechanism for ion-association complex of MTK with BTB and BCP is given in Scheme I. The experimental factors affecting the development and stability of the ion-association complexes were studied and optimized. Such factors include pH, concentration of reagents, extraction time and organic solvent for extraction. Various organic solvents used for extraction like chloroform, carbon tetrachloride, xylene, toluene, dichloromethane and ethyl acetate. Chloroform was found to be the most suitable solvent for the quantitative extraction of ion-association complex while partial extraction of the complex was achieved with other solvents. The stepwise extraction was also used for the quantitative extraction of ion-association complex and it was observed that only one step extraction was sufficient for the quantitative recovery of the complex with chloroform. Shaking time for extraction of complex form 1-5 min produced constant complex absorbance; therefore a shaking time of 2.0 min was used throughout. The absorbance of the ion-association complex remained unchanged if the order of reagent addition changed. However, the ion-association complexes were stable for 6 h for BTB and 5 h for BCP at room temperature. The influence of pH on the ion-association complexes of MTK with BTB and BCP have been studied using phthalate buffer. It has been observed that maximum absorbance of complexes were found with BTB and BCP at pH 3 and low absorbance values were observed for the pH more than or less than the optimum value. This shows that the complexes are less stable at other pH values. The effect of BTB and BCP concentration was studied by adding different volume of 0.1% solution of BTB and BCP to a constant concentration of MTK. Maximum absorbance of ion-association complex with BTB and BCP was found at 5.0 mL of 0.1% solution, beyond which absorbance remains constant.

Analytical characteristics

The Beer's law limits, the molar absorptivity, regression equations and correlation coefficient values were evaluated. The linearity of calibration graphs were proved by the high values of the correlation coefficient (r). Accuracy and precision of the two methods were determined by analyzing three different concentrations in six replicates. The percent of relative standard deviation and percent range of error are calculated for the developed methods. To determine the accuracy of these methods, three different amounts of bulk samples within the linearity limits are prepared and analyzed by the developed methods. The percent recoveries of the drug by these methods are found to be within the range which indicates that the developed methods are accurate. Optical characteristics, linear regression parameters, precision and accuracy of the proposed methods are presented in Table-1. These methods have been successfully applied for the determination of MTK in pharmaceutical preparations. Singulair 5mg was taken for the analysis. The percent of recovery of the drug is calculated and is compared with a reference method statistically by means of t-test and Ftest at 95% confidence level and found the developed methods are not significantly different. The results obtained by the developed methods are shown in Table-2.



Scheme 1 Reaction of BTB (Method A) & BCP (Method B) with MTK

TABLE -1 Quantitative parameters for determination of MTK using BTB and BCP

Parameter	Method A	Method B
λ_{max} (nm)	410	415
Beer's law limits (µg/mL)	5.0 – 25.0	4.0 – 20.0
Molar absorptivity (1 $mol^{-1}.cm^{-1}$)	5.72 x 10^3	4.95 x 10^3
Sandell's sensitivity (µg.cm^{-2}/0.001 absorbance unit)	0.0417	0.0498
Optimum photometric range (µg/mL)	7.0 - 20.0	5.0 - 17.7
Regression equation (Y=a+bc) slope (b)	0.0249	0.0262
Intercept (a)	0.00033	-0.0022
Correlation coefficient (r)	0.9999	0.9993
Relative standard deviation (%)*	1.557	1.807
% Range of error (confidence limits)		
0.05 level	1.793	2.076
0.01 level	2.802	3.254

** Y= a + bx, where'Y'is the absorbance and x is the concentration of Montelukast Sodium in µg/ml.*
*** For six replicates*

Table.2 Assay and Recovery of montelukast sodium [MTK] in dosage forms [SINGULAIR]

Method	Pharmaceutical Formulation	Labeled Amount (mg)	Proposed Method			Found by reference method±S.D	% Recovery by proposed method**
			Amount found* (mg) ±S.D	t (value)	F (Value)		
Method A	Tablet	5.0	4.90±0.39	0.27	2.53	4.98±0.62	99.19±0.33
Method B	Tablet	5.0	4.92±0.29	0.50	4.57	4.98±0.62	99.39±0.28

**Average ± standard deviation of six determinants the t and F- values refer to comparison of the proposed method. Theoretical values at 95 % confidence limits t = 2.365 and F = 4.88.*
*** Average of six determinations.*

CONCLUSION

The developed methods are simple, sensitive, accurate and economic. These methods can be successfully applied for the analysis of pharmaceutical formulations in any laboratory

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