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SIMULTANEOUS ESTIMATION OF MONTELUKAST SODIUM AND THEOPHYLLINE IN PHARMACEUTICAL DOSAGE FORM BY UV SPECTROPHOTOMETRIC METHOD

Rakesh B. Patel*, Rajesh R. Parmar, Visnu M. Patel, Dushyant A. Shah

Department of Quality Assurance, APMC College of Pharmaceutical Education and Research, College Campus, Motipura, Himmatnagar – 383001, India

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For Correspondence:

Rakesh B. Patel

Department of Quality Assurance, APMC College of Pharmaceutical Education and Research, College Campus, Motipura, Himmatnagar – 383001, India

E-mail:

rakesh_pharm24@yahoo.in

ABSTRACT

A simple, precise, accurate, rapid and economical spectrophotometric method have been developed for simultaneous estimation of Montelukast sodium and Theophylline in pure and in combined tablet dosage form. Method-1 simultaneous equations and Method-2 Q-absorbance Ratio method by using nm 287 nm and 271 nm as absorbance maxima (λ max)for Montelukast sodium and Theophylline respectively and 280 nm (isoabsorptive point). A water was used as Solvent. Linearity was observed in the concentration range of 4-24 µg/ml for Montelukast sodium and 2-24 µg/ml for Theophylline respectively. The method was validated statistically and recovery study was performed to confirm the accuracy of the method.

INTRODUCTION

Montelukast sodium is chemically 1-[({(R)-m-[(E)-2-(7- chloro-2-quinolyl) vinyl]-α-[o-(1-hydroxyl-1-methylethyl)phenethyl]benzyl}thio)methyl] cyclopropaneacetate sodium. Montelukast sodium is Anti-Asthmatic Agents, Antiarrhythmic Agents, Leukotriene Antagonists. Montelukast selectively antagonizes leukotriene D_4 (LTD_4) at the cysteinyl leukotriene receptor, $CysLT_1$, in the human airway. Montelukast inhibits the actions of LTD_4 at the $CysLT_1$ receptor, preventing airway edema, smooth muscle contraction, and enhanced secretion of thick, viscous mucus.

Theophylline is chemically 1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione. Theophylline is Vasodilator Agents, Phosphodiesterase Inhibitors, Bronchodilator Agents, Respiratory Smooth Muscle Relaxant. Theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen. Theophylline competitively inhibits type III and type IV phosphodiesterase (PDE), the enzyme responsible for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation. Theophylline also binds to the adenosine A2B receptor and blocks adenosine mediated bronchoconstriction. Like other methylated xanthine derivatives, theophylline is both are

1. Competitive nonselective phosphodiesterase inhibitor, which raises intracellular cAMP, activates PKA, inhibits TNF-alpha and inhibits leukotriene synthesis, and reduces inflammation and innate immunity
2. Nonselective adenosine receptor antagonist, antagonizing A1, A2, and A3 receptors almost equally, which explains many of its cardiac effects.

Theophylline drug is official in Indian Pharmacopeia. A survey of literature revealed that few chromatographic and Spectrophotometric methods are reported for determination Montelukast sodium and Theophylline individually and with other drug combination. The present work describe simple, precise, accurate and economical spectrophotometric method have been developed for simultaneous estimation of Montelukast sodium and theophylline form combined dosage form.

MATERIAL AND METHOD

Instrument

A shimadzu model 1700 (Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions.

Reagents and Chemicals

Reference Standards of Montelukast Sodium and Theophylline were obtained as gift samples from the Zydus Cadila Pharmaceutical Ltd. The drug sample (tablet) MONTE-THEO manufactured by Panacea Biotec Ltd. were procured from market. All other reagents were of analytical grade for Spectrophotometric method.

Procedures

Preparation of Standard Stock Solution and Calibration curve:

Standard stock solution of pure drug containing 500 µg/ml of MONTELUKAST SODIUM and 1000 µg/ml of THEOPHYLLINE were prepared separately in the distil water and final volume was adjusted with same solvent to get 100 µg/ml of each drug. Working standard solution of 20 µg/ml were scanned in the entire UV range 400-200nm to determine the λ max of both drug. The λmax of Montelukast sodium and Theophylline is 287 nm and 271 nm respectively. Five working standard solution with concentration 4,8,12,16,20,24 µg/ml of Montelukast sodium and 2,5,8,11,14,17 µg/ml of Theophylline. The absorbance of resulting solution were measured at their respective λmax and plotted a calibration curve to get linearity and regression equation.

Method-1 (Simultaneous Equation Method)

The Simultaneous Equation Method of analysis based on the absorption of the drugs Atorvastatin calcium and Aspirin at their λmax. Two wavelength selected for the development of Simultaneous Equation are 287 nm (λ1) and 271 nm (λ2). absoptivities of both the drugs at both the wavelengths were determined.Equations obtained for the estimation of concentration were,

$$Cx = \frac{A_2 a y_1 - A_1 a y_2}{a x_2 a y_1 \quad a x_1 a y_2}$$

$$Cy = \frac{A_1 a x_2 - A_2 a x_1}{a x_2 a y_1 \quad a x_1 a y_2}$$

Where A1 and A2 are absorbance of Sample solution at 287 and 271 nm respectively.
ax1= Absorptivity of Montelukast sodium at 287 nm

ax2 = Absorptivity of Montelukast sodium at 271 nm

ay1 = Absorptivity of Theophylline at 287 nm

ay2= Absorptivity of Theophylline at 271 nm

C_X and C_Y are concentration of Montelukast and Theophylline in sample solution.

Method-2 (Q-Absorbance OR Absorbance Ratio Method)

The absorbance ratio method of analysis is based on the absorbance at two selected wavelengths; one is an isosbestic point and the other being the wavelength of maximum absorption of one of the two components. From overlain spectra (Figure-1) wavelength 280 nm (isosbestic point) and 271 nm (λ max of Theophylline) are selected for Q-Absorbance equation (3 & 4).

Cx = (Qm-Qy) x A1/(Qx-Qy) x ax1 ……(3)

Cy = (Qm-Qx) x A1/(Qy-Qx) x ay1 ……(4)

Where A1 and A2 are absorbance of sample solution at 280 nm and 271 nm respectively. ax1 = Absorptivity of Montelukast sodium at 280 nm,ax_2= Absorptivity of montelukast sodium at 271 nm, ay_1= Absorptivity of Theophylline at 280 nm, ay_2= Absorptivity of Theophylline at 271 nm

C_X and C_Y are concentration of montelukast and Theophylline in sample solution.

Procedure for tablet formulation

Twenty tablet were accurately weighed, and contents were removed. Average weight of the content per tablet was calculated. The contents of a tablet were reduce to fine powder. A quantity of tablet powder equivalent to 10mg of Montelukast sodium and 200mg of Theophylline was transferred to 100ml volumetric flask and dissolved in distil water with sonicated for 20 min, was then filtered through Whatman filter. The Aliquot portion of filtrate was further diluted to get a final concentration of about 5.5µg/ml Montelukast sodium and 10 µg/ml of Theophylline For Method-1(simultaneous equation method)The absorbance of sample solution was measured at 287nm and 271nm in 1cm cell against the black and The Aliquot portion of filtrate was further diluted to get a final concentration of about 8.8µg/ml Montelukast sodium and 16 µg/ml of Theophylline For Method-2(Q-absorbance method) The absorbance of sample solution was measured at 280nm and 271nm in 1cm cell against the blank. The content of Montelukast sodium and Theophylline in a tablet was calculated by the simultaneous equation method and Q-absorption method.

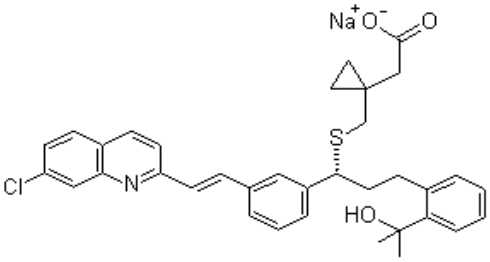

Figure-1 Montelukast sodium

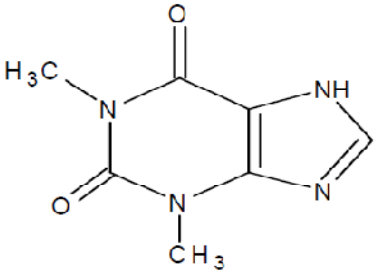

Figure-2 Theophylline

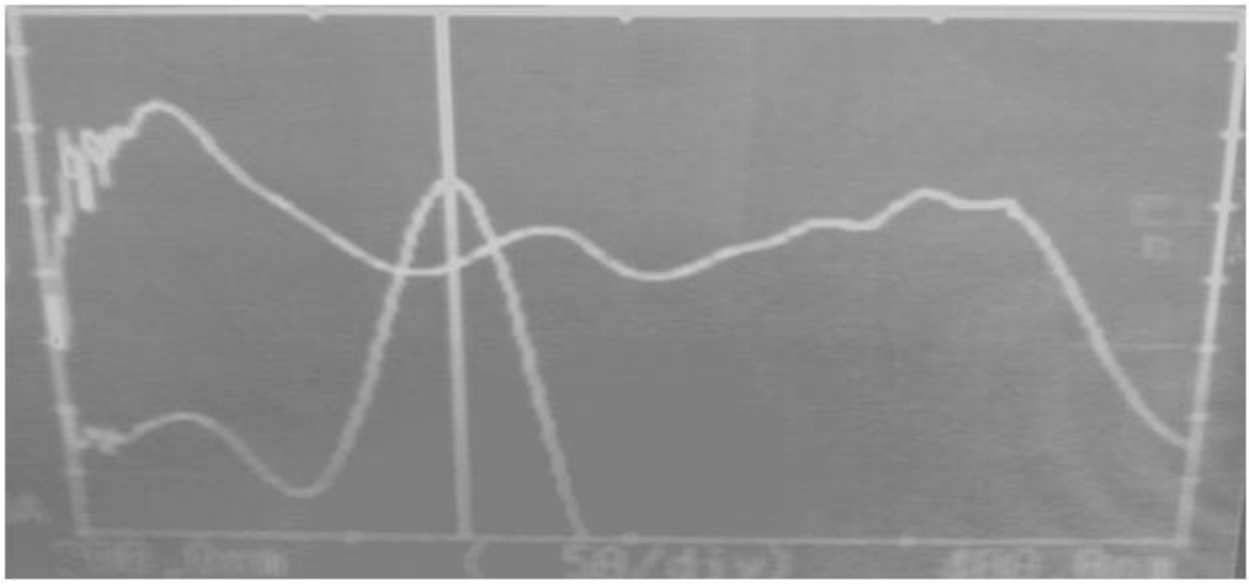

Figure-3 Overlain spectra of Montelukast sodium (10µg/ml) and Theophylline (200µg/ml)

Table-1 Optical Characteristic:

Method-1 (Simultaneous equation method)				
Parameters	**Montelukast sodium**		**Theophylline**	
Wavelength (nm)	287	271	287	271
Beer's law limit (µg /ml)	4-24	4-24	2-17	2-17
Regression equation (y = a + bc)	y = 0.033x - 0.002	y = 0.030x - 0.001	y =0.020x + 0.018	y = 0.052x + 0.010
Slope (b)	0.033	0.030	0.020	0.052
Intercept (a)	0.002	0.001	0.018	0.010

Correlation coefficient (r^2)	0.999	0.999	0.998	0.999
LOD (µg/ml)	0.15	0.20	0.36	0.20
LOQ (µg /ml)	0.48	0.63	1.10	0.61
Method-2(Q-Absorbance method)				
Parameters	**Montelukast sodium**		**Theophylline**	
Wavelength (nm)	271	280	271	280
Beer's law limit (µg /ml)	8-24	8-24	5-17	5-17
Regression equation (y = a + bc)	y=0.029x+ 0.008	y=0.030x+ 0.010	y = 0.049x- 0.013	y = 0.037x- 0.008
Slope (b)	0.029	0.030	0.050	0.037
Intercept (a)	0.007	0.012	-0.008	-0.007
Correlation coefficient (r^2)	0.9995	0.997	0.9996	0.997
LOD (µg/ml)	0.52	0.52	0.34	0.33
LOQ (µg /ml)	1.59	1.60	1.03	1.01

Table-2 Results of the recovery studies

Method	**Recovery Level**	**% Recovery**	**SD**	**% Recovery**	**SD**
		Montelukast sod.		Theophylline	
I	80%	100.0	±0.27	100.4	±0.28
	100%	100.7	±0.47	102.3	±0.40
	120%	99.41	±0.23	98.3	±0.25
II	80%	99.57	±0.98	100.5	±0.37
	100%	100.12	±0.29	99.91	±0.81
	120%	99.2	±0.97	101.21	±1.11

*SD = Standard deviation

Table-3 Results of analysis of tablet formulation

Drugs	Simultaneous equation Method	Q-Absorbance method
	%Assay ± SD(n=6)	
Montelukast sodium(10 mg)	99.8% ± 0.45	99.76%±0.71
Theophylline (200 mg)	101.0% ± 0.29	100.97 ± 0.56

Validation of the Method according to ICH Guidelines

Validation of the method was done according to ICH guidelines for Simultaneous Equation method.

Linearity

The linearity of the method is its ability to elicit test results that are directly proportional to the concentration of the analyte in the samples. MONTE was linear with the concentration range of 4-24 µg/ml at 287 nm. THEO showed the linearity in the range of 2-17 µg/ml at 271 nm.

Precision(repeatability)

The repeatability of the method was confirmed by the analysis of formulation was repeated for 6 times with the same concentration.

Intermediate precision(reproducibility):

The intraday and interday precision of the proposed method was determined by analyzing the corresponding responses 3 times on the same day and on 3 different days 3 different concentrations of standard solutions of MONTE and THEO.

Accuracy (recovery study):

To check the accuracy of the proposed methods, recovery studies carried out at 80%, 100%, and 120% of the test concentration as per ICH Guideline. The recovery study was performed three times at each level.

Limit of detection and Limit of quantification:

The limit of detection (LOD) and the limit of quantification (LOQ) of the drug were derived by calculating the signal-to-noise ratio (S/N) using the following equations designated by International Conference on Harmonization (ICH) guidelines.

$LOD = 3.3 \times \sigma/S$, $LOQ = 10 \times \sigma/S$

Where, σ = the standard deviation of the response and S = slope of the calibration curve.

RESULTS AND DISCUSSION

In this method, two wavelengths were used for the analysis of the drugs. 287 nm (λmax of MONTE) and 271 nm (λmax of THEO) are the wavelengths at which calibration curves were prepared for both the drugs. The two drugs also show an isoabsorptive wavelength at 280 nm, where both the drugs have same absorptivity value. Linear correlation was obtained between absorbances and concentrations of MONTE and THEO in the concentration ranges of 4-24 µg/ml and 2-17 µg/ml for both drugs respectively. The linearity of the calibration curve was validated by the high values of correlation coefficient of regression. (Method-1)LOD and LOQ values for MONTE were found to be 0.15 and 0.48 µg/ml and 0.20 and 0.63 µg/ml at 287 and 271 nm respectively. LOD and LOQ values for THEO were found to be 0.20 and 1.10 µg/ml and 0.36 and 0.61 µg/ml at 287 and 271 nm respectively.(Method-2)LOD and LOQ values for MONTE were found to be 0.52 and 1.60 µg/ml and 0.52 and 1.59 µg/ml at 280 and 271 nm respectively. LOD and LOQ values for THEO were found to be 0.33 and 1.01 µg/ml and 0.34 and 1.03 µg/ml at 280 and 271 nm respectively. These data show that method is sensitive for the determination of MONTE and THEO. Both drugs showed good regression values at their respective wavelengths and at isoabsorptive point, and the results of a recovery study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. The proposed validated method was successfully applied to determine MONTE and THEO in their combined dosage form. The results obtained for MONTE and THEO were comparable with the corresponding labeled amounts (Table-3).

CONCLUSION

The proposed methods are simple, rapid and validated in terms of linearity, precision, accuracy, reproducibility, and can be used successfully for routine simultaneous estimation of Montalukast sodium and Theophylline in pure and tablet dosage forms.

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