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Spectrophotometric Determination of Montelukast Sodium and Levocetirizine Dihydrochloride in Tablet Dosage Form by AUC Curve Method

Patel Nilam K.[1*] and Pancholi S. S.[2]

[1]*Department of Pharmaceutical Analysis, Shree Krishna Institute of Pharmacy, Gujarat Technological University, Shankhalpur, Gujarat, India*
[2] *Department of Pharmaceutical Analysis, Babariya Institute of Pharmacy, Gujarat Technological University, Baroda, Gujarat, India*

ABSTRACT

A simple, accurate, and precise AUC curve spectrophotometric method was developed for simultaneous determination of Montelukast sodium (MTKT) and Levocetirizine dihydrochloride (LCTZ) in combined pharmaceutical dosage forms. The principle for AUC curve method is "the area under two points on the mixture spectra is directly proportional to the concentration of the component of interest". The area selected were 263.6 to 293.6 and 222 to 242 nm for determination of MTKT and LCTZ respectively. The two drugs follow Beer-Lambert's law over the concentration range of 5-30 µg/ml for MTKT and LCTZ. The % estimation of the drugs was found near to 100 % representing the accuracy of the method. The recovery of the MTKT and LCTZ were found near to 100 %. Validation of the proposed methods was carried out for its accuracy, precision, specificity and ruggedness according to ICH guidelines. The proposed methods can be successfully applied in routine work for the determination of MTKT and LCTZ in combined dosage form.

Key words: Spectrophotometric method, Montelukast Sodium, Levocetirizine Dihydrochloride, Validation.

INTRODUCTION

Montelukast sodium 2-[1-[(R)-[3-[2(E)-(7-chloroquinolin-2-yl) vinyl] phenyl] -3-[2- (1-hydroxy-1-methylethyl) phenyl] propyl -sulfanylmethyl] cyclopropyl] acetic acid sodium salt (Figure 1) is a fast acting and potent cysteinyl leukotriene receptor antagonist which is being used in the treatment of asthma [1]. The recommended dosing of MTKT is 10mg per day.

Levocetirizine 2-[2-[4-[(*R*)-(4-chlorophenyl)-phenyl methyl] piperazinyl-1-yl]ethoxy] acetic acid, the *R*-enantiomer of racemic cetirizine, is a selective, potent, H1-antihistamine compound indicated for the treatment of allergic rhinitis and chronic idiopathic urticaria[2].The LCTZ is official in IP-2007[3].The recommended dosing of LCTZ is 5mg per day.

Literature survey revealed that only a few chromatographic methods have been reported for the determination of MTKT and LCTZ, in individual and in combination with other drugs. Liquid chromatography with fluorescence detection[4–6], stereoselective HPLC for MTKT and its S-enantiomer[7], simultaneous HPLC and derivative spectroscopic method with loratadine[8], stability indicating HPLC method for MTKT in tablets and human plasma[9] reported for MTKT..Different spectrophotometric [10], HPLC [11-14] and LCMS [15, 16] methods have been reported for the determination of cetirizine in pharmaceutical formulations and biological fluids. Simple RP-HPLC, HPTLC and ratio derivative spectroscopy for determination of MTKT and LCTZ was found [17-20].

Literature survey revealed no method reported for simultaneous determination of the two drugs by AUC curve method. The aim of the present work was to develop a simple, sensitive, accurate, and precise AUC method for routine analysis. The proposed method was validated according to ICH guidelines [21].

MATERIALS AND METHODS

Chemicals

Standard samples of MTKT and LCTZ were obtained as gifts from Zydus cadilla Healthcare, Ahmedabad, Gujarat, India. Combination tablet formulation containing MTKT equivalent to 10 mg and LCTZ 5 mg was procured from local pharmacy. Methanol (S.D. Fine Chemicals, Mumbai, India) was used. All chemicals and reagents were of analytical reagent (AR) grade.

Instrumentation

A Shimadzu (Kyoto, Japan) model UV-1700 double beam UV-Visible spectrophotometer attached with computer operated software UV probe 2.0 with spectral width of 2 nm, wavelength accuracy of 0.5 nm and pair of 1 cm matched quartz cells was used to measure absorbance of the resulting solutions. Sartorius CP224S analytical balance (Gottingen, Germany) and ultra sonic cleaner (Frontline FS 4, Mumbai, India) were used during the study.

Preparation of Stock standard solution and selection of wavelengths

MTKT(100 µg/ml) and LCTZ (100 µg/ml) stock were prepared by weighing accurately 10 mg MTKT and LCTZ powder into 2 separate 100 ml volumetric flasks; 20 ml methanol was added, shaken for a few minutes, and diluted to volume with methanol to obtain a standard solution of MTKT (100 µg/ml) and LCTZ (100 µg/ml). After proper dilutions, 10 µg/ml MTKT and LCTZ was scanned in the UV-region i.e. 400 to 200 nm. In UV –Spectrophotometric method two wavelengths 222 nm to 242 nm and 263.6 nm to 293.6 nm were selected for determination of Area Under Curve [AUC] of LCTZ and MTKT respectively **(Figure I and II)**

Study of linearity curves

Standard solution of MTKT (0.5, 1.0, 1.5, 2, 2.5, and 3.0) and LCTZ (0.5, 1.0, 1.5, 2.0, 2.5, 3.0 ml) was pipette out in to a separate series of 10 ml volumetric flask. The volume was adjusted to

the mark with methanol and mixed. The area under curve for solutions was measured between 222.0 to 242 nm and 263.6 to 293.6 nm against methanol as blank. From using this area the 'X' values of the drugs were determined for both the drugs at the selected AUC range.

Figure I: Spectra of LCTZ at wavelength range 222-242 nm

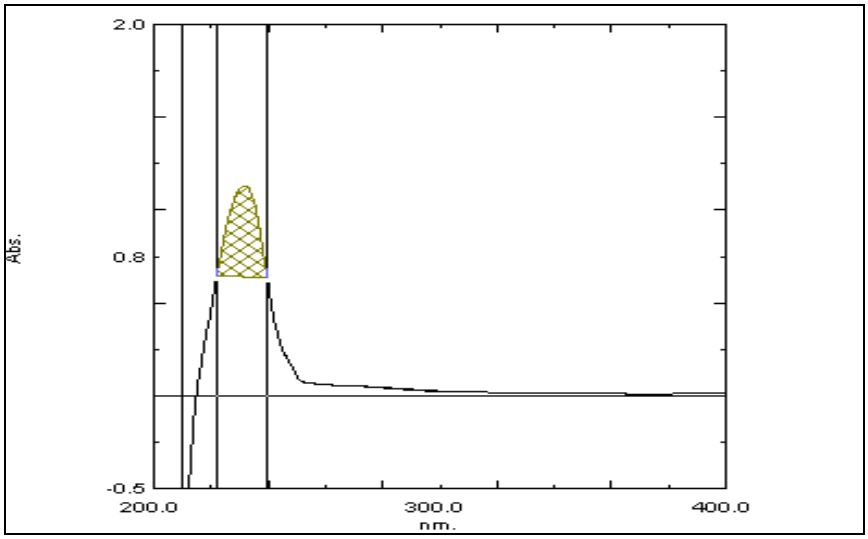
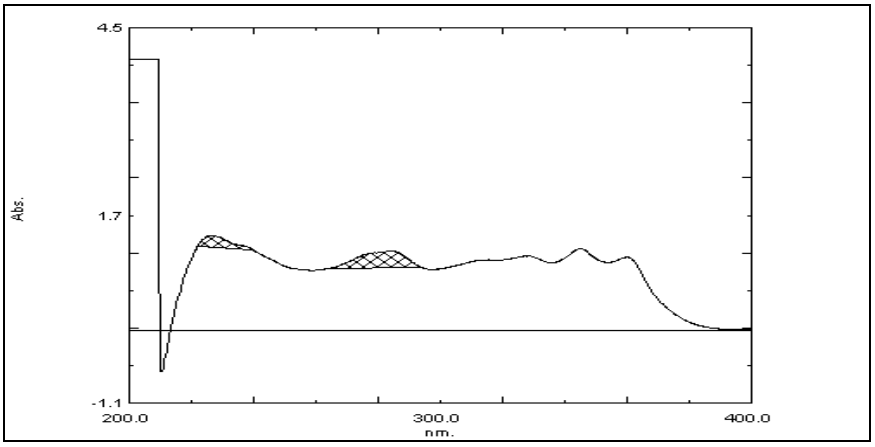


Figure II: Spectra of MTKT at wavelength range 222-242 nm and 263.6-293.6 nm



The 'X' is the ratio of area under the curve at selected wavelength ranges with the concentration of component in gm/lit. These 'X' values were the mean of ten independent determinations. A set of two simultaneous equations obtained by using mean 'X' values.

A set of two simultaneous equations obtained by using mean 'X' values are as follows:

A1 = 184.111C1 + 56.83C2 (at λ222-242nm) …….. (1)
A2 = 0 C1 + 143.833C2 (at λ263.6-293.6nm)…… (2)

Analysis of marketed formulation

For sample solution, 20 tablets were weighed; their mean weight was determined, and grounded into fine powder in a mortar. An amount of powdered mass equivalent to 10 mg MTKT and 5 mg LCTZ was accurately weighed, and transferred in to a 100 ml volumetric flask, 60 ml of methanol was added and sonicated for 20 min., the volume was diluted to mark and mixed well. The solution was filtered through Whatmann No.42 filter paper. Suitable aliquots of filtrate were analyzed by proposed method.

RESULTS AND DISCUSSION

The described method has been validated for linearity, accuracy and intermediate precision. The standard solutions for linearity were prepared 5 times at different concentration levels. The calibration curve was found to be linear in the range of 5-30 µg/ml for both drug. The limit of detection (LOD) and limit of quantification (LOQ) were determined by visual methods as suggested in ICH guidelines, which were found to be 1.6 and 4.8 at 222-242 nm, 1.06 and 3.1 at 263.6-293.6 for MTKT respectively. The LOD and LOQ were1.23 and 3.71 at 222-242 nm for LCTZ respectively. Repeatability of measurement of absorbance was evaluated using 6 replicates of same concentration. The intraday and interday variations for the determination of MTKT and LCTZ were evaluated at 3 different concentration levels (10, 20 and 30 µg/ml). The coefficient of variance (CV, %) values of within day and day to day variations for proposed method were found to be less than 2 %, revealed that proposed method was precise. Accuracy was checked by recovery study at 3 different concentration levels, i.e., a multilevel recovery study. The tablet formulations were analyzed by developed method and assay results were found to be 98.90 ± 0.61 % for MTKT and 98.75 ± 0.96 % for LCTZ of the labeled claim. The tablet samples were also spiked with an extra 50, 100 and 150 % (I, II, and III, respectively) of the standard MTKT and LCTZ, and the mixtures were analyzed by proposed method.

Table I: Summary of Validation Parameter for the Proposed Method

Parameters	Montelukast		Levocetirizine
Wavelength range (nm)	222-242 nm	263.6-293.6nm	222-242 nm
Beer's Law Limit (µg/ml)	5-30	5-30	5-30
Regression equation (y= a + bc) Slope (b) Intercept (a)	 0.0133 0.0554	 0.0267 0.1463	 0.08 0.1903
Correlation Coefficient (r^2)	0.9969	0.9988	0.9991
LOD	1.60	1.06	1.23
LOQ	4.80	3.1	3.71
Repeatability(RSD*, n=6), %	0.46	0.30	0.34
Precision (RSD) % Interday (n=6)	 0.88-0.95%	 0.52-1.07%	 0.63-1.09%
Intraday (n=6)	0.33-0.51	0.34-0.70%	0.53-0.88%
Assay±SD	98.90±0.61		98.75±0.96

**SD is relative standard deviation*

Result of all validation parameters are shown in Table I. Results of the recovery study are shown in Table II, which indicate the suitability of proposed method for routine analysis of MTKT and LCTZ from its tablet dosage forms. Assay results are shown in Table III.

Table II: Recovery study of MTKT and LCTZ

Drug	Amount present in formulation (µg/ml)	Amount Added (%)	% Recovery ± SD*
MTKT	10	50	97.87+ 0.80
	10	100	98.95+ 1.06
	10	150	98.72+ 0.80
LCTZ	5	50	98.63+0.58
	5	100	99.68+ 0.18
	5	150	99.15+ 0.65

Table III: Assay result of MTKT and LCTZ

Sample No.	Label Claim		Amount Found		% Label Claim	
	MTKT (mg/tab)	LCTZ (mg/tab)	MTKT (mg/tab)	LCTZ (mg/tab)	MTKT (mg/tab)	LCTZ (mg/tab)
1	10	5	9.98	4.93	99.77	98.67
2	10	5	9.91	4.85	99.07	96.93
3	10	5	9.91	4.95	99.07	99.10
4	10	5	9.91	4.95	99.07	99.10
5	10	5	9.84	4.95	98.38	98.99
6	10	5	9.80	4.99	98.03	99.74
Mean			9.89	4.94	98.90	98.75
S.D.			0.06	0.05	0.61	0.96

CONCLUSION

The proposed dual wavelength method gives accurate and precise results for determination of MTKT and LCTZ in marketed formulation (tablet) without prior separation and is easily applied for routine analysis. The most striking feature of the AUC curve method is its simplicity and rapidity. Method validation has been demonstrated by variety of tests for linearity, accuracy, precision and stability. The developed method has several advantages, as it is simple, accurate, precise and economical. The proposed method was successfully applied to determination of these drugs in commercial tablets.

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