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Research Article

SIMULTANEOUS SPECTROPHOTOMETRIC DETERMINATION OF MONTELUKAST SODIUM AND BAMBUTEROL HYDROCHLORIDE IN TABLETS

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ABSTRACT
The present manuscript describe simple, sensitive, rapid, accurate, precise and economical first derivative spectrophotometric method for the simultaneous determination of montelukast sodium and bambuterol hydrochloride in combined tablet dosage form. The derivative spectrophotometric method was based on the determination of both the drugs at their respective zero crossing point (ZCP). The first order derivative spectra was obtained in chloroform and the determinations were made at 241 nm (ZCP of bambuterol hydrochloride) for montelukast sodium and 258.4 nm (ZCP of montelukast sodium) for bambuterol hydrochloride. The linearity was obtained in the concentration range of 10-60 µg/ml for montelukast sodium and 10-80 µg/ml for bambuterol hydrochloride. The mean recovery was 100.1 ± 1.25 and 99.70 ± 1.38 for montelukast sodium and bambuterol hydrochloride, respectively. The method was found to be simple, sensitive, accurate and precise and was applicable for the simultaneous determination of montelukast sodium and bambuterol hydrochloride in pharmaceutical tablet dosage form. The results of analysis have been validated statistically and by recovery studies.
KEYWORDS: Montelukast sodium, Bambuterol hydrochloride, First order derivative spectrophotometric method, Tablet, Validation.

INTRODUCTION

Montelukast sodium (MTKT) is chemically 1-[({(R)-m-[(E)-2-(7- chloro-2-quinolyl) vinyl]-α-[o-(1-hydroxyl-1-methylethyl)phenethyl]benzyl}thio)methyl] cyclopropaneacetate sodium[1], is a leukotriene receptor antagonist, used in the treatment of chronic asthma and allergic rhinitis[2-3]. It is official in IP. IP[4] describes liquid chromatography method for its estimation. Literature survey reveals voltametric[5], spectrofluorimetric[6], HPLC[7-10], HPLC and derivative spectroscopic method with loratidine[11], stability indicating HPLC method[12], and LC/MS[13] methods for estimation of MTKT in pharmaceutical dosage forms as well as in biological fluids. Bambuterol hydrochloride (BAM) is chemically (RS)-5-(2-tert-butylamino-1-hydroxyethyl)–m-phenylene bis (dimethylcarbamate) hydrochloride[14], is a long acting bronchodilator for the treatment of asthma[15]. Bambuterol hydrochloride is official in BP. BP[16] describes potentiometric titration method for its estimation. Literature survey reveals HPLC[17-18], solid-state NMR[19] methods for the determination of BAM. The combined dosage forms of MTKT and BAM are available in the market for the prophylaxis and treatment of chronic asthma and chronic bronchitis in pediatrics. Literature survey reveals HPLC[20] and spectrophotometric[21-22] methods for simultaneous determination of MTKT and BAM in tablets. The present manuscript describes simple, sensitive, accurate, precise, rapid and economic first order derivative spectrophotometric method for simultaneous determination of montelukast sodium and bambuterol hydrochloride in pharmaceutical tablet dosage form.

MATERIALS AND METHODS

Apparatus

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. Spectra were automatically obtained by UV-Probe system software. A Sartorius CP224S analytical balance (Gottingen, Germany), an ultrasonic bath (Frontline FS 4, Mumbai, India) was used in the study.

Reagents and Materials

MTKT and BAM bulk powder was kindly gifted by Sun Pharmaceuticals Ltd. Vadodara, Gujarat, India. The commercial fixed dose combination product was procured from the local market. Chloroform AR Grade was procured from S. D. Fine Chemicals Ltd., Mumbai, India.

Preparation of standard stock solutions

An accurately weighed quantity of MTKT (10 mg) and BAM (10 mg) were transferred to a separate 100 ml volumetric flask and dissolved and diluted to the mark with chloroform to obtain standard solution having concentration of MTKT (100 µg/ml) and BAM (100 µg/ml).

Methodology

The standard solutions of MTKT (10 µg/ml) and BAM (10 µg/ml) were scanned separately in the UV range of 200-400 nm. The zero-order spectra thus obtained was then processed to obtain first-derivative spectra. Data were recorded at an interval of 1 nm. The two spectra were overlain and it appeared that MTKT showed zero crossing at 258.4 nm, while BAM showed zero crossing at 241 nm. At the zero crossing point (ZCP) of MTKT (258.4 nm), BAM showed a first-derivative absorbance, whereas at the ZCP of BAM (241 nm), MTKT showed a first-derivative absorbance. Hence 241 and 258.4 nm were selected as analytical wavelengths for determination of MTKT and BAM, respectively. These two wavelengths can be employed for the determination of MTKT and BAM without any interference from the other drug in their combined dosage formulations.

Validation of the proposed method

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines[23].

Linearity (Calibration curve)

The calibration curves were plotted over a concentration range of 10-60 µg/ml for MTKT and 10-80 µg/ml for BAM. Accurately measured standard solutions of MTKT (1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 ml) and BAM (1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 ml) were transferred to a series of 10 ml of volumetric flasks and diluted to the mark with chloroform. First-derivative absorbance (D1) was measured at 241 nm for MTKT and 258.4 nm for BAM. The calibration curves were constructed by plotting absorbances versus concentrations and the regression equations were calculated.

Method precision (repeatability)

The precision of the instrument was checked by repeated scanning and measurement of absorbance of solution (*n* = 6) for MTKT and BAM (40 µg/ml) without changing the parameter of the first-derivative spectrophotometry method.

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 over a period of 1 week for 3 different concentrations of standard solutions of MTKT and BAM (20, 40 and 60 µg/ml). The result was reported in terms of relative standard deviation (% RSD).

Accuracy (recovery study)

The accuracy of the method was determined by calculating recovery of MTKT and BAM by the standard addition method. Known amounts of standard solutions of MTKT and BAM were added at 50, 100 and 150 % level to prequantified sample solutions of MTKT and BAM (10 µg/ml for each drug). The amounts of MTKT and BAM were estimated by applying obtained values to the respective regression line equations. The experiment was repeated for five times.

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, i.e., 3.3 for LOD and 10 for LOQ) using the following equations designated by International Conference on Harmonization (ICH) guidelines[23].

$$LOD = 3.3 \times \sigma/S$$

$$LOQ = 10 \times \sigma/S$$

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

Analysis of MTKT and BAM in combined tablet dosage form

Twenty Tablets were weighed and powdered. The powder equivalent to 10 mg of MTKT and 10 mg of BAM was transferred to a 100 ml volumetric flask. Chloroform (50 ml) was added to it and sonicated for 20 min. The solution was filtered through Whatman filter paper No. 41 and the volume was adjusted up to the mark with chloroform. This solution is expected to contain 100 µg/ml of MTKT and 100 µg/ml of BAM. This solution (6.0 ml) was taken in to a 10 ml volumetric flask and the volume was adjusted up to mark with chloroform to get a final concentration of MTKT (60 µg/ml) and BAM (60 µg/ml). The responses of the sample solution were measured at 241 nm and 258.4 nm for quantitation of MTKT and BAM, respectively. The amounts of the MTKT and BAM present in the sample solution were calculated by fitting the responses into the regression equation for MTKT and BAM in the proposed method.

RESULTS AND DISCUSSION

The standard solutions of MTKT and BAM were scanned separately in the UV range, and zero-order spectra (Figure 1) thus obtained were then processed to obtain first-derivative spectra. Data were recorded at an interval of 1 nm. The two derivative spectra showed maximum absorbance at 241 nm (ZCP of BAM) for

MTKT and 258.4 nm (ZCP of MTKT) for BAM. First-derivative absorbances (D1) were recorded 241 nm for MTKT and 258.4 nm for BAM (Figure 2). First derivative spectra give good quantitative determination of both the drugs at their respective without any interference from the other drug in their combined dosage formulations. Second and third-ordered derivative spectra of the drugs were not tested because the first-order spectra give satisfactory ZCPs and good quantitative determination of both the drugs without any interference.

Linear correlation was obtained between absorbances and concentrations of MTKT and BAM in the concentration ranges of 10–60 µg/ml and 10-80 µg/ml, respectively. The linearity of the calibration curve was validated by the high values of correlation coefficient of regression (Table 1). The RSD values for MTKT and BAM were found to be 0.39 and 0.87 %, respectively (Table 1). The low values of relative standard deviation (less than 2 %) indicate that the proposed method is repeatable. The low RSD values of interday (0.52 – 1.98 and 0.62 – 1.84 %) and intraday (0.54 – 1.88 and 0.57 – 1.96 %) for MTKT and BAM, respectively, reveal that the proposed method is precise (Table 1). LOD values for MTKT and BAM were found to be 2.79 and 2.58 µg/ml, respectively and LOQ values for MTKT and BAM were found to be 9.2 and 8.5 µg/ml, respectively (Table 1). These data show that proposed method is sensitive for the determination of MTKT and BAM.

The recovery experiment was performed by the standard addition method. The mean recoveries were 100.1 ± 1.25 and 99.70 ± 1.38% for MTKT and BAM, respectively (Table 2). The results of recovery studies indicate that the proposed method is accurate. The proposed validated method was successfully applied to determine MTKT and BAM in their combined dosage form. The results obtained for MTKT and BAM were comparable with the corresponding labeled amounts (Table 3). No interference of the excipients with the absorbance of interest appeared; hence the proposed method is applicable for the routine simultaneous estimation of MTKT and BAM in pharmaceutical dosage forms.

CONCLUSION

Based on the results, obtained from the analysis of described method, it can be concluded that the method has linear response in the range of 10-60 µg/ml and 10-80 µg/ml for MTKT and BAM, respectively with co-efficient of correlation, (r^2)=0.9997 and (r^2) = 0.9998 for MTKT and BAM, respectively. The result of the analysis of pharmaceutical formulation by the proposed method is highly reproducible and reliable and it is in good agreement with the label claim of the drug. The additives usually present in the pharmaceutical formulation of the assayed sample did not interfere with determination of MTKT and BAM. The method can be used for the routine analysis of the MTKT and BAM in combined dosage form without any interference of excipients.

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TABLE 1: REGRESSION ANALYSIS DATA AND SUMMARY OF VALIDATION PARAMETERS FOR THE PROPOSED METHOD

PARAMETERS		**First-derivative UV Spectrophotometry**	
		MTKT at 241 nm	**BAM at 258.4 nm**
Concentration range (µg/ml)		10 - 60	10 - 80
Regression equation (y = a + bc) Slope (b) Intercept (a)		y = 0.008x-0.0007 0.008 -0.0007	y = 0.037x-0.004 0.037 -0.004
Correlation Coefficient (r^2)		0.9997	0.9998
Sandell's sensitivity (µg/cm^2/0.001 A.U.)		0.280	0.125
Accuracy (% recovery) (n = 5)	Level I	99.51 ± 0.75	99.42 ± 0.91
	Level II	100.5± 1.39	99.71 ± 1.79
	Level III	100.4 ± 1.62	99.98 ± 1.45
Repeatability (%RSD[a], n = 6),		0.39	0.87
Interday (n = 3) (%RSD)		0.52 - 1.98	0.62 - 1.84
Intraday(n = 3) (%RSD)		0.54 – 1.88	0.57 – 1.96
LOD[b] (µg/ml)		2.79	2.58
LOQ[c] (µg/ml)		9.20	8.50

[a]RSD = Relative standard deviation. [b]LOD = Limit of detection. [c]LOQ = Limit of quantification

TABLE 2: RECOVERY DATA OF PROPOSED METHOD

Drug	**Level**	**Amount taken (µg/ml)**	**Amount added (µg/ml)**	**Amount found (µg/ml)**	**% Mean recovery ± S.D. (n = 5)**
MTKT	I	10	5	14.86	99.51 ± 0.75
	II	10	10	20.10	100.5± 1.39
	III	10	15	25.10	100.4 ± 1.62
BAM	I	10	5	14.91	99.42 ± 0.91
	II	10	10	19.94	99.71 ± 1.79
	III	10	15	24.99	99.98 ± 1.45

S. D. is Standard deviation and n is number of determinations

TABLE 3: ANALYSIS OF BAM AND MTKT BY PROPOSED METHOD

Tablet	Label claim (mg)		Amount found (mg)		% Label claim ± S. D. (n = 6)	
	MTKT	BAM	MTKT	BAM)	MTKT	BAM
I	10	10	9.96	9.93	99.64 ± 0.46	99.33 ± 0.59
II	10	10	9.97	9.96	99.73 ± 0.72	99.65 ± 0.63

S. D. is Standard deviation and n is number of determination

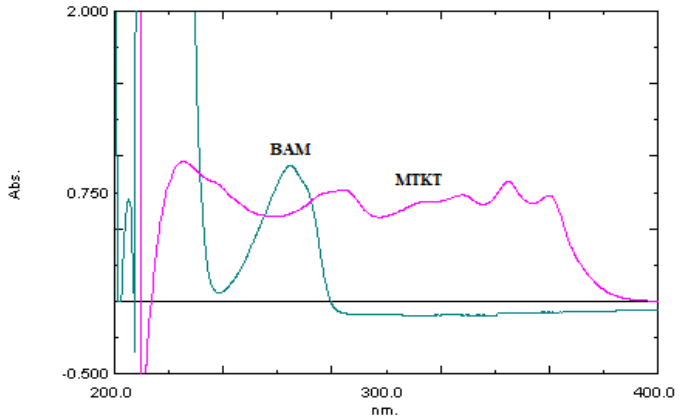

FIGURE 1: Overlain zero-order absorption spectra of MTKT and BAM in chloroform

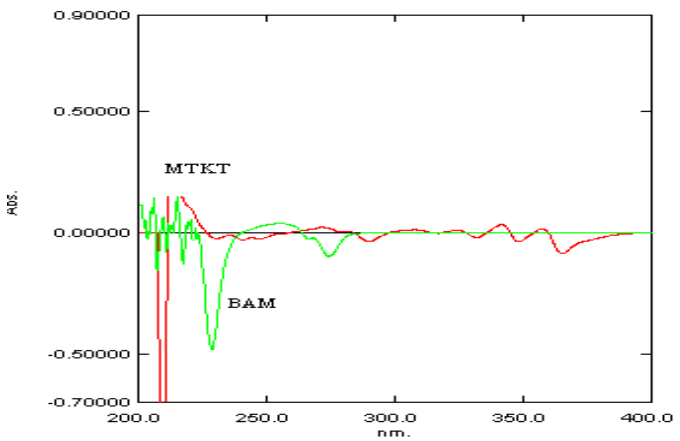

FIGURE 2: Overlain first-order derivative spectra of MTKT and BAM in chloroform

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