Research Article

Spectrophotometric Simultaneous Determination of Salbutamol Sulfate and Ketotifen Fumarate in Combined Tablet Dosage Form by First-Order Derivative Spectroscopy Method

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Received 31 May 2013; Revised 21 June 2013; Accepted 9 July 2013

Academic Editor: Rolf W. Berg

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Salbutamol sulfate and ketotifen fumarate are used in combination for the treatment of asthma. The present work deals with method development for simultaneous estimation of salbutamol sulfate and ketotifen fumarate in two-component tablet formulation by first-order derivative spectroscopy. For determination of sampling wavelength, 10 \( \mu \text{g/mL} \) of each of salbutamol and ketotifen was scanned in 200–400 nm ranges and sampling wavelengths were found to be 257 nm for salbutamol and 278 nm for ketotifen in first-order derivative spectroscopy. In this method, linearity was observed in the ranges of 5–45 \( \mu \text{g/mL} \) for salbutamol and 5–35 \( \mu \text{g/mL} \) for ketotifen. The % recovery was within the range between 98 and 102%, and % relative standard deviation for precision and accuracy of the method was found to be less than 2%. The method is validated as per international conference on harmonization guidelines. The method can be successfully applied for the simultaneous analysis of both drugs in pharmaceutical dosage forms.

1. Introduction

Salbutamol sulfate, chemically known as (rs)-1-(4-hydroxy-3-hydroxymethylphenyl)-2-(tert-butylamino) ethanol sulfate (Figure 1), is beta-adrenoceptor agonist used as an antiasthmatic drug [1]. It is official in Indian pharmacopoeia and British pharmacopoeia. It is estimated by acid-base titration method as per Indian pharmacopoeia and British pharmacopoeia [1, 2]. The literature review reveals that HPLC [3–5] and UV spectrophotometric methods [6–8] have been reported for estimation of salbutamol sulfate in pharmaceutical dosage forms.

Ketotifen fumarate, chemically known as 4-(1-methyl-4-piperidylidene)-4h-benzo[4, 5] cyclohepta [1, 2-b] thiophen-10(9h)-one hydrogen fumarate (Figure 2), is cycloheptathio- phen blocker of histamine h-1 receptors used as an antiallergic and an antiasthmatic drug [9]. It is not official in Indian pharmacopoeia, British pharmacopoeia, United States pharmacopoeia, and European pharmacopoeia. The literature review reveals that HPLC [10, II] and UV spectrophotometric methods [12, 13] have been reported for estimation of ketotifen fumarate in pharmaceutical dosage forms.

The salbutamol sulfate and ketotifen fumarate mixture is not yet official in any pharmacopoeia. As per literature, no analytical method could be traced for the analysis of salbutamol sulfate and ketotifen fumarate combination in pharmaceutical dosage forms. Therefore, simple, rapid, and reliable method for simultaneous estimation of these drugs in mixture seemed to be necessary.

Spectrophotometric methods of analysis are more economic and simpler, compared to methods such as chromatography and electrophoresis. Under computer-controlled instrumentation, derivative spectrophotometry is playing a very important role in the multicomponent analysis of mixtures by UV molecular absorption spectrophotometry. Binary mixtures can be easily resolved by means of a spectrophotometric method, which is based on the simultaneous use of “zero crossing” method. The aim of this work was to investigate the utility of derivative spectrophotometry and to develop reliable spectrophotometric procedures for the simultaneous determination of salbutamol sulfate and ketotifen fumarate either in laboratory samples or in commercial dosage forms without any prior separation of individual drugs. The present developed method is simple, rapid,
2. Materials and Methods

2.1. Apparatus and Instrument. A double beam UV-visible spectrophotometer (Shimadzu, model pharm spec 1800) having two matched quartz cells with 1 cm light path and electronic analytical balance (Shimadzu AUX-220), and ultrasonication (Branson) were used. Volumetric flasks and pipettes of borosilicate glasses were used in the study.

2.2. Chemicals and Reagents. Pure drug samples of salbutamol sulfate and ketotifen fumarate were provided as a gift sample by East West Pharma, Uttarakhand, India. Methanol and all other chemicals were provided by Sardar Patel University, Vallabh Vidhyanagar, Gujarat, India.

2.3. Marketed Formulation. The marketed formulation studied was mastifen-s tablet manufactured by East West Pharma. Each tablet contains 1 mg ketotifen and 2 mg salbutamol.

2.4. Selection of Common Solvent. Methanol of analytical reagent grade was selected as a common solvent for developing spectral characteristics of both drugs. The selection was made after assessing the solubility of both drugs in different solvents.

2.5. Preparation of Standard Solutions. Accurately weighed quantity of salbutamol sulfate (10 mg) and ketotifen fumarate (10 mg) was transferred to two separate 10 mL volumetric flasks, dissolved in little amount of methanol and diluted to the mark with methanol (stock solutions: 1000 μg/mL of salbutamol sulfate and ketotifen fumarate). 100 μg/mL of salbutamol sulfate and ketotifen fumarate solutions was prepared by diluting 5 mL of stock solution to 50 mL with methanol.

2.6. Spectrophotometric Conditions

(i) Mode: spectrum.
(ii) Scan speed: medium.
(iii) Bandwidth: 1 nm.
(iv) Wavelength range: 400–200 nm.
(v) Absorbance scale: 0.00 A–2.00 A.
(vi) Initial baseline correction: methanol.

3. First-Order Derivative Spectroscopy Method

Working standard solutions of salbutamol sulfate (100 μg/mL) and ketotifen fumarate (100 μg/mL) were diluted appropriately with methanol to obtain solution containing salbutamol sulfate (10 μg/mL) and ketotifen fumarate (10 μg/mL). Spectra of these diluted solutions were scanned in the spectrum mode between 200 nm and 400 nm using methanol as a blank. The zero-order spectra of salbutamol sulfate and ketotifen fumarate were transformed to corresponding first derivative spectra in the range of 200–400 nm. The overlay spectra (zero and first order) of salbutamol sulfate and ketotifen fumarate are shown in Figures 3 and 4.

3.1. Selection of Wavelengths. A signal at 257 nm of first derivative spectrum was selected for quantification of salbutamol sulfate where no interference due to ketotifen fumarate was observed; similarly, a signal at 278 nm was selected for quantification of ketotifen fumarate, where salbutamol sulfate did not interfere with the estimation of ketotifen fumarate.

3.2. Calibration Curves for Salbutamol Sulfate and Ketotifen Fumarate. The standard solutions of salbutamol sulfate (100 μg/mL) and ketotifen fumarate (100 μg/mL) were used
to prepare two different sets of working standard solutions of
salbutamol sulfate (5–45 μg/mL) and ketotifen fumarate (5–
35 μg/mL). For this, aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5,
4.0, and 4.5 mL of working standard solutions of salbutamol
sulfate and aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 3.5 mL
of working standard solutions of ketotifen fumarate were
transferred separately to a series of 10 mL volumetric flasks
and diluted to mark with methanol, and the absorbance was
measured at 257 nm for salbutamol sulfate and 278 nm for
ketotifen fumarate, respectively. The values of first derivative
absorbance were plotted against corresponding concentra-
tions to construct the calibration curves. First derivative
spectra of working standard dilutions and calibration curves
are shown in Figures 5, 6, 7, and 8.

3.3. Analysis of Tablet Formulation. Marketed tablet formu-
lations containing salbutamol sulfate (2 mg) and ketotifen
fumarate (1 mg) were analyzed using this method. From the
triturate of 20 tablets, an amount equivalent to 2 mg of salbu-
tamol sulfate and 1 mg of ketotifen fumarate was weighed and
dissolved in 10 mL of methanol in 100 mL volumetric flask by
sonication for 10 min. Then, final volume of the solution was
made up to 100 mL with methanol to get a solution containing
20 μg/mL of salbutamol sulfate and 10 μg/mL of ketotifen
fumarate. The solution was filtered through Whatman filter
paper no. 41, and the absorbance values were measured
at 257 nm and 278 nm for salbutamol sulfate and ketotifen
fumarate, respectively. The concentration of each analyte was
determined with the equations generated from calibration
curve of respective drugs. The first derivative spectrum of
marketed formulation and standard mixture are shown in
Figure 9. The analysis was repeated three times.

4. Results and Discussion

4.1. Selectivity. The UV spectra of standard mixture (salbu-
tamol sulfate (20 μg/mL) + ketotifen fumarate (10 μg/mL))
and sample solutions (tablet) were recorded between 200 and
400 nm and their absorbance measured. The selectivity of the
method was assessed by comparing spectra obtained from
formulation solutions with that obtained from standard drug
solution. The UV absorption spectra obtained from standard
and sample solutions were found to be identical, confirming
the selectivity of the method. The overlain UV absorption
spectra of the drugs from marketed formulation (tablet) with
the standard mixture are shown in Figure 9.
4.2. Linear correlation was obtained between absorbance versus concentrations of salbutamol sulfate and ketotifen fumarate in the concentration ranges of 5–45 μg/mL and 5–35 μg/mL for both drugs, respectively. Regression parameters are mentioned in Table 4. The linearity spectra and calibration curves of salbutamol sulfate and ketotifen fumarate are shown in Figures 5, 6, 7, and 8, respectively.

4.3. Accuracy. Recovery studies were performed by standard addition method at three levels, that is, 80%, 100%, and 120%. Known amounts of pure salbutamol sulfate and ketotifen fumarate were added to preanalyzed sample of marketed formulation, and they were subjected to analysis by the proposed method. The recovery was verified by estimation of drug in triplicate preparations at each specified concentration level and calculated %RSD. The mean recoveries were 98.82%–101.19% and 98.34%–100.81% for salbutamol sulfate and ketotifen fumarate, respectively. The low value of standard deviation indicates that the proposed method is accurate. Results of recovery studies are shown in Table 1.

4.4. Precision

4.4.1. Repeatability. The precision of the instrument was checked by repeated scanning and measurement of the absorbance of solutions (n = 6) of salbutamol sulfate (10 μg/mL) and ketotifen fumarate (10 μg/mL) without changing the parameters of the proposed method. The %RSD values for salbutamol sulfate and ketotifen fumarate were found to be 1.30% and 0.23%, respectively, at 257 nm and 278 nm (Table 2). Low relative standard deviation (<1) indicates that the proposed method is repeatable.
<table>
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<tr>
<th>Sr. no.</th>
<th>Concentration (μg/mL)</th>
<th>Salbutamol sulfate</th>
<th>Ketotifen fumarate</th>
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<tr>
<td></td>
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<td>Absorbance</td>
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<table>
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<th>Parameters</th>
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<td>Salbutamol sulfate</td>
<td>Ketotifen fumarate</td>
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<tr>
<td>Wavelength</td>
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<td>Precision (RSD) %</td>
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<td>Repeatability (n = 6)</td>
<td>0.43–1.02</td>
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<td>Interday (n = 3)</td>
<td>0.37–0.91</td>
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</table>

4.5. LOD and LOQ. LOD and LOQ of the drug were calculated as per ich guideline. LOD values for salbutamol sulfate and ketotifen fumarate were found to be 0.55 μg/mL and 0.061 μg/mL, and LOQ values for SAL and KTF were found to be 1.66 μg/mL and 0.18 μg/mL (Table 4). These data show that the proposed method is sensitive for the determination of salbutamol sulfate and ketotifen fumarate.

4.6. Analysis of Salbutamol Sulfate and Ketotifen Fumarate in Marketed Formulation. Content of salbutamol sulfate and ketotifen fumarate found in the marketed method from the proposed method is shown in Table 5. The % purity was 99.75% for salbutamol sulfate and 101.90% for ketotifen fumarate.

5. Conclusion

In this proposed methods, the linearity was observed in the concentration ranges of 5–45 μg/mL and 5–35 μg/mL with coefficients of correlation $r^2 = 0.9998$ and $r^2 = 0.9998$ for salbutamol sulfate and ketotifen fumarate at 257 nm and 278 nm, respectively. The result of the analysis of combined mixture by the proposed method was found to be highly reproducible and reliable. The additive present in the combined mixture of the assayed samples did not interfere with determination of salbutamol sulfate and ketotifen fumarate. So, the developed first the derivative UV spectroscopy method is simple, precise, accurate, and reproducible and can be used for simultaneous determination of salbutamol sulfate and ketotifen fumarate in pharmaceutical dosage forms. The method was validated as per international conference on harmonization guidelines.

Acknowledgments

The authors are thankful to East West Pharma, Uttarakhand, India for providing gratis sample of salbutamol sulfate and ketotifen fumarate as well as to the Department of Pharmaceutical Sciences, Sardar Patel University, Vallabh Vidhyanagar, Gujarat, India, for providing facilities to complete this work successfully.

References


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