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Research Article

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Spectrophotometric estimation of ketotifen and salbutamol by validated analytical method from tablet dosage form

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ABSTRACT

A Multicomponent Spectrophotometric method for simultaneous estimation of Ketotifen fumarate and Salbutamol sulphate in combined tablet dosage form has been proposed. Considering the absorption spectra of both analytes in the range of 220-360 nm in water, the four wavelengths of equal intervals of 40 nm were selected as 350 nm, 320 nm, 280 nm and 240 nm to produce calibration curves of mixture of analytes. The present method used inbuilt application of instrument (Shimadzu Pharm Spec 1700, UV-Visible Spectrophotometer) to quantify Ketotifen fumarate and Salbutamol sulphate in formulation. The mean % assay was found as 102.90% and 101.05% for Ketotifen fumarate and Salbutamol sulphate respectively. The method has been validated in accordance with ICH guidelines for accuracy and precision. The mean % recovery was found in range of 98.85 to 99.62% for Ketotifen fumarate and 99.08 to 100.65 % for Salbutamol sulphate, while % RSD was observed as less than 1% for precision study. The developed method was simple, accurate, rapid economical which make it suitable for routine analysis of Ketotifen fumarate and Salbutamol sulphate from marketed formulation.

Keywords: Ketotifen fumarate; Salbutamol sulphate; Multicomponent Spectrophotometric Method

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INTRODUCTION

Ketotifen (KETO) is a relatively selective, non-competitive histamine antagonist (H1-receptor) and mast cell stabilizer. Chemically it is 4,9-dihydro-4-(1-methylpiperidin-4-ylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophene-10-one hydrogen fumarate with molecular formula of $C_{23}H_{23}NO_5S$ and molecular weight is 425.5 g/mol (Figure 1). It is a white to brownish-yellow crystalline powder. It is sparingly soluble in water, slightly soluble in methanol and very slightly soluble in acetonitrile [1].

Salbutamol (SAL) is a short-acting, selective beta (2)-adrenergic agonist and thus it stimulates beta (2)-adrenergic receptors. Binding of SAL to beta (2)-receptors in the lungs results in relaxation of bronchial smooth muscles, it is (RS)-1-(4-hydroxy-3-hydroxy-methylphenyl)-2-(tert-butylamino) ethanol sulphate and its molecular formula is $(C_{13}H_{21}NO_3)_2H_2SO_4$ and molecular weight is 576.70g g/mol (Figure 2). It is white or almost white, crystalline powder. It is sparingly soluble in water, soluble in ethanol (96%), slight soluble in ether [2].

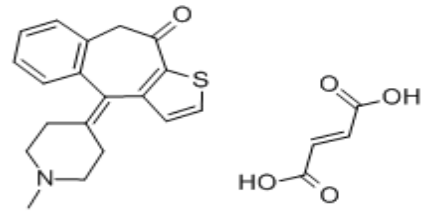

Fig 1: Chemical Structure of Ketotifen fumarate

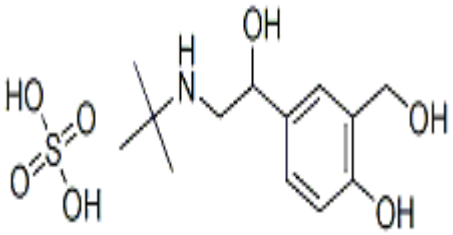

Fig 2: Chemical Structure of Salbutamol sulphate

Ketotifen fumarate (1 mg) and Salbutamol sulphate (2 mg) is available in combination as tablet dosage form and prescribed for asthma disorder. KETO is anti histamine, but when used with SAL it will allow these to be taken longer while still being effective. It does so by up regulating the body's beta-adrenergic receptors. It is extremely effective when used with SAL. Combination of KETO and SAL is used for allergic asthma mainly in children.

Literature survey reveals that few analytical methods are reported for analysis of prescribed drugs individually or in combination with other drugs like Stability indicating HPLC [3], LCMS [4], RP-HPLC [5], Colorimetric titration [6], Ion pair spectrophotometric method [7], Spectroscopic methods [8] are reported for KETO and RP-HPLC [9], Spectroscopic methods [10], Stability indicating HPLC [11] are available for SAL. As no analytical method is reported for simultaneous estimation of these drugs so an attempt has been made to develop and validate new UV-Visible Spectrophotometric method for simultaneous estimation KETO and SAL in tablet dosage form.

EXPERIMENTAL SECTION

Instrument

A Shimadzu UV- Visible double beam spectrophotometer model 1700 (Japan) with 1 cm matched quartz cells connected to a PC computer running UV-Probe 2.32 software for absorbance measurements and treatment of data was used. Sartorius digital balance for weighing and PCI analytics sonicator for extracting the drugs from the marketed formulation was used.

Chemicals and Reagents

The drug samples of KETO and SAL were obtained from East West Pharma, Haridwar and Micro Labs Pvt Ltd, Bangalore respectively. Tablets containing KETO and SAL (Mastifan-s East West Pharma, Haridwar) were purchased from local pharmacy. Double Distilled Water as a solvent and Whatmann filter paper (no.41) was used throughout the experiment.

Method

The mixed stock solution of analytes was prepared by transferring equivalent weight 10 mg of KETO and 20 mg of SAL in 10 ml volumetric flask. The drugs were dissolved in few ml of double distilled water and volume was made upto the mark with the same solvent to get the concentration of 1000 µg/ml of KETO and 2000 µg/ml of SAL. This solution was further diluted to get five serial dilutions containing 4 to 20 µg/ml of KETO and 8 to 40 µg/ml of SAL in double distilled water. All mixed standard solutions were scanned over the range of 360 nm to 220 nm in multicomponent mode of spectrophotometer at medium scanning speed. The absorbencies of solutions were measured at wavelength interval of 40 nm. The data of calibration curve was stored and processed by instrument. An overlain spectrum of mixed standard solutions is as shown in Fig 3.

Analysis of Commercial Formulation

Twenty tablets (Mastifen -S) were accurately weighed and crushed to fine powder. The tablet powder equivalent to 5 mg of KETO (2 mg of SAL) was accurately weighed, transferred to 50 ml volumetric flask, small quantity of double distilled water was added and sonicated for 15 min. The solution was made up to mark with the same solvent to get concentration of 100 µg/ml of KETO and 200 µg/ml of SAL. This solution was filtered through whatman filter paper No. 41. The filtrate was further diluted with double distilled water to get concentration of 10 µg/ml of KETO and

20 µg/ml of SAL.

Fig 3: Overlain Spectra of Mixed Standards of KETO and SAL

The sample solution was scanned over the range of 360 nm to 220 nm in multi component mode immediately after the scanning of five mixed standard solutions and concentration of each component was estimated by analysis of spectral data of sample solution with respect to that of mixed standards by the instrument. The spectrum of sample solution is given in Figure 4 and results of assay of marketed formulation are given in Table 1.

Figure 4: Spectrum of Sample Solution.

Validation

The proposed method of analysis for KETO and SAL in combination was validated as per the recommendations of ICH guidelines [12] for accuracy and precision. Recovery studies were carried out by addition of pure drug to previously analyzed tablet sample at three different concentration levels (80%, 100%, and 120%) (Fig 5). The results of recovery studies are reported in Table 2. While, precision of the method was determined by repeatability and intermediate precision (intra-day, inter-day) expressed as % Relative Standard Deviation (% RSD). Intra-day precision was evaluated by analyzing concentration of KETO (10 µg/ml) and SAL (20 µg/ml) of standard and sample solutions at three different time intervals under the same experimental conditions on the same day, while inter-day precision was determined by analyzing above mentioned concentrations of solutions on three consecutive days (Table 3).

Figure 5: Spectrum of Sample, Standard and Recovery Solution.
Where A-Standard Solution, B-Sample Solution, C-80% Recovery Solution,D-100% Recovery Solution, E-120% Recovery Solution.

Table 1: Assay of Marketed Formulation (Mastifen-S).

Analyte	Label Claim (mg)	Mean Amount Found Per Tablet(mg)	Mean Amount Found (%)	% RSD (n=6)
KETO	1	1.03	102.90	1.78
SAL	2	2.02	101.05	1.16

Table 2: Results of Recovery Studies.

analyte	Level of Recovery		
	80% (± RSD)	100% (± RSD)	120% (± RSD)
KETO	99.45± 0.16	99.21 ± 0.39	99.08 ± 0.16
SAL	99.72 ± 0.17	100.28 ± 0.38	99.22 ± 0.19

Table 3: Results of Precision Studies (Intra-Day and Inter-Day)

Analyte	Concentrations of sample solution (µg/ml) % RSD (n=3)	Intra-day precision %RSD(n=3)	Inter-day precision %RSD(n=3)
KETO	10	0.0060	0.0168
SAL	20	0.0125	0.0981

RESULTS AND DISCUSSION

The standard solutions of both drugs were prepared in Double distilled water, 0.1 N Hydrochloric acid, 0.1N Sodium hydroxide, Dichloromethane, Glacial acetic acid, Dimethylformamide and Methanol. KETO was not soluble in 0.1N Sodium hydroxide so stock solution was prepared in Double distilled water and further dilution was made with 0.1 N Sodium hydroxide and overlay spectra of these drugs were studied in each solvent. Considering the economy and satisfactory absorbance of both drugs, double distilled water was selected as solvent.

As the proposed method is specific to instrument having software for provision of such determination, two parameters are critical , one is selection of proper sampling wavelength and the other is concentrations of mixed standard solution.

Hence overlay spectra of analytes were studied carefully for selection of proper sampling wavelength. KETO has shown absorbance in the range of 220-360 nm while SAL was found to be absorbing in the range 220-320 nm. Considering common absorbance of these drugs, the wavelength range of 220-360 nm was selected for the study. The various wavelength intervals like 40, 41, 50 and 52 were tried to measure and process data by the instruments to determine

the exact concentration of standard and sample solutions. The wavelength interval of 40 nm was found to be effective to quantify both drugs in marketed formulation. The concentrations of mixed standard solutions were selected on the basis of linearity of each analyte at their wavelengths of absorption. The care was taken while selecting the concentrations of mixed solutions such that the absorbance at four selected wavelengths was not more than 1.0 (considering % relative error by instruments).

The mean content of analytes in the marketed formulation were found to be 102.90 and 101.05% for KETO and SAL respectively, while recovery was found in the range of 98.85 to 99.62% for KETO and 99.08 to 100.65% for SAL respectively. The values of relative standard deviations of inter-day and intra-day studies were found to be less than 1%. Intra-day study also indicated the standard and sample solutions were stable for measurement for longer time. The limitation of the present study is need of inbuilt software and retaining all the serial dilution of mixed standard solution for analysis of marketed formulation. The assay and validation results confirmed that the contents of KETO and SAL estimated in the tablet dosage form were free from the interference of excipients.

CONCLUSION

The developed multicomponent spectroscopy method for simultaneous estimation of Ketotifen fumarate and Salbutamol sulphate in combined tablet dosage form is simple, economical, accurate and reproducible and can be conveniently adopted for the routine quality control analysis from its pharmaceutical formulations and bulk drug.

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