

Spectrophotometric method development and validation for simultaneous analysis of Ketotifen fumarate and Cetirizine dihydrochloride in pharmaceutical dosage form

Ruchika Patel¹, Prachi Kabra^{1*}, Ritu Kimbahune², Satya Vijay Singh¹, L.V.G.Nargund¹

¹Department of Quality Assurance, Nargund College of Pharmacy, Dattatreyanagar, II Main, 100 ft Ring Road, BSK III Stage, Bangalore-85, (INDIA)

²Department of Quality Assurance, Al-Ameen College of Pharmacy, Hosur Road, Near Lal Bagh Main Gate, Bangalore-27, (INDIA)

E-mail : rituvivekk@gmail.com

ABSTRACT

In present research work, a simple Multicomponent Spectrophotometric method for simultaneous estimation of Ketotifen fumarate and Cetirizine dihydrochloride in pharmaceutical dosage was developed. The method used is inbuilt application of instrument (Shimadzu Pharm Spec 1700, UV spectrophotometer) to quantify Ketotifen fumarate and Cetirizine dihydrochloride in formulation. Considering the absorption of both analytes in the range of 200-360 nm in water, the wavelength intervals of 40 nm was selected such as 360 nm, 320 nm, 280 nm, 240 nm and 200 nm for measurements. The serial dilutions of standard were scanned and absorptions were stored and sample concentration was determined by the instrument. The mean assay was found as about 100.3 %. The method has been validated in accordance with ICH guidelines for accuracy and precision. Result of recovery study was observed in the range of 98.78% to 101.48% for Ketotifen fumarate and 98.77% to 101.48% for Cetirizine dihydrochloride. The % RSD for precision study was found as less than 1. The developed method is simple, accurate and economical so can be used for the routine analysis of Ketotifen fumarate and Cetirizine dihydrochloride from tablet dosage form. © 2013 Trade Science Inc. - INDIA

KEYWORDS

Ketotifen fumarate;
Cetirizine dihydrochloride;
Multicomponent spectroscopy.

INTRODUCTION

Chronic Urticaria is a condition where an itchy rash persists on off for six weeks or more. The cause of the rash is often not clear and many people also develop swelling of the lips, tongue or other areas of the body from time to time^[1]. The symptoms can often be eased with antihistamine tablets. The combination of Ketotifen fumarate (a relatively selective, non-competitive hista-

mine antagonist (H₁-receptor) and mast cell stabilizer) and Cetirizine dihydrochloride (an antihistamine; selective peripheral H₁ receptors inhibitor) is highly recommended for this condition.

Ketotifen fumarate (KTF) is 4,9-dihydro-4-(1-methylpiperidin-4-ylidene)-10H-benzo^[4,5]cyclohepta[1,2-b]thiophene-10-one hydrogen fumarate (Figure 1)^[2]. It is sparingly soluble in water, slightly soluble in methanol, very slightly soluble in acetonitrile^[3].

Full Paper

Cetirizine (CTZ)^[4] is chemically 2-(2-{4-[(4-Chlorophenyl)(phenyl)-methyl]piperazino}ethoxy) acetic acid dihydrochloride (Figure 2). It is very soluble in water, freely soluble in alcohol and sparingly soluble in chloroform^[5].

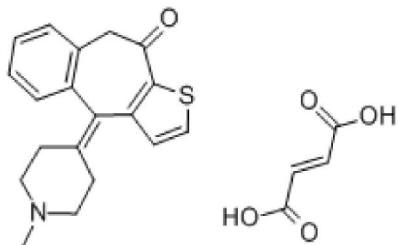


Figure 1: Chemical structure of Ketotifen fumarate

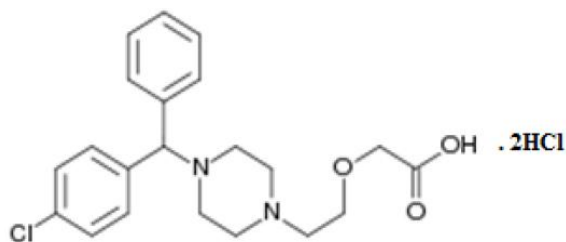


Figure 2 : Chemical structure of Cetirizine

Literature survey reveals that few analytical methods like stability indicating HPLC method^[6], HPLC method^[7,8], LC-MS method^[9], Coulometric titration^[10], HPLC/MS/MS method^[11], Spectrophotometric^[12], HPTLC^[13] methods are available to determine Ketotifen and Cetirizine individually or in combination with other drugs. There is no analytical method reported for simultaneous estimation of Ketotifen and Cetirizine in combined dosage form. Hence, investigation of new analytical methods is in need for the quantitative estimation of the drugs in combined pharmaceutical dosage form.

MATERIALS AND METHOD

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 Ketotifen fumarate and Cetirizine dihydrochloride were obtained from East West Pharma, Haridwar and Micro Labs Pvt Ltd., Bangalore respectively. Tablets containing Ketotifen fumarate (1mg) and Cetirizine dihydrochloride (10 mg) (Mastifen C) were purchased from local pharmacy.

Method

The mixed stock solution of analytes was prepared by transferring 5 mg of KTF and 50 mg of CTZ in 50 ml volumetric flask, dissolved in few ml of water and volume was made up to the mark with the same solvent to get the concentration of 100 µg/ml of KTF and 1000 µg/ml of CTZ. This solution was further diluted to get six serial dilutions containing 0.5 to 3 µg/ml of KTF and 5 to 30 µg/ml of CTZ in water. All mixed standard solutions were scanned over the range of 360 nm to 200 nm in multicomponent mode of spectrophotometer at medium scanning speed. The absorbance of solutions were measured at wavelength interval of 40 nm, processed and stored by instrument. An overlain spectrum of mixed standard solutions is as shown in Figure 3.

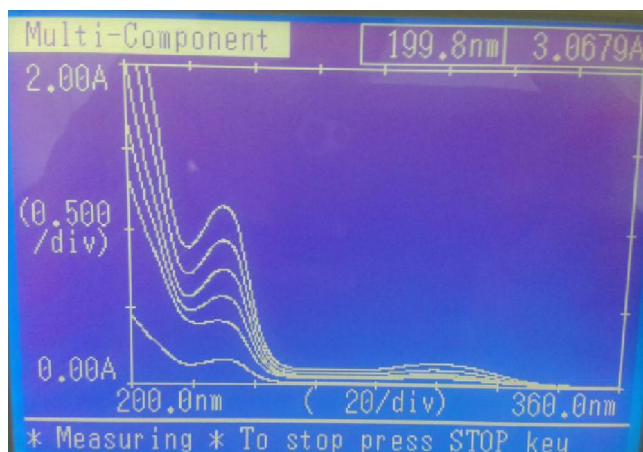


Figure 3 : Overlain spectra of mixed standards of Ketotifen and Cetirizine

Analysis of commercial formulation

Twenty tablets (Mastifen C) were accurately weighed and crushed to fine powder. The tablet powder equivalent to 2.5 mg of KTF (25 mg of CTZ) was accurately weighed, transferred to 25 ml volumetric flask, small quantity of water was added and sonicated for 10 min. The volume was made up to mark with water to get the concentration of 100 µg/ml of KTF

and 1000 µg/ml of CTZ. This solution was filtered through whatman filter paper no 41. The filtrate was further diluted with water to get concentration of 1 µg/ml of KTF and 10 µg/ml of CTZ.

The sample solution was scanned over the range of 360 nm to 200 nm in multicomponent mode immediately after the scanning of the 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 the concentration of sample was determined by the instrument on the basis of calibration data. The results of assay of marketed formulation are given in TABLE 1.

TABLE 1 : Results of assay of marketed formulation

Analyte	Label claim per tablet (mg)	Mean amount found in tablet (mg)(n=6)	Mean amount found (%) (n=6)	%R.S.D. (n=6)
KTF	1.00	1.002	100.2661	0.671
CTZ	10.00	10.03	100.2659	0.672

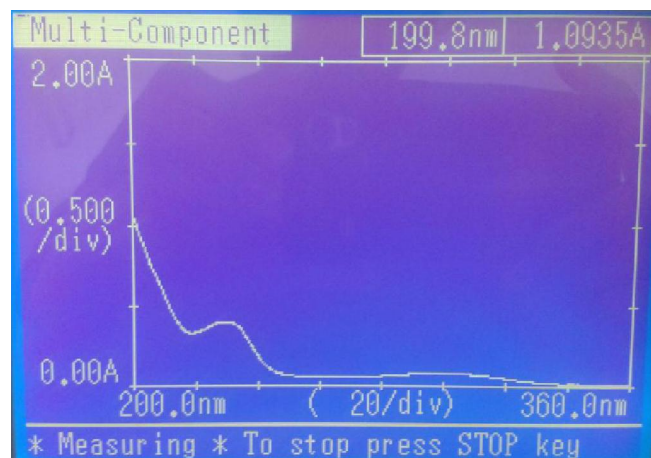


Figure 4 : Spectrum of sample solution.

Validation of method

The proposed method of analysis for KTF and CTZ in combination was validated as per the recommendations of ICH guidelines^[14] 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%) (Figure 5). The results of recovery studies are reported in TABLE 2. While, precision of the method was determined by repeatability and intermediate precision (in-

tra-day, inter-day) expressed as % Relative Standard Deviation (%RSD). Intra-day precision was evaluated by analyzing concentration of Ketotifen (1 µg/ml) and Cetirizine (10 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 the solutions on three consecutive days.

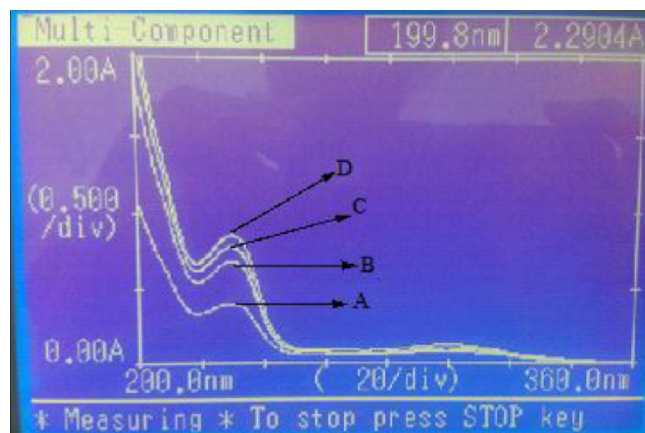


Figure 5: Overlain spectra of sample and recovery studies (A-Assay, B-80%, C-100%, D-120% addition)

TABLE 2 : Results of recovery studies

Analyte	Level Of Recovery		
	80% (±RSD) (n=3)	100% (±RSD) (n=3)	120% (±RSD) (n=3)
KTF	100.16±0.9	99.33±0.80	100.79±0.74
CTZ	99.83±0.45	99.33±0.84	100.78±0.75

TABLE 3 : Results of precision studies (Intra-day and Inter-day)

Analyte	Concentrations of sample solution (µg/ml)	Intra-day precision % RSD (n=3)	Inter-day precision % RSD (n=3)
KTF	1	0.0913	0.9351
CTZ	10	0.0913	0.9442

RESULTS AND DISCUSSION

The overlay spectra of both drugs were studied carefully in different solvents like Water, 0.1 N Hydrochloric acid, 0.1 N Sodium hydroxide, Dimethylformamide, Glacial acetic acid and methanol. Considering the economy, ease of analysis and satisfactory absorbance of both the drugs, water was selected as solvent for the present study.

Full Paper

As the proposed method is specific to instrument having software for provision of such determination, selection of proper sampling wavelength and concentrations of mixed standard solutions are critical. Hence overlay spectra of analytes were studied carefully. Both drugs have shown optimum absorbance in the range of

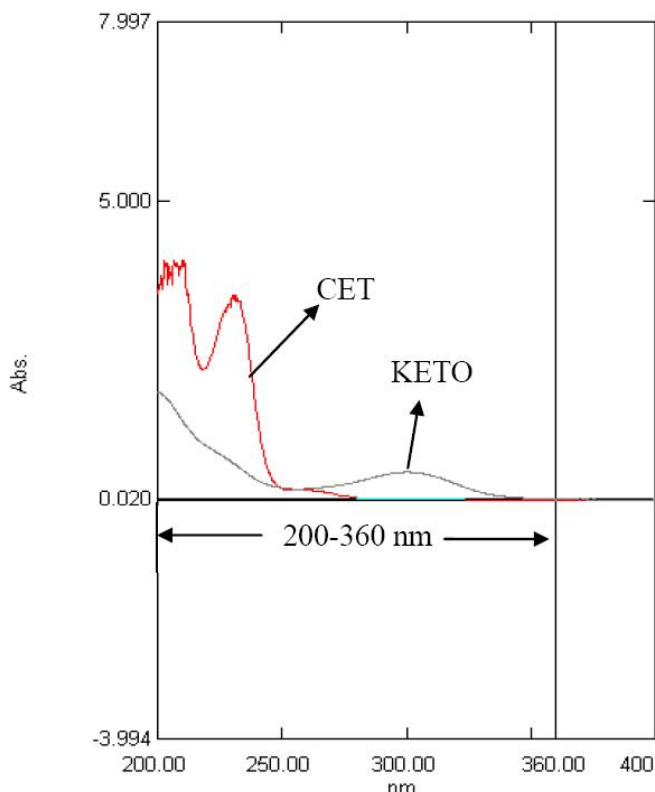


Figure 6 : Overlain spectra of Ketotifen and Cetirizine in water

360-200 nm, so the wavelength range of 360-200 nm was selected for the study (Figure 6).

The various wavelength intervals 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 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 five selected wavelengths was not more than 1 (Considering % relative error by instruments).

The mean content of analytes in the marketed formulation were found to be 100.2659 % for CTZ and 100.2661 % for KTF, while recovery was found in the range of 98.78 to 101.48 % for KTF and 98.77 to

101.48 % for CTZ 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 the spectra of mixed standards for sample analysis. The assay and validation results confirmed that the contents of Ketotifen fumarate and Cetirizine dihydrochloride estimated in the tablet dosage form were free from the interference of excipients.

CONCLUSION

The developed multi component spectroscopy method for simultaneous estimation of Ketotifen fumarate and Cetirizine dihydrochloride 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.

REFERENCES

- [1] <http://www.patient.co.uk/health/Chronic-Urticaria.htm> (access date Nov 24, 2011), (2011).
- [2] <http://www.pharmgkb.org/drug/PA450152> (access date Nov 24, 2011), (2011).
- [3] The Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Published by The Indian Pharmacopoeia commission, Ghaziabad, 2, 1546 (2010).
- [4] <http://www.canadadrugsonline.com/article-description.php?PID=160> (access date Nov 24, 2011), (2011).
- [5] <http://en.wikipedia.org/wiki/Cetirizine> (access date Nov 24, 2011), (2011).
- [6] I.P.Nnane, L.A.Damani, A.J.Hutt; *Chromatographia*, **48**, 797-802 (1998).
- [7] B.Paw, G.Misztal, H.Hopkala, J.Drozd; *Pharmazie*, **57**(5), 313-5 (2002).
- [8] A.M.Y.Jaber, H.A.Sherife, M.M.Omari, A.A.Badwan; *J.Pharm.Biomed.Anal.*, **34**(1), 87-94 (2004).
- [9] F.Q.Alali, B.M.Tashtoush, N.M.Najib; *J.Pharm.Biomed.Anal.*, **34**(1), 87-94 (2004).
- [10] W.Ciesielski, R.Zakrzewski, U.Zlobinska; *Int.J.Pharm.Sci.*, **60**(2), 237-8 (2005).

- [11] M.Ma, F.Feng, Y.Sheng, S.Cui, H.Liu; J.Chromatogra.B, **846(1,2)**, 105-111 (2007).
- [12] M.Amanlou, M.H.Nazlou, H.Azizian, E.Souri, H.Farsam; Anal let, **40(17)**, 3267-79 (2007).
- [13] P.S.Dhongle, S.J.Sahare, S.S.Dhongle, A.S.Mundhey, S.P.Wate; Der pharmacia Lettre, **3(4)**, 111-9 (2011).
- [14] ICH Guidance on Analytical Method Validation, in: Proceedings of the International Convention On Quality for the Pharmaceutical Industry, Toronto, Canada, and September, (2002).