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DETERMINATION AND QUANTIFICATION OF CETIRIZINE HCl IN DOSAGE FORMULATIONS BY RP-HPLC

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A simple, sensitive, reliable and rapid HPLC method for the determination of cetirizine hydrochloride using hyoscine butyl bromide as an internal standard has been developed. The chromatographic system consisted of Shimadzu LC-10 AT VP pump, SPD-10 AV VP with UV/visible detector and a CBM-102 Bus Module integrator. Separation was achieved on the U Bondapak 125 A C18 10μm column at room temperature. The samples were introduced through an injector valve with a 10 μl sample loop. Acetonitrile-water (1:1 v/v) was used as mobile phase, with flow rate 2 ml/minutes. pH was adjusted to 2.9 with phosphoric acid. UV detection was performed at 205 nm. The results obtained showed a good agreement with the declared content. Recovery values for cetirizine hydrochloride were 99.19 - 100.82 %. The proposed method is reliable rapid, precise, selective and may be used for the quantitative analysis of cetirizine HCl, in presence of hyoscine butyl bromide as internal standard. The method was valid was for the determination in raw materials, bulk drug and formulations. The limit of quantification was 5 - 30 nano grams, while the limit of detection was 0.4 nano grams.

Keywords: Cetirizine, hyoscine butylbromide, HPLC determination.

INTRODUCTION

Cetirizine HCl or 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-piperazin-1-yl]ethoxy]acetic acid dihydrochloride, is white or almost white powder, freely soluble in water, practically insoluble in acetone and in methylene chloride, molecular weight 461.8, molecular formula, $C_{21}H_{27}Cl_3N_2O_3$ (figure 1) [The Merck Index 2001; Martindale, The Extra Pharmacopoeia 1996; British Pharmacopoeia 2003]. Cetirizine is a piperazine derivative and metabolite of hydroxyzine, is an antihistamine, reported to be a long acting and with some mast-cell stabilizing activity. It is used for the symptomatic relief of hypersensitivity reactions including rhinitis and chronic urticaria. (Anonymous 1990; Spencer *et al.,* 1993; Barnes *et al.,* 1993; Sharpe and Shuster 1993 and Snyman *et al*., 1994). Cetirizine is rapidly absorbed from the gastro-intestinal tract after oral administration, peak plasma concentration being attained in about one hour. It is highly bounded to plasma proteins and has an elimination half-life of about 11 hours. Cetirizine has been detected in breast milk and excreted primarily in the urine mainly as unchanged drug (Awni *et al.,* 1990 and Desager *et al.,* 1993).

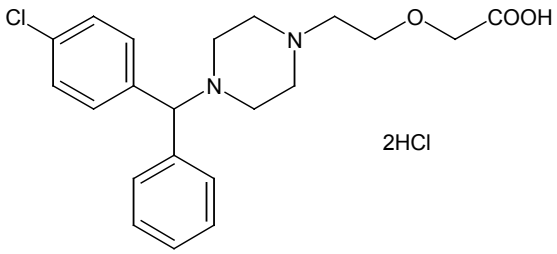

Figure 1

There are number of methods reported in the literature for the determination of drug (Zajac *et al.,* 2001) in tablets (El Walily *et al*., 1996 and Jeli *et al*., 2000), serum (Moncrieff, 1992 and Zaater *et al*., 2000), urine (Rosseel and Lefebvre, 1991; Choi *et al*., 2000), plasma (Pandya *et al.,* 1996) based on HPLC, while an HP-TLC method for the determination of drug in human plasma is also available (Moncrieff, 1992). However, the limit of detection in all these methods does not exceed 3 μg/ ml. The goal of this study was to develop a rapid, more accurate, precise reliable, less expensive and least time consuming HPLC method for the analysis of cetirizine HCl, in the form of raw materials, bulk drug samples and dosage formulations, using the most commonly employed C-18 column with UV detection and extremely low LOQ & LOD values.

EXPERIMENTAL

Material and reagents

Samples of hyoscine butylbromide, and cetirizine HCl were a kind gift from AGP (Private) Limited. All dosage formulations were purchased from market. HPLC grade acetonitrile and phosphoric acid were obtained from Merck. The mobile phase and solution were prepared in deionized double distilled water. Stock solutions of the compounds were prepared in deionized water and stored at room temperature. Fresh working solutions were prepared daily. All solution were filtered through 0.45 um filtration assembly and degassed by sonicator.

Apparatus

The HPLC system used was of LC-10 AT VP Shimadzu pump, SPD-10AV VP with Shimadzu UV visible detector, a u Bondapak 125 A C18 10 μm column (particle size 10 μm) was used for separation. The chromatographic and integrated data were recorded using a CBM-102 communication Bus Module Shimadzu on a Pentium-IV PC.

Chromatographic conditions

The mobile phase was acetonitrile-water (1:1), the pH of this mobile phase was adjusted to 2.9 with phosphoric acid (85 %). Before delivering into the system it was filtered through 0.45 μm filter and degassed using a vacuum. The analysis was carried out under isocratic conditions using a flow rate 1.7 ml/minutes at room temperature. Chromatograms were recorded at 205 nm using a detector SPD-10AV VP Shimadzu UV visible. Injector with a 10 μ liter sample loop introduced the samples.

Analytical procedure

10 mg hyoscine butylbromide and 10 mg of cetirizine HCl, were dissolved in water in 100 ml volumetric flask separately and made up volume with same solvent (stock solution 100 μg/ml). Aliquots were diluted to desired concentration of cetirizine. Twenty tablets of Rigix™ were weighed (average weight 115 mg), powdered and 115 mg of the powder equivalent to 10 mg of active substance was dissolved in 100 ml of water. Similar procedure was adopted for Alerid™, Cerizine™ and Zyrtec™ tablets. Likewise Rigix™ and Zyrtec™ oral solutions were diluted appropriately, allowed to stand for 1 hour with intermittent sonication to ensure complete solubility and volume was made up with water. These stock solutions were filtered, to obtain clear filtrate and were further diluted to desired concentrations. 10 μ liter volume of each sample was injected and chromatographed under above conditions.

RESULTS AND DISCUSSION

Chemical structure and chemical properties are the most important facts that predict chromatographic behavior. In the present investigation the best separation of the two compounds were achieved using a u Bondapak 125 A C18 (10 um) column and mobile phase acetonitrile-water (1:1 v/v). The lower percentage of acetonitrile in mobile phase resulted in peak broadening of both components and long analysis duration, while higher percentage of acetonitrile in mobile phase resulted peak splitting of cetirizine peak. Optimal retention times, 2.3 & 3.3 minutes for hyoscine Butyl bromide 2.3, cetirizine HCl respectively were achieved when the pH of mobile phase was adjusted to 2.9 with 85 % phosphoric acid. Small changes in pH of the mobile phase had a great influence to the chromatographic behavior of these substances. Higher pH of the mobile phase resulted in peak tailing, and lower pH resulted in broadening of peak in both components.

Accuracy and precision

The accuracy of the method was evaluated by analyzing independently prepared solutions of hyoscine butyl bromide and cetirizine HCl. The precision of the method wads investigated with respect to repeatability. Calibration graphs of the injected concentration of cetirizine HCl, against recovered concentration of cetirizine HCl showed a straight line, with a recovery of 99.19-100.82 ± 0.61 % of drug (figure 3). The recovery data is expressed in tables 1-4. These tables show that the method is accurate for determination of cetirizine HCl, in presence of hyoscine butylbromide as internal standard. All calibration curves have a correlation coefficient of at least 0.9999.

Table 1
Recovery of cetirizine HCl by proposed method

Injected (ppm)	<——— Reference drug ———>			<——— Dosage form ———>		
	Found	% Recov.	Mean (AUC)	Found	% Recv.	Mean (AUC)
0.5	0.4953	99.0584	24271	0.4972	99.4344	22377
1	0.9867	98.6738	48354	0.9945	99.4505	44762
1.5	1.4981	99.8702	73411	1.5123	100.823	68070
2	1.9949	99.7456	97759	2.0052	100.2617	90255
2.5	2.4846	99.3841	121756	2.48	99.1989	111623
3	3	100	147013	3	100	135068

Table 2
Inter day accuracy and precision of cetirizine HCl by proposed method

Injected (ppm)	Day 1		Day 2		Day 3		Day 4	
	RSD	% Recov	RSD	% Recov.	RSD	% Recov.	RSD	% Recov.
0.5	0.0045	99.06	0.0032	99.43	0.0014	99.57	0.0049	100.12
1	0.0076	98.67	0.0009	99.45	0.0013	99.23	0.0016	100.26
1.5	0.0006	99.87	0.0007	100.82	0.0013	100.30	0.0011	99.91
2	0.0006	99.75	0.0004	100.26	0.0008	100.52	0.0004	99.96
2.5	0.0073	99.38	0.0008	99.20	0.003	99.42	0.0042	99.67
3	0.0008	100	0.0021	100	0.0036	100	0.0015	100

For intra-day precision, six concentration of each compound were analyzed on the same day. Each concentration of sample was injected 4 times a day. Table 3 summarizes the relative standard deviation (RSD) and other regression characteristics. Generally acceptable repeatability of the results with in one day and day-to-day was observed. Data of the relative retention times obtained in a series of four consecutive injections also showed acceptable repeatability when analyzed not only on the same day but also on four consecutive days.

System suitability and specificity
System suitability of the method was evaluated by analyzing the symmetry of the hyoscine butylbromide (internal standard) and cetirizine HCl, peaks, theoretical plates of the column and the resolution between the two peaks.

The specificity and suitability of the method was also demonstrated by assaying different dosage formulations in the form of tablets and oral solutions in presence of hyoscine butylbromide (table 4). The method demonstrated well and distinct resolution between hyoscine butylbromide, which was used as internal standard and cetirizine formulations. A typical chromatogram showing separation of the cetirizine and internal standard is shown in figure 2.

Quantification limit
The limit of quantification was 5 - 30 nano grams, while the limit of detection was 0.4 nano grams. These were calculated on the basis of drug content in 10 µl of sample injected in each loop.

Ruggedness
Ruggedness of this method was evaluated on two different instruments of the same make in two different laboratories at University of Karachi. Lab 1 was in the Department of Chemistry, while Lab 2 was at the Research institute of Pharmaceutical Sciences at Faculty of Pharmacy.

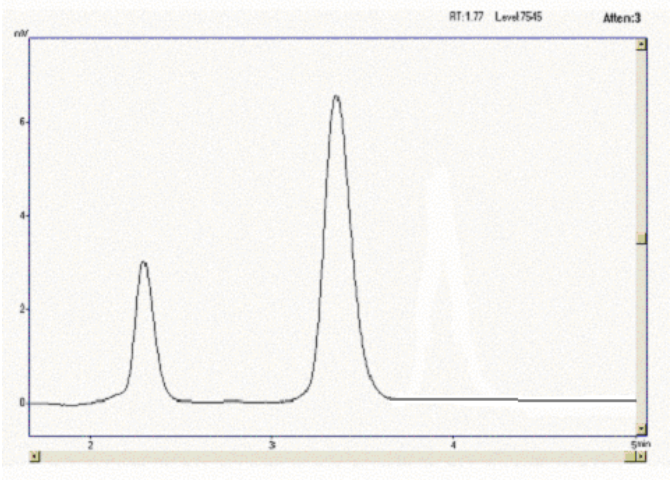

Figure 2: A typical chromatogram showing separation of internal standard (2.3 min) and cetirizine (3.3 min).

Table 3
Recovery and regression characteristics of cetirizine HCl by proposed method

Concentration injected	Recovered concentration			
(ppm)	Day 1	Day 2	Day 3	Day 4
0.5	0.4953	0.4972	0.4979	0.5006
1	0.9867	0.9945	0.9923	1.0026
1.5	1.4981	1.5123	1.5045	1.4986
2	1.9949	2.0052	2.0105	1.9993
2.5	2.4846	2.48	2.4856	2.4918
3	3	3	3	3
Correlation coefficient (R)	0.9999	0.9999	0.9999	0.9999
Standard error of estimate	0.0069	0.01201	0.00983	0.00357
Standard error	0.0064	0.01118	0.00916	0.0033
p value	0	0	0	0
Intercept	-0.00813	0.00186	-0.00117	0.00228
Slope	1	1	1	1

Table 4
Recovery of cetirizine HCl in dosage formulations by proposed method

<——— Tablets ———>								<——— Oral solutions ———>			
Rigix™		Zyrtec™		Cerizine™		Alerid™		Rigix™		Zyrtec™	
Found	% Rec.	Found	% Rec.	Found	% Rec.	Found	% Rec.	Found	% Rec.	Found	% Rec.
9.943	99.43	9.957	99.57	9.96	99.6	10.12	101.2	1.02	102	1.017	101.7
9.945	99.45	9.922	99.22	9.98	99.8	9.94	99.4	1.008	100.8	0.987	98.7
10.082	100.82	10.03	100.3	10.09	100.9	10.13	101.3	1.009	100.9	0.982	98.2
10.026	100.26	10.05	100.5	9.86	98.6	9.98	99.8	0.994	99.4	0.989	98.9
9.92	99.2	9.942	99.42	10.04	100.42	10.06	100.6	1.006	100.6	1.018	101.8
10	100	10	100	10	100	10	100	10	100	10	100

Label claim of tablets = 10 mg; Label claim of oral solutions = 1 mg/ml

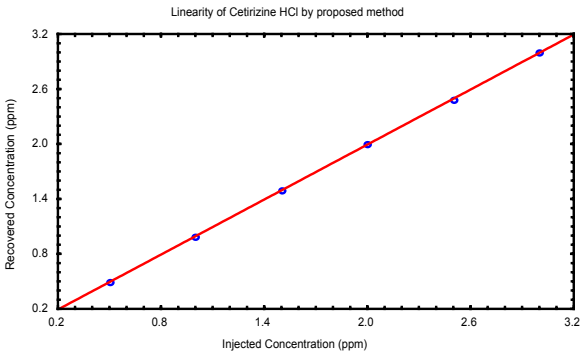

Figure 3

CONCLUSION

The present attempt is the first to describe determination and quantitation of cetirizine HCl in presence of hyoscine butylbromide by RP-HPLC. The method uses hyoscine butylbromide as internal standard because of good separation and resolution of the chromatographic peaks. The proposed method is rapid, precise and applicable to the analysis of standard drug, raw materials and dosage formulations in the form of tablets or solutions. Results obtained are accurate, precise, confirmed by the statistical parameters and in a good agreement with the declared contents.

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mastitis are *Staphylococci, Streptococci, Coliforms*, *Enterobacter spp.,* and *Pseudomonas spp*. Different diagnosis of clinical mastitis can be treated with various antibiotics (Morin *et al*., 1998). Mastitis, which is inflammation of the mammary gland, is considered the most costly disease of dairy cows Worldwide (DeOliveria *et al*., 2000).