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ESTIMATION OF IBUTILIDE FUMARATE IN BULK AND PHARMACEUTICAL FORMULATIONS BY A SIMPLE AND VALIDATED RP-HPLC

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ABSTRACT

A rapid, precise, economical, and accurate HPLC method for estimation of Ibutilide fumarate in bulk and formulations was developed and validated via system suitability method. The chromatographic resolution of Ibutilide was achieved using acetonitrile: 0.1M ammonium dihydrogen phosphate buffer PH~ 6(Phasphoricacid), (25: 75 V/V) as a mobile phase UV detection at 250 nm and Hypersil thermo C18 column at a flow rate of 1.0mL/min. The calibration curve was linear (r^2 = 0.9991) over Ibutilide concentration ranging from 20 to 120 µg/mL. The proposed method is also accurate, precise and robust. The method can be used for routine quality control analysis.

Keywords: Ibutilide Fumarate, Ant arrhythmic drug , RP-HPLC, LOD and LOQ

INTRODUCTION

The chemical name for ibutilide fumarate is methanesulfonamide, N-{4-{4-(ethylheptyl amino)-1 -hydroxybutyl} phenyl}, (+)(-), (E)-2-butenedioate (1:0.5) (hemifumarate salt). Its molecular formula is C22H38N2O5S, and its molecular weight is 442.62. Ibutilide fumarate is a white to off-white powder with an aqueous solubility of over 100 mg/mL at pH 7 or lower. It is an antiarrhythmic drug with predominantly class III (cardiac action potential prolongation) properties according to the Vaughan Williams Classification[1-3].

The drug is available in the market as injection wherein each milliliter of injection contains 0.1 mg of ibutilide fumarate (equivalent to 0.087 mg ibutilide free base), 0.189 mg sodium acetate trihydrate, 8.90 mg sodium chloride, hydrochloric acid to adjust pH to approximately 4.6 and water for injection. Various analytical methods have been reported in scientific literature for the analysis of Ibutilide fumarate human plasma including LC-MS[4] and Chiral separation of enantiomers by HPLC[5]. Thus, the aim of this study was to develop and validated a fast, simple and cost-effective HPLC method for analysis of Ibutilide fumarate from pharmaceutical formulations.

EXPERIMENTAL

Instrumentation: Quantitative analysis was performed on a binary gradient HPLC with Shimadzu LC20AT and LC20AT VP series HPLC pumps, with a 20µl injection of sample loop (manual), and SPD20 VP UV-Visible Detector. The out put signal was monitored and integrated using ShimadzuClass VP version 6.12 SP1 software. Hypersil, Thermo, C_{18} (250 x 4.6µ, 5µ) column was used for Separation**.**

Standards and chemicals: Ibutilide fumarate and its formulation capsules were gifted by two well known Analytical Testing laboratories and a formulation companies. The HPLC purity of selected test sample is higher than the 99.99%. Acetonitrile HPLC grade, Ammonium dihydrogen phosphate, and phosphoric acid were purchased from Merck chemicals for which purities are reported more than 99.5%.

Preparation of standard solution: Standard stock solution (100µg/mL) was prepared by transferring 50

mg of Ibutilide fumarate into a 50 mL volumetric flask, 20 mL of mobile phase was added, and the mixture was sonicated to dissolve and make up the volume with mobile phase. Aliquots of these standard solution was transferred using A-grade bulb pipette into 100 mL volumetric flasks and made up to volume with methanol to get final concentration of 20-120 µg/mL.

Chromatographic conditions: The mobile phase used in this study was a mixture of acetonitrile and 0.1M ammonium dihydrogen phosphate buffer PH~ 6(Phasphoricacid) 25:75 v/v, then the content was solicited for 30 min for degassing purpose and then filtered through 0.45 µ (pore diameter) Whitman filter paper. The mobile phase was pumped from the solvent reservoir to the column at a flow rate of 1.0mL/min. The eluents were monitored at 250 nm. The column temperature was maintained ambient throughout the experiment.

Linearity: By appropriate aliquots of the standard solution with mobile phase, six working solutions ranging between 20-120 µg/mL were prepared. Each experiment was performed in triplicate according to optimized chromatographic conditions. The peak area of the chromatogram was plotted against the concentration of Ibutilide fumarate to obtain the calibration curve (Table1).

Estimation of Ibutilide fumarate from its Formulation: Twenty injections were accurately weighed and mixed. The sample equivalent to 10 mg Ibutilide was taken in volumetric flask contains 50 mL acetonitrile. This solution was diluted with mobile phase, so as to obtain a concentration in the range of linearity previously determined. All determinations were carried out in five replicates. The represented data was shown in table 2.

RESULTS AND DISCUSSION

Specificity and selectivity of the method was assessed by preparing a drug concentrationof 100 µg/mL from pure drug stock and commercial sample stock in selected mobile phase and analyzed. The HPLC chromatograms recorded for the drug matrix showed almost no other peaks within a retention time range of 8 min (Figure 1). Thus the HPLC method developed in this study is selective for Ibutilide fumarate. The method is linear in the concentration range 20 to 120 µ g/ml. Precision was studied by five replicate measurements at three different concentration levels. Accuracy of the method was determined by calculating recovery studies. Statistical evalution revealed that relative standard deviation (%RSD) of the drug at different concentration levels. Precision and accuracy data were shown in Table 3 respectively. For system suitability, five replicates of standard sample were injected and different parameters were studied (table 1).

CONCLUSIONS

In this study, a simple, efficient and reliable HPLC method was developed and fully validated for the analysis of Ibutilide fumarate in tablets. The linearity range, limit of detection and quantification, precision, accuracy, specificity, selectivity, and ruggedness were performed to determine the suitability of the method. These full validation assays have been concluded that the developed HPLC method is linear, sensitive, accurate, precise, selective and rugged for the determination of Ibutilide fumarate. These advantages encourage the application of this method in routine analysis of Ibutilide fumarate in pharmaceutical formulations.

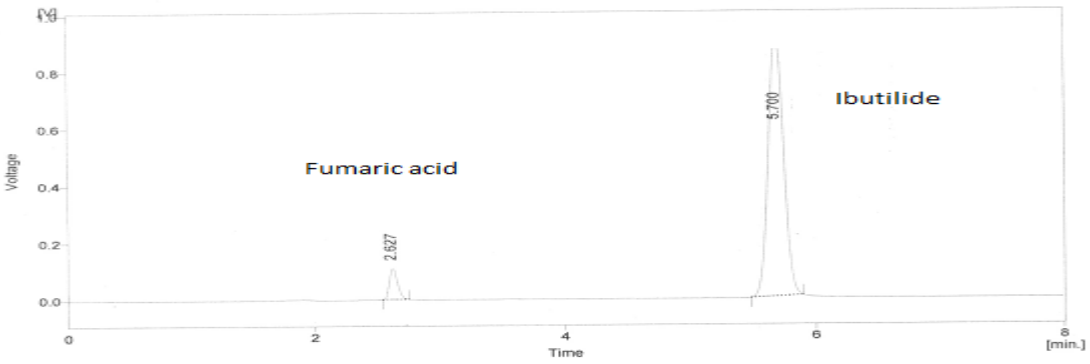

Figure 1: Chromatogram of Ibutilide fumarate

Table 1: Linearity data of Ibutilide fumarate

Conc. (µg/mL)	Peak area ratio	Statistical Analysis
20	1352	Y= 64.62X + 90.73
40	2706	Correlation co-efficient: 0.9991
60	4038	Asymmetric factor : 1.118
80	5146	Theoretical Plates(N):10125
100	6623	
120	7825	

Table 2: Amount of Ibutilide fumarate in formulation dosage By HPLC Method

Tablet Formulation	Label Claim per injection (mg)	% Drug found ± SD (n=6)	RSD (%)	SEM
Corvert	0.1	99.58±0.7526	0.7245	0.3136

Table3. Results of recovery studies and precision

Actual Conc. (µg/mL)	% Recovery		Precision			
	Mean±SD	%RSD	Intra-day		Inter-day	
			*Mean±SD	%RSD	*Mean±SD	%RSD
30	100.22±1.3153	1.31	100.45±1.3741	1.37	99.5±0.9765	0.98
40	100.48±0.7136	0.71	100.82±0.6713	0.67	100.14±1.1736	1.17
50	99.57±1.4488	1.46	100.11±1.3493	1.35	100.52±0.4028	0.4

*Concentration (µg/mL)

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