Spectrophotometric Determination of Ibutilide Fumarate in Bulk Drug substance form

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Abstract

A simple and cost effective spectrophotometric method is described for the determination of Ibutilide fumarate in bulk drug substance form. The method is based on 'complex formation' concept under acidic conditions with acid dyes e.g. TPOOO. The colored species have absorption maxima at 485nm and obeys Beer's law in the concentration range of 2.5 – 20 □g mL^{-1}. The absorbance was found to be increasing linearly with increasing concentration of Ibutilide, which is corroborated by the calculated correlation coefficient value of 0.9995 (n=8). The molar absorptivity and Sandell's sensitivity are $3.611x10^4$ 1 mole cm^{-1} and 0.024 □g cm^{-2} respectively. The slope and intercept of equation of regression line are 0.0403 and 0.0144 respectively. The limit of detection was 0.561 □g mL^{-1}. The optimum experimental parameters for the reaction were studied and also validity of the described procedure was assessed. The statistical analysis of results revealed high accuracy and good precision. The proposed method was successfully applied to the determination of Ibutilide Active Pharmaceutical Ingredient (API) in bulk drug substance form.

Key words: Ibutilide fumarate (IF), bulk drug substance, Active Pharmaceutical Ingredient (API), spectrophotometry, acid dyes, TPOOO, ion association complex

Introduction

Ibutilide fumarate (IF) is a novel class III methane sulphonamide anti arrhythmic agent recently introduced in therapy for the treatment of cardiovascular diseases and its activity is 30 times to that of Sotolol. The IF is chemically known as (±)-N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl] phenyl] methane sulfonamide whose structure is presented in Fig 1. The drug is available as fumarate salt. Currently, IF and its pharmaceutical dosage forms are not found in any official compendia (pharmacopoeia)[1-2]. However, the chiral separation of IF enantiomers by derivatization technique was published in the literature[3]. Furthermore, an analytical profile was found in a survey of literature which includes elemental analysis, mass spectral data, ^{1}H NMR and ^{13}C NMR and FT-IR data and also the preparation of Ibutilide fumarate[4-5]. There was some literature available on treatment, efficacy and applications [6-11].

Literature survey reveals that there is only one report on chiral separation of Ibutilide enantiomers by derivatization with 1-naphthyl isocyanate and high performance liquid chromatography on a chiral Pirkle column[3] No spectrophotometric methods were published till date for the quantification of IF to the best of our knowledge. Hence, an attempt was made to develop simple and sensitive spectrophotometric method for the estimation of Ibutilide fumarate in bulk drug substance form. The purpose of this investigation was to develop a reliable, reproducible and quick and less expensive method for routine quantification by exploiting the properties of analytically useful function groups in the drug substance IF. The method uses the well known 'complex formation' concept under acidic conditions with the acid dyes e.g. TPOOO.

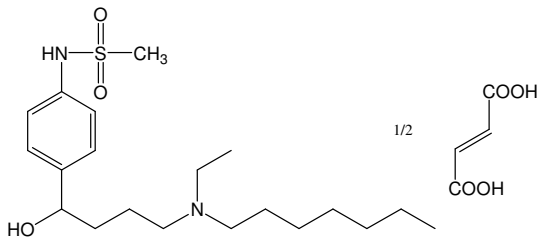

Figure-1: Structure of Ibutilide fumarate

Material and Methods

All spectral and absorbance measurements were made on a Shimadzu UV-Visible Spectrophotometer 1601 with cm matched quartz cell. A systronics digital pH meter 361 was used for pH measurements.

All the chemicals used throughout the experimentation are of analytical reagent grade and Millipore distilled water. The IF sample was obtained from SAPL and TPOOO was obtained from Fluka (0.2%, 5.70×10^{-3} M).0.1M HCl solution was obtained from E-Merck and Chloroform from Qualigens. The TPOOO solution was prepared by dissolving 200mg of Trapaeolin OOO in 100mL of distilled water. The HCl solution was prepared by diluting 8.6mL of Conc. HCl in 1000 mL of distilled water and standardized.

General procedure: Into a series of 125mL separating funnels containing aliquots of standard IF solution (1.0-4.0mL; 50□g/mL), 6.0mL of 0.1M HCl and 2.0mL of dye solution (TP OOO) were added. The total volume of aqueous phase in each separating funnel was adjusted to 15mL with distilled water and 10mL of chloroform was added. The contents were shaken for 2 minutes. The two phases were allowed to separate and the absorbances of the separated organic layer were measured at 485nm (λ_{max}) against a similar reagent blank. The color species was stable for 1 hour. The amount of IF in sample solution was obtained from the Beer's-Lambert's plot (Fig 2). The Ringbom plot was also presented in Fig 3.

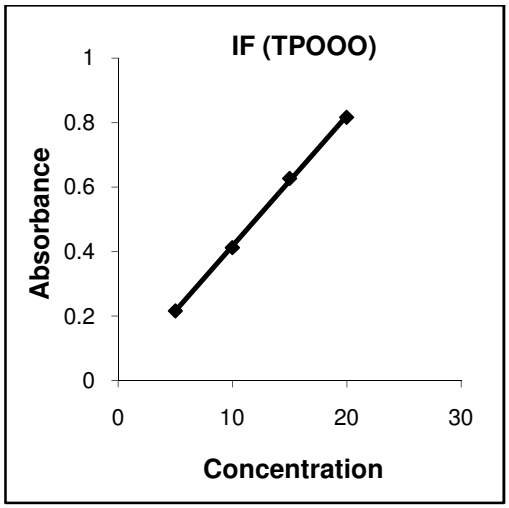

Figure-2: Beer Lambert's plot

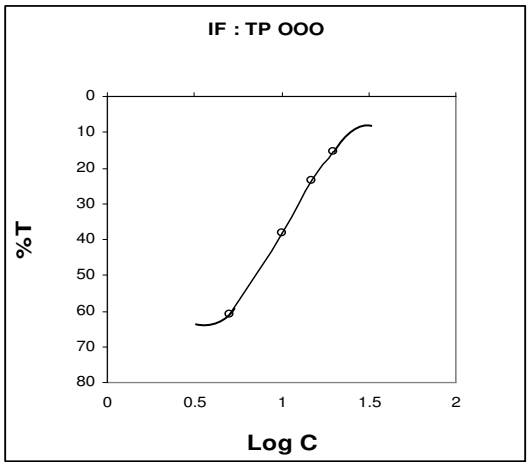

Figure-3: Ringbom plot

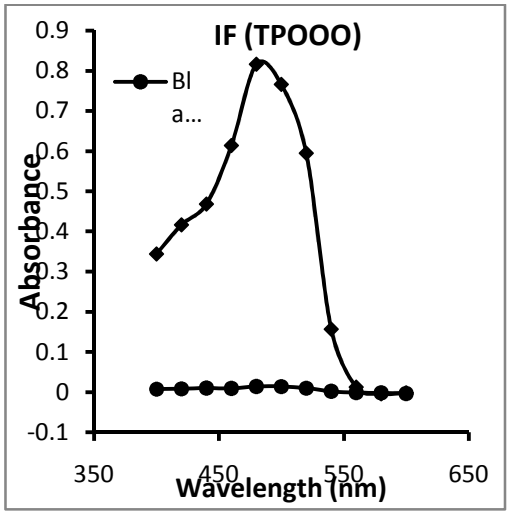

Fig 4. Absorption spectra

Results and discussion

In order to ascertain the optimum wavelength of maximum absorption (λ_{max}) of the colored specifies formed, 20 g/mL of final IF dilution was taken and the color was developed. The absorption spectra were scanned at the wavelength region of 360-850nm against a corresponding reagent blank. The reagent blank absorption spectrum was recorded against distilled water. The results are graphically presented (Fig 4). The absorption curves of colored specify formed in each method shows characteristic absorption maximum where as the blank in each method has low or no absorption in this region.

The optimum conditions for the method were fixed based on the study of effects of various parameters such as type of acid, buffer, concentration of acid, concentration of dye, choice of organic solvent, ratio of organic phase to aqueous phase, shaking time, temperature, intensity and stability of the colored species in organic phase. The control experiments were executed by measuring the absorbance at 485nm of series of solutions varying one and fixing the other parameters. The results are presented in Table 1.

The chemistry of colored species: Ibutilide slightly under acidic conditions forms ion-association complex with acid dyes, i.e., TP OOO which is extractable into chloroform from aqueous phase. The protonated nitrogen (of positive charge) of Ibutilide is expected to attract the oppositely charged part of the dye and behave as a single unit being held together by electrostatic attraction as represented in scheme (fig 5).

Statistical illustration of the method: The Beer-Lambert and Ringbom plots of the system were illustrated graphically in fig 2 and fig 3. Least square regression analysis was carried out for slope, intercept and correlation coefficient. Beer-Lambert's limits, molar absorptivity; Sandell's sensitivity and optimum photometric range for IF were calculated and presented in table 2.

Precision: The precision of the established method was studied by determining the absorbance values for 8 replicates of a fixed concentration of 20 g/ml. The present relative standard deviation and percent range of errors (at 0.05 and 0.01 confidence limits) were calculated and presented in table 2.

Accuracy: The accuracy of the method was determined by taking the different amounts of IF sample within the Beer-Lambert's law limits and by analyzing as per the proposed methods. The results (percent error) are recorded in table 2.

Conclusions

The proposed method is thus simple, rapid, precise and inexpensive and hence the same can be used for routine analysis of Ibutilide fumarate in bulk drug substance.

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Table-1: Optimum conditions of method

Parameter	Conditions in procedure	Optimum range
λ_{max} (nm)	485	480-490
Effect of acid conc. on color development	0.1M HCl	0.08-0.12 M HCl
Volume of acid required for color development	6.0	5.0-7.0
Effect of volume of dye, TP OOO (mL)	2.0	1.8-2.2
Choice of organic solvent for extraction	Chloroform	Chloroform*
Effect of ratio of organic phase on extraction	1:1.5	1:1.5**
Effect of shaking time (min)	2	1-5
Effect of temperature on colored species (^oC)	28 ± 5^oC	28 ± 5^oC ***
Stability of colored species	5 min	Immediate to 60min

** The other solvents tried are chloro benzene, dichloromethane, carbon tetrachloride, benzene and n-butanol out of which chloroform was preferred.*
*** The extraction was incomplete when ratio of aqueous to organic phase is more than specified*
**** at 20^oC the extraction was found to be improper and at $>35^oC$, the stability of colored species found to be less.*

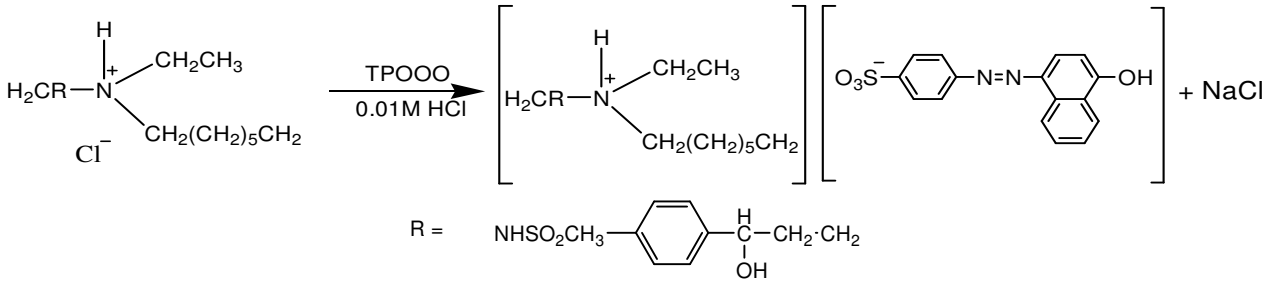

Figure-5: chemistry scheme for colored species

Table-2: Statistical illustration of the method

Parameter	Values
λ_{max} (nm)	485
Beer's law limits (□g mL^{-1})	2.5-20
Detection limits (□g mL^{-1})	0.561
Molar absorptivity (1mol cm^{-1})	$3.611x10^{4}$
Sandell's sensitivity □g cm^{-2}/0.001 absorbance unit)	0.024
Optimum photometric range (□g mL^{-1})	7.5-17.5
Regression equation (Y=a+bC) Slope (b)	0.0403
Standard deviation of slope (S_b)	$5.504x10^{-4}$
Intercept (a)	0.0144
Standard deviation of intercept (S_a)	$7.5369x10^{-3}$
Standard error of estimation (S_e)	$6.1538x10^{-3}$
Correlation coefficient (r^2)	0.9995
Relative Standard Deviation (%)	0.875
% Range of error (confidence limits of 6 determinations, 0.05 level, 0.01 level	0.919, 1.442
% Error in bulk samples (average of 3 determinations)	0.211