



Research Article

DEVELOPMENT AND VALIDATION OF NEW FT-IR SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF AMBROXOL HYDROCHLORIDE AND CETIRIZINE HYDROCHLORIDE IN COMBINED PHARMACEUTICAL SOLID TABLET DOSAGE FORM

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ABSTRACT

Infrared spectroscopy is also known as vibrational spectroscopy. FTIR is a non-destructive, highly sensitive, highly specific and robust analytical technique by which almost any solid, liquid or gas samples can be analyzed. The given research work is related with successful development and validation of newer, accurate, precise and sensitive FT-IR analytical method for estimation of cetirizine hydrochloride and ambroxol hydrochloride in their combined tablet dosage form. Literature survey reveals that, there is no FT-IR spectrophotometric method was developed and validated until now for this combination. KBr (Ar) grade was used as diluent. The functional groups were selected as AR-NH (1631 cm^{-1}) for ambroxol HCl and C=O (1741 cm^{-1}) for cetirizine HCl. The method was validated as per ICH guidelines. The linearity was developed at 6.0-36.0 % w/w for AMB HCl and 0.5-3.0 % w/w for CET HCl respectively. The correlation coefficients were found to be 0.9993 and 0.9995 respectively. The precision was found to be within acceptable limit. The developed method was found to be accurate and repeatable the % RSD was found to be within 2 %.

Keywords: Ambroxol hydrochloride, cetirizine hydrochloride, FT-IR, ICH guidelines.

INTRODUCTION

The ambroxol hydrochloride is chemically known as Trans-4-[(2-amino-3, 5-dibromobenzyl) amino] cyclohexanol hydrochloride¹. It is metabolite of bromhexine a derivative of alkaloid vasicine obtained from *Adhatoda vasica*⁴. It has potent mucolytic and mucokinetic activity^{3,4}.

The cetirizine hydrochloride is [2-[4-[(4-Chlorophenyl) phenylmethyl] -1-piperaziny] ethoxy] acetic acid dihydrochloride². It is metabolite of hydroxyzine. It acts as antihistaminic by blocking the peripheral H₁ receptor^{3,4}.

Literature survey reveals all analytical method development and validations available for single cetirizine HCl, ambroxol HCl and their combination dosage forms⁵⁻¹². There is no FT-IR spectrophotometric method was developed and validated up till now. The aim of research work is to develop new FT-IR method for routine analysis of cetirizine hydrochloride and ambroxol hydrochloride in bulk and combined solid tablet dosage form

MATERIALS AND METHOD

Apparatus and instruments

FT-IR spectrophotometer (IR-Affinity-1, Shimadzu Corp., Japan) equipped with diffuse reflectance sampling interface and attached with computer operated Shimadzu IR solution software was used for collection and analyze the data. It also equipped with detector-DLATGS and uses a high-energy long life ceramic light source. FT-IR spectrum was recorded in range of 400-4000 cm^{-1} with 45 scans and resolution of 8 cm^{-1} . Analytical weighing balance: A named; Model AA-2200. [Max. 200g, Min. 0.01g; e = 0.0001g]

Chemical and reagent

Working standard / drug sample was obtained as a gift samples from Bidwai Chemicals, Nanded, marketed formulation Cetzine A (cetirizine HCl IP 5 mg, ambroxol HCl IP 60 mg) of Glaxo Smith Kline Pharma. Limited, was purchased from local market. Pure KBr analytical grade was used as diluent, all calibrated glass wares were used throughout the work.

Solvent selection

Both the drugs were found to be compatible with potassium bromide. Solid sampling method was used for FT-IR method development and validation. So KBr is selected as solvent or diluent because it is transparent to IR- radiation and its peaks does not interfere with peaks of drugs.

Preparation of working standard (6.0% w/w AMB and 0.5 % w/w CET):

Accurately weighed ambroxol hydrochloride (60 mg) and cetirizine hydrochloride (5 mg) pure drugs were mixed separately with 940 mg and 995 mg of KBr (spectroscopic grade) respectively and triturated well to made homogenous mixture.

Selection of analytical wave number

Working standards of both drugs was scanned in IR range of 4000-400 cm^{-1} with resolution of 4 and 45 scans. Wave number was selected in such a way that one functional group of one drug should not present in another drug so that one can avoid interference of one drug in another. Wave number (peak

intensities) parameter is selected for both drugs, in that one can select a wave number. Functional group selected for AMB HCl was $-ArNH$ and wave number found in range of $1600-1670\text{ cm}^{-1}$. Functional group selected for CET HCl was $-COOH$ and wave number found in range of $1700-1800\text{ cm}^{-1}$.

Analysis of marketed tablet formulation

Accurately weighed 20 tablets of marketed formulation and average weight was determined and found to be 168 mg. Then these tablets were crushed to fine powder and powder weighed equivalent to 60 mg of AMB HCl and 5 mg of CET HCl was taken. It has been mixed with 832 mg of KBr such that concentration made was 6.0 % w/w for AMB HCl and 0.5 % w/w for CET HCl respectively.

METHOD VALIDATION

Linearity

The linearity study was performed by preparing standard dilution of 6, 12, 18, 24, 30 and 36 % w/w for AMB HCl and 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 % w/w for CET HCl. The calibration graph was plotted for diluted concentrations versus peak intensities of AMB HCl and CET HCl respectively.

Precision

The precision of the method was evaluated by inter-day and intraday variation studies. In intraday studies, working dilutions of sample were analyzed triplicate in a day and percentage relative standard deviation (% RSD) was calculated. In the inter-day variation studies, working dilutions of sample were analyzed

on three consecutive days and percentage relative standard deviation (% RSD) was calculated.

Accuracy

To ascertain the accuracy of the proposed methods, recovery studies were carried at three different levels (80%, 100% and 120%) as per ICH guidelines.

As per the label claim, tablet contains 60 mg of AMB HCl and 5 mg of CET HCl. For recovery studies 6 mg of AMB HCl and 0.5 mg of CET HCl had been selected, and different levels of the standard concentration according to 80%, 100% and 120% were added to pre-quantified sample and it was mixed thoroughly, analyzed and their % mean recoveries were calculated.

LOD and LOQ

ICH guideline describes several approaches to determine the detection and quantitation limits. These include visual evaluation, signal to noise ratio and the use of standard deviation of the response and the slope of the calibration curve. In the present study, the LOD and LOQ were based on the third approach and calculated with use of the following equations:

$$LOD = \frac{3.3\sigma}{S}$$

$$LOQ = \frac{10\sigma}{S}$$

Where σ is the standard deviation of the peak areas of the drugs, taken as a measure of noise, and S is the slope of the corresponding calibration curve.

Table 1: Analysis of Marketed Tablet Formulation

Name of the drug	Mean*	SD*	% RSD*
AMB	103.4081	0.68142	0.6589
CET	107.520325	1.22626855	1.1405

* Indicates average of six determinations

Table 2: Linear Regression Data for Calibration Curve of AMB and CET

Name of the drug	Linearity range (%w/w)	r ²	Slope	Intercept
AMB	6.0-36.0	0.9999	0.0127	0.2822
CET	0.5-3.0	0.999	0.2049	0.1464

Table 3: Repeatability Data (Intra-Assay Precision)

Name of the drug	Mean*	SD*	% RSD*
AMB	99.9945	0.652318	0.6524
CET	100.00	0.9797	0.9798

* Indicates average of six determinations

Table 4: Intra-Day Precision Data

Name of the drug	Mean*	SD*	% RSD*
AMB	103.4233	0.1415	0.1367
CET	106.9067	0.6987	0.6535

* Indicates average of three determinations

Table 5: Inter-Day Precision Data

Name of the drug	Mean*	SD*	% RSD*
AMB	103.8467	0.7858	0.9148
CET	108.9467	1.0849	0.9958

* Indicates average of three determinations

Table 6: Recovery Study (Accuracy) Data

Level of Recovery	% Mean Recovery *		SD*		% RSD*	
	AMB	CET	AMB	CET	AMB	CET
80%	100.75	99.23	0.2914	0.3207	0.2893	0.3233
100%	100.45	100.27	0.2040	0.1155	0.2031	0.1152
120%	99.20	99.34	0.5802	0.4619	0.5849	0.4649

* Indicates average of three determinations

Table 7: LOD & LOQ

Name of the drug	LOD(% w/w)	LOQ(% w/w)
AMB	0.6118	0.9268
CET	0.03818	0.1157

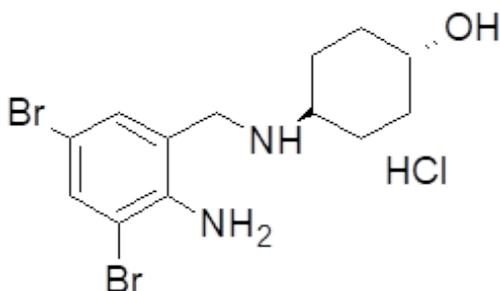


Figure 1: Chemical structure of Ambroxol hydrochloride

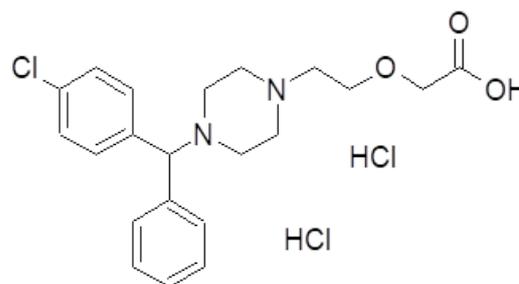


Figure 2: Chemical structure of Cetirizine hydrochloride

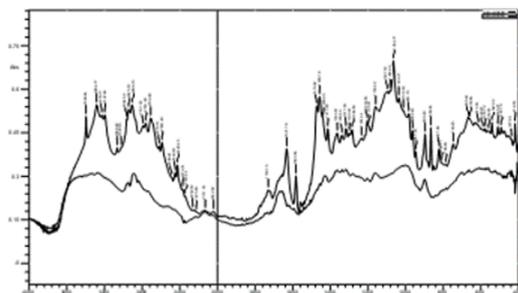


Figure 3: Overlay of excipients and tablet spectra respectively

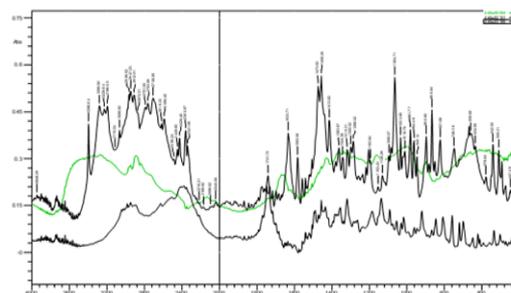


Figure 4: Overlay of CET, AMB, and excipients Spectra respectively

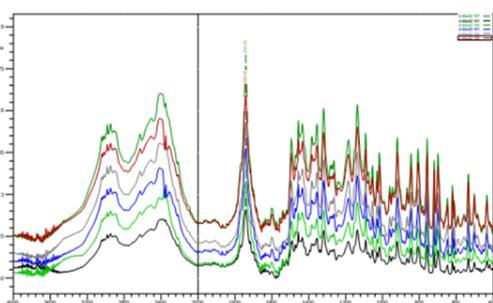


Figure 5: Overlay of linearity spectra of CET HCl of concentration range (0.5-3.0 %w/w)

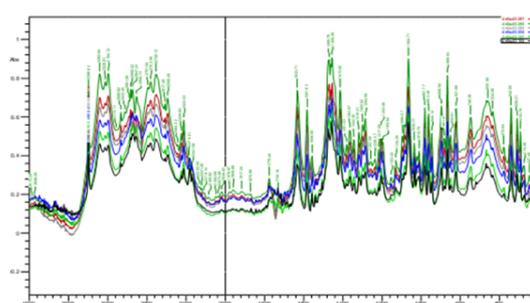


Figure 6: Overlay of linearity spectra of AMB HCl of concentration range (6.0-36.0 % w/w)

RESULT AND DISCUSSION

The FTIR spectrum for pure sample of AMB HCl and CET HCl exhibited absorbance bands in the range of 1600-1670 cm^{-1} and 1700-1800 cm^{-1} . The low intensity absorbance bands arising from AMB HCl and CET HCl were not much affected by dilution in dry potassium bromide; therefore, in the present study we have used dry potassium bromide as a diluent.

The most prominent absorbance band corresponding to the aromatic $-\text{NH}$ group centered in the range of 1600-1670 cm^{-1} for diluted samples of AMB HCl and $-\text{COOH}$ group in the range of 1700-1800 cm^{-1} for diluted samples of CET HCl in dry potassium bromide was within the 2.0 absorbance units.

Analysis of tablet formulation

The proposed validated method was applied for the quantification of ambroxol HCl and cetirizine HCl in combined tablet dosage form. The FTIR spectrum in figure 3 and 4 indicates that there is no interference of excipients used in the formulation of tablet dosage form. The pharmaceutical dosage form was analyzed using developed method and the result of analysis is shown in table 1. The average recoveries of CET HCl were in the range of 98-102 % w/w label claim and the % RSD values were in the range of 0.3233 – 0.4649. The % recovery of label claim was in good argument and within the acceptable limits of USP (not less than 90 % and not more than 110 % of stated amount of AMB HCl and CET HCl).

Method Validation

Linearity

The calibration curves were found to be linear over concentration range of 6, 12, 18, 24, 30 and 36 %w/w and 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 %w/w for AMB HCl and CET HCl respectively. The results of linearity study are given in table 2. Figure 5 and 6 are shown its overlays.

Repeatability

For the repeatability study, the detector response from the standard and sample were used to calculate the amount of the drug in the tablet, & estimation was near to 100 % and below 2 % indicates the method is repeatable.

Precision

The precision was expressed by coefficient of variation (% RSD) and accuracy by mean and standard deviation. For day 1 precision studies, the % RSD value for five sample 0.6589 % was observed while for day 3 precision studies the 1.1405 % was observed. The intraday and interday precision results were within the accepted variable limits.

Accuracy

The accuracy of the assay method was evaluated with the recovery of pure drug excipients at three different level (80 %, 100 %, 120 % w/w of label claim) by standard addition method and the recovery data is summarized in table 39, 40. Good recoveries of AMB HCl were obtained in the range of 98-102 % with the % RSD range of 0.2893 – 0.5849 at various added concentration.

LOD and LOQ

LOD was 0.6118 % w/w and 0.03818 %w/w while LOQ was 0.9268 % w/w and 0.1157 % w/w for AMB HCl and CET HCl.

CONCLUSION

Traditionally, FTIR spectroscopy is employed for the qualitative analysis of pharmaceuticals, however, with advantage in sampling techniques. FTIR spectroscopy may serve as useful technique for quantitative and qualitative analysis of solid-state pharmaceutical. In present work, we reported the development and validation of FTIR method for the quantification ambroxol hydrochloride and cetirizine hydrochloride in solid-state pharmaceutical and successfully applied to pharmaceutical dosage form.

The proposed method was found to be precise, accurate and suitable for the analysis of ambroxol hydrochloride and cetirizine hydrochloride in bulk and pharmaceutical formulation. The developed method was solvent free eco-friendly and cost effective. The developed method can be used for routine quality control analysis of both drugs in pharmaceutical dosage form.

ABBREVIATIONS

AMB HCl: Ambroxol hydrochloride
 CET HCl: Cetirizine hydrochloride
 FT-IR: Fourier transform infra-red
 ICH: International conference on harmonization
 SD: Standard deviation
 RSD: Relative standard deviation
 LOD: limit of detection
 LOQ: Limit of quantification

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