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Stability-Indicating LC Method for Simultaneous Estimation of Rabeprazole Sodium Hydrochloride and Itopride Hydrochloride in Combined Dosage Form

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ABSTRACT

A simple, sensitive and precise stability indicating HPLC method has been developed for the estimation of rabeprazole and itopride in combined dosage form. A Phenomenex Gemini C-18, 5 µm column with a mobile phase containing 0.02 M ammonium acetate (pH 6): acetonitrile: methanol (45: 20: 35, v/v/v) was used. The flow rate was 1.0 mL min^{-1} and effluents were monitored at 284 nm. Rabeprazole and itopride stock solutions were subjected to acid and alkali hydrolysis, chemical oxidation and dry heat degradation. The proposed method was validated with respect to linearity, accuracy, precision and robustness. The retention times of rabeprazole and itopride were 8.8 and 3.8 min, respectively. The method was linear in the range of 0.4–20 µg mL^{-1} for rabeprazole and 0.8–150 µg mL^{-1} for itopride. The degraded product peaks were well resolved from the pure drug peak with significant differences in their retention time values. Stressed samples were assayed using the developed HPLC method. The method was successfully applied to the estimation of rabeprazole and itopride in combined capsule dosage forms.

Keywords: reversed phase liquid chromatography, validation, forced degradation
Abbreviations: ITC, itopride hydrochloride; **LC**, liquid chromatography; **RAB**, rabeprazole sodium

INTRODUCTION

Rabeprazole sodium (RAB) is chemically 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridynyl]-methyl]sulfinyl]-1H-benzimidazole sodium. Rabeprazole is a substituted benzimidazole proton pump inhibitor. It does not exhibit anticholinergic or histamine H2 receptor antagonist properties but suppress gastric acid secretion by inhibiting the gastric H^+, K^+ ATPase at the secretory surface of the gastric parietal cell. Itopride hydrochloride (ITC) is chemically N-[P-[2-[dimethyl amino]ethoxyl]benzyl] veratramide hydrochloride. Itopride has anticholinesterase (AchE) activity as well as dopamine D2 receptor antagonistic activity and is being used for the symptomatic treatment of various gastrointestinal motility disorders. Various prokinetic studies were conducted in patients of non ulcer dyspepsia (NUD), reflux esophagitis and chronic gastritis, diabetic gastroparesis and functional dyspepsia. The results of these studies indicated that itopride is an effective prokinetic agent for the treatment of symptoms caused by altered gastrointestinal motility in all the above mentioned conditions (Gupta *et al.* 2004).

Proton pump inhibitors are drug of choice in the treatment of peptic ulcer diseases, GERD and non ulcer-dyspepsia (Bukowska *et al.* 2002; Van *et al.* 2004). Itopride has been proved to be effective prokientic agent for the treatment of non ulcer dyspepsia, GERD, gastritis caused by altered gastric motility. Proton pump inhibitors are combined with prokinetics which induces peristalsis to achieve synergistic effect in the treatment of GERD and peptic ulcer diseases (Harikumar *et al*. 2004).

A literature survey regarding quantitative analysis of these drugs revealed that attempts have been made to develop analytical methods for the estimation of RAB using LC (Garcia *et al.* 2004; Mehta *et al.* 2005; Garcia *et al.* 2006; Vasu *et al.* 2009), spectrophotometry (Rahman *et al.* 2008; Syed *et al.* 2008) and LC-MS (Shao *et al.* 2007). Methods have been reported for the estimation of ITC by HPLC (Singh *et al.* 2005; Dighe *et al.* 2006; Ptacek *et al.* 2009; Ma *et al.* 2009), LC-MS (Lee *et al.* 2007) and spectrophotometry (Smitha *et al.* 2007). For estimation of rabeprazole and itopride in combination, RP-HPLC (Gandhi *et al.* 2008), HPTLC (Suganthi *et al.* 2008) and spectrophotometric (Pattanayak *et al.* 2007; Heralgi *et al.* 2008; Sabnis *et al.* 2008) methods have been reported.

The International Conference on Harmonization (ICH) guidelines (Q2R1, 2005) require the implementation of stress testing procedures for the identification of degradation products that are potentially occurring in drug substances which can help to understand the possible degradation pathway for the drugs. The apparent lack of a suitable stability indicating method for the estimation of RAB and ITC in combination prompted us to develop accurate, specific and sensitive stability indicating LC method. This study reports forced degradation of rabeprazole and itopride under a variety of conditions such as acid and alkali hydrolysis, oxidative stress hydrolysis and dry heat degradation.

EXPERIMENTAL

Apparatus

The liquid chromatographic system consisted of a Shimadzu HPLC model (VP series) containing LC-10AT (VP series) pump, variable wavelength programmable UV/VIS detector SPD-10AVP and Rheodyne injector (7725i) with 20 µL fixed loop. The analytes were monitored at 284 nm. Chromatographic analysis was performed on Phenomenex Gemini C-18 column having 250 × 4.6 mm i.d. and 5 µm particle size. All the drugs and chemicals were weighed on Shimadzu electronic balance (AX 200, Shimadzu Corp., Japan).

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Techniques Paper

Chemicals and reagents

Analytically pure RAB and ITC were obtained as gift samples from Mepro Pharmaceutical Ltd., India and Torrent Pharmaceutical Ltd., India, respectively. HPLC grade acetonitrile, methanol and water were obtained from E. Merck Ltd., Mumbai, India while analytical reagent grade acetic acid and ammonium acetate were obtained from S. D. Fine chemicals, Mumbai, India. Capsule formulation 1 Rabium Plus (Intas Pharmaceutical ltd., India) and 2 Zorite (Indoco Remedies Ltd., India) containing 20 mg of rabeprazole sodium and 150 mg of itopride hydrochloride were procured from local market.

Chromatographic conditions

A reverse phase C-18 column (Phenomenex, Gemini) equilibrated with mobile phase 0.02M ammonium acetate (pH 6): acetonitrile: methanol (45: 20: 35, v/v/v) was used. Mobile phase flow rate was maintained at 1 mL min^{-1} and effluents were monitored at 284 nm. The sample was injected using a 20 µL fixed loop, and the run time was 15 min.

Preparation of standard stock solutions

Stock solutions were prepared by accurately weighing 25 mg each of RAB and ITC and transferring to two separate 25 mL volumetric flasks containing a few mL of methanol. The flasks were swirled to dissolve the solids. Volumes were made up to the mark with methanol to yield a solution containing 1000 µg mL^{-1} of RAB and ITC. Aliquot from the stock solution of RAB and ITC were appropriately diluted with mobile phase to obtain solutions of 100 µg mL^{-1} of each.

Method validation

The method was validated for accuracy, precision, linearity, specificity, detection limit, quantitation limit and robustness as per ICH guideline (Q2R1, 2005).

1. Linearity

Appropriate aliquots of RAB working standard solution were taken in different 10 mL volumetric flasks. Appropriate aliquots of ITC working standard solution were added to the same flasks. The volumes were made up to the mark with mobile phase to obtain final concentrations of 0.4, 1, 5, 10, 15, 20 µg mL^{-1} of RAB and 0.8, 4, 8, 40, 80, 150 µg mL^{-1} of ITC, respectively. The solutions were injected using a 20 µL fixed loop system and chromatograms were recorded. Calibration curves were constructed and regression equations were computed for RAB and ITC.

2. Precision

The intra-day and inter-day precision study of RAB and ITC was carried out by estimating the corresponding responses three times on the same day and on three different days for three different solutions containing RAB (1, 10, 20 µg mL^{-1}) and ITC (4, 80, 150 µg mL^{-1}) in mixture, and the results are reported in terms of RSD. The instrumental precision was evaluated by injecting mixed solutions containing three different concentrations of RAB (1, 5, 15 µg mL^{-1}) and ITC (4, 40, 120 µg mL^{-1}) six times and results are reported in terms of RSD.

3. Accuracy

The accuracy of the method was determined by calculating recoveries of RAB and ITC by method of standard additions. Known amount of RAB (0, 1, 5, 15 µg mL^{-1}) and ITC (0, 0.8, 40, 80 µg mL^{-1}) were added to a pre quantified sample solution, and the amount of RAB and ITC were estimated by measuring the peak areas and by fitting these values to the straight-line equation of calibration curve.

4. Detection limit and quantitation limit

The limit of detection (LOD) is defined as the lowest concentration of an analyte that can reliably be differentiated from background levels. Limit of quantification (LOQ) of an individual analytical procedure is the lowest amount of analyte that can be quantitatively determined with suitable precision and accuracy. LOD and LOQ were calculated using following equation as per ICH guidelines:

$LOD = 3.3 \times \sigma/S$; $LOQ = 10 \times \sigma/S$

where σ is the standard deviation of y-intercepts of regression lines and S is the slope of the calibration curve.

5. Robustness

Robustness of the method was studied by observing stability of the sample solution at 25 ± 2°C for 24 h.

6. Specificity

Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities and degradation products. Commonly used excipients (starch, microcrystalline cellulose and magnesium stearate) were spiked into a pre weighed quantity of drugs. The chromatogram was taken by appropriate dilutions and the quantities of drugs were determined.

Specificity was also studied by performing forced degradation study using acid and alkali hydrolysis, chemical oxidation and dry heat degradation studies and interference of the degradation products were investigated. Stock solutions were prepared by accurately weighing 25 mg each of RAB and ITC and transferring to two separate 25 mL volumetric flasks containing few ml of methanol. The flasks were swirled to dissolve the solids diluted up to the mark with methanol. These stock solutions were used for forced degradation studies.

a) Base hydrolysis: Forced degradation in basic media was performed by taking 1 mL stock solutions of RAB and ITC in two different 25 mL volumetric flasks and 5 mL of 0.1 N NaOH was added. Similarly, 1 mL aliquots of stock solutions of RAB and ITC were taken in the same 25 mL volumetric flask to obtain mixture and 5 mL of 0.1 N NaOH was added. All flasks were stored at room temperature for 24 h. Solutions were neutralized with 0.1 N HCl using pH meter and diluted up to the mark with mobile phase. Appropriate aliquots were taken from above solutions and diluted with mobile phase to obtain final concentration of 6 µg mL^{-1} of RAB and ITC separately and in the mixture.

b) Acid hydrolysis: Forced degradation in acidic media was performed by taking appropriate aliquots of stock solutions of RAB and ITC in two different 25 mL volumetric flasks and 5 mL of 0.1 N HCl was added. Similarly, appropriate aliquots of stock solutions of both the drugs were taken in the same 25 mL volumetric flask to obtain mixture and 5 mL of 0.1 N HCl was added. All flasks were stored at room temperature for 70 min. Solutions were neutralized with 0.1 N NaOH using pH meter and suitably diluted with mobile phase to obtain final concentration of 10 µg mL^{-1} of RAB and 75 µg mL^{-1} of ITC separately and in the mixture.

To another 25 mL volumetric flask, 1 mL stock solution of ITC was taken and 5 mL of 0.1 N HCl was added. The solution was heated at 80°C for 1 h and allowed to cool to room temperature. Solution was neutralized with 0.1 N NaOH using pH meter and suitably diluted with mobile phase to obtain final concentration of 6 µg mL^{-1} of ITC.

c) Oxidative stress degradation: To perform oxidative stress degradation, 1 mL stock solutions of RAB and ITC were taken in two different 25 ml volumetric flasks and 5 ml of 3% hydrogen peroxide was added. Similarly, 1 mL stock solutions of RAB and ITC were taken in the same 25 mL volumetric flask to obtain mixture and 5 mL 3% hydrogen peroxide was added. All the mixtures were heated in a water bath at 80°C for 1 h and allowed to cool to room temperature. Solutions were appropriate diluted with mobile phase

to obtain final concentration of 6 µg mL^{-1} of RAB and ITC separately and in mixture.

d) Dry heat degradation: To study dry heat degradation, solid drugs were exposed in oven at 80°C for 1 h. The solids were allowed to cool and 25 mg each of RAB and ITC were weighed, transferred to two separate volumetric flasks (25 mL) and dissolved in few mL of methanol. Volumes were made up to the mark with the methanol. Appropriate aliquots were taken from above solutions and diluted with mobile phase to obtain final concentration of 40 µg mL^{-1} of ITC and 10 µg mL^{-1} of RAB.

All the reaction solutions were injected in the liquid chromatographic system and chromatograms were recorded.

Analysis of marketed formulations

The content of 20 capsules were weighed. Powder equivalent to 20 mg RAB (and 150 mg ITC) was accurately weighed and transferred to a 50 mL volumetric flask. A few mL (20 mL) of mobile phase was added to the above flask and flask was sonicated for 5 min. The solution was filtered using Whatman filter paper No. 1 in another 50-ml volumetric flask and volume was diluted to the mark with the mobile phase.

Appropriate volume of the aliquot was transferred to a 25-mL volumetric flask and the volume was made up to the mark with mobile phase to obtain 10 µg mL^{-1} of RAB and 75 µg mL^{-1} of ITC. The solution was sonicated for 10 min. The solution was injected at above chromatographic conditions and peak areas were measured. The quantification was carried out by keeping these values to the straight line equation of calibration curve.

RESULTS AND DISCUSSION

Optimization of mobile phase

The objective of the method development was to resolve chromatographic peaks for active drug ingredients (RAB and ITC) and degradation products produced under stressed conditions with less asymmetric factor. Various mixtures containing aqueous buffer-methanol, acetonitrile were tried as mobile phases.

Different mobile phases tried were acetonitrile: water (70: 30, v/v) which gave peak for RAB at 3.36 min and for ITC at 2.29 min with unsatisfactory peak resolution. Methanol: 0.02 M ammonium acetate (pH 6) (70: 30, v/v) was tried which gave broad peak for RAB and ITC. 0.02 M ammonium acetate (pH 6): acetonitrile: methanol (40: 20: 40, v/v/v) were tried which gave peak for RAB at 7.2 min and for ITC at 3.58 min with more asymmetry. 0.02 M ammonium acetate (pH 5): acetonitrile: methanol (40: 20: 40, v/v/v) was tried which gave peak for RAB 7.0 min and for ITC 3.2 min.

The mobile phase consisting of 0.02 M ammonium acetate (pH 6 using 0.1 M acetic acid): acetonitrile: methanol (45: 20: 35, v/v/v) was selected which gave sharp, well resolved peaks for RAB and ITC. The flow rate was maintained at 1.0 mL min^{-1}. The retention times for RAB and ITC were 8.8 and 3.8 min, respectively with the resolution of 17.8 (**Fig. 1**).

UV overlain spectra of both RAB and ITC showed that both the drugs absorbed appreciably at 284 nm, so the same was selected as the detection wavelength during chromatographic studies.

Method validation

The calibration curves were obtained by plotting the peak area versus concentration over the range of 0.4-20 µg mL^{-1} for RAB and 0.8-150 µg mL^{-1} for ITC, respectively. Instrument precision was determined by performing repeatability test and the RSD values for RAB and ITC were found out. The intra-day and inter-day precision studies were carried out and the results are reported in terms of RSD (**Table 1**). The low RSD values indicate that the method is precise.

The accuracy of the method was determined by calculating recoveries of RAB and ITC by method of standard addition. The recoveries were found to be 98.28–99.73 and 98.23–100.70% for RAB and ITC, respectively. The values indicate that the method is accurate. The detection limits for RAB and ITC were 0.1 and 0.3 µg mL^{-1}, respectively, while quantitation limits were 0.4 and 0.8 µg mL^{-1}, respectively. The above data shows that a nanogram quantity of both the drugs can be accurately and precisely determined.

Table 1 Summary of validation and system suitability parameters.

Parameters	RAB	ITC
Retention time (min)	8.8	3.8
Asymmetry	1.3	1.6
Resolution	17.8	-
Theoretical Plates	11469	4627
Detection limit (µg mL^{-1})	0.1	0.3
Quantitation limit (µg mL^{-1})	0.4	0.8
Accuracy (%)	98.28 - 99.73	98.23 - 100.70
Precision (%RSD)		
Intra-day (n=3)	0.85 - 1.72	0.32 - 1.52
Inter-day (n=3)	1.10 - 1.88	0.82 - 1.93
Instrument precision (%RSD)	0.39 - 0.83	0.26 - 0.97
Specificity	97.32 - 99.63%	98.18 - 100.27%

The specificity study was carried out to check the interference from the excipients used in the formulations by preparing synthetic mixture containing both the drugs and excipients. The chromatogram showed peaks for both the drugs (RAB and ITC) without any interfering peak and the recoveries of both the drugs were above 97%. System suitability studies were carried out on freshly prepared standard stock solution of ITC and RAB and parameters obtained are summarized in **Table 1**. The solution stability study revealed that RAB was unstable and underwent hydrolysis with a percentage recovery of 45.23%, while ITC was stable for 24 h without detectable degradation. Percentage recovery of ITC was found to be 98.72%.

Forced degradation study

The chromatograms of base degraded sample showed degradation product peaks at retention time (RT) 3.137, 3.867, 5.093 min for RAB while ITC was found to be stable (**Figs. 2, 3**).

RAB was highly susceptible to acid hydrolysis and the treated samples turns brown in color after acid hydrolysis. The chromatogram of acid degraded samples showed degradation products peaks at RT 3.347, 5.89 and 7.383 min for RAB at room temperature. ITC was found to be stable to acid hydrolysis at room temperature and at 80°C (**Figs. 4, 5**).

The chromatogram of hydrogen peroxide degraded samples showed degradation product peaks at RT 3.33, 3.547, 4.967, 8.18 min for RAB with complete degradation of drug while degradation peak ITC was observed at 3.673 min (**Fig. 6**). Both the drugs were found to be stable to dry heat degradation and no degradation peak was observed. Physical appearance of RAB powder was changed to brown after dry heat degradation.

The degradation study thereby indicated that RAB was stable to dry heat degradation while it was susceptible to acid hydrolysis, base hydrolysis and oxidative stress degradation. ITC was found to be susceptible to oxidative stress degradation (**Table 2**).

Analysis of marketed formulations

The proposed method was applied to the determination of RAB and ITC in their combined dosage form (Capsule 1 and 2). The results for RAB and ITC were comparable with the corresponding labeled amounts (**Table 3**).

Literature survey revealed that for estimation of RAB and ITC in combination, RP-HPLC (Gandhi *et al*. 2008), HPTLC (Suganthi *et al.* 2008) and spectrophotometric (Pattanayak *et al.* 2007; Heralgi *et al.* 2008; Sabnis *et al.*

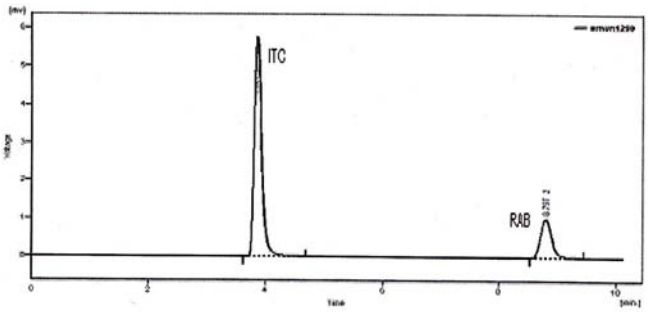

Fig. 1 Liquid chromatogram of ITC (40 µg mL^{-1}; 3.8 min) and RAB (5 µg mL^{-1}; 8.8 min).

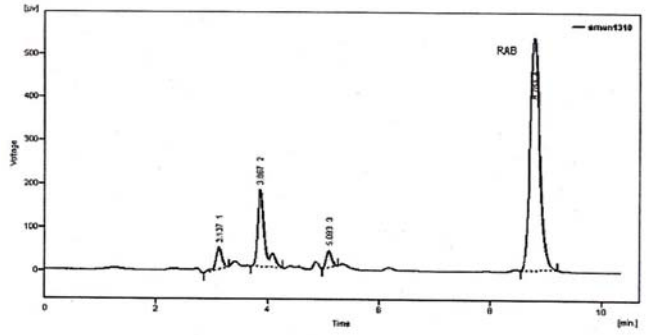

Fig. 2 Chromatogram of base treated RAB (6 µg mL^{-1}) at room temperature for 24 h.

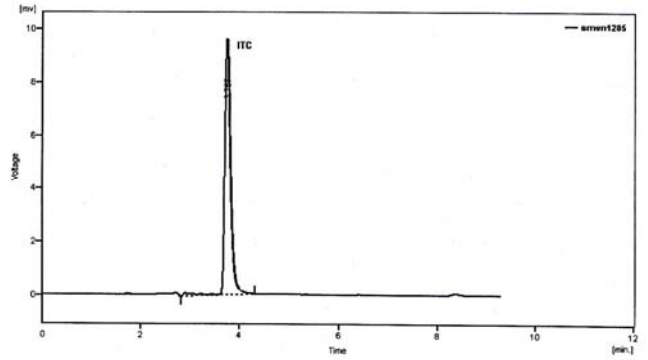

Fig. 3 Chromatogram of base treated ITC (6 µg mL^{-1}) at room temperature for 24 h.

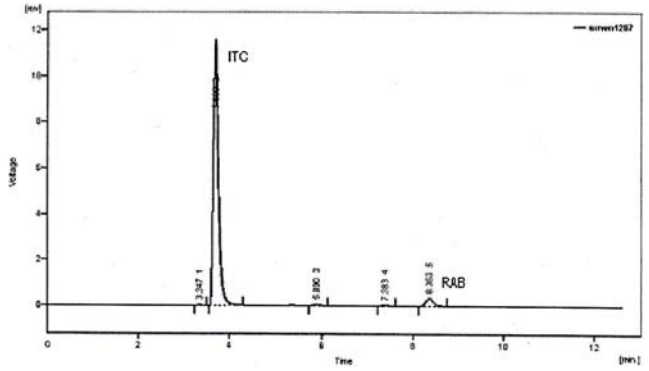

Fig. 4 Chromatogram of acid treated RAB (10 µg mL^{-1}) and ITC (75 µg mL^{-1}) at room temperature for 70 min.

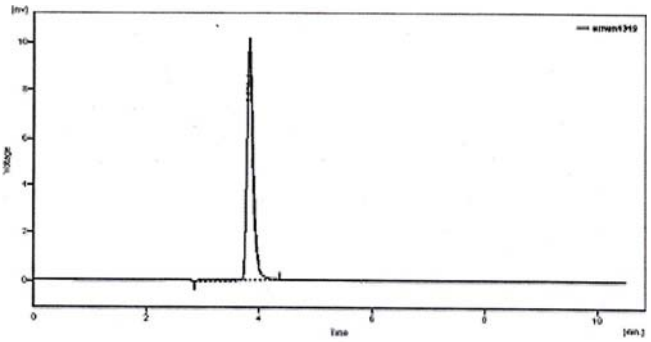

Fig. 5 Chromatogram of acid treated ITC (6 µg mL^{-1}) at 80° C for 1 h.

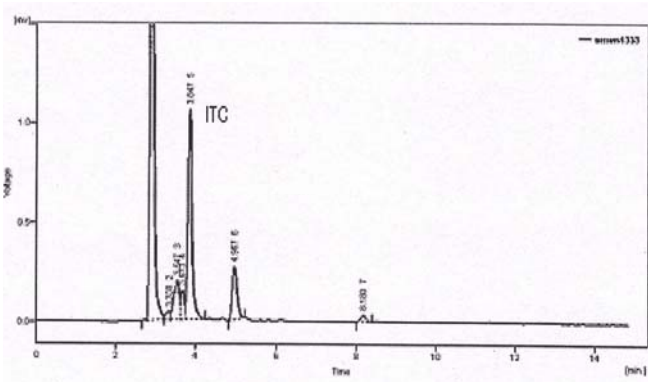

Fig. 6 Chromatogram of hydrogen peroxide (3%) treated RAB (6 µg mL^{-1}) and ITC (6 µg mL^{-1}) at 80°C for 1 h.

Table 2 Forced degradation study of RAB and ITC for the proposed LC method.

Conditions	Time (hrs)	Recovery (%)		Retention time of Degradation products	
		RAB	ITC	RAB	ITC
Base 0.1 N NaOH	24 h at 25°C	40.64	97.56	3.137, 3.867, 5.093	-
Acid 0.1 N HCl	70 min at 25°C	16.60	98.12	3.347, 5.89, 7.383	-
3% hydrogen peroxide [a]	1	0	96.78	3.330, 3.547, 4.967, 8.18	3.673
Dry heat [a]	1	98.12	99.45	-	-

[a] Samples were heated at 80°C for specified period of time.

Table 3 Assay results of combined dosage form.

Formulations	Labeled amount (mg)		Amount found (mg) [b]		% of drug found ± SD [b]	
	RAB	ITC	RAB	ITC	RAB	ITC
1	20	150	20.03	147.64	100.13 ± 1.11 b	98.42 ± 0.87 b
2	20	150	19.73	149.90	98.65 ± 0.69 b	99.93 ± 0.61 b

[b] :mean value ± standard deviation of three determinations; Formulation 1: Rabium Plus, Intas Pharmaceutical Ltd., India and formulation 2: Zorite, Indoco Remedies Ltd., India.

2008) methods have been reported. Compared to the reported RP-HPLC method the developed method is more sensitive and stability indicating. The spectrophotometric methods reported for the estimation of RAB and ITC includes derivative spectrophotometry, simultaneous equation and Q-absorbance method. The reported spectrophotometric methods and HPTLC methods are less sensitive and less specific compared to developed LC method. The developed

method is stability indicating which has advantage that the method can be used for degradation studies and stability studies conducted to predict shelf life of dosage form.

CONCLUSIONS

Proposed study describes stability indicating LC method for the estimation of RAB and ITC combination in mixture. The method was validated and found to be simple, sensitive, accurate and precise. Statistical analysis proved that method was repeatable and selective for the analysis of RAB and ITC in combination with out any interference from the excipients. The method was successfully used for determination of drugs in their pharmaceutical formulations. Also the above results indicate the suitability of the method for acid, base, dry heat and wet heat degradation study. As the method separates the drugs from its degradation products, it can be used for analysis of stability samples.

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