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Research Article

Development And Validation of Stability Indicating Assay Method for Simultaneous Determination of Ranitidine and Dicyclomine in Combined Dosage Form

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ABSTRACT

The present research work is focussed on the development of FT-IR Spectrophotometric method for estimation and validation of ranitidine (RANI) and dicyclomine (DICY). It is simple, fast, accurate, cost efficient and reproducible Spectrophotometric method, developed for the estimation of RANI and DICY. The wave numbers selected were in range of 1361 cm^{-1}(Nitro) for RANI and 1716 cm^{-1} (Ester) for DICY. The linearity for these drug at the selected wave numbers lies between 3-18 (% w/w) for RANI and 0.2-1.2 (% w/w) for DICY respectively, with correlation coefficient of 0.998 for RANI and 0.998 for DICY. The accuracy and precision of the method were determined and validated according to ICH guidelines. The method has good reproducibility with % RSD less than two. Thus proposed method can be successfully applied for RANI and DICY in routine analysis work.

Keywords: FT-IR Spectrophotometric method; Ranitidine; Dicyclomine; ICH guidelines.

1. INTRODUCTION

RANI, chemically N-(2-{[(5-dimethylamino) methyl]-2furanyl}-methylthioethyl)-N'-methyl-2-nitro-1, 1'ethane diamine, is the active compound of manypharmaceutical formulations. It competitively inhibits the action of histamine on the H_2 receptors of parietal cells, reducing gastric acid secretion under daytime and nocturnal basal conditions and also when stimulated by food, insulin, histamine or pentaglandin (1). RANI is an synthetic H_2 receptor antagonist(2). DICY, chemically (bicyclohexyl]-1-carboxylic acid is an antispasmodic and anticholinergic(antimuscarinic) agent. It acts in two ways: a specific anticholinergic effect (antimuscarinic) at the acetylcholine-receptor sites, a direct effect upon smooth muscle (musculotropic) (3). It is used to treat a certain type of intestinal problem called irritable bowel syndrome. It helps to reduce the symptoms of stomach and intestinal cramping. This medication works by slowing the natural movements of the gut and by relaxing the muscles in the stomach and intestines (4,5). Combination of RANI and DICY is used in treatment of acute ulcer (6). The numbers of assay methods areavailable for determination of RANI in pharmaceutical formulations (7). DICY is medication which helps in slow down the movements of guts and by relaxing muscles in stomach and intestines (8). DICY inhibits gastrointestinal propulsive motility and decreases gastric acid secretion and controls excessive pharyngeal, tracheal and bronchial secretions (9).Chemical structure of RANI given in fig.1 (a) and DICY given in fig. (b).

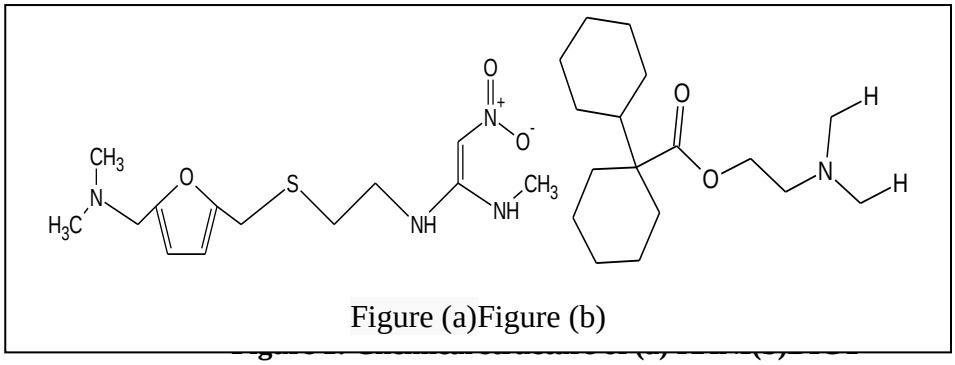

Figure (a)Figure (b)

2. MATERIALS AND METHODS

2.1 Apparatus and Instruments

Spectroscopic measurements were carried on FT-IR spectrophotometer serial no- A213747 (IR-Affinity-1, Shimadzu corp., Japan) attached with computer operated software IR solution. FT-IR spectrum was recorded in range of 400-4000 cm^{-1} with 45 scans and resolution of $8cm^{1}$. Analytical weighing balance (AA-200) and hot air oven were used during the study.

2.2 chemicals and reagents

Potassium bromide IR grade was obtained from MERCK chemicals Pvt. Ltd. Mumbai. Standard bulk sample of Ranitidine and Dicyclomine were purchased as a gift sample from Orchev pharma Pvt. Ltd. Rajkot Gujarat and Wockhardt Pvt. Ltd Aurangabad respectively.RANILA-SPAS (Ranitidine150 mg, Dicyclomine10mg) of Akums drugs &pharma Ltd, was obtained from market.

2.3 Solvent selection

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

3. FT-IR SPECTROPHOTOMETRIC METHOD

Working standard (0.5 % w/w) of both drugs was scanned in IR range of 400-4000 cm^{-1} with resolution of 8 and 45 scans.Wave numbers selected were in range of 1361 cm^{-1} (Nitro)for RANI and 1716 cm^{-1} (Ester) for DICY.

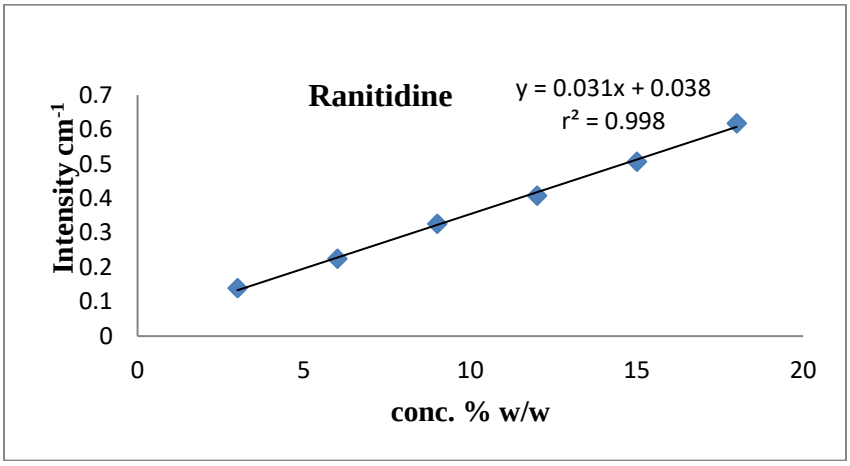

Fig. 2 Calibration curve of RANI

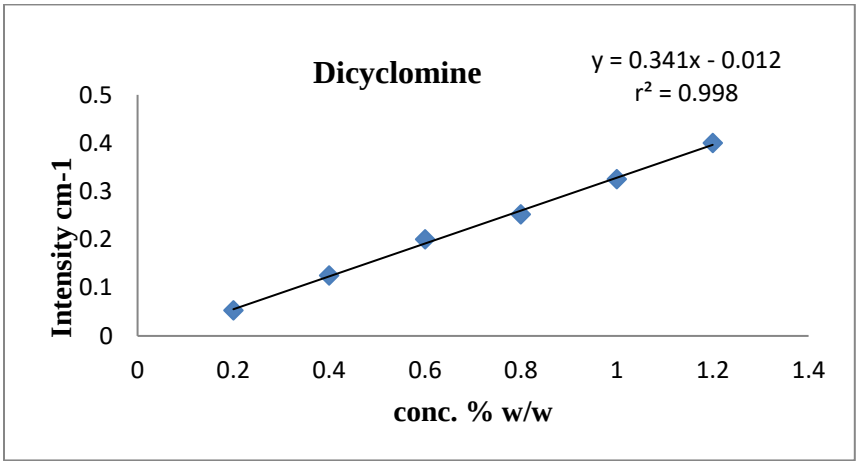

Fig. 3 Calibration curve of DICY

3.1 METHOD VALIDATION

3.1.1 Linearity

The linearity of this method was found to be 3-18 % w/w for RANI and 0.2-1.2% w/w for DICY.For this method equations generated were y = 0.031x + 0.038 (R^2 = 0.998) and y = 0.341x - 0.012 (R^2 = 0.998) for RANI and DICY respectively. Results are shown in Table.1

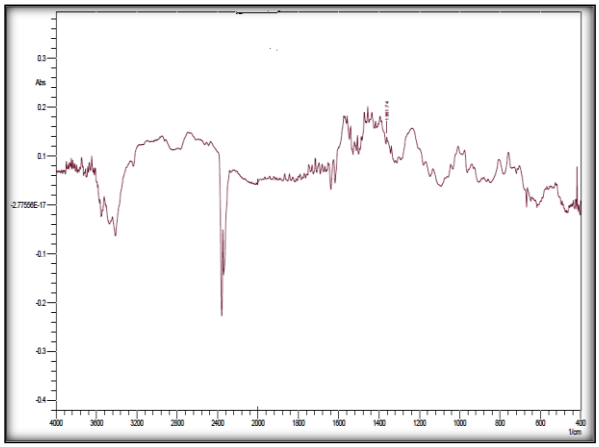

Fig. 4 spectrum of RANI (3% w/w)

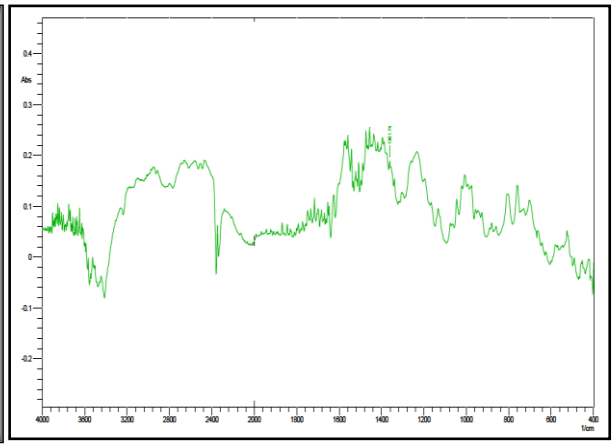

Fig. 5 spectrum of RANI (6 % w/w)

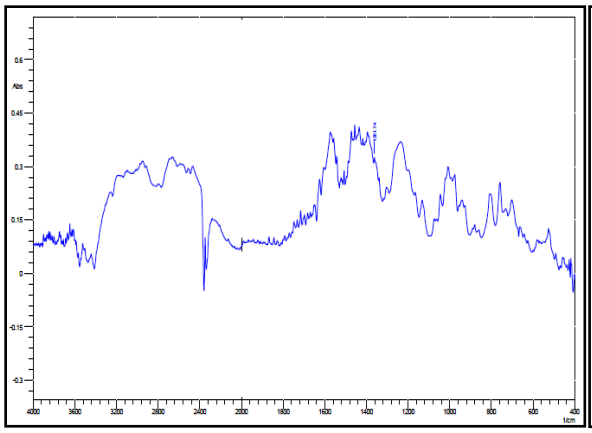

Fig. 6 spectrum of RANI (9 % w/w)

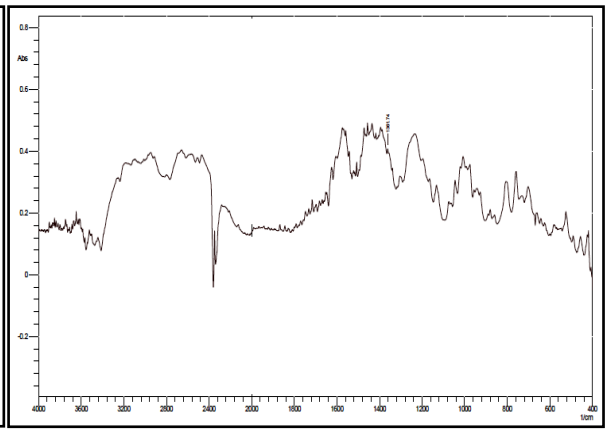

Fig. 7 spectrum of RANI (12 % w/w)

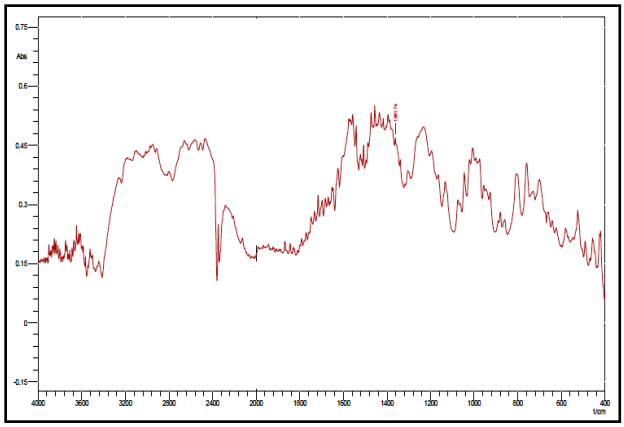

Fig. 8 spectrum of RANI (15 % w/w)

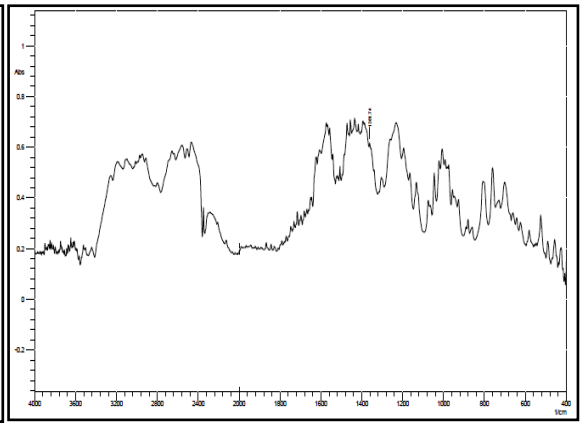

Fig. 9 spectrum of RANI (18 % w/w)

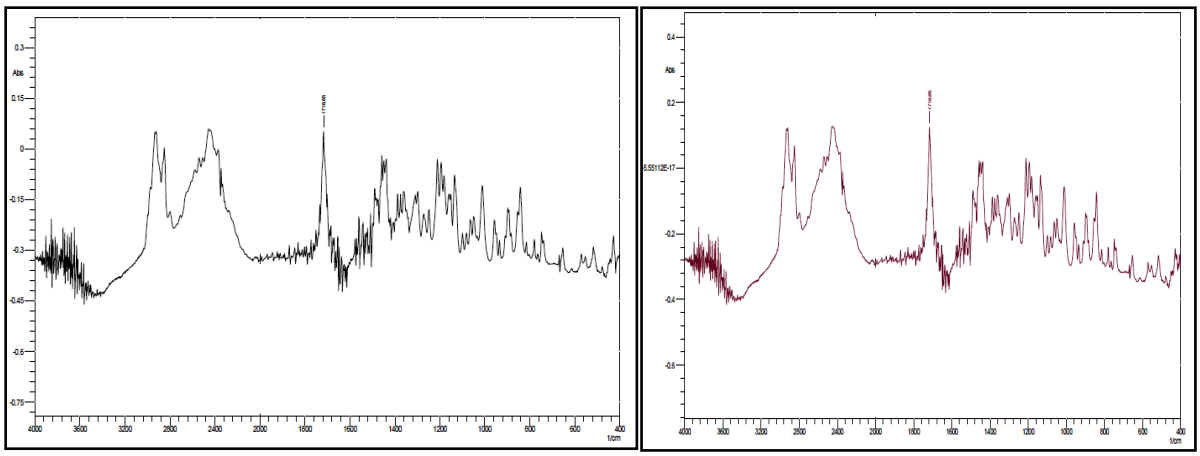

Fig. 10spectrum of DICY (0.2 % w/w)Fig. 11 spectrum of DICY (0.4 % w/w)

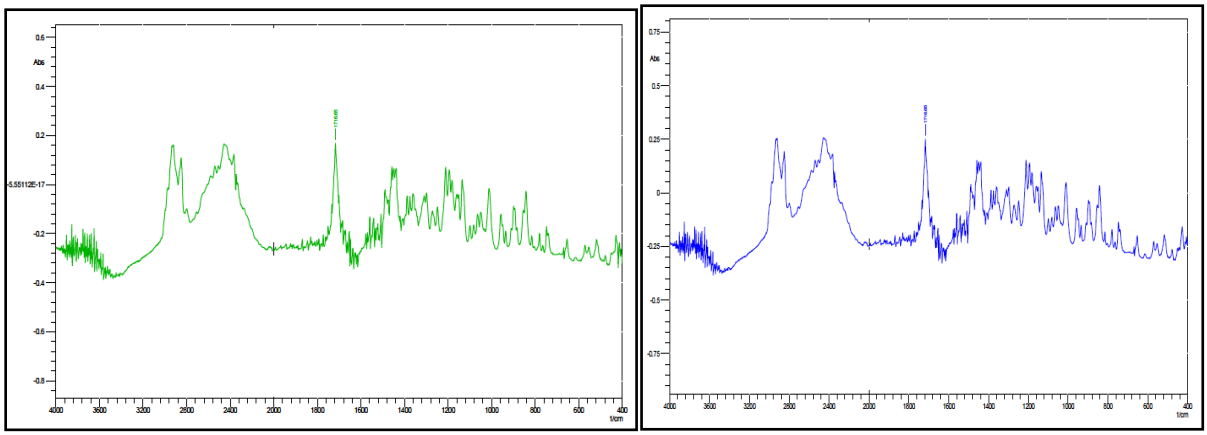

Fig. 12 spectrum of DICY (0.6 % w/w)Fig. 13 spectrum of DICY (0.8 % w/w)

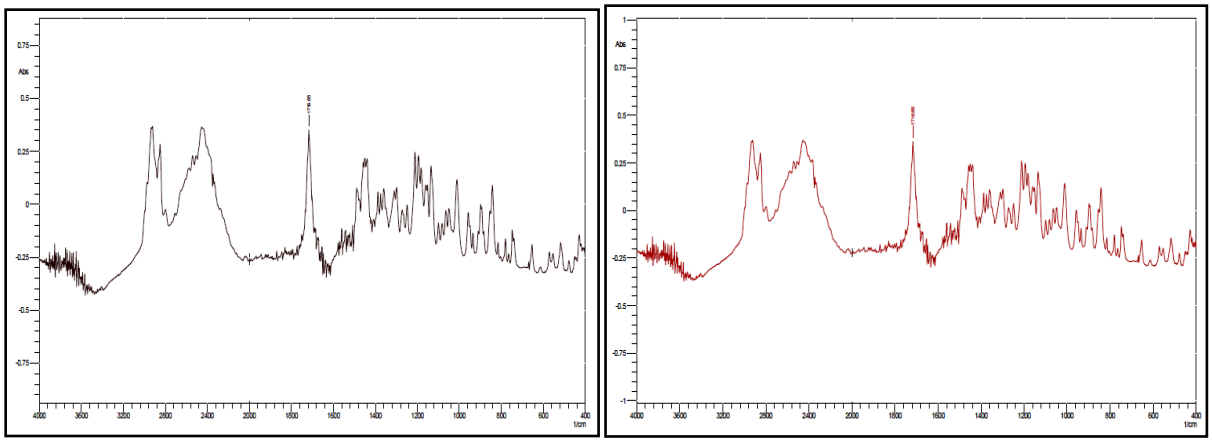

Fig. 14 spectrum of DICY (1.0 % w/w)Fig. 15 spectrum of DICY (1.2 % w/w)

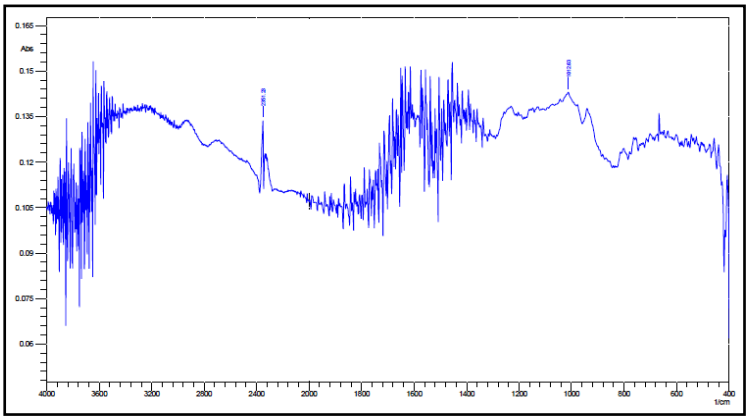

Fig. 16 Spectrum of tablet Excipients

Table 1: Linear regression data for calibration curve of RANI and DICY

Name of the drug	Linearity range (% w/w)	r^2	Slope	Intercept
RANI	3-18	0.998	0.031	0.038
DICY	0.2-1.2	0.998	0.341	0.012

3.1.2 Precision

Precision of the method was evaluated by inter-day and intraday variation studies. In intraday studies, working solutions of standard and sample were analyzed in triplicate for a day and percentage relative standard deviation (% RSD) was calculated. In the inter-day variation studies, working solution of standard and sample were analyzed on two consecutive days and percentage relative standard deviation (% RSD) was calculated. Precision study was carried on formulation. Precision data is shown in Table.2

Table 2: Precision data of marketed formulation

Sr. No.	Interval of Time	Concentration (% w/w)		% Recovery	
		RANI	DICY	RANI	DICY
I	Intra-day	3	0.2	99.49	99.20
II		3	0.2	99.23	99.60
III		3	0.2	99.49	100
I	Inter-day	3	0.2	99.49	99.20
II		3	0.2	99.49	99.20
III		3	0.2	99.23	100.39
INTRADAY			Mean*	99.40	99.6
			SD*	0.1501	0.4

	%RSD*	0.1510	0.401
INTERDAY	**Mean***	99.40	99.59
	SD*	0.1501	0.6870
	%RSD*	0.1510	0.6898

* Indicates average of six determinations

3.1.3 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.

To perform recovery study at 80% tablet powder is weighed about 327 mg having equivalent weight of 150 mg of RANI and 10 mg of DICY and to this standard 120 mg of RANI and 8 mg of DICY was added. The mixture is triturated well and added into 485 mg kbr and again triturated well and by serial dilution technique required concentration was prepared containing 3.0% w/w of RANIand 0.2% w/w of DICY.

To perform recovery study at 100% tablet powder is weighed about 327 mg having equivalent weight of 150 mg of RANI and 10 mg of DICYand to this standard 150 mg of RANI and 10 mg of DICYwas added. The mixture is triturated well and added into 485 mg kbr and again triturated well and by serial dilution technique required concentration was prepared containing 3.0% w/w of RANI and 0.2% w/w of DICY.

To perform recovery study at 120% tablet powder is weighed about 327 mg having equivalent weight of 150 mg of RANIand 10 mg of DICY and to this standard 180 mg of RANIand 12 mg of DICYwas added. The mixture is triturated well and added into 485 mg kbr and again triturated well and by serial dilution technique required concentration was prepared containing 3.0% w/w of RANI and 0.2% w/w of DICY.Accuracy data is shown in Table. 3

Table 3: Recovery study data

Level of Recovery	**Amount present (mg)**		**Added concentration (mg)**		**Amount recovered (mg)**		**% Recovery**	
	RANI	**DICY**	**RANI**	**DICY**	**RANI**	**DICY**	**RANI**	**DICY**
80%	150	10	120	8	268.62	17.92	99.49	99.60
	150	10	120	8	267.92	17.85	99.23	99.20
	150	10	120	8	268.62	17.78	99.49	98.81
100%	150	10	150	10	299.22	20	99.74	100
	150	10	150	10	297.69	20.07	99.23	100.39
	150	10	150	10	300	20.07	100	100.39
120%	150	10	180	12	330.82	21.91	100.25	99.60
	150	10	180	12	330	22.17	100	100.79
	150	10	180	12	330	22.17	100	100.79
	% Mean Recovery *		**SD***			**% RSD***		

	RANI	DICY	RANI	DICY	RANI	DICY
80%	99.40	99.20	0.1501	0.3950	0.1510	0.3981
100%	99.65	100.26	0.3917	0.2251	0.3930	0.2245
120%	100.08	100.39	0.1443	0.6870	0.1442	0.6843

* Indicates average of three determinations

3.1.4 LOD and LOQ

The LOD and LOQ of RANI and DICY were calculated by mathematical equation:

LOD= 3.3 X Standard deviation / Slope

LOQ= 10 X Standard deviation / Slope

LOD and LOQ are shown in Table. 4

Table 4: LOD & LOQ

Name of the drug	LOD (% w/w)	LOQ (% w/w)
RANI	0.1062	0.3219
DICY	0.0096	0.0292

3.2 Analysis of marketed tablet formulation

Accurately weighed 20 tablets of marketed formulation and average weight were found 327 mg. Then these tablets were crushed to fine powder and from this 327 mg of powder weighed containing equivalent weight of 150 mg of RANI and 10 mg of DICY. It has been mixed with 485 mg of kbr and dilution made was 3.0 % w/w for RANI and 0.2 % w/w for DICY respectively.Analysis of marketed tablet formulation is shown in Table. 5

Table 5: Analysis of tablet formulation

Sr. No.	Label claim (mg/tab)		Amount found (mg/tab)		% of Label claim	
	RANI	DICY	RANI	DICY	RANI	DICY
1	150	10	149.2	9.92	99.49	99.20
2	150	10	148.8	9.96	99.23	99.60
3	150	10	149.2	10	99.49	100
4	150	10	149.2	9.92	99.49	99.20
5	150	10	149.2	9.92	99.49	99.20
6	150	10	148.8	10.03	99.23	100.39
				Mean*	99.40	99.59
				SD*	0.1342	0.5028

	%RSD*	0.1350	0.5048

* Indicates average of six determinations

4. FORCED DEGRADATION STUDIES

Forced degradation studies were performed on RANI and DICY to prove the stability indicating property of the method. The stress conditions applied for degradation study involved thermal, photolytic and sunlight degradation [ICH Q1A(R2) 2003].

4.1 Thermal degradation

Thermal degradation was carried out by exposing pure drugs to dry heat at 80ºC for 3 hrs. Samples are withdrawn at interval of 30 min. The samples after exposure to heat were diluted or mixed with kbr to get RANI(3.0 % w/w) and DICY (0.2 % w/w). Wave number was measured at 1361 cm^{-1} and 1716 cm^{-1} for RANI and DICY respectively. Finally peak area of sample was compared with standard peak area and percent degradation and percent assay was calculated.

4.2 Photolytic degradation

Pure drugs were exposed to UV radiations for 3 hrs and samples were withdrawn at interval of 30 min. The samples after exposure to light were diluted with kbr to get RANI(3.0% w/w) and DICY (0.2 % w/w). Wave number was measured at 1361 cm^{-1} and 1716 cm^{-1} for RANI and DICY respectively. Finally peak area of sample was compared with standard peak area and percent degradation and percent assay was calculated.

4.3 Degradation in Sunlight

Sunlight degradation is performed by exposing the pure drugs to sunlight in open space for 3 hrs. Samples are withdrawn at interval of 30 min. The samples after exposure to sunlight were diluted or mixed with kbr to get RANI(3.0 % w/w) and DICY(0.2 % w/w). Wave number was measured at 1361 cm^{-1} and 1716 cm^{-1} for RANI and DICYrespectively. Finally peak area of sample was compared with standard peak area and percent degradation and percent assay was calculated.Forced degradation data is shown in Table. 6

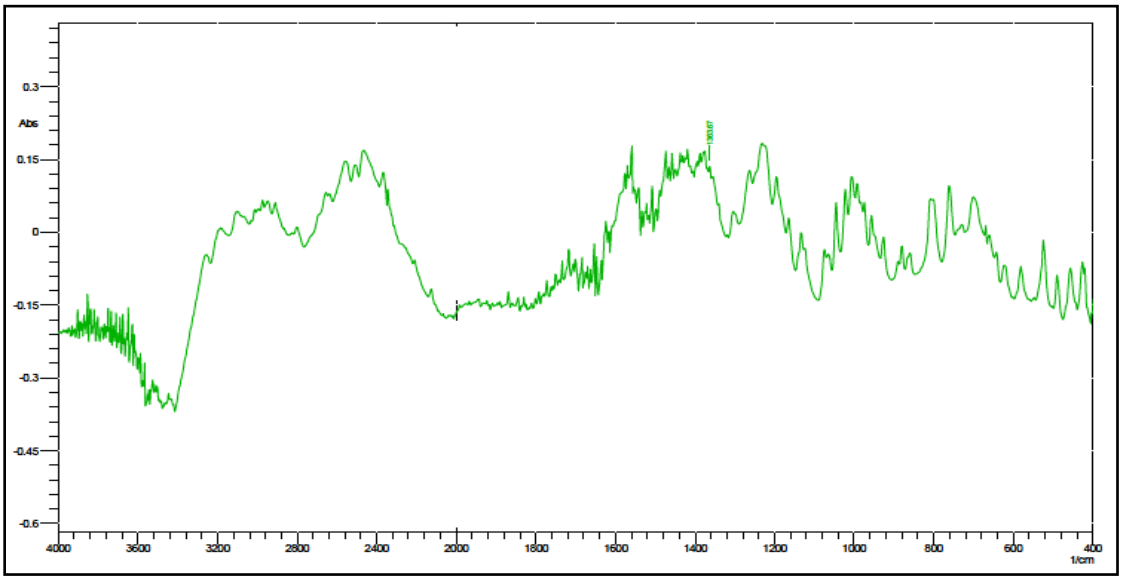

Fig. 17Thermal degradation of RANI

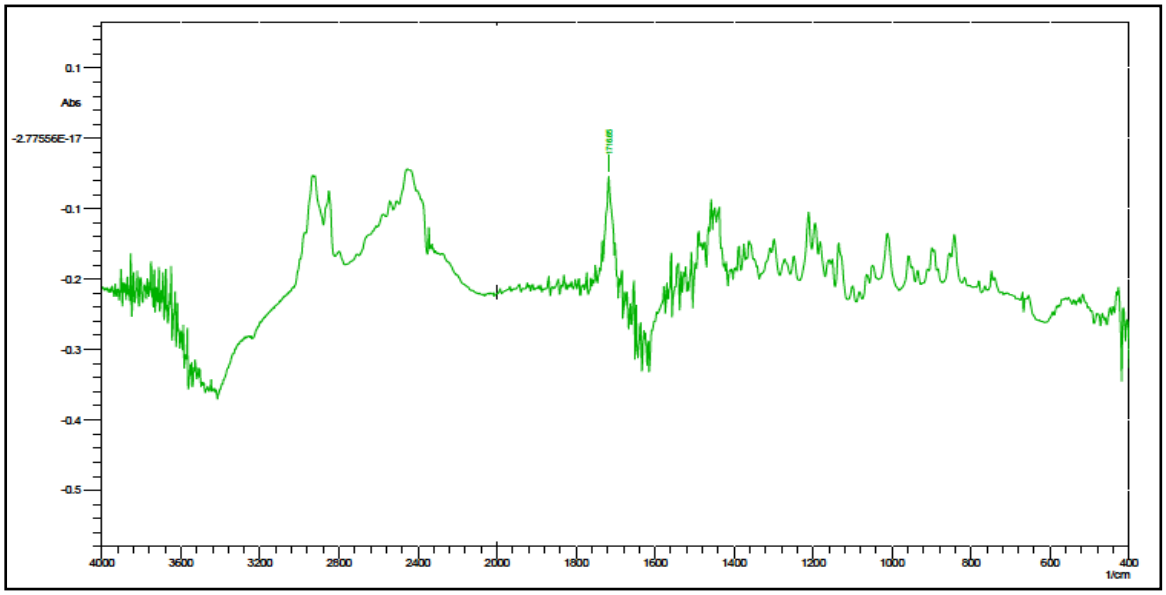

Fig. 18Thermal degradation ofDICY

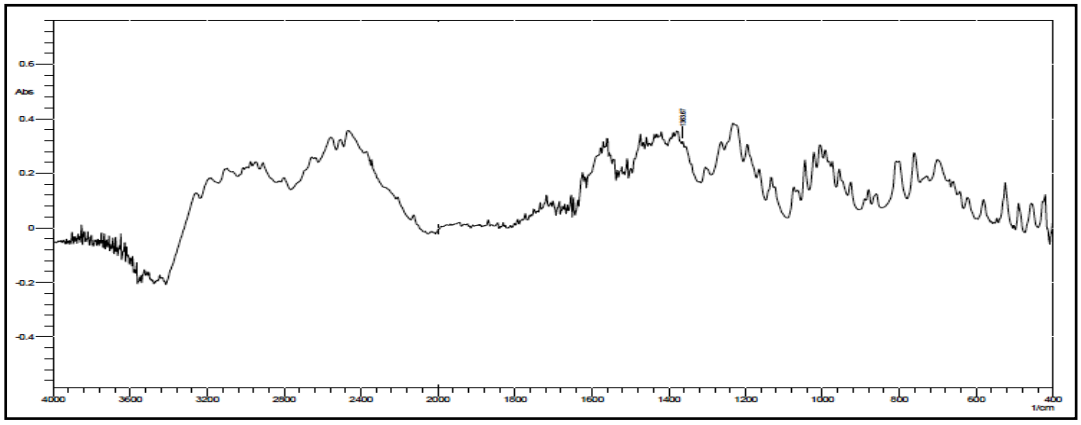

Fig. 19Photolytic degradation of RANI

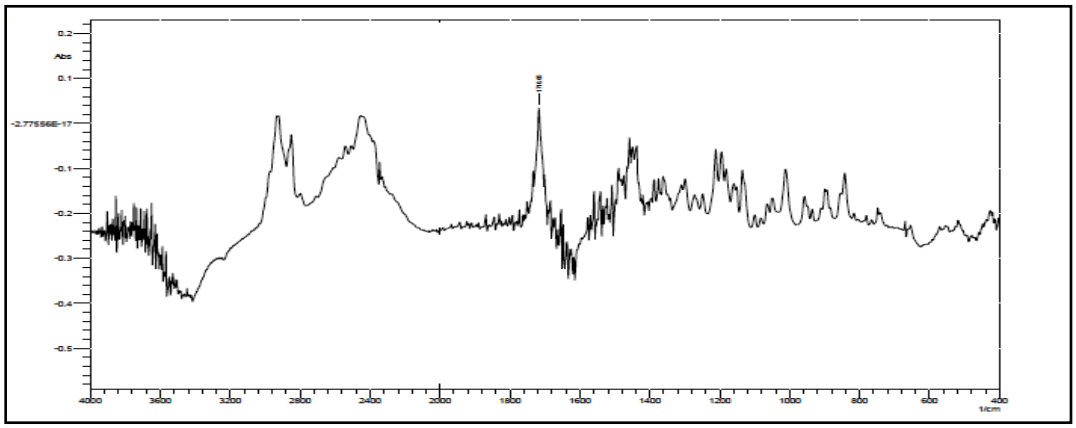

Fig. 20Photolytic degradation ofDICY

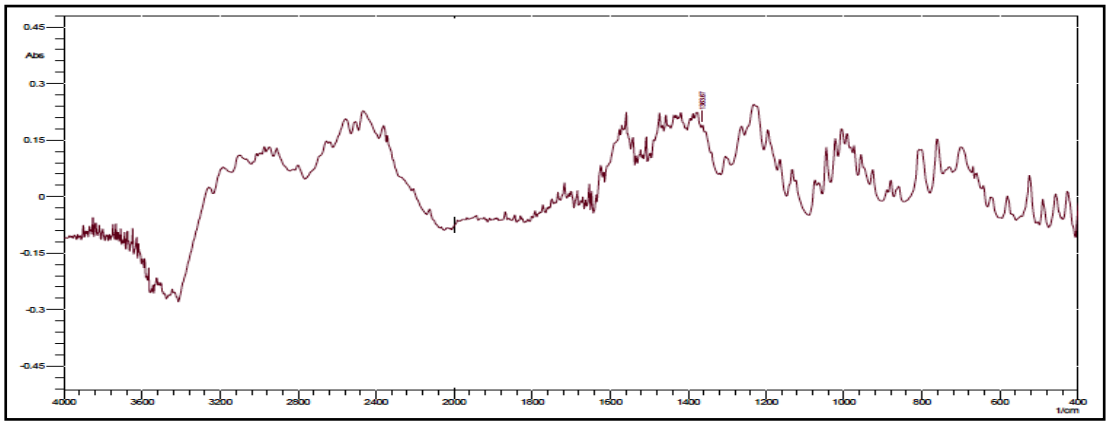

Fig. 21 Degradation of RANI in sunlight

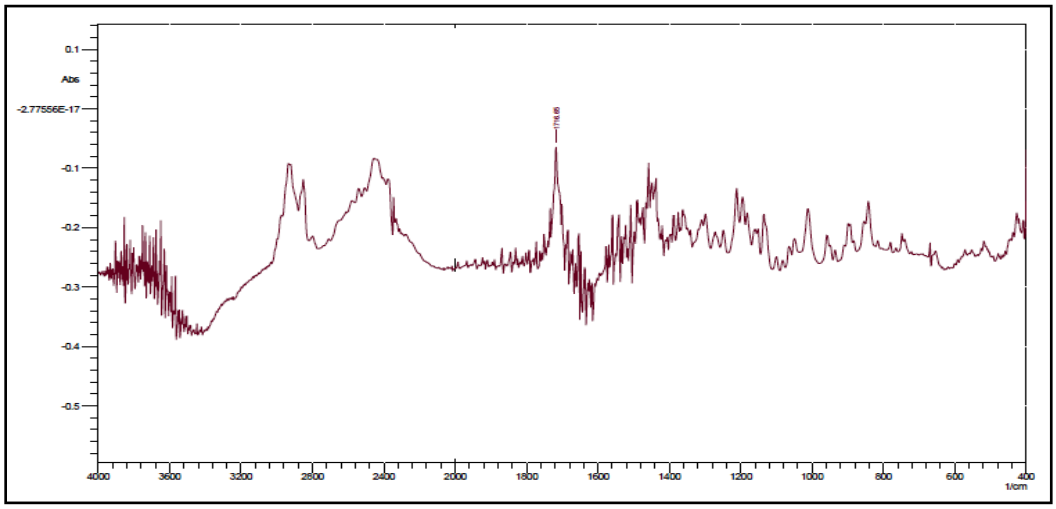

Fig. 22Degradation of DICY in sunlight

Table 6: Force degradation study data

Sr.no.	Condition	% Degradation		% Assay	
		RANI	DICY	RANI	DICY
1	Sunlight degradation (RANI 60 min) and (DICY 30 min)	47.83	25.39	52.17	74.61
2	Photolytic degradation In UV chamber (RANI 60 min) and (DICY 30 min)	78.88	13.88	21.12	86.12
3	Thermal degradation (DICY 30 min) and (RANI 60 min)	32.82	21.42	67.18	78.58

5. RESULTS AND DISCUSSION

Linearity of RANI was found to be 3-18 % w/w while for DICY 0.2-1.2% w/w. The wave numbers selected were in range of 1361 cm^{-1} (Nitro)for RANI and 1716 cm^{-1} (Ester) for DICY. Further precision was calculated as inter and intraday variations and %RSD was less than two. The accuracy of the method was determined by calculating mean percentage recovery it was found to be 99.40, 99.65, 100.08 for RANI of 80%,100%,120% level while for DICY99.20, 100.26, 100.39of 80%, 100%, 120%. LOD value was found to be 0.1062 for RANI while for DICY 0.0096 and LOQ value was found to be 0.3219 for RANI while for DICY0.0292. Forced degradation study was also carried out which involved thermal, photolytic and sunlight degradation.

6. CONCLUSION

The method used was simple, rapid and does not involve the use of complex instruments. The low value of standard deviation shows that the method was precise, high percentage of recovery and accurate as shown in table.Thus from the results, it can be concluded that above developed FT-IR method was suitable for estimation of RANI and DICY in tablet formulation.The estimated method was sensitive, precise, accurate, specific and economic. Hence, the method can be used successfully for quality control and routine analysis of finished pharmaceutical dosage form.

7. ACKNOWLEDGEMENT

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