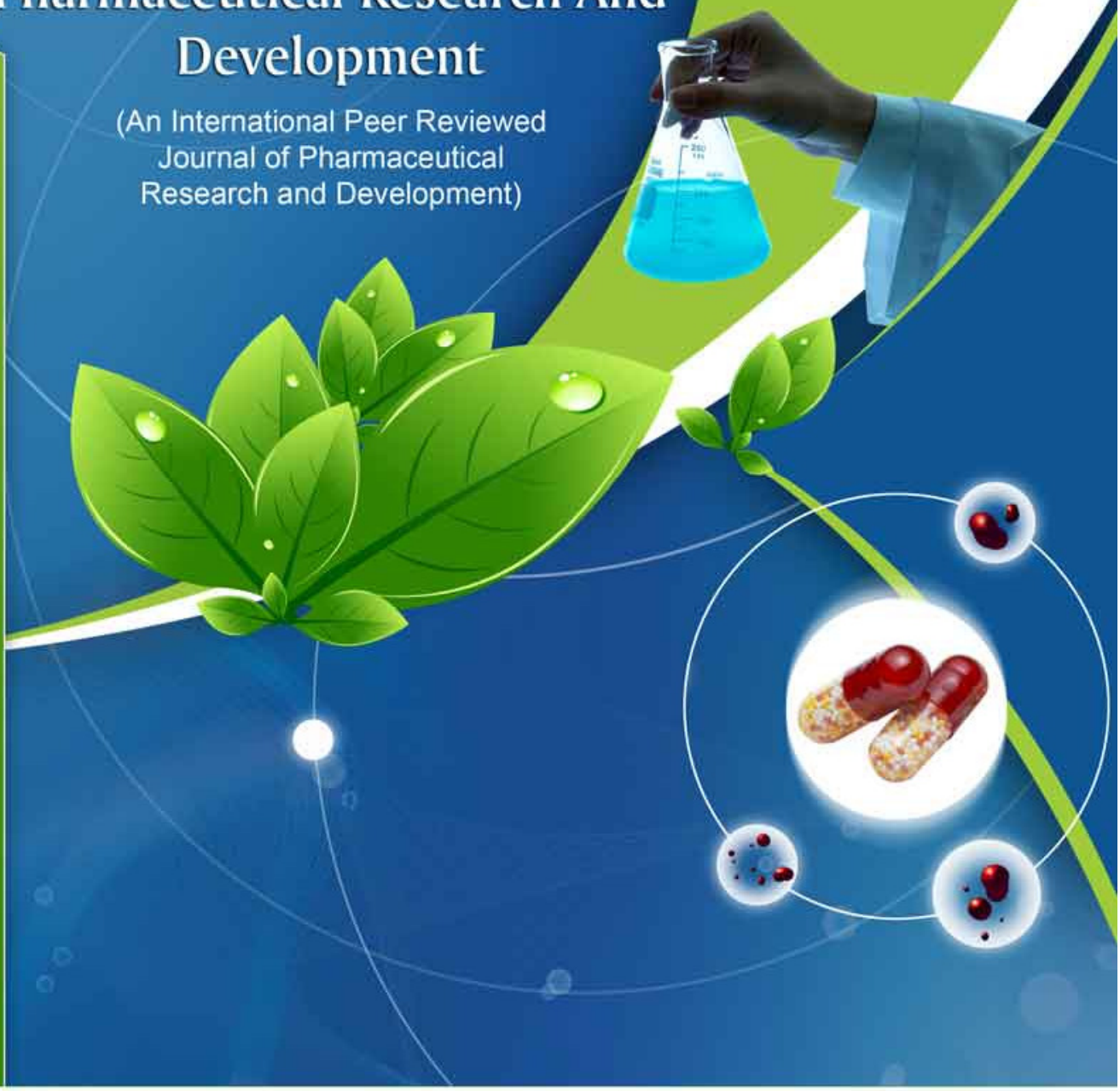
ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD



Volume - 01 Issue - 04 JULY-AUG 2013

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

DEVELOPMENT AND VALIDATION OF STABILITY INDICATING RP-HPLC ASSAY METHOD FOR SIMULTANEOUS ESTIMATION OF RABEPRAZOLE SODIUM AND ACECLOFENAC IN CAPSULE DOSAGE FORM

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Received: 22June 2013, ***Revised and Accepted: 2 July 2013***

ABSTRACT

A simple, rapid, and precise Reverse Phase HPLC method has been developed for determination of Rabeprazole Sodium (RBP sodium) and Aceclofenac (ACE) in combined Dosage form. The RP-HPLC method carried out on Hypersil BDS C18 (150 mm x 4.6 mm, 5µm) as stationary phase by using mobile phase consisting of 0.02M Phosphate buffer (pH 6with orthophosphoric acid) : acetonitrile (67:33). Mobile phase was maintained at a flow rate 1.0 ml/min. The UV detector was operated at 280nm. Retention time was found to be 4.3min for RBP Sodium and 5.9 min for Aceclofenac. The specificity studies shows that the analyte peaks were well resolved from the intermediates. Developed method was found to be linear over the range of 100-300µg/ml and 10-30µg/ml for Aceclofenac and Rabeprazole Sodium respectively; the correlation coefficient was found to be 0.9995 and 0.9995 for Aceclofenac and Rabeprazole Sodium. The precision study showed that the percentage relative standard deviation was within the range of acceptable limits, and the mean recovery was found to be 100.45 % and 99.63 % for Aceclofenac and Rabeprazole Sodium respectively. Statistical analysis proves that the method is reproducible & selective for the estimation of said drug, as the method could effectively separate the drug from its degradation product.

Key words: RP-HPLC, Rabeprazole Sodium, UV detector, Aceclofenac

INTRODUCTION

Rabeprazole sodium is a Proton Pump Inhibitor having the chemical name of 2-[4-methoxypropoxy3methyl- 2-pyridinyl]- methyl] sulfinyl]-1- H-benzimidazole Sodium[1].The chemical structure given in Fig. No.1. The use of Rabeprazole sodium is Proton Pump Inhibitor [3,4,5]. Another active component of the combination is Aceclofenac, with anti-inflammatory activity having the chemical name {[2-(2', 6'-dichlorophenyl) amino] phenyl acetoxyacetic acid}[2] .The chemical structure is given in Fig. 2. Such a combination is used an antacid and pain relief. Literature survey revealed that various analytical methods have been published for determination of Rabeprazole sodium such as UV[6,7],HPLC[8,9,10,11] and for determination of Aceclofenac in bulk & tablet dosage form single or in combination by HPLC[12,13,14,15] and UV[16] method are found. So far, no stability indicating RP-HPLC assay method has been reported for combination drug product of Aceclofenac& Rabeprazole sodium . Therefore, it was

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proposed necessary to a new rapid and stability-indicating method for simultaneous determination of aceclofenac& Rabeprazole sodium in its capsule dosage form and to validate the Proposed method as per ICH guidelines[17].

EXPERIMENTAL PROCEDURE

Reagents & Materials

The active pharmaceutical ingredients Aceclofenac and Rabeprazole sodium were supplied by Elder Pharma Pvt. Ltd. and Capsule (Label claim: 20µg/capsule of Rabeprazole sodium& 200µg/capsule of Aceclofenac, Product name: Altraday capsule & Manufacturer: Ranbaxy Healthcare) were procured from the market. HPLC grade Acetonitrile, ,Methanol were obtained from Merck specialties Pvt. Ltd,). HPLC system of Waters-alliance instrument equipped with Empower software, inbuilt solvent degasser system, quaternary pump and photodiode array detector with variable injector and auto sampler was used. Column used was Hypersil C18 (150 x 4.6 mm, 5µm) G.L. Science Inc. Japan.

CHROMATOGRAPHIC CONDITIONS

Chromatographic separation was achieved at ambient temperature on a reversed phase column using mobile phase consisting of mixture of dipotassium hydrogen phoshphate buffer pH 6.0 (6.9672g dipotassium hydrogen phoshphate buffer in 2 lit. purified water) & Acetonitrile in the ratio of 67:33' the pH of mobile phase was adjusted to 6.0 ± 0.1 with Ortho phosphoric acid at a flow rate maintained at 1 ml/min. and detection was carried out at 280nm.Diluent-(methanol (80) : water (20) : diethyl amine (0.1) .The injection volume was 20 µl for assay and degradation level.

PREPARATION OF STANDARD SOLUTIONS

Preparation of standard stock solution

Weighed of 200.0 mg of Aceclofenac was dissolved in diluent (methanol (80): water (20): diethyl amine (0.1) and volume was made up to 100.0 ml with same solvent. A 5.0 ml of resultant solution was diluted to 50.0 ml with mobile phase to give a solution of aceclofenac (Concentration 200 µg/ml). Similarly 20.0 mg of RBP Sodium was dissolved in diluent (methanol (80): water (20) : diethyl amine (0.1) and diluted to 100.0 ml. A 5.0 ml of resultant solution was diluted to 50.0 ml with diluents (Concentration 20 µg/ml).

Working standard preparation

An accurately weighed quantity of ACF (200.0 mg) and RBP Sodium (20.0 mg) were transferred to 100.0 ml volumetric flask and dissolved in about 50.0 ml diluent and the volume was made up to the mark with diluent (methanol (80) : water (20) : diethyl amine (0.1).

Working mixed standard solution

From the above solution 5.0 ml was further diluted to 50.0 ml by diluent (methanol (80) : water (20) : diethyl amine (0.1) to get concentration of 200 µg/ml and 20 µg/ml for ACF and RBP Sodium respectively.

ANALYSIS OF MARKETED FORMULATION

Twenty capsules were weighed and the pellets were removed and crushed to obtain fine powder. An accurately weighed quantity of pellet powder equivalent to 200 mg ACF and 20 mg RBP Sodium was transferred into 100.0 ml volumetric flasks, 60 ml of diluent was added and ultrasonicated for 10 minutes and diluted up to the mark with same solvent the solution was mixed and filtered through 0.45 µ membrane filter. The filtrate was further diluted with diluent to obtain final concentration of 200 µg/ml ACF and 20 µg/ml RBP Sodium. The diluted solution (20 µl) was injected into the column and chromatographed using optimized chromatographic conditions. The corresponding chromatograms were recorded and area of each peak for ACF and RBP Sodium was measured at 280.0 nm. Each sample solution was chromatographed in triplicate and the mean peak area for ACF and RBP Sodium was calculated. Sample solutions chromatogram are shown in Fig. No.3.and results of assay method shown in (Tablel. 9)

Amount of drug estimated in mg/tablet and percent label claim was calculated using following formula:

$$\text{Content of drug in sample (mg/cap.)} = \frac{PA_{Spl}}{PA_{Std}} \times \frac{\text{Weight of std. (mg)}}{d_f} \times \frac{\text{Avg. Weight of capsule}}{\text{Powder taken (mg)}} \times \text{capsule (mg)}$$

Where, PA_{Spl} - Peak area of sample,
PA_{Std} - Peak area of standard,
d_f - Dilution factor.

Percent label claim was calculated using formula:

$$\text{Percent label claim} = \frac{\text{Content of drug in sample}}{\text{Label claim}} \times 100$$

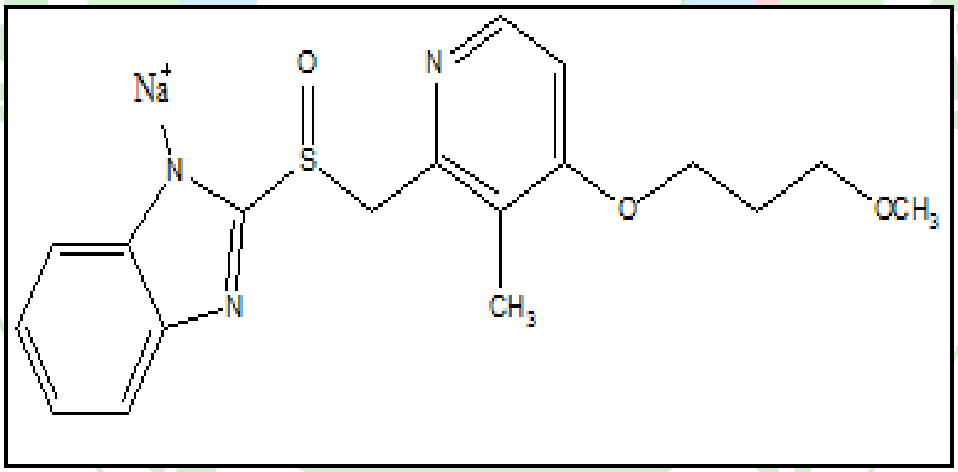

Fig. 1: chemical structure of RBP Sodium

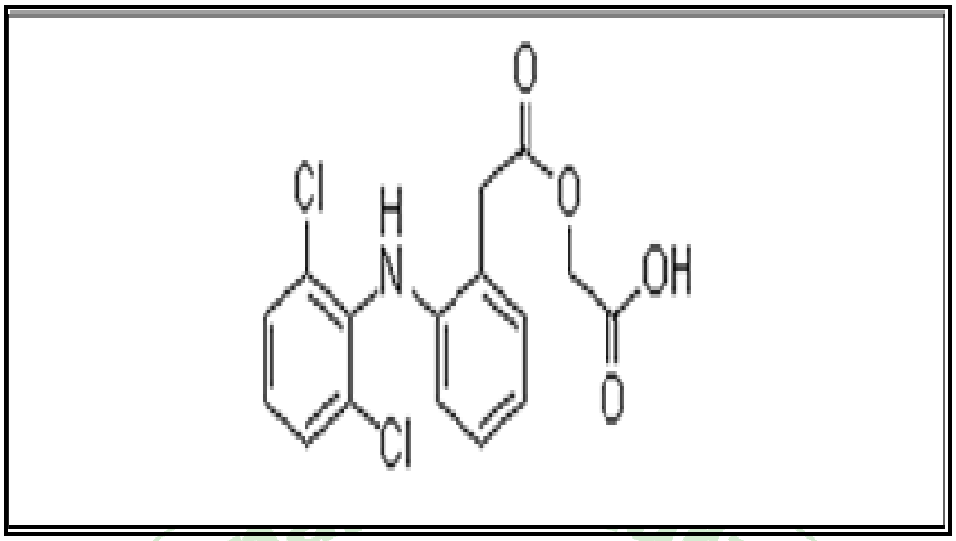

Fig. 2: chemical structure of Aceclofenac

Table 9: Assay results for analysis of marketed formulation

Component	*Label claim (mg)*	*Retention Time*	*Average Area*	*S.D.*	*% R.S.D.*	*% Assay*
Aceclofenac	200	5.6	5968580	35378	0.6	100.99
Rabeprazole sodium	20	4.3	717189	10856	1.5	99.48

FORCED DEGRADATION STUDIES

Acid Hydrolysis

The 450 mg of sample was taken in each of three 100 ml volumetric flasks. Then 50 ml of diluents was added them. Samples were allowed completely mix into the diluent. 1 ml each of 0.01 M HCl, 0.1 M HCl, 1 M HCl were added in first, second and third volumetric flask simultaneously. The volumetric flasks were kept aside for 1 hr. After 1 hr 0.01 M NaOH, 0.1 M NaOH, 1 M NaOH were added in simultaneous manner into the volumetric flasks for neutralization of sample solution. Then volume made up to the mark with diluent. After that 5ml of the above solutions were diluted upto 50 ml. So as to obtain the working standard of 200 µg/ml (ACE) & 20 µg/ml (RBP Sodium) and subjected to HPLC analysis[11].

Base hydrolysis

The 450 mg of sample was taken in each of three 100 ml volumetric flasks. Then 50 ml of diluents was added them. Samples were allowed completely mix into the diluent. 1 ml each of 0.01 M NaOH, 0.1 M NaOH, 1 M NaOH were added in first, second and third volumetric flask simultaneously. The volumetric flasks were kept aside for 1 hr. After 1 hr to that solutions 0.01 M HCl, 0.1 M HCl, 1 M HCl were added in simultaneous manner into the volumetric flasks for neutralization of sample solution. Then volume made up to the mark with diluent. After that 5ml of the above solutions were diluted upto 50 ml. So as to obtain the working standard of 200 µg/ml (ACE) & 20 µg/ml (RBP Sodium) and subjected to HPLC analysis.

Peroxide degradation (H2O2 30 % w/v)

The 450 mg of sample was taken into the 100 ml volumetric flask. Then added 50 ml of diluent and mixed well. Then 1 ml H2O2 was added into the volumetric flask. After that volumetric flask was kept aside for 1 hr. Further volume made up to 100 ml of volumetric flask. Then 5ml of the above solution was diluted upto 50ml So as to obtain the working standard of 200 µg/ml (ACE) & 20 µg/ml (RBP Sodium) and subjected to HPLC analysis.

UV light degradation (UV chamber)

The 450 mg sample was kept UV chamber for 24 hr. After this was transfer to volumetric flask. Allowed dissolved with the diluents. Then volume was made upto 100 ml of volumetric flask. From that solution 5 ml of were taken into 50 ml of volumetric flask and volume was made upto 50 ml of diluent. So as to obtain the working standard of 200 µg/ml (ACE) & 20 µg/ml (RBP Sodium) and subjected to HPLC analysis.

Thermal degradation

The 450 mg of sample was kept in c at 105 ˚C in hot air oven for 24 hr. Then 450 mg were taken from this sample into the 100 ml of volumetric flask. Diluent was added to dissolve the sample completely into diluent. Volume was made upto 100 ml . Then 5 ml of this solution was taken into 50 ml of volumetric flask volume was made upto 50 ml with diluent. So as to obtain the working standard of 200 µg/ml (ACE) & 20 µg/ml (RBP Sodium) and subjected to HPLC analysis.

RESULTS AND DISCUSSION

HPLC method development and optimization

Optimization of the chromatographic conditions in order to develop stability indicating assay method for the simultaneous estimation of Aceclofenac (ACE) & Rabeprazole sodium (RBP) was found to be a challenging task because of their combination ratio of approximately 200;20. Wavelength of detection selected to be 280 nm from overlaid spectrum of ACE & RBP. Diluents is selected upon solubility of both drugs -(methanol (80) : water (20) : diethyl amine (0.1) . Two chromatographic columns were tried such as Hypersil BDS-C18 (150 x 4.6 mm, 5µm), Hypersil BDS-C18 (250 x 4.6 mm, 5µm), and different mobile phases (containing buffers like Dipotassium hydrogen phosphate,) like Buffers (pH 6-7): Acetonitrile, Acetonitrile:Water, Methanol:Water, in different composition by isocratic elution. The chromatographic separation was achieved using C18 (150 x 4.6 mm, 5µm) column with isocratic elution having mobile phase composition containing 0.02 M buffer pH 6.0 & Acetonitrile in the ratio of 67:33 gave good peak shape, resolution and theoretical plates with less than 2% tailing factor. Chromatogram is shown in Fig. No. 3.

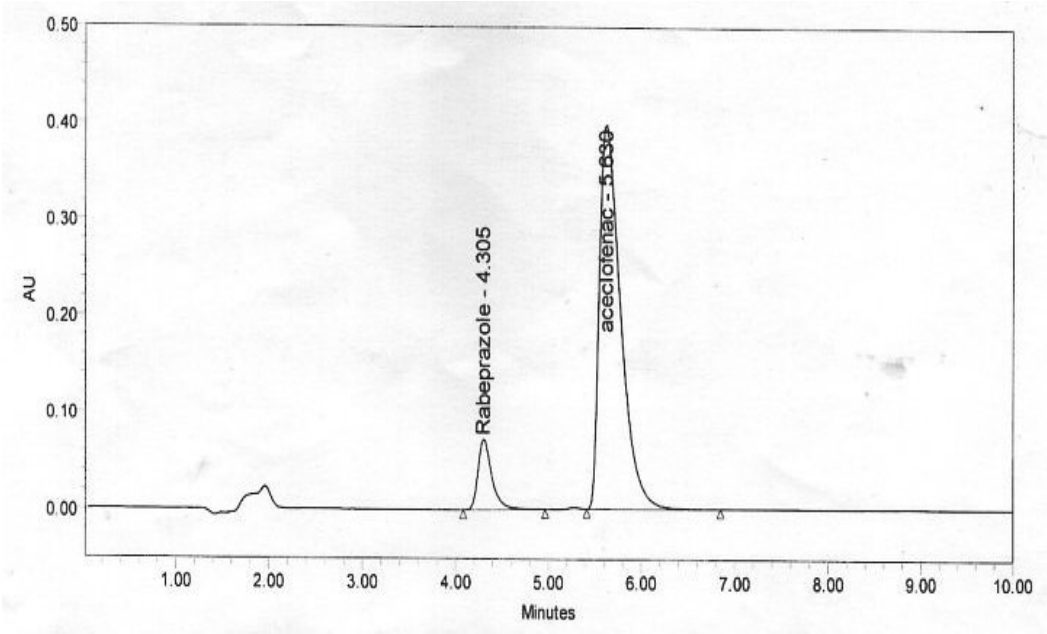

Fig.3: Typical chromatogram of Rabeprazole sodium & Aceclofenac sample solution

Forced degradation study:

The sample solution containing Rabeprazole sodium &Aceclofenac subjected to acidic stress condition using 0.1 M HCL showed 20.61% degradation of Rabeprazole (fig.No.4) . The sample solution subjected to degradation by basic condtion using 1M NAOH for 1hr showed 48 .79% degradation of both drugs (fig.No.5). When subjected to degradation by using 30% H2O2 for 1hr in which Aceclofenac shows 1.77% degradation (fig.No.6). Similarly the sample solution on thermal degradation showed degradation of 0.60% (fig.No.7). And on photolytic degradation by exposure to UV radiation showed 0.59% degradation (fig.No.8).

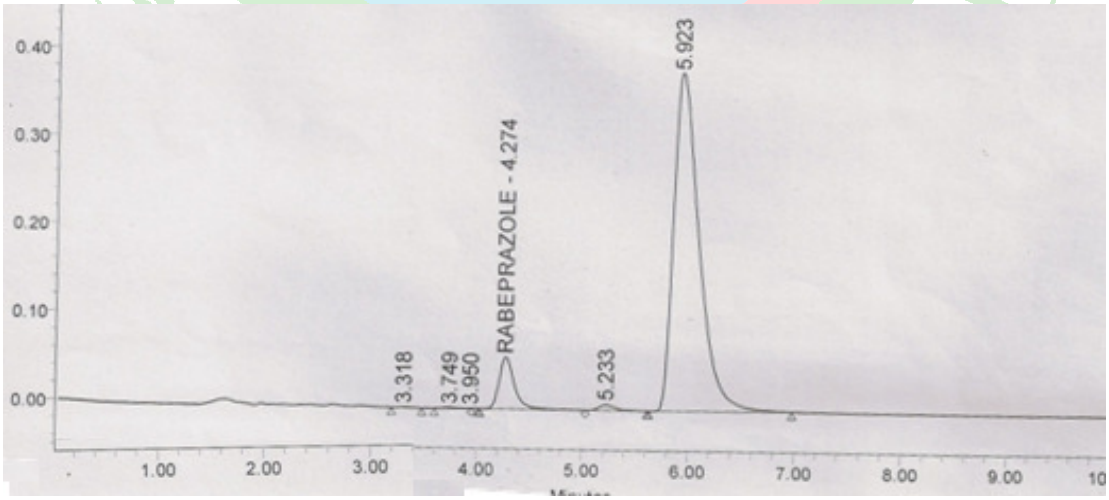

Fig.4: Acid Hydrolysis for 1 hour in 0.1M HCl

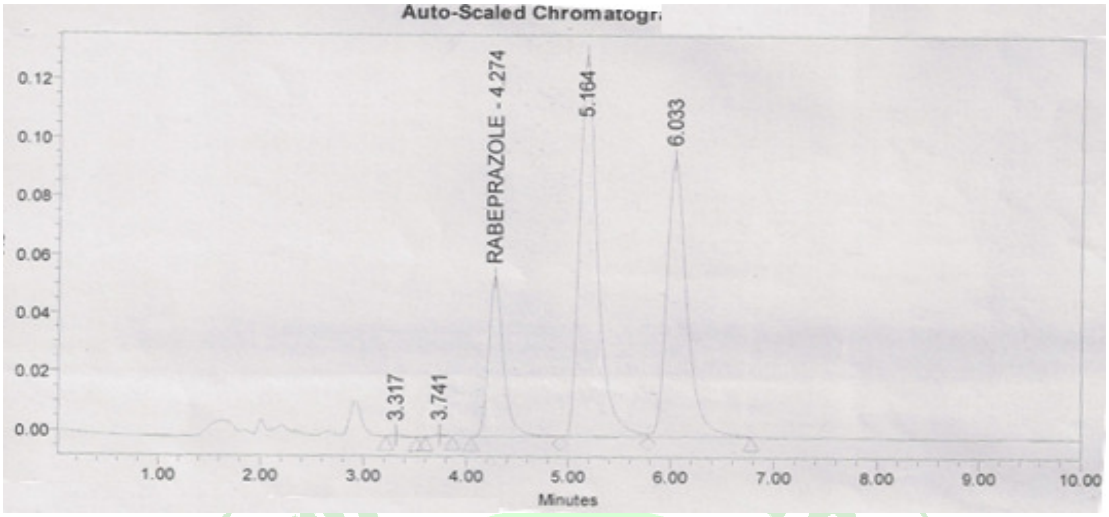

Fig. 5: Base Hydrolysis for 1 hr in 1M NaOH

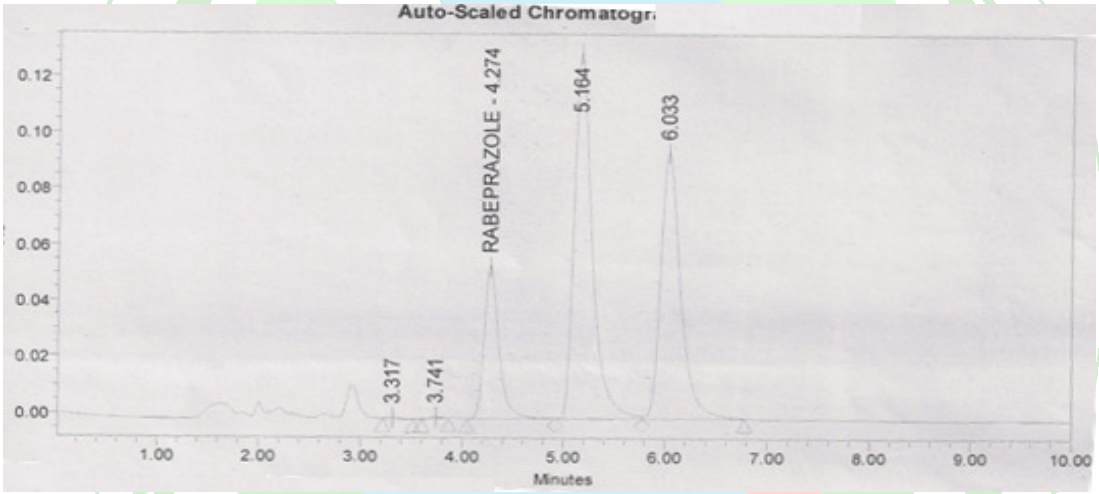

Fig. 6: Oxidation for 1hr minutes in 30% H_2O_2

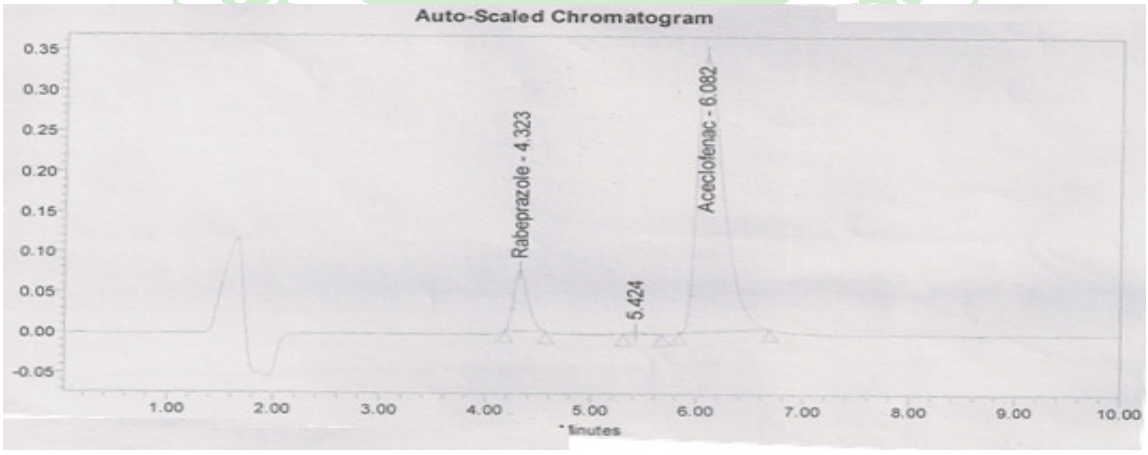

Fig. 7: Thermal degradation for 24 hours

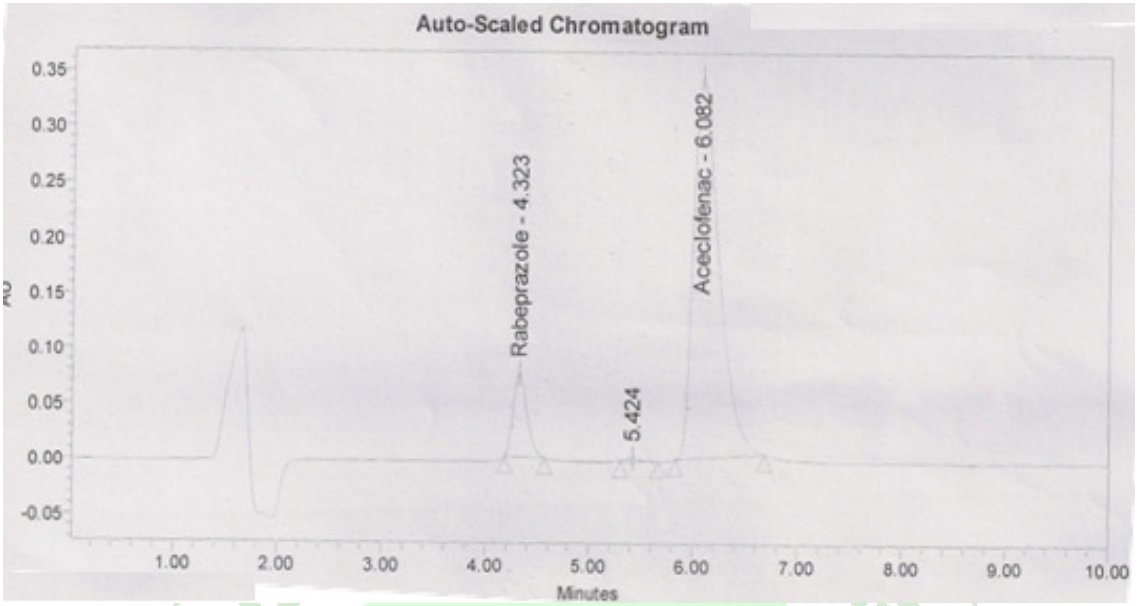

Fig.8: Photolytic degradation by exposure to UV radiations for 12 hours

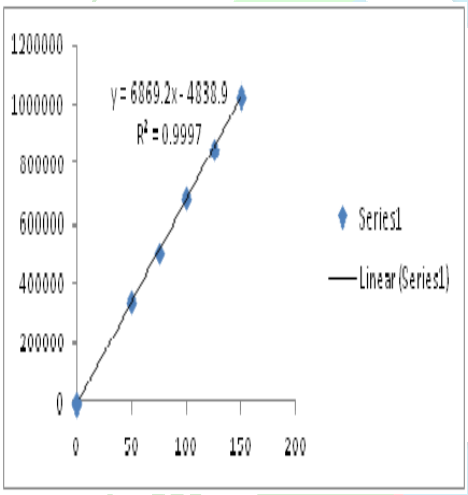

Fig. 9: Linearity plot for Rabeprazole Sodium

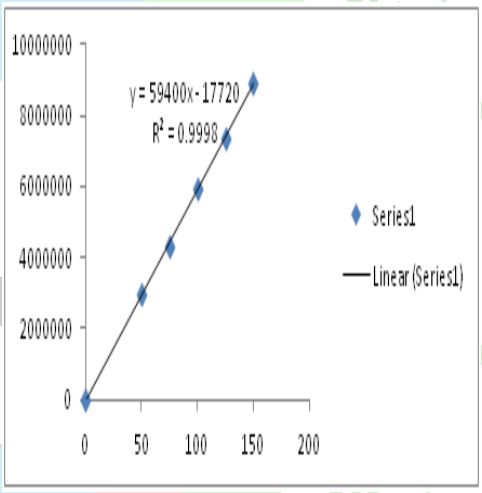

Fig. 10: Linearity plot for Aceclofenac

VALIDATION OF THE METHOD

The method was validated with respect to following parameters.

linearity

Linearity of the proposed method was carried out over the range of 50 % to 150 % of samples assay concentration (200 µg/ml and 20 µg/ml for Aceclofenac and Rabeprazole Sodium, respectively) and the linearity plots were recorded in fig 9 & 10. Table No1 shows the result for the linearity of the proposed method. The calibration curve was prepared by the plot of concentration against the peak area counts. The slope, intercept and regression coefficient are as shown in Table 1. The results indicated that the method is linear in the concentration range of 100-300µg/ml for Aceclofenac and 10-30 µg/ml for Rabeprazole Sodium, respectively[13].

Table 1: The linearity levels for Aceclofenac and Rabeprazole Sodium.

Sr. No	*ACF Conc. µg/ml*	*ACF Area*	*RBP Sodium Conc. µg/ml*	*RBP Sodium Area*
1	100	2985909	10	339981
2	150	4340942	15	497396
3	200	5948976	20	684496
4	250	7402087	25	853195
5	300	8915780	30	1030413
Slope		29842		34733
Intercept		49616		13569
Correlation Coefficient		0.9995		0.9995

Precision

System precision (Repeatability)

The system precision was checked by using standard chemical substance to ensure that the analytical system is working properly. The retention time, number of theoretical plates, tailing factor and area of six determinations of standard preparation were measured and % RSD was calculated. It is observed from the data tabulated in Table 2, that the Rt and area response are consistent as evidenced by the values of RSD. Hence, it can be concluded that the system precision parameter meets the requirement of method validation.

Table 2: The results of the system precision

	ACF				*RBP Sodium*			
Inj. No.	*Area*	*Rt (Min)*	*Theoretical Plate/meter*	*Tailing Factor*	*Area*	*Rt (Min)*	*Theoreticl Plate/metr*	*Tailing Factor*
1	6258130	5.63	2945	1.84	739101	4.30	4384.78	1.42
2	6178566	5.62	2955	1.81	722927	4.30	4390.1	1.45
3	6185420	5.61	2940	1.79	730662	4.30	4381.46	1.4
4	6194966	5.61	2945	1.8	741408	4.30	4385.25	1.41
5	6168152	5.62	2953	1.82	734665	4.30	4389.65	1.46
6	6204780	5.63	2954	1.83	741461	4.30	4386.12	1.44
Mean	6198335	5.6	-	-	735037	4.3	-	-
RSD	0.51	0.16	-	-	0.98	0.04	-	-

Method precision (Reproducibility)

To perform this parameter of validation study homogenous sample of a single batch was analyzed six times. This indicates whether a method is giving consistent results for a single batch. For assay, the sample of Aceclofenac and Rabeprazole Sodium capsule were analyzed six times of a same batch as per analytical procedure. The assay for the same was calculated against standard preparation and the % RSD was calculated. The results

tabulated in Table 3 shows that method is precise as the % RSD for assay value were found to be 0.54 % and 0.52 % for Aceclofenac and Rabeprazole Sodium respectively.

Table 3: The results of the method precision.

	ACF	*RBP Sodium*
Set No.	***% Assay***	***% Assay***
1	100.43	99.45
2	100.66	99.26
3	101.41	99.53
4	101.53	99.45
5	100.98	99.18
6	100.13	100.62
Mean	100.85	99.58
RSD	0.54	0.52

Intermediate Precision (Ruggedness)

The procedure followed for assay method in method precision was repeated on two different days, by two different analysts, using two different columns and using two different HPLC systems. The Intermediate precision of the proposed method and % RSD for inter-day condition were found to be 0.54 % and 0.62% for Aceclofenac and 0.52 % and 0.57 % for Rabeprazole Sodium in standard preparation in case of analyst-I and analyst-II, respectively, which illustrated the reproducibility of the method. The results for comparison of method precision and intermediate precision are shown in Table 4. The acceptance criterion was 2.0 % and the outcomes of the experiments were within the acceptable limits. The method was seen to be rugged and this shows that it complies with the regulatory requirements

.

Table 4: Comparison of method precision and intermediate precision

Parameters	***ACF***	***RBP Sodium***	***ACF***	***RBP Sodium***
Analyst	Analyst 01		Analyst02	
Day	05/07/12		07/07/12	
Instrument	HPLC 01		HPLC 02	
Column	Hypersil BDS C18 003		Hypersil BDS C18 005	
Mean Peak Area	5646748	628351	5686528	635382
% Assay	100.85	99.58	100.45	99.96
% RSD	0.54	0.52	0.62	0.57

Robustness of the method

The robustness of the method was evaluated by varying method parameters such as percent organic content, pH, ionic strength, temperature, etc., and determining the effect on the results of the method. From the results (Table 5), it can be concluded that, the method is robust.

Accuracy

The accuracy of the method was performed by recovery studies. The retention time of Aceclofenac and Rabeprazole Sodium were found to be 4.3min and 5.6 min respectively. The known amount of standard drug was spiked in triplicate to the 50% samples and the recovery of the drug was calculated. The accuracy of the method was calculated at three concentrations such as 100 µg/ml, 200 µg/ml and 300µg/ml for Aceclofenac and 10 µg/ml, 20µg/ml and 30 µg/ml for Rabeprazole Sodium. The recoveries at three different concentrations were found to be 100.61, 100.33 and 100.4 %; with mean % recovery was found to be 100.45 %for Aceclofenac and

99.44, 99.53 and 99.91 %; with mean % recovery was found to be 99.63 % for Rabeprazole Sodium. The %RSD was less in all the three spiked levels. The higher percentage mean recovery indicated that the proposed method was accurate and reliable. The results of recovery experiments of the method are depicted in the Table 6 and Table 7. The chromatogram for 50, 100 and 150 % spiking[16,17].

Table 5: Robustness & Ruggedness results

Parameters	*The Relative Standard Deviation should NMT 2.0 % for 5 replicate injections.*	
	ACF	*RBP Sodium*
Decrease in flow rate	0.33	0.78
Increase in flow rate	0.59	0.43
Decrease in Buffer pH	0.48	1.02
Increase in Buffer pH	0.79	1.15
Decrease in Organic Phase	0.04	0.28
Increase in Organic Phase	0.08	1.85

Table 6: Accuracy of the assay method for Aceclofenac

Sr. No.	*Level (about)*	*Area Response*	*% Recovery*	*Mean % Recovery*	*% RSD*
1	50%	2830357	101.12	100.61	0.49
2		2801846	100.12		
3		2815682	100.6		
4	100%	5263521	100.05	100.33	0.23
5		5399750	100.47		
6		5292546	100.46		
7	150%	8191107	100.39	100.4	0.03
8		8058625	100.44		
9		8091465	100.37		
Across all levels				100.45	0.25

Table 7: Accuracy of the assay method for Rabeprazole Sodium

Sr. No.	*Level (about)*	*Area Response*	*% Recovery*	*Mean % Recovery*	*% RSD*
1	50%	293332	99.63	99.44	0.21
2		294834	99.22		
3		298356	99.46		
4	100%	629532	99.95	99.53	0.40
5		626599	99.48		
6		621451	99.16		
7	150%	952553	99.83	99.91	0.16
8		959995	100.1		
9		943098	99.82		
Across all levels				99.63	0.25

System suitability

The overall system was evaluated for the system suitability of the proposed method. The 10 % asymmetry of Aceclofenac and Rabeprazole Sodium was less than 2.5 which indicated that the peak shape is symmetrical. The high counts of theoretical plates revealed the column efficiency. The % RSD showed that the proposed method is precise. For summary of system suitability studies see Table 8.

Table.8: Summary of system suitability studies of Assay method by HPLC.

System Suitability Parameter	*Observation*		*Acceptance Criteria*
	ACF	*RBP Sodium*	
Tailing factor	1.85	1.42	NMT 2.0
Peak asymmetry (10%)	2.43	1.64	NMT 2.5
Theoretical plates (N)	2943.40	4384.78	NLT 2000
% RSD of 6 injections	0.59	0.98	NMT 2.0

CONCLUSION

A simple, economical, precise and accurate RP-HPLC method for the estimation of Rabeprazole sodium & Aceclofenac has been developed. This method was validated as per ICH guidelines. Results suggest that the developed method can be used for routine quality control studies for assay of Rabeprazole sodium & Aceclofenac in bulk and capsule dosage form.

ACKNOWLEDGEMENT

The authors would like to convey regards to Elder Pharma Pvt. Ltd.,Nerul, Navi Mumbai, for providing the gift sample of the pure drug and Principal, Sinhgad college of Pharmacy, Vadgaon (Bk.), Pune for providing the necessary facilities for carrying out the research work.

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