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DEVELOPMENT AND VALIDATION OF STABILITY INDICATING RP-HPLC METHOD FOR THE SIMULTANEOUS ESTIMATION OF DOLUTEGRAVIR AND RILPIVIRINE BY FORCED DEGRADATION STUDIES

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Keywords:

API, Dolutegravir, Inertsil ODS column, Precision, Forced Degradation, Rilpivirine

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ABSTRACT: Background: Dolutegravir and Rilpivirine are two antiretroviral drugs that have been approved for the treatment of HIV Infection. An error-free, accurate, precise and valid reverse-phase liquid chromatography method was developed for the quantitation of Dolutegravir and Rilpivirine in its bulk form as well as in combined dosage form by forced degradation studies. **Methods:** Chromatographic separation of these two drugs Dolutegravir and Rilpivirine, was achieved with an INERTSIL ODS C18 (250 × 4.6 mm, 5 µm) reverse-phase analytical column with a 10 min analytical run time using a mixture of 0.1% OPA: Acetonitrile in the ratio of (60:40 v/v) as mobile phase. The mobile phase was streamed at a flow rate of 1.0 mL min^{-1} with a column temperature of 250 °C, and detection wavelength was carried out at 230 nm. The retention time was found to be 3.4 min for Dolutegravir and 4.3 min for Rilpivirine. **Results:** The linearity limit of Dolutegravir and Rilpivirine was found to be in the range of 0.999 and 0.999. The method validation was carried out in terms of accuracy, linearity, precision, specificity, LOD, LOQ as per ICH Guidelines. **Conclusion:** The results obtained from the validation parameters show that the method developed can be useful in the quality control test of bulk and combined dosage forms of Dolutegravir and Rilpivirine. Dolutegravir and Rilpivirine were exposed to different stress conditions like acidic, basic, neutral, thermal and peroxide. Amongst all, the drug was found to be more degraded under thermal as well as photodegradation conditions.

INTRODUCTION: Dolutegravir is chemically called as (3S, 7R)-N-[(2, 4-difluorophenyl) methyl]-11-hydroxy-7-methy l-9, 12-dioxo-4-oxa-1, 8-diazatricyclo [8.4.0.03, 8] tetradeca-10, 13-diene-13-carboxamide. **Fig. 1** Dolutegravir is a class of antiretroviral drugs approved for the treatment of the human immune deficiency virus (HIV).

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Dolutegravir is an integrase inhibitor and a class of antiretroviral agent that targets the viral integrase. Dolutegravir can be used only in combination with other antiretroviral drugs. It is associated with a low rate of serum aminotransferase elevations during treatment, but it has no significant effect on acute liver injury[1].

Dolutegravir is an integrase strand transfer inhibitor (INSTI), which is effective against human immunodeficiency virus type 1 (HIV-1) infection. Dolutegravir is an orally bioavailable drug that binds to the active site of integrase; this is an HIV enzyme that catalyzes the transfer of viral genetic material into human chromosomes. This enzyme blocks the strand transfer step and prevents

integrase from binding to retroviral deoxyribonucleic acid (DNA), which is essential for the HIV replication cycle. This enzyme is responsible for preventing HIV-1 replication [2, 3]. Rilpivirine is chemically called as (4-[[4-[4- [(E)-2-cyanoethenyl]-2, 6-dimethylanilino] pyrimidin-2-yl] amino] benzonitrile) **Fig. 2**. Rilpivirine is an antiretroviral drug classified under a non-nucleoside reverse transcriptase inhibitor (NNRTI) which is used in the treatment of HIV-1 infections [4]. Rilpivirine resembles pyrimidine nucleotide found in the DNA; it is a class of diarylpyrimidine derivative [5]. The plasticity and flexibility of rilpivirine interacting binding site give it a very high efficacy and resistance compared to other NNRTI's [6].

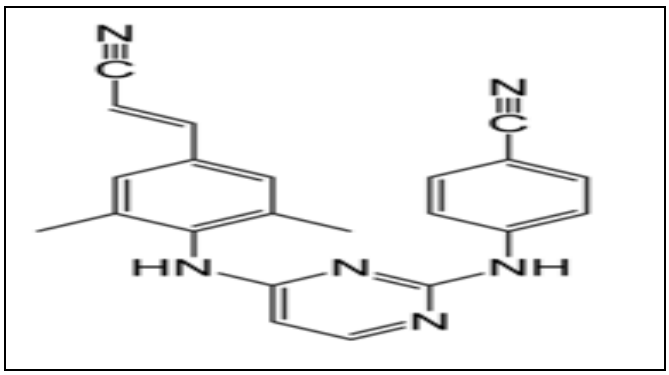

FIG. 1: STRUCTURE OF DOLUTEGRAVIR

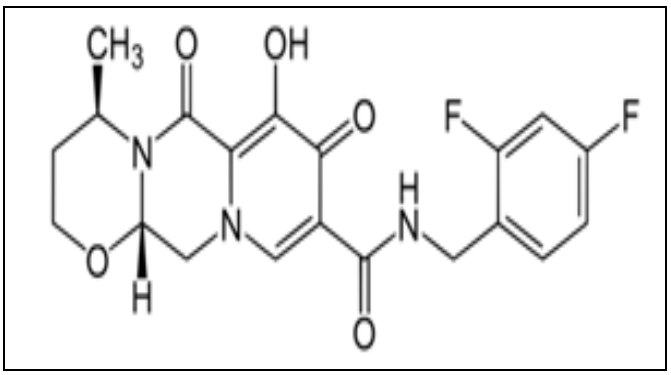

FIG. 2: STRUCTURE OF RILPIVIRINE

From the available literature, we found that only a few analytical methods have been reported for simultaneous determination of Dolutegravir and Rilpivirine by RP-HPLC methods either in single and combined dosage forms, which include UV7, HPLC, 8-15 HPTLC, 16 UPLC, LC-MS, 17-18 and UPLC 19-20 methods. Some analytical methods were found to be less economical in terms of run times, mobile phase composition and column dimensions. Hence, an error-free, accurate, precise and valid reverse-phase liquid chromatography method was developed for the quantitation of Dolutegravir and Rilpivirine in its bulk form and as well as in pharmaceutical dosage form.

MATERIALS AND METHODS:

Instruments Used: HPLC WATERS, software: Empower, 2695 separation module, UV detector. UV/VIS spectrophotometer LABINDIA UV 3000+ pH meter Adwa – AD 1020 Analytical balance Afcoset ER-200A.

Chemicals and Reagents: Potassium dihydrogen phosphate procured from finer chemical ltd AR grade, sodium hydroxide procured from Merck AR grade, hydrochloric acid procured from Merck GR grade, orthophosphoric acid procured from Merck GR grade, hydrogen peroxide procured from Merck GR grade, acetonitrile procured from Merck HPLC grade, water millipore HPLC grade.

Standard Preparation: Dolutegravir 50 mg and Rilpivirine 25 mg were weighed and transferred into a 100 mL volumetric flask. Then 7 mL of diluent was added and sonicated. The volume was made up to the mark with the same solvent. Then 3.0 mL of the above stock solution was transferred into a 10 mL volumetric flask and the volume was adjusted up to the mark with diluent.

Sample Preparation: Dolutegravir 50 mg and Rilpivirine 25 mg were weighed and transferred into a 100 mL volumetric flask and about 7 mL of diluent was added and sonicated. The volume was adjusted up to the mark with the same solvent. It was kept aside for few minutes until the un-dissolved excipient from the tablets gets settled at the bottom of the flask. Slowly the supernatant fluid was collected using a syringe and the solution was filtered with a 0.45 nylon membrane filter, which further removes any excipients present in the solution. Then 3.0 ml of the above stock solution was transferred into a 10 mL volumetric flask, and the volume was adjusted with diluent.

Preparation of OPA Buffer: Orthophosphoric acid 1 ml was taken in a 1000 ml volumetric flask, and the volume was made up with HPLC water and degassed in an ultrasonic water bath for 10 min and then filtered through a 0.45 µ filter under vacuum filtration.

Preparation of Mobile Phase: Accurately measured 600 mL (60%) of the above Buffer and 400 mL (40%) of Acetonitrile were mixed and degassed in an ultrasonic water bath for 10 min and then filtered through 0.45 µ filter under vacuum filtration.

Diluent Preparation: The mobile phase was used as the diluent.

Method Development: Different chromatographic trials were performed with different columns and mobile phases. A number of trials were performed before choosing the chromatographic condition, with different solvents ratios, flow rate and temperatures to check the retention time (RT), peak shape, theoretical plates of the analyte and tailing factor (peak symmetry). The optimized chromatographic is shown in **Fig. 3.**

TABLE 1: CHROMATOGRAPHIC TRIALS

Parameters	Trial 1	Trial 2	Trial 3	Trial 4
Column Used	symmetry, C18 4.6 × 150 mm, 5 µm	Zodiacsil C18 4.6 × 150 mm, 5 µm	Hypersil RPC8 4.5 × 150 mm, 5.0 µm	Zodiac sil RPC18 4.6×250 mm, 5 µm
Mobile phase	MeOH: H_2O (50:50%v/v)	ACN: H_2O (50:50%v/v)	Buffer ACN: pH 6.8 phosphate buffer (50:50)	30% 0.1% OPA buffer: 70% Methanol
Buffer				OPA
Flow rate	1 ml/min	1 ml/min	1 ml/min	1 ml/min
Wavelength	230 nm	230 nm	230 nm	230 nm
Temperature	30 °C	30°C	30 °C	30 °C
Injection Volume	20 µl	20 µl	20 µl	20 µl
Run time	5.0 min	5.0 min	10.0 min	8 min

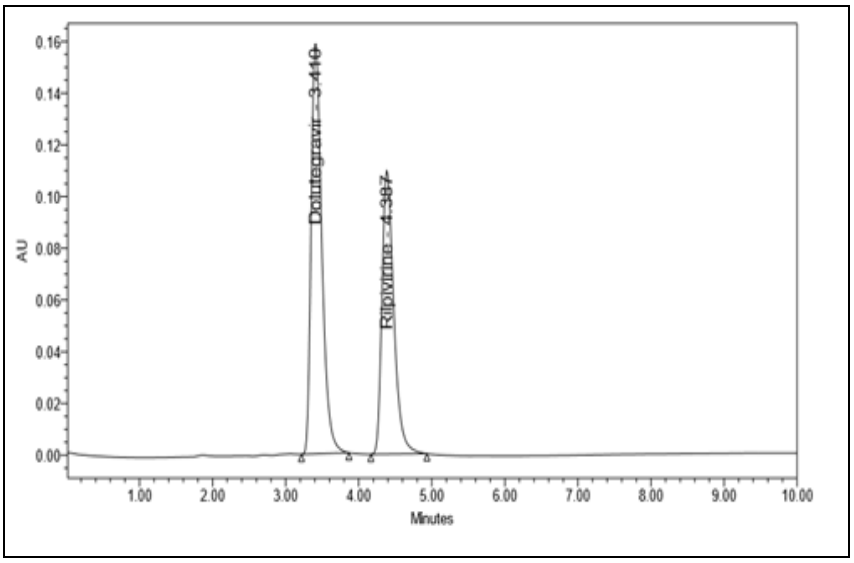

FIG. 3: OPTIMIZED CHROMATOGRAM

Optimized Chromatographic Conditions:

Temperature	:	Ambient (25 °C)
Mode of separation	:	Isocratic mode
Column	:	Inertsil ODS, column (200 × 4.6 mm, 5 µm)
Buffer	:	0.1% OPA
Mobile phase	:	0.1% OPA: Acetonitrile (60: 40)
Flow rate	:	1.0 mL per min
Wavelength	:	230 nm
Injection volume	:	20 µl
Run time	:	10 min.

RESULTS AND DISCUSSION:

Validation:

Precision: Precision is expressed in terms of the degree of agreement between replicate analyses of a homogenous sample, usually measured as the relative standard deviation (RSD). The precision was determined by taking 50 mg of Dolutegravir and 25 mg of Rilpivirine working standards. Both the working standards were transferred into a 100 mL clean, dry volumetric flask and about 7 mL of diluent was added and sonicated to dissolve it completely and the volume was adjusted up to the mark with the same solvent. (Stock solution) then

3.0 ml of the above stock solutions were transferred into a 10 mL volumetric flask and adjusted up to the mark with diluent. The results are summarized for Dolutegravir and Rilpivirine in **Table 2** & **3**

TABLE 1: SUMMARIZED PRECISION RESULTS FOR DOLUTEGRAVIE AND RILPIVIRINE

Injection	RT (Dolutegravir)	Area for Dolutegravir	RT (Rilpivirine)	Area for Rilpivirine
Injection-1	3.410	1610934	4.364	1228406
Injection-2	3.418	1609985	4.373	1223300
Injection-3	3.419	1619309	4.378	1213803
Injection-4	3.423	1608645	4.380	1201667
Injection-5	3.424	1610885	4.388	1228897
Injection-6	3.433	1618951	4.391	1220372
Average		1613118.2		1219407.5
Standard Deviation		4731.4		10327.1
%RSD		0.3		0.8

TABLE 2: SUMMARIZED ID PRECISION RESULTS FOR DOLUTEGRAVIE AND RILPIVIRINE

Injection	RT (Dolutegravir)	Area for Dolutegravir	RT (Rilpivirine)	Area for Rilpivirine
Injection-1	3.409	1604507	4.362	1214125
Injection-2	3.412	1594158	4.376	1210517
Injection-3	3.420	1591505	4.382	1212127
Injection-4	3.422	1601953	4.385	1211539
Injection-5	3.425	1598025	4.391	1219177
Injection-6	3.426	1604821	4.393	1203992
Average		1599161.5		1211912.8
Standard Deviation		5538.0		4950.5
%RSD		0.3		0.4

Specificity: The system suitability for specificity was carried out to determine whether there was any interference of any impurities in the retention time of the analytical peak.

The study was performed by injecting blank and standard into the system. There was no interference of any peak in the blank with the retention time of the analytical peaks.

Accuracy: Accuracy is expressed as the nearness of agreement between the values found and values that are already available. Accuracy can be expressed in terms of closeness between the true value and precision.

It can be determined by using at least a minimum of 3 concentrations and 9 determinations over the specified range. 50 mg of Dolutegravir and 25 mg of Rilpivirine working standard were accurately weighed and transferred into a 100 mL volumetric flask, and about 7 mL of diluent was added and sonicated to dissolve it completely, and the volume was adjusted with the same solvent.

(Stock solution) Further, 3.0 ml of the above stock solutions were transferr**e**d using a pipette into a 10 mL volumetric flask and diluted up to the mark with diluent. The accuracy results for Dolutegravir and Rilpivirine are shown in **Tables 4** & **5.**

TABLE 3: ACCURACY RESULTS FOR DOLUTEGRAVIR

%Concentration (at specification Level)	Area	% RSD	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	809552.3	0.8	25	25.21	100.82	100.39
100%	1611682	0.2	50	50.18	99.36	
150%	2408440.7	0.3	75	74.99	99.98	

TABLE 4: ACCURACY RESULTS FOR RILPIVIRINE

%Concentration (at specification Level)	Area	% RSD	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	617877.7	0.9	12.5	12.59	100.75	100.04
100%	1224225.3	0.1	25	24.95	99.81	
150%	1831657.7	0.3	37.5	37.33	99.55	

Linearity: Linearity may be defined as the capacity of an analytical method to produce outcomes that are directly related to the concentration of an analyte. Linearity was determined by taking 50 mg Dolutegravir, and 25 mg of Rilpivirine working standards both the standards were transferred into a 100 mL volumetric flask and 7 mL of diluent was added and sonicated for 10 min and the volume was adjusted with the same solvent. The linearity results for Dolutegravir & Rilpivirine are shown in Tables 6 & 7 and **Fig. 4** & **5**.

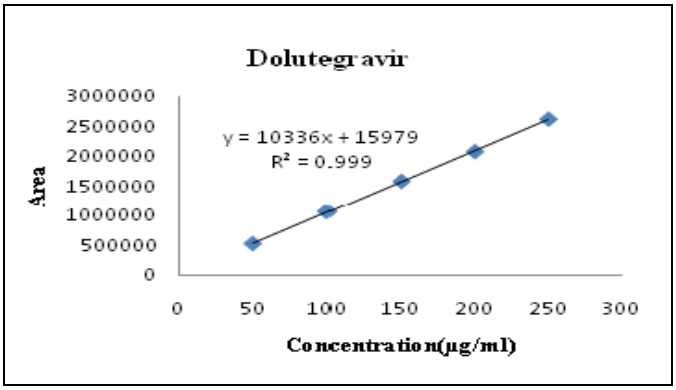

FIG. 4: LINEARITY GRAPH OF DOLUTEGRAVIR

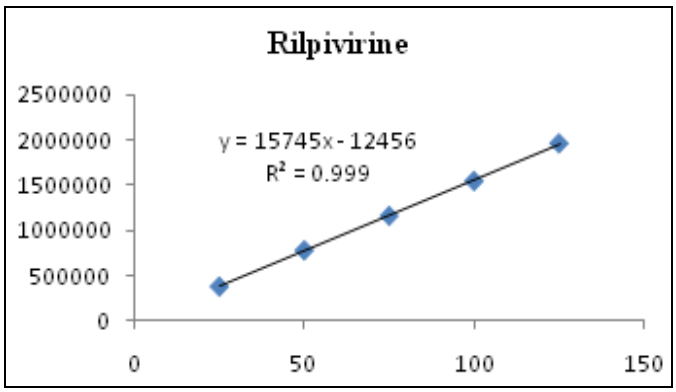

FIG. 5: LINEARITY GRAPH OF RILPIVIRINE

TABLE 5: LINEARITY RESULTS OF DOLUTEGRAVIR

S. No	Linearity Level	Concentration	Area
1	I	50	524876
2	II	100	1059982
3	III	150	1574201
4	IV	200	2068062
5	V	250	2604868
	Correlation Coefficient		0.999

TABLE 6: LINEARITY RESULTS OF RILPIVIRINE

S. no	Linearity Level	Concentration	Area
1	I	25	380761
2	II	50	782401
3	III	75	1164038
4	IV	100	1549472
5	V	125	1965315
	Correlation Coefficient		0.999

Robustness: As part of the robustness, deliberate change in the flow rate, mobile phase composition, temperature variation was made to evaluate the impact on the method. The robustness limit for mobile phase variation and flow rate variation is well within the limit; the % degradation results are in limits.

LOD & LOQ: LOD is expressed in terms of the lowest quantity of an analyte which can be detected by the chromatographical separation. A blank resolution is injected and the quantitative noise and peak-to-peak relation can be calculated from blank chromatograms. The limit of quantitation is the concentration level above which the concentration can be estimated with acceptable exactness and precision.

Degradation Studies: The International Conference on Harmonization (ICH) guideline entitled stability testing of new drug substances and products requires that stress testing be carried out to elucidate the inherent stability characteristics of the active substance. The aim of this work was to perform the stress degradation studies on the Dolutegravir and Rilpivirine using the proposed method.

Preparation of stock solution: Dolutegravir 50 mg and 25 mg of Rilpivirine working standards were accurately weighed and transferred into a 100 mL clean dry volumetric flask and about 7 mL of Diluent was added and sonicated to dissolve it completely and volume was adjusted up to the mark with the same solvent. (Stock solution)

Hydrolytic Degradation under Acidic Condition: A stock solution of 3 mL was pipetted out into a 10 mL volumetric flask and 3 mL of 0.1N HCl was added. Then, the volumetric flask was kept at 60 ºC for 24 h and then neutralized with 0.1 N NaOH and volume was made up to 10 ml with diluent. The solution was filtered with 0.44 microns syringe filters and placed in vials.

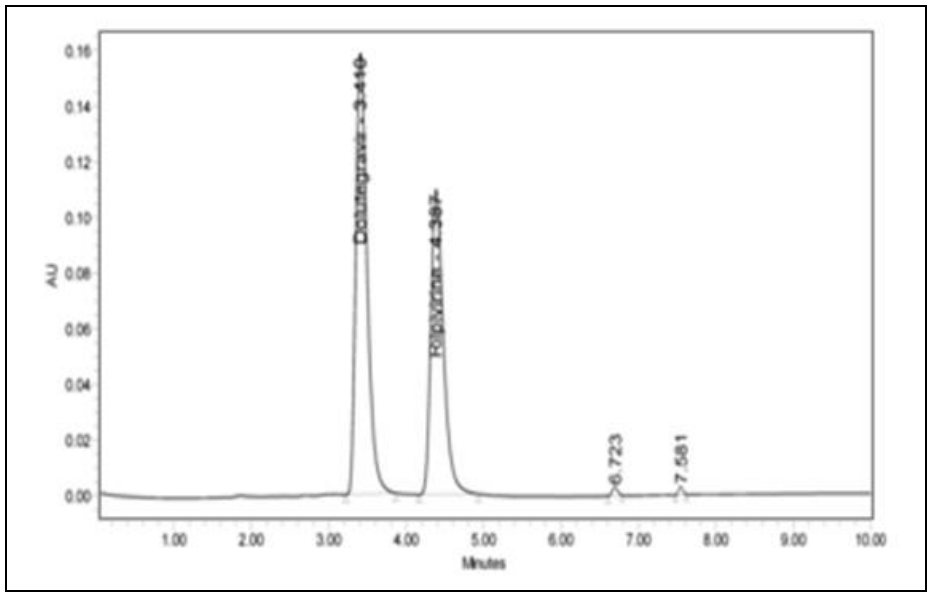

FIG. 6: ACID DEGRADATION CHROMATOGRAM

TABLE 7: ACID DEGRADATION RESULTS OF DOLUTEGRAVIR AND RILPIVIRINE

S. No	Peak Name	RT	Area	Height	USP Resolution	USP Tailing	USP Plate Count
1	Dolutegravir	3.410	1583722	156664		1.42	2657.20
2	Rilpivirine	4.387	1207822	108152	3.52	1.40	3669.74
3		6.723	1243	182	10.47	1.01	9475.45
4		7.581	1417	161	1.06	0.87	2966.35

Hydrolytic Degradation Under Alkaline Condition: Stock solution of 3 mL was pipetted out into a 10 mL volumetric flask, and 3ml of 0.1N NaOH was added in 10 mL volumetric flask. The volumetric flask was kept at 60 ºC for 24 h and neutralized with 0.1N HCl and volume was made up to 10 ml with diluent. The solution was filtered with 0.44 microns syringe filters and placed in vials.

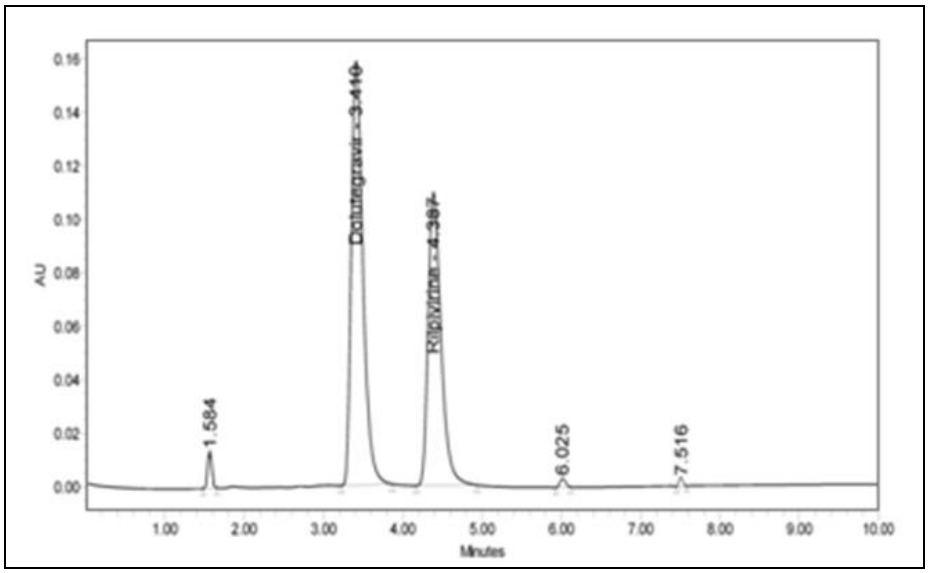

FIG. 7: BASE DEGRADATION CHROMATOGRAM

TABLE 8: ALKALINE DEGRADATION RESULTS OF DOLUTEGRAVIR AND RILPIVIRINE

S. no	Peak Name	RT	Area	Height	USP Resolution	USP Tailing	USP Plate Count
1		1.584	2570	680		1.07	3141.32
2	Dolutegravir	3.410	1528333	151184	8.08	1.42	2657.20
3	Rilpivirine	4.387	1173832	105108	3.52	1.40	3669.74
4		6.025	1137	161	5.87	1.18	4220.48
5		7.516	1053	111	7.31	1.01	6559.29

Thermal Induced Degradation: Dolutegravir and Rilpivirine sample was taken in petridish and kept in Hot air oven at 1100 °C for 3 h. Then the sample was taken and diluted with diluents and injected into HPLC and analyzed.

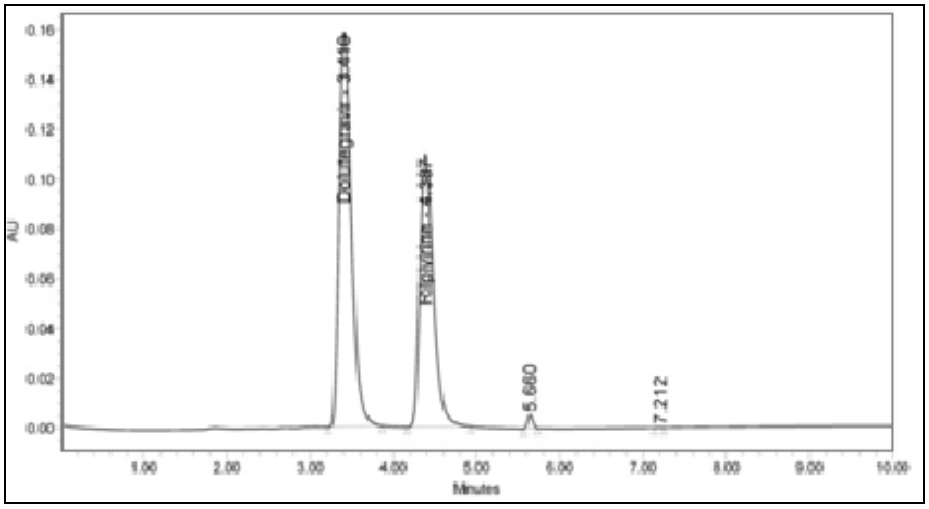

FIG. 8: THERMAL DEGRADATION CHROMATOGRAM

TABLE 9: THERMAL DEGRADATION RESULTS OF DOLUTEGRAVIR AND RILPIVIRINE

S. no	Peak Name	RT	Area	Height	USP Resolution	USP Tailing	USP Plate Count
1	Dolutegravir	3.410	1492533	147643		1.42	2657.20
2	Rilpivirine	4.387	1196732	107159	3.25	1.40	3669.74
3		5.660	1460	190	5.60	0.91	8780.52
4		7.212	1819	215	8.13	0.73	7690.48

Oxidative Degradation: The stock solution of about 3 mL was pipetted into a 10 mL volumetric flask, and 1 mL of 30% w/v of hydrogen peroxide was added in 10 mL volumetric flask and the volume was made up to the mark with diluent. The volumetric flask was then kept at room temperature for 15 min. The solution was filtered with 0.45 microns syringe filters and place in vials.

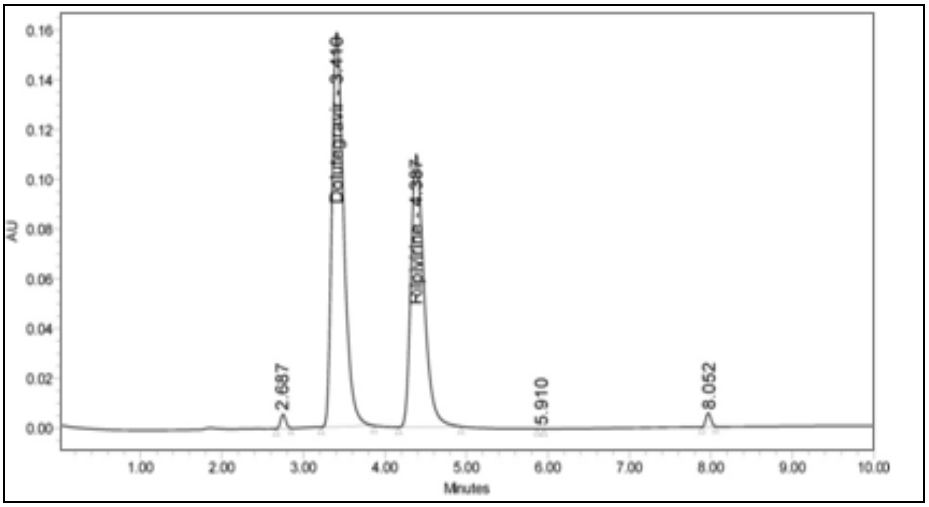

FIG. 9: OXIDATIVE DEGRADATION CHROMATOGRAM

TABLE 10: OXIDATIVE DEGRADATION RESULTS OF DOLUTEGRAVIR AND RILPIVIRINE

S. no	Peak Name	RT	Area	Height	USP Resolution	USP Tailing	USP Plate Count
1		2.687	2229	212		1.51	3424.52
2	Dolutegravir	3.410	1558673	154186	3.23	1.42	2657.20
3	Rilpivirine	4.387	1146223	102636	3.52	1.40	3669.74
4		5.910	1113	171	8.35	0.96	8299.87
5		8.052	1216	182	13.38	0.49	7297.85

Photo Degradation: About 3 ml of the stock solution was pipetted out into a 10 mL volumetric flask and exposed to sunlight for 24 h and the volume was made up to the mark with diluent. The solution was filtered with 0.45 microns syringe filters and place in vials.

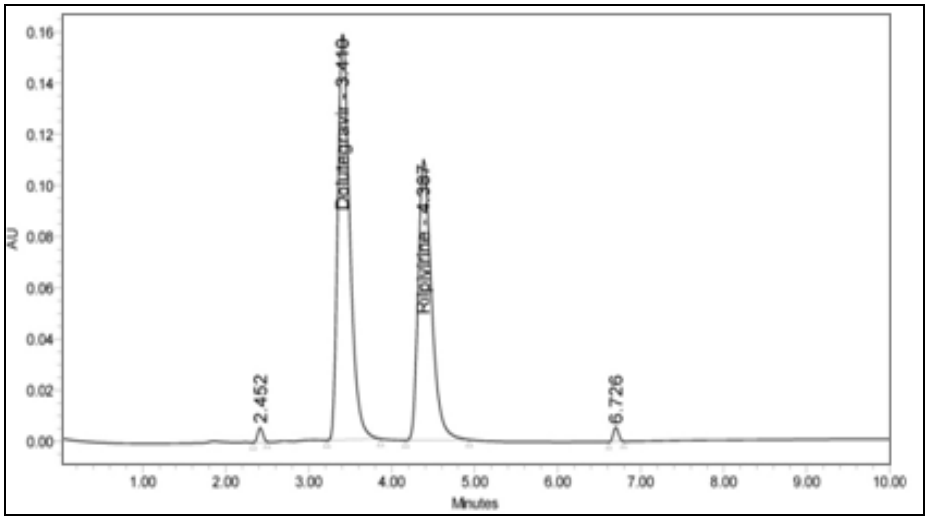

FIG. 10: PHOTODEGRADATION CHROMATOGRAM

TABLE 11: PHOTODEGRADATION RESULTS OF DOLUTEGRAVIR AND RILPIVIRINE

S. no	Peak Name	RT	Area	Height	USP Resolution	USP Tailing	USP Plate Count
1		2.452	1286	170		0.86	7322.54
2	Dolutegravir	3.410	1509356	149307	5.05	1.42	2657.20
3	Rilpivirine	4.387	1127897	100995	3.52	1.40	3669.74
4		6.726	1167	162	11.40	0.79	4664.85

TABLE 12: DEGRADATION RESULTS OF DOLUTEGRAVIR AND RILPIVIRINE

	Dolutegravir		Rilpivirine	
Sample Name	Area	% Degraded	Area	% Degraded
Standard	1602702		1224118	
Acid	1583722	1.18	1207822	1.33
Base	1528333	4.64	1173832	4.11
Peroxide	1558673	2.75	1146223	6.36
Thermal	1492533	6.87	1196732	2.24
Photo	1509356	5.82	1127897	7.86

DISCUSSION: A simple, precise and selective RP-HPLC method was developed for the determination of Dolutegravir and Rilpivirine. Chromatographic separation was achieved by using mobile phase consisting of a mixture of 0.1% OPA, of Acetonitrile (60: 40) on Inertsil ODS, column (200 × 4.6 mm, 5 µm) column, with a detection limit of 230 nm. Linearity was observed in the range 50-150 µg /ml for Dolutegravir and 25-125 µg/ml for Rilpivirine for the amount of drugs estimated by the proposed methods were in good agreement with the label claim. The proposed method was validated. The accuracy of the methods was assessed by recovery studies at three different levels. Recovery experiments indicated the absence of interference from commonly encountered pharmaceutical additives or excipients. The method was found to be precise as indicated by the

repeatability analysis, showing % RSD less than ^{2}. All statistical data proves the validity of the methods and can be used for routine analysis of pharmaceutical dosage form.

CONCLUSION: The proposed HPLC method was found to be rapid, simple, specific, precise, accurate, and economical for simultaneous estimation of Dolutegravir and Rilpivirine in the pharmaceutical dosage form. From the above experimental results and parameters, it was concluded that a new method was established for simultaneous estimation of Dolutegravir and Rilpivirine by the RP-HPLC method. Precision and recovery studies were also found to be within the range.

The drug gets more degraded under Thermal degradation in Dolutegravir and photodegradation in Rilpivirine degradation studies. There was a decrease in retention times and so the run time also decreased, so the method developed was simple and economical that can be adopted in regular quality analysis tests in Industries.

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CONFLICTS OF INTEREST: The authors declare no conflict of interest

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