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# Simultaneous Estimation of Cabotegravir and Rilpivirine in Combined Formulation by RP-HPLC Method

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**Abstract:**

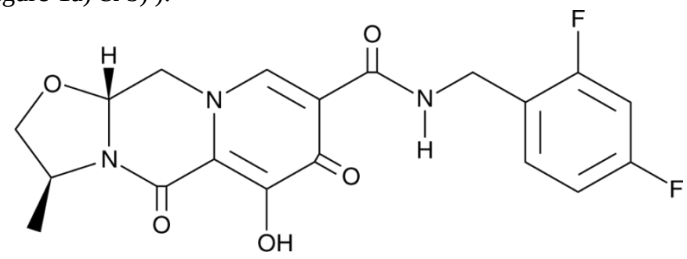
For the simultaneous estimate of Rilpivirine and Cabotegravir in pharmaceutical dosage form, Rilpivirine and Cabotegravir were quantified in active pharmaceutical ingredients using a high-performance liquid chromatographic technology that was created and verified. Agilent C18 150 × 4.6 mm, 5µm Column was applied to run the Chromatographic technique. At a flow rate of 1.0 ml/min and mobile phase made up of Buffer of AmmoniumFormate: Acetonitrile in the proportion 70:30 was pumped through the column. 30°C was kept as the temperature. The obtained optimized wavelength was 257 nm. The retention times of rilpivirine and Cabotegravir were determined to be 2.322 minutes and 2.904 minutes respectively, Recovery was 99.84% and 100.14%, respectively of Rilpivirine and cabotegravir's and LOD and LOQ values through Regression equations yielded was 0.19, 0.59, and 0.20, 0.61, respectively.Rilpivirine's regression equation is y = 6645.3x + 720.01 and Cabotegravir'sis y = 6696x + 327.18. As a result of shorter retention times and shorter run times, the method was created to be straightforward and cost-effective, and it may be used for routine Quality Control Tests in Industries.

**Keywords:**Cabotegravir, Rilpivirine, RP-HPLC, Method Validation

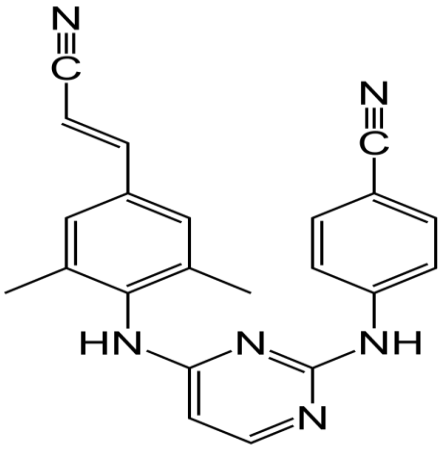
## 1. Introduction:

HIV is more globally expanded and virulent and they are two types one is less virulent and one is more virulent. A single-stranded RNA genome with two copies is present in the enveloped retrovirus known as the human immunodeficiency virus (HIV)[1,2]. The final stage of HIV disease, acquired immunodeficiency syndrome (AIDS), is brought on by it. HIV infections and AIDS are treated with highly active retroviral therapy (HAART), which involves multiple antiretroviral drug combinations [4]. The U.S. Food and Drug Administration (FDA) have approved the prescription drug Cabenuva for the treatment of HIV infection [3]. Cabotegravir and rilpivirine, two distinct medications, are both found in Cabenuva, [5].The FDA approved Cabotegravir with rilpivirine as a treatment for HIV-1 infection in people with virological suppression.Cabenuva is a long-acting drug that may continue to work in your body up to 12 months after your previous injection [6,7]. Cabotegravir-Chemically known as $C_{19}H_{17}F_2N_3O_5$.An HIV-1 Integrase inhibitor called Cabotegravir is used to treat and prevent HIV-1 infection before exposure.Rilpivirine, a non-nucleoside reverse transcriptase inhibitor,[8] is administered along with Cabotegravir. They are many dosage indications are been implemented for the usage of theses drug Intramuscular action shows greater regimen than oral form for the treatment of HIV-1 infection. Mainly Cabotegravir acts as an inhibitor of HIV Integrase, as it stops the replications of viral cells by binding of active sites and preventing transformation of viral cells into host cells so that replication process will be stopped[9,10]. Rilpivirine- Chemically known as $C_{22}H_{18}N_6$, a non-nucleoside reverse transcriptase inhibitor (NNRTI), which is used in conjunction with other antiretroviral to treat HIV-1 specifically.Rilpivirine,[11] a diarylpyrimidine derivative, is approved for the treatment of HIV-1 infections in antiretroviral therapy-naive individuals with HIV-1 RNA below 100,000 copies per milliliter and CD4+ cell count

greater than 200 cells per millimeter. The recommended full regimen for the treatment of HIV-1 infection includes rilpivirine and cabotegravir.A non-nucleoside reverse transcriptase inhibitor called rilpivirine prevents HIV-1 from replicating.[12, 13]HIV-1 replication and other RNA and DNA-dependent DNA polymerase activities are inhibited as a result of its binding. It does not exhibit activity against the following human DNA:Cabotegravir, Rilpivirine shown in (figure-1a) & b) ).




**1) Cabotegravir**




**2)Rilpivirine**

**Figure 1) Structure of Cabotegravir & 2) Structure of Rilpivirine**

## 2. Objectives:

A thorough literature discovered that several analytical methods have been reported in the literature, more economical methods were observed and there is no method reported for the estimation stability studies. Hence a simple, cost-effective stability-indicating simultaneous estimation of Cabotegravir, Rilpivirine and by RP-HPLC [14,15,16,17,18,19,20,21,22] pharmaceutical dosage form has to be developing and validated as per the guidelines of ICH (Q2 specification) [23].

## 3. Methods and Materials:

Cabotegravir, Rilpivirine and pure drugs were obtained from Spectrum Pharma research solutions. The combination tablet Cabotegravir, and Rilpivirine (Cabenuva**)** was brought from India Mart Hyderabad. All the chemical and buffers used in this estimation are procured from Rankem, India.

**Instrumentation**

WATERS HPLC, model:2695 SYSTEM with Photo diode array detector was used for the development and method validation, with an automated sample injector with software Empower 2.

**Chromatographic Conditions:**

| | | |
|---|---|---|
| Column | : | Agilent C18 150x 4.6mm, 5µm. |
| Mobile phase | : | 0.01M ammonium formate buffer : acetonitrile in the proportion of 70:30 |
| Diluent | : | Water and acetonitrile in the ratio of 40:60 |
| HPLC flow program | : | Isocratic |
| Flow rate (mL/min.) | : | 1.0 |
| Wavelength (nm) | : | 257 |
| Column temperature (°C) | : | 25 |
| Injection volume (µL) | : | 10 |
| Run time (minutes) | : | 6.0 |

**Preparation of Buffer**

**Preparation of 0.01Mammonium formate Buffer:**

Add 0.66 g of ammonium formate to the solution of 1000ml of distilled water in suitable container adjust the pH 5.0 with 0.1% acetic acid, Sterilize the solution by passing it through a 0.22 µ membrane filter. Store the solution in tightly sealed bottles at 4°C or at room temperature. Ammonium formate decomposes in hot water and solutions containing it should not be autoclaved.

**Preparation of Standard solution:**

Accurately Weighed and transferred 37.5mg of Rilpivirine, and 25mg of Cabotegravir working Standards into a 50 ml clean dry volumetric flasks, add10mlof diluent, sonicated for 10 minutes and make up to the final volume with diluent (750µg/ml Rilpivirine, and 500µg/ml of Cabotegravir)

**Preparation of Standard working solution:**

1ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent. (75µg/ml Rilpivirine and 50µg/ml of Cabotegravir)

**Preparation of Sample solution:**

Add 1ml of Rilpivirine and Cabotegravir injection sample into a 100 volumetric flask, 50ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters. (375µg/ml Rilpivirine and 250 µg/ml of Cabotegravir)

**Preparation of Sample working solution:**

0.2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent.(75µg/ml Rilpivirine and 50 µg/ml of Cabotegravir).

**Preparation of Linearity Solution:**

**25% Standard solution:**

0.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (18.75µg/ml of Rilpivirine and 12.5µg/ml of Cabotegravir)

**50% Standard solution:**

0.5ml each from two standard stock solutions was pipetted out and made up to 10ml. (37.5µg/ml of Rilpivirine and 25µg/ml of Cabotegravir)

**75% Standard solution:**

0.75ml each from two standard stock solutions was pipetted out and made up to 10ml. (56.25µg/ml of Rilpivirine and 37.5µg/ml of Cabotegravir)

**100% Standard solution:**

1.0ml each from two standard stock solutions was pipetted out and made up to 10ml. (75µg/ml of Rilpivirine and 50µg/ml of Cabotegravir)

**125% Standard solution:**

1.25ml each from two standard stock solutions was pipetted out and made up to 10ml. (93.75µg/ml of Rilpivirine and 62.5µg/ml of Cabotegravir)

**150% Standard solution:**

1.5ml each from two standard stock solutions was pipetted out and made up to 10ml (112.5µg/ml of Rilpivirine and 75µg/ml of Cabotegravir)

**Preparation of degradation solution:**

**Oxidation:**

To 1 ml of stock solution of Rilpivirine and Cabotegravir, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 600c. For HPLC study, the resultant solution was diluted to obtain 60µg/ml & 40µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

**Acid Degradation Studies:**

To 1 ml of stock solution Rilpivirine and Cabotegravir, 1ml of 2N Hydrochloric acid was added and refluxed for 30mins at 600°C. The resultant solution was diluted to obtain 75µg/ml & 50µg/ml solution and 10 µl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

**Alkali Degradation Studies:**

To 1 ml of stock solution Rilpivirine and Cabotegravir, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 600°c. The resultant solution was diluted to obtain 60µg/ml & 40µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

**Dry Heat Degradation Studies:**

The standard drug solution was placed in oven at 105°C for 1 h to study dry heat degradation. For HPLC study, the resultant solution was diluted to 75µg/ml & 50µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

**Photo Stability studies:**

The photochemical stability of the drug was also studied by exposing the 750µg/ml & 500µg/ml solution to UV Light by keeping the beaker in UV Chamber for 1days or 200 Watt hours/m2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 75µg/ml & 50µg/ml solutions and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

**Neutral Degradation Studies:**

Stress testing under neutral conditions was studied by refluxing the drug in water for 1hrs at a temperature of 60ºC. For HPLC study, the resultant solution was diluted to 75µg/ml & 50µg/ml solution and 10 µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

## 4. Results and Discussion:

The validation of HPLC method was carried out for the simultaneous estimation of Cabotegravir, Rilpivirine drug substance as per the ICH guidelines to demonstrate that the method is proposed for the routine analysis.

**System suitability:**

The system suitability was performed for eachvalidation parameters by injecting standard solution containing Rilpivirine 25 µg/mland Cabotegravir12.5 µg/ml. System suitability chromatogram was shown in figure 3 and values are mentioned in the table 1.

**Specificity (Selectivity):**

Checking of the interference in the optimized method. We haven't found interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific. Representative chromatogram is shown in Figure 4, 5 and experimental data is given in Table 2.

**Table 1: System suitability Results**

| Peak Name | RT (mins) | Area | USP Resolution | USP tailing | USP Plate count |
|---|---|---|---|---|---|
| Rilpivirine | 2.332 | 309439 | | 1.7 | 3493 |

| | | | | | |
|---|---|---|---|---|---|
| Cabotegravir | 2.946 | 119817 | 3.3 | 1.2 | 4181 |

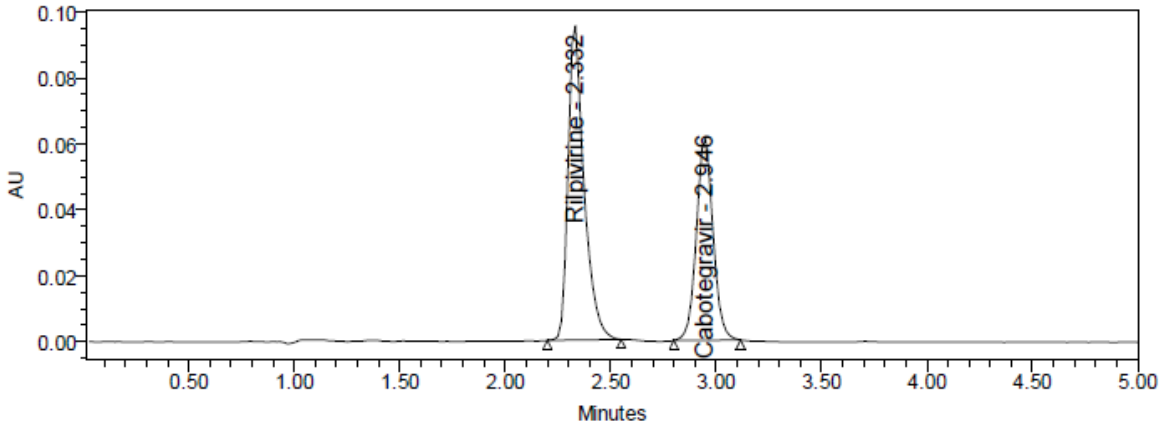



**Figure 3: System suitability chromatogram of Cabotegravir, and Rilpivirine**

**Table 2: Specificity Data**

| Sample name | Retention time(mins) | Area |
|---|---|---|
| Rilpivirine | 2.346 | 496123 |
| Cabotegravir | 2.978 | 332589 |

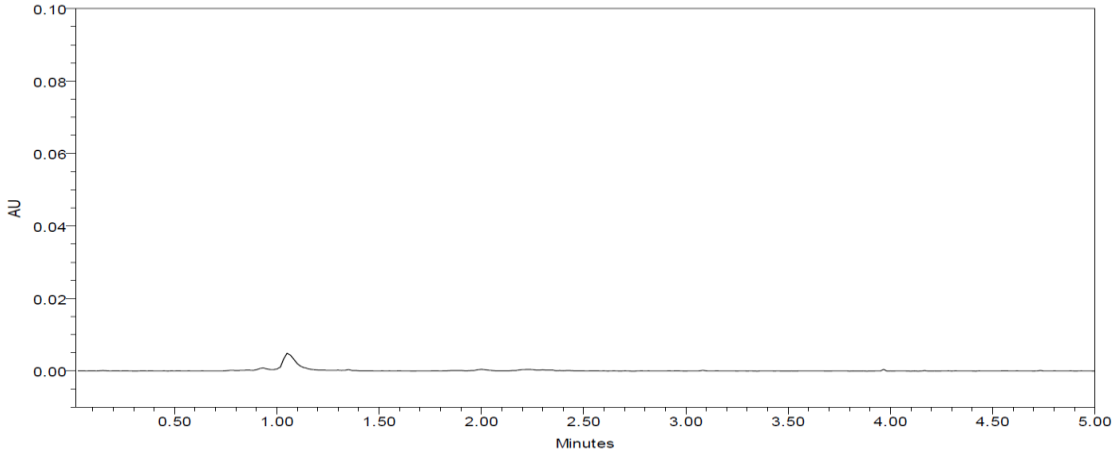



**Figure 4: Placebo Chromatogram**

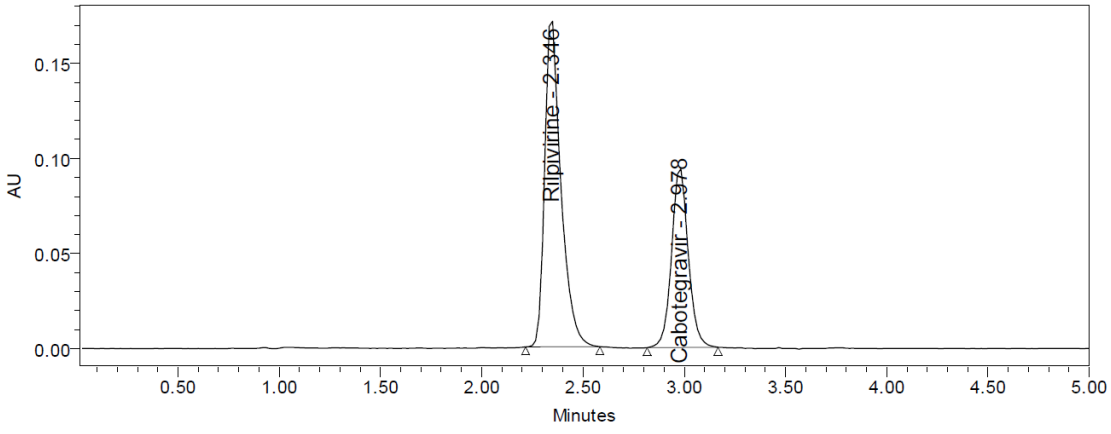


**Figure 5: Specificity chromatogram of Cabotegravir, and Rilpivirine**

**Linearity:**

A series of linearity solutions were prepared by quantitative dilutions of the stock solution of the main drugs to obtain solutions at 25 to150 % of the sample concentration. Each solution was injected and the peak area was recorded. The Regression coefficient, slope and Y-intercept were calculated. The regression coefficient for both drugs was found 0.999. The results indicate excellent linearity for cabotegravir and Rilpivirine shown in Table 3 and the graphs were shown in figure 6 and 7.

**Table 3: Cabotegravir Linearity**

| % Level | Concentration(ppm) | Area |
|---|---|---|
| 25% | 12.5 | 83663 |
| 50% | 25 | 167035 |
| 75% | 37.5 | 254603 |
| 100% | 50 | 337253 |
| 125% | 62.5 | 411622 |
| 150% | 75 | 505826 |
| **$R^2$ value** | | **0.999** |

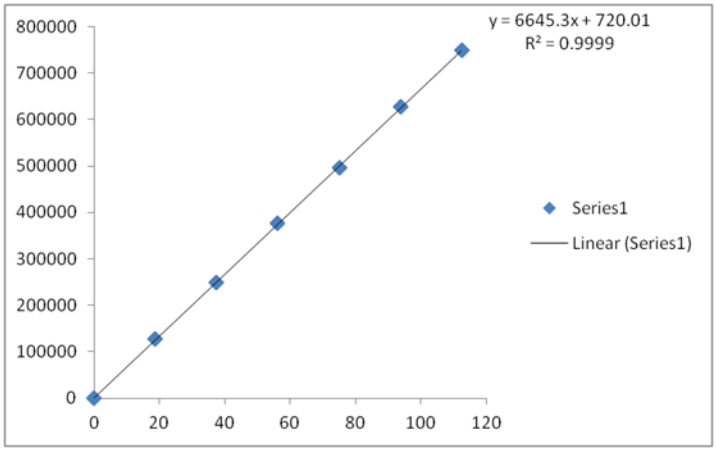



**Figure 6: Cabotegravir calibration curve**

**Table 4: Rilpivirine Linearity**

| % Level | Concentration (ppm) | Area |
|---|---|---|
| 25% | 18.75 | 127706 |
| 50% | 37.5 | 248178 |
| 75% | 56.25 | 375460 |
| 100% | 75 | 495693 |
| 125% | 93.75 | 627108 |
| 150% | 112.5 | 747493 |
| **$R^2$ value** | | **0.999** |

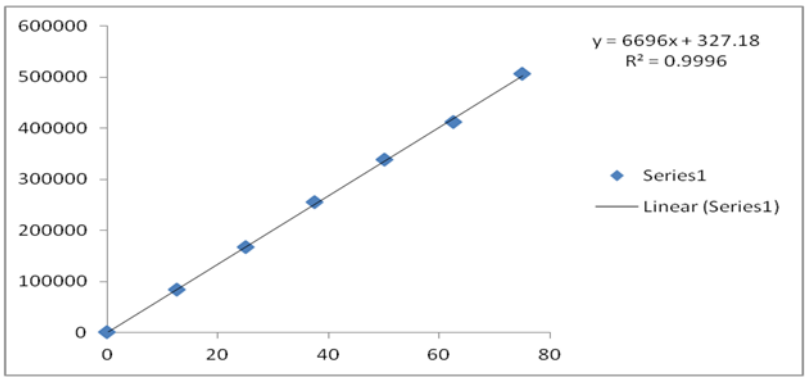



**Figure 7: Rilpivirine Calibration curve**

**Accuracy:**

The accuracy of the method was determined by using solutions containing spiked samples of cabotegravir and Rilpivirine at 50%, 100% and 150% of the working strength. All the solutions were prepared in triplicate and analyzed. The percentage recovery results obtained for each analyte was listed in Table 6

**Table 6: Accuracy Data (%Recovery data)**

| **%Level** | **Recovery Data** | | | | | |
|---|---|---|---|---|---|---|
| | **Cabotegravir** | | | **Rilpivirine** | | |
| | Amt added | Amt found | % Rec | Amt added | Amt found | % Rec |
| 50% Level | 25 | 25.09 | 100.37 | 37.5 | 37.5 | 100.1 |
| | 25 | 25.00 | 100.01 | 37.5 | 37.7 | 100.5 |
| | 25 | 24.96 | 99.84 | 37.5 | 37.3 | 99.5 |
| 100%Level | 50 | 50.17 | 100.35 | 75 | 74.3 | 99.0 |
| | 50 | 50.17 | 100.33 | 75 | 75.2 | 100.2 |
| | 50 | 50.41 | 100.82 | 75 | 74.9 | 99.9 |
| 150%Level | 75 | 75.19 | 100.25 | 112.5 | 111.8 | 99.4 |
| | 75 | 75.01 | 100.01 | 112.5 | 113.2 | 100.6 |
| | 75 | 74.44 | 99.26 | 112.5 | 111.7 | 99.3 |
| **Mean%** | | | **100.14** | | | **99.84** |

**System Precision:**

The system precision was performed by analyzing six replicate injections of standard solution at 100% of the specified limit with respect to the working strength of Cabotegravir andRilpivirine. Results of peak area are summarized in Table 7

**Table 7: System precision data**

| **Injection** | **Cabotegravir** | **Rilpivirine** |
|---|---|---|
| 1 | 330322 | 494907 |
| 2 | 335919 | 496596 |
| 3 | 338270 | 498956 |
| 4 | 333288 | 496943 |
| 5 | 335016 | 495340 |
| 6 | 336649 | 493994 |
| **Avg** | 334911 | 496123 |
| **Stddev** | 2793.7 | 1763.3 |
| **%RSD** | **0.8** | **0.4** |

The % RSD for the peak areas of Cabotegravir andRilpivirineobtained from six replicate injections of standard solution was within the limit.

**Method Precision:**

The precision of the method was determined by analyzing a sample of Cabotegravir andRilpivirine(Six individual sample preparations). Data obtained is summarized in Table 8.

**Table 8:** Method precision data

| Injection | Cabotegravir | Rilpivirine |
|---|---|---|
| 1 | 337686 | 498898 |
| 2 | 336693 | 495757 |
| 3 | 333342 | 499749 |
| 4 | 336649 | 495164 |
| 5 | 339595 | 495340 |
| 6 | 336089 | 498719 |
| **Avg** | 336676 | 497271 |
| **Stddev** | 2049.5 | 2066.1 |
| **%RSD** | **0.6** | **0.4** |

From the above results, the % RSD of method precision study was within the limit for Cabotegravir andRilpivirine.

**Robustness:**

Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus (65Buffer:35Acetonitirle), mobile phase plus (75Buffer:25Acetonitrile), temperature minus (25°C) and temperature plus(35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit. Results are tabulated in Table-9.

**Table 9:** Robustness Results

| Chromatographic condition | Cabotegravir (%RSD) | Rilpivirine (%RSD) |
|---|---|---|
| Flow(-) | 0.5 | 0.5 |
| Flow(+) | 0.6 | 0.8 |
| Temp(Ambient-) | 0.6 | 0.7 |
| Temp(Ambient+) | 0.8 | 0.6 |
| Mobile phase(-) | 0.6 | 0.3 |
| Mobile phase (+) | 0.8 | 0.5 |

**Forced degradation:**

It is defined as degradation of new drug substance and drug product at conditions more severe than accelerated conditions. It is required to demonstrate specificity of stability indicating methods and also provides an insight into degradation pathways and degradation products of the drug substance and helps in elucidation of the structure of the degradation products. Forced degradation studies show the chemical behavior of the molecule which in turn helps in the development of formulation and package. The conditions are mentioned Table10.

**Table 10:** Forced degradation conditions for Cabotegravir andRilpivirine.

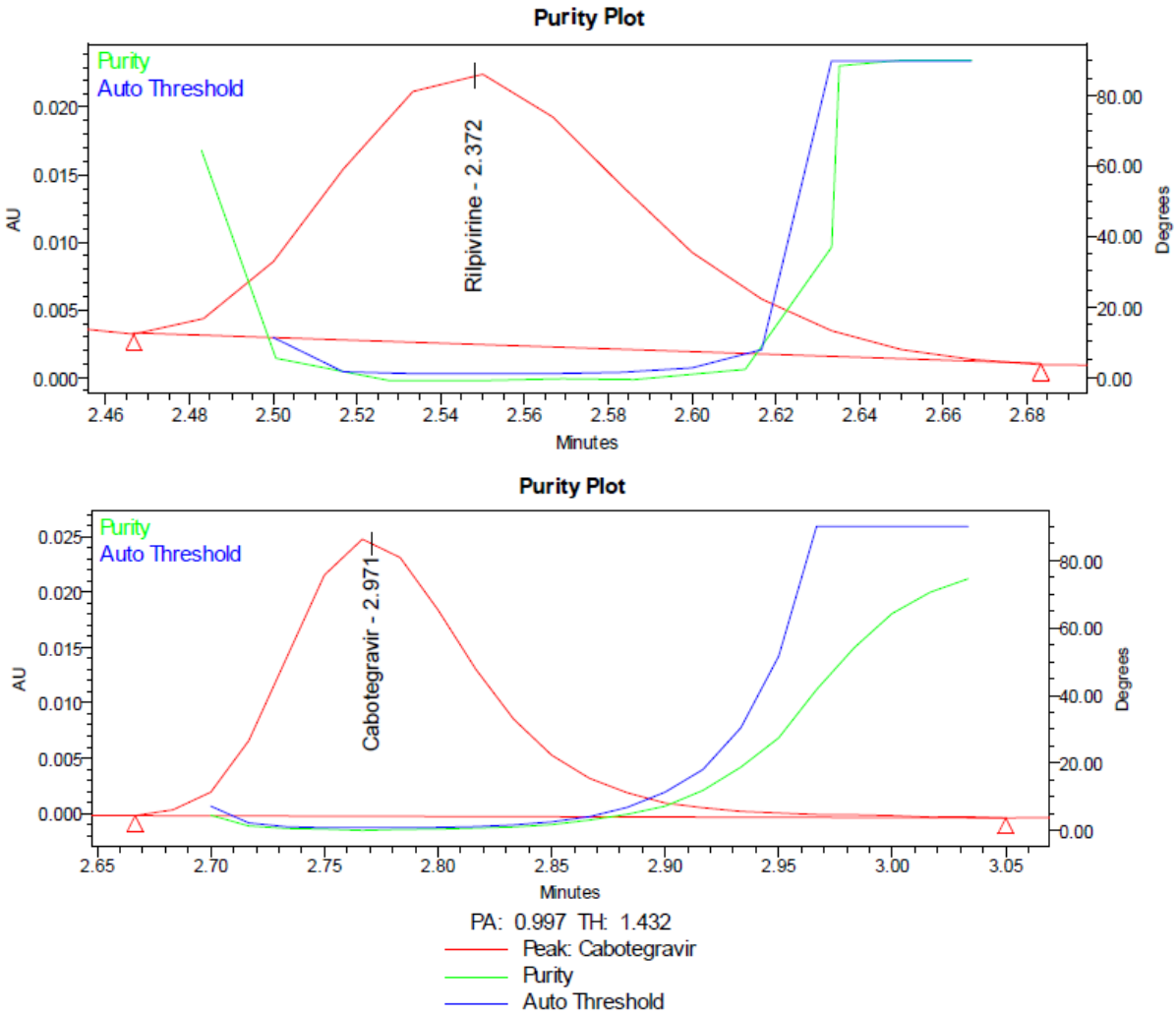
| Stress condition | Solvent | Temp($^0$C) | Exposed time |
|---|---|---|---|
| Acid | 2N HCl | 60$^0$C | 30 mins |
| Base | 2N NaOH | 60$^0$C | 30 mins |
| Oxidation | 20% $H_2O_2$ | 60$^0$C | 30 mins |

| | | | |
|---|---|---|---|
| Thermal | Diluent | $105^0$C | 6 hours |
| Photolytic | Diluent | - | - |
| Hydrolytic | Water | $60^0$C | - |

From the results, no degradation was observed when the samples were exposed to acid, base, hydrolysis, thermal, light and water. According to the stress study, none of the degradant co-eluted with the active drug peaks formed.

**Table 11:** Degradation profile results

| **Type of degradation** | **Rilpivirine** | | | **Cabotegravir** | | |
|---|---|---|---|---|---|---|
| | Area | %Recovered | % Degraded | Area | %Recovered | % Degraded |
| Acid | 473856 | 95.42 | 4.58 | 318125 | 94.89 | 5.11 |
| Base | 484984 | 97.66 | 2.34 | 319246 | 95.23 | 4.77 |
| Peroxide | 462450 | 93.12 | 6.88 | 312595 | 93.24 | 6.76 |
| Thermal | 481143 | 96.88 | 3.12 | 324874 | 96.91 | 3.09 |
| UV | 489745 | 98.62 | 1.38 | 329797 | 98.37 | 1.63 |
| Water | 491746 | 99.02 | 0.98 | 334697 | 98.37 | 1.63 |



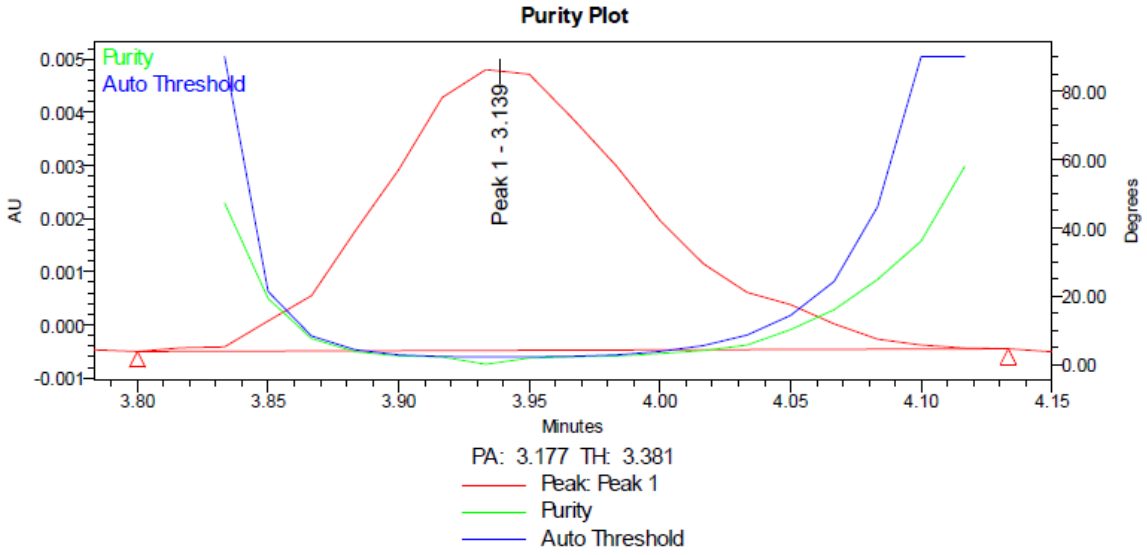



**Fig. 8 Purity Plot of Degraded of peroxide Sample**.

**Assay was performed:**

Add 1ml of Rilpivirine and Cabotegravir injection sample into a 100 volumetric flask, 50ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters. (375µg/ml Rilpivirine and 250 µg/ml of Cabotegravir).0.2ml of filtered sample stock solution was transferred to 10ml volumetric flask and made up with diluent.75 (µg/ml Rilpivirine, and 50 µg/ml of Cabotegravir). The obtained results are below tabulated

**Table 12: Assay results for Cabotegravir, and Rilpivirine**

| | **Label claim dose** | **%Assay** |
|---|---|---|
| **Cabotegravir** | 400/2ml | 100.43 |
| **Rilpivirine** | 600/2ml | 100.16 |

## 5. Conclusion:

By using the RP-HPLC methodology, a new stability indicating analytical approach was created and verified. The information provided in the study will be very helpful for the quality monitoring of Cabotegravir and Rilpivirine in pharmaceutical dosage forms because the sample preparation is straightforward, uses a small amount of mobile phase, and only requires a short period of time for analysis. When two medications were assay from a combination dose form, the results were close to 100% according to the newly discovered approach. Recovery studies were successful, demonstrating that excipient influence is nonexistent.

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