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# A REVIEW ON ANALYTICAL PROFILE OF CABOTEGRAVIR AND RILPIVIRINE IN PHARMACEUTICAL FORMULATIONS AND BIOLOGICAL MATRICES

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***Abstract:*** The chase to improve the quality of life has stimulated desirable changes in research to design and develop a new drug and enhance its safety and effectiveness. Thus, there is a gradual rise in demand to develop susceptible and specific analytical techniques for newly developed drugs. Thus, analysts are striving very hard to develop new and efficient analytical methods to achieve these targets. The antiretroviral agents Rilpivirine (RPV) and cabotegravir (CAB) are approved as a combined treatment regimen against human immunodeficiency virus (HIV). This review article represents the collection and discussion of various analytical methods available in the literature for the estimation of the CAB and RPV in pharmaceutical formulations and biological samples consisting of HPLC, UPLC and hyphenated techniques such as LC-MS, LC-MS/MS. Moreover, we discuss about CAB and RPV chemical structure, mechanism of action, activity against drug-sensitive and -resistant HIV, and pharmacodynamics/pharmacokinetics properties. The present review can be effectively explored to conduct future analytical investigation for the estimation of Cabotegravir and Rilpivirine.

**Keywords -** Cabotegravir and Rilpivirine, Analytical Methods, RP-HPLC, LC-MS/MS.

## INTRODUCTION

More than 75 million people worldwide have been infected with human immunodeficiency virus (HIV), and there are now approximately 37 million individuals living with the infection.Untreated HIV replication causes progressive CD4+ T cell loss and a wide range of immunological abnormalities, leading to an increased risk of infectious and oncologicalcomplications. HIV infection also contributes to cardiovascular disease, bone disease, renal and hepatic dysfunction and several other common morbidities. Antiretroviral drugs are highly effective at inhibiting HIV replication, and for individuals who can access and adhere to these drugs, combination antiretroviral therapy leads to durable (and probably lifelong) suppressionof viral replication. Viral suppression enables immune recovery and the near elimination of therisk for developing acquired immune deficiency syndrome (AIDS). Despite effective treatment, HIV-infected individuals have a higher-than-expected risk of heart, bone, liver, kidney and neurological disease [1].

The recent approval of a combined treatment regimen utilizing prolonged-release suspensions of the antiretroviral agents Rilpivirine (RPV) and cabotegravir (CAB) for monthly intramuscular injections was a great step forward towards improved HIV treatment regimens. A further important aspect is that HIV requires lifelong treatment, as current ART options canonly effectively control viral replication in the systemic blood circulation. Drug permeation to specific viral reservoirs, such as lymph nodes, is limited and therapy interruption leads to viralrebounds [2].

**Cabotegravir** (Fig.1) is a second-generation non-nucleoside reverse transcriptase inhibitor which is more potent with fewer side effects and has a longer half-life. it is the first antiretroviral medications to be formulated for injection and to have extended half-life [2]. Its Chemical structure and formula are 3R,6S)-N-[(2,4-difluorophenyl) methyl]-10-hydroxy-6- methyl-8,11-dioxo-4-oxa-1,7-diazatricyclo [7.4.0.0] trideca-9,12-diene-12-carboxamide and C19H17F2N3O5 and its molecular weight is about 405.358 g/mo. It has white to off-whit crystalline powder, insoluble in aqueous solutions under pH 9, and slightly soluble above pH 10. with p*Ka* 7.8 [3].

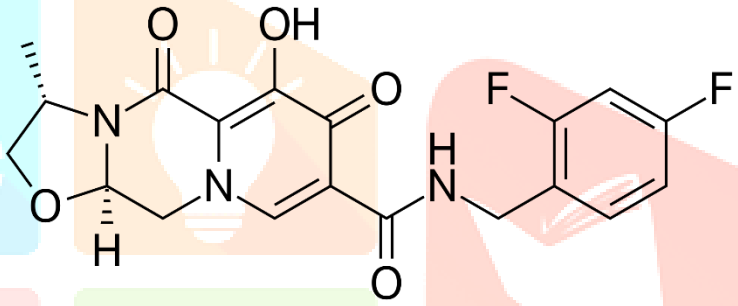


**Figure 1: Chemical structure of Cabotegravir**

**PHARMACOKINETICS DATA OF CABOTEGRAVIR [4]:**

**Absorption:** Oral cabotegravir has a *Tmax* of 3 hours, reaches a *Cmax* of 8.0 µg/mL, and has an AUC of 145 µg h/mL. Intramuscular extended-release cabotegravir has a *Tmax* of 7 days, reaches a *Cmax* of 8.0 µg/mL, and has an AUC of 1591 µg h/mL.

**Protein Binding:** It is >99.8% bound to proteins in plasma, usually albumin.

**Metabolism:** It is O-glucuronidated to two metabolites, with 67% of glucuronidation performed by UGT1A1, and 33% by UGT1A9.

**Route of elimination:** An oral dose of cabotegravir is 58.5%is recovered in faces and 26.8% is recovered in urine.

**Half-life:** Oral: 41 hrs; Intramuscular extended release: 5.6-11.5 weeks.

**Mechanism of action:** As an antiretroviral drug, Cabotegravir belongs to the integrase strandtransfer inhibitor (INSTI) class. It works by inhibiting the activity of the integrase enzyme, which is essential for the replication of the HIV virus. By blocking this enzyme, Cabotegravirhelps to prevent the virus from integrating its genetic material into the host's DNA, thereby reducing viral replication and the progression of HIV/AIDS [5].

**Adverse effects**:

- Difficulty breathing,
- Swelling of your face, lips, tongue, or throat,
- Severe dizziness, extreme tiredness,
- Fever, rash, blisters or sores in or around your mouth,
- Muscle or joint pain,
- Red or puffy eyes,
- Thoughts of self-harm,
- Loss of appetite,
- Nausea, vomiting,
- Yellowing of the skin or eyes [5].

**Rilpivirine** (Fig.2) is non-nucleoside reverse transcriptase inhibitor with fewer side effects likerashes, insomnia, fever and it is more potent which helps to fight with infection. Its chemical structure and molecular formula are 4-{[4-({4-[(E)-2-cyanovinyl]-2,6-dimethylphenyl} amino) pyrimidin-2-yl] amino} benzonitrile and $C_{22}H_{18}N_6$.Its molecular weight is about 366.42g/mol. It has p*ka* of 11.43. However multiple drug therapy can control the HIV infection effectively. Cabotegravir is combined along with Rilpivirine under the brand name Cabenuva[6].

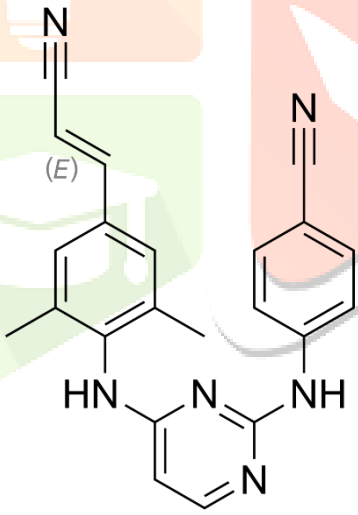


**Figure 2: Chemical structure of Rilpivirine**

**PHARMACOKINETICS DATA OF RILPIVIRINE [7]:**

**Absorption:** When taken by mouth, Rilpivirine reaches highest levels in the blood plasma afterabout four to five hours. Taking the drug without food lowers its plasma levels by 40% as compared to taking it with food, which is considered to be clinically relevant. Therefore, patients are advised to take the medication together with a meal. After injection into the muscle,the substance reaches highest plasma levels after three to four days.

**Distribution:** Rilpivirine is almost completely bound to plasma proteins (99.7%), mostlyto albumin.

**Metabolism:** It is metabolized mainly by the liver enzyme CYP3A4. Metabolites include several oxidation products, glucuronides, and glucuronides of oxidized metabolites.

**Biological half-life:** It is approximately 45 hours for the tablets and 13 to 28 weeks for the injection.

**Elimination:** has only been studied for oral administration: Most of the drug is excreted via the faces (85%), partly in unchanged form (25%), partly in form of its metabolites (60%). A minor amount is excreted via the urine (6%), almost exclusively as metabolites.

**Mechanism of Action:** Rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

**Adverse Effects:**

- The most common side effects of the injectable formulation are reactions at theinjection site (in up to 84% of patients) such as pain and swelling, as well as headache(up to 12%) and fever or feeling hot (in 10%).
- Less common (under 10%) are depressive disorders, insomnia, and rashes.
- The most common side effects of the tablets are also depressive disorders (4.1%), headache (3.5%), insomnia (3.5%) and rashes (2.3%).

**Table1: List of marketed formulations of Cabotegravir and Rilpivirine [8]**

| S.No. | Drug | Trade Name | Name of the manufacturer | Dosage form and strength |
|---|---|---|---|---|
| 1 | Cabotegravir | Apretude | Viiv healthcare | ɔn and Suspension200 mg/mL |
| 2 | Cabotegravir | Vocabria | Viiv healthcare | Injection; 200 mg/mL |
| 3 | Rilpivirine | Edurant | Janssen pharmaceuticals | Tablet; 25 mg |
| 4 | Rilpivirine | Rekambys | Janssen pharmaceuticals | Injection 600 mg/mL; 900 mg/mL |
| 5 | abotegravir& Rilpivirine | Cabenuva | Viiv healthcare | Injection 400 mg/600 mg; 600 mg /900 mg of Cabotegravir and Rilpivirine |

**Table 2: List of analytical methods for the estimation of Cabotegravir**

| S.No. | Method | Column | Mobile phase | Flow rate (mL/min) | Wavelengthh (nm) | Linearity(µg/mL) | Retention time (Rt) | LOD (µg/mL) | LOQ (µg/mL) | RefNo. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | RP-HPLC | Kinetex C18 column (250 x 4.6 nm, 5 µm) | Methanol: 20 mM phosphate buffer (pH 3) 70:30 v/v | 1.00 | 243 | 2-12 | 4.7 | 0.49 | 1.47 | 10 |

**Table 3: List of analytical methods for the estimation of Rilpivirine**

| S.No. | Method | Column | Mobile phase | Flow rate (mL/min) | velength(nm) | inearity (µg/mL) | Retention time (min) | LOD (µg/mL) | LOQ µg/mL | RefNo. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | RP-HPLC | 8 Column (4.6 x250 nm, 5 µm) | le and Phosphate(60:40) | 1 | 282 | 10-50 | 2.75 | 0.005 | 0.17 | 11 |
| 2 | LC | Zodiac C18 (250x4.6 nm,5 µm) | Methanol: water: 0.1% ortho phosphoric acid (80:10:10 v/v/v) | 1.5 | 230 | 4-10 | 3.80 | 0.06 | 0.2 | 12 |
| 3 | UPLC-MS/MS | UPLC HSS T3 column (150 mm x 2.1 mm) 1.8 µm | cetonitrile (50:50v/v) | 0.5 | m/z 367.14 | 3.9- 2000 ng/mL | 3.51 | 3.8 ng/mL | 7.8 ng/mL | 13 |
| 4 | LC-MS/MS | Restek Pinnacle DB BiPh Column (50 mm × 2.1 mm, 5 µm) | Acetonitrile: formic acid (0.1%)v/v (50:50) | 1 | m/z 367.2 → 195.1 | 5–2000 ng/mL | 4.02 | 5 ng/mL | - | 14 |
| 5 | RP-HPLC | gilent C18 (4.6 x 150mm, 5µm) | r 50% OPA: 50%Acetonitrile | 1 | 257 | 6.25-37.5 | 2.853 | 0.56 | 1.69 | 15 |
| 6 | RP-HPLC | Phenomenex C18 (150x4.6mm, 5µm). | A mixture of 0.1% Ortho phosphoric acid and acetonitrile 60:40 v/v | 1 | 262 | 5-75 | 7.73 | 0.005 | 0.5 | 16 |
| 7 | RP-HPLC | XBridge C18 column. (4.6 · 150 mm, particle size: 3.5 mm;Waters) | Acetonitrile (solvent A) and 50-mM acetate buffer at pH 4.5 (solvent B) a linear gradient from 40% to 70% of acetonitrile in 15 minutes. | 1 | 305 | 20-2000ng/mL | 12.9 | - | 20 ng/mL | 17 |

**Table 4: List of analytical methods for the Simultaneous estimation of Cabotegravir and Rilpivirine**

| S. No. | Method | Column | Mobile phase | Flow rate (mL/min) | velength(nm) | Linearity (µg/mL) | Retentiontime (Rt) | LOD (µg/mL) | LOQ (µg/mL) | Assay | Ref.No. |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | RP-HPLC | Phenomenex Gemini (250 nm x 4.6 nm) 5µm | Methanol and Phosphate Buffer (pH-4.2) 20: 80 v/v | 1.0 | 246 | 20–100 & 40–120 | CBR: 2.45 min RLP: 4.31 min | 0.98 & 2.94 | 1.27 & 3.81 | 99.98% | 18 |
| 2 | RP-HPLC | Agilent C 18 column (BDS) (150 X 4.6 nm, 5µm) | 0.01 N $KH_2P0_4$ buffer(pH: 4.8): acetonitrile (70:30 v/v). | 0.9 & 1.0 | 260 | 25-150 & 37.5-225 | CBR: 2.30 min RLP: 3.187 min | 0.24 & 1.10 | 0.74 & 3.34 | 100.25% and 99.79% | 19 |
| 3 | RP-HPLC | Kromasil C18 150 x 4.6 mm, 5µ. | 0.01N Potassium dihydrogen phosphate: Acetonitrile 60:40 | 1.0 | 257 | 18.75-112.5 & 12.5- 75 | CBR: 2.642 minRLP: 2.257 min | 0.54 & 0.18 | 0.46 & 0.15 | 100.43% and 100.13% | 20 |
| 4 | RP-HPLC | Kinetex C18 column (250 mm x 4.6 mm, 5µm) | Acetonitrile: Sodium Dihydrogen Phosphate buffer (0.05M) of pH 4.5 35:65 v/v | 1.0 | 242.5 | to 15& 3.75 to 22.5 | CBR: 2.14 min RLV: 3.12 min | 1:3; 0.263 & 0.202 | 1:10; 0.798 & 0.613 | 99.64-99.80% &- 99.52-99.95% | 21 |
| 5 | HPLC | Symmetry C18 (4.6×150 nm, 3.5 µm) | Acetonitrile, and 0.1% formic acid in a 20:80v/v ratio with a photodiode array | 1.0 | 231 | 30–450 & 20–300 | CBR: 3.942 min RLV: 2.050 min | 0.375 & 0.25 | 1.238 & 0.825 | 100.9% 100.6% | 22 |
| 6 | HPLC-MS | Apex ScientificInertsil ODS-3 column (4.6 mm x250 mm, 5 µm) | Acetonitrile and 0.1% trifluoroacetic acid inwater (81:19, v/v) | 0.3 | 257 | 5 to 500ng/mL & 500 to 10,000 ng/mL | RPV (m/z) of 367.4 andCAB at 406.3 | RPV:4.77 ng/mL CAB: 4.93 ng/mL | 12 ng/mL 664 ng/mL | RLV: 96.0% - 104.0% CAB: 98.3% - 106.2% | 23 |
| 7 | UPLC | ibar C18 (100 x2.1nm, 2 µm) | r: acetonitrile(55:45 v/v) | 0.3 | 257 | 12.5 & 112.5 | CBR: 1.152 min RLV: 0.618 min | 0.43 & 0.78 | 1.30 & 2.37 | 99.79% 99.58% | 24 |

## CONCLUSION:

The present review provides a summary of various analytical methods reported in the literature for the determination of Cabotegravir and Rilpivirine in bulk, pharmaceutical formulations and also in various biological matrices like blood plasma and urine. Analytical methods consisting of chromatography, hyphenated techniques, were employed for determination of Cabotegravir and Rilpivirine in bulk, pharmaceutical dosage forms and biological matrix. The primary objective of the compilation of review is to collect maximum available on analytical methods of CAB, RLP and study it in detail. From this survey, it is revealed that a handful of analytical methods are obtainable on HPLC, UPLC and very few articles are available based on hyphenated methods (LC-MS/MS). The reported data for analysis of CAB And RLP revealed that HPLC with UV detection is the most frequent technique employed for the determination of CAB and RLP in pharmaceutical dosage forms. For analysis of CAB and RLP in biological matrices like blood plasma, urine LC-MS with MS detection is appropriate since this strategy gives precise outcomes and minimal effort. Furthermore, employing MS techniques in LC offered unique selectivity and sensitivity as well as a choice of method for analysis of CAB, RLP and its metabolites in biological samples. Hyphenated techniques such as LC-MS, LC-MS/MS, and UPLC-MS/MS methods are also reported for quantification of CAB and RLP in plasma and other biological fluids. This review will be useful in further development of the analytical methods for this combination and also gives a glimpse of the drug Profile.

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## CONFLICTS OF INTEREST STATEMENT:

All the authors declare that they do not have any conflicts of interest.

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