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A REVIEW ON DOLUTEGRAVIR & RILPIVIRINE IN BULK & PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

Day by day may Antiviral and Anti retroviral drugs are emerging in markets as per etiologic and viral conditions. One of them is Dolutegravir and Rilpivirine, both the drug have different mode of action, i.e Dolutegravir is an HIV-1 antiviral agent. It inhibits HIV integrase by binding to the active site and blocking the strand transfer step of retroviral DNA integration in the host cell. The strand transfer step is essential in the HIV replication cycle and results in the inhibition of viral activity. Rilpivirine contains non-nucleoside reverse transcriptase inhibitor (NNRTI). The drug works by restraining the HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase. Fewer methods of analytical research has been reported for estimation of above drugs, which are HPLC, HPTLC, UPLC- UV, RP – UPLC. The Objective behind these review work is to study the analytical work done on Dolutegravir and Rilpivirine

KEYWORDS: Dolutegravir, Rilipivrine, HPLC, HPTLC, UPLC- UV, RP – UPLC.

1. INTRODUCTION

The World is encountering with various epidemics with every coming decade, and the most common causative agent is virus. There are various types of Virus know to humans and most of the viruses don't have specific drug to cure it, one of them is Human immunodeficiency virus (HIV). These virus causes disease called Acquired Immune deficiency syndrome. (AID's). Till date there is no complete cure for the disease, but only life span of the patient can be increased. HIV is a retrovirus that infects and replicates primarily in human CD4+ T cells and macrophages.[1]

1.1 Dolutegravir

Dolutegravir sodium chemically, (4R,12aS)-9-{[(2,4difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo3,4,6,8,12,12a- Hexahydro-2H-pyrido [1',2':4,5]pyrazino[2,1-b][1,3]oxazin-7-olate, is a novel integrase stand transfer inhibitor active against Human Immunodeficiency Virus. The drug is active against HIV type 1 (HIV-1) and also has some in vitro activity against HIV type 2 (HIV-2).[1]

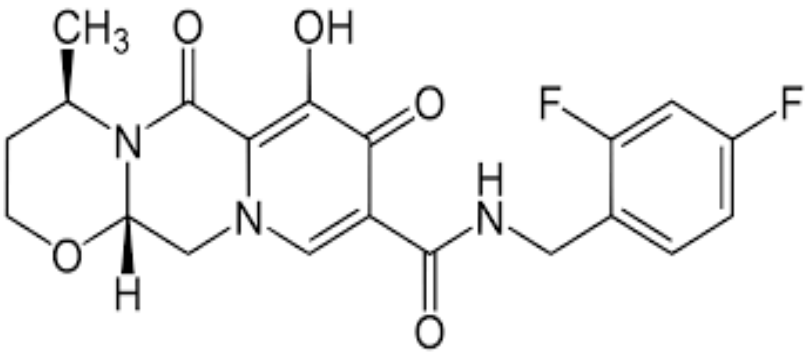

Fig: Structure of Dolutegravir.

Drug Profile

Sr.No	Parameters	Description
01	Category	Anti-Retro viral
02	Chemical formula	C20H19F2N3O5
03	IUPAC Name	2,4-[difluorophenyl] methyl carbamoyl]-4-methyl - 6,8,dioxo-3,4,12,12a -tetrahydro-2H-pyrido[5,6] pyrazin [2,6-b][1,3] oxazin -7-olate.
04	Molecular weight	419.385 g/mol
05	Characteristic	Off-White to Pale Yellow Solid
06	Solubility	Slighty Soluble in Water
07	Log P & pKa	2.2 and 8.2
08	Melting Point	190^0 -193^0 C
09	CAS No.	1051375-16-6
10	Indication	For the treatment of HIV infection. By preventing replication of HIV

Mechanism of action

Dolutegravir is an HIV-1 antiviral agent. It inhibits HIV integrase by binding to the active site and blocking the strand transfer step of retroviral DNA integration in the host cell. The strand transfer step is essential in the HIV replication cycle and results in the inhibition of viral activity.[2]

Pharmacokinetics

The dolutegravir pharmacokinetic profile under single dose and steady state conditions ranging from 2 to 100 mg per day has been assessed in healthy and HIV infected adults.[3,4]

Dolutegravir exhibits rapid absorption, with a median time to maximum concentration (t_{max}) ranging from 0.5 to 2 hours. Dolutegravir also displays extensive protein binding with >99% of the dolutegravir blood plasma concentrations bound to albumin and alpha 1-acid glycoprotein (AAG).[6,5] The terminal elimination half-life ($t_{½}$) of dolutegravir was 13 to 14 hours in healthy subjects and 11 to 12 hours in HIV infected subjects. Single doses of 5, 10, 25, 50 and 100 mg achieved plasma dolutegravir concentrations greater than the *in vitro,* protein-adjusted IC_{90} of 0.064µg/ml for more than 30 hours following oral administration. Multiple daily doses ranging from 10 to 50 mg in both uninfected and infected subjects yielded trough plasma concentrations (C_{trough}) 3–25 times greater than this *in vitro* threshold.[3,4]

DOSAGE AND ADMINISTRATION

Dolutegravir/Rilpivirine Tablet

- 50mg/25mg (equivalent to 52.6mg Dolutegravir sodium/27.5mg Rilpivirine hydrochloride).[1]

1.2. Rilpivirine

Rilpivirine is chemically known as 4-{[4-({4-[(1E)-2cyanoeth-1-en-1-yl]-2, 6-dimethylphenyl} amino) pyrimidin-2-yl] amino} benzonitrile{http://www.drugbank.ca/drugs/DB08864}. Rilpivirine is non-nucleoside reverse transcriptase inhibitor (NNRTI) which is used for the treatment of HIV-1 infections in treatment-naive patients.[7] It is a diarylpyrimidine derivative, a class of molecules that resemble pyrimidine nucleotides found in DNA.[8] The internal conformational flexibility of rilpivirine and the plasticity of it interacting binding site gives it a very high potency and an unlikely generation of resistance compared to other NNRTI's.[9] Rilpivirine was developed by Tilbotec, Inc. and FDA approved on May 20, 2011.[10] On November 21, 2017, Rilpivirine, in combination with dolutegravir, was approved as part of the first complete treatment regimen with only two drugs for the treatment of adults with HIV-1 named Juluca.[11,12]

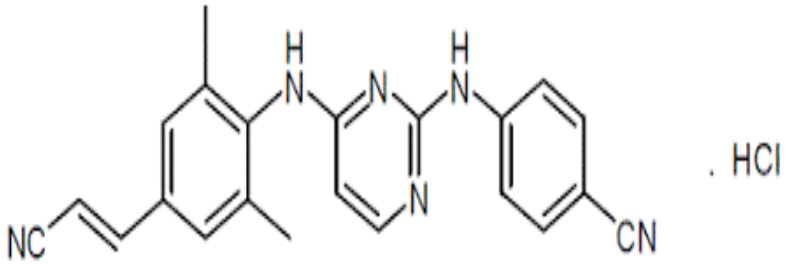

Fig: Structure of Rilpivirine.

Drug Profile

Sr.No	Parameters	Description
01	Category	Anti-Retroviral
02	Chemical formula	C22H18N6
03	IUPAC Name	4[4-4[(E)-2 cynoethenyl]2,6, dimethylanilino]pyrimidine-2-yl]amino]benzonitile HCl
04	Molecular weight	366.428 g/ mol
05	Characteristic	Slightly Yellow Crystalline powder.
06	Solubility	Readily soluble in Dimethyl sulfoxide (DSMO), moderately soluble in PEG. Practically insoluble in water.
07	Log P & pKa	4.86 & 5.6
08	Melting Point	241^0 -243^0 C
09	CAS No.	500287-72-9
10	Indication	For the treatment of HIV infection. By preventing replication of HIV

Mechanism of action

Rilpivrine is an antiviral drug that contains non-nucleoside reverse transcriptase inhibitor (NNRTI). The drug works by restraining the HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase.[13] It does not inhibit the human cellular DNA polymerases alpha, beta, and gamma.[14]

It is a diarylpyrimidine derivative, a class of molecules that resemble pyrimidine nucleotides found in DNA.[7] The internal conformational flexibility of rilpivirine and the plasticity of it interacting binding site gives it a very high potency and an unlikely generation of resistance compared to other NNRTI's.[15]

Pharmacokinetics

Rilpivirine is highly protein-bound, and more than 99% may be bound to human plasma proteins in a concentration-dependent manner.[16] Under fasting conditions, the maximum plasma concentration of rilpivirine (C_{max}) decreased by 46% and the area under the rilpivirine

plasma concentration curve (AUC) decreased by 43%. Similarly, rilpivirine C_{max} and AUC are reduced by 50% when given with a protein-rich nutritional drink.[17]

Absorption

Peak plasma concentration: 3.67 mcg/mL (dolutegravir); 0.13 mcg/mL (rilpivirine)

Peak plasma time: 3 hr (dolutegravir); 4 hr (rilpivirine)

AUC ratio, moderate-fat meal: 1.87 (dolutegravir); 1.57 (rilpivirine)

AUC ratio, high-fat meal: 1.87 (dolutegravir); 1.72 (rilpivirine).[19]

Metabolism

Dolutegravir: Primarily metabolized by UGT1A1; CYP3A (minor)

Rilpivirine: Primarily metabolized by CYP3A.[19]

Exceration

Half-life: 14 hr (dolutegravir); 50 hr (rilpivirine)

Excretion, urine: 31% (dolutegravir), <1% (unchanged dolutegravir); 6.5% (rilpivirine), <1% (unchanged rilpivirine)

Excretion, feces: 64% (dolutegravir), 53% (unchanged dolutegravir); 85% (rilpivirine), 25% (unchanged rilpivirine).[19]

Adverse reaction

Adverse reactions of a more intense character including epigastric, discomfort, nausea, and vomiting followed by diarrhoea, drowsiness, weakness, dizziness, malaise and headache might be seen.[6]

2. Reported Method is categorized depending on the following considerations

Sr. no	Drug	Method	Description	Ref. no.
1	Dolutegravir and Rilpivirine in pharmaceutical Dosage form.	RP-HPLC	**Column:** Agilent C18 column (4.6×150mm)5µ, **Mobile phase:** (70:30 v/v) methanol: Phosphate buffer pH 3.0 **Flow rate:** 1.0 ml/min **Wavelength:** 240 nm **Retention time:** 4.029 (Dol) min and 2.767 min.(Ril)	[20]
2	Dolutegravir and Rilpivirine in rat plasma.	RP-HPLC	**Column :** Phenomenex C18 [150 x 4.6mm, 5um] **Mobile phase:** Ortho phosphoric Acid (0.1%) :Acetonitrile 60:40 v/v **Flow rate:** 1.0 ml/min **Wavelength:** 262 nm **Retention time:** 4.35 (Dol) mins and 7.73 mins.(Ril)	[21]
			Column: XBridge C18 Column (150 x 4.6 mm)	[22]

3	Dolutegravir and Rilpivirine in human Plasma	HPLC-UV	**Mobile phase :** Acetonitrile: Acetate Buffer pH4.5 **Flow rate:** 1 min **Wavelength:**260 (Dol), 305(Ril) **Run time:** 25 min	
4	Dolutegravir and Rilpivirine in human in bulk and dosage form.	RP-UPLC	**Mobile phase:** 0.1% ortho phosphoric acid: Acetontrile (55:45%) **Column:** SB C8 column **Flow rate:** 1 min/ml **Retention time:** 1.25 min (dol), 1.69 (ril). **Wavelength :** 260	[23]
5	Dolutegravir in bulk and tablet dosage form	UPLC – UV	**Mobile phase :** Ammonium acetate : Formic acid 50% (A) Acetonitrile 100 % (B) **Column:** EHB C8 column(2.1 x100mm **Flow Rate :** 0.3 ml / min **Wavelength :** 258 nm.	[24]
6	Dolutegravir in bulk and pharmacutical dosage form	HPLC & HPTLC	**HPLC –** **Column:** ODS C18 column(150 x 4.6 mm) **Mobile phase:** acetonitrile: water pH7.5 (80:20 %) **Flow Rate :** 1 ml / min **U.V. detection range :**260. nm. **HPTLC –** **Column:** G 60 F_{254} column **Mobile phase:** Methanol: Chloroform: Formic acid (8:2:0.5%) **U.V. detection range: 265** nm.	[25]
7	Dolutegravir in Human Plasma	HPLC	**Column :** ODS 2 C18 column (150 x 4.6) **Mobile phase :** Sodium Acetate (pH4.0) : Methanol (30:70) **Flow Rate :** 1.0 ml /min **Retention time :** 2.08 min **Wavelength :** 254 nm	[26]
8	Dolutegravir Pharmaceutical Dosage Form	RP-UPLC	**Column :** BEH C18 (50 cmX 3.0 mm) **Mobile phase :** Dipotassium HydrogenOrthoposphate : Methanol (30:70) **Retention time :** 2.857 min **Wavelength :** 260 nm	[27]
9	Rilipivirine in Dosage form	RP-HPLC	**Column :** C18 column (4.6 cm x 250 mm) **Mobile phase :** Acetonitrile : Phosphate Buffer (60:40) **Flow Rate :** 1.0 ml /min **Retention time :** 2.75 min **Wavelength :** 282 nm	[28]
10	Rilipivirine in Bulk and Dosage form	RP-HPLC, HPTLC	**HPLC-** **Column :** YMC C18 column (20 cm X 10 cm) **Mobile phase :**: Phosphate Buffer : Acetonitrile (60:40 % v/v) **Flow Rate :** 1.0 ml /min **Wavelength :** 272 nm **HPTLC** **Column :** YMC C18 column (20 cm X 10 cm) **Mobile phase :** Ethyl Acetate : methanol : Chloroform, (8:1:1) **Flow Rate :** 1.0 ml /min **Wavelength :** 2 nm	[29]
11	Rilipivirine in Dosage	RP-	**Column :** ODS HG 5 RP C18 column (15cm x 4.6mm)	[30]

	form	HPLC	**Mobile phase :** Acetonitrile : Potassium Dihydrogen Phosphate (40:60) **Flow Rate :** 1.0 ml /min **Retention time :** 4.50 min **Wavelength :** 282 nm	
12	Rilipivirine in Dosage form	RP-HPLC	**Column :** ODS HG-5 C18 column (15cm x 4.6mm) **Mobile phase :** Acetate (pH4.0) : Acetonitrile : Acetate Buffer(4 pH) (63:35% v/v) **Flow Rate :** 1.0 ml /min **Wavelength :** 260 nm	[31]

3. CONCLUSION

Many methods for determination of Dolutegravir and Rilpivirne have been reported. Some HPLC assay methods were used to monitor Dolutegravir and Rilpivirne. Methods for the analysis of active and inactive metabolites of Dolutegravir and Rilpivirne in Rat and Human plasma have also been reported. Some articles related to the determination of Dolutegravir and Rilpivirne alone or in combination pharmaceutical dosage forms have been mentioned. Dolutegravir and Rilpivirne are antiviral drug used to restrict the replication of virus. A sensitive UPLC -UV, method was developed for the estimation of Dolutegravir and Rilpivirne in bulk and pharmaceutical dosage form and also from single one. Along with the above technique HPTLC, RP –UPLC has been also studied for the analysis. Validation of the developed method was done as per the ICH guidelines.

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