Chapter 3

REVIEW OF LITERATURE

3.1 LITERATURE REVIEW FOR DRUGS & THEIR COMBINATIONS

The Anti-Microbial agents are those medicinal agents & drug substances that are utilized in the therapy for the infectious diseases caused due to the micro-organisms like bacteria, virus, fungus, protozoa, parasites, and other organisms that causes illness & health problems in the individuals. These medicinal agents are widely used in the preventions as well as for the therapy of diseases in the body. They are also referred as chemotherapeutic agents.

The literatures have been reviewed for the analytical methods found for the selected class of drugs. The Review of the literatures [42-63] have been done for the triple drug combination of **Doravirine, Lamivudine, Tenofovir**. These drugs belong to the class of NNRTI Non Nucleoside Reverse Transcriptase Inhibitors-class and that been used into therapy to the HIV virus infections in the adults and juvenile patients. These drugs are used individually as well as in the combinations with the other class of antiviral drugs for the therapy of HIV AIDS in the patients. There are reported methods for these drugs in different formulations with other class of drugs, UV, spectrophotometric, RP-HPLC , LCMS and other methods are reported. But none of them includes stability indicating RP-HPLC- method, for triple drugs Doravirine, and- Tenofovir, Lamivudine together- combined tablet dosage forms along with the application in the *in-vitro* dissolution applicable by the developed HPLC method.

For the combination of **Cabotegravir & Rilpivirine** the literature reviews [64-78] have been done, they belong to NNRTI Nucleoside-Reverse-Transcriptase-Inhibitors- drug-class that are been applied-used in HIV infections, for which LCMS, UV Spectroscopic, HPLC methods have been present for the individual drugs as well as with the other drug combinations, but there are no reported methods for the stability indicating assay method by RP-HPLC applied-made for the injectable dosage form of the Cabotegravir & Rilpivirine along within combined dosage forms.

Review of the literature [79-90] has been done for the dugs **Dolutegravir, Rilpivirine & Tenofovir** combinations which are used in the HIV type-1 virus infections as well as in hepatitis virus infections. These drugs are available in tablet oral dosage forms with

different drug combinations. There are reported LC/MS/MS, UV spectrophotometric, HPLC , method for individual and with other drug combinations, but no reported stability indicating HPLC method in combinational-combined dosages available for them. Hence there is need for the analytical method for these drugs in combined-forms.

Fexinidazole drug is a nitro-imidazole derivative used as a Anti-trypanosomal class of drug, used in HAT disease known as HAT Human African Typanosomiasis sleeping sickness which is induced by *Trypanosoma brucei gambiense* organism. Its *in vivo* metabolites are helpful in treatment of infectious disease induced by *Trypanosoma brucei* and *Leishmania donovani*. The literature review [91-95] there is RP-HPLC method for tablet dosage form. For this drug, no stability indicating RP-HPLC -method as well as in-vitro dissolution applicable HPLC method for this drug.

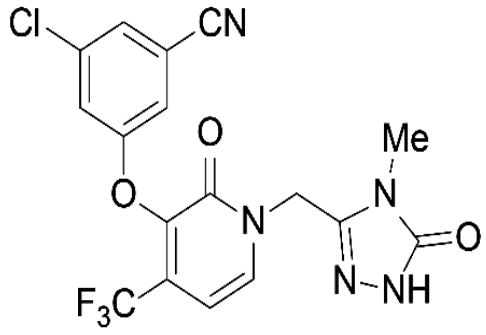
Molnupiravir is a is a drug which applied for the therapy of COVID-19 infections due to SARS COV 2 virus. The drug is effectively used in the therapy for patients in which new mutated viruses are made in active through inhibiting viral replication due to miss-interpretation in replication as drug is a nucleoside analogue of cytidine. The drug Molnupiravir is a isopropyl ester of hydroxyl cytidine and its acts by blocking RNA Polymerase to stop viral replication. The drug is approved therapy in viral infections. Literature reviews [96-105] show RP-HPLC method as well as micellar UV spectrophotometric method in plasma as well as with combination with ritonavir darunavir, HP-TLC method is available but no in-vitro dissolution applicable RP-HPLC method are available for the drug.

The Triple Pak combination of the drugs **Amoxicillin, Clarithromycin, Vonoprazan**, is used in the the therapy of the *Helicobacter pylori* infections employs the use of new combinational these drugs. The Triple Pack drug combination is effective in the treatment as the drugs Amoxicillin, Clarithromycin are anti-microbial agents eradicates the microbial infections. Vonoprazan drug is competitive acid blocker helps in the treating hyper acidity and gastric-duodenal ulcer's along with the combination with Amoxicillin and Clarithromycin induced by *Helicobacter pylori* infections**.** The review of literature [106-119] for these drugs shows, HPLC, LC/MS, UV spectroscopic methods for Amoxicillin, Clarithromycin with other combinations like ornidazole, metronidazole, tinidazole, omeprazole, and other drugs. There are no reported methods for with vonoprazan drug in the triple pak combination.

3.2 DRUG PROFILE

3.2.1 Doravirine

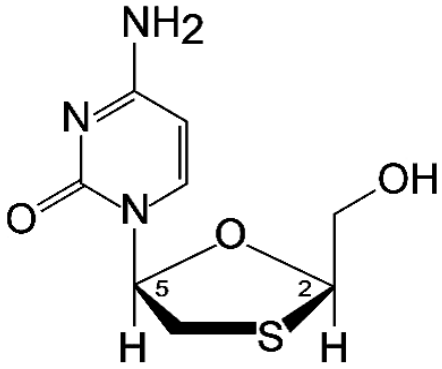
Structure



Molecular Formula	$C_{17}H_{11}ClF_3N_5O_3$
Chemical Name	3 -Chloro - 5 - (- (-1 -(4 – methyl - 5 – oxo -4,5 - di-hydro-1H-1,2,4- triazol -3- yl-) – methyl) – 2 – oxo – 4 -(tri-fluoro- methyl) -1- , -2- dihydro- pyridin - 3 – yl)-oxy -) benzonitrile
Mol. Wt.	425.7
CAS No.	1338225-97-0
Melting Point	284.8 ^{0}C
Solubility	Insoluble in water, and is soluble in DMSO, Freely soluble in 50:50 Water : Methanol
pKa	9.47-9.66
Therapeutic Class	Antiviral, Anti-HIV, NNRTI Nucleoside-Reverse-Transcriptase-Inhibitor

3.2.2 Lamivudine

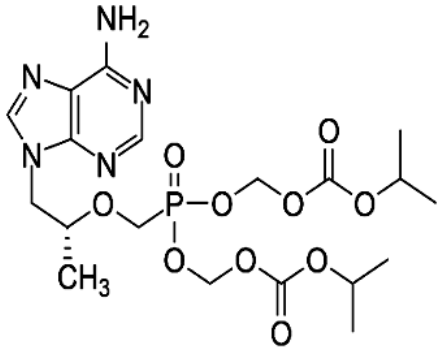
Structure



Molecular Formula	$C_8H_{11}N_3O_3S$
Chemical Name	(-) -1 - [- (- 2 – *R* , 5 – *S* -) – 2 - (- hydroxyl – methyl -) -1- , 3 - oxathiolan - 5 - yl] - cytosine
Mol. Wt.	229.26
CAS No.	134678-17-4
Melting Point	160-162 ^{0}C
Solubility	Sparingly soluble in water, Slightly soluble in solvents ethanol and methanol
pKa	4.08-4.30
Therapeutic Class	Antiviral, Anti-HIV, NNRTI Non-Nucleoside-Reverse-Transcriptase-Inhibitor, Anti-Hepatitis B

3.2.3 Tenofovir

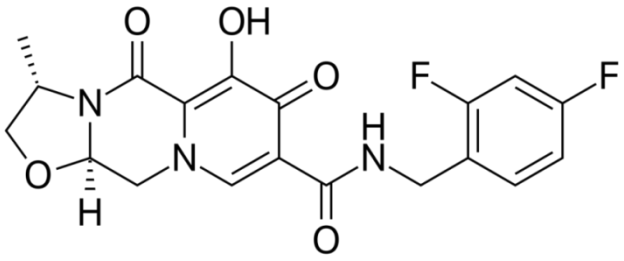
Structure



Molecular Formula	$C_8H_{14}N_5O_4P$
Chemical Name	Bis - { - [- (- isopropoxy – carbonyl -) - oxy] – methyl - } - ({ [(- 2 – R) – 1 - (- 6 - amino - 9H - purin - 9 - yl) - 2 - propanyl-] - oxy} methyl) phosphonate
Mol. Wt.	287.21
CAS No.	201341-05-1
Melting Point	113-115 ^{0}C
Solubility	Soluble in ethanol DMSO, sparingly soluble water, soluble in methanol & in phosphate buffer
pKa	3.75, 6.8
Therapeutic Class	Antiviral, Anti-HIV, NNRTI Nucleoside-Reverse-Transcriptase-Inhibitor

3.2.4 Cabotegravir

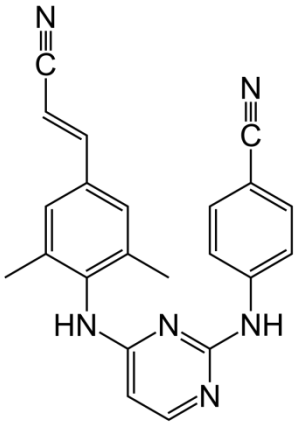
Structure



Molecular Formula	$C_{19}H_{17}F_2N_3O_5$
Chemical Name	N - ((-2,4 – Di-fluoro-phenyl -) – methyl -) – 6 - hydroxyl – 3 – methyl -5,7 – di-oxo - 2,3,5,7,11,11 – a – hexahydro - (1,3) – oxazolo - (3,2-a) – pyrido - (1,2-d) – pyrazine – 8 - carboxamide
Mol. Wt.	405.4
CAS No.	1051375-10-0
Melting Point	241-243 ^{0}C
Solubility	Soluble in DMF, DMSO, sparingly soluble in water, soluble in ACN & in ACN : phosphate buffer 50:50 ratio
pKa	7.7, 10.04, 11.1
Therapeutic Class	Antiviral, Anti-HIV, NNRTI Nucleoside-Reverse-Transcriptase-Inhibitor

3.2.5 Rilpivirine

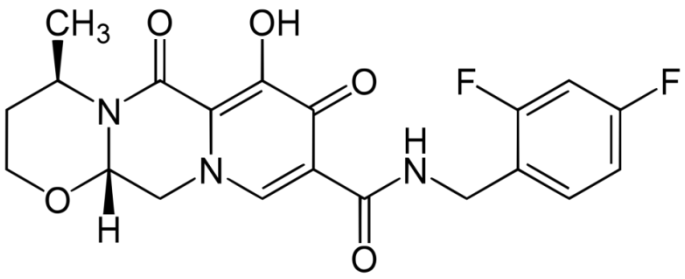
Structure



Molecular Formula	$C_{22}H_{18}N_6$
Chemical Name	4 - {[4 - ({ 4 - [(*E*) – 2 – cyanovinyl] - 2,6 - di- methyl- phenyl } – amino -) – pyrimidin – 2 – yl -] - amino} - benzonitrile
Mol. Wt.	366.42
CAS No.	500287-72-9
Melting Point	248-251 ^{0}C
Solubility	Slightly soluble in methanol and DMF, insoluble in water, soluble in 20:80 Methanol : ACN
pKa	5.6
Therapeutic Class	Antiviral, Anti-HIV, Integrase-Inhibitor

3.2.6 Dolutegravir

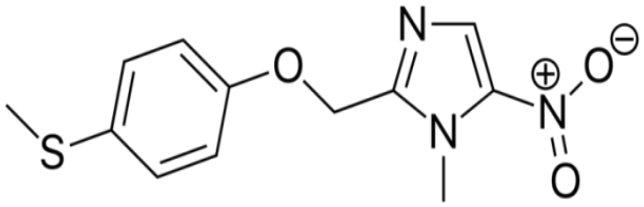
Structure



Molecular Formula	$C_{20}H_{19}F_2N_3O_5$
Chemical Name	(4-R, 12a - S) – N - (2,4 – di – fluorobenzyl) – 7 – hydroxyl – 4 – methyl - 6,8 – dioxo -3, 4 ,6 ,8 , 12 ,12 a – hexahydro - 2H – pyrido - [1',2':4,5] – pyrazino - [2,1 - b] - [1,3] – oxazine – 9 - carboxamide
Mol. Wt.	419.4
CAS No.	1051375-16-6
Melting Point	190-193 ^{0}C
Solubility	Soluble in ACN and methanol, and slightly soluble in water, soluble DMSO & DMF
pKa	8.2
Therapeutic Class	Antiviral, Anti-HIV, Integrase-Inhibitor

3.2.7 Fexinidazole

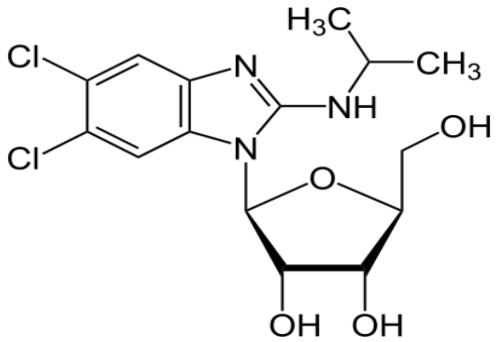
Structure



Molecular Formula	$C_{12}H_{13}N_3O_3S$
Chemical Name	1 – Methyl – 2 - ((- 4 - (methyl – thio) – phenoxy -) – methyl -) - 5 – nitro - 1H - imidazole
Mol. Wt.	279.32
CAS No.	59729-37-2
Melting Point	110-120 ^{0}C
Solubility	Soluble in ethanol methanol DMSO, insoluble in water
pKa	1.03-1.3
Therapeutic Class	Anti-parasitic, Anti-Trypanosomal, nitro-reductase

3.2.8 Maribavir

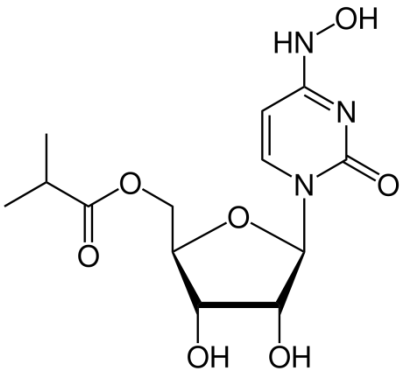
Structure



Molecular Formula	$C_{15}H_{19}Cl_2N_3O_4$
Chemical Name	(2S, 3S, 4R, 5S) - 2 - (5,6 – dichloro – 2 - (isopropylamino) - 1H – benzo - [d] – imidazol – 1 -yl) -5- (hydroxymethyl) – tetrahydrofuran - 3,4 - diol
Mol. Wt.	376.2
CAS No.	176161-24-3
Melting Point	198 ^{0}C
Solubility	Insoluble in water, soluble in methanol & DMSO
pKa	6.38, 12.45-13.20
Therapeutic Class	Anti-viral, Cytomegalovirus CMV UL97 kinase inhibitor

3.2.9 Molnupiravir

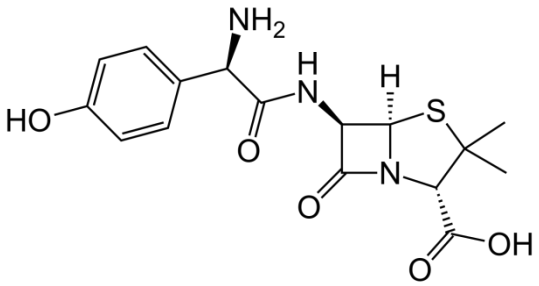
Structure



Molecular Formula	$C_{13}H_{19}N_3O_7$
Chemical Name	((2R, 3S, 4R, 5R) - 3,4 – dihydroxy – 5 - ((4Z) – 4 - (hydroxyimino) – 2 – oxo -3,4 – dihydropyrimidin -1(2H) -yl) – oxolan – 2 - yl) – methyl – 2 - methylpropanoate
Mol. Wt.	329.31
CAS No.	2349386-89-4
Melting Point	156-159 ^{0}C
Solubility	Soluble in water, DMSO, DMF, soluble in PBS-pH-7.2
pKa	8.21
Therapeutic Class	Anti-viral, RNA-polymerase mutation SARS-Cov-2

3.2.10 Amoxicillin

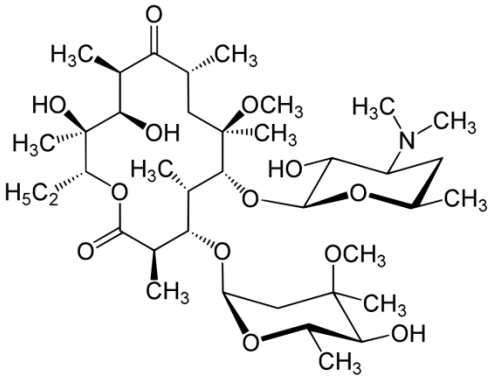
Structure



Molecular Formula	$C_{16}H_{19}N_3O_5S$
Chemical Name	(2*S*, 5*R*, 6*R*) – 6 - [[(2*R*) – 2 – amino – 2 - (4 – hydroxyphenyl) acetyl] amino] - 3,3 – dimethyl – 7 – oxo – 4 – thia – 1 – azabicyclo - [3.2.0] – heptanes – 2 - carboxylic acid
Mol. Wt.	365.4
CAS No.	26787-78-0
Melting Point	194 ^{0}C
Solubility	Freely Soluble water, soluble methanol, sparingly soluble in ethanol, soluble in methanol
pKa	2.6, 3.23, 7.22, 11.7
Therapeutic Class	Anti-bacterial, Cell-wall synthesis inhibitor

3.2.11 Clarithromycin

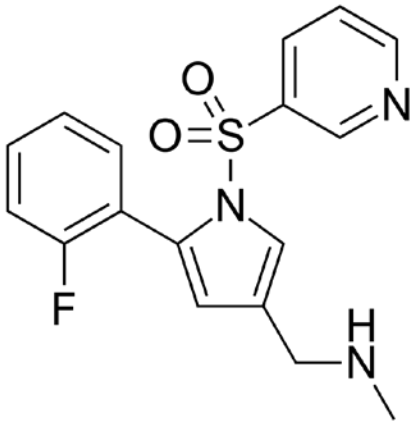
Structure



Molecular Formula	$C_{38}H_{69}NO_{13}$
Chemical Name	(3*R*, 4*S*, 5*S*, 6*R*, 7*R*, 9*R*, 11*R*, 12*R*, 13*S*, 14*R*) – 6 - [(2*S*,3*R*,4*S*,6*R*) – 4 - (dimethyl - amino) – 3 – hydroxyl -6 – methyloxan – 2 – yl] – oxy – 14 – ethyl - 12,13 –dihydroxy – 4 - [(2*R*, 4*R*, 5*S*, 6*S*) – 5 – hydroxyl – 4 – methoxy - 4,6 – dimethyl- oxan – 2 – yl] – oxy – 7 – methoxy -3,5,7,9,11,13 – hexamethyl – oxa - cyclo - tetradecane - 2,10 - dione
Mol. Wt.	478
CAS No.	81103-11-9
Melting Point	217-220 ^{0}C
Solubility	**S**paringly soluble in ethanol, Slightly soluble in water, soluble in methanol,
pKa	8.38, 8.99, 12.46
Therapeutic Class	Anti-bacterial, Protein synthesis inhibitor

3.2.12 Vonoprazan

Structure



Molecular Formula	$C_{17}H_{16}FN_3O_2S$
Chemical Name	1 - [5 - (2 – fluoro – phenyl) – 1 – pyridine – 3 –yl- sulfonyl – pyrrol – 3 –yl] – *N* – methyl - methanamine
Mol. Wt.	345.4
CAS No.	881681-01-2
Melting Point	192-195 ^{0}C
Solubility	Soluble DMSO, Slightly soluble in water, DMSO, slightly soluble in methanol & DMF
pKa	9.06-9.6
Therapeutic Class	Antacid, Competitive potassium proton pump inhibitor