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EFFICACY AND TOLERABILITY OF TENOFOVIR DISOPROXIL FUMARATE BASED REGIMEN AS COMPARED TO ZIDOVUDINE BASED REGIMENS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract:

Background: *Few data are available regarding the use of tenofovir disoproxil fumarate (TDF) during pregnancy for the prevention of mother-to-child transmission of hepatitis B virus (HBV).*

Methods: *In this trial, we included 200 mothers who were positive for hepatitis B e antigen (HBeAg) and who had an HBV DNA level higher than 200,000 IU per milliliter. Participants were randomly assigned, in a 1:1 ratio, to receive usual care without antiviral therapy or to receive TDF (at an oral dose of 300 mg per day) from 30 to 32 weeks of gestation until postpartum week 4; the participants were followed until postpartum week 28. All the infants received immunoprophylaxis. The primary outcomes were the rates of mother-to-child transmission and birth defects. The secondary outcomes were the safety of TDF, the percentage of mothers with an HBV DNA level of less than 200,000 IU per milliliter at delivery, and loss or seroconversion of HBeAg or hepatitis B surface antigen at postpartum week 28.*

Results: *The EAP enrolled 10 343 patients; serious adverse events (SAEs) were reported in 631 (6%). A renalSAE of any type was observed in 0.5% of patients, and graded elevations in serum creatinine occurred in 2.2% of the patients evaluated. In a multivariate analysis, baseline risk factors for the development of increased serum creatinine on-study were elevated serum creatinine, concomitant nephrotoxic medications, low body weight, advanced age, and lower CD4 cell count. For postmarketing safety data (455 392 person-years of exposure to tenofovir DF) the most commonly reported serious adverse drug reactions were renal events, with a distribution by type similar to that observed in the EAP. Bone abnormalities were infrequently reported in either the EAP or the postmarketing safety databases. No new unexpected toxicities were identified in postmarketing safetysurveillance.*

Conclusions: *The data demonstrate a favorable safety profile for tenofovir DF in the treatment of adults with HIVinfection. Risk factors for development of nephrotoxicity can be identified and may be useful in managing those patients at greatest risk.*

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INTRODUCTION:

Pharmaceutical analysis plays a vital role in the Quality Assurance and Quality control of bulk drugs. [1]Analytical chemistry involves separating, identifying, and determining the relative amounts of components in a sample matrix. Pharmaceutical analysis is a specialized branch of analytical chemistry. Pharmaceutical analysis derives its principles from various branches of sciences like physics, microbiology, nuclear science, and electronics etc. Qualitative analysis reveals the chemical identity of the sample. Quantitative analysis establishes the relative amount of one or more of these species or analytes in numerical terms. Qualitative analysis is required before a quantitative analysis can be undertaken. A separation step is usually a necessary part of both a qualitative and quantitative analysis. The results of typical quantitative analysis can computed from two measurements. One is the mass or volume of sample to be analyzed and second is the measurement of some quantity that is proportional to the amount of analyte in that sample and normally completes the analysis.

Assay of drugs in dosage forms:

Assay is the process of determing the percent amount of the analyte present in the sample by its name. Dosage forms require a variety of tests and standards and to assure therapeutic benefit.

According to WHO, a drug[2] may be defined as any substance or product that is used or intended to be used for modifying or exploring physiological systems or pathological states for the benefit of the patient.

The enormous number of drugs available for the treatment of various diseases has made it necessary to classify them. Hence, a sharp division into the following two classes has been made.

Pharmacodynamics agents:

These drugs have certain effects upon animal organs but are not specific remedies for particular diseases. They may be further sub-divided into different classes like central nervous system modifiers (depress or stimulate), adrenergic stimulants and blocking agents, cholinergic and anticholinergic agents, cardio-vascular agents, diuretics, anti-inflammatory agents, antispasmodics, antihistamines, anticoagulants etc.

Chemotherapeutic or anti-infective agents:

Anti-infective agents treat infection by suppressing or destroying the causative microorganisms like bacteria, mycobacterium, fungi, protozoa, or viruses. Anti-infective agents derived from natural substances are called as antibiotics and those produced from synthetic substances are called antimicrobials. However, these two terms are now used interchangeably. An anti-infective agent should be chosen on the basis of its pharmacological properties and spectrum of activity as well as on various host (patient) factors. A combination of drugs should be given only when clinical experience has shown such therapy to be more effective than single-agent therapy in a particular treatment. A multiple agent regimen can increase the risk of toxic drug effects and in a few cases result, a drug antagonism and subsequent therapeutic ineffectiveness.

AIM AND SCOPE OF PRESENT WORK

Since the first clinical evidence of AIDS was reported over 25 years ago, an estimated 25 million people have died as a result of HIV infection, making it one of the most destructive epidemics in recorded history. In 2005, there were an estimated 3.1 million deaths due to AIDS. Current estimates suggest that some 40.3 million people worldwide are infected with HIV, up from an estimated 37.5 million in 2003, and twice as many as compared to 1995. In 2005, it is estimated that an additional 4.9 million individuals worldwide became infected with HIV, and 700,000 of these new infections were in children <15 years of age.

Of major concern is the prevalence of HIV/AIDS in developing countries. Approximately 95% of all HIV-infected people live in low and middle-income countries. Although there is new evidence that adult HIV infection rates have decreased in certain countries, the overall trends in HIV transmission are still increasing, and the overall number of people living with HIV has continued to increase in all regions of the world except the Caribbean.

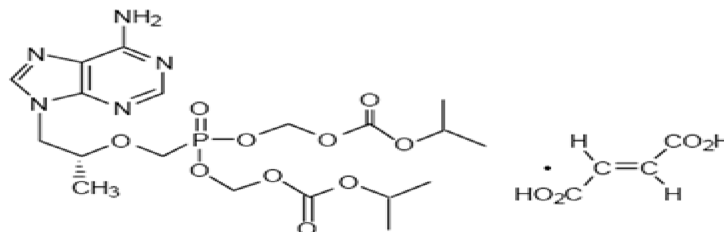
The antiretroviral drugs do not cure the HIV infection; they only temporarily suppress viral replication and improve symptoms. They have various adverse effects and patients receiving these drugs require careful monitoring by adequately trained health professionals. For these reasons, continued rigorous promotion of measures to prevent new infections is essential and the need for this has not been diminished in any way by the addition of antiretroviral drugs. Adequate resources and trained health professionals are a prerequisite for the introduction of this class of drugs. Effective therapy requires commencement of three or four drugs simultaneously, and alternative regimens are necessary to meet specific requirements at start-up, to substitute for first-line regimens in the case of toxicity, or to replace failing regimens. The use of fixed-dose combinations can help simplify treatment,

facilitate storage and distribution, and improve patients adherence to the treatment plan.

Tenofovir disoproxil fumarate(Tenofovir DF):

Tenofovir is a derivative of adenosine monophosphate lacking a complete ribose ring and is the only nucleotide analog currently marketed for the treatment of HIV infection. Because the parent compound had very poor oral bioavailability, tenofovir is available only as the disoproxil fumarate prodrug, which has improved oral absorption and cellular penetration substantially. Like lamivudine and emtricitabine, tenofovir is active against HIV-1, HIV-2, (Human immunodeficiency viruses) and HBV (Hepatitis B virus). The IC_{50} of tenofovir disoproxil fumarate against laboratory strains of HIV-1 ranges from 2 to 7 nM, making the prodrug about one hundredfold more active in vitro than the parent compound.

Structure:



Chemical Name : 9-[(R)-2-[[bis[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]-methoxy]propyl]adenine fumarate (1:1)

Empirical Formula : C19H30N5O10P • C4H4O4

Molecular weight : 635.52

Description : Tenofovir DF is a white to off-white crystalline powder. The Partition coefficient for tenofovir disoproxil is1.25 and the pKa is 3.75.

Mechanism of Action:

Tenofovir disoproxil fumarate is hydrolyzed rapidly to tenofovir and then is phosphorylated by cellular kinases to its active metabolite, tenofovir diphosphate. The active moiety is, in fact, a triphosphate compound because the parent drug starts out as the monophosphate. The intracellular diphosphate is a competitive inhibitor of viral reverse transcriptases and is incorporated into HIV DNA to cause chain termination because it has an incomplete ribose ring. Although tenofovir diphosphate has broad-spectrum activity against viral DNA polymerases, it has low affinity for human DNA polymerases, which is the basis for its selective toxicity.

Resistance:

Virus replication in the presence of suboptimal concentrations of drug can select for mutations conferring resistance to tenofovir. Specific resistance occurs with a single substitution at codon 65 of reverse transcriptase (K65R). This mutation reduces in vitro sensitivity by only three- to fourfold but has been associated with clinical failure of tenofovir-containing regimens. Tenofovir sensitivity and virologic efficacy also are reduced in patients harboring HIV isolates with high-level resistance to zidovudine or stavudine, specifically those having three or more Thymidine analog mutations (TAMs), including M41L or L120W. However, HIV variants that are resistant to zidovudine show only partial resistance to tenofovir, possibly a reflection of the much less efficient excision of tenofovir diphosphate by pyrophosphorolysis. The M184V mutation associated with lamivudine or emtricitabine resistance partially restores susceptibility in tenofovir-resistant HIV harboring the K65R mutation.

Absorption, Distribution, and Elimination:

Tenofovir disoproxil fumarate has an oral bioavailability of 25%. A high-fat meal increases the oral bioavailability to 39%, but the drug can be taken without regard to food. Tenofovir is not bound significantly to plasma proteins. The plasma elimination half-life ranges from 14 to 17 hours. The reported half-life of intracellular tenofovir diphosphate is 11 hours in activated peripheral blood mononuclear cells and 49 hours or longer in resting cells. The drug therefore can be dosed once daily.

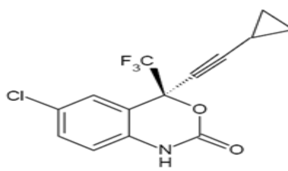
Tenofovir undergoes both glomerular filtration and active tubular secretion. Between 70% and 80% of an intravenous dose of tenofovir is recovered unchanged in the urine. Doses should be decreased in those with renal insufficiency.

Untoward Effects:
Tenofovir generally is well tolerated, with few significant adverse effects reported except for flatulence. In placebo-controlled, double-blinded trials, the drug had no other adverse effects reported more frequently than with placebo after treatment for up to 24 weeks; tenofovir was significantly less toxic than stavudine. However, rare episodes of acute renal failure and Fanconi syndrome have been reported with tenofovir, and this drug should be used with caution in patients with preexisting renal disease. Because tenofovir also has activity against HBV and may lower plasma HBV DNA concentrations, caution is warranted in using this drug in patients co infected with HBV; discontinuation of tenofovir may be associated with a rebound of HBV replication and exacerbation of hepatitis.

Drug Interactions and Precautions:
Tenofovir is not metabolized to a significant extent by CYPs and is not known to inhibit or induce these enzymes. However, tenofovir has been associated with a few potentially important pharmacokinetic drug interactions. A 300-mg dose of tenofovir increased the didanosine AUC by 44% to 60% probably as a consequence of inhibition of the enzyme purine nucleoside phosphorylase by both tenofovir and tenofovir monophosphate. These two drugs probably should not be used together, or if this is essential, the dose of didanosine should be reduced from 400 to 250 mg/day. In addition, low-dose ritonavir (100 mg twice daily) increases the tenofovir AUC by 34%, and atazanavir increases the tenofovir AUC by 25%. The mechanism of these interactions is unknown.

Efavirenz:
Efavirenz is a non nucleoside reverse transcriptase inhibitor (NNRTI) with potent activity against HIV-1. The in vitro IC_{50} of this drug ranges from 3 to 9 nM. Like other compounds in this class, efavirenz does not have significant activity against HIV-2 or other retroviruses.

Structure:



Chemical Name: (S)-6-chloro-4-(cyclopropylethynyl)-1, 4-dihydro-4-(trifluoromethyl)-2H-3, 1-benzoxazin-2-one

Molecular formula: C14H9ClF3NO2

Molecular weight: 315.68.

Description: Efavirenz is a white to slightly pink crystalline powder

Resistance:
Because the target site is HIV-1-specific and is not essential for the enzyme, resistance can develop rapidly. The most common resistance mutation seen clinically is at codon 103 of reverse transcriptase (K103N), and this decreases susceptibility up to one hundredfold or greater. Additional resistance mutations have been seen at codons 100, 106, 108, 181, 188, 190, and 225, but either the K103N or Y181C mutation is sufficient to produce clinical treatment failure. Cross-resistance extends to all FDA-approved NNRTIs.

Absorption, Distribution, and Elimination:
Efavirenz is well absorbed from the gastrointestinal tract and reaches peak plasma concentrations within 5 hours. There is diminished absorption of the drug with increasing doses. Bioavailability (AUC) is increased by 22% with a high-fat meal. Efavirenz is more than 99% bound to plasma proteins and, as a consequence, has a low CSF-plasma ratio of 0.01. The clinical significance of this low CNS penetration is unclear, especially since the major toxicities of efavirenz involve the CNS. It is recommended that the drug be taken initially on an empty stomach at bedtime to reduce side effects. Efavirenz is cleared via oxidative metabolism, mainly by CYP2B6 and to a lesser extent by CYP3A4. The parent drug is not excreted renally to a significant degree. Efavirenz is cleared slowly, with an elimination half-life of 40 to 55 hours at steady state. This safely allows once-daily dosing.

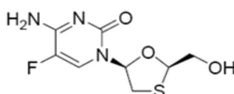
Untoward Effects:
Rash occurs frequently with efavirenz, in up to 27% of adult patients. Rash usually occurs within the first few weeks of treatment and rarely requires drug

discontinuation. Life-threatening skin eruptions such as Stevens-Johnson syndrome have been reported during postmarketing experience with efavirenz but are rare.

Drug Interactions and Precautions:
Efavirenz is a moderate inducer of hepatic enzymes, especially CYP3A4. It undergoes limited autoinduction, but because of its long half-life, there is no need to alter drug dose during the first few weeks of treatment. Efavirenz decreases concentrations of phenobarbital, phenytoin, and carbamazepine; the methadone AUC is reduced by 33% to 66% at steady state. Rifampin concentrations are unchanged by concurrent efavirenz, but rifampin may reduce efavirenz concentrations. Efavirenz reduces the rifabutin AUC by 38% on average. Efavirenz has a variable effect on HIV protease inhibitors. Indinavir, saquinavir, and amprenavir concentrations are reduced, but ritonavir and nelfinavir concentrations are increased. Drugs that induce CYP2B6 or CYP3A4 (e.g., phenobarbital, phenytoin, and carbamazepine) would be expected to increase the clearance of efavirenz and should be avoided.

Emtricitabine:
Emtricitabine is a cytosine analog that is chemically related to lamivudine and shares many of that drug's pharmacodynamic properties. Like lamivudine, it has two chiral centers and is manufactured as the enantiomerically pure (2R, 5S)-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (FTC). Emtricitabine is active against HIV-1, HIV-2, and HBV. The IC_{50} of emtricitabine against laboratory strains of HIV-1 ranges from 2 to 530 nM, although, on average, the drug is about 10 times more active in vitro than lamivudine.

Structure:



Chemical Name: 5-fluoro-1-(2R, 5S)-[2-(hydroxymethyl)-1, 3-oxathiolan-5-yl] cytosine

Molecular formula: C8H10FN3O3S

Molecular weight: 247.24.

Description: Emtricitabine is a white to off-white crystalline powder

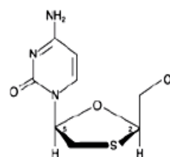
|

Solubility: Practically soluble in water and methanol.

Therapeutic Use:
Emtricitabine is FDA approved for treating HIV infection in adults in combination with other antiretroviral agents. Two small monotherapy trials showed that the maximal antiviral effect of emtricitabine (mean 1.9 log unit decrease in plasma HIV RNA concentration) was achieved with a dose of 200 mg/day. Several large trials have confirmed the antiretroviral activity of emtricitabine in three-drug regimens with other agents, including nucleoside or nucleotide analogs, protease inhibitors, and/or NNRTIs. In two randomized comparison studies, emtricitabine- and lamivudine-based triple-combination regimens had similar efficacy**.**

Lamivudine:
Lamivudine is a cytosine analog reverse transcriptase inhibitor that is active against HIV-1, HIV-2, and HBV. The molecule has two chiral centers and is manufactured as the pure 2R, cis(-)-enantiomer. The racemic mixture from which lamivudine originates has antiretroviral activity but is less potent and substantially more toxic than the pure (-)-enantiomer. Compared with the (+)-enantiomer, the phosphorylated (-)-enantiomer is more resistant to cleavage from nascent RNA/DNA duplexes by cellular exonucleases, which may contribute to its greater potency.

Structure:



Chemical Name: (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one and L-2',3'-dideoxy-3'-thiacytidine

Molecular formula: $C_8H_{11}N_3O_3S$

Molecular weight: 229.26

Description: Lamivudine is a white to off-white crystalline solid

Solubility: Practically soluble in water and methanol.

Careful sampling and sample preparation
Before beginning method development, it is need to review what is known about the sample in order to define the goals of separation. The sample related information that is important is summarized in Table: 2.1

Table 1.1

1.Number of compounds present
2.Chemical structures
3.Molecular weights of compounds
4.pK_a values of compounds
5.UV spectra of compounds
6.Concentration range of compounds in samples of interest
7.Sample solubility

The chemical composition of the sample can provide valuable clues for the best choice of initial conditions for an HPLC separation.

Separation goals

The goals of HPLC separation need to be specified clearly, which include:

- ❖ The use of HPLC to isolate purified sample components for spectral identification or quantitative analysis
- ❖ It may be necessary to separate all degradants or impurities from a product for reliable content assay or not
- ❖ In quantitative analysis, the required levels of accuracy and precision should be known (a precision of ± 1 to 2% is usually achievable)
- ❖ Whether a single HPLC procedure is sufficient for raw material or one or more different procedures are desired for formulations
- ❖ When the number of samples for analysis at one time is greater than 10, a run time of less than 20 minutes often will be important.
- ❖ Knowledge on the desired HPLC equipment, HPLC experience and academic training do the operators have?

Sample preparation

Samples come in various forms

- ❖ Solutions ready for injection
- ❖ Solutions that require dilution, buffering, addition of an internal standard or other volumetric manipulation
- ❖ Solids must be dissolved or extracted
- ❖ Samples that require pretreatment to remove interferences and/or protect the column or equipment from damage.

Table 1.2

Sample	Requirements
Inorganic ions	Detection is primary problem; use ion chromatography.
Isomers	Some isomers can be separated by reversed-phase HPLC and are then classified as regular samples; better separations of isomers are obtained using either (1) normal-phase HPLC or (2) reversed-phase separations with cyclodextrin-silica columns.
Enantiomers	These compounds require "chiral" conditions for their separation.
Biological	Several factors make samples of this kind "special": molecular conformation, polar functionality, and a wide range of hydrophobicity.
Macromolecules	"Big" molecules require column packings with large pores (>>10-nm diameters); in addition, biological molecules require special conditions as noted above.

SUMMARY AND CONCLUSION:

Development of new analytical methods for the determination of drugs in pharmaceutical dosage forms is more important in pharmacokinetic, toxicological and biological studies. Today pharmaceutical analysis entails much more than the analysis of active pharmaceutical ingredients or the formulated product. The pharmaceutical industry is under increased scrutiny from the government and the public interested groups to contain costs and at consistently deliver to market safe, efficacious product that fulfill unmet medical needs. The pharmaceutical analyst plays a major rule in assuring identity, safety, efficacy, purity, and quality of a drug product. The need for pharmaceutical analysis is driven largely by regulatory requirements. The commonly used tests of pharmaceutical analysis generally entail compendia testing method development, setting specifications, and method validation. Analytical testing is one of the more interesting ways for scientists to take part in quality process by providing actual data on the identity, content and purity of the drug products. New methods are now being development with a great deal of consideration to worldwide harmonization. As a result, new products can be assured to have comparable quality and can be brought to international markets faster.

Pharmaceutical analysis occupies a pivotal role in statuary certification of drugs and their formulations either by the industry or by the regulatory authorities. In industry, the quality assurance and quality control departments play major role in bringing out a safe and effective drug or dosage form. The current good manufacturing practices (CGMP) and the Food Drug Administration (FDA) guidelines insist for adoption of sound methods of analysis with greater sensitivity and reproducibility. Therefore, the complexity of problems encountered in pharmaceutical analysis with the importance of achieving the selectivity, speed, low cost, simplicity, sensitivity, specificity, precision and accuracy in estimation of drugs.

RP-HPLC method development: A simple reverse phase HPLC method was developed for estimation of related substances of Tenofovir and Lamivudine present in their pharmaceutical formulation. An Cronosil-M (250 × 4.6 mm), 5μ column along with 65min gradient elution of pH 3.0$NH_4H_2PO_4$ Buffer as mobile phase- A and Acetonitrile and Methanol in the ratio of 90:10 as mobile phase- B. The flow rate was 1.0 ml/min and effluent was monitored at 262 nm. . The impurities identified were Fumaric acid, Carboxylic acid, Stereoisomer of Lamivudine, MONO POC, Salicylic acid, nPOC-POC The retention times were 9.31 min, 10.49 min, 12.86 min, 14.01 min, 26.23 min, 35.05 min, 50.27 min and 51.25 min for Fumaric acid, Carboxylic acid, Stereoisomer, Lamivudine, MONO-POC, Salicylic acid, Tenofovir and nPOC-POC respectively.

Analysis of drugs present in combined pharmaceutical dosage forms is a quite challenging problem and hence attempts were made to develop analytical methods for relative substances of drugs Tenofovir, Efavirenz and Emitracitabine present in combined dosage forms.

All the proposed methods are simple, selective, reproducible, sensitive and accurate with good precision. Some of the methods were proved to be superior to most of the reported methods. All these proposed methods for estimation of selected drugs such as Tenofovir, Efavirenz, Emtricitabine and Lamivudine were successfully applied in pharmaceutical formulations.

The proposed methods can be used as alternative methods to the reported ones for the routine determination of selected drugs under the study in pharmaceutical dosage forms.

Observation:

The retention times and relative retention times for the peaks were as follows:

Name of the peak	Retention time(min)	RRT
Fumaric acid	9.31	0.66
Carboxylic acid	10.49	0.74
Stereoisomer	12.86	0.92
Lamivudine	14.01	1.00
MONO-POC	26.23	1.87
Salicylic acid	35.05	2.50
Tenofovir	50.27	3.58
nPOC-POC	51.25	3.65

The separation and peak shapes were found to be satisfactory.

Conclusion: The above method was finalized for related substances of Tenofovir and Lamivudine. See figures 8.1, 8.2, 8.3, 8.4 and 8.5.

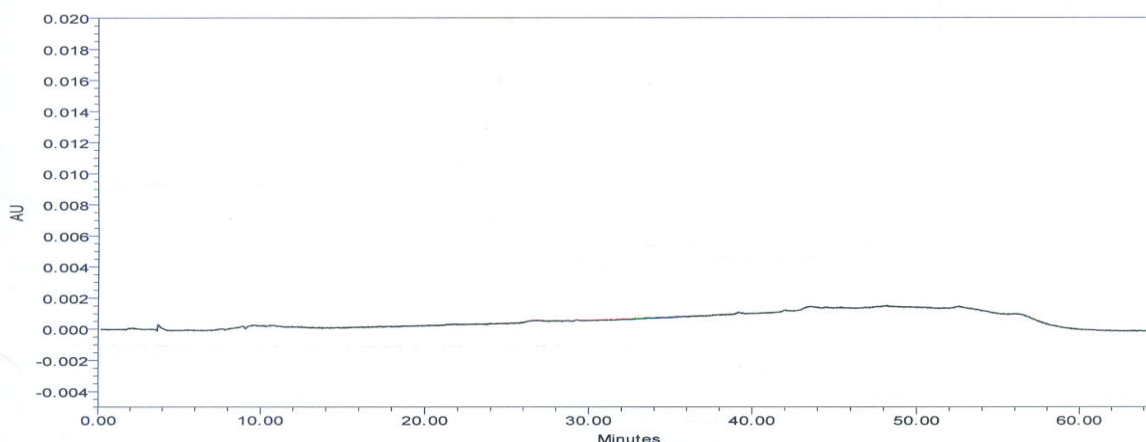


Fig: 8.1 Typical chromatogram of Tenofovir and Lamivudine(Blank)

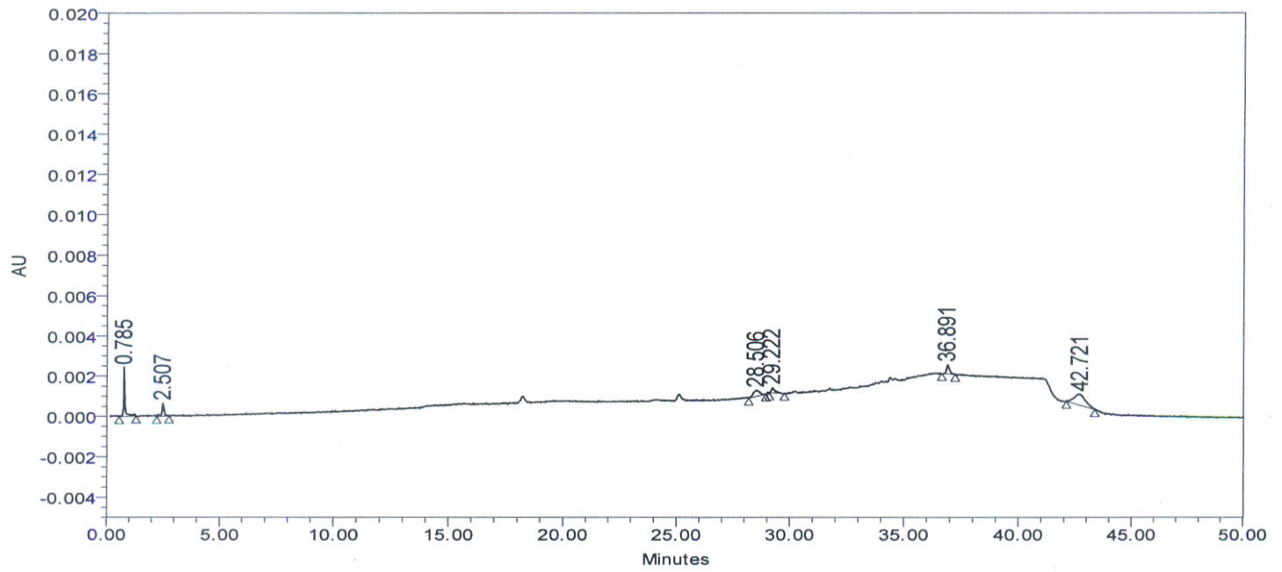


Fig: 8.2 Typical chromatogram of Tenofovir and Lamivudine(Placebo)

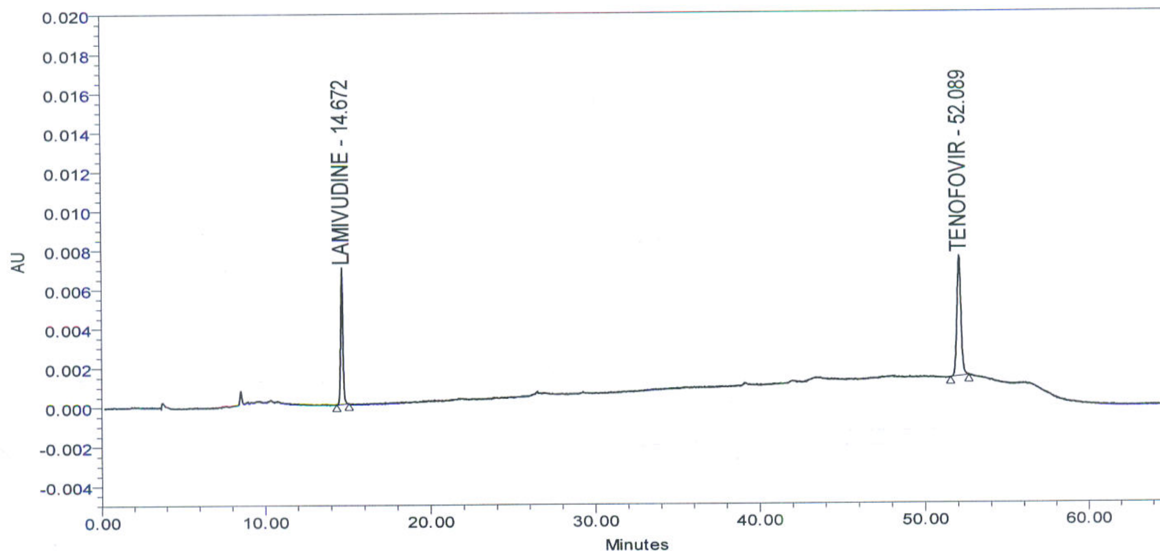


Fig: 8.3 Typical chromatogram of Tenofovir and Lamivudine(Standard)

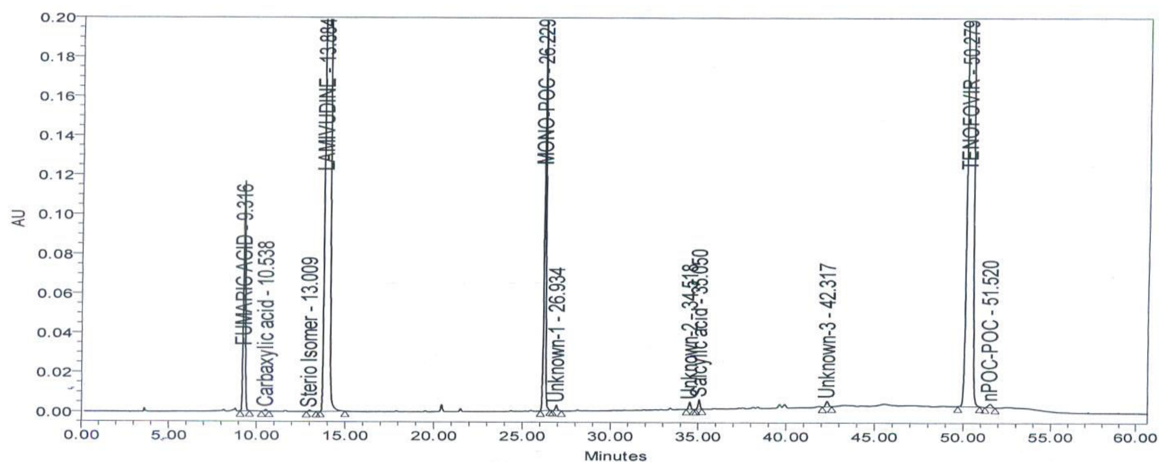


Fig: 8.4 Typical chromatogram of Tenofovir and Lamivudine (Spiked Sample)

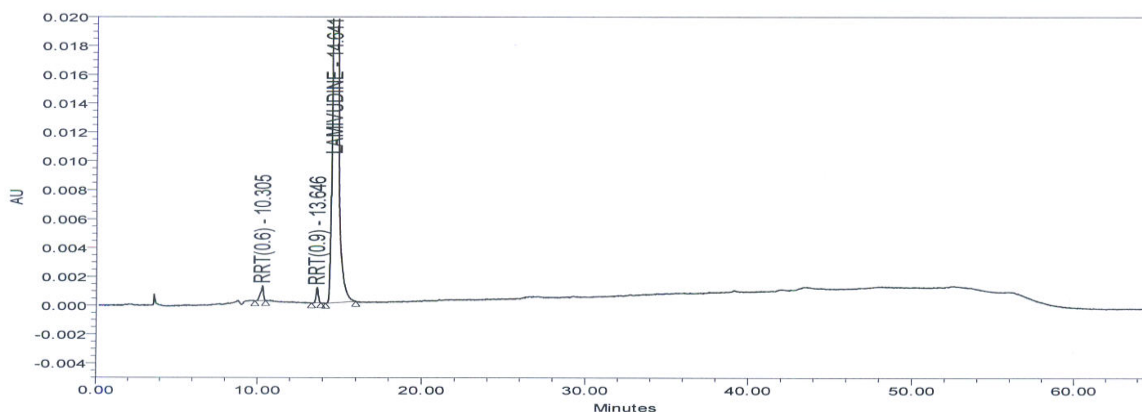


Fig: 8.5 Typical chromatogram of Lamivudine Resolution Mixture

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