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A Review on Antiretroviral Tablets

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ABSTRACT

The usage of fixed dose combination (FDC) tablets of Lamivudine, Dolutegravir and Tenofovir Disoproxil Fumarate (TDF) is increasing due to increased incidences of HIV/Hepatitis B and HIV/TB co-infections. This is likely to increase the financial crisis due to limited resources for funding procurement of ready-made products from the pharmaceuticals manufacturing leading countries. Therefore, production of local oral tablets containing Lamivudine and TDF FDC is inevitable. Lamivudine 300 mg/TDF 300 mg tablets were developed and optimized by D-optimal mixture design and produced by direct compression technique. The first-ever 2-drug regimen approved for the treatment of HIV-1 infection for treatment-naive people living with HIV (PLWH), consisting of the integrase inhibitor dolutegravir (DTG) and the nucleoside reverse transcriptase inhibitor (NRTI) lamivudine (3TC), is reviewed in this paper. The chemical composition and properties, pharmacokinetic and pharmacodynamics profile, and clinical trial data on efficacy and safety of DTG/3TC are presented. An expert opinion aims to highlight important considerations for the use of DTG/3TC in the context of existing and emerging ARV options.

Keywords: Lamivudine, Dolutegravir, Tenofovir Disoproxil Fumarate, Nucleoside reverse transcriptase inhibitor.

I. INTRODUCTION

Remarkable advancements have occurred in the development of combination antiretroviral therapy (cART) for the treatment of HIV infection since the approval of the first antiretroviral agent, zidovudine, in 1987. Since then, more potent, effective and better tolerated treatment regimens which require less frequent dosing and/or that are co-formulated into single-tablet regimens (STRs) have revolutionized the treatment of HIV and led to significant gains in life expectancy among people living with HIV (PLWH).

Given the expanded treatment options, regimen selection by HIV care providers include considerations such as
dosing frequency, food requirement, drug–drug interaction (DDI) potential, short- and long-term

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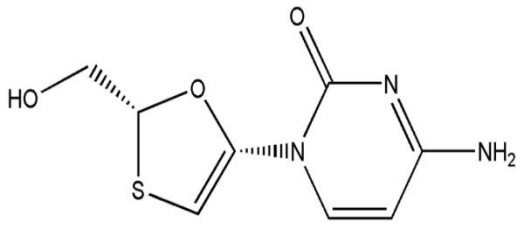
toxicities as well as costs of what is expected to be life-long treatment. These considerations and regimen characteristics are also important for drug development and inform what drugs and treatment strategies should be advanced for clinical. HIV (human immunodeficiency virus) is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing equipment, drug, injection. If left untreated, HIV can lead to the disease AIDS (acquired immunodeficiency syndrome). There is no proven HIV cure and HIV cannot be eliminated by the human body. Thus, if you have HIV, you will always have it. Fortunately, antiretroviral medication, or ART, an effective HIV treatment, is now accessible.

HIV medication can significantly lower the viral load, or the amount of HIV in the blood, if taken as directed. We refer to this as viral suppression. An undetectable viral load is one in which an individual's viral load is so low that it cannot be detected by a typical lab. Individuals with HIV who take their medication as directed, achieve and maintain an undetectable viral load, and avoid sharing HIV with partners who are HIV-negative can lead long, healthy lives. The advanced stage of HIV infection known as AIDS is brought on by the virus severely impairing the immune system of the body. Since taking HIV medication as directed halts the disease's progression, the majority of HIV-positive individuals in the United States do not get AIDS. An individual with HIV is said to have advanced to AIDS if and when their CD4 cell count is less than 200 cells per milliliter of blood (200 cells/mm3). (An individual with a healthy immune system has a CD4 count of 500–1,600 cells/mm3.) OR, regardless of their CD4 count, they get one or more opportunistic infections. In the absence of HIV medication, persons with AIDS usually live for three years. Without treatment, a deadly opportunistic sickness reduces a person's life expectancy to around one year. Even at this stage of HIV infection, medication can still be life-saving for some patients. However, those who begin taking HIV medication immediately after being diagnosed benefit more, which is why HIV testing is crucial.

Chemical Structure of Lamivudine



Lamivudine is a cytidine analogue with a chemical formula (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one, formulated as a sulfur salt (Figure 2). Its molecular formula is C8H11N3O3S with an exact mass of 229.3 g/mol. It appears as an off-white to white crystal that is water soluble with a melting point of 160–162°C.26

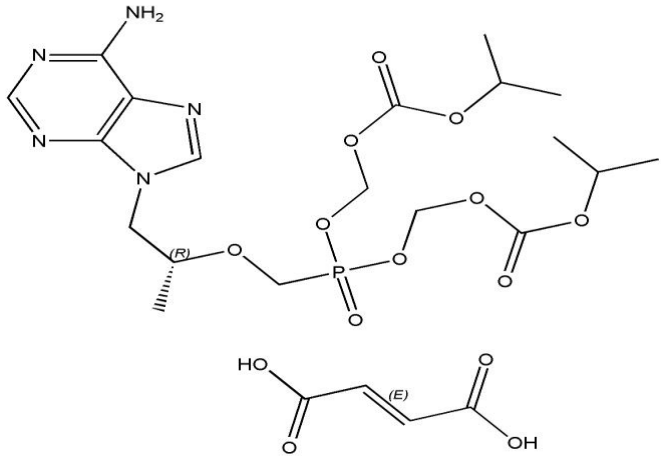
Pharmacodynamics:

3TC competitively inhibits HIV-1 reverse transcriptase by incorporation of its active tri-phosphorylated form into the viral DNA producing chain termination. It has excellent activity against HIV-1 and HIV-2 virus with an EC50 value of 120 nM for HIV-1 and HIV-2 in cell lines including PBMCs and monocytes. 3TC has activity against hepatitis B virus, although monotherapy is associated with the rapid development of resistance.

Pharmacokinetics:

Following oral ingestion, 3TC is rapidly absorbed with excellent bioavailability (87% approximately) that is not significantly impacted by meal intake and with a Tmax of 1 hr. It distributes mainly to the extravascular spaces with a peak time of approximately 3.2 hrs and a volume of distribution of 96 L. Its half-life of 13–19 hrs allows for once-daily dosing. 3TC does not undergo hepatic metabolism and is excreted primarily through the kidneys, hence dose adjustments are required in the setting of compromised renal function. 3TC exhibits linear pharmacokinetics, achieving steady state by day 15 of administration.

Chemical Structure of Tenofovir Disoproxil



Tenofovir disoproxil 201341-05-1 PMPA prodrug Bis (POC)PMPA 9-((R)-2-((Bis(((isopropoxycarbonyl)oxy)methoxy)phosphinyl) methoxy)propyl)adenine. Molecular Weight 519.4 g/mol. Store at 25°C. MIMS Class -Antivirals. ATC Classification J05AF07 - tenofovir disoproxil ; Belongs to the class of nucleoside and nucleotide reverse transcriptase inhibitors. Used in the systemic treatment of viral infections. Tenofovir disoproxil is an organic phosphonate that is the disoproxil ester of tenofovir. A prodrug for tenofovir, an HIV-1 reverse transcriptase inhibitor, tenofovir disoproxil is used as the fumaric acid salt in combination therapy for the treatment of HIV infection. It has a role as a prodrug, a HIV-1 reverse transcriptase inhibitor and an antiviral drug. It is functionally related to a tenofovir (anhydrous).

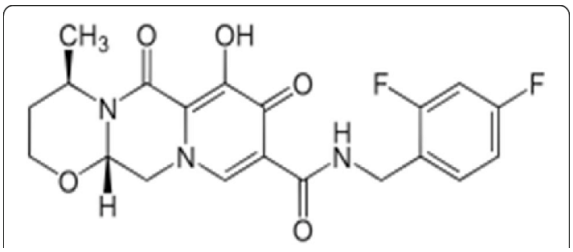
Pharmacodynamics:

This drug prevents viral DNA chain elongation through inhibition of enzymes necessary for host cell infection viral replication in HIV-1 and Hepatitis B infections. In vitro effects-The antiviral activity of tenofovir against in laboratory and clinical isolates of HIV-1 was studied in lymphoblastoid cell lines, primary monocyte/macrophage cells, in addition to peripheral blood lymphocytes. The EC50 (50% effective concentration) values of tenofovir against HIV-1 virus ranged between 0.04 μM to 8.5 μM. Combination of tenofovir disoproxil with other drugs-In drug combination studies of tenofovir with nucleoside reverse transcriptase inhibitors (abacavir, didanosine, lamivudine, stavudine, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), additive and synergistic effects were seen. Tenofovir demonstrated antiviral activities in cell cultures against HIV-1 Label.

Pharmacokinetics:

Absorption- Rapidly absorbed from the gastrointestinal tract. Increased bioavailability when taken with a high fat meal. Bioavailability- Approx 25%. Time to peak plasma concentration: 36-84 minutes (fasting); 96-144 minutes (with high fat meal). Distribution- Widely distributed into body tissues, particularly the kidneys and liver. Volume of distribution: 1.2-1.3 L/kg. Plasma protein binding: <7%. Metabolism- Tenofovir disoproxil fumarate is rapidly converted intracellularly to tenofovir via hydrolysis, and subsequently phosphorylated to the active form, tenofovir diphosphate. Excretion- Via urine (70-80%, as unchanged drug). Elimination half-life- 17 hours.

- **Chemical Structure of Dolutegravir**



DTG sodium is monocarboxylic acid amide and an organic heterocyclic compound with a chemical formula– sodium(4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2Hpyrido[1′,2′:4,5]pyrazino[2,1 b][1,3]oxazin-7-olate (Figure 1). It has a sodium moiety with the molecular formula – C20H18F2N3NaO5 with an exact mass of 441.36 g/mol. It is light yellow to white powder in appearance and is slightly water soluble.

Pharmacodynamics:

DTG is a potent integrase inhibitor that employs divalent cations (Mg2+) to couple with the enzymatic active site of the viral integrase. Its structure allows DTG to penetrate the active and recently vacated enzymatic pocket where it binds farther in than prior drugs in its class. This provides a more stable and lasting bond compared to other precursor integrase inhibitors such that its dissociation constant (mean dissociation constant 2.7 x 10–6 s–1) is slower compared to either raltegravir (RAL) or elvitegravir (EVG) – 22 and 71 x 10–6 s–1, respectively. It also has a lower half-maximal inhibitory concentration (IC50) for HIV-1 of 1.6 nM compared to 3.3 and 6 nM for RAL and EVG, respectively.

Pharmacokinetics:

Following ingestion, DTG peaks in 2–3 hrs. Low-, medium- and high-fat meals increase DTG's AUC by 33%, 41% and 66%, respectively. The median time to maximal concentration (Tmax) is 2.5 hrs. It is tightly protein bound (99%) in plasma and has a medium volume of distribution of 17 L. Its elimination half-life is about 14 hrs which allows for once-daily dosing. DTG is excreted mainly via feces (64%) and urine (31%). DTG is metabolized by UGT1A1 (major pathway) and CYP 3A (minor pathway) but does not inhibit UGT1A1 or inhibit or induce any CYP enzymes, therefore possesses a limited drug–drug interaction profile. However, it is a substrate of BCRP, P-gp, UGT1A3 and UGT1A9.25

II. METHODS AND MATERIAL

Materials

Analytical grade solvents are used like methanol, glacial acetic acid and acetonitrile are generally used. Acetone, diaminoethane, ammonium hydroxide are also used.

Instruments

Densitometer , planar chromatograph software fluid bed dryer , tablet press and tubular mixer are used .

Formulation And Develpoment

For the purpose of this formulation the particle size distribution for Lamivudine and Tenofovir Disoproxil Fumarate (TDF) was set at D90 > 250 μm to prevent the possibility of capping, picking and sticking of formulation during direct compression process. Excipients are the common ones and most of them were utilized by the innovator. Lower and upper limits of pharmaceutical formulation excipients are proposed based on literature search and provided as design constraints . Independent variables and dependent variables are pointed out and presented .

Method of Preparation of Matrix Tablets

Following passage through #40 mesh, lamivudine, HPMC K4M, HPMC K15M, HPMC K100M, dicalcium phosphate, and Povidone K30 were collected individually in a plastic bag. Matrix tablets

were prepared in batches using the wet granulation process. After all of the ingredients were sifted, they were combined at an optimal pace for 20 minutes in a quick mixing granulator. Using a mechanical stirrer, povidone K30 was dissolved in hot water. To get wet mass, the binder solution mentioned above was added to the dry mix and stirred for 15 minutes. The resulting wet mass was then put through a multi-mill and dried for 60 minutes at an input temperature of 40°C to 55°C. Aerosil, magnesium stearate, and talc were used to lubricate the ground granules after they had been processed for ten minutes in an octagonal blender. Finally, a tablet compression machine with a 12 mm flat punch was used to compress the lubricated granules into tablets.

Preformulation Studies :

As a part of preformulation studies, the aim of this work is to examine the solubility and stability of a series of 5′-O-carbonates of lamivudine with proven antihuman immunodeficiency virus activity. Solubility studies are carried out using pure solvents (water, ethanol and polyethylene glycol 400 [PEG 400]), as well as cosolvents in binary mixture systems (water–ethanol and water–PEG 400). These ionizable compounds shows that their aqueous solubility is decreasing as the carbon length of the substituent moiety increases, but being enhanced as the pH is reduced. In addition, the solubility is enhanced significantly by using ethanol and PEG 400 as cosolvents. Stability-indicating high-performance liquid chromatography procedure is found to be selective, sensitive and accurate for these compounds and good recovery, linearity and precision isalso observed.

III.CONCLUSION

The Lamivudine and Tenofovir Disoproxil Fumarate FDC tablets and dolutegravir formulation was developed by using D-optimal design through quality testing assessment involved disintegration, friability, assay and dissolution.

Recommendations

Further formulation development trials could be conducted by varying ratios of binders and disintegrants which were not tried in this study. The undertaking of the proposed trials could lead into other optimized drug formulations and hence providing alternative formulations to the proposed formulation in this study.

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