



Estimation Of Tenofovir Disoproxil Fumarate By Analytical Method:A Review

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Absrtact

Tenofovir disoproxil fumarate (TDF) belongs to the class of antiretroviral drugs known as nucleotide analogue reverse transcriptase inhibitors. It is used in combination with other antiretroviral agents for the treatment of AIDS. Tenofovir and lamivudine are also effective against hepatitis B Virus. Tenofovir disoproxil fumarate is rapidly absorbed from the gastrointestinal tract and is converted to tenofovir with peak plasma concentration occurring within 2 hours. Tenofovir is widely distributed in the body tissues, particularly in kidneys and liver. It is excreted mainly in urine. The objective of this review is to summarize and collect a number of studies that have already been published in various national and international literature platforms for the purpose of estimating the amount of Tenofovir disoproxil fumarate in pharmaceutical formulations and bulk, with a particular emphasis on UV spectrometric methods. There are several parameters employed with the UV Spectrophotometric technique, but two important parameters are λ max and solvent. This compilation review covers all of the analytical techniques that have been utilized to estimate Tenofovir disoproxil fumarate along with their key parameters. This will be helpful for researchers and will further the body of knowledge in this area.

Keywords:

Tenofovir Disoproxil Fumarate , UV spectro photometric method, λ max , viral disease, AIDS, Lamivudin , Emtricitabine , Efavirenz

Introduction

Tenofovir (nucleotide reverse transcriptase inhibitor). It is a nucleotide analogue of adenosine. It undergoes intracellular phosphorylation and inhibits viral reverse transcriptase enzyme resulting in termination of chain elongation of HIV DNA. Flatulence can occur with Tenofovir It should be cautiously used in patients with renal disease. It is used in combination with other antiretroviral agents for the treatment of AIDS. Tenofovir and lamivudine are also effective against hepatitis B Virus.^[1]

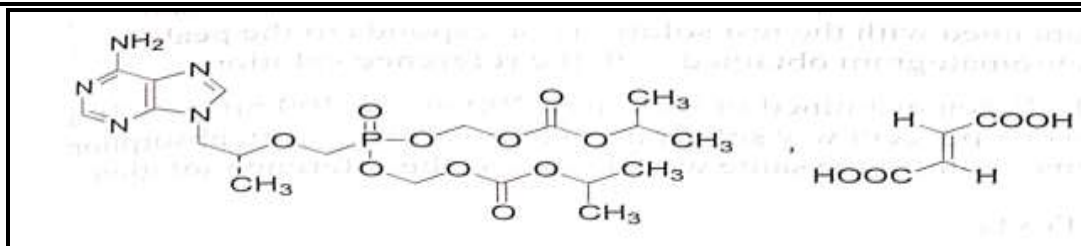


Fig.No-1 Tenofovir Disoproxil Fumarate

MolecularFormula: $C_{19}H_{30}N_5O_{10}P, C_4H_4O_4$ **Molecular**

Weight: 635.5gm/mol

Category: Antiviral

Dose: 300 mg daily

Description: A white to off-white crystalline powder

Solubility: Water

Tenofovir Disoproxil Fumarate contain not less than 97.0 % and not more than 102.0 % of $C_{19}H_{30}N_5O_{10}P, C_4H_4O_4$ calculated on the anhydrous basis. Tenofovir Disoproxil Fumarate salt of bis(isopropoxy- carbonyloxymethyl ester of (R)-9-(2-phosphonomethoxy- propyl) adenine with fumaric acid.^[2]

Tenofovir Disoproxil Fumarate, IP Fumarate Salt of bis(isopropoxycarbonyloxymethyl ester of (R)- 9-(2-phosphonomethoxypropyl) adenine. It is a white to off-white crystalline powder. Tenofovir disoproxil fumarate is rapidly absorbed from the gastrointestinal tract and is converted to tenofovir with peak plasma concentration occurring within 2 hours. Tenofovir is widely distributed in the body tissues, particularly in kidneys and liver. It is excreted mainly in urine. The usual dose of tenofovir disoproxil fumarate is 300 mg once daily with food for the treatment of HIV infection.

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Each film coated tablet contains:
 Tenoxicam Disproxiol
 Fumarate IP 300mg
 Emeticitabine IP 200mg
 Excipients q.s.
 Colour: Yellow Oxide of Iron &
 Titanium Dioxide IP
 Dosage:
 As directed by the Physician.
 Storage:
 Store protected from moisture if at
 temperature not exceeding 30°C
 Keep out of reach of children.
 Keep the container tightly closed.

Tenofovir & Emtricitabine Tablets.IP^[3]

The objective of the current project is to develop simple, accurate, and precise analytical techniques for the quantitative determination of TDF from different body fluid simulations in bulk and solid dosage forms. A single UV-spectrophotometric method for identifying the drug in pharmaceuticals, bulk, or other simulated physiological body fluids like double-distilled water, stomach, or vaginal fluids is not identified in the literature review.

In this paper, a study on the development of new validated UV-spectrophotometric methods for the estimation of TDF in bulk and solid dosage form in various simulated buffer media—namely, double distilled water, pH 6.8, phosphate buffer (PB) at pH 6.8, and gastric simulated fluid (HCl) at pH 1.5—is reported. The International Conference on Harmonization (ICH) requirements were followed in the validation of the procedures.^[4]



Tenofovir disoproxil fumarate is an orally accessible ester prodrug of Tenofovir (also known as PMPA), an acyclic nucleotide analog with action invitro against retroviruses, including HIV-1, HIV-2, and hepatitis B virus (HBV). Tenofovir's negative charge at neutral pH is caused by the presence of a phosphonate group, which restricts its oral bioavailability. After absorption, Tenofovir Disoproxil Fumarate quickly transforms Tenofovir, which is metabolized intracellularly, into Tenofovir diphosphate, an active metabolite that inhibits HIV-1 reverse transcriptase (RT) and stops the DNA chain from growing.^[5]

The current study's objectives were to create a stability-indicating assay (Carstensen.*et.al.*, 2000, Singh and Bakshi. *et.al.*, 2002, Singh et al., 2006) and determine the intrinsic stability of tenofovir disoproxil fumarate through stress studies conducted under a range of ICH-recommended test conditions (International Conference on Harmonization, 1996; Singh and Bakshi et al., 2000, International Conference on Harmonization, 2003).^[6]

Human immunodeficiency virus (HIV):

Human Immunodeficiency Virus is known as HIV.

H: It exclusively infects people and is spread by humans, not by animals. It cannot be spread by mosquito, bat, or other animal bites.

I. The immune system in our bodies works to defend us against pathogens, diseases, and other threats. However, HIV-positive individuals are incapable of fighting off illnesses. But the immune system starts to weaken.

V. virus is a tiny, simple object that exists outside of the body in an inactive state before becoming active once it enters the body. AIDS is brought on by the HIV virus. Our body's immune system typically fights off germs and viruses.

White blood cells in our immune system shield us against pathogens. Helper cells, or T cells, or CD4+ cells are found in white blood cells. An infected individual will have the capacity to grow. These infections prey on the immunological system of the body. These infections can result in a number of health issues and even death. Although there isn't a cure for AIDS, several medications can help the disease progress more slowly and keep you healthier for longer^[7]

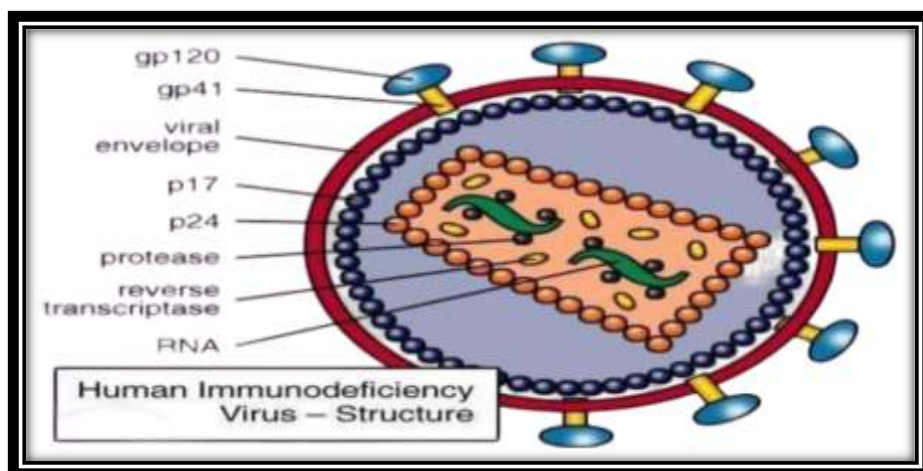


Fig No:2 Human Immunodeficiency Virus-Structure

Origin Of HIV:

It is thought by scientists that a particular kind of chimpanzee found in West Africa is the source of the HIV infection in humans. The immunodeficiency virus that affects chimpanzees is known as SIV (Simian Immunodeficiency Virus). It is thought that when people hunted SIV-infected chimpanzee for meat and came into touch with its blood, the virus spread and changed into HIV in humans. 1959 saw the discovery of what is most likely the first known instance of HIV-1 type infection in humans from a man's blood sample in Kinshasa, Democratic Republic of Congo.

According to the blood sample's genetic analysis, the individual may have contracted a virus in the late 1940s or early 1950s.

Stages Of HIV:

There are 3 stages of infections and severity increases as the stage of disease increases.

- ☐ **Stage: 1** (Acute HIV infection)
- ☐ **Stage:2** (Chronic infection)
- ☐ **Stage: 3** (Acquired immunodeficiency syndrome).

Stage 1: Acute HIV Infection

Acute HIV infection is the initial stage of the virus. usually appears two to four weeks after the patient contracts the HIV infection. During this initial phase of infection, the virus grows and travels quickly throughout the body. The HIV begins to target and eliminate the CD4 cells that fight infection. The immune system gradually declines as a result. High blood levels of HIV enhance the likelihood of HIV transmission during the acute phase.

Stage 2: Chronic HIV Infection

This is the second stage of HIV infection, sometimes referred to as clinical latency or asymptomatic HIV. The virus continues to replicate during this second stage of infection, but extremely slowly.

Stage 3: AIDS

The third stage of HIV infection is actually known as AIDS and is the most serious. The body is unable to fight off opportunistic infections at this point because HIV has seriously compromised the immune system. When a person's CD4 count is less than 200 cells/mm, they are diagnosed with AIDS.

Life Cycle Of HIV

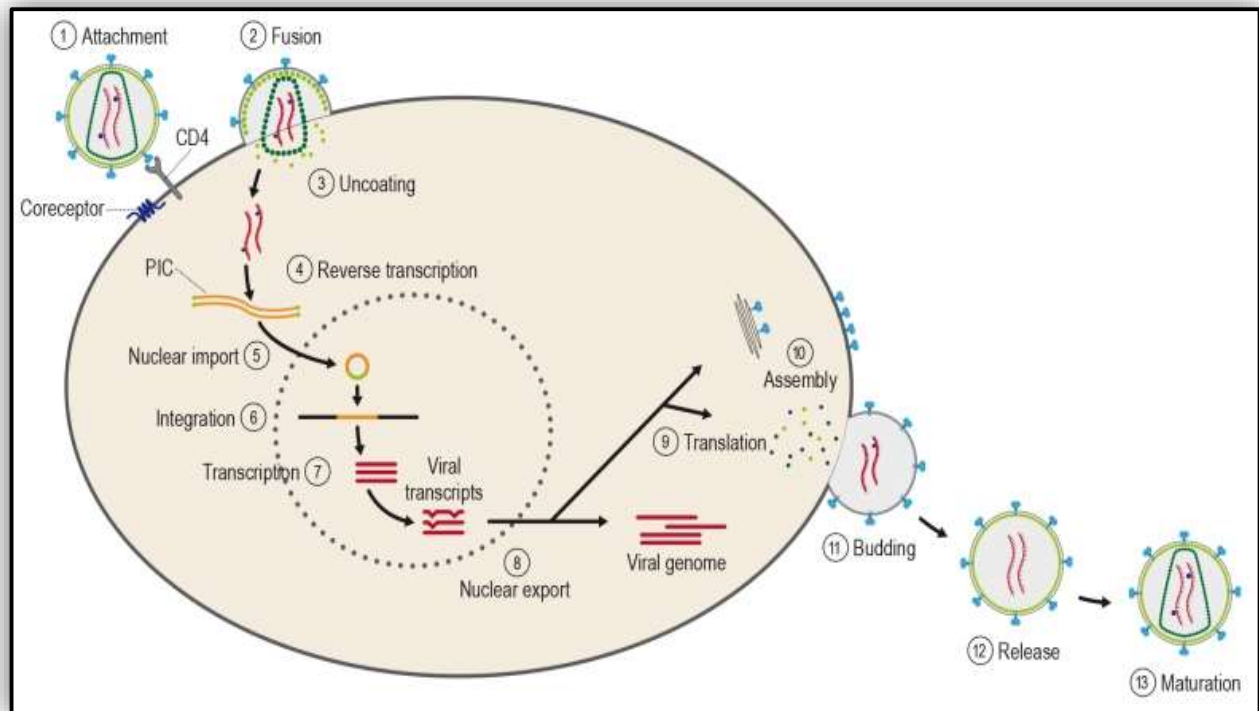


Fig.No-3 Life Cycle of HIV

Entry to Human Cells

The HIV virus is unique in that it replicates within human cells. When this virus attaches itself to a cell that has the CD4 protein on its surface, the process starts. HIV attaches itself to the cd4 receptor, allowing the two to unite. T-helper cells, which make up the body's immune system, are the immunological cells that HIV mostly infects. As HIV infects more cells, the immune system deteriorates.

Reverse transcription

Reverse transcriptase is an enzyme that facilitates reverse transcription. Reverse transcriptase's primary job is to transform viral RNA into DNA. After that, the enzyme integrase transports the DNA to the cell's nucleus, where it is inserted.

Transcription and translation

At this point, transcribing happens. HIV virus produces messenger RNA via conversion.

Assembly, budding and maturation

After HIV copies combine with freshly produced HIV protein and enzymes, new viral particles are formed, which bud out from the original CD4 cell. HIV protein's lengthy chains are broken up into smaller pieces by the enzyme protease. These recently discovered viruses are able to find and infect additional CD4 cells.^[8]

Literature Review:

Swati .K.et.al.(2018)

Tenofovir Disoproxil Fumarate was estimated using a novel, straightforward, precise, and accurate zero order derivative spectroscopic method that has an absorption maximum at 258 nm in 0.1 N H₂SO₄. The method was developed and validated for use in bulk and pharmaceutical dosage forms. It was discovered that the linearity fell within the 5 concentration range. 40 µg/ml, with a correlation coefficient of 0.9995 and strong linearity, was discovered. precision and repeatability in this concentration range. It was discovered that the regression equation was $Y = 0.0243 X + 0.0134$. The accuracy of the method was demonstrated by the recovery values, which fell within the range of 99.82 to 100.14%. It was discovered that the LOD and LOQ were, respectively, 0.3266 and 0.9800 mcg / ml. Less was the % RSD values^[9]

Mondal.N.et.al.(2014)

Tenofovir Disoproxil fumarate (TDF), an anti-HIV medication, has been identified in raw material and in tablets using straightforward, sensitive, and precise UV spectrophotometric techniques. In four distinct media, namely stomach fluid simulated (HCl) pH 1.5, vaginal fluid simulated (VFS) pH 4.2, phosphate buffer (PB) pH 6.8, and double distilled water, the medication exhibits its highest absorption at 259 nm. Within the 5-45 µg/mL drug concentration range, Beer's law is followed. The results show that the limits of detection and quantification are, respectively, 1.37 and 4.17 µg/ml in the simulated stomach fluid, 1.27 and 3.85 µg/ml in the simulated vaginal fluid. The techniques have been effectively used to measure TDF in tablets and pharmaceuticals in bulk. The ICH recommends statistical validation of the results. The commercial formulation's ingredients are found to not interfere with the methodologies; as a result, the UV-method enables quick and affordable drug measurement in tablet and bulk dose form., 1.22 and 3.71 µg/ml in the phosphate buffer, and 1.30 and 3.95 in the double-distilled water.^[10]

Himaja.M.et.al.(2014)

The goal is to provide a straightforward and accurate derivative spectrophotometric approach for figuring out how much tenofovir disoproxil fumarate is in both bulk and prescription dosage forms.

Techniques: Standard and sample solutions were made in an azeotropic combination (methanol: water, 40:60 v/v). Zero order derivative values were recorded at 260 nm and first order derivative values were measured at 273 nm (n-6) in order to quantitatively determine the medication.

Results: For both the zero order and first order derivative spectro photometric methods, calibration graphs created at their wavelengths of determination were linear within the concentration range of 4-24 µg/mL ($r^2 = 0.999$ and $r^2 = 0.998$).

In conclusion, there is no apparent variation in the suggested approaches' performance

with respect to mean values and standard deviations, making them appropriate for the regular quality control of pharmaceutical formulations containing tenofovir disoproxil fumarate^[11]

Combination Emtricitabine+TDF

Choudhari .V. P *et.al.*(2013)

A novel UV-visible spectrophotometric base line manipulation technique has been devised that is easy to use, affordable, precise, and accurate for determining tenofovir disoproxil fumarate (TE) and emtricitabine (EM) in combination tablet dose form simultaneously. This approach uses distilled water as the solvent and is based on baseline manipulation (difference) spectroscopy, where amplitudes at 261 and 289.9 nm were chosen to calculate TE and EM, respectively, in a combined formulation. In the concentration ranges of 4–20 $\mu\text{g/mL}$ for TE and 6–30 $\mu\text{g/mL}$ for EM, both medications follow Beer's rule. The analytical data have undergone statistical validation, and recovery experiments have confirmed the accuracy of the suggested approach, which adhered to ICH requirements.^[12]

Vishwanath.V.*et.al.*(2013)

Tenofovir disoproxil fumarate (TDF) and emtricitabine (EMT) can now be estimated simultaneously in a single tablet dosage form thanks to the development and validation of a new, straightforward, sensitive, accurate, and U.V. Spectrophotometric absorbance correction method. The solvent was 50% v/v methanol. 260 nm and 290 nm were the chosen wavelengths for absorption correction method. For TDF, the method was found to be linear between 5 and 25 $\mu\text{g/mL}$, and for EMT, between 7 and 35 $\mu\text{g/mL}$. For TDF and EMT, respectively, the mean percentage recovery was found to be between 99.24% and 100.42% and 100.03 and 101.04% at three distinct levels of standard additions. The method's precision (both intra- and inter-day) was found to be within acceptable bounds ($\text{RSD} < 2\%$).^[13]

Ingale K.D.*et.al.*(2009)

Two techniques have been developed to measure emtricitabine and tenofovir disoproxil fumarate simultaneously using spectroscopy. The two methods are the absorbance ratio method and the simultaneous equation method. Based on investigations into the solvent effect and the spectral characteristics of emtricitabine and tenofovir disoproxil fumarate, methanol was chosen as the solvent. Tenofovir Disoproxil Fumarate exhibits maximum absorbance at 259 nm, while emtricitabine exhibits maximum absorbance at 281 nm. Linearity was demonstrated for Tenofovir Disoproxil Fumarate and Emtricitabine in the concentration ranges of 6–48 $\mu\text{g/mL}$ and 4–32 $\mu\text{g/mL}$, respectively. The first method used a simultaneous equation to determine the drug concentration, while the second method used the ratio of absorbances at the isoabsorptive point and the λ_{max} of one drug to determine the drug concentration. Recovery studies and statistical validation were used to verify the analysis's findings. Using the developed methods, a tablet containing both drugs was assayed with good accuracy and precision.^[14]

Combination Lamivudin+TDF

Gupta Rakesh.*et.al.*(2019)

A For the simultaneous determination of Lamivudine (LAM) and Tenofovir disoproxil fumarate (TDF) in mixed dosage form, a straightforward, exact, accurate, and cost-effective spectrophotometric approach was devised and validated. Using the absorptivity values at certain wavelengths 276 nm and 260 nm, respectively—in a water solvent system, LAM and TDF were quantified using the simultaneous equation approach. In the concentration range of 5–25 $\mu\text{g/mL}$, LAM and TDF fulfilled Beer's law. The ICH criteria (Q2A & Q2B) were followed in determining several analytical parameters, including linearity, precision, accuracy, limit of detection (LOD), and limit of quantification (LOQ). Both medications' percentages of recovery fell between 98.31 and 98.94%, demonstrating exceptional accuracy. The procedures were exact, with a relative standard deviation of

less than 2% for both drugs. The simultaneous equation approach can be utilized for regular analysis since it makes it easy, quick, and direct to determine LAM and TDF in commercially accessible combination dosage form without the need for prior separations.^[15]

Three combination Lamivudine +TDF + Efavirenz

Edebi.N.V.et.al.(2022)

The task of calculating individual drugs in formulations with many components using a single spectroscopic analytical method is challenging. Lamivudine (3TC), Tenofovir disoproxil fumarate (TDF), and efavirenz (EFV) were among the antiretroviral (ARV) drugs analyzed in a fixed drug combination (FDC) using a simultaneous UV-spectrophotometric method. Maximal absorptions of TDF, EFW, and 3TC were observed in 0.1 HCl at 230, 247, and 270 nm, respectively. The method validation resulted in robustness and repeatability, with linearity ranging from 1-5 ug mL⁻¹ for TDF, 10-50 ug mL⁻¹ for EFV, and 2-10 ug mL⁻¹ for 3TC, respectively, with correlation coefficients (r) of 0.998, 0.999, and 0.998. For 3TC, TDF, and EFV, the corresponding percentage drug contents were 98.44±1.26%, 97.52±0.72%, and 99.43±1.44%. Excipient interference was absent from the method, which made it possible to identify multicomponent ARVs in FDCs.^[16]

Three combination Emtricitabine +TDF+Efavirenz

Mishra.R.et.al.(2021)

The simultaneous equation method is predicated on drug absorption (X, Y, and Z) at the opposing drug's maximal wavelength. The three wavelengths selected for the approach are 240 nm, 256 nm, and 316 nm for Efavirenz (EFV), Emtricitabine (EMT), Tenofovir disoproxil fumarate (TDF) λ max. and The established method was then validated using various parameters. A straight forward, accurate, dependable, repeatable, and effective UV spectrophotometric method has been developed and validated. The reliability and validity of suggested methods have been examined by recovery studies. It was discovered that the recovery of additional standards (80 %, 100 %, and 120 %) occurred at three replication and three concentration phases. It is implied that the procedure is accurate only if the percent number is close to 100, SD, and less than 2 % RSD. Repeatability and intermediate precision were used to calculate accuracy. Consistency over a brief period of time in the same operating environment is implied by the effect of repeatability. The intermediate precision analysis is expressed in terms of variation in the laboratory on different days and variation in analysts by different analysts.^[17]

Table No-1**Comparison of UV Technique of Tenofovir Disoproxil Fumarate & Emtricitabine**

Parameter	Method 1(UV) Choudhari.V.P	Method 2(UV) Vishwanath.V.P	Method 3(UV) Ingale.K.D
Wavelength	161&289nm	260&290nm	259&281nm
Concentration Of Range	TDF 4-2µg/ml EMT 6-30µg/ml	TDF 5-25µg/ml EMT 7-35µg/ml	TDF 6-48µg/ml EMT 4-32µg/ml
Mean%	-	99.24%, 100.42%, 100.03%&101.04%	-

Table No-2**Comparison of UV Technique of Tenofovir Disoproxil Fumarate**

Parameter	Method 1(UV) Swati.K	Method 2(UV) Mondal.N	Method 3(UV) Himaja.M
wavelength	258 nm	259nm	260nm
Mobile Phase	-	Hcl-PH(1-5) (VFS) PH (4-9) phosphate Bufferr PH (6.8)	Methanol: Water 40:60v/v
Range	99.82%To100.14%	-	-
Drug Concentration Range	40 µg /m	5-45 µg/ml	-
LOD	0.3266 mcg/ml	Stomach Fluid 1.31 µg /ml Vaginal Fluid 1.27 µg /ml	-
LOQ	0.9800mcg/ml	Stomach Fluid 4.17 µg /ml Vaginal Fluid 5.83 µg /ml	-

Conclusion

For The Study of Tenofovir Disoproxil Fumarate In Bulk And Pharmaceutical Dose Form, A Number Of UV Methods Have Been Reported. The Current Review Collected All of The Methods Described In The Literature, With An Accent on UV Spectrophotometric Tenofovir Disoproxil Fumarate Estimation. The Development of New Techniques Will Lessen The Analytical Issues That Currently Exist, Such As Increasing Resolution, Reducing Retention Time And Run Time, And Others. These Techniques Will Be More Accurate, Precise, Cost-Effective, And Efficient, And They Will Be Suitable For Routine Analysis. This Paper Discusses UV Spectrophotometric Techniques For Tenofovir Disoproxil Fumarate Dosage Estimation In Both Pharmaceutical And Bulk Form. As A Result, This Evaluation Will Aid In Future Research And Serve As A Manual For Developing New Tenofovir Disoproxil Fumarate Research Methods. The Three Proposed Methods Are Accurate, Precise, Rapid, Reproducible And Economical And Can Be Employed For Routine Quality Control of Emtricitabine And Tenofovir Disoproxil Fumarate In Combined Dosage Formulation. The Method Is Simple, Rapid, Accurate And Precise And Can Be Used For Routine Analysis of Tenofovir From Tablet Formulations

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