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Method Development and Validation for the Simultaneous Estimation of Doravirine, Lamivudine and Tenofovir Bulk and Pharmaceutical Dosageform

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ABSTRACT
A simple, precise, accurate, sensitive, reliable and cost effective Stability indicating RP-HPLC method was developed and validated for the the simultaneous estimation of the Lamivudine, Tenofovirand Doravirine in Api and Tablet dosage form. Chromatogram was run through Zorbax C18 150x4.6mm, 5m. Mobile phase containing 0.1% Formic acid and Acetonitrile in the ratio of 70:30 v/v was pumped through column at a flow rate of 1ml/min. Temperature was maintained at 30°C. Optimized wavelength for Lamivudine, Tenofovir and Doravirinewas260.0 nm.Retention time of Lamivudine, Tenofovir and Doravirine were found to be 2.383 min, 2.977 minand3.926 min respectively. The linearity was established over the concentration ranges of 20–100 µg/ml and 30–150 µg/ml with correlation coefficient%RSD of method precision for Doravirine, Lamivudine and Tenofovir were and found to be 1.6, 1.1 and 1.0 respectively. % recovery was obtained as 100.56%, 99.98% and 99.35% for Doravirine, Lamivudine and Tenofovir respectively. LOD values are obtained from regression equations of Doravirine, Lamivudine and Tenofovir.were 0.21 ppm, 0.64 ppm, 0.55 pmandLOQvalues are obtained from regression equations of Doravirine, Lamivudine and Tenofovirwere0.65ppm,1.94ppm,1.67ppmrespectively.PercentageassayofDoravirine, Lamivudine and Tenofovir was found to beObtainedwas 99.95%. 100.19% and 100.43% respectively.Doravirine, Lamivudine and Tenofovir were subjected to stress conditions like Acidic, Alkaline, Oxidation, Thermal and Photo degradation and results showed that Doravirine,Lamivudine,Tenofovir was more sensitive towards Acid degradation and The % degradation results were within the limits Hence the developed method can be successfully employed for the routine analysis of Doravirine,Lamivudine and,Tenofovir in bulk and pharmaceutical dosageform

KEYWORDS: Doravirine. Lamivudine, Tenofovir, RP-HPLC

I. INTRODUCTION

Doravirine ischemically3-chloro-5-({1-[(5-hydroxy-4-methyl-4H-1,2,4-triazol-3-yl)methyl]-2-oxo-4-(trifluoromethyl)- 1,2-dihydropyridin-3-yl}oxy)benzonitrile .And its molecular formula $C_{17}H_{11}ClF_3N_5O_3$,Molecular Weight 425.749

Doravirine has been used in trials studying the treatment of HIV-1, HIV-1 Infection, Renal Impairment, and Human Immunodeficiency Virus (HIV) Infection.

Lamivudin is chemically4-amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin- 2-onemolecular formula is $C_8H_{11}N_3O_3S$its molecular weight is 229.256 A reverse transcriptase inhibitor and zalcitabine analog in which a sulfur atom replaces the 3' carbon of the pentose ring. It is used to treat Human Immunodeficiency Virus Type 1 (HIV-1) and hepatitis B (HBV)

Tenofovir is chemically ({[(2R)-1-(6-amino-9Hpuryl)propanyl]oxy}methyl) phosphonicacid Its molecular formula is $C_9H_{14}N_5O_4P$ and its molecular weight is 287.2123 Tenofovir is in a class of medications called nucleoside reverse transcriptase inhibitors (NRTIs). It works by decreasing the amount of HIV and HBV in the blood. Tenofovir may not prevent the spread of hepatitis B to otherpeople

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Image 1: Structure of Doravirine

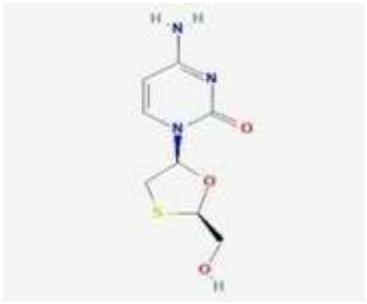

Image2:Structureof Lamivudine

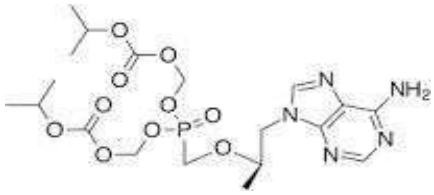

Image3: Structure of Tenofovir,

Doravirine. Lamivudine, and,Tenofovir, were introduced into the market in combined dosage form (**Delstrigo**) it is a fixed-dose combination antiretroviral medication used to **treat HIV/AIDS** doravirine, Lamivudine, and Tenofovir. Doravirine belongs to a class of drugs known as non- nucleoside reverse transcriptase inhibitors (NNRTIs). Lamivudine is called a nucleoside reverse transcriptase inhibitor and Tenofovir is called a nucleotide reverse transcriptase inhibitor. Lamivudine and Tenofovirare often called NRTIs. Doravirine/ Lamivudine/ Tenofovir is not a cure for HIV infection. To decrease your risk of spreading HIV disease toothersThe literature review reveals that few analytical methods have been reported for the simultaneous estimation Doravirine, Lamivudine, and Tenofovir.of in bulk, pharmaceutical dosage forms and in biological samples. They are UV Spectrophotometric, HPLC and LC-MS/MS methods. Few analytical methods are reported for the Doravirine, Lamivudine, and Tenofovir in bulk and pharmaceutical formulations. They are UV Spectrophotometric, HPLC and UPLC methods. But still there is a need for the development of more sensitive and cost effective analytical method for simultaneous estimation Doravirine, Lamivudine, and Tenofovir of Hence an attempt has been made to develop a simple, precise, accurate, sensitive, reliable and cost effective stabilityindicating RP- HPLC method for the simultaneous estimation of Doravirine, Lamivudine, and Tenofovir in bulk and pharmaceutical dosage form.

II. MATERIALS AND METHODS

Chemicals and reagents

Drug Samples\Were obtained from Spectrum pharma research solutions pvt.ltd

Chemicals and Solvents Used : Water –HPLC grade Acetonitrile - HPLC grade, Triethyl amine– AR grade Potassium dihydrogenortho phosphate – AR grade, Orthophosphoric acid – Argrade, All the above chemicals and solvents are From Ranchem

Instrumentation

- Electronics Balance -Denver
- BVK enterprises, India, P^H meter
- Waters HPLC 2695 series with quaternary pumps, Photo Diode array detector and auto sampler integrated with empower software
- BVK enterprises, Ultrasonicator.
- Lab India UV double beam spectrophotometer with UV win5

Selection of wavelength

UV spectrum of 10µg/ml Doravirine and 10µg/ml of Lamivudine and10µg/ml of Tenofovir in Methanol were recorded by scanning in the range of 200nm to 400nm against blank separately. Then the suitable wavelength for the detection of Doravirine, Lamivudine and Tenofovir was selected as 259 nm by overlapping the spectrum of

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drugs. At this wavelength of the drugs showed good absorbance.

Chromatographic Condition

The chromatographic separation of Doravirine. Lamivudine, Tenofovir, was performed by using a Zorbax C_{18} 150x4.6mm, 5m. Mobile phase containing 0.1% Formic acid and Acetonitrile in the ratio of 70:30 v/v was pumped through column at a flow rate of 1ml/min. Temperature was maintained at 30°C. Detection of wavelength was carried out at 259 nm. The retention time of Doravirine, Lamivudine, Tenofovir was found to be 2.650min,3.191min and 4.123 min.

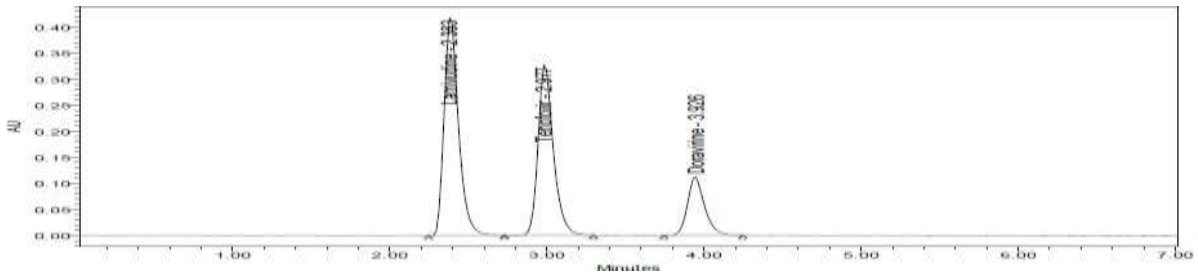

Image 4: Chromatogram of Doravirine. Lamivudine, Tenofovir Standard

Preparation of Standard Solution

Accurately weighed 12.5mg of Doravirine, 37.5 mg of Lamivudine and 37.5mg of Tenofovir and transferred to three 25ml volumetric flasks separately 10ml of Diluent was added to flasks and sonicated for 20mins. Flasks were made up Diluent and labeled as Standard stock solution 1, 2 and 3. (Doravirine 250ppm, Lamivudine 750ppm&Tenofovir750ppm).

Preparation of Sample Solution

5 tablets were weighed and calculate the average weight of each tablet then the weight equivalent to 1 tablet wastransferred into a 100 ml volumetric flask, 25ml of diluent added and sonicated for 50min, further the volume made up with diluent and filtered. (Doravirine 1000ppm, Lamivudine 3000ppm&Tenofovir3000ppm)

III. RESULTSAND DISCUSSION

Method validation

The developed method was validated with respect to system suitability, specificity, linearity, precision, accuracy, limit of detection, limit of quantification and robustness in accordance with the ICH Q2 (R1)guidelines.

System suitability

System-suitability tests are an integral part of method development and were used to ensure adequate performance of the chromatographic system. Retention time (RT), number of theoretical plates (N), tailing factor (T), and peak asymmetry (AS), resolution (RS) were evaluated. The results are shown in Table1

Property	Doravirine	Lamivudine	Tenofovir	Acceptance Criteria
Retention-time (Rt)	3.926	2.383	2.977	-
Resolution	4.9	4.9	4.9	NLT 2.0
Tailing factor (T)	1.22	1.29	1.27	NMT 2.0
Theoreticalplates (N)	6431	3247	4633	NLT 2000

data it was found that all the system suitability parameters for developed method were within the limit

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. It was found that there is no interference of any blankpeaks with the drugs of the analysis concern. Hence method was specific

Linearity

The linearity of an analytical method is its ability to elicit test results which are directly proportional to the concentration of analyte in the

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sample. Standard solution of Doravirine. Lamivudine, Tenofovir were prepared in such a way that the final concentration of Doravirine. Lamivudine, Tenofovir is in the range of 20-100µg/ml

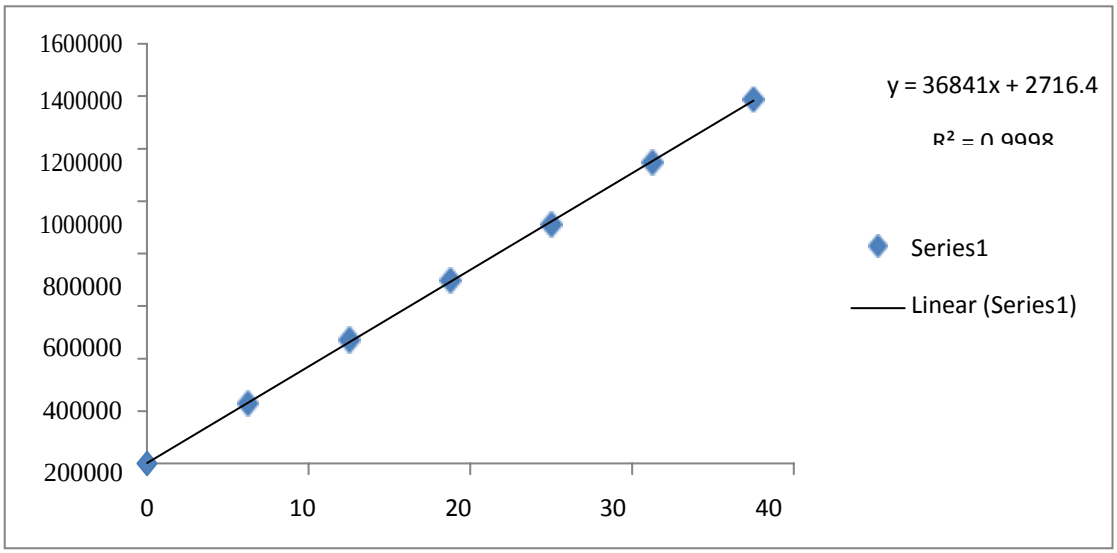


Image 5: Calibration curve of Dorarvine

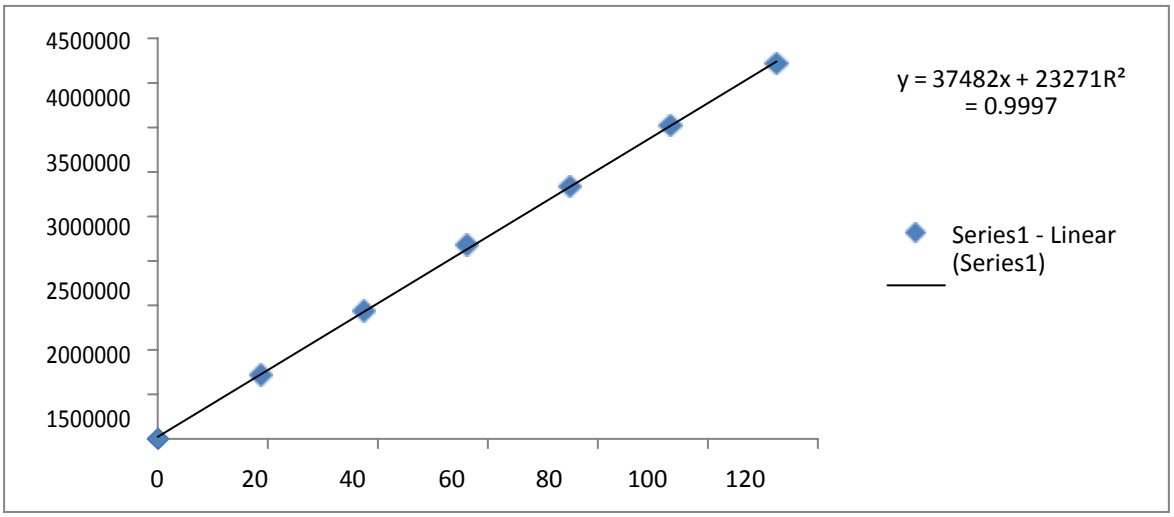
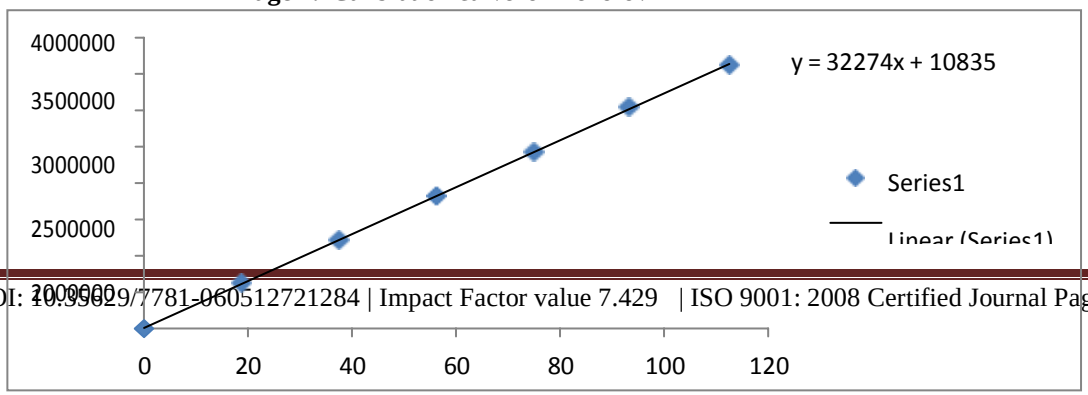


Image 6: Calibration curve of Lamivudine

Image 7: Calibration curve of Tenofovir



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The correlation co-efficient of Dorarviine. Lamivudine and Tenofovir were found to be 0.999 for all the threedrugs which were in the acceptance limit. Hence the proposed method was linear.

Precision

From a single volumetric flask of working standard solution six injections were given and the obtained areas were mentioned above. Average area, standard deviation and % RSD were calculated for three drugs and obtained as 1.6%, 1.1% and 1.0% respectively for Doravirine, Lamivudine and Tenofovir. As the limit of Precision was less than "2" the system precision was passed in this method.

Table 2: Results of Intra-day Precision and Intermediate Precisionfor Dorarviine. Lamivudine, Tenofovir

S.NO	Area of Doravirine.	Area of Lamivudine	Area of Tenofovir
1.	895372	2787576	2335711
2.	902124	2787410	2358731
3.	909957	2758102	2343435
4.	882637	2775102	2291171
5.	890792	2783950	2339936
6.	899430	2746886	2368458
Mean	896719	2773171	2339574
S.D	9455.7	17018.5	26736.1
%RSD	1.1	0.8	1.0

Multiple sampling from a sample stock solution was done and six working sample solutions of same concentrations were prepared, each injection from each working sample solution was given on the next day of the sample preparation and obtained areas were mentioned in the above table. Average area, standard deviation and % RSD were calculated for three drugs and obtained as 1.1%, 0.8% and 1.0% respectively for Doravirine, Lamivudine and Tenofovir. As the limit of Precision was less than "2" the system precision was passed in this method.

Accuracy

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. Accuracy may often express as percent recovery by the assay of known added amounts of analyte. Accuracy of the developed method was confirmed by doing recovery study as per ICH guideline at three different concentration levels 50%, 100%, 150% and the Values were measured. This performance was done in triplicate. The results were shown in Table.

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Table 3: Accuracy table of Doravirine**.**

% Level	AmountSpiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	12.5	12.67	101.43	100.56%
	12.5	12.610	100.89	
	12.5	12.59	100.76	
100%	25	25.097	100.39	
	25	25.033	100.13	
	25	25.106	100.43	
150%	37.5	37.185	99.16	
	37.5	37.762	100.70	
	37.5	37.916	101.11	

Table 4 : Accuracy table of Lamivudine

% Level	AmountSpiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	37.5	37.384	99.69	99.98%
	37.5	37.362	99.63	
	37.5	37.557	100.15	
100%	75	74.948	99.93	
	75	75.317	100.42	

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	75	75.137	100.18	
150%	112.5	113.449	100.84	
	112.5	110.969	98.64	
	112.5	112.859	100.32	

Table 5 : Accuracy table of Tenofovir

% Level	**AmountSpiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	**Mean %Recovery**
50%	37.5	37.328	99.54	99.35%
	37.5	37.471	99.92	
	37.5	37.498	99.99	
100%	75	74.556	99.41	
	75	74.164	98.89	
	75	74.106	98.81	
150%	112.5	112.512	100.01	
	112.5	110.409	98.14	
	112.5	111.859	99.43	

Three levels of Accuracy sample were prepared by standard addition method. Triplicate injections were given for each level of accuracy and mean %Recovery was obtained as 100.56%, 99.98% and 99.35% for and Doravirine, Lamivudine and Tenofovir. Respectively.

Limit of detection and Limit of quantification (LOD & LOQ)

Detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated, under the stated experimental conditions. Quantification limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. LOD and LOQ of Doravirine, Lamivudine and Tenofovir were determined based on signal-to-noise ratio.

The S/N ratio value for LOD solution shall be 3 and for LOQ solution shall be 10. The S/N ratio values for LOD and LOQ of Doravirine, found to be 4.054&4.099, Lamivudine found to be 2.398&2.418 and Tenofovir were found to be 2.947&2.978 for respectively. The results obtained were within the limit, which showed that the method was sensitive

Robustness

The robustness of the proposed method was determined by analysis of aliquots from

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homogenous lots by differing physical parameters like flow rate (±0.1ml/min), mobile phase ratio (±10%). The results were shown inTable

Table 6: Robustness data for Doravirine, Lamivudine and Tenofovir

S.No	Condition	%RSD of Doravirine.	%RSD of Lamivudine	%RSDof Tenofovir
1	**Flow rate (-) 0.9ml/min**	1.5	1.3	1.0
2	**Flow rate (+) 1.1ml/min**	0.7	1.2	0.8
3	**Mobile phase (-) 55W:45M**	1.3	1.5	1.4
4	**Mobile phase (+) 45W:55M**	0.5	1.0	1.8
5	**Temperature (-) 25°C**	0.2	0.8	1.4
6	**Temperature (+) 35°C**	1.5	0.9	1.1

Results for actual flow rate and Mobile phase composition have been considered from Accuracy standard. The Retention time, USP plate count, USP tailing factor obtained for change of flow rate, variation in mobile phase were found to be within the limit. Hencethe method was robust.

Assay: Assay was performed to determine the content of Dorarviine. Lamivudine, Tenofovir in combined dosage form. The % assay should be within range of 98-102%. The % assay of Doravirine, Lamivudine and Tenofovir were found to be 99.95&100.19&100.43

FORCED DEGRADATION STUDIES

The International Conference on Harmonization (ICH) guidelines entitled stability testing of new drug substances and products requires that stress testing be carried out to elucidate the inherent stability characteristics of the active substance. The specificity of the method was demonstrated through forced degradation studies conducted on the sample using acid, alkaline, oxidative, thermal and photolytic degradations. The sample was exposed to these conditions and the percentage degradation was calculated

Table 7 : Degradation Data of Doravirine

S.NO	Degradation Condition	Area	% Area Recovery	% Drug Degraded
1	Acid	862645	94.31	5.69
2	Alkali	870138	95.13	4.87
3	Oxidation	882060	96.43	3.57

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4	Thermal	894310	97.77	2.23
5	UV	896479	98.01	1.99
6	Water	908160	99.29	0.71

Table 8 : Degradation Data of Lamivudine

S.NO	**Degradation Condition**	**Area**	**% Area Recovery**	**% Drug Degraded**
1	Acid	2656715	94.68	5.32
2	Alkali	2679921	95.51	4.49
3	Oxidation	2700114	96.23	3.77
4	Thermal	2727901	97.22	2.78
5	UV	2767856	98.64	1.36
6	Water	2786005	99.29	0.71

Table 9: Degradation Data of Tenofovir

S.NO	**Degradation Condition**	**Area**	**% Area Recovery**	**% Drug Degraded**
1	Acid	2282531	94.83	5.17
2	Alkali	2302391	95.65	4.35
3	Oxidation	2347091	97.51	2.49
4	Thermal	2356755	97.91	2.09
5	UV	2375068	98.67	1.33
6	Water	2389070	99.25	0.75

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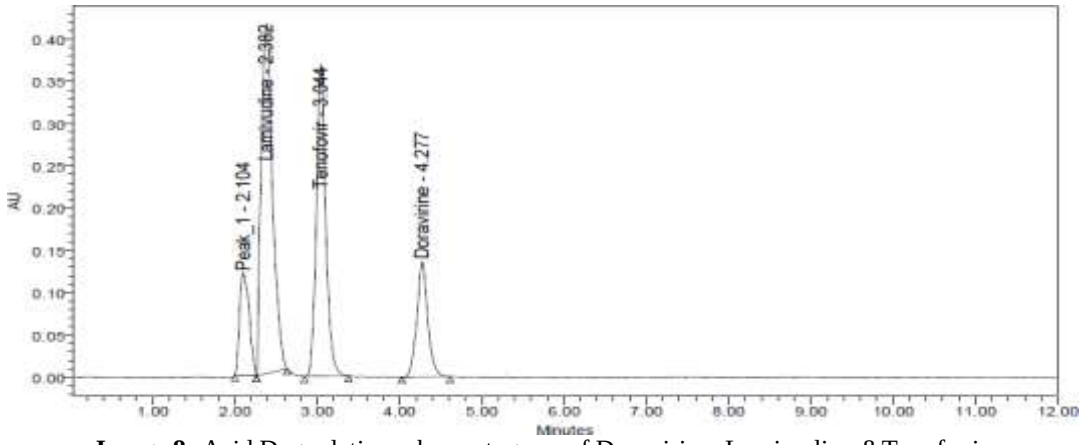

Image 8: Acid Degradation chromatogram of Doravirine, Lamivudine &Tenofovir

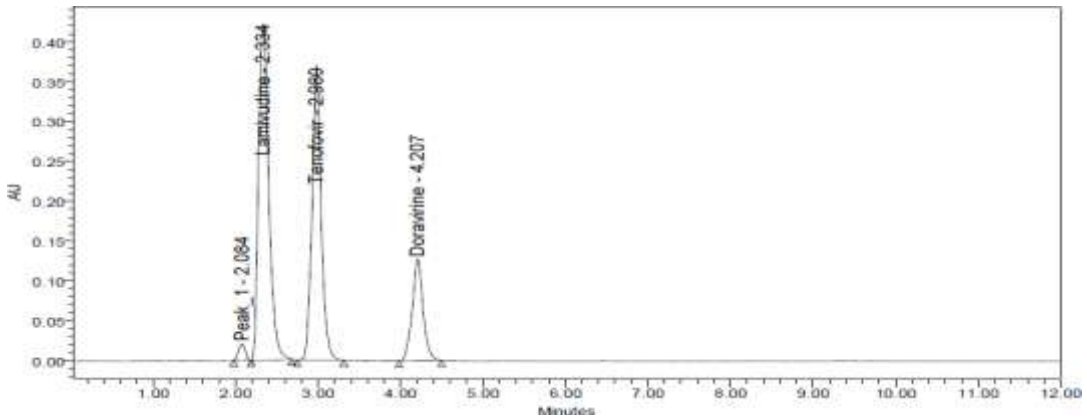

Image 9: Base Degradation chromatogram of Doravirine, Lamivudine &Tenofovir

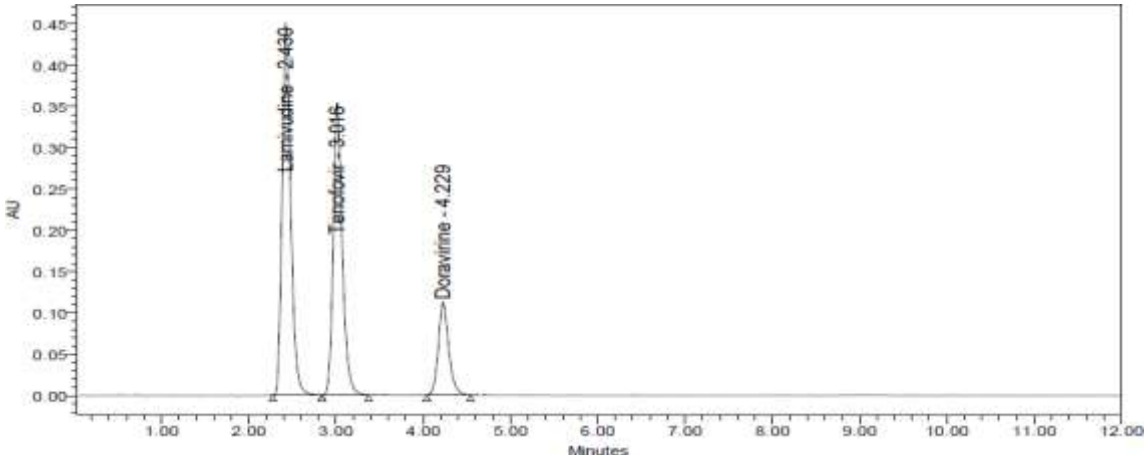

Image 10 : PeroxideDegradation chromatogram of Doravirine, Lamivudine &Tenofovir

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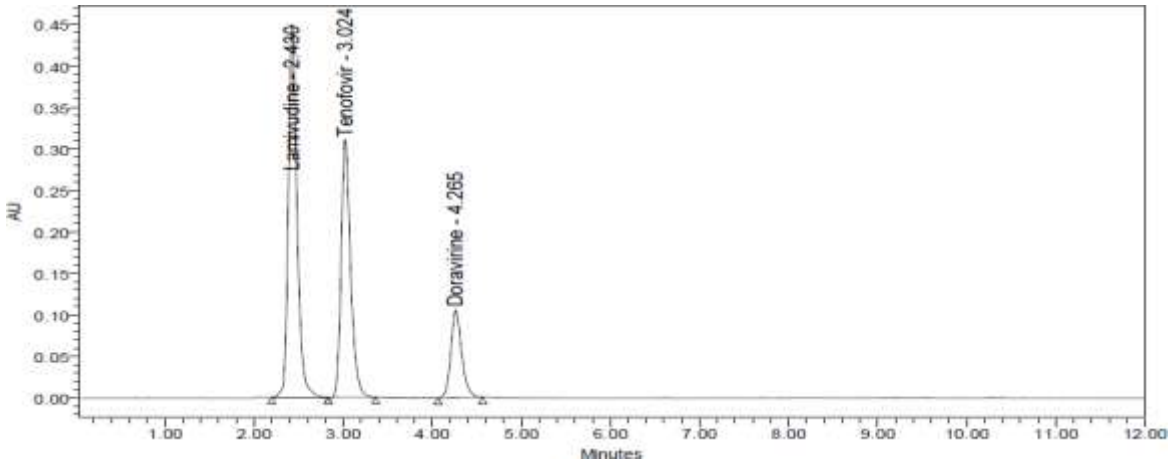

Image 11: Thermal Degradation chromatogram of Doravirine, Lamivudine &Tenofovir

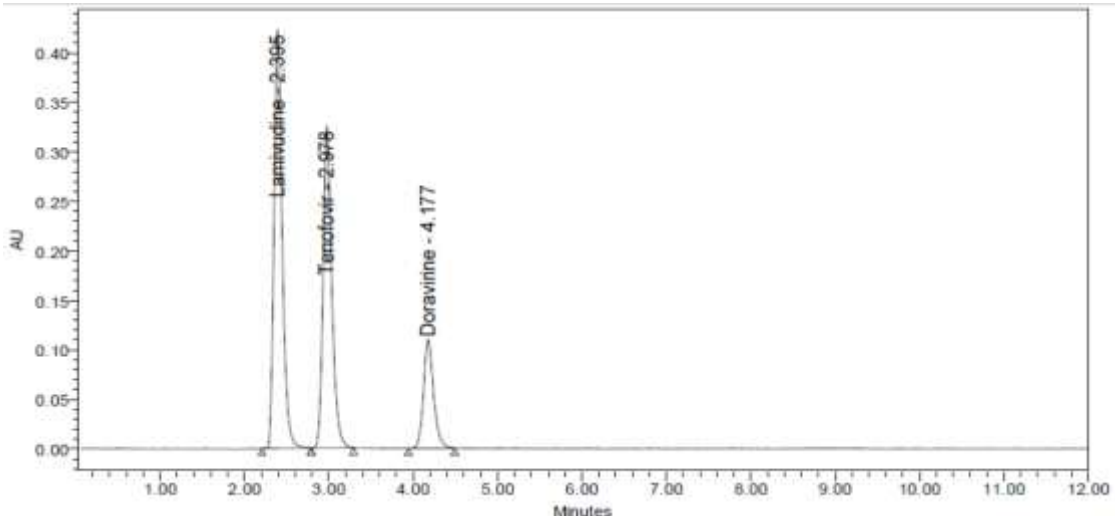

Image 12 : UV Degradation chromatogram of Doravirine, Lamivudine &Tenofovir

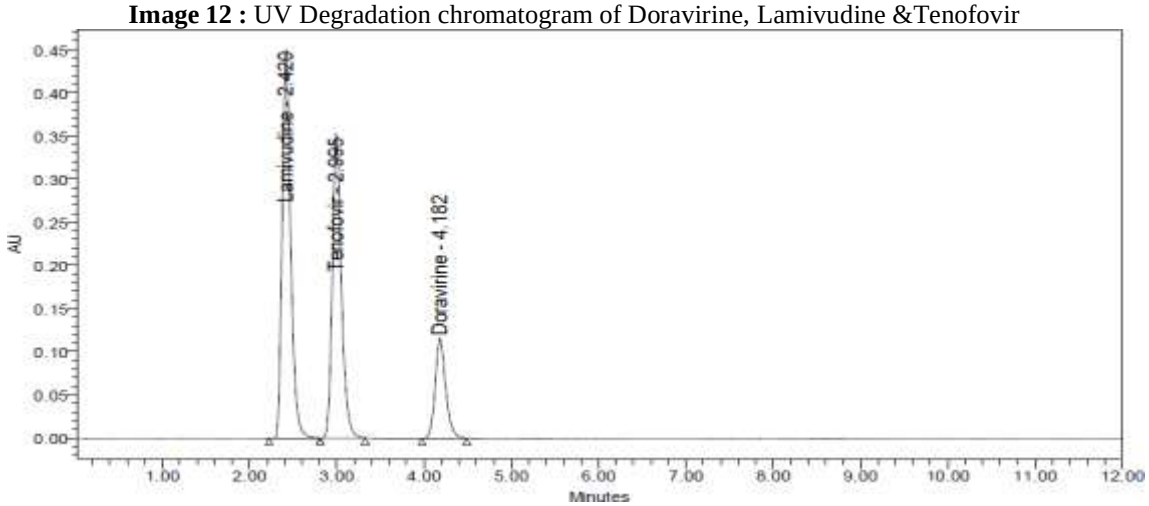

Image 13 : Water Degradation chromatogram of Doravirine, Lamivudine &Tenofovir

Results for Stability studies of Doravirine, Lamivudine and Tenofovir

The results showed that Doravirine, Lamivudine andTenofovirwasmore sensitive towards acid degradation Degradation of drug up to 10% is

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generally accepted. The % degradation results of Doravirine, Lamivudine and Tenofovir were with in limits.

IV. CONCLUSION

The developed RP-HPLC method was simple, precise, accurate, sensitive, reliable and cost effective for the simultaneous estimation of Doravirine, Lamivudine andTenofovir in bulk and pharmaceutical dosage form. The developed method was stability indicating and can separate degradants. Therefore this RP-HPLC method can be used for the routine analysis of these drugs in bulk, pharmaceutical formulations and also for stability studies in research institutions, quality control department in industries, testinglaboratories

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