Emtricitabine, Tenofovir, and Rilpivirine from their degradation products Analysis by HPLC

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ABSTRACT
A simple, expeditious, and explicit stability-indicating High-Performance Liquid Chromatography (HPLC) analytical test method was developed for the quantitative analysis of Emtricitabine, Tenofovir, and Rilpivirine in bulk drugs and combined dosage formulations. Using the ICH guidelines method was validated using a C18 column of size 250 mm X 4.6 mm, 5μ, maintained at 25°C. The total run time maintained was 10 min. Acetonitrile and 0.1% TEA prepared in water adjusted with pH 3.0 was adapted as a mobile phase. The injection volume of samples was 20μL and UV-DAD detector system set at 265 nm used for UV detection. As per the ICH guidelines method was validated. The retention times were observed as 2.52, 3.27, 6.70 min for Emtricitabine, Rilpivirine, and Tenofovir disoproxyl fumarate, respectively. Linearity ranges were observed 24-56 μg/mL Emtricitabine, 3-7 μg/mL Rilpivirine and 30-70 μg/mL Tenofovir. Relative Standard Deviation not exceed 2%. In contrast to the conventional method of HPLC, a method developed was able to give better resolution of swift retention times in the separation of various degradation products along with the pure active pharmaceutical ingredients. The proposed method exhibited excellent reproducibility and repeatability. The stress studies performed by following ICH guidelines indicated that the present HPLC method is explicit and stability-indicating. Since the present HPLC method has the capacity to separate the drugs with high resolution in tablet dosage forms, hence the method can be exploited for routine analysis of quality control sample and stability analysis.

INTRODUCTION

Emtricitabine

Emtricitabine (EMCB) with chemical name 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid. Emtricitabine is the (-) - enantiomer of a thioanalog of cytidine, which differs from other cytidine analogs in that has a fluorine in the 5-position as shown in Figure 1.

In adults, the Emtricitabine is used for the HIV infection treatment and is an inhibitor of a nucleoside reverse transcriptase inhibitor (NRTI) (Emtricitabine, 2018). C_{18}H_{10}FN_{3}O_{3}S, and 247.25 are the molecular formula and molecular weight of Emtricitabine respectively. The approximate solubility of Emtricitabine in the water at 25 °C is 112mg/mL, and physical appearance is a crystalline powder with white to off-white colour.

Rilpivirine

Rilpivirine
Rilpivirine with chemical name 4-[(4-[(E)-2-cyanoethyl]-2,6-dimethylanilino]pyrimidin-2-yl] amino] benzonitrile shown in Figure 2. Rilpivirine (TMC278, Trade name Edurant) (Rilpivirine, 2018) used for the treatment of HIV infection and is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) of with higher potency, longer half-life and reduced side-effect profile compared with older NNRTIs, such as Efavirenz. The molecular weight and its molecular formula of Rilpivirine are 366.43 and C22H18N6O2, respectively. The appearance of Rilpivirine is a white to off-white crystalline powder, and the solubility Rilpivirine is 1.62 mg/mL in the water at 25°C.

Figure 1: Chemical Structure of Emtricitabine

![Chemical Structure of Emtricitabine](image)

Figure 2: Chemical Structure of Rilpivirine

![Chemical Structure of Rilpivirine](image)

Figure 3: Chemical Structure of Tenofovir disoproxil fumarate

![Chemical Structure of Tenofovir disoproxil fumarate](image)

**Tenofovir disoproxil fumarate**

Tenofovir disoproxil fumarate chemical name of Tenofovir DF is \([([2R]-1-(6-aminopurin-9-yl) propan-2-yl] oxymethyl-(propan-2-yloxycarbonyloxymethoxy) phosphoryl) oxymethylpropan-2-yl carbonate \(E\)-but-2-enedioic acid shown in Figure 3. Tenofovir disoproxil fumarate (Tenofovir disoproxil, 2018) is known as nucleotide analogue reverse transcriptase inhibitors (NRTIs) which belongs to an anti-retroviral class of drug. Molecular formula and molecular weight of Tenofovir disoproxil fumarate...
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C_{19}H_{30}N_{10}O_{10} P. C_{4}H_{4}O_{4} and 635.51. The physical appearance of this drug is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in the water at 25 °C.

MATERIALS AND METHODS

Drug substance

Working standards Emtricitabine (99.7%), Rilpivirine (99.5%), and Tenofovir disoproxyl fumarate (99.5%) were procured from Chandra Labs, Hyderabad, India.

Instrumentation

An Agilent-1100, High-Performance Liquid Chromatography consisting of quaternary pump (G1376A), Column compartment (G1315B), Autosampler (G1387A), and Diode array detector (G1315B), supplied by M/s. Agilent Technologies, USA. Mettler-Toledo analytical balance, model AG-245 capable of weighing 0.01 mg, supplier: M/s. Mettler AG, Switzerland. Sonicator supplied by M/s. Serwell instrument, India. Digital pH meter supplied by M/s. Serwell instruments, India.

Chemicals and reagents

Acetonitrile (HPLC grade) was purchased from J.T. Baker, India. Triethyl amine (AR grade) supplied by M/s. Sigma-Aldrich, Bangalore, India. Water (HPLC grade) supplied by M/s. Sigma-Aldrich, India. Sodium hydroxide and Hydrogen peroxide (GR grade) supplied by M/s. Merck, India.

Preparation of the mobile phase

Mobile Phase composition: A– Acetonitrile, B–0.1% TEA prepared in water (pH 3.0).

Standard solution preparation:

Weigh, and transferred 13 mg of Emtricitabine, 1.62 mg of Rilpivirine, and 20 mg of Tenofovir standards into a 100 mL volumetric flask added 3/4th volume of diluent, sonicated for 5 minutes till the sample was dissolved and made up to the final volume with the diluent. Prepared 34.62 μg/mL of solution by diluting 1mL to 10mL with the diluent.

Chromatographic conditions

The mixture of A– Acetonitrile, and B–0.1% TEA prepared in water (pH 3.0) used as Mobile Phase. The mobile phase was filtered through 0.45μm membrane filter, degassed for 10 min, and flushed the column with a mobile phase with flow rate, 1.0 mL/min in C18 column, (250mm X 4.6 mm, 5μ). The total run time used was 10min, and the temperature of the column was set at 25°C. The volume of the sample injected was 20μL. Wavelength was set at 265nm in a UV-DAD detector.

Method development

After a number of experiments, prime chromatographic conditions were fixed for better separations (Ilango and Sunitha, 2012; Budawari, 2006). For each drug, separate standard calibration lines were erected. From the stock solution, various aliquots were prepared with the concentration ranging from 24-56μg/mL Emtricitabine, 30-70 μg/mL Tenofovir, 3-7 μg/mL Rilpivirine were prepared using the mobile phase. Each concentration was injected 6 times, and for all three drugs, retention time and peak area were recorded each time separately. Construction of Calibration curves for all three drugs were done separately by taking the average peak area on Y-axis and concentration on X-axis. The regression equations, as shown in Figures 4 and 5 and Figure 6, were calculated from the calibration curves. The drug content of the combined tablet dosage form was calculated from the above regression equations.

Pharmaceutical formulation estimation

For Solid drug dosage form analysis (Lakshmi et al., 2016; Choudhari et al., 2011), 10 tablets were weighed, powdered in a mortar and 200mg of powder Emtricitabine, 25 mg of Rilpivirine and 300 mg of Tenofovir taken into a 50 mL volumetric flask. The whole mixture was dissolved in a sufficient quantity of diluent, and finally, the solution was diluted to 50ml by adding the same diluent up to the mark. The solution was subjected to sonication for 5 min. Using 0.45 mm nylon membrane, the solution was filtered. From the above solution, 34.62 μg/mL of each EMCB, TDF, and Rilpivirine was prepared by dissolving 1mL of the above solution into 10 mL volumetric flasks and diluted with the mobile phase. Injected 6 times into the column, chromatograms and respective peak areas were measured. The content of EMCB, TDF, and Rilpivirine were calculated by using the regression equation, which was indicated as % Assay. The results are tabulated in Table 1.

Validation

In this analytical method, validation proved repeatability reproducibility, and accuracy of the method and will steadily harvest a result meeting its intended analytical applications (ICH Guidelines, 2005). ICH guideline was adapted for validation for this method, which provided the information system suitability, linearity, and limit of detection (LOD), the limit of quantification (LOQ), precision, selectivity, robustness, and accuracy.

Accuracy

The recoveries of each drug at three different lev-
### Table 1: Estimation of Pharmaceutical Formulation

| Drug name  | Labelled claim (mg) | Test Conc. (μg/mL) | Mean Amount estimated(μg/mL) | Estimatedamount (%) |
|------------|---------------------|--------------------|-------------------------------|---------------------|
| Emtricitabine | 200                | 200                | 200.08                        | 100.04              |
| Tenofovir  | 300                | 300                | 307.23                        | 102.41              |
| Rilpivirine | 25                 | 25                 | 24.93                         | 99.74               |

### Table 2: Results of the Recovery Studies

| Drugs name | Pre analysed Conc. (μg/mL) | % Recovery levels | Added Amount (μg/mL) | Found Amount (μg/mL)(n=3) | % Recovery |
|------------|---------------------------|-------------------|----------------------|---------------------------|------------|
| Emtricitabine | 40                    | 80                | 32                   | 39.7                      | 124.1      |
|             | 100                       |                   | 48                   | 120.1                     |
|             | 120                       |                   | 55.6                 | 115.8                     |
| Rilpivirine | 05                        | 80                | 04                   | 05.0                      | 125.8      |
|             | 100                       |                   | 05                   | 122.1                     |
|             | 120                       |                   | 06                   | 115.9                     |
| Tenofovir  | 50                        | 80                | 40                   | 49.0                      | 122.6      |
|             | 100                       |                   | 50                   | 121.7                     |
|             | 120                       |                   | 60                   | 115.5                     |

### Table 3: Method Precision

| S. No. | Emtricitabine | Rilpivirine | Tenofovir |
|--------|---------------|-------------|-----------|
| RT     | Area          | RT          | Area      | RT          | Area      |
| 1      | 2.520         | 1087.803    | 3.277     | 1094.372    | 6.707     | 1753.454  |
| 2      | 2.517         | 1089.666    | 3.270     | 1101.764    | 6.690     | 1774.741  |
| 3      | 2.523         | 1067.836    | 3.277     | 1073.595    | 6.707     | 1729.087  |
| 4      | 2.520         | 1097.279    | 3.273     | 1108.428    | 6.707     | 1774.492  |
| 5      | 2.517         | 1059.014    | 3.270     | 1079.236    | 6.693     | 1729.167  |
| 6      | 2.517         | 1071.854    | 3.273     | 1075.584    | 6.693     | 1727.320  |
| Avg    | 2.5190        | 1078.909    | 3.273     | 1088.830    | 6.700     | 1748.044  |
| SD     | 0.0024        | 14.836      | 0.003     | 14.708      | 0.008     | 22.745    |
| %RSD   | 0.10          | 1.38        | 0.10      | 1.35        | 0.12      | 1.30      |

### Table 4: Calibration Data

| Mcg   | Emtricitabine | Rilpivirine | Tenofovir |
|-------|---------------|-------------|-----------|
|       | Area          | Mcg         | Area      | Mcg         | Area      |
| 24    | 631.586       | 3           | 659.236   | 30          | 1229.584  |
| 32    | 907.713       | 4           | 919.393   | 40          | 1482.509  |
| 40    | 1091.004      | 5           | 1086.050  | 50          | 1750.266  |
| 48    | 1339.312      | 6           | 1348.518  | 60          | 2124.626  |
| 56    | 1549.123      | 7           | 1552.332  | 70          | 2413.579  |

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Table 5: Optical Characteristics of Emtricitabine, Rilpivirine and Tenofovir

| Parameters                        | Emtricitabine | Rilpivirine | Tenofovir |
|----------------------------------|---------------|-------------|-----------|
| Linearity range (µg/mL)          | 24-56         | 3-7         | 30-70     |
| Regression line equation         | y = 28.33x + 29.589 | y = 221.53x + 5.4473 | y = 30.101x + 295.06 |
| Correlation coefficient (r)      | 0.9969        | 0.9963      | 0.9951    |
| LOD (µg/mL)                      | 1.47          | 0.28        | 4.16      |
| LOQ (µg/mL)                      | 4.46          | 0.86        | 12.61     |

Table 6: LOD & LOQ

|       | Emtricitabine | Rilpivirine | Tenofovir |
|-------|---------------|-------------|-----------|
| LOD   | 1.47          | 0.28        | 4.16      |
| LOQ   | 4.46          | 0.86        | 12.61     |

Table 7: Robustness Studies of Emtricitabine, Rilpivirine, and Tenofovir

| Method parameters | Conditions | Emtricitabine | Rilpivirine | Tenofovir |
|-------------------|------------|---------------|-------------|-----------|
| Flow Rate         | 1.4mL/min  | 2.99          | 3.88        | 7.89      |
| Flow Rate         | 1.0mL/min  | 2.17          | 2.81        | 5.70      |
| Wavelength        | 260nm      | 2.49          | 3.24        | 6.63      |

Table 8: System Suitability Parameters

| Parameter          | Emtricitabine | Rilpivirine | Tenofovir |
|--------------------|---------------|-------------|-----------|
| Retention time     | 2.99          | 3.88        | 7.89      |
| Asymmetry          | 1.77          | 1.31        | 1.609     |
| Plates             | 3559          | 2418        | 5817      |
| Resolution         | -             | 2.90        | 11.09     |

Table 9: Results of stress degradation studies

| Stress conditions  | Emtricitabine | Active present after degradation (%) | Rilpivirine | Tenofovir |
|--------------------|---------------|--------------------------------------|-------------|-----------|
| Acid               | 27.7          | 28.0                                 | 44.3        |
| Base               | 27.5          | 27.6                                 | 44.9        |
| Thermal            | 27.6          | 27.7                                 | 44.7        |
| Photolytic         | 27.8          | 27.9                                 | 44.3        |
| Photocatalytic     | 27.7          | 27.6                                 | 44.7        |

was done, ranging from (80% to 120%) with target concentration EMCB, TDF, and Rilpivirine. The recovery range was tabulated, as indicated in Table 2.

**Precision**

The system precision was tested by six (n=6) injections, and the assay value, % RSD, RT, and areas were determined in Table 3. Assay value calculated, and the obtained % RSD were 1.38%, 1.35%, and 1.30% respectively. The %RSD value were found to be <2.0%. Statistical results revealed that the proposed HPLC method having worthy precision. The results are shown in tabular form, i.e., Table 3.

**Linearity and Range**

The linearity and range of the method was established in the range of 24-56µg/mL for Emtricitabine,
30-70 µg/mL for Tenofovir disoproxil fumarate, and 3-7 µg/mL for Rilpivirine concentrations. The graph plotted peak area versus concentration. The data were statistically analyzed by using linear regression. The results were tabulated in Table 4 and Table 5.

LOD and LOQ
Limit of detection (LOD) and Limit of quantification (LOQ) represents the concentration of the analyte that would yield signal to noise ratio of 3 for LOD and 10 for LOQ, respectively. The results were tabulated in Table 6.

Robustness
The assay method’s robustness was set up by introducing small changes in the chromatographic condition, which included the percentage of wavelength (260 nm and 264 nm), 1.0 mL/min, and 1.4 mL/min of flow rates. The results were tabulated in Table 7.

Solution stability
The solution stability (Jampala R R et al., 2014; Rao P P et al., 2014) of Emtricitabine, Rilpivirine, and Tenofovir for the assay method was conceded out by parting both the sample and standard solutions in compactly capped volumetric flasks at room temperature for 24 h. The same sample solution was surveyed at 6-hour intervals over the study period. The RSD% of the Emtricitabine, Rilpivirine, and Tenofovir assay was calculated.

System suitability parameters
For gaging system suitability, six replicates of standards samples of Emtricitabine, Rilpivirine, and Tenofovir were injected and various parameters, i.e., resolution, plate number (N), peak asymmetry and relative retention time of the samples were premeditated. The results were recorded in Table 8.

Specificity and selectivity
Specificity is the degree to which the procedure applies to check in each analysis by examining blank matrix samples for any interfering peaks and evaluated with regard to interference due to the presence of any other placebos and proved no interfering peaks within retention time ranges shows the respective chromatogram (Figure 7).

Degradation studies
Stock solution preparation
In 50 mL volumetric flasks, 200 mg of Emtricitabine, 25 mg of Rilpivirine, and 300 mg of Tenofovir were weighed. The mixture was dissolved in the mobile phase. The solution was finally diluted to the mark in 50 mL volumetric flasks using the same diluent.

Acid degradation
In a 50 mL round bottom flask, 5 mL of stock solution was pipetted, and 2.5 mL of 0.1 N HCl was added. At 60°C, the flask was refluxed for 30 min and then allowed to cool. The solution was neutralized using 0.1N NaOH and made up to the mark using the mobile phase and intended the percentage of degradation.

Alkali degradation
In 50 mL round bottom flask, 5.0 mL of stock solution was pipetted, and 2.5 mL of 0.1 N NaOH was added. The flask was refluxed at 60 °C for 30 min and allowed to cool. Neutralized with 0.1N HCl solution, using a mobile phase, the solution was made up to the mark and intended the percentage of degradation.

Photocatalytic degradation under UV
Weighed and transferred 300 mg of Emtricitabine, 50 mg of Rilpivirine, 500 mg of Tenofovir into different Petri dish and kept in UV light. Weighed and transferred 200 mg of Emtricitabine, 25 mg of Rilpivirine, 300 mg of Tenofovir into 50 mL volumetric flasks, dissolved and diluted up to the mark with the mobile phase. In 50 mL volumetric flasks, 5 ml stock solution was transferred into and diluted up to the mark with the mobile phase.

Thermal condition
In different Petri dishes, 300 mg of Emtricitabine, 50 mg of Rilpivirine, and 500 mg of Tenofovir were weighed. Dishes were incubated in hot air oven maintained at 105°C for 6 h, and the samples were placed in a desiccator till it reaches room temperature. After reaching room temperature again from above plates, 200 mg of Emtricitabine, 25 mg of Rilpivirine, 300 mg of Tenofovir were weighed and transferred into a 50 mL volumetric flask. The mixture was dissolved in the mobile phase and diluted with the same till the mark. In a 50 mL volumetric flasks, 5 mL of each stock solution was transferred into and diluted up to the mark with the mobile phase.

Photolytic condition
Pipetted, 5 mL stock solution, was bared to sunlight for about 6 hours and diluted with 5 mL of the mobile phase. Calculated the percentage of degradation was calculated.

RESULTS AND DISCUSSION

Chromatographic conditions optimization
The optimized chromatographic conditions are mentioned above. The finest peak shape and supreme separation were achieved with mobile conditions.
The phase composition is A–Acetonitrile, B–0.1% TEA in water with Column: C18 (250 mm x 4.6 mm, 5µ), a wavelength at 265 nm and flow rate of 1.0 mL/min. As per our knowledge till date majority of HPLC methods uses C-18 or C-8 columns and most their mobile phase are complex in compositions. Hence endeavoured were deviated towards the simple method development and enhanced with the C18 column with virtuous resolution. To get good separation, different logical variations were tried among the individual drugs and the solid drug dosages and some modifications in mobile phase composition, flow rate, and temperature in gradient modes on different C18 columns with HPLC.

**Accuracy**

The percentage recovery was covered in the range from 80.00% to 120.00% for Emtricitabine, Rilpivirine, and Tenofovir in the combined dosage forms. The RSD% value of replicated injections was less than 2.0%, which indicates that this method is highly accurate. Table 2 indicates the results obtained.

**Precision**

The method precision and intermediate precision of Emtricitabine, Rilpivirine, and Tenofovir standard solution checked, and %RSD were less than 2%, which signifies that this method is highly precise. The results obtained are recorded in Table 3.

**Linearity**

The calibration curve plotted for the Emtricitabine, Rilpivirine, and Tenofovir were linear over the samples concentrations range of 24-56µg/mL, 3-7µg/mL, and 30-70µg/mL, respectively. The data subjected towards the peak area versus concentration by linear regression analysis, and the correlation coefficient (r) was obtained (0.99). The statistical analysis revealed that the proposed method was linear, and Table 4 & Table 5 indicates the results obtained.

**LOQ and LOD**

The results of LOQ and LOD data was established for all analytes, and the signal-to-noise ratio for the LOQ and LOD were well within the acceptance criteria. The results were as tabulated in Table 6.

**Robustness**

The robustness of the assay method was established by introducing minor changes in the chromatographic condition, which covered the percentage of flow rate, 1.0 and 1.4 mL/min and wavelength, 260 nm, and 264 nm. The developed method was unaffected by the minor deliberated changes, which indicates the proposed method was robust. The results were tabulated in Table 7.

**Degradation studies**

Upon performance of degradation studies, Emtricitabine, Rilpivirine, and Tenofovir were active after degradation. The active present after degradation studies results were shown in Table 9.

**CONCLUSIONS**

Stress testing (or forced degradation studies) one of the most critical criteria in pharmaceutical industries in method development. A simple, expeditious, rapid, and precise stability-indicating analytical method of HPLC was developed, and the methods were validated for the quantitative analysis of Emtricitabine, Rilpivirine, and Tenofovir in bulk drugs and combined dosage forms. The better separation of various types of degradation products along with pure drugs can be achieved. The method is also has capacity of giving swift retention times with upright resolution. Excellent performance with respect to Sensitivity, repeatability, and swiftness can be achieved by this method. Thus method could be useful not only for assay but also for monitoring and degradation products during development as per the ICH guidelines. Hence using this method, routine QC samples and control samples can be analyzed. When compared with other methods, this method will decrease the consumption of solvent, time, man, and power. Hence the method is fit for regular pharmaceutical use.

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