Development and Application of Liquid Chromatographic Method for Simultaneous Determination of Elvitegravir, Tenofovir Disoproxil Fumarate, Emtricitabine, and Cobicistat in Fixed Dosage Form

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ABSTRACT

Introduction: Quad pill is fixed-dose combinations containing four drugs in a single tablet with the intention of reducing the number of tablets that need to be taken. Elvitegravir/ Cobicistat/ Emtricitabine/ Tenofovir disoproxil fumarate (“QUAD”) – is a complete regimen intended for treatment of HIV infection. Developing a single analytical method for the estimation of individual drugs in a quad pill is very challenging, due to the formation of drug-drug and drug-excipient interactions.

Method: Chromatographic separation of the four antiviral drugs was achieved by using a gradient elution at a flow rate of 1.0 mL/min on Inertsil ODS 3V C18 column (250 m×4.6 mm, 5 μm particle size, 100Å pore size) at ambient temperature. Mobile phase A of the gradient solvent system was KH₂PO₄ (0.02M) in 1000 ml of water and by adjusting the pH to 2.5 with dilute orthophosphoric acid and mobile phase B was acetonitrile. UV detection at 240nm was employed to monitor the analytes.

Results: A linear response was observed for emtricitabine over the concentration range 20-240 μg/mL, for tenofovir disoproxil fumarate over the concentration range of 30-360 μg/mL, for elvitegravir and cobicistat over the concentration range of 15-180 μg/mL. Limit of detection (LOD) for emtricitabine, Tenofovir disoproxil fumarate, elvitegravir and cobicistat were 0.02 μg/mL, 0.03 μg/mL, 0.75 μg/mL and 3 μg/mL respectively. Limit of quantification (LOQ) for emtricitabine, Tenofovir disoproxil fumarate, elvitegravir and cobicistat were 0.06 μg/mL, 0.09 μg/mL, 2.25 μg/mL and 9 μg/mL respectively.

Conclusion: The present study demonstrates the applicability of chromatographic method to develop a new, sensitive, single HPLC method for the simultaneous quantitative determination of four antiviral agents in fixed pharmaceutical dosage form.

Keywords: Cobicistat, elvitegravir, emtricitabine, gradient-high performance liquid chromatography, quadpill, tenofovir disoproxil fumarate

INTRODUCTION

STRIIBILD* is a fixed-dose combination tablet containing elvitegravir (ELVT), cobicistat (COB), emtricitabine (EMCB), and tenofovir disoproxil fumarate (TDF) for oral administration. STRIBILD* is a one-pill, once-a-day prescription medicine used as a complete HIV-1 treatment. It is used to treat HIV-1 in adults who have never taken HIV-1 medicines before. STRIBILD does not cure HIV-1 or AIDS. ELVT¹ (2S)-1-hydroxy-3-methylbutan-2-yl]-(7-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid, is a newly introduced HIV-1 integrase strand transfer inhibitor (Figure 1). COB¹ 1,3-Thiazol-5-ylmethyl [(2R,5R)-5-[(2S)-2-[(methyl[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl] carbamoyl] amino]-4-(morpholin-4-yl) butanoyl][amino]-1,6-diphenylhexan-2-yl]carbamate is a mechanism-based inhibitor of cytochrome P450 (CYP) enzymes of the CYP3A family. EMCB¹ 4-amino-5-fluoro-1-(2S,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one, is a synthetic nucleoside analog of cytidine. TDF¹ is a fumaric acid salt of the bisiso propoxy carbonyloxymethyl ester derivative of tenofovir. The chemical name of TDF is 9-[(R)-2-[(bis [[isopropoxy carbonyl] oxy]methoxy]phosphinyl]methoxy) propyl]adenine fumarate. TDF² is converted in vivo to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5’-monophosphate.

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DOI: 10.5530/phm.2014.1.2
A survey of literature has revealed several analytical methods for the determination of tenofovir and EMMC in combination with efavirenz in biological fluids and in pharmaceutical products. These include high-performance liquid chromatography (HPLC).\textsuperscript{8,9} On the contrary, to the best of our knowledge, there is no method reporting the simultaneous determination of TDF, ELVT, COB, and EMMC in pharmaceutical formulation. In this paper, we report the very first reversed-phase-HPLC (RP-HPLC) method for the assay of EMMC, ELVT, TDF, and COB in fixed dosage form. The new method is capable of separating all four active ingredients present in the tablet. Validation of the current method will be performed according to the requirements of unique selling proposition (USP) for assay determination which include accuracy, precision, selectivity, linearity, and range.

**EXPERIMENTAL**

**Chemicals and reagents**

EMCB, ELVT, TDF, COB are obtained as kind gift samples from Mylan Laboratories Limited, Hyderabad. Potassium dihydrogen orthophosphate, acetonitrile and orthophosphoric acid were obtained from Merck, Mumbai, India. All the solutions were prepared in Milli Q water (Millipore, USA). Test samples composed of Stribilid\textsuperscript{®} film-coated tablet contains 150 mg of ELVT, 150 mg of COB, 200 mg of EMMC and 245 mg of TDF (equivalent to 300 mg of TDF or 136 mg of tenofovir) are obtained from Gilead Sciences, Kuala Lumpur, Malaysia.

**HPLC instrumentation and chromatographic conditions**

Waters Alliance 2695 separation module (Waters Corporation, Milford, USA) equipped with 2489 ultraviolet (UV)/visible detector or 2998 Photodiode Array detector (PDA) with Empower 2 software was used for the analysis. The HPLC system was equipped with a column compartment with temperature control and an on-line degasser. Inertsil ODS 3V C18 column (250 × 4.6 mm, 5 μm, Waters Corporation, Milford, USA) and a gradient mixture of solvent A and B were used as stationary and mobile phases, respectively. Buffer contains 0.02 M potassium dihydrogen phosphate and its pH was adjusted to 2.5 with orthophosphoric acid. Buffer was used as solvent A. Acetonitrile was used as solvent B. The gradient program (T/%B) was given in Table 1, was adjusted at 1.0 ml/min flow rate and 20 μl injection volume were maintained. The eluted compounds were monitored at 240 nm. The column oven temperature was maintained at 30°C. Data acquisition, analysis, and reporting were performed by Empower 2 (Waters) chromatography software.

**Preparation of solutions**

**Standard and stock solutions**

Standard solution of the four active ingredients of the drug was prepared in the following manner: Transfer 200 mg of EMMC, 300 mg of TDF, and 150 mg of COB, and 150 mg of ELVT working standards into a 100 ml volumetric flask, dissolve and dilute with acetonitrile and buffer in the ratio of 30:70 as diluent. 5 ml of the resulting solution is further diluted up to 50 ml in the volumetric flask with diluents. The resulting solution contains 200 μg/ml of EMMC, 300 μg/ml of TDF, and 150 μg/ml each of the ELVT and COB as working standard solutions. The prepared stock solutions were stored at 4°C and protected from light.

**Preparation of the sample solution**

Twenty tablets were weighed, and their average weight was calculated. The tablets were crushed to a homogeneous state.

<table>
<thead>
<tr>
<th>Time</th>
<th>Mobile phase-A</th>
<th>Mobile phase-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

**Figure 1.** Chemical structures of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate.
powder, and a quantity equivalent to one tablet (1000.2 mg) was weighed and transferred into a 100 ml volumetric flask, extracted in diluent by sonication, and filtered through Whatman no. 41 filter paper. The filtrate (5 ml) was quantitatively transferred to a 50-ml volumetric flask, and the solution was diluted to volume with the diluents.

**Solutions for the validation study**

*Calibration and quality control samples*

Calibration standards (20-240 μg/ml for EMCB, 30-360 μg/ml for TDF and 15-180 μg/ml each of ELVT and COB were prepared from working standard solutions by appropriate dilution with acetonitrile and buffer in the ratio of 30:70 as diluents. Quality control samples are prepared at three concentrations of the linearity range (160 μg/ml, 200 μg/ml, and 240 μg/ml) for EMCB, (240 μg/ml, 300 μg/ml, and 360 μg/ml) for TDF, and (120 μg/ml, 150 μg/ml, and 180 μg/ml) each for ELVT and COB were prepared from the standard solutions.

**Method validation**

The developed chromatographic method was validated for selectivity, linearity, precision, accuracy, sensitivity, robustness, and system suitability.

**Specificity**

The terms selectivity and specificity are often used interchangeably. The specificity of the developed liquid chromatography (LC) method for quantification of all the four drugs was determined in the presence of excipients present in pharmaceutical products. In specificity study, interference between drugs and tablet excipients were evaluated from the comparison of spectral purity obtained from the analysis for the standard solutions and sample solutions.

**System suitability**

The system suitability was assessed by six replicate analyses of the drugs at concentrations of 200 μg/ml for EMCB, 300 μg/ml for TDF, and 150 μg/ml each for ELVT and COB. The acceptance criterion was ±2% for the relative standard deviation (RSD) for the peak area and retention times (RTs) for all four analytes. The system suitability parameters with respect to theoretical plates, tailing factor, repeatability and resolution between EMCB peak and peaks of the other three analytes were defined.

**Linearity**

Linearity of the method was evaluated at seven equispaced concentration levels by diluting the standard solutions to give solutions over the ranges 10-120% target concentration for all four analytes, respectively. The calibration curves were constructed at seven concentrations between 20-240 μg/ml for EMCB, 30-360 μg/ml for TDF and 15-180 μg/ml each of ELVT and COB. These were injected in triplicate, and the peak areas were inputted into a Microsoft Excel® spreadsheet program to plot calibration curves. The linearity was evaluated by linear regression analysis, which was calculated by the least square regression method. The peak areas of drugs to drugs concentration were used for plotting the linearity graph. The linearity data is reported in Table 2.

**Precision**

Precision was evaluated in terms of intra-day repeatability and inter-day reproducibility. The intra-day repeatability was investigated using six separate sample solutions prepared, as reported above, from the freshly reconstructed tablet formulations at 100% of the target level. Each solution was injected in triplicate, and the peak areas obtained were used to calculate means and RSD% values. The inter-day reproducibility was, by preparing and analyzing in triplicate sample solutions from the reconstructed formulations at the same concentration level of intra-day repeatability; the means and RSD% values were calculated from peak areas (Table 3).

**Accuracy**

The accuracy of the method was determined by measuring the recovery of the drugs by the method of standard additions. Known amounts of each drug corresponding to 80%, 100%, and 120% of the target test concentrations (20 μg/ml of EMCB, 30 μg/ml of TDF, and 15 μg/ml each of ELVT and COB) were added to a placebo mixture to determine whether the excipients present in the formulation led to positive or negative interferences. Each set of additions was repeated 3 times at each level.

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**Table 2** Linearity data for the Stirbilid®-fixed dosage form

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Emtricitabine</th>
<th>Tenofovir disoproxil fumarate</th>
<th>Cobicistat</th>
<th>Elvitegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration range (μg/ml)</td>
<td>20-240</td>
<td>30-360</td>
<td>15-180</td>
<td>15-180</td>
</tr>
<tr>
<td>Regression equation</td>
<td>y=37191.7x−18469</td>
<td>y=21547.9x+4705.3</td>
<td>y=6768.1x+2063.9</td>
<td>y=13270.2x−4708.5</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>LOD (μg/ml)</td>
<td>0.02</td>
<td>0.03</td>
<td>3</td>
<td>0.75</td>
</tr>
<tr>
<td>LOQ (μg/ml)</td>
<td>0.06</td>
<td>0.09</td>
<td>9</td>
<td>2.25</td>
</tr>
</tbody>
</table>

LOD: Limit of detection, LOQ: Limit of quantification
Extraction sample preparation procedure is followed and assayed against qualified reference standard. The accuracy was expressed as the percentage of the analytes re-covered by the assay (Table 4).

Sensitivity

Limits of detection (LOD) and quantification (LOQ) were estimated from the signal-to-noise ratio. The detection limit was determined as the lowest concentration level resulting in a peak area of 3 times the baseline noise. The LOD was determined, by injecting progressively low concentrations of four analytes of interest. The quantification limit was determined as the lowest concentration level that provided a peak area with signal-to-noise.10

Robustness

To determine the robustness of the developed method, experimental conditions were deliberately changed, and the RSD for replicate injections of EMCB, TDF, ELVT and COB peaks and the USP resolution factor between EMCB and the other three peaks were evaluated. The mobile phase flow rate was 1.0 ml/min. This was changed by ±0.2 units to 0.8 and 1.2 ml/min. The effect of stationary phase was studied by the use of LC columns from different batches at 35°C. The effect of buffer pH was studied at pH 2.3 and 2.7 (±0.2 units). The chromatographic variations were evaluated for resolution between EMCB and the other three analytes in a system suitability solution with respect to RT and % assay of drugs.

Solution stability

To assess the solution stability, standard and test solutions were kept at 25°C (laboratory temperature) for 24 h. These solutions were compared with freshly prepared standard and test solutions.

RESULTS AND DISCUSSION

HPLC method development

All the four drug solutions were prepared in diluent at a concentration of 100 μg/ml and scanned in UV-Visible spectrometer; all the drugs were having UV maxima at around 240 nm. Hence detection at 240 nm was selected for method development purpose. Some important parameters, pH of the mobile phase, concentration of the acid or buffer solution, percentage and type of the organic modifier, etc., were tested for a good chromatographic separation. The main analytical challenge during development of a new method was obtaining adequate retention of the polar parent compounds, TDF, EMCB, and ELVT while maintaining a reasonable elution time for the less-polar COB. Trials showed that acidic mobile phase with reverse phase column gives symmetric and sharp peaks. For this reason, potassium dihydrogen phosphate buffer with pH-2.5 was adjusted with orthophosphoric acid was preferred as acidic buffer solution. Acetonitrile was chosen as the organic modifier because it dissolves drugs very well. Mobile phase composition in gradient mode at a flow rate of 1.0 ml/min was observed for a good resolution. Then method was optimized to separate all the active ingredients by changing to gradient mode. Several gradient conditions were tried before optimizing the final gradient program as: Time (min)/% solution B: 0/20, 3/50, 5/80, 12/80, 15/20, and 18/20. The satisfactory chromatographic separation, with good peak shapes were achieved on Inertsil ODS 3V-C18 (250 × 4.6) mm with 5 μm particles, using 0.02 m potassium dihydrogen phosphate buffer (adjusted to pH 2.5 with 1% orthophosphoric acid) as mobile phase A and acetonitrile as solution B with a flow rate of 1.0 ml/min. The HPLC gradient program was optimized as: (time (min)/% solution B: 0/5, 10/60, 15/80, 17/60, 20/5, and 25/5. The column temperature as maintained at 35°C and the detection was monitored at a wavelength of 240 nm. The injection volume was 20 μl. Buffer: acetonitrile (70:30, v/v)
was used as diluent. In the optimized gradient conditions EMCB, ELVT, TDF and COB were well separated with a resolution (Rs) of >2 and the typical RTs of EMCB, ELVT, TDF and COB were about 3.7, 7.6, 8.1, 10.7, and 12.9, respectively, the typical chromatogram of system suitability shown in Figure 2.

Method validation

The developed method was validated, as described below, for the following parameters: System suitability, selectivity, linearity, precision, accuracy, and LOD/LOQ.

Selectivity

Selectivity of the current method was demonstrated by good separation of the four active ingredients (EMCB, TDF, ELVT and COB). Furthermore, matrix components, e.g., excipients, do not interfere with the four analytes as they have no absorbance. The representative chromatogram (Figure 3) of the fixed dosage form solution containing excipients showed no peak interfering with analytes; moreover, the adjacent chromatographic peaks were separated with resolution factors >3. Overall, these data demonstrated that the excipients did not interfere with the active ingredients peaks, indicating selectivity of the method.

System suitability

The RSD values of peak area and RT for the analytes are within 2% indicating the suitability of the system (Table 5).

Linearity and range

Five concentration levels within 10-120% of the target concentration range for analytes were considered to study the linearity. The calibration curves were prepared by plotting the peak area of the drug to the respective concentrations, which were linear in the range of 20-240 μg/ml for EMCB, 30-360 μg/ml for TDF, and 15-180 μg/ml each of ELVT and COB. Peak areas of the active ingredients and concentrations were subjected to least square linear regression analysis to calculate the calibration equations and correlation coefficients. The mean regression equations were found as $y = 37191.7x - 18469$ for EMCB, $y = 21547.9x + 4705.3$ for TDF, $y = 6768.1x + 2063.9$ for COB and $y = 13270.2x - 4708.5$ for ELVT. The square of the correlation coefficient ($r^2 > 0.999$) demonstrated a significant correlation between the concentration of analytes and detector response. The results show that there is an excellent correlation between the peak area ratios and the concentrations of drugs in the range tested.

Precision

Precision of this method was determined by injecting the standard solution of the four analytes 6 times. The RSD of peak area of six replicates was found to be <2. The results obtained are shown in Table 3. In all instances, the %RSD values were <2%.

Accuracy

Percentage recovery of the four active ingredients using this method was determined using the fixed dose combination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Emtricitabine</th>
<th>Tenofovir disoproxil fumarate</th>
<th>Cobicistat</th>
<th>Elvitegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention time (min)</td>
<td>3.719</td>
<td>5.539</td>
<td>7.994</td>
<td>11.180</td>
</tr>
<tr>
<td>Theoretical plates</td>
<td>10200.95</td>
<td>21995.12</td>
<td>12673.23</td>
<td>28136</td>
</tr>
<tr>
<td>Tailing factor</td>
<td>1.27</td>
<td>1.31</td>
<td>1.30</td>
<td>1.13</td>
</tr>
<tr>
<td>HETP</td>
<td>2.45×10^{-5}</td>
<td>1.137×10^{-5}</td>
<td>1.973×10^{-5}</td>
<td>8.886×10^{-6}</td>
</tr>
<tr>
<td>USP plates/meter</td>
<td>40803.8</td>
<td>87980.48</td>
<td>50692.92</td>
<td>112544.6</td>
</tr>
<tr>
<td>Resolution</td>
<td>------------</td>
<td>1.20</td>
<td>1.13</td>
<td>1.16</td>
</tr>
<tr>
<td>Peak area</td>
<td>7317542</td>
<td>6477640</td>
<td>1020802</td>
<td>2099145</td>
</tr>
<tr>
<td>% of peak area</td>
<td>43.44</td>
<td>38.17</td>
<td>6.02</td>
<td>12.37</td>
</tr>
</tbody>
</table>

USP: Unique selling proposition, HETP: Height equivalent to theoretical plate.
tablet dosage forms. The results of accuracy studies from standard solution and excipient matrix are shown in Table 4; recovery values demonstrated that the method was accurate within the desired range.

**Sensitivity**

LOD for EMCB, TDF, ELVT and COB were 0.02 μg/ml, 0.03 μg/ml, 0.75 μg/ml, and 3 μg/ml respectively. LOQ for EMCB, TDF, ELVT and COB were 0.06 μg/ml, 0.09 μg/ml, 2.25 μg/ml, and 9 μg/ml, respectively. The results of LOD and LOQ were indicating a high sensitivity of the method.

**Robustness**

The HPLC parameters were deliberately varied from normal procedural conditions including the mobile phase flow rate was 1.0 ml/min. This was changed by ±0.2 units to 0.8 and 1.2 ml/min. The effect of stationary phase was studied by the use of LC columns from different batches at 35°C. The effect of buffer pH was studied at pH 2.3 and 2.7 (±0.2 units). Under these variations, all analytes were adequately resolved, and elution orders remained unchanged. The testing solution maintained a signal-to-noise ratio over 10 in all varied conditions. The peak resolution between EMCB and other three analytes were all larger than 1.5 under each variation.

**Analysis of the fixed dose combination tablet**

Twenty tablets contents were accurately weighed, their mean weight were determined, and they were then finely powdered. An amount of the homogenous powder equivalent to one tablet (1000.2 mg) was transferred into a 100 ml volumetric flask, added 40 ml of diluents (acetonitrile: potassium dihydrogen orthophosphate adjusted pH 2.5 with orthophosphoric acid), sonicated for 30 min, diluted to 100 ml with methanol and a 5-ml sample taken from this solution was centrifuged at 3000 rpm for 15 min. A 1-ml aliquot from supernatant was then decanted to another 10 ml volumetric flask. Test solutions were then made up to volume with the mobile phase. The amounts of COB, EMCB, TDF, and ELVT in ternary mixtures or dosage forms were individually calculated using the related linear regression equations.

On the basis of above results, the proposed method was applied to the simultaneous determination of and four antiviral drugs present in fixed dosage forms which comprised the ternary mixture (Stribild® film-coated tablet contains 150 mg of ELVT, 150 mg of COB, 200 mg of EMCB, and 245 mg of TDF (equivalent to 300 mg of TDF). Figure 3 shows representative chromatograms obtained from the analysis of Stribild® tablets. The differences between the amount claimed and those assayed were very low, and the RSD values were within the acceptable range mentioned by pharmacopoeias. The mean percentage recoveries obtained after six repeated experiments were found between 97.53 and 100.98 (Table 6), indicating that the results are accurate and precise, and there is no interference from the common excipients used in the pharmaceutical dosage forms.

**CONCLUSION**

In this study, a validated simple and reliable RP-HPLC-PDA procedure was described for the assay of a complex multidrug combination consisting of ELVT, COB, EMCB, and TDF for oral administration which is indicated as one-pill, once-a-day prescription medicine used as a complete HIV-1 treatment. To our present knowledge, no attempts have yet been made to estimate this multidrug mixture by analytical procedure. All the four active ingredients were successfully resolved and quantified using Inertsil ODS 3V C18 column (250 × 4.6 mm, 5 μm) in a relatively short run time of 18 min in gradient mode of chromatographic method. The proposed method provides a good resolution between active ingredients. The developed method reported herein was validated by parameters as described in ICH-Q2B guideline. System suitability, specificity, linearity, LOD, LOQ values, within- and between-day precision and accuracy of the proposed technique were obtained during the validation studies. The proposed method has the advantages of simplicity, repeatability, sensitivity, and requires less expensive reagents.

**REFERENCES**


**Table 6** Assay results of emtricitabine, tenofovir disoproxil fumarate, Cobicistat and elvitegravir in tablets

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Label claim (mg/tablet)</th>
<th>Amount found in (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMT TDF COB ELV EMT TDF COB ELV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stribild® a fixed-dose combination tablet</td>
<td>200 300 150 150 198.5 295 149.2 148.9</td>
<td></td>
</tr>
</tbody>
</table>

EMT: Emtricitabine, TDF: Tenofovir disoproxil fumarate, COB: Cobicistat, ELV: Elvitegravir


