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RAPID ANALYSIS OF RILPIVIRINE, EMTRICITABINE AND TENOFOVIR ACTIVE INGREDIENTS BY NOVEL HPLC METHOD

RİLPİVİRİN, EMTRİSİTABİN VE TENOFOVİR AKTİF BİLEŞENLERİNİN YENİ HPLC YÖNTEMİYLE HIZLI ANALİZİ

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ABSTRACT

Objective: *A novel high-performance liquid chromatography (HPLC) method was developed for the simultaneous determination of Emtricitabine (EMT), Tenofovir (TNF), and Rilpivirine (RLP).*
Material and Method: *The analysis was performed using a Waters XBridge C18 (3.5 µm, 4.6 × 150 mm) column. The mobile phase consisted of methanol and triethylamine buffer (pH 3.15) in a 60:40 (v/v) ratio, with a flow rate of 1.2 ml/min. The developed method was successfully applied to standard mixtures and pharmaceutical tablet formulations containing EMT, TNF, and RLP, without matrix interference.*
Result and Discussion: *The proposed technique exhibited good linearity, with correlation coefficients (R^2) of 0.999 for EMT, 0.999 for TNF, and 1.000 for RLP. The calibration ranges were 10.0–600.0 µg/ml for EMT, 2.0–75.0 µg/ml for TNF, and 2.0–75.0 µg/ml for RLP. The method was validated in accordance with ICH guidelines, demonstrating high sensitivity, precision, and accuracy. It was found to be a rapid, economical, and efficient approach for the simultaneous determination of these active pharmaceutical ingredients.*
Keywords: *Emtricitabine, rilpivirine, RP-HPLC, simultaneous determination, tenofovir*

ÖZ

Amaç: *Emtrisitabin (EMT), Tenofovir (TNF) ve Rilpivirin (RLP) aktif bileşenlerinin eş zamanlı tayini için yeni bir yüksek performanslı sıvı kromatografisi (HPLC) yöntemi geliştirilmiştir.*
Gereç ve Yöntem: *Analizler, Waters XBridge C18 (3.5 µm, 4.6 × 150 mm) kolon kullanılarak gerçekleştirilmiştir. Mobil faz, metanol ve trietilamin tamponunun (pH 3.15) 60:40 (v/v) oranındaki karışımından oluşmuştur. Akış hızı 1.2 ml/dak olarak ayarlanmıştır. Geliştirilen yöntem, EMT, TNF ve RLP içeren standart çözelti karışımları ve farmasötik tablet formlarına başarıyla uygulanmış ve matris girişimi gözlenmemiştir.*
Sonuç ve Tartışma: *Önerilen yöntem mükemmel doğrusallık sergilemiş olup korelasyon katsayıları*

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(R^2) EMT için 0.999, TNF için 0.999 ve RLP için 1.000 olarak belirlenmiştir. Kalibrasyon aralıkları EMT için 10.0–600.0 µg/ml, TNF için 2.0–75.0 µg/ml ve RLP için 2.0–75.0 µg/ml olarak bulunmuştur. Yöntem, ICH kılavuzlarına uygun olarak valide edilmiş ve yüksek seçicilik, doğruluk ve kesinlik göstermiştir. EMT, TNF ve RLP'nin eş zamanlı tayini için hızlı, ekonomik ve verimli bir yöntem olduğu tespit edilmiştir.
Anahtar Kelimeler: *Emtrisitabin, eş zamanlı tayin, rilpivirin, RP-HPLC, tenofovir*

INTRODUCTION

The human immunodeficiency virus (HIV) is a type of retrovirus that leads to acquired immunodeficiency syndrome (AIDS), a disease marked by the gradual deterioration of the immune system [1]. The primary aim of antiretroviral therapy in managing HIV infection is to suppress viral replication. Studies have shown that initiating treatment with a combination of two or more antiretroviral drugs is the most effective approach to achieve this goal [2].

In 2011, the U.S. Food and Drug Administration and the European Medicines Agency approved a fixed-dose combination of emtricitabine (EMT), rilpivirine (RLP), and tenofovir disoproxil fumarate (TNF). Since its approval, this combination has been used globally by individuals living with HIV [3].

The combination of EMT, TNF, and RLP in a single regimen has shown significant virological and immunological effectiveness, along with favorable lipid profile outcomes for most patients [4]. In HIV therapy, the use of multiple drugs is a common approach. To improve patient adherence and simplify daily treatment, pharmaceutical companies strive to formulate single-dose preparations containing multiple active ingredients.

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI) and a synthetic cytidine analog with a fluorinated oxathiolane ring [5]. Its chemical designation is 5-fluoro-1-[2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine (Figure 1A). Once inside the cell, it undergoes phosphorylation by cellular kinases, producing emtricitabine 5'-triphosphate, its active form. This metabolite competes with the natural substrate deoxycytidine 5'-triphosphate for incorporation into the viral DNA by HIV-1 reverse transcriptase [6]. The incorporation of emtricitabine 5'-triphosphate results in premature chain termination, thereby inhibiting viral replication. By blocking reverse transcription, emtricitabine indirectly supports the preservation of immune function by reducing viral load [7].

Tenofovir disoproxil fumarate (Figure 1B), formally known as {9-[(R)-2-[bis(isopropoxycarbonyl)oxy]methoxy]phosphonyl]methoxy]propyl]adenine fumarate}, is classified as a nucleotide analog reverse transcriptase inhibitor employed for the treatment of HIV infection in adults [8]. After administration, it undergoes diester hydrolysis to generate tenofovir, which is subsequently phosphorylated by cellular enzymes into its active form, tenofovir diphosphate. This metabolite exerts its antiviral effect by competing with deoxyadenosine 5′-triphosphate for incorporation into viral DNA during replication, ultimately causing chain termination and inhibiting the activity of HIV-1 reverse transcriptase [9].

Rilpivirine (Figure 1C), known chemically as benzonitrile 4-[4-[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]hydrochloride, is classified as a second-generation non-nucleoside NRTI. It provides enhanced efficacy, a longer half-life, and a more favorable side effect profile than older NNRTIs like efavirenz [10].

A review of the literature revealed that LC-MS has been used for the simultaneous determination of three active compounds in biological samples [11]. In addition, capillary electrophoresis has been employed for the analysis of these substances [12], and HPLC methods have been applied in studies involving pharmaceutical preparations [13,14].

High-performance liquid chromatography (HPLC) is a fundamental tool in pharmaceutical analysis due to its simplicity, versatility, and minimal sample preparation. In this method, analytes dissolved in a solvent are separated within a chromatographic column, producing a chromatogram where each compound appears as a distinct peak at a defined retention time. Its high resolution, excellent recovery, and adaptability to compounds with various polarities, molecular weights, volatilities, and thermal sensitivities make HPLC indispensable-not only for routine analysis but also for drug stability assessments [15].

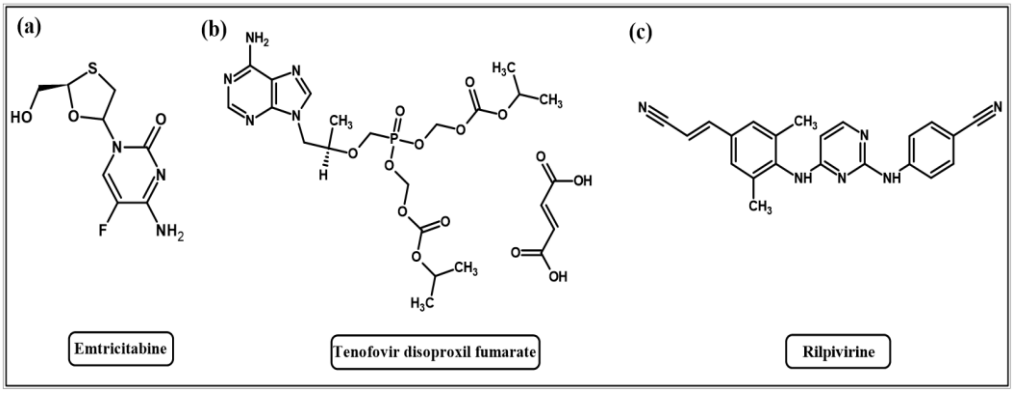


Figure 1. Chemical structure of EMT (a), TNF(b), and RLP (c)

In our study, HPLC is employed to simultaneously determine multiple drugs, demonstrating its robustness and efficiency in complex analytical applications. In this study, we introduce a novel HPLC method for the simultaneous quantification of EMT, TNF, and RLP in pharmaceutical preparations. This method offers a rapid, economical, and efficient approach to analyzing these active ingredients, ensuring high specificity and sensitivity without interference from the tablet matrix.

MATERIAL AND METHOD

Instrument

HPLC was performed using a Dionex Ultimate 3000 series system. Separation was achieved on an XBridge® C18 column (3.5 µm, 4.6 × 150 mm). The mobile phase consisted of a buffer solution containing triethylamine and trifluoroacetic acid (pH 3.15) mixed with acetonitrile, delivered at a flow rate of 1.2 ml/min. Detection was carried out using a DAD detector set at wavelengths of 285.0 nm for EMT, 261.0 nm for TNF, and 290.0 nm for RLP.

Materials

Materials used in this study were HPLC grade. EMT, TNF, and RLP standards were bought from USP. Triethyl amine (TEA), trifluoroacetic acid (TFA), and HPLC grade acetonitrile were obtained from Merck (Darmstadt, Germany). Prepared buffer solution and methanol were filtered using a 0.22 µm PES membrane filter.

Preparation of Mobile Phase

For mobile phase A, 3.5 ml of TEA was added to 2.00 l of type I pure water and filtered through a 0.22 µm PES membrane filter. Finally, 2.0 ml of TFA was added to this solution, the bottle was immediately capped, and then the bottle was gently shaken to make it homogeneous. For mobile phase B, acetonitrile for gradient grade HPLC was used.

Preparation of Standard Solutions

The stock solution of EMT was prepared by accurately weighing 50 mg of the USP standard and dissolving it in 10.0 ml of a solvent mixture containing MPA and MPB in a 1:1 (v/v) ratio, resulting in a final concentration of 5000 µg/ml. Stock solutions of TNF and RLP were prepared similarly by accurately weighing the appropriate amounts of reference standards and dissolving them in 20.0 ml of the same solvent mixture, yielding final concentrations of 1000 µg/ml. All stock solutions were stored at 5°C and protected from light.

Preparation of Laboratory-Made Solution

The excipients in the formulation were accurately weighed, mixed, and transferred to a 100 ml volumetric flask. They were then dissolved using an ultrasonic bath with a solvent mixture. A 2 ml of

this solution was subsequently diluted to 20 ml with the same solvent mixture, resulting in final concentrations of 300, 150, and 300 µg/ml for the respective analytes. All prepared solutions were filtered through a 0.22 µm membrane filter before injection into the HPLC system.

Calibration Curve Preparation

Calibration solutions at seven different concentrations were prepared from each stock solution. A 5 µl volume of each analyte solution was injected into the HPLC column at a flow rate of 1.2 ml/min. The corresponding peak areas were measured and recorded. Calibration curves were constructed by plotting peak area against concentration, and the concentrations of the samples were determined using the resulting calibration equations.

Validation Parameters of the Technique

The suggested method was questioned according to the ICH (Q2B) guideline by checking the accuracy, precision, linearity, sensitivity, and stability of the method [16].

RESULT AND DISCUSSION

Optimization of Chromatographic Method

Various mobile phases, column types, and temperature conditions were evaluated to achieve optimal chromatographic performance in terms of peak shape, symmetry factor, and retention time. The final optimized system parameters are summarized in Table 1. Separation of the active substances was carried out on an XBridge® C18 HPLC column (3.5 µm, 4.6 × 150 mm). Before analysis, the stationary phase was conditioned for approximately 1.0 hours with the mobile phase, during which the flow rate was gradually increased from 0.2 ml/min to 1.2 ml/min. A 5.0 µl injection volume was used for all standard and sample solutions. System suitability parameters are presented in Table 2. All data were obtained at the specific detection wavelengths for each analyte. The optimized chromatogram, shown in Figure 2, demonstrates the precision and suitability of the method for the simultaneous analysis of EMT, TNF, and RLP.

Table 1. HPLC parameters

Analytical column	Waters XBridge® C18, (3.5 µm 4.6x150 mm)
Mobile phase A	0.175 % TEA and 0.1 % TFA in water
Mobile phase B	Acetonitrile
Mobile phase Ratio	MPA: MPB (60:40; v/v)
Flow rate	1.2 ml/min
Injection	5 µl
T_{column}	40°C
$T_{Autosampler}$	20°C and 5°C*
Runtime	5 minutes
Wavelengths	λ_1:261 nm for RLP, λ_2:285 nm for EMT, λ_3:290 nm for RLP

* The autosampler was maintained at 5°C during system operation, and inter-day samples were stored at the same temperature to ensure consistency and stability

Table 2. System suitability parameters of the HPLC method at the mean concentration

Parameters	Retention time	Theoretical plates	Asymmetry	Capacity Factor)	Resolution
EMT	1.26	4418	1.22	5.28	7.32
TNF	1.88	6192	1.15	8.42	11.72
RLP	3.18	10302	1.01	14.88	-

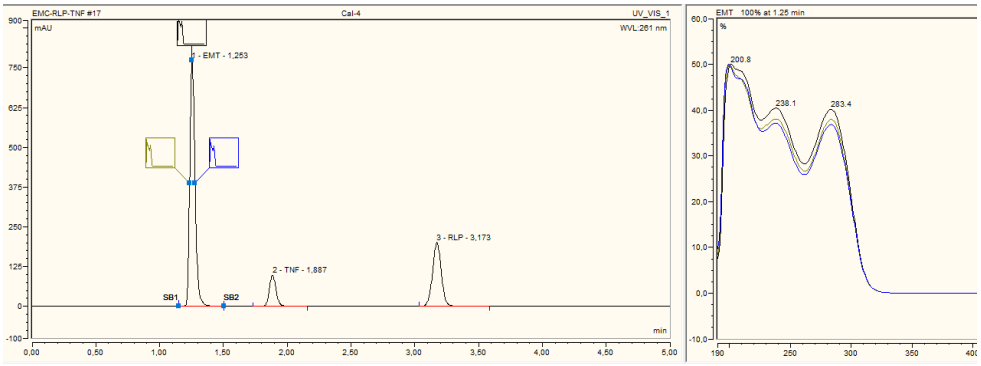


Figure 2. Representative peaks of active ingredients with suggested conditions

Validation of Developed Analytical Methods

Following the International Conference on Harmonization ICH guidelines, the developed method was validated for accuracy, precision, linearity, sensitivity, and stability.

Linearity and Sensitivity

The linearity of the analytical approach was evaluated by establishing calibration curves for EMT (10.0–600.0 µg/ml), TNF (2.0–75.0 µg/ml), and RLP (2.0–75.0 µg/ml), with regression equations and correlation coefficients derived from the mean peak areas of various concentrations. The high correlation coefficients ($R^2 > 0.999$) confirm a strong linear relationship. Additionally, the limits of detection (DL) and quantification (QL) were determined according to ICH Q2(R2) guidelines, as presented in Table 3. These results highlight the method's high sensitivity, allowing reliable detection of EMT, TNF, and RLP at low concentrations, which is essential for accurate pharmaceutical and chemical analyses.

Table 3. Parameters of the suggested HPLC technique

Parameters	EMT	TNF	RLP
Calibration range (µg/ml)	10.0-600.0	2.0-75.0	2.0-75.0
Wavelength, nm	285.0	261.0	290.0
Intercept value	1.0331	0.1836	-0.4557
Slope value	0.2459	0.2285	1.0978
Correlation coefficient, R^2	0.999	0.999	1.000
DL (µg/ml)	0.06	0.05	0.02
QL (µg/ml)	0.19	0.14	0.07

Accuracy Studies for the HPLC Technique

The accuracy of the proposed HPLC method was determined through recovery studies. Recovery was assessed by preparing synthetic solutions in which two of the analytes were maintained at their mean concentrations, while the analyte under investigation was varied to 50%, 100%, and 150% of its mean concentration. The calculated recovery values are presented in Table 4. The results showed that the percentage recoveries were within the acceptable range, confirming the high accuracy of the developed method.

Table 4. The calculated value of recovery for the laboratory mixture

Active Substance	%50	%100	%150
EMT	98.1	99.3	98.3
TNF	99.4	98.2	99.1
RLP	100.6	100.0	101.2

Precision Results of the HPLC Technique

The precision of the proposed method was evaluated by analyzing two sets of samples prepared at three different concentration levels. For the intra-day precision study, the samples were stored at 20°C. For the inter-day precision study, the samples were divided into two groups: one stored at 20°C and the other at 5°C. Both sets were protected from light throughout the study. The calculated values are presented in Tables 5 and 6.

Table 5. Precision values of the suggested HPLC method of EMT, TNF, and RLP at 20°C (Intra-day results)

EMT at 20°C	**Level 50%**	**Level 100%**	**Level 150%**
2. Hour	100.4	99.8	101.1
4. Hour	97.5	98.9	98.9
6. Hour	99.2	94.6	95.6
8. Hour	100.0	95.5	95.8
12. Hour	100.1	96.5	94.0
16. Hour	99.8	101.4	93.0
20. Hour	100.1	100.3	92.1
24. Hour	100.0	101.8	91.7
Standard Dev.	0.9	2.7	3.3
TNF at 20°C	**Level 50%**	**Level 100%**	**Level 150%**
2. Hour	100.2	96.9	101.7
4. Hour	99.4	94.6	99.2
6. Hour	98.9	91.5	95.5
8. Hour	99.6	92.4	95.7
12. Hour	99.6	93.4	93.7
16. Hour	99.4	98.0	92.5
20. Hour	99.6	96.9	91.5
24. Hour	99.4	98.2	90.8
Standard Dev.	0.4	2.6	3.8
2. Hour	98.9	94.7	97.5
4. Hour	98.3	92.6	95.2
6. Hour	97.9	89.7	91.9
8. Hour	98.5	90.6	92.1
12. Hour	98.6	91.6	90.3
16. Hour	98.4	95.9	89.2
20. Hour	98.6	94.9	88.3
24. Hour	98.5	96.2	87.8
Standard Dev.	0.3	2.5	3.4

Performance of the Suggested HPLC Method in Stability Analysis

To evaluate the performance of the proposed method in stability analysis, some synthetic solutions were prepared and analysed. For this purpose, at the mean concentration, the sample solutions were forced to be degraded by 0.1 N HCl, 0.1 N NaOH, 3.0% Hydrogen peroxide solution, and by keeping the sample solution at 50°C. The method demonstrated reliable performance in analyzing the

degraded samples, indicating its suitability for stability studies and its robustness in detecting potential degradation products.

Table 6. Precision values of the suggested HPLC method of EMT, TNF, and RLP at 5°C and 20°C (Inter-day results)

EMT at 20°C Inter-day Results				**EMT at 5°C Inter-day Results**			
Day	**Level 50%**	**Level 100%**	**Level 150%**	**Day**	**Level 50%**	**Level 100%**	**Level 150%**
1. Day	100.0	101.8	91.7	1. Day	98.0	99.5	98.1
2. Day	99.6	102.8	91.1	2. Day	99.7	98.0	96.7
3. Day	101.5	102.9	94.0	3. Day	100.8	102.9	97.9
4. Day	101.5	101.9	92.9	4. Day	97.4	99.9	97.0
5. Day	98.9	103.4	96.0	5. Day	97.9	101.2	96.3
Std Dev.	1.2	0.7	2.0	**Std Dev.**	1.4	1.8	0.8
TNF at 20°C Inter-day Results				**TNF at 5°C Inter-day Results**			
Day	**Level 50%**	**Level 100%**	**Level 150%**	**Day**	**Level 50%**	**Level 100%**	**Level 150%**
1. Day	99.4	98.2	90.8	1. Day	97.4	96.2	97.9
2. Day	98.7	99.1	89.9	2. Day	98.5	94.7	96.2
3. Day	100.2	99.0	92.7	3. Day	100.0	98.9	97.3
4. Day	100.1	97.8	91.3	4. Day	96.6	100.2	96.5
5. Day	98.1	99.8	95.2	5. Day	101.1	97.1	90.1
Std Dev.	0.9	0.8	2.1	**Std Dev.**	1.9	2.2	3.1
RLP at 20°C Inter-day Results				**RLP at 5°C Inter-day Results**			
Day	**Level 50%**	**Level 100%**	**Level 150%**	**Day**	**Level 50%**	**Level 100%**	**Level 150%**
1. Day	98.5	96.2	87.8	1. Day	97.5	94.3	94.1
2. Day	98.0	97.2	87.0	2. Day	97.4	93.2	92.7
3. Day	99.7	97.4	89.9	3. Day	100.0	96.0	93.7
4. Day	99.7	96.4	88.7	4. Day	97.1	97.3	93.0
5. Day	98.2	97.4	91.8	5. Day	100.7	95.7	93.3
Std Dev.	0.8	0.6	1.9	**Std Dev.**	1.7	1.6	0.6

Comparison with Reported HPTLC and LC–MS/MS Methods

To evaluate the relative strengths of the developed RP-HPLC method, a comparison was made with two previously published analytical techniques: an LC–MS/MS method [11] and a high-performance thin-layer chromatography (HPTLC) method [13]. The LC–MS/MS method, although highly sensitive with a lower limit of quantification of 10 ng/ml and broad calibration ranges (10–2000 ng/ml for all analytes), was primarily designed for bioanalytical applications using dried blood spots and required complex sample preparation and costly instrumentation. This limits its practicality for routine pharmaceutical quality control. On the other hand, the HPTLC method, while more economical, demonstrated lower resolution and was less suited for high-throughput workflows. It reported LODs of approximately 4.25–5.51 ng/band and LOQs of 12.88–16.69 ng/band, with acceptable accuracy and precision. However, its reliance on densitometric detection and limited automation may restrict its reproducibility and broader applicability in pharmaceutical analysis. Compared to both methods, the proposed RP-HPLC method provides a favorable balance of precision, sensitivity, and operational simplicity. With linear calibration ranges of 10.0–600.0 µg/ml for Emtricitabine, 2.0–75.0 µg/ml for Tenofovir, and 2.0–75.0 µg/ml for Rilpivirine, along with excellent correlation coefficients ($R^2 \geq 0.999$), the method ensures reliable quantification over therapeutically relevant concentrations. Furthermore, its

rapid analysis time, straightforward sample preparation, and cost-effectiveness position it as an efficient alternative for routine quality control in pharmaceutical laboratories.

Conclusion

The proposed HPLC method was successfully developed and validated for the simultaneous quantification of EMT, TNF, and RLP in laboratory-prepared and synthetic pharmaceutical samples. The method offers a straightforward and rapid procedure without the need for derivatization or complex sample preparation, making it both time- and energy-efficient. It demonstrated high sensitivity, with detection at lower concentrations than some previously reported methods and exhibited excellent accuracy and precision across the studied range. In comparison to more sophisticated techniques such as LC–MS/MS, which require costly instrumentation and complex workflows, the HPLC method provides a practical alternative that is more accessible and cost-effective for routine pharmaceutical quality control. Additionally, it offers significant advantages in terms of shorter analysis time and reduced energy consumption, aligning with environmentally conscious analytical practices. Overall, the developed method is reliable, economical, and well-suited for the routine or individual determination of EMT, TNF, and RLP in combined dosage forms.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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