INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Review On Various Analytical Approaches For The Estimation Of Rilpivirine And Its Combination In Bulk And Dosage Forms

Srinija Naluka[1], Soujanya Chaganti[2]*, Karuna Devi Barla[2], Durga Panikumar Anumolu[1]

[1]Department of Pharmaceutical Analysis, Gokaraju Rangaraju College of Pharmcay, Hyderabad.
[2]Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmcay, Hyderabad.

ARTICLE INFO

Received: 16 March 2024
Accepted: 20 March 2024
Published: 23 March 2024
Keywords:
Rilpivirine ,Linearity, Spectroscopic method, HPLC, LCMS.
DOI:
10.5281/zenodo.10863534

ABSTRACT

Rilpivirine is non-nucleoside reverse transcriptase inhibitor (NNRTI) which is used for the treatment of HIV-1 infections in treatment-naive patients. It is a diarylpyrimidine derivative. The chemical name of rilpivirine is 4-{[4-({4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl}amino)-pyrimidinyl]amino}benzonitrilemonohydrochloride. Present review is focused on method conditions, linearity offered, sensitivity, accuracy, precision and assay results of various analytical methods such as UV-Visible spectroscopy, HPLC and LCMS for the estimation of rilpivirine.

INTRODUCTION

Rilpivirine is non-nucleoside reverse transcriptase inhibitor (NNRTI) which is used for the treatment of HIV-1 infections in treatment-naive patients. It is a diarylpyrimidine derivative. The chemical name of rilpivirine is 4-{[4-({4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl}amino)-pyrimidinyl]amino}benzonitrilemonohydrochloride[3,4].

Its molecular is C22H18N6.

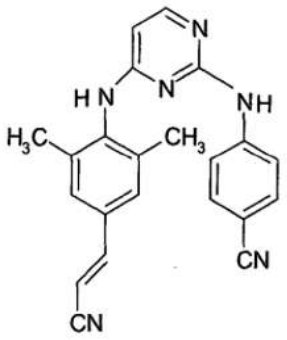

Figure 1: Chemical Structure of Ripivirine

***Corresponding Author:** Soujanya Chaganti
Address: *Department of Pharmaceutical Chemistry, Gokaraju Rangaraju College of Pharmcay, Hyderabad.*
Email ✉: Soujanya.chaganti18@gmail.com.

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Rilpivirine was developed by Tilbotec, Inc. and FDA approved on May 20, 2011. The internal conformational flexibility of rilpivirine and the plasticity of it interacting binding site gives it a very high potency and reduces the chance of resistance compared to other NNRTIS. Treatment of HIV-1 infections in treatment-naive patients with HIV-1 RNA ≤100,000 copies/mL in combination with at least 2 other antiretroviral agents. Literature survey reveals few analytical methods for the estimation of rilpivirine such as chromatographic techniques [1-18], spectrophotometric techniques [19-21], hyphenated techniques [22-25].

CHROMATOGRAPHIC TECHNIQUES1-18

Sr. No	Mobile phase [v/v]	Flow rate & Detection wave length	Column	Linearity [µg/ml]	Accuracy	Precision & Retention time	LOD & LOQ
1	MeCN, potassium dihydrogen phosphate buffer (20 mM, pH 3.3), & triethylamine 58.72: 41.23: 0.05 (v/v)	1.7 mL/min & 270 nm	Phenomenex Gemini C18 column (150 mm × 4.6 mm i.e., 5 μm)	**HPLC** Emtricitabine [EMT]: 28–84 µg /ml, Tenofovir disoproxil fumarate [TDF]: 42–126 µg /ml, & Rilpivirine [RPV]: 3.5–10.5 µg /ml	EMT: 99.50% TDF: 99.90% & RPV: 99%	%RSD: intraday & interday precision ≤2% & **RT:** -	LOD & LOQ: EMT-1.90, 0.43 ng/mL TDF-2.18, 0.54 ng/mL RPV-3.12, 1.78 ng/mL
2	Phosphate buffer: Acetonitrile 40:60	1.2 mL/min & 262 nm	INERTSIL column, C18 (150x4.6 ID) 5µm	**HPLC** Emtricitabine: 24-56 µg /ml, Rilpivirine: 3-7 µg /ml & Tenofovir disoproxil fumarate: 30-70 µg /ml	EMT: 100.19%, RPV: 101.30% & TDF: 99.70%	%RSD: <2% & **RT:** EMT: 2.523 min RPV: 3.270 min TDF: 6.653 min	LOD & LOQ: EMT-22.19, 30.31 µg/ml RPV-3.85, 17.12 µg/ml TDF-17.23, 50.91 µg/ml
3	Mobile phase A: 0.02M sodium dihydrogen	1.5 ml/min & 261 nm	Inertsil ODS 3V column	**RP-HPLC** Emtricitabine: 8-120µg/ml, Tenofovir disoproxil	**Sol 1:** EMT: 99.2 TDF: 99.2 RPV: 99.59 **Sol 2:**	%RSD: EMT: 0.21% TDF: 0.099% RPV: 0.34% & **RT:**	LOD & LOQ: EMT - 0.06, 0.14 µg/ml

	orthophosphate & Mobile phase B: Methanol and water (85:15)			fumarate: 12-180µg/ml, & Rilpivirine: 20-360µg/ml	EMT: 98.92 TDF: 100.56 RPV: 101.32 **Sol 3:** EMT: 100.36 TDF-: 99.42 RPV: 100.95 **Sol 4:** EMT: 99.71 TDF: 99.32 RPV: 99.99 **Sol 5:** EMT: 101.07 TDF: 99.09 RPV: 99.85	EMT: 5.88 min TDF: 8.796 min RPV: 12.015 min	TDF - 0.07, 0.12 µg/ml RPV - 0.08, 0.15 µg/ml
4	Acetonitrile, Potassium dihydrogen phosphate buffer (pH2.8) & orthophosphoric acid (40:60)	1.0 ml/min & 282 nm	Develosil ODS HG-5 RP C18, 5µm, 15cmx4.6 mm	**RP-HPLC** Rilpivirine: 0 – 30 µg/ml	%RSD: 0.202152, 0.331525, 0.331159	**Intraday** **solution** / **%RSD** **10** / **0.96** **20** / **0.4** **30** / **0.33** **Interday** **10** / **0.97** **20** / **0.42** **40** / **0.14** **RT:** RPV: 4.50 min	**LOD & LOQ: RPV - 0.05, 0.15 µg/ml**
5	0.1% Orthophosphoric & acetonitrile (60:40 v/v)	1.0ml/min & 262nm	Phenomenex C18 (150x4.6mm, 5µm)	**RP-HPLC** Dolutegravir (DTG): 10–150 µg/ml & Rilpivirine (RPV): 5–75 µg/ml	DTG: 100.22–100.45% & RPV: 100.37–100.58%	% RSD: DTG: 0.15% RPV: 0.26% **RT:** DTG: 4.349 min RPV: 7.730 min	LOD & LOQ: DTG - 0.01, 0.1 µg/ml RPV - 0.005, 0.05 µg/ml
6	Mobile phase A: 0.03M di potassium hydrogen orthopho	1.0 ml/min & 284 nm	Zorbax Eclipse XDB-C18, 250x4.6mm,5 µm	**RP-HPLC** Rilpivirine: 100-300µg/ml	RPV: 93.50-119.10 %	%RSD: intraday & interday precision ≤2% **RT:** RPV: 7.19 min	LOD & LOQ: RPV - 0.05µg/ml, 0.15 µg/ml

	sphate (pH 2.5) & dilute ortho-phospho ric acid & Mobile phase B: acetonitr ile (15: 85 v/v)						
7	0.1% OPA: Acetonit rile (60:40 v/v)	1.0 mL min-1 & 230 nm	INERTSIL ODS C18 (250 × 4.6 mm, 5 µm)	**RP-HPLC** Dolutegravir: 50-150 µg /ml & Rilpivirine: 25-125 µg/ml	DTG:100.3 9% RPV:100.0 4%	% RSD: <2% **RT:** DTG: 3.410 min RPV: 4.387 min	_
8	KH2PO 4 buffer (pH 3.5) & Acetonit rile (45:55 v/v)	1mL/min & 240.0 nm	Agilent C18 column (4.6x150m m, 5µm)	**RP-HPLC** Dolutegravir: 12.5 -75 µg/mL & Rilpivirine: 6.25-37.5 µg/mL	DTG: 99.33% & RPV: 100.5%	%RSD: DTG - 0.9% & RPV - 0.6% **RT:** RPV: 2.239 min DTG: 2.899 min	LOD & LOQ: DTG - 0.2, 0.6 µg/ml RPV - 0.02, 0.06 µg/mL
9	Acetonit rile & Phosphat e buffer (pH 3.5), (60:40)	1 ml/min & 282 nm	C8 Column (4.6 x 250 mm, 5 µm)	**RP-HPLC** Rilpivirine: 10-50 µg/mL	RPV: 99-101%	%RSD: Precision: 0.13, ID Precision: 0.004 **RT:** RPV: 2.755 min	LOD & LOQ: RPV - 0.005µg/m l, 0.17µg/ml
10	0.01N KH2PO 4 buffer (pH: 4.8): acetonitr ile (70:30v/ v)	260 nm	Agilent - C18 column (BDS) (150 X 4.6 mm, 5µm)	**RP-HPLC** Cabotegravir: 25-150 µg/mL & Rilpivirine: 37.5-225µg/mL	Cabotegrav ir: 100.25% & RPV: 99.79%	%RSD: Cabotegravir - 0.3% & RPV - 0.4% Intraday & interday precision ≤2 **RT:** RPV: 2.300 min Cabotegravir: 3.187 min	LOD & LOQ: Cabotegra vir - 0.24, 0.74 µg/mL RPV – 1.10, 3.34 µg/mL
11	Acetonit rile: ammoni um	0.8 ml/minut es &	Shim-pack C18 column	**RP-HPLC** Rilpivirine HCL: 5–50 µg/ml	RPV HCL: 98%–102%	%RSD: RPV HCL - 0.709% **RT:** RPV:	LOD & LOQ: RPV HCL - 0.104

	acetate buffer (0.05 M) (pH-3.5 equalized with glacial acetic acid), (60:40 v/v)	291 nm	(150 × 4.6 mm; 5 µ)			4.5 min	µg/ml, 0.315 µg/ml
12	0.01N ammonium acetate buffer (pH 3) & acetonitrile (65:35 v/v)	1.0 ml/min & 257 nm	Inertsil C18 (150 x 4.6 mm, 5 µm) column	**RP-HPLC** Cabotegravir: 10-60 µg/ml & Rilpivirine: 15-90 µg/ml	Cabotegravir: 100.71 % & RPV: 100.01 %	%RSD: < 2% **RT:** Cabotegravir: 2.250 min RPV: 2.823 min	LOD & LOQ: Cabotegravir - 0.13 µg/ml, 0.38 µg/ml RPV - 0.16 µg/ml, 0.48 µg/ml
13	0.01N Potassium dihydrogen phosphate: Acetonitrile (60:40)	1.0 ml/min & 257 nm	Kromasil C18 150 x 4.6 mm, 5µ	**RP-HPLC** Cabotegravi:18.75-112.5µg/ml Rilpivirine: 12.5- 75µg/ml	RPV: 100.13% & Cabotegravir: 100.43%	%RSD: RPV: 0.5% & Cabotegravir: 1.4% **RT:** RPV: 2.257 min Cabotegravir: 2.642 min	LOD & LOQ: RPV - 0.18 µg/ml, 0.54 µg/ml Cabotegravir - 0.15 µg/ml, 0.46 µg/ml
14	Mobile phase: phosphate buffer: acetonitrile (60:40% v/v), (pH 6.8)	1.0ml/min & 272nm	Ymc C18 short column	**RP-HPLC** Rilpivirine:1-10µg/ml	RPV: 0.6397%	%RSD: RPV: 0.6845 **RT:** RPV: 3.137 min	LOD & LOQ: RPV - 0.0427µg/ml, 0.724 µg/ml
15	Chloroform: ethyl acetate: methanol: glacial acetic acid (5:2:1:0.	272 nm	Aluminium plates: silica gel 60 F254	**HPTLC** Emtricitabine: 600-2400 ng band^{-1} Rilpivirine: 50-300 ng bands^{-1} Tenofovir disoproxil	EMT: 100.01% RPV: 100.32% TDF: 100.14%	%RSD: intraday and interday precision% (<2%) EMT: 99.91% RPV: 98.72% TDF: 99.34%	LOD & LOQ: EMT – 5.0164, 15.2012 ng/band RPV -

	1 v/v/v/v)			fumarate: 600-3600 ng band^{-1}		**RT:** -	4.25, 12.8790 ng/band TFV – 5.5063, 16.6890 ng/band
16	35% of 0.1M tri ethyl amine buffer & 65% Acetonitrile	0.3 ml/min & 260 mμ	Thermosil Octa Decyl Column (4.6 x 50mm, 1.7 mm)	**RP-UPLC-PDA** _	Mean recovery: 100.48%	%RSD: <2 **RT:** Emtricitabine: 0.965 min, Tenofovir Alafenamide: 1.528 min, RPV: 2.186 min	LOD & LOQ: 3.00 µg/ml, 9.98 µg/ml
17	0.1% ortho phospho ric acid & acetonitrile (55:45% v/v)	1 mL/min & 260 nm	SB C8 column (100 x 3 mm, 1.8 mm)	**RP-UPLC** Dolutegravir: 12.5 – 75.0 µg/mL Rilpivirine: 6.25 – 37.5 µg/mL	% Recovery: DOL: 99.04 - 99.79% RIL: 99.20 - 99.92%	%RSD: <2.0 **RT:** Dolutegravir: 1.25 min RPV: 1.69 min	LOD & LOQ: DOL: 0.281 & 0.852 µg/ml RIL: 0.281 & 0.152 µg/ml
18	methanol: water: 0.1% ortho phospho ric acid (80:10:10 v/v/v)	1.5ml/min & 230nm	Zodiac C18 (250x4.6mm, 5µm in particle size)	**LC** Rilpivirine:4-10 µg/ml	Mean recovery: 98.3 to 100.1%	%RSD: <1.0% Intraday: 0.8 - 1.08 Interday: 0.9 - 1.27 **RT:** RPV: 3.83 min	LOD & LOQ: 0.06 µg/ml, 0.2µg/ml
19	HPTLC: ethyl acetate: methanol: chloroform (8.0:1.0:1.0%v/v/v)	254nm	_	**HPTLC** Rilpivirine:5-30 µg/spot	%RSD: 0.8692%	%RSD: 0.3044 **RT:** -	LOD & LOQ: 0.317 µg/ml, 0.513 µg/ml

SPECTROPHOTOMETRIC TECHNIQUES19-21

S.NO	Solvents	Linearity [µg/ml]	λmax (nm)	Comment
20	Methanol	**UV**	EMT: 240.8nm	UV region

		Emtricitabine: 4–12 μg/ml, Tenofovir disoproxil fumarate: 6–18 μg/ml, Rilpivirine HCl: 0.5–1.5 μg/ml	TDF: 257.6nm RPV: 305.6nm	
21	Acetonitrile: Water (50:50)	**UV** 4-20µg/ml	304nm	UV region
22	Methanol	**UV** 2-8µg/ml	282nm	UV region

HYPHENATED TECHNIQUES22-25

Sr. NO	Mobile phase (v/v)	Flow rate (ml/min)	Column	Linearity & Retention Time
23	5 mM Ammonium acetate, 20.0% & Acetonitrile, 80% (20:80% v/v)	0.70 ml/min	Zorbax 5 µ, C18, 100×4.60 mm	**LC-MS-MS** Tenofovir: 5.000 - 600.00 ng/mL Rilpivirine: 1.000-203.00 ng/mL **RT:** Tenofovir: 0.85 min RPV: 2.80 min
24	Acetonitrile & 0.1% (v/v) trifluoroacetic acid in water (81:19, v/v)	0.3 mL/min	Apex Scientific Inertsil ODS-3 column (4.6 mm × 250 mm, 5 µm particle size)	**HPLC-MS** Rilpivirine: 0-150 ng/ml Cabotegravir: 0-25000 ng/ml **RT:** RPV: 6.846 min Cabotegravir: 9.835 min
25	55% of water (0.05% formic acid, v/v) and 45% of methanol (0.05% formic acid, v/v)	0.5mL/min	Kinetex phehyl-hexyl column	**HPLC-MS-MS** Darunavir (DRV): 60 to 15000 ng/mL Dolutegravir (DTG) & Elvitegravir (ELV): 20 to 5000 ng/mL

				Raltegravir (RAL), Raltegravir-β-D-glucuronide (RAL-GLU), Ritonavir (RTV) and Rilpivirine (RPV): 10 to 2500 ng/mL **RT:** RAL-GLU: 2.8 min, RPV: 4.0 min, RAL: 5.3 min, DRV: 6.1min, DTG: 6.7 min, ELV: 9.1 min, RTV: 9.4 min

CONCLUCSION:

Upon extensive literature survey, it was found that quite a good spectrophotometric, chromatographic as well as hyphenated techniques were reported for the quantification of Rilpivirine. Therefore, this study may help researchers in developing a simple, precise and robust method for the quantification of rilpivirine and its combinations.

REFERENCES

1. Venkatesan S, Kannappan N, Mannemala SS. Stability-indicating HPLC method for the simultaneous determination of HIV tablet containing emtricitabine, tenofovir disoproxil fumarate, and rilpivirine hydrochloride in pharmaceutical dosage forms. Int Sch Res Notices. 2014.
2. Karunakranth D, Midha AK, Babu RS, Kishore D. Development and validation of HPLC method for simultaneous estimation of emtricitabine, rilpivirine and tenofovir disoproxil fumarate tablet dosage form. IJRPB. 2018;6(1):8-15.
3. Kavitha KY, Geetha G, Hariprasad R, Venkatnarayana R, Subramanian G. Development and validation of rp-hplc analytical method for simultaneous estimation of emtricitabine, rilpivirine, tenofovir disoproxil fumarate and its pharmaceutical dosage forms. IJCP. 2013;4(1):1.
4. Kumar BR, Subrahmanyam KV. A validated stability-indicating rp-hplc method for the determination of rilpivirine. JGTPS. 2014;5(3):1822-6.
5. Veeraswami B, Naveen VM. Development and validation of RP-HPLC method for the estimation of dolutegravir and rilpivirine in bulk and pharmaceutical dosage form and its application to rat plasma. Development. 2019;12(2).
6. Kumar BM, Rajkamal B, Chandramowli B. Development and validation of Rilpivirine in pharmaceutical formulation by RP-HPLC. Am J PharmTech Res. 2019;9(03):345-53.
7. Babu MN, Chandrasekar R. Development and validation of stability indicating RPHPLC method for the simultaneous estimation of dolutegravir and rilpivirine by forced

degradation studies. Int. J. Pharm. Sci. & Res. 2021;12(9):4954-63.
8. Pravalika P, Rani GT, Sree PT, Saritha Y. Development and validation of RP-HPLC method for the estimation of dolutegravir and rilpivirine in bulk and its tablet dosage form. J. Pharm. Res. 2021 jul;20(3):19.
9. Ghosh S, Bomma S, Prasanna VL, Vidyadhar S, Banji D, Roy S. Method development and validation of rilpivirine in bulk and tablet doses form by RP-HPLC method. RJPT. 2013;6(3):240-3.
10. Suneetha A, Lakshmi MV, Jyothi K, Priyanka BY. Development and validation of stability indicating RP-HPLC method for the simultaneous determination of cabotegravir and rilpivirine in bulk and injection dosage form. J. Pharm. Res. 2022 oct;21(4):145.
11. Patel S, Nagappan K, Reddy GS. A new quantitative Reverse phase high-performance liquid chromatographic method for the quantification of Rilpivirine hydrochloride in bulk and dosage form. J. Appl. Pharm. Sci. 2018 Nov 30;8(11):157-62.
12. Vemuluri PC, Dodda S. Stability indicating Reverse phase-high performance liquid chromatography method for simultaneous estimation of cabotegravir and rilpivirine. Ind. J. Pharm. Edu. Res. 2023;57(3s):s766-71.
13. Prasanna A, Rani SS. A validated stability indicating RP-HPLC method development for simultaneous estimation of cabotegravir and rilpivirine in pharmaceutical dosage form: https://doi. Org/10.54037/wjps. 2022.101003. WJPPS. 2022 oct 1:22-9.
14. Sudha T, Shanmugasundram P. Reverse phase high performance and HPTLC methods for the determination of rilpivirine bulk and in tablet dosage form. WJPPS. 2012 Jul 17;1(4):1183-96.
15. Saminathan J, Vetrichelvan T. Development and validation of HPTLC method for simultaneous estimation of emtricitabine, rilpivirine and tenofovir disoproxil fumarate in combined dosage form. Bangladesh J. Pharmacol. 2016 Aug 10;19(1):114-21.
16. Pasha SI, Varanasi MB, Mohammed I. Stability indicating RP-UPLC-PDA method development, validation of multi drug combination of emtricitabine, tenofovir alafenamide and rilpivirine in bulk drug and its tablet formulation. Orient. J. Chem. 2017 Jan 1;33(2):925-9.
17. Khaleel N, Rahaman SA. Stability-indicating RP-UPLC method for simultaneous determination of dolutegravir and rilpivirine in bulk and pharmaceutical dosage form. Indian drugs. 2019 oct 1;56(10).
18. Kumar KR, Suneetha A, Srilakshmi N. A validated LC method for the Estimation of Rilpivirine in API and Pharmaceutical Dosage form. J. Pharm. Res. 2012 Aug;5(8):4434-6.
19. Sudha T, Shanmugasundram P. Reverse phase high performance and HPTLC methods for the determination of rilpivirine bulk and in tablet dosage form. World J. Pharm. Res. 2012 Jul 17;1(4):1183-96.
20. Venkatesan S, Kannappan N. Simultaneous spectrophotometric method for determination of emtricitabine and tenofovir disoproxil fumarate in three-component tablet formulation containing rilpivirine hydrochloride. Int. Sch. Res Notices. 2014;2014.
21. Ghurghure SM, Dhange A, Mhetre R, Phatak AA. Method development and validation of rilpivirine in bulk and solid dosage form by using uv-visible spectrophotometric method.
22. Ghosh S, Kumar M, Jena S, Banji D, Roy S. Method development and validation of Rilpivirine in bulk and Pharmaceutical Tablet Dosage Form by using UV–Visible Spectrophometric Method. AJRC. 2012;5(12):1472-5.

23. Kumar BM, Bigala BR. A Simple, selective, rapid and rugged method development and validation of tenofovir and rilpivirine in human plasma using liquid chromatography coupled with tandem mass spectrometry. EJPMR. 2017;4(7):605-13.
24. Ramöller IK, Abbate MT, Vora LK, Hutton AR, Peng K, Volpe-Zanutto F, Tekko IA, Moffatt K, Paredes AJ, McCarthy HO, Donnelly RF. HPLC-MS method for simultaneous quantification of the antiretroviral agents rilpivirine and cabotegravir in rat plasma and tissues. J. Pharm. Biomed. Anal. 2022.10;213:114698.
25. Zheng Y, Aboura R, Boujaafar S, Lui G, Hirt D, Bouazza N, Foissac F, Treluyer JM, Benaboud S, Gana I. HPLC-MS/MS method for the simultaneous quantification of dolutegravir, elvitegravir, rilpivirine, darunavir, ritonavir, raltegravir and raltegravir-β-d-glucuronide in human plasma. J. Pharm. Biomed. Anal. 2020.15;182:113119.

HOW TO CITE: Srinija Naluka, Soujanya Chaganti, Karuna Devi Barla, Durga Panikumar Anumolu, Review On Various Analytical Approaches For The Estimation Of Rilpivirine And Its Combination In Bulk And Dosage Forms, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 3, 915-924. https://doi.org/10.5281/zenodo.10863534