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ANALYTICAL METHODS FOR RALTEGRAVIR IN PHARMACEUTICALS: A REVIEW

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ABSTRACT

The main aim of this review is to provide a brief overview of analytical methods like spectrophotometric and chromatographic methods for the analysis of Raltegravir in pharmaceuticals to researchers. Integrase inhibitors, also called as integrase strand transfer inhibitor (INSTI) are one of the class of antiretroviral (HIV) drugs intended to block integrase action. Integrase is a viral enzyme that inserts viral genome into DNA of host cell. Integration is an important step in retroviral replication, blocking of integrase enzyme can halt further spread of virus. Various analytical methods for Raltegravir are reviewed in this article along with their experimental conditions in bulk, pharmaceutical dosage forms.

Keywords: Raltegravir, spectrophotometric, chromatographic, HIV, analytical methods

INTODUCTION

Raltegravir is chemically N- [(4-fluorophenyl) methyl]-5-hydroxy-1-methyl-2- {2- [(5-methyl-1,3,4-oxadiazol-2-yl) formamido] propan-2-yl}-6-oxo-1,6-dihydropyrimidine-4-carboxamide. The molecular formula is $C_{20}H_{21}FN_6O_5$ and molecular weight is 444.42g/mol. Raltegravir targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV. The drug is metabolized away via glucuronidation. In present study, analytical methods with better detection range for estimation of Raltegravir in its pure form and its pharmaceutical formulations **[1]**.

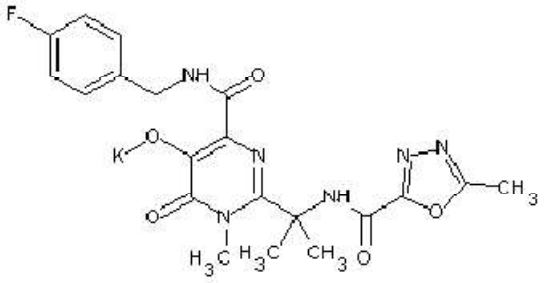

Figure 1: Structure of Raltegravir [2]

METHODS

S. No.	Drug and reference	Method	Inference
1.	Raltegravir in bulk and tablet dosage form [1]	UV-Spectrophotometric method	λmax:290nm Solvent: 0.1N NaOH
2.	Raltegravir potassiumin tablets [3]	Spectrophotometric estimation	λmax:328nm Linearity: 3-55µg/mL
3.	Raltegravir potassium in bulk and pharmaceutical formulation [4]	Spectrophotometric method	λmax:331.6nm Linearity: 1-100µg/mL
4.	Raltegravir in film coated tablets [5]	Derivative and difference spectrophotometry	Diluent: Borate buffer (P^H 9), HCl, sodium acetate buffer solutions Linearity: 1-150, 10-150, 10-150µg/mL in all the buffers in zero, first order derivative & different spectroscopy
5.	Raltegravir and Lamivudine in bulk and pharmaceutical dosage form [6]	RP-HPLC	Mobile phase (M.P): ACN:phosphate buffer, P^H 3.0, (45:55%v/v) Column:Inetrsil ODS 3V C18 (4.6×150mm, 5µm) Detector and wavelength: PDA, 275nm Flow rate: 1.0mL/min Linearity:Raltegravir 150-450µg/mL, Lamivudine 50-150µg/mL
6.	Lamivudine and Raltegravir in laboratory prepared binary mixture [7]	RP-HPLC	M.P: Methanol:ACN: 0.05mM phosphate buffer P^H 3.0, (75:15:10%v/v) Column: Phenomenex C18 (150mm×4.6mm id, 5µ particle size) wavelength: 275nm Flow rate: 1.0mL/min
7.	Lamivudine and Raltegravir in bulk and tablet dosage form [8]	RP-HPLC	M.P: ortho phosphoric acid: ACN: P^H 2.45 adjusted with triethyl amine, (40:60%v/v) Column: symmetry C18 (250mm×4.6mm, 5µ) Flow rate: 1.0mL/min Detector and wavelength: PDA, 260nm Retention Time: Lamivudine and Raltegravir 2.355min, 3.400min respectively Linearity: 50-150µg/mL
8.	Raltegravir in pharmaceutical preparations [9]	RP-HPLC	Column: symmetry C8 (150mm×4.6mm, 5µ particle size) M.P: Methanol: phosphate buffer P^H 2.5: ACN, (40:60v/v), isocratic mode Flow rate: 0.6mL/min, wavelength: 247nm Injection volume: 20µL Retention Time: 2.881min Linearity: 5-25µg/mL
9.	Antiretroviral agents in the plasma of HIV-infected Patients [10]	HPLC-UV method for simultaneous quantification	Internal standard: Quinoxaline, solid phase extraction M.P: ACN: sodium acetate buffer, gradient mode Column: reverse phase analytical C18 Run time: 25min
10.	Raltegravir in human plasma [2]	RP-HPLC	Internal standard: Metronidazole, liquid-liquid extraction

			Column: Phenomenex C18 (250mm×4.6mm, 5µm) M.P: 10mM phosphate buffer P^H 3.5±0.05: ACN (60:40v/v) Linearity: 40.0-4003.9ng/mL
11.	**Related substances of raltegravir in tablets [11]**	**Quality by Design (Qbd) approach-chromatographic method**	**Column: Inertsil C18×2.5µ Resolution: NLT1.8 M.P, flow rate, temperature: carried out by multivariate approach**
12.	**Raltegravir Potassium in Bulk and in Tablet Dosage form [12]**	**RP-HPLC- UV**	**Column: Symmetry C18 (4.6 x 150mm, 5 µmXTerra) M.P: phosphate buffer (pH 3.0): Methanol (45:55% v/v) Flow rate: 0.6mL/min wavelength: 219nm**
13.	**Lamivudine and Raltegravir In Solid Dosage Form [13]**	**RP-HPLC by forced degradation studies**	**Column:Inertrsil ODS C18 (4.6×150mm) M.P: ortho phosphoric acid (OPA): ACN (50:50v/v) Retention Time: Lamivudine and Raltegravir 1.99min, 4.34min respectively Linearity: Lamivudine and Raltegravir 15-75µg/mL, 30-150µg/mL.**
14.	**Raltegravir and others in the plasma of HIV-infected Patients[14]**	**HPLC-PDA method**	**Internal standard: Quinoxaline, solid phase extraction M.P: ACN: phosphate buffer Column: reverse phase analytical C18 Run time: 28min, gradient mode**
15.	**Raltegravir in bulk and pharmaceutical dosage form [15]**	**RP-HPLC**	**Column: Agilent C18(100mm×2.5mm,3µm) M.P: ACN: water (80:20v/v) Detector and wavelength: UV, 240nm Flow rate: 0.8mL/min**
16.	**Raltegravirand Maraviroc in bulk form [16]**	**RP-HPLC**	**Column:RPSymmetry C18 (150mm×4.6mm) M.P: ACN: phosphate bufferpH 3.5 (40:60v/v) Flow rate:1.0mL/min Injection volume: 20µL Wavelength: 239nm Linearity:Raltegravir and maraviroc 10-50µg/mL, 5-25µg/mL respectively**
17.	**Raltegravir in bulk and dosage form [17]**	**RP-HPLC**	**Column:Symmetry Develosil ODS C18 HG-5RP 5µm, 15cmx4.6mm i.d. M.P:Phosphate buffer (pH=3.0): Methanol with 30:70 Flow rate:1.0mL/min Run time: 5.0min Injection volume: 10µL wavelength: 246nm Linearity:Raltegravir 20-70µg/mL**
18.	**Raltegravir potassium in bulk and dosage form [18]**	**RP-HPLC**	**Column: RP Shim packC18 (150mm×4.6mm; 5µm) M.P: ACN: ammonium acetate buffer (pH4 adjusted with glacial acetic acid): Methanol with 50:50v/v Flow rate:0.8mL/min Retention Time: 4.31min wavelength: 271nm Linearity:Raltegravir 10-50µg/mL**
19.	**Lamivudine and Raltegravir in bulk and pharmaceutical dosage form [19]**	**RP-HPLC**	**Column: Inertsil ODS C18 (150mm×4.6mm, 5µm) M.P: ACN: 0.1% ortho phosphoric acid buffer (50:50v/v) Detector and wavelength: PDA, 242nm Flow rate:0.9mL/min Retention Time: Lamivudine 1.9±0.3min, Raltegravir 4.3±0.3min Linearity: Lamivudine and Raltegravir 15-75µg/mL, 30-150µg/mL**
20.	**Raltegravir in human blood plasma [20]**	**HPLC**	**Solid phase extraction Linearity: 20-10,000ng/mL**

21.	**Raltegravir [21]**	**LC-MS**	**Concentration range: 0.010-7.680µg/mL in Plasmaconcentrations**
22.	**Raltegravir in spraguedawley rat serum [22]**	**LC-MS/MS**	**Liquid-liquid extraction Internal standard: Didanosine M.P: ACN: methanol: 0.1% acetic acid in water (40:30:30), isocratic mode Column: waters, Exterra C18 (50mm×4.6mm, 5µm) Flow rate:0.5mL/min Sample volume:50 µL Linearity: 1-1000ng/mL**
23.	**Raltegravir potassium pharmaceutical dosage form [23]**	**RP-HPLC and HPTLC**	**HPLC; M.P:Phosphate buffer (pH3.0 adjusted with phosphoric acid): Methanol with 40:55%v/v, isocratic Column:Symmetry C185µm, 15cmx4.6mm i.d. HPTLC; M.P: Toluene: ethyl acetate: methanol: glacial acetic acid (4:5:0.6:0.4%v/v) S.P: precoated plate of silica gel 60F 254 Quantified by: densitometric absorbance at 218nm, R_f value: 0.12**
24.	**Raltegravir and its impurities in bulk drug and dosage forms [24]**	**RP-HPLC**	**M.P: 0.1% perchloric acid and ACN at 30^0C, gradient mode Column: purosphere star RP 18 Flow rate:1mL/min Wavelength: 300nm**
25.	**Raltegravir in human blood plasma [25]**	**HPLC with fluorescence detection**	**Liquid-liquid extraction Internal standard: Delavirdine RT: 5.0min Column:Symmetry shield RP C18150x4.6mm, gradient mode M.P: ACN:0.1% v/v triethylamine in water pH 3.0 Flow rate: 1mL/min Retention Time: 6.4min Fluorimetric detection: 299&396nm as excitation and emission wavelength**
26.	**Degradation products of Raltegravir [26]**	**LC, LC-MS/TOF, MS^N**	**Column: C18 Mode: Gradient**
27.	**Forced degradation studies of Raltegravir [27]**	**RP-HPLC and LC-MS/MS**	**M.P: Buffer& ACN (60:40v/v) Column: Hypersil BDS, C18, 100x4.6mm, 5µm UV detection: 213nm**
28.	**Maraviroc and Raltegravir in human plasma [28]**	**HPLC-UV**	**Solid phase extraction M.P: 0.01M KH_2PO_4& ACN (50:50v/v) Column: Analytical d C18 Atlantis 150x4.6mm, 5µm, isocratic mode Flow rate:1mL/min Run time: 10min UV wavelength: Maraviroc 197nm and Raltegravir 300nm**
29.	**Raltegravir, other antiretroviral drugsin human plasma [29]**	**UPLC-MS/MS**	**Internal standard:stable labelled isotope Run time:10min**
30.	**Raltegravir, other antiretroviral drugsin human plasma[30]**	**UPLC-MS/MS**	**Internal standard (IS):Adapted deuterated IS Electron spray ionisation mode Retention Time:4.2min for all compounds**
31.	**Raltegravir, other antiretroviral drugsin human plasma[31]**	**Electron spray ionisation LC-MS/MS**	**Internal standard: Ritonavir analog, Methyl indinavir, lopinavir-d8 Column:C18 HPLC (waters sunfire100x2.1mm, 3.5µm, gradient mode Flow rate:0.3mL/min Injection volume: 5µL**
32.	**Raltegravirin human plasma[32]**	**UPLC-MS/MS**	**Liquid-liquid extraction Column:Aquity UPLC C18, isocratic mode Run time: 1min M.P:0.1% formic acid& ACN 50:50v/v**
33.	**Raltegravir, Dolutegravir and Elvitegravir**	**HPLC-Tandem MS**	**Internal standard: Raltegravir d_3 Column:X Bridge C18, 50x2.1mm, 3.5µm**

	concentrations in human plasma and CSF [33]		**M.P:ACN: water 7:3v/v with 0.1% formic acid Flow rate:0.2mL/min Run time: 5min**
34.	**Raltegravirin human plasma [34]**	**LC-Tandem MS**	**Internal standard: Raltegravir d_3 Column:Chromolith RP-18e endcapped C18 100x4.6mm Run time: 2min m/z: 443.1-316.1 for raltegravir, 446.1-319.0 for IS**
35.	**Raltegravir and Raltegravir glucuronide in human plasma [35]**	**LC-Tandem MS**	**Column:ZORBAX Eclipse XRB-C8 Run time: 9min, gradient mode Flow rate:0.4mL/min MS at positive electron spray ionisation condition**
36.	**Raltegravir and othersin human plasma [36]**	**HPLC-MS/MS**	**Column:kinetex phenyl-hexyl M.P:55% water (0.05% formic acid):45% Methanol (0.05% formic acid) Flow rate:0.5mL/min**
37.	**Raltegravir, maraviroc, darunavir, and etravirinein human plasma [37]**	**LC-Tandem MS (electron spray ionisation)**	**Column:waters Atlantis-TM-dc18, 50x2.1mm, 3µm M.P:2mM ammonium acetate containing 0.1% formic acid & ACN with 0.1% formic acid, gradient mode Injection volume: 10µL**
38.	**Raltegravirin human plasma [38]**	**HPLC-MS/MS**	**Internal standard:Stable isotope labelled $_6C^{13}$-MK-0518 Column:Ace C18(50x3mm, 3µm, titanium fits) M.P:42.5/57.5 v/v 0.1mMEDTA in 0.1% formic acid/methanol Flow rate:0.5mL/min**
39.	**Raltegravir and othersin human plasma [39]**	**LC-Tandem MS**	**Column:RP-C18 (50x1.5mm, 5µm) M.P:5mM formic acid -35% v/v ACN Run time: 6min Flow rate:0.2mL/min Retention Time: 2.5min Linearity:1-10,000ng/mL**
40.	**Raltegravir and othersin human plasma and tissue [40]**	**LC-Tandem MS**	**Column:Waters BEH C8, 50x2.1mm, 1.7µm**
41.	**RaltegravirandLamivudine in pharmaceutical dosage form [41]**	**UPLC**	**Column:BEH Shield RP18, 100x2.1mm, 1.7µm M.P:Buffer potassium dihydrogen orthophosphatepH3.0 adjusted with orthophosphoric acid: methanol 30:70%v/v, isocratic mode Run time: 4min Flow rate:0.230mL/min Detector and wavelength: PDA, 254nm**
42.	**Raltegravir potassium [42]**	**UPLC and degradation**	**Column:BEH Shield, 100x2.1mm, 1.7µm M.P: sodium perchlorate pH 2.5: ACN 65:35%v/v, isocratic mode Flow rate:0.3mL/min Injection volume: 0.3µL wavelength: 240nm Column temperature: 30^0 C**

CONCLUSION

The above table is summary of research work on various analytical methods for estimation of Raltegravir, though various spectrophotometric and chromatographic methods are available but there is need for continuous development of accurate, sensitive, precise, efficient, economic, fast methods, to optimise the utilisation of solvents and to enhance the researchers to utilize the available methods for estimation

of Raltegravir as alone or as combination in dosage forms and in biological fluids.

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REFERENCES

[1] Siddartha B,Sudheer Babu I, UV - Spectrophotometric method for estimation of raltegravir in bulk and tablet dosage form, International journal of pharmaceutical, chemical and biological sciences, 4 (4), 2014, 807–811.

[2] Rama BabuG, Srirama Murthy P, Panakala Rao V. V, Development and Validation of RP- HPLC Method for the Determination of Raltegravir In Human Plasma, Journal of Applicable Chemistry,6 (4), 2017, 559-567.

[3] Baheti K. G, Kore P. P, Gamepatil M. M, Nimje H. M, Spectrophotometric Estimation of Raltegravir Potassium in Tablets, Indian Journal of Pharmaceutical Sciences, 76 (6), 2014, 557-559.

[4] GirijaBhavar B, Sanjay Pekamwar S, Kiran Aher B, Sanjay Chaudhari R, Simple Spectrophotometric Method for Estimation of Raltegravir Potassium in Bulk and Pharmaceutical Formulations, Journal of Applied Pharmaceutical Science 3 (10), 2013, 147-150.

[5] Mathrusri Annapurna Mukthinuthalapati, Ravi Teja Gunnam, Krishna Phani Sri Ponnekanti, Chaitanya Boni, Determination of Raltegravir by derivative and difference spectrophotometric techniques in film coated tablets, Research Journal of Pharmacy and Technology, 10 (4), 2017.

[6] Sunil Junapudi, Nagaraju P, Ganesh K, Nagesh M, Method development and validation for simultaneous estimation of raltegravir and lamivudine by using RP-HPLC in bulk and pharmaceutical dosage form, Inventi Rapid - Pharm Analysis & Quality Assurance, 2018, 1-5

[7] Veena Singh D, Sanjay Daharwal J, Optimization of RP-HPLC method for simultaneous estimation of lamivudine and raltegravir in binary mixture by using design of experiment, Eurasian Journal of Analytical Chemistry, 12 (3), 2017, 179-195.

[8] Priyanka B, Sahithi K, Srihitha G, Vyshnavi G, SravanthiBijjiga, Analytical Method Development and Validation for the Simultaneous Estimation of Lamivudine and

Raltegravir by RP-HPLC Method, Pharma Research Library.

[9] Lakshmana Rao A, Raghu Ram MS**,** Validated reverse phase HPLC method for determination of raltegravir in pharmaceutical preparations,International Journal of Research in Pharmacy and Chemistry, 2 (1), 2012, 217-221.

[10] Nitin Charbe, Sara Baldelli, Valeria Cozzi, Simone Castoldi, Dario Cattaneo, Emilio Clementi, Development of an HPLC–UV assay method for the simultaneous quantification of nine antiretroviral agents in the plasma of HIV-infected patients, Journal of Pharmaceutical Analysis, 6, 2016, 396–403.

[11] Prasad Kancherla, Sateesh Babu Dhulipalli,Pallavi Alegete, Seshagiri RaoJVLN, Development and Validation of Chromatographic Method for Related Substances of Raltaglavir in Raltaglavir Tablets by Using Quality by Design (Qbd) Approach,International Journal of Pharmaceutical Sciences Review and Research, 40 (1), 2016, 259-265.

[12] Sudha T, Raghupathi T, Reverse Phase–High Performance Liquid Chromatography and Ultra Violet Spectrophotometric Method for the Estimation of Raltegravir Potassium in Bulk and in Tablet Dosage form, Global Journal of Medical research, 11 (2), 2011.

[13] Krishna Dutta TejaswiJuluri,GovindaRajan R, RP-HPLC method development and validation for simultaneous estimation and forced degradation studies of lamivudine and raltegravir in solid dosage form, International Journal of Applied Pharmaceutics, 10 (6), 2018, 242-248.

[14] Antonio D'Avolio, Lorena Baietto, Marco Siccardi, Mauro Sciandra, Marco Simiele, An HPLC-PDA method for the simultaneous quantification of the HIV integrase inhibitor raltegravir, the new nonnucleoside reverse transcriptase inhibitor etravirine, and 11 other antiretroviral agents in the plasma of HIV-infected patients, Therapeutic Drug Monitoring, 30 (6), 2008, 662-9.

[15] Vijaya Sri K, Ravinderreddy S, Suresh K, Rapid RP-HPLC Method Development and Validation for Analysis of Raltegravir in Bulk and Pharmaceutical Dosage Form,

Asian Journal of Research in Chemistry, 8(5), 2015, 335-339.

[16] Sridhar Raavi, Dr.Padmalatha H, RP-HPLC method development and validation for the simultaneous estimation of raltegravir and maraviroc in bulk form, International Journal of Innovative Pharmaceutical Sciences and Research, 3 (8), 2015, 990-997.

[17] Shirisha Bhavani, Srinivasa Rao A, Sharone Aneeta B,Method development and validation of raltegravir by RP-HPLC method, International Journal of Pharmacy and Analytical Research, 8 (3), 2019, 320-328.

[18] Krishnaveni Nagappan, Sonam Patel, Santhosh Reddy Gouru, Quantitative Reverse-phase High-performance Liquid Chromatographic Method for the Quantification of Raltegravir Potassium in Bulk and Dosage Forms, Journal of Young Pharmacists, 11 (3), 2019, 274-278.

[19] Lavanya K, Koteswararao N, Srinivasa rao V,RP-HPLC method development and validation for simultaneous estimation of Lamivudineand Raltegravirin bulk and pharmaceutical dosage form, Asian Journal of Pharmaceutical Analysis and Medicinal Chemistry, 5 (1), 2017, 49- 59.

[20] NaserRezk L, Nicole White, AngelaKashuba D M, An accurate and precise high-performance liquid chromatography method for the rapid quantification of the novel HIV integrase inhibitor raltegravir in human blood plasma after solid phase extraction, Analytica Chimica Acta, 628 (2), 2008, 204-213.

[21] Tsuguhiro KANEDA, Masaaki TAKAHASHI, Yuichi KUDAKA, A conventional LC-MS method developed for the determination of plasma raltegravir concentrations, Biological and Pharmaceutical Bulletin, 31(8), 2008, 1601-1604.

[22] Vijaya Raju A.D, Appala Raju Nemala,Development and Validation of a LC-MS/MS Method for the Determination of Raltegravir in Sprague Dawley Rat Serum and Its Application to Pharmacokinetic Study, American Journal of Biomedical Sciences, 5(3), 2013, 197-207.

[23] Sudha T, Shanmugasundram P, Development and validation of RP-HPLC and HPTLC chromatographic methods of analysis for the quantitative

estimation of Raltegravir potassium in pharmaceutical dosage form, Research Journal of Pharmacy and Technology, 2011.

[24] Balaji M, AppaRao K.M. Ch, Ramakrishna K, Srinivasarao V, Development and validation of RP- HPLC method for determination of raltegravir and its impurities in bulk drug and dosage forms, pharma science monitor-an international journal of pharmaceutical sciences, 5 (3), 2014, 187-196.

[25] Poirier Jean Marie, Robidou Pascal, Jaillon Patrice, Quantification of the HIV-integrase inhibitor raltegravir (MK-0518) in human plasma by high-performance liquid chromatography with fluorescence detection, Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 867(2), 2008, 277-281.

[26] Ravi TiwariN, Chandrakant Bonde G, & Kailash Bothara G, Identification and characterization of degradation products of Raltegravir using LC, LC–MS/TOF, AND MS^N, Journal of Liquid Chromatography & Related Technologies, 36 (8), 2013, 1078-1095.

[27] BhavyasriKhagga, Murali Balaram V, Nageswarao R, Rambabu D, Development and Validation of Forced Degradation Studies of Raltegravir using RP-HPLC and Characterization of Degradants by LC-MS/MS, Journal of Pharmaceutical Sciences and Research, 7(9), 2015, 685-689.

[28] Stefania Notari, Chiara Tommasi, Emanuele Nicastri, Simultaneous determination of maraviroc and raltegravir in human plasma by HPLC-UV, IUBMB Life, 61 (4), 2009, 470–475.

[29] Pauline Bollen D J, Marga J A de Graaff-Teulen, Development and validation of an UPLC-MS/MS bioanalytical method for simultaneous quantification of the antiretroviral drugs dolutegravir, elvitegravir, raltegravir, nevirapine and etravirine in human plasma, Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 2019, 76-84.

[30] Zoubir Djerada, Catherine Feliu et al, Validation of a fast method for quantitative analysis of elvitegravir, raltegravir, maraviroc, etravirine, tenofovir, boceprevir and 10 other antiretroviral agents in human

plasma samples with a new UPLC-MS/MS technology, Journal of Pharmaceutical and Biomedical Analysis, 86, 2013, 100-111.

[31] Sylvie Quaranta, Christian Woloch et al, Validation of an Electrospray Ionization LC-MS/MS Method for Quantitative Analysis of Raltegravir, Etravirine, and 9 Other Antiretroviral Agents in Human Plasma Samples, Therapeutic Drug Monitoring, 31 (6), 2009, 695-702.

[32] Fortuna Serena, Ragazzoni Enzo, Lisi Lucia, Navarra Pierluigi et al, Validation of an UPLC-MS/MS method for quantitative analysis of raltegravir in human plasma samples, Therapeutic Drug Monitoring, 35 (2), 2013, 258-263.

[33] Kiyoto Tsuchiya, Mayu Ohuchi et al, High-performance liquid chromatography–tandem mass spectrometry for simultaneous determination of raltegravir, dolutegravir and elvitegravir concentrations in human plasma and cerebrospinal fluid, Biomedical Chromatography, 32 (2), 2017.

[34] Mallika Sanyal, Ajay Gupta, Swati Guttikar et al, Selective and rapid determination of raltegravir in human plasma by liquid chromatography-tandem mass spectrometry in the negative ionization mode, Journal of Pharmaceutical Analysis, 5 (2), 2015, 101–109.

[35] Ling-Zhi Wang, Lawrence Soon-U Lee et al, Simultaneous determination of raltegravir and raltegravir glucuronide in human plasma by liquid chromatography–tandem mass spectrometric method, Journal of Mass Spectrometry, 46 (2), 2011.

[36] Yi Zheng, RadiaAboura, HPLC-MS/MS method for the simultaneous quantification of dolutegravir, elvitegravir, rilpivirine, darunavir, ritonavir, raltegravir and raltegravir-β-D-glucuronide in human plasma, Journal of Pharmaceutical and Biomedical Analysis, 182, 2020.

[37] Decosterd L.A, Fayet A et al, A LC-tandem MS assay for the simultaneous measurement of new antiretroviral agents: Raltegravir, maraviroc, darunavir, and etravirine, Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 877 (11-12), 2009, 1057-1069.

[38] Merschman S.A, Vallano P.T et al, Determination of the HIV integrase inhibitor, MK-0518 (raltegravir), in human plasma using 96-well liquid-liquid extraction and HPLC-MS/MS, Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 857 (1), 2007, 15-24.

[39] Shingo Kato, Eiko Yamada, et al, Determination of abacavir, tenofovir, darunavir, and raltegravir in human plasma and saliva using liquid chromatography coupled with tandem mass spectrometry, Journal of Pharmaceutical and Biomedical Analysis, 114, 2015, 390-397.

[40] Teresa Parsons L, Mark Marzinke A, Development and validation of a liquid chromatographic-tandem mass spectrometric method for the multiplexed quantification of etravirine, maraviroc, raltegravir, and rilpivirine in human plasma and tissue, Journal of Pharmaceutical and Biomedical Analysis, 131, 2016, 333-344.

[41] Sarif Niroush Konari, Jane Jacob T, Stability indicating validated UPLC technique for the simultaneous analysis of raltegravir and lamivudine in pharmaceutical dosage forms, HIV and AIDS Review, 15 (4), 2016, 161-169.

[42] Rami Reddy B. V, Reddy B. S et al, Validated stability-indicating UPLC assay method and degradation Behavior of Raltegravir Potassium, International Journal of Pharmacy and Technology, 4 (1), 2012, 4045-4049.