

A Review on Analytical Methods for the estimation of Rizatriptan, an Antimigraine Drug

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ABSTRACT

Rizatriptan is a selective serotonin receptor agonist of the 1B and 1D sub types used in the acute treatment of migraine attacks. Effective analytical procedures are required for qualitative and quantitative determination of a drug. An extensive literature survey has been conducted in various analytical and pharmaceutical journals and the analytical methods which were developed and used for estimation of Rizatriptan in single or in combination with other drugs in bulk drugs, pharmaceutical formulations, biological fluids, stability indicating and impurity profiling methods have been reviewed. Various analytical methods used for the estimation of Rizatriptan reviewed in this paper includes Ultraviolet spectrometry, Visible spectrometry, High performance thin layer chromatography, High performance liquid chromatography, Liquid chromatography- mass spectrometry.

Keywords: Rizatriptan, Spectrophotometry, HPLC, Chromatography

INTRODUCTION

Migraine is a common recurring headache of moderate to severe intensity that interferes with normal functioning i.e., gastrointestinal, neurological and autonomic symptoms [Barbara G Wells et al., 2005]. Migraine attack consists of an initial visual disturbance (aura), in which a flickering pattern, followed by a blind spot. This visual disturbance is followed for about 30min, later by a severe throbbing headache, often accompanied by photophobia, nausea, vomiting and prostration which lasts for several hours [Rang H P et al., 2012]. Migraine is a common condition affecting 5% of men and 15% of women [Clive Page et al., 2009]. Migraine headaches are subclassified according to the presence or absence of aura symptoms. Most persons who suffer from migraine do not experience aura symptoms [Brain K. Alldredge et al., 2013].

Pathophysiology:

Migraine may be due to

- I. Neuronal dysfunction characterized by a wave of depressed electrical activity that advances across the cerebral cortex i.e., cortical excitation.

- II. Trigeminal afferents from the dural vasculature are activated and sensitized by the local release of neuropeptides and inflammatory mediators.
- III. Imbalance in the activity of serotonin containing neurons in brainstem nuclei that modulate cerebral vascular tone and nociception. This imbalance may result in vasodilation of intracranial blood vessels and action of trigemino vascular system [Barbara G Wells et al., 2005, David E. Golan et al., 2012].

5-hydroxytryptamine or 5-HT or serotonin is a neurotransmitter which is the target for many of the drugs used to treat psychiatric disorders such as depression and it play critical roles in modulating mood, sleep-wake cycle, motivation, pain, perception, neuroendocrine function [David E. Golan et al., 2012].

Serotonin is synthesized from the amino acid tryptophan by the enzyme tryptophan hydroxylase which converts tryptophan to 5-hydroxytryptophan. Aromatic L-amino acid decarboxylase then converts 5-hydroxytryptophan to serotonin. These enzymes are present throughout the cytoplasm of

serotonergic neurons, both in cell body and in cell processes [David E. Golan et al., 2012].004@yahoo.c Abnormalities in 5-HT/serotonin activity play a role in migraine headache. Plasma 5-HT levels decrease by nearly half during a migraine attack, with a corresponding risk in the urinary excretion of 5-hydroxyindole acetic acid, the primary metabolite of 5-HT [Brain K. Alldredge et al., 2013].

Drugs used for treatment of Migraine [Tripathi K D. 2006]:

Mild: Simple analgesics/ NSAIDs such as Aspirin, Naproxen sodium, Tolfenamic acid, Indomethacin, Mefenamic acid etc. with antiemetic.

Moderate: Combination of NSAIDs such as Aspirin with codeine, Aspirin with oxycodone. Combination of Aspirin, Acetaminophen and caffeine was found to be more efficient. Combination of Acetaminophen, Caffeine and Butabital is given only for short periods since the combination can cause dependence [Clive Page et al., 2009].

Severe: Ergot alkaloids, Triptans.

Ergotamine is an adrenergic agonist with affinity for 5-HT₁ receptors, stimulation of which leads to vasoconstriction. These drugs are contraindicated in patients with coronary artery or peripheral vascular disease [Clive Page et al., 2009].

TRIPTANS:

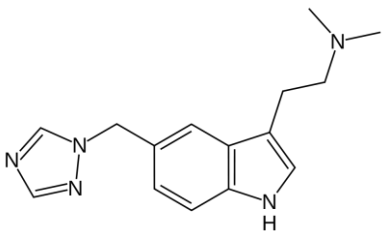
Triptans are 5-HT₁ receptor agonists, very active against mild to moderate attacks of migraine. This is the first choice of specific drugs in the symptomatic treatment of migraine.

First Generation Triptans: Sumatriptan is the first generation triptan that is approved for use.

Second Generation Triptans: Zolmitriptan, Naratriptan, Rizatriptan, Almotriptan, Frovatriptan, Elatriptan [Waldman and Terzic 2009].

Rizatriptan

Drug Profile[www.wikipedia.com]

Structure	
Chemical name	N,N-dimethyl-2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethanamine
Molecular weight	269.345 g/mol
Molecular formula	C ₁₅ H ₁₉ N ₅
Melting point	178-180 °C
Storage conditions	Store at room temperature away from light and moisture [www.medicinenet.com]
Dosage forms available	Tablets (orally disintegrating and film coated)
Solubility	Soluble in water; sparingly soluble in alcohol; slightly soluble in methylene chloride.[www.drugfuture.com/Pharmacopoeia/USP35]

Mechanism of Action:

It works by narrowing blood vessels in the brain, stopping pain signals from being sent to the brain, and blocking the release of certain natural substances that cause pain, nausea, and other symptoms of migraine.

[www.nlm.nih.gov/medlineplus]

Pharmacokinetics:

Rizatriptan is readily absorbed from the gastrointestinal tract. The biological half-life of Rizatriptan is approximately 2-3hours. After absorption, rizatriptan (oral) is rapidly eliminated in urine[www.drugs.com].

ANALYTICAL METHODS FOR RIZATRIPTAN

Various analytical methods have been developed for the estimation of Rizatriptan in single and in combination which includes Spectrophotometric, HPLC, HPTLC, LC-MS methods.

Spectrophotometric Methods

S.No	Drug	Method	Description	Ref No.
1.	Rizatriptan Benzoate	UV first and second derivative, amplitude method	Solvent: 0.1N NaOH Detection: 227, 281, 233,238nm. Correlation coefficient (r^2) =0.999 Linearity Conc. : 0.5-80mcg/ml	Acharjya Sasmita Kumari et al., 2010
2.	Rizatriptan Benzoate	UV zero and first derivative, AUC method	Solvent: distilled water Detection: 225, 231,217, 210-232 nm. Correlation coefficient (r^2) =0.999 Linearity Conc. : 2-10mcg/ml	Ishan K Chinnapurkar et al., 2015
3.	Rizatriptan Benzoate	UV Spectroscopic method	Solvent: Phosphate buffer pH 6.8 Detection: 226 nm. Correlation coefficient (r^2) =0.9956 Linearity Conc. : 1-8mcg/ml	Sunil S Khanchandani et al., 2013
4.	Rizatriptan Benzoate	UV Spectroscopic method, AUC	Solvent: 0.1N NaOH Detection: 280 nm. Correlation coefficient (r^2) = 0.999 Linearity Conc.: 0.5-80mcg/ml	Sethy Prasanta et al., 2013
5.	Rizatriptan	UV spectroscopic method	Solvent: 0.1NHCl Detection: 226 nm. Correlation coefficient (r^2) = 0.996 Linearity Conc.: 1-5mcg/ml	Dev prakash et al., 2011
6.	Rizatriptan	UV Spectrophotometric method	Solvent: Distilled water Detection: 230 nm. Correlation coefficient (r^2) = 0.9905 Linearity Conc.: 50- 250mcg/ml	Bafna SR et al., 2013
7.	Rizatriptan Benzoate	Stress Degradation Studies	Solvent: Distilled water Detection: 224nm Correlation coefficient (r^2) = 0.9988 Linearity Conc.: 0.5-2.5mcg/ml	Kempwade Amolkumar et al., 2015
8.	Rizatriptan Benzoate	AUC method	Solvent: Distilled water Detection: 280nm Correlation coefficient (r^2) = 0.999 Linearity Conc.: 6-36mcg/ml	Pritam S Jain et al., 2016
9.	Rizatriptan Benzoate	Stability Indicating Spectrophotometric method	Solvent: Methanol Detection: 278nm Correlation coefficient (r^2) = 0.9997 Linearity Conc.: 10-80mcg/ml	Uttam Prasad Panigrahy and Divya Swetha M, 2013
10.	Rizatriptan	UV spectrophotometric, derivative and spectrofluorimetric methods	Solvent: Distilled Water Detection: 225nm(zero order), 232nm first derivative), 280 and 362nm (fluorimetry, emission and absorption) Correlation coefficient (r^2) = 0.9997 Linearity Conc.: 0.1-15mcg/ml (zero and first order), 0.03- 10mcg/ml (Fluorimetry)	Altinoz S et al., 2002
11.	Rizatriptan Benzoate	UV Spectrophotometric	Solvent: 0.1NHCl Detection: 225nm	Vivek rajendra et al. 2010

		method	Correlation coefficient (r^2) = 0.999 Linearity Conc.: 1-10mcg/ml	
12	Rizatriptan Benzoate	UV Spectrophotometric method	Solvent: 0.1NHCl & 0.1N NaOH Detection: 226nm Correlation coefficient (r^2) = 0.999 Linearity Conc.: 0.4-10mcg/ml, 0.25-10mcg/ml	Kudige N Prashanth and Nagaraju Swamy, 2014
13.	Rizatriptan Benzoate	UV Spectrophotometric method	Solvent: Methanol Detection: 226nm Correlation coefficient (r^2) = 0.999 Linearity Conc.: 2-8mcg/ml	Suneetha A and Syama Sundar B, 2009
14.	Rizatriptan Benzoate	UV Derivative method	Solvent: 0.1N HCl, Distilled water Detection: 216.64, 233.78nm (0.1NHCl), 216.8, 234.06nm (DW) Correlation coefficient (r^2) = 0.998 Linearity Conc.: 1-30mcg/ml (0.1NHCl), 0.1-35mcg/ml (DW)	Mathrusri Annapurna M et al., 2012
15.	Rizatriptan Benzoate	UV Spectrophotometric method	Solvent: Methanol Detection: 278nm Correlation coefficient (r^2) = 0.998 Linearity Conc.: 10-50mcg/ml	Jane Jacob et al., 2012
16.	Rizatriptan Benzoate	Visible	Reagents: Bromocresol Green Solvent: buffer pH 3.0 Detection: 416nm Correlation coefficient (r^2) = 0.999 Linearity Conc.: 0.5-100mcg/ml	Effat Sourı et al., 2013
17.	Rizatriptan Benzoate	Visible	Reagents: Vanillin in acidic medium Solvent: Distilled water Detection: 579nm Correlation coefficient (r^2) = 0.9997 Linearity Conc.: 50-250mcg/ml	Avula Prameela Rani et al., 2012
18.	Rizatriptan Benzoate	Visible	Reagents: Methyl Orange, 2, 2'-Bipyridyl Solvent: Distilled water Detection: 420nm (MO), 490nm(BPL) Correlation coefficient (r^2) = 0.9999 Linearity Conc.: 10-50mcg/ml (MO), 4-20mcg/ml(BPL)	Sanmukha kumar JV, 2010
19.	Rizatriptan Benzoate	Visible	Reagents: p-Chloranilic Acid (p-CA) and 2,3-Dichloro-5,6-dicyano-p-benzoquinone (DDQ) Solvent: Acetonitrile Detection: 530nm(p-CA), 590nm (DDQ) Correlation coefficient (r^2) = 0.9999 Linearity Conc.: 14 - 245mcg/ml (p-CA), 4-70mcg/ml (DDQ)	Kudige N Prashanth and Kanakapura Basavaiah, 2012
20.	Rizatriptan Benzoate	Visible	Reagents: Chloramine-B in HCl Solvent: Distilled Water Detection: 490nm Correlation coefficient (r^2) = 0.9999	Malini S et al, 2015
21.	Rizatriptan	Visible	Reagents: bromophenol blue (BPB),	Prashanth KN et

	Benzoate		bromocresol purple (BCP), bromothymol blue (BTB) in chloroform medium Solvent: chloroform Detection: 425 nm (BPB, BCP) 420 nm (BTB). Correlation coefficient (r^2) = 0.999 Linearity Conc.: 0.8–16mcg/ml (BPB), 1.0–20mcg/ml (BCP) and 1.2–24mcg/ml (BTB)	al., 2011
22.	Rizatriptan Benzoate	Visible	Reagents: N-bromosuccinimide (NBS), janus green (JG), calmagite (CMG) Solvent: Distilled water Detection: Iodometric titration (NBS), 620 nm (JG), 540 nm (CMG) Correlation coefficient (r^2) = 0.999 Linearity Conc.: 1–10 mg (NBS), 0.5–8.0 mcg/ml (JG), 1.5–30.0 mcg/ml (CMG)	Kudige Nagaraj Prashanth and Kanakapura Basavaiah, 2012
23.	Rizatriptan Benzoate	Visible	Reagents: Sodium Nitro prusside-Acetaldehyde (SNP-ACD), Cobalt thiocyanate (CTC) Solvent: Distilled water Detection: 560nm, 635nm Correlation coefficient (r^2) = 0.9999 Linearity Conc.: 0.5–2.5 mcg/ml (SNP-ACD, CTC)	Sastry CSP et al., 2012
24.	Rizatriptan Benzoate	Visible	Reagents: Vanillin in sulphuric acid, 4-aminophenazone Solvent: Acetonitrile and methanol (1:1) Detection: 560nm, 635nm Correlation coefficient (r^2) = 0.9999 Linearity Conc.: 0.5–2.5 mcg/ml	Jane Jacob et al., 2012

CHROMATOGRAPHIC METHODS

S.No	Drug	Method	Chromatographic Conditions	Ref. No
1.	Rizatriptan Benzoate	RP-HPLC	Column: Zorbax SB phenyl (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume : 10 μ l Detection: 255 nm Mobile Phase: Sodium dihydrogen orthophosphate buffer (pH 3.5): Acetonitrile (80:20) Elution: Isocratic	Haarika B and Prabhakar Reddy V, 2014
2.	Rizatriptan Benzoate	RP-HPLC	Column: Water's XBridge C18 (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 0.8 ml/min Injection volume : 20 μ l Detection: 227 nm Mobile Phase: phosphate buffer pH 2.5: methanol 70:30.	Sirisha V et al., 2013

			Elution: Isocratic	
3.	Rizatriptan Benzoate	RP-HPLC	Column: Inertsil ODS 3V C18 (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 225 nm Mobile Phase: acetonitrile: methanol: 10 mM aqueous phosphate buffer (58:34:08%v/v) Elution: Isocratic	Punna Venkateshwarlu and Srikanth Gajam, 2011
4.	Rizatriptan Benzoate	RP-HPLC	Column: Inertsil DBC C18 (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 225 nm Mobile Phase: Phosphate buffer pH 6.5: Acetonitrile : Methanol -87:7.8:5.2 (v/v/v) Elution: Isocratic	Jitendra kumar P et al., 2014
5.	Rizatriptan Benzoate	RP-HPLC	Column: Inertsil ODS (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 225 nm Mobile Phase: Phosphate buffer pH 6.5: Acetonitrile:Methanol-87:7.8:5.2 (v/v/v) Elution: Isocratic	Kannappan N et al., 2009
6.	Rizatriptan Benzoate	RP-HPLC	Column: Zorbex - eclips XDB, C18, (150 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 278 nm Mobile Phase: acetonitrile, methanol, phosphate buffer pH 2.5- 45:30:25 Elution: Isocratic	Jane Jacob et al., 2012
7.	Rizatriptan Benzoate	RP-HPLC	Column: Hiper C18, (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 278 nm Mobile Phase: phosphate buffer (20 mM pH adjusted to 3.2 \pm 0.005 with OPA): Methanol - 70:30 v/v Elution: Isocratic	Bhagawati ST et al., 2015
8.	Rizatriptan	RP-HPLC	Column:	Devprakash et

	Benzoate		XTerra-Symmetry C18, (150 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 0.8 ml/min Injection volume :20 μ l Detection: 226 nm Mobile Phase: acetonitrile and potassium dihydrogen orthophosphate buffer pH 3.0 - 50:50 (v/v) Elution: Isocratic	al., 2012
9.	Rizatriptan Benzoate	RP-HPLC	Column: XTerra-Symmetry C18, (250 x 4.6mm, 5 μ) Temp. : Ambient Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 227 nm Mobile Phase: Sodium dihydrogen ortho phosphate dihydrate (adjusted to pH 7 \pm 0.5 with NaOH) and Acetonitrile (85:15v/v) Elution: Isocratic	Sundar BS et al., 2009
10.	Rizatriptan Benzoate	RP-HPLC	Column: Inertsil ODS 3v, (250 x 4.6mm, 5 μ) Temp. : 40 $^{\circ}$ C Flow rate: 1.0 ml/min Injection volume :20 μ l Detection: 225 nm Mobile Phase: buffer, acetonitrile and water(87:7.8:5.2v/v) Elution: Isocratic	Sai Krishna U et al., 2013
11.	Rizatriptan Benzoate	RP-HPLC	Column: C18, (250 x 4.6mm, 5 μ) Temp. : 50 $^{\circ}$ C Flow rate: 1.5ml/min Injection volume :20 μ l Detection: 280 nm Mobile Phase: Phosphate Buffer (pH 5.5) : Acetonitrile 90:10 (v/v) Elution: Isocratic	Prasad E Funde and Chandramohan Nibe, 2013
12.	Rizatriptan Benzoate	RP-HPLC Impurity Profiling (2 impurities)	Column: C ₁₈ XTerra™ (150 \times 3.9 mm, 5 μ m) Temp. : 20 $^{\circ}$ C Flow rate: 1.2ml/min Detection: 225 nm Mobile Phase: methanol, TEA (1%) and 10 mM KH ₂ PO ₄ (adjusted to pH 5.5 with 85% OPA) -5:9.5:85.5 v/v/v Elution: Isocratic	Jocic B et al., 2007
13.	Rizatriptan	RP-HPLC Impurity		Joseph

	Benzoate	Profiling (3 process related impurities)		SunderRaj T et al., 2009
14.	Rizatriptan Benzoate	RP-HPLC Stability indicating Assay	Column: C ₁₈ XTerra 150 × 3.9 mm, 5 μm Temp. : 20°C Flow rate: 1.2 ml/min Detection: 225 nm Mobile Phase: methanol, TEA and 0.01 mol L ⁻¹ KH ₂ PO ₄ pH adjusted to 6 with 85%OPA (6:9.4:84.6 v/v) Elution: Isocratic	Mira Zecevic et al., 2008
15.	Rizatriptan Benzoate	RP-HPLC Impurity Profiling	Column: C ₁₈ 150 × 3.9 mm, 5 μm Temp. : 40°C Flow rate: 1.2 ml/min Detection: 225 nm Mobile Phase: 0.1% triethylamine(pH 7.0, adjusted with phosphoric acid)-acetonitrile (90:10) Elution: Isocratic	Chen Jun et al., 2004
16.	Rizatriptan Benzoate	RP-HPLC Impurity Profiling 2 isomers and one impurity	Column: C8	Antonucci V et al., 1998
17.	Rizatriptan Benzoate	RP-HPLC Stability indicating Assay	Column: Zorbax SB-CN (250 mm × 4.6 mm, 5 μm) Mobile Phase: potassium di hydrogen ortho phosphate (pH 3.4), acetonitrile and methanol. Elution: Isocratic	Mallikarjuna Rao B et al., 2006
18.	Rizatriptan Benzoate	RP-HPLC Stability indicating Assay	Column: Zorbax SB CN 250 mm x 4.6 mm, 5μ. Temp. : 25°C Flow rate: 1.0 ml/min Injection volume : 10 μl Detection: 225 nm Mobile Phase: acetonitrile: pH 3.4 phosphate buffer (20:80 v/v) Elution: Isocratic	Chandra shekhar K Gadewar et al., 2013
19.	Rizatriptan Benzoate	RP-HPLC Stability indicating Assay	Column: Perfectsil (C18, 250 mm × 4.6 mm, 5.0 μ) Temp. : ambient Flow rate: 1.0 ml/min Injection volume : 10 μl Detection: 225 nm Mobile Phase: Phosphate Buffer pH 3.5 (adjusted with 85% OPA): methanol (80:20 v/v) Elution: Isocratic	Sachin S Jagtap et al., 2010
20.	Rizatriptan Benzoate	RP-HPLC Bioanalytical	Sample: Rabbit Plasma Column: Hibar C18 4.6x250mm, 5μm Flow rate: 1.1ml/min Detection: 231nm Mobile Phase:	Vishal P Awari et al., 2014

			10mM di-potassium hydrogen ortho phosphate buffer (pH 3.2) and methanol - 77:23 Elution: Isocratic Internal Standard: Zolmitriptan	
21.	Rizatriptan Benzoate	RP-HPLC Bioanalytical	Sample: urine sample Sample Processing: Solid Phase extraction Column: Macherey nagel column C18 (150 mm × 2.50 mm, 4µm) Detection: λ _{ex} - 280nm λ _{emm} - 365nm Mobile Phase: Acetonitrile and DDW, with added 1.0 mL of trifluoroacetic acid -16:84v/v. Elution: Isocratic	Mohammad Soleimani et al., 2017
22.	Rizatriptan Benzoate	RP-HPLC Bioanalytical	Sample: Human Plasma Sample Processing: Liquid –liquid extraction with methyl tertiarybutyl ether Detection: λ _{ex} - 225nm λ _{emm} - 360nm Mobile Phase: 0.05% (v/v) triethylamine in water (adjusting to pH 2.75 with 85% phosphoric acid) and acetonitrile (92:8, v/v) Elution: Isocratic	JunChen et al., 2014
23.	Rizatriptan Benzoate	RP-HPLC Bioanalytical	Sample: Human Plasma Sample Processing: Liquid –liquid extraction with dichloromethane Column: Luna C8 (250mm ×4. 6mm,5µm) Detection: λ _{ex} - 290nm λ _{emm} - 356nm Mobile Phase: 0.02mol·L ⁻¹ potassium dihydrogen phosphate-acetonitrile-methanol(87:10:3) Flow rate: 1ml/min Elution: Isocratic	Qin Yong-ping et al., 2006
24.	Rizatriptan Benzoate	UPLC impurity profiling (3 impurities)	Column: Acquity UPLC BEH C18, 100 mm x 2.1 mm, 1.7µm Temp. : 45°C Flow rate: 0.3 ml/min Injection volume : 1µl Detection: 225 nm Mobile Phase: 10mM potassium dihydrogen ortho phosphate and 2 ml triethyl amine, pH adjusted to 3.0 with OPA and acetonitrile Elution: Gradient	Koti Reddy Y et al., 2012
25.	Rizatriptan Benzoate	HPTLC	SP: aluminum plates precoated with silica gel 60 F254 Mobile Phase: dichloromethane-acetone-acetic acid 3:2:0.2(v/v/v)	Syama Sundar B and Suneetha A, 2010
26.	Rizatriptan	HPTLC	SP: aluminum plates precoated with silica	Ganesh Sarowar

			gel 60 F254 Mobile Phase: Benzene: Methanol (8: 2, v/v)	et al., 2016
27.	Rizatriptan Benzoate	HPTLC	SP: aluminum plates precoated with silica gel 60 F254 Mobile Phase: Methanol: n-Propane: Triethylamine (3:5:2 v/v/v)	Pritam S Jain et al., 2016
28.	Rizatriptan Benzoate	HPTLC	SP: aluminum plates precoated with silica gel 60 F254 Mobile Phase: toluene-methanol-triethylamine 9:3:1 (v/v/v)	Sharma S and Sharma MC, 2011
29.	Rizatriptan	HPTLC	SP: aluminum plates precoated with silica gel 60 F254 Mobile Phase: Methanol: Ammonia (9:1, v/v)	Devprakash Dahiya et al., 2011
30.	Rizatriptan	LC-MS/MS	Sample: Human Plasma Sample Processing: Liquid-liquid extraction Column: ACE C18 column, (150 X 4.6 mm, 3 μ m) Mobile Phase: acetonitrile: 10 mM aqueous ammonium acetate-acetic acid (90:10:0.5% v/v/v) Flow rate: 1ml/min Internal Standard: Zolmitriptan Elution: Isocratic	Shankarananth Velusamy et al., 2013
31.	Rizatriptan	LC-MS/MS	Sample: Human Plasma Sample Processing: Liquid-liquid extraction Column: Hypurity C18 (50 X 4.6 mm, 5 μ m) Mobile Phase: methanol: deionized water: 1.0M ATFA solution (60 : 40 : 0.1, v/v/v) Flow rate: 0.35ml/min Internal Standard: Sumatriptan Elution: Isocratic	Dinesh S Patel et al., 2012
32	Rizatriptan	LC-MS/MS	Sample: Human Plasma Sample Processing: Liquid-liquid extraction Column: Zorbax XDB C ₈ column (150 x 4.6 mm, 5 μ m) Internal Standard: Zolmitriptan Elution: Isocratic	Ji-fen Guo et al., 2006
33	Rizatriptan	LC-MS/MS	Sample: Dog Plasma and urine	Barrish A et al., 1996
34	Rizatriptan	LC-MS/MS	Sample: Human Plasma Sample Processing: Liquid-liquid extraction Column: Ascentis Express RP Amide C18, 50 x 4.6 mm, 2.7 μ m Mobile Phase: 10 mM ammonium formate:acetonitrile (20:80 v/v) Internal Standard: Rizatriptan d ₆ Elution: Isocratic	Ramakotaiah Mogili et al., 2011

35	Rizatriptan	LC-MS/MS Impurity profile (3 impurities)	Column: C-18 (100 mm x 4.6 mm, 3.5 μ m) Mobile Phase: A: 0.2% Formic Acid B: Methanol: Acetonitrile (5:95) Flow rate: 0.8ml/min Internal Standard: Sumatriptan Elution: gradient	Narasimha Rao K et al., 2017
36	Rizatriptan	GC-MS/MS Impurity profile (3 impurities)	Linearity: 15-75ppm	Raman NVVSS et al., 2017
37	Rizatriptan	LC-MS/MS	Sample: Human Plasma Sample Processing: Liquid –liquid extraction Column: Lichrospher C18 column (4.6mm \times 50 mm,5 μ m) Mobile Phase: acetonitrile–10mMaqueous ammonium acetate–acetic acid (50:50:0.5, v/v/v) Flow rate: 1.0ml/min Internal Standard: Granisetron Elution: Isocratic	Yi Chen et al., 2006

OTHER METHODS

S.No	Drug	Method	Chromatographic Conditions	Ref. No
1.	Rizatriptan Benzoate	Electro chemical method	Working electrode: glassy carbon electrode	Tayyebeh Madrakian et al., 2016
2.	Rizatriptan Benzoate	Electro chemical method	Working electrode: glassy carbon electrode	Nagappa L Teradal et al., 2014
3.	Rizatriptan Benzoate	Electro chemical method	Working electrode: glassy carbon electrode	Rajeev Jain et al., 2013
4	Rizatriptan	Preparative Chromatography	---	Srinivasula Reddy Maddula et al., 2009

ANALYTICAL METHODS FOR RIZATRIPTAN IN COMBINATION WITH OTHER DRUGS

S.No	Drug	Method	Conditions	Ref. No
1.	Rizatriptan Benzoate and Naproxen	RP-HPLC	Column: Symmetry shield C18, (250 x 4.6mm, 5 μ) Temp. : ambient Flow rate: 1.5ml/min Injection volume : 20 μ l Detection: 235nm Mobile Phase: Acetonitrile : water 60:40%v/v Elution: Isocratic	Sathis Kumar Dinakaran, 2014
2.	Rizatriptan, Almotriptan, Eletriptan	HPTLC	SP: aluminum plates precoated with silica gel 60 F254 Mobile Phase: methanol: acetonitrile:	Ramzia I El-Bagary et al., 2012

			ammonia (9:4:1 v/v)	
3.	Rizatriptan, Almotriptan, Eletriptan	RP-HPLC	Column: Hypersil C18, (250 x 4.6mm, 5 μ) Temp. : ambient Flow rate: 2ml/min Injection volume : 20 μ l Detection: 235nm Mobile Phase: Methanol: Acetonitrile : Phosphate buffer pH 3(1:1:2v/v/v) Elution: Isocratic	Ramzia I El- Bagary et al., 2012
4	Rizatriptan	RP-HPLC	Column: Symmetry C18, (250 x 4.6mm, 5 μ) Temp. : ambient Flow rate: 0.5-1.5ml/min Injection volume : 20 μ l Detection: 280nm Mobile Phase: Acetonitrile : Sodium Phosphate buffer pH adjusted to 2.5ith OPA Elution: Gradient	Vivek Sagar P et al., 2010
5	Rizatriptan and naproxen	UV- Spectrophotometric method	Solvent: Phosphate buffer pH 7.4 Detection: 216.34 nm and 230.19nm Correlation coefficient (r^2) = 0.9905, 0.9998 LinearityConc.: 2- 4.5mcg/ml	Dinakaran Sathis Kumar et al., 2013
6.	Almotriptan, Rizatriptan, Sumatriptan, Zolmitriptan	Spectrofluorimetric method	Fluorescent Reagent: Eosin Solvent: Distilled water Detection: λ_{ex} =301.3 nm, λ_{em} =542.8 nm. Correlation coefficient (r^2) = 0.9905, 0.999 LinearityConc.: 0.07- 1.0mcg/ml	Hammad MA et al., 2016
7.	Triptans	Review article	-----	Cafer Saka, 2009
8.	Naratriptan, Sumatriptan, Rizatriptan, Zolmitriptan	Colorimetry	Reagent: 4-aminoantipyrine	Karuna A Rawat et al., 2014
9.	Naratriptan, Sumatriptan, Rizatriptan, Zolmitriptan	Colorimetry	Reagent: citrate capped silver nanoparticles	Sweta K Laliwala et al., 2014
10.	Almotriptan, Rizatriptan, sumatriptan, Eletriptan, Zolmitriptan	LC-MS	Sample: Hair	Daniele Vandelli et al., 2016
11.	Naratriptan, Sumatriptan, Rizatriptan, Zolmitriptan	Colorimetry	Reagent: p-Chloranil (Tetrachloro-1,4 Benzoquinone) Detection: 558nm	Mahmoud A Omar et al., 2017

12.	Naratriptan, Sumatriptan, Rizatriptan, Zolmitriptan	LC-MS	Sample: Human Serum Sample Processing: Solid phase extraction Internal Standard: Bufotenine	Karthick Vishwanathan et al., 2000
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DISCUSSION

The presented exhaustive review covers the analytical methods for the determination of Rizatriptan and its combination in pharmaceutical and biological samples like serum and plasma. Various spectrophotometric and chromatographic conditions are presented in table.

CONCLUSION

The presented information is useful for the future study for researcher involved in qualitative and quantitative analysis of rizatriptan in single and in combination.

Conflict of Interest: None

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