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REVIEW OF ANALYTICAL METHODS FOR IDENTIFICATION AND QUANTIFICATION OF ZOLMITRIPTAN

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ABSTRACT: Zolmitriptan is a selective serotonin receptor agonist of 1B and 1D receptors belonging to the triptan class. Zolmitriptan binds to the serotonin (5-HT) 1B receptors, receptor binding leads to inhibition of nociceptive transmission, constriction of cranial vessels, and reduction of vessel pulsation, thereby providing relief of migraine headaches, as Zolmitriptan holds great importance in migraine headaches, it is necessary to compile the various analytical methods that have been reported in the literature for its analysis in pharmaceuticals or bulk products and in bioanalysis. Analytical techniques are used for pharmaceutical analysis and therapeutic drug monitoring to study bioavailability and bioequivalence. Most of the analytical methods reported for its determination are the ones that utilize HPLC and other hyphenated techniques like LC-MS, UPLC-MS, LC-MS/MS. Therefore, the present review provides a summary of the HPLC-based methods used in the determination and quantification of Zolmitriptan in different matrices since the time of its discovery.

INTRODUCTION: Zolmitriptan (ZMT), 4(S)-4-[3-(2-dimethyl aminoethyl)-1H- 5-indolyl-methyl]-1, 3-oxazolin-2-one belongs to Serotonin 5-HT1D receptor agonists [1]. It stimulates the serotonin receptors in the brain. Serotonin is a natural substance in the brain that causes blood vessels in the brain to narrow. It is used to treat severe migraine headaches; it is currently available as conventional or oral dispersible tablets and nasal sprays [2].

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The determination of Zolmitriptan was reported by different analytical methods, which include HPLC with mass spectrometry detection, electron spray ionization mass spectrometry, tandem mass spectrometry, fluorescence detectionin pharmaceutical preparations, and biological fluids [2-10].

The spectrometric methods for the determination of Zolmitriptan in pharmaceutical dosage forms were determined by complexation [11].

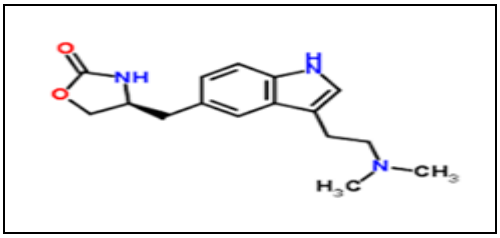

FIG. 1: STRUCTURE OF ZOLMITRIPTAN

The structure of the Zolmitriptan **Fig. 1** and the empirical formula of Zolmitriptan (ZMT) is $C_{16}H_{21}N_3O_2$, and its molecular weight was found to be 287.36. The physicochemical properties of Zolmitriptan are it is slightly soluble in water (1.3mg/ml at 25°C) and 0.1M hydrochloric acid (33mg/ml at 25°C), the melting point of Zolmitriptan is found to be 136°C, and the dissociation constant (pKa) found to be 9.64 ± 0.01.13.

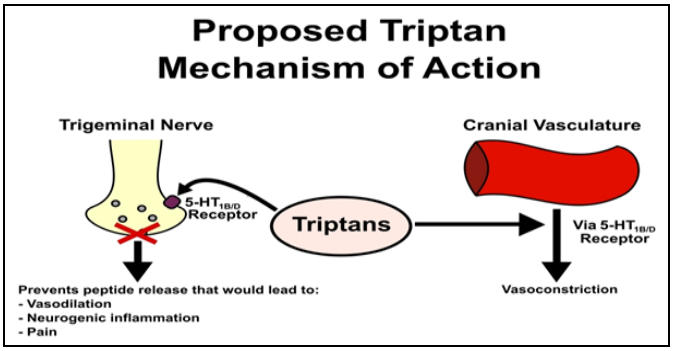

FIG. 2: MECHANISM OF ACTION OF ZOLMITRIPTAN

Mechanism of Action: Zolmitriptan is one of the agents of triptans with anti-migraine properties. Zolmitriptan inhibits the pro-inflammatory neuropeptide release and relieves migraine headaches [12]. Zolmitriptan binds to the serotonin (5-HT) 1B receptors and 5-HT 1Dreceptors and it shows agonistic action trigeminal sensory nerve terminals in the meninges and central terminals in brainstem sensory nuclei [13-15]. Receptor binding leads to inhibition of nociceptive transmission, stimulates the constriction of cranial vessels, thereby leads to a reduction of vessel pulsation, thereby providing relief of migraine headaches [12] **Fig. 2**.

Synthesis: (5)-4-(4-amino benzyl)Oxazolidine-2-one (1) is diazotization of(1) using aqueous sodium nitrite and concentrated HCl at -5 to 0°C gave the desired diazonium chloride salt(2). Reduction of (2) using stannous chloride di-hydride and concentrated HCl followed by adjustment of pH of the reaction mass to 1.7-1.85 with 55% sodium hydroxide solution afforded the hydrazine hydrochloride salt (3). Zolmitriptan (5) was obtained by reflux condensation of compound (3) with 4-4-dimethoxy-N, N-dimethylbutane-1-amine (4) in high yield. It was observed that the Zolmitriptan crude yield was only obtained when the pH of the reaction mixture was adjusted to 1.7 to 1.85. Recrystallization of this crude material from IPA/n-heptane gives Zolmitriptan (5) **Fig. 3** [16].

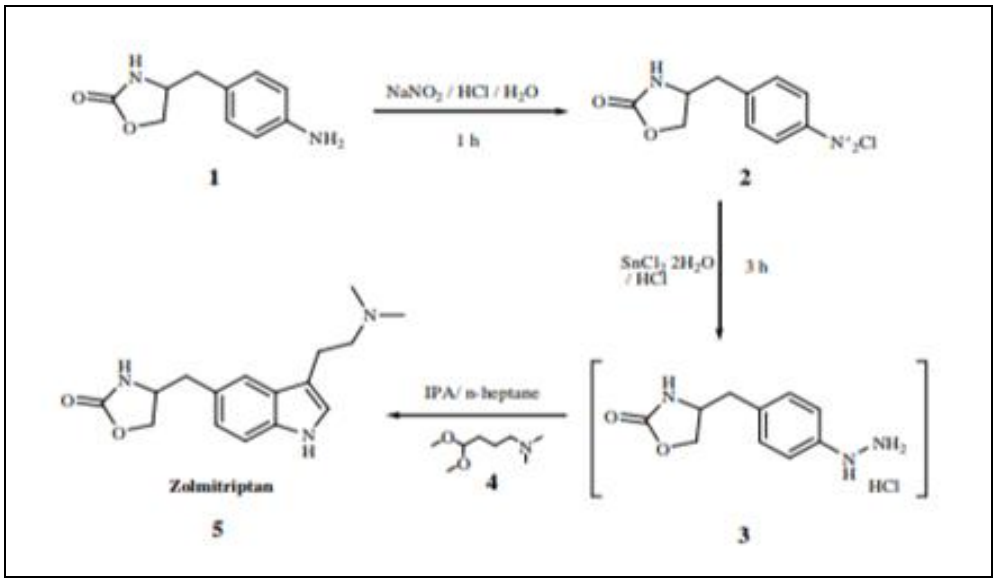

FIG. 3: SYNTHESIS OF ZOLMITRIPTAN

Pharmacokinetics: The mean oral bioavailability of Zolmitriptan was found to be 40%, with having no effect on the rate of absorption. The dosing kinetics are found to be linear over a range of 2.5 to 50 mg with 75% of the C_{max} attained within 1 hour of dosing [17]. It is rapidly absorbed and detectable in the plasma, within 2 to 5 minutes for the nasal spray and within 15 minutes for the tablet [18, 19]. Zolmitriptan peak plasma levels are obtained in 2–4 hours, and it is maintained for up to 6 hours [20]. The time to peak concentration (T_{max}) is approximately 2 hours for tablet, 3 hours for orally

disintegrating tablet, and 3-4 hours for nasal spray formulation [18–22]. The metabolism of Zolmitriptan is mostly hepatic, and only 25% of Zolmitriptan is bound to plasma proteins. Thus it is unlikely for drug interactions involving the displacement of highly protein-bound drugs [23].

Analytical Methods: Annapurna *et al.,* developed an RP-HPLC method for the determination of Zolmitriptan. The chromatographic conditions for the determination of Zolmitriptan were a Hypersil ODS C18 column (250mm × 4.8mm, 5µm) used for separation and the mobile phase was composed of 10mM tetra butyl ammonium hydrogen sulfate (TBAHS): methanol 50:50 v/v at a pH of 3.4, the flow rate was maintained at 0.8 ml/minute and the detection wavelength was 224nm. The calibration curve for Zolmitriptan was linear from 1 to 100µg/ml. The values of LOD & LOQ were 0.2687µg/ml & 0.8134µg/ml respectively [6].

Chen *et al*., developed a method for the determination of Zolmitriptan in human plasma using the liquid chromatography-tandem mass spectrometry method. The calibration curve for Zolmitriptan was linear with 0.05 to 30ng/ml with diphenhydramine as an internal standard. The mobile phase was composed of Acetonitrile: water: formic acid 70:30:0.5 and at a flow rate of 0.5ml/minute. The inter and intraday precision (%RSD) were less than 8.5%, and accuracy was less than -2.5%, and the LLOQ of Zolmitriptan was found to be 0.05ng/ml [24].

Champaneria *et al*., developed an RP-HPLC method for the estimation of Zolmitriptan in its pharmaceutical dosage form and validated it. The chromatographic conditions for the determination of Zolmitriptan were a C18 column, and the mobile phase was composed of methanol: water in the ratio of 75:25 v/v at a pH of 5 and the flow rate was maintained at 1ml/minute and detection wavelength was 222nm. The calibration curve for Zolmitriptan was linear from 10-50µg/ml. The LOD and LOQ were 2.84µg/ml and 8.62µg/ml respectively [25].

A simple, sensitive and specific RP-HPLC method for the estimation of Zolmitriptan in tablet dosage forms was developed by Nageswara Rao *et al*. The chromatographic conditions were achieved on a Kromasil C18 column with a mobile phase composed of 750ml of 0.01M anhydrous dipotassium hydrogen orthophosphate and 250ml of methanol adjusted to a pH of 7.5 and the flow rate was maintained at 1ml/minute, and detection wavelength was 230nm. The linearity for zolmitriptan was observed in the range of 0.01 to 2µg/ml. The LOD and LOQ for Zolmitriptan were found to be 0.01µg/ml and 0.03µg/ml, respectively [26].

Validation of the developed method for zolmitriptan tablets in pharmaceutical dosage form by RP-HPLC was developed by JK Ega. The chromatographic conditions for the developed method were performed on waters X-terra column with a mobile phase composed of 0.2M sodium dihydrogen orthophosphate buffer at a pH of 7.8 and acetonitrile in the ratio of 80:20 v/v, which was maintained at a flow rate of 1ml/minute and detection wavelength was 225nm [27].

Simultaneous estimation of Rizatriptan, Sumatriptan, and Zolmitriptan by RP-HPLC method was developed by P. Vivek Sagar *et al*. The chromatographic conditions were achieved on an ODS C18 column with a gradient mobile phase composed of sodium phosphate buffer: acetonitrile 70:30v/v at a flow rate of 1ml/minute and detection wavelength was 280nm. The linearity range was from 0-150µg/ml, and the LOD and LOQ were found to be 0.1ppm and 2ppm respectively [8].

A selective and sensitive UPLC-MS/MS approach for trace level quantification of four potential genotoxic impurities in zolmitriptan drug substance was developed by Vijaya Bhaskar reddy *et al*. The chromatographic conditions were achieved on a Hypersil BDS C8 column with a gradient mobile phase composed of 5mM ammonium acetate buffer (A) and a mixture of acetonitrile: methanol 90:10 v/v (B), the flow rate was maintained at 0.5ml/minute. The detection was carried out using a mass spectrometer with an m/z ratio of 288.2 [28].

Vishwanathan *et al*., had developed a method for the determination ofanti-migraine compounds rizatriptan, Sumatriptan, and Zolmitriptan in human plasma by liquid chromatography-electrospray tandem mass spectrometry. The chromatographic conditions were achieved on C8 column with a mobile phase composed of buffer 20mM ammonium acetate at a pH of 2.70 (adjusted with

glacial acetic acid to pH 4 and then with formic acid to pH 2.70): methanol: acetonitrile 80:10:10 v/v/v and the flow rate was maintained at 300µl/minute, and the detection was performed using a mass spectrometer and the m/z value of Zolmitriptan (molecular ion) was found to be 288 and the m/z value of the fragment ion was found to be 58 and the retention time of the Zolmitriptan was found to be 2.95 minutes, and the LOD was found to be 100µg/ml [29].

Simultaneous LC-MS/MS determination of Zolmitriptan and its active metabolite N-desmethyl zolmitriptan in human plasma was developed by Kilic B *et al*. The chromatographic conditions were achieved on XTerra RP18 column with a mobile phase composed of acetonitrile: 5mM ammonium acetate: formic acid 50:50:0.05 v/v/v with a flow rate of 0.25ml/minute and the detection was performed using a mass spectrometer and the m/z value of the Zolmitriptan was found to be 288 and the fragment ion was found to be 58. The retention time of the Zolmitriptan was found to be 1.87 minutes and the LOQ was found to be 0.25ng/ml [30].

E. K. S. Vijayakumar *et al*., was developed a new stability-indicating HPLC method for related substances in Zolmitriptan. The chromatographic conditions were achieved on waters X-Terra C18 column with a mobile phase consisted of a mixture of 0.02M ammonium formate containing 0.1% n-propyl amine and acetonitrile in 80:20v/v and performed at a flow rate of 1ml/minute and detection wavelength was 225nm. The linearity was established in the range of 150ng/ml to 1000ng/ml and the LOD and LOQ were determined to be 50ng/ml and 150ng/ml, respectively [5].

Dalpiaz A *et al*., was developed a quantitative determination of Zolmitriptan in rat blood and cerebrospinal fluid by reverse phase HPLC coupled with tandem mass spectrometer with electrospray ionization technique and application to *in-vivo* preclinical pharmacokinetic study. The chromatographic conditions were achieved on Luna HST C18 column with a gradient mobile phase composed of 0.1%v/v formic acid in water as component A and 0.1%v/v formic acid in acetonitrile as component B, and the flow rate was maintained at 150µl/minute and the detection was performed using a mass spectrometer, and the m/z value of Zolmitriptan was found to be 288 and the retention time was found to be 1.5 minutes. The LOD and LOQ in the water matrix were found to be 6.6ng/ml and 11ng/ml, and in blood extracts, it was found to be 26.5ng/ml and 44.2ng/ml, respectively [31].

B.M.Rao *et al*., had developed a stability-indicating LC method for the determination of Zolmitriptan. The chromatographic conditions were achieved on Waters X-terra RP18 column with a gradient mobile phase composed of phosphate buffer with a pH of 9.85: methanol: acetonitrile 70:20:10 v/v/v as component A and phosphate buffer pH of 9.85: acetonitrile 30:70 v/v with a flow rate of 1ml/minute with DAD detection at a wavelength of 225nm and the retention time was found to be 13.96 minutes [32].

Srinivasu M.K *et al*., developed a validated chiral LC method for the determination of Zolmitriptan and its potential impurities. The chromatographic conditions were achieved by normal phase HPLC with Chiralpak ADH column with a mobile phase composed of hexane: isopropanol: methanol: diethylamine 75:10:15:0.1 v/v/v/v at a flow rate of 1ml/minute with PDA detection at a wavelength of 225nm and the retention time was found to be 8.2 minutes [33].

Pragathi Ranjan *et al*., developed an RP-HPLC method for the assay of Zolmitriptan. The chromatographic conditions were achieved on Symmetry C18 column with a mobile phase composed of buffer and methanol in the ratio of 35:65 v/v and degas it and filter through 0.45µ filter and at a flow rate of 0.8ml/minute with UV detection at a wavelength of 240nm and the retention time was found to be 2.46 minutes and the linearity concentrations were observed at a range of 30-70µg/ml. the LOD and LOQ were found to be 3.04µg/ml and 10.3µg/ml [34].

Rahul sagde M *et al*., developed an analytical method development and validation for the estimation of Zolmitriptan by RP-HPLC method. The chromatographic conditions were achieved on the Phenomenex C18 column (150mm × 4.6 mm, 5µm) with a mobile phase composed of Phosphate buffer (pH 3.5): Methanol in the ratio of 85:15 v/v degas it and with a flow rate of 0.9 ml/minute with

UV detection at a wavelength of 224 nm and the retention time was found to be 3.57 minutes. The developed method is validated according to ICH Q2R1 guidelines and the LOD and LOQ results were found to be 2.45 and 7.42 µg/ml, respectively [35].Hammad MA *et al*., developed a validation method for rapid and sensitive spectrofluorimetric assay for the determination of four triptans in pure and dosage forms. The procedure was established on a determination of quenching process by developing a binary complex reaction, the relative fluorescence capacity was determined at an excitation wavelength and emission wavelength of 301.3 nm and 542.8 nm, respectively. The calibration graphs were linear to an extent from 0.1-1.0 µg/ml. The detection limit and quantitation limit were found to be 0.032 and 0.096 µg/ml, respectively [36].High sensitivity spectrophotometric methods for the determination of Zolmitriptan in pharmaceutical formulations were developed by sakur AA *et al*. The simple, sensitive, rapid spectrophotometric method was based on the formation of ion-pair complexes between Zolmitriptan and two dyes (thymol blue, phenol red) with absorption maximum at 398 nm and 418 nm for thymol blue and phenol red respectively. The concentration ranges for 0.125-9.0 and 1.25-40 µg/ml with Thymol blue and phenol red, respectively [37]. Sakura A *et al*., developed a sensitive spectrophotometric method for the determination of Zolmitriptan in bulk or tablet form by complex formation with sulphonpthalein acid dyes. The sulphonpthalein dyes used are Bromo cresol green (BCG) and Bromo cresol purple (BCP). The solvents used for the dilution are chloroform and dichloromethane for BCG and dimethyl sulfoxide and dichloromethane for BCP. The maximum absorbance obtained for Zolmitriptan with BCG was found to be 411nm of the visible region and 403nm with BCP and the LOD and LOQ with BCG was found to be 0.0627µg/ml and 0.19µg/ml and for BCP was found to be 0.0495µg/ml and 0.15µg/ml [11]. A novel spectrophotometric method for the determination of Zolmitriptan in pharmaceutical formulations was developed by Raza A *et al*. In this method, the detection was performed by the charge transfer between Zolmitriptan and 0.2% 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone in acetonitrile. The diluent used for the solubility of Zolmitriptan was acetonitrile, as the charge transfer occurs between the Zolmitriptan and acetonitrile medium, the detection *i.e.,* maximum absorbance of Zolmitriptan was found to be 555nm in the visible region. The LOD of the zolmitriptan was found to be 6µg/ml [38].

Rao R.N *et al*., developed enantiomeric discrimination and quantification of Zolmitriptan by proton NMR spectroscopy using (R)-(-)-α-methoxy phenylacetic acid as the chiral solvating agent. In this method, the detection was performed by the Diastereomic complexation between zolmitriptan and (R)-methoxy phenylacetic acid (MPA). The diluent used to solubilize the Zolmitriptan and for the suitable method was Deuterated chloroform. The detection was performed at 499.13MHZ frequency. The LOD and LOQ of (R)-zolmitriptan and (S)-zolmitriptan was found to be 0.05 & 0.14mg/0.6ml and 0.06 & 0.15mg/0.6ml respectively [39].

TABLE 1: HPLC-BASED METHODS OF ZOLMITRIPTAN IN PHARMACEUTICAL AND BIOLOGICAL ANALYSIS

Method	Matrices	Column	Mobile phase	Flow rate	Detection	Retention time	LOD & LOQ
RP-HPLC [6]	Standard	Hypersil ODS C18 column	10mM tetra butyl ammonium hydrogen sulphate: methanol 50:50 v/v	0.8ml/ min	UV at wavelength 224nm	3.308 min	0.2687µg/ml & 0.8134µg/ml
LC-MS/MS [24]	Human plasma	Zorbax SB C8 column	Acetonitrile: water: formic acid 70:30:0.5v/v	0.5ml/min	MS using m/z 288>58	2.38 min	NA & 0.05 ng/ml(LLOQ)
RP-HPLC ESI MS/MS [31]	Rat plasma and cerebrospinal fluid	Luna HST C18 column	Gradient elution A-0.1%v/v, formic acid in water B- 0.1%v/v, formic acid in acetonitrile	150 µl/ min	MS using m/z 288>243	1.5 min	For water matrix in HPLC-ms and HPLC -ms/ms 4.8,6.6ng/ml & 3.2, 11ng/ml For blood extracts 24.4, 26.5ng/ml & 13.2, 44.2ng/ml
RP-	Standard	C18	Methanol: water 75:25 v/v	1ml/min	UV detection at	3.6 min	2.84 & 8.62µg/ml

HPLC [25]		column	and pH adjusted to 3 using 10% orthophosphoric acid		wavelength 222nm	
RP-HPLC [26]	Standard	Kromasil C18 column	750ml of dipotassium hydrogen orthophosphate added 2ml of triethylamine adjusted to7.5 pH and 250ml of methanol	1ml/min	UV detection at wavelength 230nm	8.1 min	0.01 & 0.03 µg/ml
RP-HPLC [27]	Standard	Waters X- terra column	Sodium dihydrogen orthophosphate buffer with 0.2 M of 7.8 pH and acetonitrile 80:20 v/v	1ml/min	DAD detection at wavelength of 225nm	4.2 min	NA
Normal phase HPLC [33]	Standard	Chiral Pak AD-H column	Hexane: isopropanol:methanol: diethylamine 75:10:15:0.1 v/v/v/v	1ml/min	PDA detection at wavelength of 225nm	8.2min	NA
RP-HPLC [32]	Standard	Waters X-terra RP18 column	Gradient A- phosphate buffer pH 9.85:methanol:acetonitrile 70:20:10 v/v B- phosphate buffer pH 9.85: acetonitrile 30:70 v/v	1ml/min	DAD detection at 225nm	13.96 min	NA
LC/ESI-MS/MS [29]	Human serum	C8 column	20mM ammonium acetate pH 2.70 (adjusted with glacial acetic acid to pH 4 and then with formic acid to pH 2.70):methanol: acetonitrile 80:10:10 v/v/v	300µl/min	MS using m/z 288>58	2.95 min	100µg/ml &NA
RP-HPLC [8]	Standard	ODS C18 column	Gradient mobile phase sodium dihydrogen phosphate, pH adjusted to 2.5 using ortho phosphoric acid (buffer) acetonitrile 70:30 v/v	1ml/min	PDA detection at 280 nm	9.185 min	0.1 ppm & 2 ppm
LC-MS-MS [30]	Human plasma	XTerra RP18 column	Acetonitrile: 5mM ammonium acetate: formic acid 50:50:0.053 v/v/v	0.25ml/min	MS using m/z 288.06>57.99	1.87 min	NA & 0.25ng/ml
UPLC-MS/MS [28]	In Zolmitriptan drug substance	Hypersil BDS C8 column	Gradient 5mM ammonium acetate buffer Mixture of acetonitrile: methanol 90:10 v/v	0.5ml/min	MS in SIR mode using m/z 288.2	9.45 min	NA
HPLC [5]	Related substances in Zolmitriptan	Waters XTerra column	0.02M ammonium formate containing 0.1% n- propyl amine and acetonitrile 80:20 v/v	1 ml/min	UV detector at wavelength of 225nm	11 min	50ng/ml &150ng/ml
HPLC [34]	Standard	Symmetry C18	Mixture of buffer and methanol 35:65 v/v	0.8ml/min	UV detector at a wavelength of 240nm	2.637 min	3.04 &10.3µg/ml
RP-HPLC [35]	Standard	Phenomenex C18	Phosphate buffer (pH 3.5): methanol 85:15 v/v	0.9 ml/min	UV detector at a wavelength of 224 nm	3.57 min	2.45 & 7.42 µg/ml

TABLE 2: SPECTROSCOPIC METHODS OF ZOLMITRIPTAN IN PHARMACEUTICAL AND BIOLOGICAL ANALYSIS

Title	Method	Wavelength for Zolmitriptan	LOD & LOQ	Solvent
Sensitive spectrophotometric methods for determination of Zolmitriptan in bulk form and in tablets via complex formation with two sulphonthalein acid dyes [11]	BCG (Bromo Cresol Green)	411nm	0.0627µg/ml & 0.19µg/ml	Chloroform & dichloromethane
	BCP (Bromo Cresol Purple)	403nm	0.0495µg/ml & 0.15µg/ml	Dimethylsulfoxide& dichloromethane
A novel spectrophotometric method for the determination of Zolmitriptan in pharmaceutical formulations [38]	Charge transfer reaction of Zolmitriptan in acetonitrile medium with 0.2% 2,3- dichoro-	555nm	6 µg/ml &NA	Acetonitrile

Enantiomeric discrimination and quantification of Zolmitriptan by ^{1}H-NMR spectroscopy using (R)- (-)-α-methoxy phenyl acetic acid [(R)-MPA] chiral solvating agent [39]	5,6-dicyano-1,4-benzoquinone Diastereomic complexation between Zolmitriptan and (R)-MPA	499.13MHZ frequency	(R)- ZMT: 0.05 & 0.14 mg/ 0.6ml (S)-ZMT: 0.06 & 0.15 mg/0.6ml	Deuterated chloroform ($CDCl_3$)
Validation of rapid and sensitive Spectrofluorometric assay for determination of four triptans in pure and dosage forms [36]	Based on the binary complex reaction between the triptans and Eosin Y in 0.2 M acetate buffer of pH 3.5	Excitation wavelength -301.3 nm Emission wavelength – 542.8 nm	LOD – 0.032 µg/ml LOQ – 0.096 µg/ml	Double distilled water

LOD- Limit of Detection, LOQ- Limit of Quantification, N.A.-Not Available, PDA- Photo Diode Array detector, DAD- Diode Array Detector

Among the available methods, HPLC-based methods are the most widely used and therefore the most common techniques used in pharma-ceutical analysis. Ultraviolet-Visible (UV) detectors coupled with HPLC systems are most frequently used for drug analysis. Currently, the use of mass spectrometers as detectors gives high levels of analytical sensibility and a low limit of detection and it is able to provide for drug quantification and identification. The present review highlights the analytical methods used for the quantification and identification of Zolmitriptan in pharmaceuticals and biological samples by different HPLC-based methods. Therefore, the present review describes only those analytical methods that were published in the scientific literature for Zolmitriptan since its discovery **Table 1**.

The review also highlights the analytical methods used for the quantification and identification of Zolmitriptan in pharmaceutical and biological samples by different spectroscopy-based methods that were published in the scientific literature for Zolmitriptan since its discovery **Table 2** [11, 35, 36].

In the methods involving simultaneous analysis of Zolmitriptan and other serotonin 5-HT1D receptor agonists using UV detectors, the switch of wavelength for each drug was frequently accomplished through the use of diode array detectors (DAD). On the other hand, in the methods that used mass spectrometry as a detection method, the quantitative determination was performed using the multiple reaction monitoring (MRM) scanning modes of transition. The m/z value for each drug was analyzed according to the fragment ions generated. In the case of Zolmitriptan, the main fragments generated upon ionization presented as an m/z value of 243; nevertheless the ions of other fragments could be observed, including those presenting m/z values of 58 and 288 [8, 11, 30].

The analytical methods described in the present review cover several HPLC-based methods that have been used for the analysis and quantification of Zolmitriptan in different human samples, including plasma, serum, and rat plasma, cerebrospinal fluid as well as in pharmaceuticals. The use of the mobile phase is the most common difference in the analytical methods described. In these methods, a number of solvents and buffers, including acetonitrile, formic acid, methanol, ammonium acetate buffer, phosphate buffer, hexane, isopropanol, tetra butyl ammonium hydrogen sulfate, triethylamine, have been used as mobile phase. There are other parameters that differentiate certain methods from others such as flow rate, wavelength, and fragment ions. The stationary phase used in most of the methods was the reversed-phase C18 column.

The wide range of options available for use as solvents in the mobile phases in these analyses is an advantage as the analyses may be required to perform under different conditions. However, it remains necessary to use solvents that are less toxic and environmentally friendlier. Contrastingly, the data presented in the table exemplify the opposite, as most of the methods included in the table had reported using methanol and acetonitrile, the two most notoriously toxic solvents, as the mobile phase. Methods for the recovery of these toxic

solvents should be developed in order to minimize environmental damage. Additionally, the development of novel analytical methods for drug detection and quantification for economically and environmentally advanced and superior to the old methods should be developed. Nevertheless, the methods that are validated imparts the concepts of analyzing Zolmitriptan for its determination and quantification.

CONCLUSION: Zolmitriptan is one of the most Serotonin 5-HT 1D Receptor Agonists that belongs to the class of triptans. Zolmitriptan exhibits suitable pharmacokinetic properties and high stability. Zolmitriptan binds to serotonin (5-HT) 1B receptors. Receptor binding leads to inhibition of nociceptive transmission, stimulates the constriction of cranial vessels, thereby leads to a reduction of vessel pulsation, thereby providing relief of migraine headaches.

The HPLC-based methods coupled with UV or mass spectrometry are the major analytical techniques available in the literature for the determination of Zolmitriptan in pharmaceuticals as well as in biological samples. Most of the methods described in the present review have used HPLC systems coupled with UV detectors. The analytical methods that use mass spectrometers as detectors have developed in recent years, but due to their high cost of mass spectrometers, it remains a major difficulty for their use in several laboratories across the world, rendering this detection technique non-feasible in developing countries. The advantages of the methods based on HPLC coupled with UV detectors or mass spectrometers due to the high specificity, speed of analysis, accuracy, and sensitivity provided by these methods. Several HPLC-based methods highlighted in the present review were developed for the simultaneous determination of Zolmitriptan and various other triptans. The present review aimed at presenting an overview of the current state-of-the-art analytical methods available for the determination and quantification of Zolmitriptan in both pharmaceuticals and biological samples.

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REFERENCES:

1. Clement EM and Franklin M: Simultaneous measurement of Zolmitriptan and its major metabolites N-desmethylzolmitriptan and Zolmitriptan N-oxide in human plasma by high-performance liquid chromatography with coulometric detection. J Chromatogr B Anal Technol Biomed Life Sci 2002; 766(2): 339-43.
2. Yao J and Qu XZ: determination of Zolmitriptan in human plasma by high performance liquid chromatography electro spray mass spectrometry and study on its pharmacokinetics. J Chinese Pharm Sci 2005; 14(1): 25-8.
3. Zhang Z, Xu F, Tian Y, Li W and Mao G: Quantification of Zolmitriptan in plasma by high-performance liquid chromatography-electrospray ionization mass spectrometry. J Chromatogr B Anal Technol Biomed Life Sci 2004; 813(1–2): 227-33.
4. Wang D and Ouyang DS: HPLC-MS determination of Zolmitriptan in human plasma and research of its bioequivalence. chinese J Pharm Anal 2007; 27(2): 171-3.
5. Vijayakumar EKS, Samel MA, Bhalekar SB and Pakhale SM: A new stability indicating HPLC method for related substances in Zolmitriptan. Indian Journal of Pharmaceutical Sciences 2010; 72: 119-22.
6. Mathrusri-Annapurna M and Nanda B: Validated RP-HPLC method for the determination of Zolmitriptan - A serotonin 5-HT receptor agonist. J Pharm Nutr Sci 2011; 1(1): 9-14.
7. Sankar DG, Babu AN, Rajeshwari A and Krishna MV: Development and validation of RP-HPLC method for estimation of Zolmitriptan in tablet dosage forms. Asian J Chem 2009; 21(7): 5019-22.
8. Sagar PV, Dey DKS and Samal HB: simultaneous estimation of rizatriptan, sumatriptan and Zolmitriptan by RP-HPLC method in bulk form. J Pharm Res 2010; 3(12): 2930-3.
9. Induri M, Bhagavan RM, Rajendra PY, Pavankumar RK, Boddu R and RS: A Validated RP HPLC method for the quantification of Zolmitriptan in tablet dosage form. Der Pharma Chem 2010; 2(5): 351-7.
10. Reddy YK, Reddy GVS and KNJ: A new stability indicating RP-UPLC method for related substances in Zolmitriptan. African J Sci Res 2011; 1(1): 50-62.
11. Sakur A and Obaydo RH: Sensitive spectrophotometric methods for Determination of Zolmitriptan in bulk form and in tablets via complex formation with tow sulphonphthalein acid dyes. Int J Acad Sci Res 2015; 3(4): 106-14.
12. Summary C. 8/16/2020 Zolmitripta C16H21N3O2 - PubChem. 2020; 1–50.
13. De Hoon JNJM, Willigers JM, Troost J, Struijker-Boudier HAJ and Van Bortel LMAB: Vascular effects of 5-HT(1B/1D)-receptor agonists in patients with migraine headaches. Clin Pharmacol Ther 2000; 68(4): 418-26.
14. Humphrey PPA, Feniuk W, Perren MJ, Connor HE and Oxford AW: The pharmacology of the novel 5-HT1-like receptor agonist, GR43175. Cephalalg 1989; 9(S9): 23-33.
15. Spencer CM, Gunasekara NS and Hills C: Zolmitriptan. A review of its use in migraine. Drugs 1999; 58(2): 347-74.
16. Siva Prasad A, Mohonty S and Satyanarayana B: A cost effective and large-scale synthesis of Zolmitriptan: An anti-migrane drug. Der Pharma Chem 2012; 4(1): 347-51.

17. Ferrari MD: 311C90: Increasing the options for therapy with effective acute antimigraine 5HT(1B/1D) receptor agonists. Neurology 1997; 48(3 S3): 1-5.
18. Dahlof C: Clinical applications of new therapeutic deliveries in migraine. Neurology 2003; 61(8 s4): 1-4.
19. Yates R, Nairn K, Dixon R and Seaber E: The Journal of Clinical and Tolerability of Zolmitriptan Nasal Spray in Healthy Volunteers 2008; 1237-43.
20. Zingmark PH and Yates RHC: True nasopharyngeal absorption of Zolmitriptan following administration of Zolmitriptan nasal spray. Eur J Neurol 2003; 10(suppl. 1): 6-7.
21. Gillotin C and Bagnis CMJ: No need to adjust the dose of Zolmitriptan a novel anti migraine treatment in patients with renal failure not requiring dialysis. J Clin Pharmacol Ther 1997; 35(11): 6-22.
22. AM: Management of migraine in clinical practice. Precriber 1998; 19(49): 17.
23. Kalanuria AA and Peterlin BL: A review of the pharmacokinetics, pharmacodynamics and efficacy of Zolmitriptan in the acute abortive treatment of migraine. Clin Med Ther 2009; 1: CMT.S2056.
24. Chen X, Liu D, Luan Y, Jin F and Zhong D: Determination of Zolmitriptan in human plasma by liquid chromatography-tandem mass spectrometry method: Application to a pharmacokinetic study. J Chromatogr B Anal Technol Biomed Life Sci 2006; 832(1): 30-5.
25. Champaneria RI, Gharia BK, Mishra AD and Shah SA: Development and validation of HPLC method for estimation of Zolmitriptan in its pharmaceutical dosage form. Pharm Anal Acta 2019; 10(02): 1-5.
26. Rao TN, Parvathamma T and Patrudu TB: Estimation of Zolmitriptan by a new RP-HPLC method. Der Pharm Lett 2012; 4(3): 1022-6.
27. Ega JK and Siddoju K: Validation of developed method for ZOLMITRIPTAN tablets in pharmaceutical dosage form by RP-HPLC. Int J Res Appl 2015; 2(8): 376-81.
28. Reddy AVB, Venugopal N, Madhavi G, Reddy KG and Madhavi V: A selective and sensitive UPLC-MS/MS approach for trace level quantification of four potential genotoxic impurities in zolmitriptan drug substance. J Pharm Biomed Anal 2013; 84: 84-9.
29. Vishwanathan K, Bartlett MG and Stewart JT: Determination of antimigraine compounds rizatriptan, Zolmitriptan, naratriptan and sumatriptan in human serum by liquid chromatography/electrospray tandem mass spectrometry. Rapid Commun Mass Spectrom 2000; 14(3): 168-72.
30. Kiliç B, Özden T, Toptan S and Özilhan S: Simultaneous LC-MS-MS determination of Zolmitriptan and its active metabolite N-desmethylzolmitriptan in human plasma. Chromatographia 2007; 66(S1): 129-33.
31. Dalpiaz A, Marchetti N, Cavazzini A, Pasti L, Velaga S and Gavini E: Quantitative determination of Zolmitriptan in rat blood and cerebrospinal fluid by reversed phase HPLC-ESI-MS/MS analysis: Application to in vivo preclinical pharmacokinetic study. J Chromatogr B Anal Technol Biomed Life Sci [Internet] 2012; 901: 72-8.
32. Rao BM, Srinivasu MK, Sridhar G, Kumar PR, Chandrasekhar KB and Islam A: A stability indicating LC method for Zolmitriptan. J Pharm Biomed Anal 2005; 39(3–4): 503-9.
33. Srinivasu MK, Rao BM, Sridhar G, Kumar PR, Chandrasekhar KB and Islam A: A validated chiral LC method for the determination of Zolmitriptan and its potential impurities. JPBA 2005; 37(3): 453-60.
34. Satpathy PR, Rao AS, Ravikumar P, Sharma JVC and Goud M: Development and Validation of RP-HPLC Method for the Assay of Risedronate Sodium 2014; 4(1): 438-41.
35. Sagde RM, Karwa PN, Thorat VM and Jadhav SS: Analytical Method Development and Validation for the Estimation of Zolmitriptan by RP HPLC Method. Int J Trend Sci Res Dev [Internet] 2019; 3(5): 804-10.
36. MA H and MA O: Validation of rapid and sensitive spectrofluorimetric assay for determination of four triptans in pure and dosage forms; application to human plasma and content uniformity testing. Pharm Anal Acta 2016; 7(7).
37. Banana Alfares AAS: High Sensitivity Spectrophotometric Methods for the Determination of Zolmitriptan in Pharmaceutical Formulations. Res J Pharm Technol [Internet] 2021; 14(3): 1215-20.
38. Raza A, Ansari TM and Niazi SB: A novel spectrophotometric method for the determination of Zolmitriptan in pharmaceutical formulations. J Chinese Chem Soc 2007; 54(6): 1413-7.
39. Rao RN, Santhakumar K and Ramachandra B: Enantiomeric discrimination and quantification of Zolmitriptan by H NMR spectroscopy using (R)-(-)-α-Methoxy phenyl acetic acid as chiral solvating agent. J Chem Pharm Res 2016; 8(1): 56-65.

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