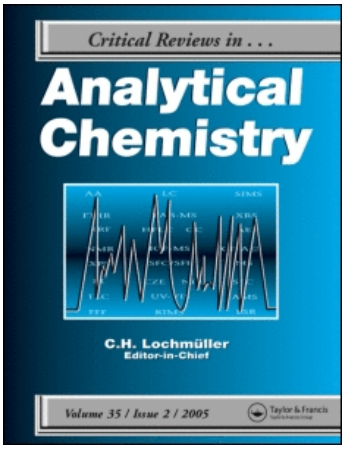

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Review of Analytical Methods for Identification and Determination of Triptans

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A review of analytical methods for identification and determination of triptans which are a group of tryptamine based drugs used in the acute treatment of migraine headaches is presented. In this review article, various methods used for determination of triptans have been covered. The methods have been divided into four groups accordingly to the applied analytical techniques: chromatographic, electrochemical, spectrometric, and capillary electrophoretic.

Keywords Review, Triptans, serotonin, migraine, identification and determination methods

INTRODUCTION

Analytical chemists have increasingly turned their attention to drug discovery and drug analysis and to solve fundamental questions of biological significance in physiology and genetics. New technologies have been developed, and a variety of instruments have been redesigned for biomedical applications. The changing nature of technologies and methods used for chemical analysis is directly relevant to the pharmaceutical industry today. Successful application of such technologies opens new opportunities for drug discovery. Migraine is a syndrome that affects a substantial part of world's population, which is three times more common in women than men (1).

Of the chemical neurotransmitter substances, serotonin (5-hydroxytryptamine, or 5-HT) is perhaps the most implicated in the treatment of various disorders, including anxiety, depression, obsessive-compulsive disorder, schizophrenia, stroke, obesity, pain, hypertension, vascular disorders, migraine, and nausea. The observation or serotonin led to the development of drugs acting on the serotonergic receptors. Historically, ergot derivatives were the first class of drug acting on a range of receptors: dopaminergic, adrenergic, and serotonergic. Triptans were a novel class of drugs acting as selective agonists of 5-HT 1B–1D receptors (2,3).

Triptans are a group of tryptamine-based drugs used in the acute treatment of migraine headaches. Structurally related to the neurotransmitter serotonin, triptans acts by selectively binding to serotonin type-1D receptors (serotonin agonist). The mechanism of action of triptans drugs is not exactly known. However, it is thought to involve (a) the cranial blood vessels, (b) the trigeminal innervation of these vessels, and (c) the reflex connection of the trigeminovascular system in the cranial parasympathetic outflow (4). Sumatriptan was the first of these compounds to be developed. Later, second-generation triptans were developed, namely, zolmitriptan, naratriptan, rizatriptan, almotriptan, eletriptan, and frovatriptan.

The most serious side effects of triptans are heart attacks and strokes. Triptans can interact with other drugs which cause a serotonin syndrome when given together with a selective serotonin reuptake inhibitor.

In this paper a review of the analytical methods and techniques for determination of triptan drugs is presented. The methods and techniques were divided into four groups: chromatographic, electrochemical, spectrometric, and capillary electrophoretic.

The chemical structures of triptans follows.

ANALYTICAL METHODS AND TECHNIQUES

The review of the papers showed that four analytical techniques have been applied for determination of triptan drugs, namely, chromatography, voltammetry, capillary electrophoresis and spectrometric methods. However, the most common method used for determination of triptan drugs is chromatography with reverse-phase high performance liquid chromatography (RP-HPLC) and/or tandem technigues. The analytıcal methods and techniques used for determination of triptans have been focused on sumatriptan, zolmitriptan and rizatriptan.

Chromatographic Methods

Chromatographic techniques belong to the most often employed group of analytical methods for identification and

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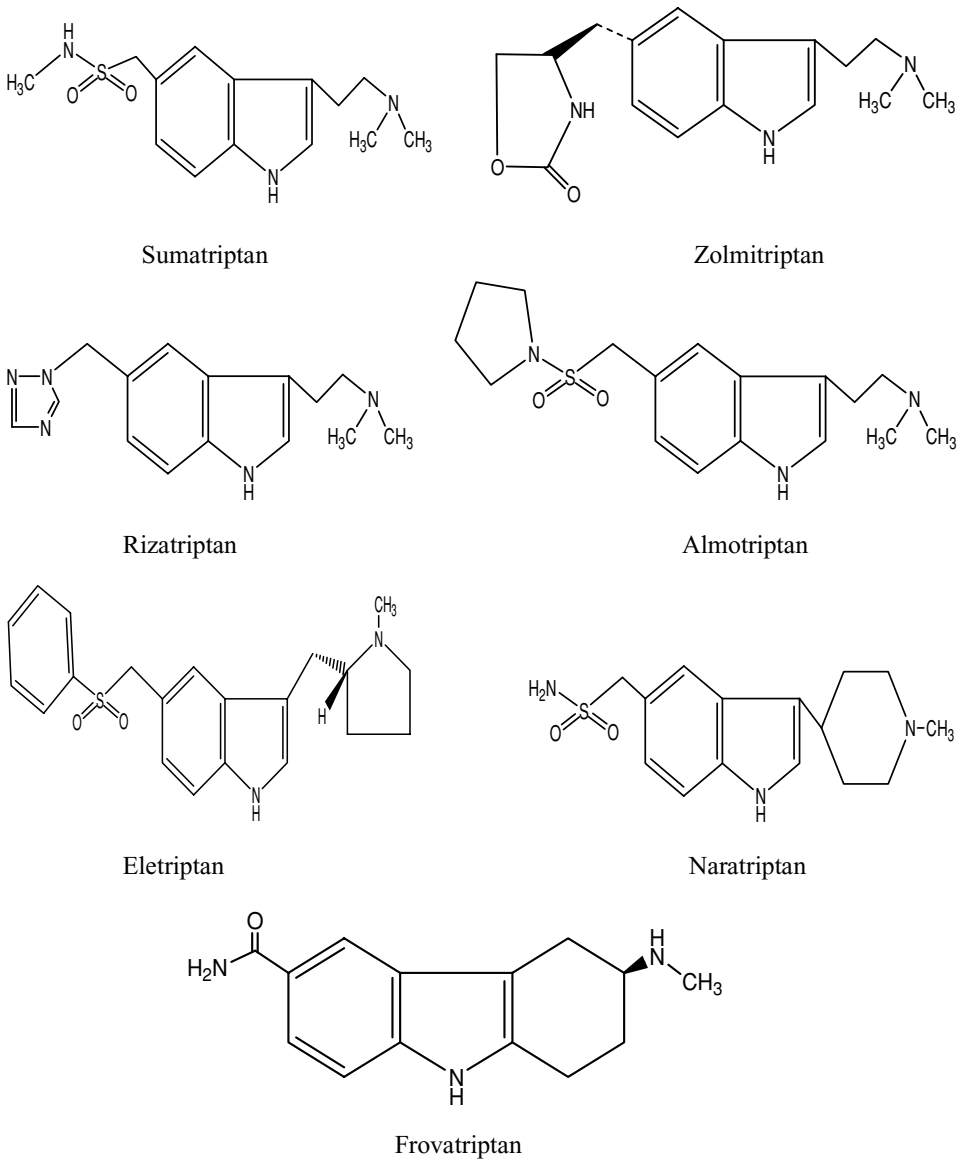

FIG. 1. Chemical Structures of Triptans.

determination of triptan drugs in biological material. Chromatography is the general term for various separatory methods, all of which have in common the distribution of a component between a mobile phase (a liquid or gas) and a stationary phase (a solid or liquid). The analyte is injected into a mobile phase (liquid for HPLC or gas for gas chromatography), which is then forced under pressure though a column.

Chromatography can be divided into two categories, namely, gas and liquid chromatography. Gas chromatography (GC) is used for the analysis of volatile samples, and liquid chromatography (LC) for non-volatile samples with a molecular weight smaller than 2000.

Many samples simply cannot be handled by GC. Either they are insufficiently volatile and cannot pass through the column, or they are thermally unstable and decompose under the conditions of separation. It has been estimated that only 20% of known organic compounds can be satisfactorily separated by GC, without prior chemical modification of the sample. On the other hand, LC is not limited by sample volatility or thermal stability (5).

LC in chromatographic methods is a separation method of great importance to the chemical, pharmaceutical and biotechnological industries. The principle is that a sample of a solution of the substances is injected into a column of a porous material (stationary phase) and a liquid (mobile phase) is pumped through the column. The separation of substances is based on differences in rates of migration through the column arising from different partition of the substances between the stationary and the mobile phase.

LC technique became a rapidly powerful separation technique and is today called high performance liquid chromatography (HPLC). The development of HPLC opened a new era

in bio-related fields and allowed faster separations of fragile macromolecules (6).

Reversed-phase liquid chromatography (RPLC) is the most popular mode of chromatography for the analytical and preparative separations of compounds of interest in the chemical, biological, pharmaceutical and biomedical sciences (7, 8). In reversed-phase gradient HPLC, the mobile phase changes composition over a specified time. A steady increase in the percentage of organic solvent (acetonitrile, methanol, propanol) leads to an increase in the mobile phase eluotropic strength and this makes it possible for highly retained non-polar analytes to be analyzed within the same run as poorly retained polar analytes. This approach has been extremely successful (9, 10) and has been widely adopted, particularly for drug metabolites (11).

A wide variety of RP-HPLC columns are available. Most columns are silica based. Silica offers good mechanical stability. A typical stationary phase is formed by chemically bonding a long-chain hydrocarbon group to porous silica. Typical ligands are n-octadecyl (C18), n-octayl (C8), n-butyl (C4), diphenyl, and cyano propyl (12).

For rapid analysis HPLC, it is important to decrease column length, increase flow rate, and use fast gradient elution. Current HPLC column technology is focused on the use of smaller particles ($<2\ \mu$m). The increased efficiency of these particles will give a sufficient increase in resolution so that columns can be shortened and flow rates increased (13).

Common detectors used for HPLC are UV absorbance, refractive index detectors, fluorescence detectors, electrochemical detectors (including amperometric and conductivity), radioactivity detectors, and a variety of light-scattering detectors including multi-angle laser light scattering and evaporative light scattering. More recently, mass spectrometry (MS) has been introduced as a highly sensitive and specific detector for HPLC analyzes. During the past 10 years several approches have tried to interface LC to MS, including thermospray particle beam and electrospray (ES) interfaces. Recently, the most important detection used in biopharmaceutical analysis is MS with the electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) techniques.

Sumatriptan

Oxford and Lant (14) reported the LC-MS for the determination of sumatriptan in plasma. The assay was linear over the calibration range 2–50 ng/ml with a limit of quantification of 2 ng/ml. The results were obtained only by using a co-eluting deuterium-labelled internal standard.

A RP-HPLC method with electrochemical detection for quantification of the determination of sumatriptan succinate in plasma and urine was presented by Andrew et al. (15) The analytical range for the plasma assay is 1–30 ng/mL and that for the urine assay is 0.2–1 2 μg/mL. For the plasma assay, intra-assay data ($n = 6$) indicate a maximum coefficient of variation (Cv) and bias across the calibration range of 6.0 and 3.0%, respectively.

McLoughlin et al. (16) developed a method with LC-atmospheric pressure chemical ionization MS for quantitation of the 5HT1D agonists MK–462 and sumatriptan in plasma with lower quantifiable limits of 0.5 ng/mL. The assay has been based on HPLC with tandem MS-MS detection. MK-462 and sumatriptan have been extracted using an automated solid-phase extraction (SPE) technique. The n-diethyl analogues of MK-462 and sumatriptan have been used as internal standards.

Dunne and Andrew (17) developed a fully automated RP-HPLC with electrochemical detection method for determination of sumatriptan serum by SPE on a Zymate XP robot linked online to the HPLC system in human. The assay is linear over the analytical range 1–30 ng/mL and selective for sumatriptan with respect to endogenous plasma components and the major circulating metabolite. The intra-assay data demonstrate a maximum bias and precision across the calibration range of 10 and 6.6%, respectively.

A rapid and sensitive HPLC method with fluorescence detection has been developed for the determination of sumatriptan in human plasma (18). The method consisted of a liquid-liquid extraction of sumatriptan and terazosin (internal standard) from human plasma with ethyl acetate. The separation of the compound was performed by isocratic reverse phase separation on a C18 column with an excitation wavelength of 225 nm and an emission wavelength of 350 nm. The linearity was over a working range of 1–100 ng/mL. The limit of quantitation (LOQ) of this method was 1 ng/mL. The authors suggested that the proposed method is simple, sensitive and suitable for pharmacokinetics or bioequivalence studies.

Sumatriptan has also been developed by HPLC method in swabs (19). The chromatographic separation involves a C18 column using a mobile phase consisting of a mixture of ammonium phosphate monobasic (0.05 M)–acetonitrile (84:16, v/v) and UV detection at 228 nm.

Shirsat et al. (20) presented a method for the quantitative determination of sumatriptan succinate with RP-HPLC method in pharmaceutical preparations. Analysis was carried out on a Hypersil C18 column 25 cm $\times$ 4.6 mm with mobile phase using a phosphate buffer: acetonitrile (80:20) as a maintained at pH 6.0. The flow rate was 1.4 mL/min and effluent was monitored at 227 nm.

Acid, base, heat, oxidation and UV irradiation stress methods to estimate the stability of the bulk drug form of sumatriptan succinate were applied by Xu et al. (21). LC coupled with MS (LC-MS and LC-MS-MS) was used to analyze the degraded samples. The authors demonstrated that sumatriptan succinate was found to be stable to exposure of acid, base, oxidation and UV irradiation at ambient conditions. However, the authors found the sample was degrading under acidic, basic and oxidative conditions at 90°C.

Boulton et al. (22) presented a sensitive and convenient high-performance liquid chromatography-tandem mass spectrometry

(HPLC-MS/MS) assay for sumatriptan in human plasma. The method was performed on the analytical Partisil C8 column (4.6 × 100 mm) by liquid-liquid extraction using a mixture of methanol-water-formic acid (90:10:0.1, v/v/v) as mobile phase. The flow rate was 0.3 mL/min. The standard curve was linear from 0.7 to 70.4 ng/mL. The lower limit of quantitation (LLOQ) was 0.7 ng/mL. According to the authors, assay was specific, accurate, precise and reproducible.

A rapid and sensitive ultraviolet HPLC method for the determination of sumatriptan in rat plasma and brain homogenate samples has been reported by Majıthıya et al. (23). After a liquid-liquid extraction (LLE) of sumatriptan and internal standard (ofloxacin), the compounds were separated on a RP C18 column by eluting with 22% of acetonitrile and 78% of ammonium phosphate buffer (0.04 M, adjusted pH 3.7) and detected at 228 nm. The limit of quantification concentration was 3 ng/mL. According to the authors, the method is simple, rapid and sensitive.

Tan et al. (24) developed an evaporation-free SPE method for sumatriptan by using high organic washing (50% methanol) and low organic elution (20% methanol) on a C18 column. The calibration curve was 1–100 ng/mL. The inter-day and intra-day precisions ranged from 4.53 to 9.12% and 1.72 to 6.93%, respectively.

A LC-MS/MS method for the quantitative determination of sumatriptan in human biolgical fluids has also been reported by Cheng et al. (25). Sumatriptan and its internal standard (D3-sumatriptan) were extracted from human matrices using C2 solid phase cartridges. The extracts which ionized using atmospheric pressure ionization (API) interface were chromatographed on a C18 column. The authors demonstrated that the method is robust, accurate, precise and specific for the direct quantification of sumatriptan in human fluids.

Franklin et al. (26) reported a method for determination of sumatriptan succinate in human plasma by using HPLC with coulometric detection. In the assay SPE was used by using internal standard (naloxone). The standard curve was linear over the range 0–100 ng/mL of sumatriptan succinate in plasma. The sensitivity was 0.5 ng/ml.

Vishwanathan et al. (27) developed a method with LC-MS/MS for the determination of anti-migraine drugs (sumatriptan, naratriptan, zolmitriptan and rizatriptan) and the internal standard bufotenine from serum. SPE using Oasis HLB was used to extract the drugs. Linear calibration curves were generated from 1–100 ng/mL. The limits of detection (LOD) for the method were 250 pg/mL for sumatriptan and 100 pg/mL for the remaining analytes based on a signal-to-noise ratio of 3.

Tipre and Vavia (28) presented the estimation of sumatriptan succinate in pharmaceutical dosage form by spectrophotometric and HPTLC (high-performance thin liquid chromatography) method. The absorption of the blue colored chromogen formed with Folin Ciocaltaeu's phenol indicator with a maximum measured at 760 nm. The colored product was stable over 4 hours at room temperature. HPTLC was carried out on silica gel with chloroform-methanol-ethyl acetate-ammonia (7,2:1:1,8:0,2 v/v/v/v). The analyte was detected at wavelength 247 nm. The drug showed a linearity at range 100–1000 ng.

Singh and Jain (29) developed a stabılıty ındıcatıng RP HPLC method for the determınatıon of sumatrıptan succınate ın pharmaceutıcal preparatıons and ıts applıcatıon ın dıssolutıon rate studıes. The method was carried out on the ODS (C18) column and at wavelengths 223 nm. Separation of the compound was performed with the mobile phase consisting of 0.0025 M orthophosphoric acid adjusted to pH 3.0 ± 0.1 with triethylamine and acetonitrile (95:5, v/v)

A HPLC method for determination in vitro transdermal absorption of sumatriptan succinate with UV detection has been reported by Femenía-Font et al. (30). The method was carried out on a 250 mm Kromasil C18 column at room temperature. The detector response was monitored at 282.7 nm. The standard curve was found in a concentration range between 0.145 and 145 μM. The LOD was 0.019 μM and the LOQ was 0.145 μM.

Zolmitriptan

Ding et al.(31) reported a HPLC-MS method for the determination of zolmitriptan in plasma and tablets. The method was analyzed by a Nucleodur C18 column using a mobile phase containing a mixture of acetonitrile-(0.05%) acetic acid (10:90,v/v). The calibration curve was linear over the range of 0.25–40 μg/L. The method recovery was in the range of 102.2–106.0% (n = 5), inter-day and intra-day Relative Standard Deviation (RSDs) were 2.3–3.4% (n = 5) and 3.4–5.4% (n = 5), respectively. According to the authors, the HPLC-MS method is accurate and sensible for zolmitriptan determination.

A specific and sensitive LC-ESI tandem mass spectrometry method for the determination of zolmitriptan and N-desmethylzolmitriptan in human plasma has been reported by Kılıç et al. (32). After a liquid-liquid extraction with a mixture of saturated ethyl acetate-dichloromethane (4:1), the analytes and the internal standard paroxetine were separated using an isocratic a mixture of acetonitrile-5 mM ammonium acetate-formic acid (50:50:0.053, v/v/v) as mobile phase on a XTerra RP18 column. Zolmitriptan and N-desmethylzolmitriptan in a range of 0.25–20 ng/mL were quantified. According to the authors, the validated method can be applied to pharmacokinetic and bioequivalence studies.

Srinivasu et al. (33) developed a chiral HPLC method for the determination of zolmitriptan and its potential impurities (R-enantiomer and Imp-1) in pharmaceutical formulations and in bulk drugs. HPLC separation was performed by normal phase chromatography on a Chiralpak column using a mixture of hexane-isopropanol-methanol-diethylamine (75:10:15:0.1, v/v/v/v) as mobile phase. Flow rate was 1.0 ml/min. The values of the LOD and LOQ of (R)-enantiomer and Imp-1 were 100, 250 ng/mL and 30, 1000 ng/ml, respectively, for 10 microl injection volume.

A new and accurate chiral LC method for the enantiomeric separation of ZTR-5 (a key starting material in the synthesis of

zolmitriptan and also chiral in nature) in bulk drugs has also been reported by Srinivasu et al. (34). The method was performed on a Chiralpak AD-H column using a mobile phase system consisting of hexane-ethanol (70:30, v/v). The LOD and LOQ of ZTR–5 were found to be 250 and 750 ng/ml, respectively, for 10 μL injection volume. According to the authors, the validated method yielded good results regarding precision, linearity, accuracy and ruggedness.

Mallikarjuna Rao et al. (35) presented a gradient, (RPLC) assay method for the quantitative determination of zolmitriptan. The chromatographic separation was achieved on a Waters X Terra RP18, 250 $\times$ 4.6 mm, 5 μm column. The gradient LC method employs Solutions A and B as mobile phase. The Solution A contains a mixture of phosphate buffer (pH 9.85)-methanol-acetonitrile (70:20:10, v/v/v) and Solution B contains a mixture of phosphate buffer (pH 9.8)-acetonitrile (30:70). The flow rate was 1.0 ml/min and the detection wavelength was 225 nm.

A sensitive and selective LC-MS/MS method for the determination of zolmitriptan in plasma has been developed by Chen et al. (36) using diphenhydramine as the internal standard. The standard curve was over the linearity range 0.05–30 ng/mL with 0.5 ml. LLE to extract the drug and the internal standard was used. The mobile phase consisted of acetonitrile-water-formic acid (70:30:0.5), at a flow rate of 0.5 mL/min. According to the authors, the method had a LLOQ of 0.05 ng/ml for zolmitriptan compared with existing methods.

Chen et al. (37) developed a RP-HPLC method for determination zolmitriptan with fluorescence detection in plasma using an isocratic system. After a single step LLE with methyl tertiary butyl ether, separation of compounds was performed with 0.05% (v/v) triethylamine in water (adjusting to pH 2.75 with 85% phosphoric acid) and acetonitrile (92:8, v/v) as mobile phase. Flow rate was 1.5 ml/min. Fluorescence detection (FD) was monitorated at 225 nm (excitation) and 360 nm (emission). The calibration curve for zolmitriptan was linear from 0.2 to 40 ng/mL. The values of the LOD and LOQ were 20 and 40 pg, respectively.

A sensitive and specific liquid chromatography electrospray ionization mass spectrometry (LC-ESI-MS) method for the identification and quantification of zolmitriptan in human plasma has been developed by Zhang et al. (38). The compounds extracted with methylene chloride-ethyl acetate mixture (20:80, v/v) were separated on a prepacked Lichrospher CN (5 μm, 150 $\times$ 2.0 mm) column using a mixture of methanol-water (10 mM NH_4AC, pH 4.0) (78:22) as mobile phase. Linearity was 0.30–16.0 ng/mL with a coefficient of determination of 0.9998. The LLOQ was 0.30 ng/mL.

Clement and Franklin (39) developed a HPLC for simultaneous determination of zolmitriptan and its major metabolites (N-desmethylzolmitriptan and zolmitriptan N-oxide) with coulometric determination (CD) in human plasma. After a SPE, separation was performed using isocratic RP-HPLC. The standard curves were linear over the range 2–20 ng/mL for zolmitriptan. The assay sensitivity was 0.5 ng for each analyte.

Hu et al. (40) developed an analytical method and quality control for determination of zolmitriptan and related substances. Zolmitriptan and related substances were separated on a shimadzu CLC-C(8) column (150 $\times$ 6 mm, 10 μm) using a mixture of acetonitrile–10 mmol/L phosphate buffer (25:75 pH 7.5) as mobile phase. Flow-rate of 1 mL/min; the UV-VIS detector was operated at 229 nm. The LOD for the related substances was 0.5 ng. Calibration curve was 4–40 μg/mL.

A selective chiral HPLC method for determination the enantiomers of *S*-zolmitriptan with FD in rat liver microsomes has been reported by Yu et al. (41). After a extraction from rat hepatic microsomal incubates with chloroform-isopropanol (75:25, v/v), the separation of compounds were separated on a normal phase Chiralpak AD-H column (250 $\times$ 0.46 mm) using a mixture of hexane–isopropanol–triethylamine (72:28:0.25, v/v/v) as mobile phase. FD was 350 nm (emission) and 291 nm (excitation). The LOQ were 0.1 μg/mL.

Rizatriptan

Guo et al. (42) presented a sensitive LC-MS-MS method for the determination of rizatriptan in human plasma. The plasma samples were prepared by LLE and separated on a Zorbax XDB C_8 column (150 $\times$ 4.6 mm) and detected by MS-MS with an ESI interface. Zolmitriptan was used as the internal standard. The method had a LLOQ of 50 pgmL for rizatriptan compared with reported methods. The within-day and between-day precision was measured to be below 11.71% and accuracy was between -5.87 and 0.86% for all quality control samples.

An analytical method based on LC with positive ion ESI coupled to LC-MS/MS for the determination of rizatriptan in human plasma using granisetron as the internal standard has been developed by Chen et al. (43). After a (LLE), the separation performed on a Lichrospher C18 column (4.6 mm $\times$ 50 mm, 5 microm) with a mixture of acetonitrile-10mM aqueous ammonium acetate-acetic acid (50:50:0.5, v/v/v) as mobile phase Flow rate was 1.0 mL/min. The assay was validated over the concentration range of 0.05–50 ng/mL.

Barrish et al. (44) developed a method based on HPLC of rizatriptan in plasma and urine with MS/MS detection. The procedure has been modified to include the simultaneous determination of the [triazole-$^{13}C_2$, $^{15}N_3$-] stable-isotope-labelled analogue for which the lower quantifiable limit was 0.1 ng/mL. The assay has been applied to study the pharmacokinetics of MK-0462 after simultaneous oral and intravenous administration of the drug and its stable-isotope-labelled analogue to dogs.

The RP chromatographic behavior of rizatriptan benzoate and its potential impurities has been reported by Antonucci et al. (45). Van't Hoff plots for a mixture of the two regiosiomers and one potential process impurity were non-linear (R = 0.937–0.965) when chromatographed on an SB-Phenyl column. However, van't Hoff plots for the same analytes were linear (R $\geq$ 0.996) when chromatographed on C8 column.

Chen et al. (46) developed a HPLC method with FD for the determination of rizatriptan in human plasma. After a single-step LLE with methyl tertiarybutyl ether, the analytes were separated using a mobile phase consisting of 0.05% (v/v) triethylamine in water (adjusted to pH 2.75 with 85% phosphoric acid) and acetonitrile (92:8, v/v). FD was performed at an excitation wavelength of 225 nm and an emission wavelength of 360 nm. The standard curve was within the concentration range of 0.5–50 ng/mL. The intra- and inter-day precisions of the method were not more than 8.0%. The LLOQ was 0.5 ng/mL for rizatriptan. According to the authors, the method was sensitive, simple and repeatable enough to be used in pharmacokinetic studies.

Mallikarjuna Rao et al. (47) developed a RP-LC method for the quantitative determination of rizatriptan benzoate. According to the authors, the developed method can be also employed for the related substance determination in bulk samples. Forced degradation studies were performed on bulk sample of rizatriptan benzoate using acid (0.5 N hydrochloric acid), base (0.1 N sodium hydroxide), oxidation (3.0% hydrogen peroxide), water hydrolysis, heat (60°C) and photolytic degradation. Mild degradation of the drug substance was observed in base hydrolysis and considerable degradation observed during oxidative stress. The chromatographic method used the samples generated from forced degradation studies on Agilent Zorbax SB-CN column with a mobile phase consisting of a mixture of aqueous potassium di hydrogen ortho phosphate (pH 3.4), acetonitrile and methanol.

Eletriptan

Cooper et al. (48) presented a HPLC method of eletriptan in plasma and saliva with Automated Sequential Trace Enrichment of Dialysate (ASTED). A mixture of acetonitrile-potassium phosphate–water (30:6:64, v/v/v) was used as the mobile phase at flow-rate of 1.0 mL/min. Linearity was over the range 0.50–250 ng/mL. At these plasma analyte concentrations, the overall inaccuracy (% bias) of the procedure ranged from −5.00 to 1.50%. Similar performances were observed for the estimation of eletriptan in saliva.

A simple and rapid method for the determination of eletriptan in tablets has been reported by Sagırlı et al. (49). Chromatography was carried out on a 250 mm × 4.6 mm C_{18} column at 30°C with acetonitrile–15 mM triethylamine solution (adjusted to pH 7.0) using concentrated *o*-phosphoric acid (60:40, v/v) mixture as mobile phase at 1.0 mL min flow rate. UV detector was set at 225 nm. A linear was observed in the range of 0.1–1.6 μg mL. The method showed good recoveries (100.08%) and the RSD values for intra- and inter-day precision were 0.78–1.93 and 1.10–2.15%, respectively. According to the authors, the method can be used for quality control assays and in vitro dissolution studies of eletriptan in tablets.

Zecevic et al. (50) presented a rapid and sensitive RP HPLC method for the routine control analysis of eletriptan hydrobromide and its organic impurity in tablets. The separation was performed on a C18 XTerra^{TM}(5 μm, 150 × 4.6 mm) column with a mixture of triethanolamine (I %)–methanol (adjusted to 6.8 with 85% orthophosphoric acid)(67.2:32.8, v/v) as mobile phase at a flow rate 1.0 mL/min The drug and its impurity were detected at 225 nm. Linearity was over the concentration range of 0.05–1.00 mg/mL for eletriptan hydrobromide and from 0.10–1.50 μg/mL.

Frovatriptan.

Laugher et al. (51) developed an analytical method using HLPC-UV of frovatriptan in rat blood. Subsequently validated in dog and mouse blood to analyze samples generated from preclinical studies. The method was also evaluated in rabbit blood, however the method proved insufficiently selective/specific for this particular matrix.

Khan et al. (52) developed a stereospecific HPLC method for separation of frovatriptan enantiomers in bulk drug and pharmaceutical formulations. Calibration curves were linear over the range of 200–6150 ng/mL. The LOD and LOQ were 65 ng/mL and 200 ng/mL, respectively. According to the authors the proposed method, compared to other methods with the results obtained by using a validated chiral capillary electrophoresis (CE) method, found to be in very good agreement.

Almotriptan.

Phanı et al. (53) reported an isocratic RP-LC method for the determination of almotriptan malate and its process-related impurities. Separation was a carried out with a C18 column and sodium phosphate buffer (pH adjusted to 7.6)–acetonitrile (80:20, v/v) as eluent, at a flow rate of 1.5 mL/min. UV detection was performed at 227 nm. Linearaty is over a range of LOQ, 1.5 ug/mL for all the process-related impurities. The method precision for the determination of related compounds was below 1.0% R.S.D.

Naratriptan

Dulery et al. (54) developed of a method based on LC-MS/MS for the determination of anti-migraine drugs [MDL 74,721 (I), with a high affinity for the 5-HT1A receptor, sumatriptan(II), naratriptan (III)] from human serum. After a SPE, separation (for the analysis of I and III) was achieved using a 150 × 2 mm Nova-Pak C8 column (4 μm particle size) and for the analysis of II, separation was achieved using a 150 × 2 mm Nova-Pak C18 column (4 μm particle size). The gradient LC method employs solutions A and B as mobile phase. The Solution A contains a mixture of 20 mM ammonium acetate-acetonitrile (90:10, v/v) and Solution B contains a mixture of acetonitrile-20 mM ammonium acetate (80:20, v/v).

Altria and McLean (55) reported a micellar electrokinetic capillary chromatography method for the determination of water soluble and insoluble acidic, basic and neutral drugs and excipients without excepting naratriptan. Optimal sensitivity was obtained by using low UV wavelength detection. According to

the authors the proposed method had the advantage of cost and time saving.

Electrochemical Methods

Electrochemical methods have proven to be useful for the development of very sensitive and selective methods for the determination of organic molecules; including drugs. Addition application of electroanalytical techniques includes the determination of electrode mechanisms. Redox properties of drugs can give insights into its metabolic fate or their *in vivo* redox processes or pharmaceutical activity (56, 57). Most electrochemical techniques, especially voltammetry and polarography but also those of electrochemical stripping, have extremely good sensitivities and detection limits. They could determine electroactive species at 10^{-3}–10^{-11} mol L^{-1} concentration levels (58).

Only two electroanalytical methods have been described in literature for analysis of tripans which consist of examining the redox properties of naratriptan and sumatriptan at the glassy carbon electrode.

Saka and Şentürk (59) examined the redox properties of naratriptan at the glassy carbon electrode. Cyclic and differential pulse voltammetry were used to investigate the dependence of electrode response on supporting electrolyte, pH, scan rate and concentration. The oxidation of the compound was shown to be irreversible and diffusion-controlled with adsorption characteristic over the entire pH = 2–12 range. The results in phosphate (pH = 7) and Britton Robinson (pH = 8) buffer allowed a new method to be developed for the determination of naratriptan, with the detection limits of 4.95×10^{-6} M and 1.80×10^{-5} M, respectively, by differential pulse voltammetry.

Sagar et al. (60) presented a voltammetric study of the oxidation of sumatriptan succinate (1:1) at the glassy carbon electrode in tablet dosage form. It was concluded that the compound exhibited a single wave in Britton-Robinson buffer solutions of pH 2–11, with a maximum current at pH 5.0. The mechanism of oxidation was connected to oxidation of the N-H group in the indole ring.

Spectrometric Methods

Spectrophotometric methods are simple and rapid so these methods can be successfully used for pharmaceutical analysis. These methods are mostly based on the formation of colored complexes between drug and the reagent which can be determined by visible spectrophotometry. UV, derivative, photometry, fluorimetry spectrophotometric methods have been used for triptans. These methods are applied for determination of triptans in pure forms and pharmaceutical formulations.

AydoğmuŞ and İnanlı (61) developed two simple and sensitive extractive spectrophotometric methods for determination of zolmitriptan in tablets. These methods are based on the formation of yellow ion-pair complexes between zolmitriptan and tropaeolin OO and bromothymol blue in citrate-phosphate buffers of pH 4.0 and 6.0, respectively. The formed complexes were extracted with dichloromethane and measured at 411.5 and 410 nm for tropaeolin OO and bromothymol blue, respectively. Correlation coefficients were 0.9998 and 0.9999 for tropaeolin OO and bromothymol blue methods, respectively. LOD of the tropaeolin OO and bromothymol blue methods were 0.341 and 0.344 μg/mL, respectively, and the LOQ were 1.034 and 1.051 μg/mL, respectively.

Altınöz et al. (62) developed two spectrophotometric and a spectrofluorimetric methods for the determination of rizatriptan in its tablet forms. Rizatriptan showed an absorption peak at 225 nm, a first-order derivative signal at 232 nm, and a fluorescence emission peak at 362 nm. Linearity ranges were found a 0.10–15.00 μg/mL for the UV, 0.05–15.00 μg/mL for the first-order derivative UV spectrophotometric and 0.03–10.00 μg/mL for the spectrofluorimetric methods. The LOQ was determined as 0.1 μg/mL for UV spectrophotometric, 17 ng/mL for first-order derivative UV spectrophotometric and 28 ng/mL for spectrofluorimetric methods. The LOD was calculated as 72 ng/mL, 5.6 ng/mL and 8.6 ng/mL, respectively. The authors demonstrated that proposed methods were successfully applied to the assay of rizatriptan in pure and tablet dosage forms and assessed as to be simple, rapid, sensitive, accurate and relatively inexpensive.

Avadhanulu et al. (63) reported spectrophotometric and RP HPLC methods for the quantitative estimation of sumatriptan succinate in its pure form using ferric chloride (1.5 M) and sulphuric acid. A purple-colored chromogen was formed which has an absorption maximum at 550 nm and it was stable for 2 hours. The chromogen was over the concentration range of 5–25 mcg/mL. In the RP = HPLC method, a Shim Pak Phenyl Column (15 cm × 6.0 mm) with a mobile phase consisting of phosphate buffer-methanol (40:60) was used. Prazosin hydrochloride was used as an internal standard. The detection wavelength is 230 nm and linearity is found to be in the range of 0.5–16 mcg/mL.

Four stability-indicating methods for the determination of sumatriptan succinate in the presence of its degradation products have been developed by Bebawy et al. (64). The first method depends on the quantitative densitometric evaluation of TLC of sumatriptan succinate using a mixture of cyclohexane–dichloromethane–diethylamine (50:40:10, v/v/v) as mobile phase and the chromatogram was scanned at 228 nm. This method determines sumatriptan succinate in the concentration range l–8 g per spot with mean percentage recovery 100.52 ± 1.23%. The second and third methods depend on the use of first-derivative (D_1) and second-derivative (D_2) spectrophotometry at 234 and 238 nm, respectively. These methods determine the drug in the concentration range 1.25–10 g mL with mean percentage recovery 99.91 ± 1.01% and 99.96 ± 1.13% for (D_1) and (D_2), respectively. The fourth method depends on the use of the ratio derivative spectrophotometric technique. The calibration graph is linear in the concentration range 1.25–10 g mL with mean percentage recovery 100.19 ± 1.19%.

Rochholz et al. (65) investigated sumatriptan and its main metabolite with TLC, ultraviolet spectroscopy, and GC/MS. The resulting analytical data [correlated hRf-values, UV solvent

spectra, remission spectra, GC retention indices, and electron impact (EI) mass spectra], including an extraction procedure and different derivatization methods, are presented. Their applicability is described for urine analysis.

Capillary Electrophoretic Methods

CE, also known as capillary zone electrophoresis (CZE), can be used to separate ionic species by their charge and frictional forces. CE is a simple analysis technique which is applied to the separation of a wide variety of compound types, including pharmaceuticals. In this area two separation modes of CE, CZE and micellar electrokinetic capillary chromatography (MECC), are mostly used. (66–67). Two papers concerning the determination of triptans drugs by CE have appeared.

Khan et al. (68) developed a cyclodextrin-modified capillary zone electrophoretic method for the evaluation of chiral purity of frovatriptan using sulfobutyl ether beta cyclodextrin as the chiral selector. The optimized method was validated in solution using imidazole as the internal standard. The LOD and LOQ were 1.0 and 5.0 μg/mL, respectively, for each isomer. According to the authors, the method is highly specific, accurate and reproducible.

Altria and Filbey (69) determined the levels of the anti-migraine agent sumatriptan in injection solutions by CE and HPLC. An internal standard was employed to provide improved precision. Detector linearity in the range of 5–150% of target concentration was 0.9993. Peak area ratio data was 0.1–0.8% and 0.5–0.7% RSD for sample and standard solutions, respectively. Inter-day repeatability gave assay data repeatability within 1%. A range of synthetic and degradative impurities was simultaneously separated and detection limits of $<0.1\%$ were possible.

Wu et al. (70) developed a practical chiral CE method for the quantitative determination of the unwanted enantiomer(R)-enantiomer in zolmitriptan. The method was carried out with a fused-silica capillary (60 cm $\times$ 50 μm ID, effective length 51.5 cm) at 20°. The applied voltage was -30 kV. UV was measured at 220 nm. The linearity was over the concentration range from 4–80 μg/mL($r = 0.9998$) of (R)-enantiomer. The injection precision (expressed as CV%) was 2.83%. The average recovery was 99.97% ($n = 9$). The LOD was 1.5 μg/mL. The host-guest complex binding constants were 964 and 905 mol -1 for (R)-enantiomer and zolmitriptan, respectively.

CONCLUSIONS

Triptans, which are effective in the acute treatment of migraine headaches, are serotonin agonist drugs. The review of literature has showed that a variety of analytical procedures for identification and determination of triptans have been developed and described. The analytıcal methods and techniques used for determination of triptans have been focused on sumatriptan, zolmitriptan and rizatriptan. On the contrary, the number of the assays found in the research literature of analytıcal methods and techniques used for other triptans (eletriptan, naratriptan, almotriptan, frovatriptan) are rather limited.

HPLC with various detection systems among the chromatographic techniques is the most common group for determination of triptan drugs. On the contrary, the research of literature for determination of triptans with gas chromatography has been founded only one assay. HPLC establish high separation potential, selectivity and sensitivity. Assays with HPLC-UV, HPLC-FL, HPLC-EC, HPLC-CE, LC-MS or LC-MS-MS detection have been reported for determination of triptan drugs. Coupling HPLC with single MS or MS-MS, which is very sensitive, selective and specific, gives the most reliable results for determination of triptans HPLC. Despite being a versatile, sensitive and reproducible technique, HPLC is tedious and time consuming because it requires previous purification of the samples and the use of several columns.

In recent years, the electrochemical techniques have led to the advancement in the field of analysis because of their sensitivity, low cost and relatively short analysis time when compared with other techniques such as chromatographic techniques. Although the triptans are being electrochemically active, there are only two literature references regarding triptans determination with electrochemical techniques. However, due to the importance of these compounds, they are very likely to be widely studied and developed in future years with electrochemical techniques as well as HPLC-EC methods for determination of triptan drugs.

Spectrophotometric methods have several advantages, the such as low interference level, good analytical selectivity, and they are easier, less expensive, and less time consuming compared with most of the other methods. However, the spectrophotometric methods are less sensitive compared with most of the other methods.

Since the last decade of the 20th century, dynamic development of the CE methods for analysis of drugs in biological and non-biological material has been observed. However, the position of CE methods in triptan drugs analysis has not been settled yet. The basic limitation of the CE techniques stem from a relatively low sensitivity. However, the combination of CE and MS-MS may gain considerable importance in triptan drugs analysis.

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