TOLVAPTAN LITERATURE SURVEY

Literature survey revealed that there were few methods reported for quantitation of tolvaptan in biological matrices [17-27]. As of now, a few studies about tolvaptan pharmacokinetics have been reported [17-27], the LC–MS/MS methods for determination of tolvaptan described in these papers had several obvious shortcomings. Firstly, the LLOQs in these reports were 0.457 [17], 2[23], 5 [18–22, 25, 26] and 10 ng/mL [24], respectively. The low sensitivity could not meet the requirement of the pharmacokinetic study of low dose tolvaptan. Secondly, the time-consuming and expensive solid-phase extraction was used for pretreatment of samples in these methods [18–26], PPT method [17] which was not suitable for high-throughput determination in pharmacokinetic study. Finally, chromatography and validation details were not provided in these reports [18–26], which might have little guiding significance for reproducing or developing the determination methods of tolvaptan. This was achieved by Qi et al., V.R.Derangula et al., [17, 27].

Q.Peia, B.Zhang (2013) et.al., [17] described the development and validation of an LC-MS/MS method for the determination of tolvaptan in human plasma. Sample preparation involved protein precipitation with acetonitrile containing
2-demethyl tolvaptan (internal standard, IS). Chromatographic separation was performed on a Zorbax XDB C(18) column with an isocratic mobile phase consisting of water (containing 0.1% formic acid) and methanol (25:75, v/v). Determination of the analytes was achieved by They have successfully applied to a pharmacokinetic study in healthy volunteers.

S.E. Shoaf, S.R. Kim, (2012) et.al., [18] compare the pharmacokinetics and pharmacodynamics of tolvaptan in Caucasian and Japanese healthy male subjects under fasting and non-fasting conditions. They have reported the plasma tolvaptan C(max) and AUC(∞) geometric mean ratios (90 % confidence interval) were 1.105 (0.845-1.444) and 1.145 (0.843-1.554) for Japanese compared to Caucasian subjects in the fasted state.

S.E. Shoaf, P. Bricmont, S. Mallikaarjun, (2012) et.al., [20] describes the changes in tolvaptan PK and PD following inhibition or induction of CYP3A4 and explores the mechanisms behind the disparity seen between tolvaptan PK and effects on urine output. It also discusses the concentrations at which tolvaptan produces its maximal response on urine output and the timing of the onset and offset of this response.
S.E. Shoaf, Y. Ohzone, S. Ninomiya, (2011) et.al., [21] reported Interactions between tolvaptan and digoxin in an open-label, sequential study where 14 healthy subjects received tolvaptan 60 mg once daily (QD) on days 1 and 12 to 16 and digoxin 0.25 mg QD on days 5 to 16.


S.R. Kim, T. Hasunuma (2011) et.al., [23], reported Pharmacokinetics, pharmacodynamics and safety of tolvaptan in healthy japanese male volunteers.

S. Yi, H. and Jeon, S.H (2012) et.al., [24] evaluated the effect of renal insufficiency on the pharmacokinetics/pharmacodynamics of tolvaptan. Thirty-seven patients were grouped by a 24-h creatinine clearance (CrCL) and evaluated for 48 h after a single 60 mg oral dose in the fasting state.

S.E. Shoaf (2012) et.al., [25] explained about effect of grapefruit juice on the pharmacokinetics of tolvaptan, a non-peptide arginine vasopressin antagonist, in healthy subjects. They designed a single-center, randomized, crossover trial of 60-mg tolvaptan with 240 mL of water or with 240 mL of reconstituted
grapefruit juice (washout period of 72 h between doses) was conducted in 20 healthy subjects.

S.E. Shoaf (2007) et.al., [26] explained about the explained about the pharmacokinetic and pharmacodynamic interactions between tolvaptan and furosemide or hydrochlorothiazide (HCTZ) were determined in a single-center, randomized, open-label, parallel-arm, 3-period crossover study conducted in healthy white (Caucasian) men.

V.R. Derangula (2014) et.al., [27] developed a simple, rapid and sensitive liquid chromatography/electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) assay method for the determination of tolvaptan in human plasma samples using tolvaptan d7 as internal standard (IS). Analyte and the IS were extracted from 100 μL of human plasma via simple liquid-liquid extraction. The chromatographic separation was achieved on a C18 column using a mixture of methanol and 0.1% formic acid buffer (80:20, v/v) as the mobile phase at a flow rate of 1.0 mL/min. The calibration curve obtained was linear (r(2) ≥ 0.99) over the concentration range of 0.05-501 ng/mL. The analyte and IS were eluted before 2.0 min. The method was successfully applied to a pharmacokinetic study of 15 mg and 60 mg tolvaptan tablet
formulation in healthy South Indian male subjects under fasting condition.

**ESZOPICLONE LITERATURE SURVEY**

Literature survey reveals that, very few methods were reported for quantification of Eszopiclone by LC-MS (40-44) and LC (45-59). However they reported in biological (40-43, 46-49), pharmaceutical formulations (44, 45, 50-59). Among the developed methods quantification of Eszopiclone by using LC-MS/MS in biological samples reported by (40-44). Based on sensitivity aspect, Hotha KK, et.al (41) developed the method at 0.1 -120.0 ng/mL., Min Meng et al., (42) achieved at 0.1 -120.0 ng/mL.

Selection of suitable internal standard for comparison of drug is most important in bioanalytical methods. For this was achieved by Min Meng et al., (42), they used deuterated internal standard comparison of drug. Based on reported methods, all were used SPE for extraction of drug and IS from biological samples. There is no method reported for quantification of Eszopiclone by using LC-MS/MS in Rabbit plasma.

**Ikeda N, Hayashida M, Kudo k and Ishida T. (2009) et.al., [40]**

Developed a rapid and quantitative screening method for 43 benzodiazepines, their metabolites, zolpidem and zopiclone in human plasma by LC-MS/MS with a small particle column. Drugs
were successfully separated within 12 min using combined scan and selected ion recording (SIR) mode. The calibration curves of were linear in the concentration range 0.5-250 ng/mL with correlation coefficients exceeding 0.99.

**Hotha KK, Vijaya Bharathi D, (2012) et.al.,[41]** Developed a highly reproducible, specific and cost-effective LC-MS/MS method was developed for simultaneous estimation of eszopiclone (ESZ) with 50 μL of human plasma using paroxetine as an internal standard (IS). The API-4000 LC-MS/MS was operated under the multiple reaction-monitoring mode using the electrospray ionization technique. A simple liquid-liquid extraction process was used to extract ESZ and IS from human plasma. The total run time was 1.5 min and the elution of ESZ and IS occurred at 0.90 min; this was achieved with a mobile phase consisting of 0.1% formic acid-methanol (15:85, v/v) at a flow rate of 0.50 mL/min on a Discover C(18) (50 × 4.6 mm, 5 μm) column. The developed method was validated in human plasma with a lower limit of quantitation of 0.1 ng/mL for ESZ. A linear response function was established for the range of concentrations 0.10-120 ng/mL (r > 0.998) for ESZ. The developed assay method was applied to an oral bioequivalence study in humans.
Min Meng, Lisa Rohde, (2012) et al., [42] describes the application of computer software ACD Lab® to facilitate the development of chiral separation for the quantitation of eszopiclone using LC–MS/MS technology. Assisted by ACD/Chrom Manager and LC Simulator software, the optimal chiral chromatographic development was completed within hours. The baseline chiral separation was achieved with a total cycle time of 3 min. For sample extraction method development, a Waters Oasis® Sorbent Selection Plate containing four different sorbents was utilized. Optimal conditions were determined using a single plate under various load, wash and elution conditions. This was followed by a GLP validation which demonstrated excellent intra- and inter-day accuracy and precision for the quantitation of eszopiclone in human plasma at 1.00–100 ng/mL range using LC/MS/MS technology. This method was utilized to support multiple clinic bioequivalence studies.

Hiren N. Mistri, Arvind G. Jangid, (2008) et al., [43] developed and validated method for simultaneous quantification of zopiclone and its metabolites, N-desmethyl zopiclone and zopiclone-N-oxide in human plasma by using HPLC–ESI-MS/MS. The analytes were extracted using solid phase extraction, separated on Symmetry shield RP8 column (150 mm × 4.6 mm i.d., 3.5 μm
particle size) and detected by tandem mass spectrometry with a turbo ion spray interface. Metaxalone was used as an internal standard. The method had a chromatographic run time of 4.5 min and linear calibration curves over the concentration range of 0.5–150 ng/mL for both zopiclone and N-desmethyl zopiclone and 1–150 ng/mL for zopiclone-N-oxide. The intra-batch and inter-batch accuracy and precision evaluated at lower limit of quantification and quality control levels were within 89.5–109.1% and 3.0–14.7%, respectively, for all the analytes. The recoveries calculated for the analytes and internal standard were ≥90% from spiked plasma samples. The validated method was successfully employed for a comparative bioavailability study after oral administration of 7.5 mg zopiclone (test and reference) to 16 healthy volunteers under fasted condition.

Andrea E. Schwaningera, (2012) et.al., [44] reported on analytical approaches published in 2002–2012 for chiral drug analysis and their relevance in research and practice in the field of clinical and forensic toxicology. Separation systems such as gas chromatography, high performance liquid chromatography, capillary electro migration, and supercritical fluid chromatography, all coupled to mass spectrometry, are discussed. Typical applications are reviewed for relevant chiral analytes such as
amphetamines and amphetamine-derived designer drugs, methadone, tramadol, psychotropic and other CNS acting drugs, anticoagulants, cardiovascular drugs, and some other drugs. Usefulness of chiral drug analysis in the interpretation of analytical results in clinical and forensic toxicology is discussed as well.

L. Asensi-Bernardia, Y. Martín-Biosca, (2011) et.al., [45] explained, a methodology for the chiral separation of zopiclone (ZPC) by electrokinetic chromatography (EKC) using carboxymethylated-β-cyclodextrin as chiral selector has been developed and applied to the evaluation of the enantioselective binding of ZPC enantiomers to HSA and total plasma proteins. Two mathematical approaches were used to estimate protein binding (PB), affinity constants (K₁) and enantioselectivity (ES) for both enantiomers of ZPC. Contradictory results in the literature, mainly related to plasma protein binding reported data, suggest that this is an unresolved matter and that more information is needed. Discrepancies and coincidences with previous data are highlighted.

Yang LJ and Rochholz G. (2002) et.al., [46] developed for the determination of zopiclone in serum by reverse-phase high performance Liquid chromatography. After the selective extraction with n-butyl chloride, this compound was chromatographed on a LiChroCART 125-4 column packed with LiChrospher 60 RP select
B(5 microns) using acetonitrile-monopotassium phosphate (20:80, V/V) as mobile phase. The eluting compound was measured by an ultraviolet detector at 254 nm. Spiked with zopiclone of 400 micrograms/L, 1,600 micrograms/L and 6,400 micrograms/L in serum, the recoveries of zopiclone were (73.4 +/- 3.2)%, (82.2 +/- 4.1)% and (90.3 +/- 4.5)% respectively. The detection limit of the method was 15 micrograms/L. The method is simple and rapid for the determination of zopiclone in forensic toxicology.

**RT Foster, Caille G, (1994) et.al.,** [47] developed high-performance liquid chromatographic (HPLC) assay for the analysis of the enantiomers of zopiclone (ZPC), a cyclopyrrolone hypnotic, in plasma chlordiazepoxide used as an internal standard (I.S.), was extracted by liquid-liquid extraction at an alkaline pH. After evaporation of the organic layer, the drug and I.S. were reconstituted in ethanol-hexane (80:20, v/v) and injected onto the HPLC column. The enantiomers were separated at ambient temperature on a 25-cm Chiralcel OD-H column with ethanol-hexane (60:40, v/v) as the mobile phase pumped at a flow-rate of 0.6 ml/min. The enantiomers of ZPC were quantified by fluorescence detection with excitation and emission wavelengths of 300 and 470 nm, respectively. The assay described allows for the direct quantitation of ZPC without pre-column derivatization, and
is suitable for clinical studies of ZPC in humans after administration of therapeutic doses.

**Gebauer MG and CP Alderman (2002) et.al., [48]** reported a modification of an HPLC method reported by Foster et al. using a closely related structural analogue of zopiclone as internal standard. Zopiclone was detected at 306 nm and linear calibration curves were constructed in the range of 1.0-250 ng/mL for each enantiomer. The % CV at 2.5 ng/mL was 12.0% for (-)-zopiclone and 14.3% for (+)-zopiclone, and the limit of quantification of each enantiomer was 2.5 ng/mL. At higher concentrations, the coefficient of variation was less than 10%. The nominal concentration of quality control samples was predicted with an accuracy within a range of +/-11.6%. The method was used in the analysis of plasma obtained from psychiatric patients.

**Tracqui A, Kintz P (1993) et.al.,[49]** developed a high performance liquid chromatographic assay with diode-array detection for the toxicological screening of the newly developed non-benzodiazepine hypnotics and anxiolytics, zopiclone, zolpidem, suriclone. After single-step liquid-liquid extraction of plasma at pH 9.5 using chloroform-2-propanol-n-heptane (60:14:26, v/v), the substances are separated on a Nova-Pak C18 4-microns column (300 mm x 3.9 mm, I.D.), with methanol-tetrahydrofuran-pH 2.6
phosphate buffer (65:5:30, v/v) as the mobile phase (flow-rate 0.8 ml/min). Full ultraviolet spectra from 200 to 400 nm are recorded on-line during the entire analysis and may be automatically compared to spectra stored in a library. The retention times of the four drugs are 4.05 min (zopiclone), 4.66 min (zolpidem), 6.74 min (suriclone) and 10.97 min (alpidem). The analysis is performed in 15 min.

Kumar R.N., Rao G.N. (2010) et.al., [50] developed an isocratic stability indicating liquid chromatographic method and validated for the determination of Eszopiclone in bulk drug and its pharmaceutical dosage form. Separation of the drug with degradation products was achieved using Peerless HT, C8, 50 x 4.6 mm; 1.8 µm column as stationary phase and PH 4.5(±0.05) buffer: Acetonitrile: Tetrahydrofuran (81:18:1,v/v) as mobile phase at a flow rate of 1.0 mL/min. UV detection was performed at 304 nm. The method was linear over the range of 10 - 150 µg/mL. The percent recovery of drug in dosage forms was ranged from 97.7 to 100.5.

Anandakumar K., Kumaraswamy G., (2010) et.al., [51] developed a simple, selective, linear, precise and accurate RP-HPLC method and validated for rapid assay of Eszopiclone (ESZ) in bulk and in tablet dosage form. Isocratic elution at a flow rate of 1ml/
min was employed on a Phenomenax Luna C18 column (150 × 4.6 mm; 5µ) at ambient temperature. The mobile phase consisted of Acetonitrile: phosphate buffer adjusted to pH 2.5 (25:75% v/v). The UV detection wavelength was 304 nm and 20 µl of sample was injected. The retention time for ESZ was 3.92 min. The method obeys Beer's law in the concentration range of 4-24 µg/ml.

Sunil R. Dhaneshwar, (2011) et.al., [53], carried out comprehensive stress testing of Eszopiclone and validated according to ICH guideline Q1A (R2). Eszopiclone is subjected to stress conditions of hydrolysis, oxidation, photolysis and neutral decomposition. Successful separation of drug from degradation products formed under stress conditions is achieved on a Thermo Hypersil BDS-C18 (250 mm Ǻ— 4.6 mm, 5.0 Î¼) from Germany with isocratic conditions and simple mobile phase containing methanol : water pH adjusted to 2.5 with ortho phosphoric acid (40 : 60) at flow rate of 1 mL/min using UV detection at 304 nm.

D. Ravi, JVLN. Seshagiri Rao, (2014) et.al., [54] developed and validated a new simple, reliable, inexpensive, and accurate method for the quantification of Eszopiclone in pharmaceutical dosage form. The separation was achieved on Purospher® Star RP18e,(150 x 4.6 mm; 5µ)in isocratic elution mode with the mobile phase consisting of 8.1 g of Sodium lauryl sulphate and 1.6 g
Sodium dihydrogen phosphate monohydrate was dissolved in 1000 mL of Milli-Q water and Ph was adjusted to 3.5 and acetonitrile in the ratio of 50: 50 (v/v) and the column was maintained at 30°C. The detection of eluent from the column was detected using photo diode array detector (PDA) at 303nm and the flow rate was maintained at 1.5 ml/min. The developed method was very sensitive as limit of quantification and limit of detection were found to be 0.132 µg/mL and 0.054 µg/mL, respectively.

**FROVATRIPTAN LITERATURE SURVEY**

Literature survey reveals that very few analytical methods have been reported for the determination of frovatriptan, including a high–performance liquid chromatography (HPLC) method and a capillary zone electrophoretic method. To date, no LC–MS/MS method has been reported for the determination of frovatriptan in any of the matrices.

*Khan, B. Viswanathan, (2007) et.al., [70]* developed and validated a stereospecific HPLC method for separation of Frovatriptan enantiomers in bulk drug and pharmaceutical formulations on a normal-phase amylose derivertized chiral column. Calibration curves were linear over the range of 200-6150 ng/mL, with a regression coefficient (R(2)) of 0.9998. The limit of
detection (LOD) and limit of quantification (LOQ) were 65 ng/mL and 200 ng/mL, respectively.

**M. Khan, B. Viswanathan, (2006) et.al., [71]** reported a cyclodextrin modified capillary zone electrophoretic method for the evaluation of chiral purity of Frovatriptan using sulfobutyl ether beta cyclodextrin (SB-beta-CD) as the chiral selector. The method is highly specific, accurate and reproducible. The optimized method was validated for specificity, precision, linearity, accuracy and stability in solution using Imidazole as the internal standard. The limit of detection (LOD) and limit of quantification (LOQ) were 1.0 µg/mL and 5.0 µg/mL respectively for each isomer.

**ALISKIREN LITERATURE SURVEY**

As of now, only a few methods were reported [77-79] for quantification Aliskiren. Burckhardt BB et al. [77] developed and validated for the quantification of Aliskiren in biological matrices by LC-MS/MS. Ashok S. et al. [78], Dousa M. et al., [79] developed the methods in pharmaceutical compounds by using HPLC[78] and HILIC[79]. Among all Burckhardt BB et al. [77] achieved best method for quantification of Aliskiren in human serum. They developed with linearity range 0.146-1200ng/mL at a total run time of 5 minutes for each injection. They used solid phase
extraction method (SPE) for extraction of drug and internal standard.

**Burckhardt BB, (2013) et.al., [77]**, published a method Determination of aliskiren in human serum quantities by HPLC-tandem mass spectrometry appropriate for pediatric trials. They have used mixed-mode solid-phase extraction and used 100 μL of serum. The chromatographic separation was performed on Xselect (TM) C18 CSH columns with mobile phase consisting of methanol-water-formic acid (75:25:0.005, v/v/v) and a flow rate of 0.4 mL/min.

**Ashok S, Varma MS (2013) et.al., [78]**, developed and validated LC method for the determination of the enantiomeric purity of aliskiren hemifumarate in bulk drug samples. In this they used an immobilized-type Chiralpak IC chiral stationary phase under both polar organic and reversed-phase modes. They used a mixture of acetonitrile-n-butylamine 100:0.1 (v/v/) as a mobile phase with a flow rate maintained at 1.0 mL/min. Ultraviolet detection was carried out at 228 nm.

**Dousa M, Brichac J, (2012) et.al., [79]**, reported a Rapid HILIC method with fluorescence detection using derivatization reaction utilizing o-phthaldialdehyde for determination of degradation product of aliskiren. A rapid procedure based on direct
extraction and HILIC separation of aliskiren (ALI) degradation product - 3-amino-2,2-dimethylpropanamide (ADPA) with fluorescence detection has been developed. The formation of ADPA from ALI under different conditions was studied. The evaluation of HILIC method robustness was performed using multi factorial experiments with fixed factors (one-level Plackett-Burman design). XBridge HILIC column with isocratic elution using mobile phase 10 mM K(2)HPO(4) pH 7.2-acetonitrile (26:74; v/v) was employed. Fluorescence detection after post column derivatization using o-phthaldialdehyde (OPA) reagent was performed at excitation and emission wavelength of 345 nm and 450 nm, respectively. This method was successfully applied for the analysis of commercially available ALI samples.