Review Article

ANALYTICAL METHODOLOGIES FOR DETERMINATION OF TELMISARTAN: AN OVERVIEW

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ABSTRACTS

Telmisartan, an angiotensin II receptor antagonist, is used for the treatment of essential hypertension; the drug has fewer side effects compare to Angiotensin converting enzyme inhibitors.

Telmisartan has been determined in formulations and biological fluids by a variety of methods such as spectrophotometry, High-performance liquid chromatography with ultraviolet and flourimetry detection, liquid chromatography coupled with tandem mass spectrometry, densitometry, immune assay methods and electrochemical methods such as hydrogen wave polarography. The overview includes the most relevant analytical methodologies used in its determination since the origin still today.

Keywords: Telmisartan, Pharmaceutical analysis, Analytical methodologies

INTRODUCTION

Telmisartan (TLM) (4-((2-n-propyl-4-methyl-6-(1-methylbenzimidazol-2-yl)-benzimidazol-1-yl) methyl)-biphenyl- 2-carboxylic acid) (Fig. 1), a substituted benzimidazole compound, is an angiotensin II type-I receptor antagonist blocker, widely used in treatment of hypertension [1]. It could have effect on those patients who have no ability of taking ACE inhibitors. It acts through interfering with the binding of angiotensin II to the angiotensin II AT$_1$-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland [2-4]. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Its elimination half-life from plasma is reported to be about 24 h, so duration of action is much longer allowing it to be used in single daily dose.
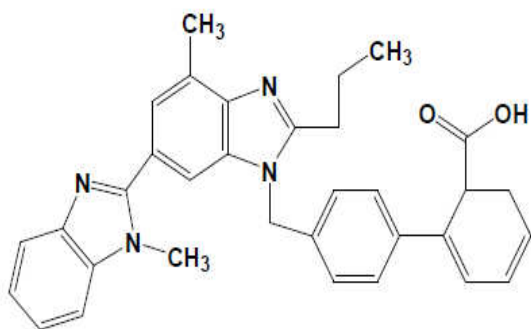

Fig. 1: Structure of Telmisartan

It is a white to slightly yellowish colored powder, practically insoluble in water but freely soluble in organic solvents. TLM has no chiral centers and exhibits no stereoisomerism. The recommended dose for treating hypertension is 20-80 mg daily. TLM is not official in IP, BP, and USP, so not any official method for determination is available. The development of new methods capable of determining drug concentration in pharmaceutical formulations and biological samples is important.

SPECTROPHOTOMETRIC METHODS

TLM has been assayed by the UV spectrophotometric (*A*max) method directly [5]. The *A*max method has been proved to be inaccurate due to matrix interference. In view of the fact that sensitive and accurate visible spectrophotometric methods were viewed as essential to avoid interference due to UV absorbing compounds in the determination of TLM in bulk samples or pharmaceutical dosage forms.

In this way, Rami Reddy et al. [6] has given two simple and sensitive methods based on the formation of colored compound with wool fat blue and 2,5-dichloro,3,6-dihydroxy,1,4-benzoquinone(DDB) with linearity of 50-250 μg/ml.

Tulja Rani, et al. [7] describe one another extractive spectrophotometric method, based on the formation of colored ion association complex of the drug with eriochrome black-T in acidic buffer of pH 3.5 followed by extraction into chloroform. (Linearity ranges 50 – 250 μg/ml).

TLM exists in two different forms in acidic and basic mediums that differ in their UV spectra. MS Palled et al [8], describe difference spectrophotometric method for the estimation of TLM in bulk drug and in pharmaceutical formulations. Difference spectrum, obtained by keeping TLM in 0.01 N NaOH in reference cell and TLM in 0.01 N HNO$_3$ in sample cell, showed two characteristic peaks at 295 nm and 327 nm with positive and negative absorbance respectively. Difference of absorbance between these two maxima was calculated to find out the amplitude, which was plotted against concentration.

The order of sensitivity among the wool fat blue(A) and DDB method(B) ,Extractive spectrophotometric method(C), UV reference method (R) and difference spectroscopy method(D) in the determination of TLM is R>D>A=B=C. The λmax order is A>C>B>D>R. The higher λmax of the proposed methods is a decisive advantage since the interference from the associated ingredients shall be far less at higher wavelengths. The validity of each method was tested by analyzing TLM in Tablets.

Mixtures

Telmisartan and Hydrochlorthiazide

Lories I. Bebawy et al. [9] use sensitive methods for the direct determination of TLM and hydrochlorothiazide (HCT) in combined dosage forms without prior separation. The first method is a first derivative spectophotometry (1D) using a zero- crossing technique of measurement at 241.6 and 227.6 nm for TLM and HCT, respectively. The second method is the first derivative of ratio spectrophotometry where the amplitudes were measured at 242.7 nm for TLM and 274.9 nm for HCT. Both methods were applied for Tablet dosage form.

KS Lakshmi et al [10] utilize Chemometric-Assisted Spectrophotometric for the simultaneous determination of TLM and HCT. The chemometric methods applied were principal component regression (PCR) and partial least square (PLS-1). These approaches

were successfully applied to quantify the two drugs in the mixture using the information included in the UV absorption spectra of appropriate solutions in the range of 200-350 nm with the intervals Δλ = 1 nm. The PCR and PLS-1 methods require neither any separation step, nor any prior graphical treatment of the overlapping spectra of the two drugs in a mixture.

Telmisartan and Atorvastatin

Absorbance correction method (I), first order derivative spectroscopic method (II) and duel wavelength method (III) have been described by Patil U.P et al.[11] The first method employs wavelength 328 nm for direct estimation of TLM where Atorvastatin Calcium(ATV) shows nil absorbance. Estimation of ATV is carried out after correction for absorbance of TLM at 241 nm. The second method is based on first order derivative spectroscopy. Wavelengths 297 nm and 241.8 nm were selected for the estimation of the ATV and TLM, respectively. In the third method, ATV was determined by plotting the difference in absorbance at 258 and 291 nm (difference is zero for TLM) against the concentration of ATV. Similarly for the determination of TLM, the difference in absorbance at 225 and 252 nm (difference is zero for ATV) was plotted against the concentration of TLM.

Analytical data for some methods described in the text find in Table 1.

Table 1: Spectrophotometric methods: analytical data

Method	Analytical data		Samples	Reference
	λmax of range(nm)	DL^a or linear range(μg/ml)		
*A*max method	230	1-8	Tablets	[5]
Charge transfer reaction of drug with DDB as acceptor	460	50-250	Tablets	[6]
Chloroform Extractable complex of drug with wool fat blue	585	50-250	Tablets	[6]
Extractive visible method by complex of drug with eriochrome black-T in acidic buffer of pH 3.5	510	50-250	Tablets	[7]
Difference spectrophotometric method	295, 327	2-12	Tablets	[8]
first derivative spectrophotometry	241.6	2.50–12.50	Tablets	[9]
Ratio derivative spectrophotometry	242.7	2.50–12.50	Tablets	[9]
Chemometric-AssistedSpectrophotometric	-	1-6	Tablets	[10]
absorbance correction method	241	5-30	Tablets	[11]
first order derivative spectroscopic method	241.8	5-30	Tablets	[11]
duel wavelength method	Difference in abs. at 225 and 252	5-30	Tablets	[11]

^{a} Detection limit

ELECTROCHEMICAL METHODS

Electrochemical methods have proved to be very sensitive for the determination of organic molecules, including drugs and related molecules in pharmaceutical dosage forms and biological fluids. The advance in experimental electrochemical techniques in the field of analysis of drugs is due to their simplicity, low cost and relatively short analysis time as compared with the other techniques. However, since most drugs are less active electrochemically, little attention has been paid so far to the use of electrochemical detection methods.

M. Xu et al. [12] use catalytic hydrogen wave method for determination of TLM using 0.8 mol/l $NH_3 \cdot H_2O$–NH_4Cl (pH = 8.9) supporting electrolyte. These authors demonstrated that the reduction peak is obtained at ca. -1.30V, which corresponds to a catalytic hydrogen wave. These authors also applied the developed method for rapid determination of the TLM in capsule forms and biological sample without pre-separation.

Authors modify above method and develop new method which has 60 times higher sensitivity using 0.8 mol L^{-1} $NH_3.H_2O$–NH_4Cl (pH 8.9)–0.01 mol/l H_2O_2 as supporting electrolyte. The results demonstrate that the polarographic reduction wave at ca. –1.30 V in the absence of H_2O_2 is a catalytic hydrogen wave, and the reduction wave enhanced by H_2O_2 is a so-called parallel catalytic hydrogen wave. The calibration curve is linear in the range 2.0×10^{-8}–2.0×10^{-6} mol L^{-1} and the detection limit is 1.0×10^{-8} mol L^{-1}. The proposed method has been proved to be advantageous over existing CZE and MEKC methods in simplicity, rapidity, and reproducibility.

Analytical data for some methods described in the text find in Table 2.

Table 2: Electrochemical Methods

Method	DL and/or Linearity range	Samples	References
Catalytic hydrogen wave method	Linearity:2.0×10^{-7} to 3.0×10^{-6} mol/l DL: 1.0×10^{-7} mol/l	Capsules and biological sample	[12]
parellal catalytic hydrogen wave method	Linearity:2.0×10^{-8}– 2.0×10^{6} mol/l DL: 1.0×10^{-8} mol/l	capsules and biological sample	[13]

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

TLM is subject to a very limited phase-I-metabolism so that the potential of interaction of this pharmaceutical is also low with respect to other drugs (e.g. paracetamol). Ebner et al., among others, investigated the chemical stability of TLM in the human body. It undergoes only minimal biotransformation in the liver to form its major inactive metabolite, TLM acylglucuronide. However, only few studies on the decomposition of TLM in the human body, on the dose as well as on the combination of TLM with other drugs, have been published to date.

During synthesis of TLM small quantity of unreacted intermediates may left over during the variety of reaction steps and finally decrease the yield and quality of the finished products. Recently, in an attempt to produce impurity free TLM, the original process was modified and the number of steps were reduced [14]. Monitoring of reactions as well as the yield the purity is very important to assess the viability of such processes for commercial production of TLM. Thus, there is a great need for development of analytical methods for separation and determination of TLM, and related substances for process development and quality control of TLM in pharmaceutical dosage form. Several HPLC methods have been available for the

determination of TLM and its metabolites in biological fluids with UV, floresencence, and electrochemical detection system.

UV detection

Ferreirós N et al. [15] describe SPE-HPLC method coupled to photodiode array detection in human urine matrix, in order to monitor four antihypertensive angiotensin II receptor antagonist drugs using experimental design. No interferences from other endogenous compounds or co-administered drugs were found.

For determination of related substances of TLM during synthesis was developed by Nageswara Rao. [16]. Here the related substances relate to a novel synthetic route and different from those A-H impurities reported by European Pharmacopeia. The modified synthetic process of TLM followed in the present investigation. It could be seen from that there are 8 steps and 7 intermediates are produced during the process. Thus the 7 intermediates except starting material were considered for method development. This developed method is suitable for quality assurance of TLM during synthesis.

Florescence Detection

TLM is self florescent drug. Sensitivity of florimetry is higher than spectrophotometric method and decrease interference of the selection of excitation and emission wavelength.

Nie J. et al. [17] establish simple HPLC method by using poly (methacrylic acid-ethylene glycol dimethacrylate, MAA-EGDMA) monolithic capillary. An advantage of said method is that it is possible direct and on-line extraction of TLM from rat tissue (heart, kidney, and liver) homogenates. The determination of TLM in treated rat tissues was achieved by using the proposed method.

Torrealday N. et al. [18] describes HPLC with florimetric detection applying statistical analysis by central composite design. Chemometric approach allowed us to reduce the number of experiments needed for chromatographic optimization, as well as the attainment of a true optimum set of conditions. Chromatographic variables were optimized by means of experimental design. A clean-up step was used for urine samples consisting of a solid-phase extraction procedure with C8 cartridges and methanol as eluent. This procedure is very simple, effective and provided no interference peaks for endogenous components, so method was proved to be selective.

By determination of drug in less plasma quantity Yunyun Jiang et al,[19] describe a rapid, high throughput, sensitive and accurate HPLC method using a monolithic column with fluorescence for the determination of TLM in human plasma. Advantage of monolithic column is faster separation compare to traditional chromatographic columns. The method was capable of estimating accurately TLM down to 1 ng/mL in human plasma with an analytical time of only 2min. The disadvantage of the method was that the linearity domain was not high enough, so some samples needed dilution and reanalysis. After full validation it was successfully applied to a bioequivalence study. A simple protein precipitation with acetonitrile ensured a high absolute recovery (>84%) and good purification from matrix interference.

Mixtures

Del Rosario Brunetto M.et al. [20] developed column-switching high-performance liquid chromatography (HPLC) for Losartan, TLM, and Valsartan in human urine. The use of a dual column LC system with restricted access precolumn packing allows efficient and rapid clean-up of urine sample, thus reducing the concentration of interferences and minimizing matrix-induced effects. The overlap of sample cleanup, analysis and recondition of the precolumn increases the sample throughput to 12 samples/h, increasing the usefulness of the method for routine analysis. It allows measuring the analytes in 20μL of human urine sample. The method permits simultaneous trace analysis of ARA-IIs, in less than 4min., which is a significant improvement in comparison to the methods reported previously.

Table 3: High Performance liquid chromatography methods

Procedure	Analytical data	Samples	Reference
SPE-HPLC-DAD method for angiotensin II receptor antagonist drugs:	LOQs: 113 ng/ml	human urine	[15]
Column: Lichrospher RP-18 column (250 × 4.6 mm, 5 μm), M.P.:20 mM ammonium acetate containing 0.1% (v/v) triethylamine (pH: 3.0) : acetonitrile at 25 °C.	Linearity:0.37-500 μg/ml LOD:0.11 μg/ml LOQ:0.37 μg/ml Retention Time of TLM: 16.42 min	Tablet	[16]
Column:C18 column with flourimetric detection	Linearity: 1.25-1500 ng/g in heart and kidney , 12.5-15 000 ng/g in liver LOD: 0.24 to 1.8 ng/g.	Rat tissue	[17]
Column: Novapak C18 column 3.9μm/150 mm, 4 mm. Mobile phase: Acetonitrile: phosphate buffer with pH 6.0, 5 mM (45:55, v/v) pumped at a flow rate of 0.5 ml/ min. λem:365 nm, λex:305nm	Linearity:1-1000 μg/l LOQ: 1μg/ml Run Time: Less than 5 min	Urine Sample	[18]
Column: Chromolith (RP-18e 100mm×4.6mm,Merck, Germany) at 25 °C Mobile Phase: Acetonitrile–methanol–water–aceticacid (30:20:50:0.05, v/v) at a flow rate of 3ml/min. λem:385 nm, λex:300nm	IS: Naproxen Linearity: 1–200 ng/ml LLOQ:1 ng/ml	Human Plasma	[19]
Column: Chromolith RP-18e monolithic column Mobile Phase: 5mM phosphate buffer (pH 3.8)–acetonitrile–methanol (65:20:15, v/v/v) at a flow-rate of 3.0 ml/min	Linearity: 0.001–2.5μg/ml Run Time: 8 min LOD: 0.0002 μg/ml(signal-to-noise ratio of 5:1)	Urine Sample	[20]
Column: Betasil C18 column (250mm×4.6mm i.d.; 5μm) Mobile phase: acetonitrile–5mM NaAc buffer solution at pH 3.5 (40:60; v/v) at flow rateof 1.0 ml/min. UV detection :250 nm λem: 380 nm, λex: 250nm.	Linearity: 0.5–200 ng/ml LOD: 0.1 to 15.3 ng/ml	Human plasma and Urine	[21]

LOD: Limit of detection, LOQ: Limit of quantification

An in-tube SPME coupled to HPLC method using a (methacrylic acid-ethylene glycol dimethacrylate, MAA-EGDMA) polymer monolithic capillary as the extraction medium was developed for the direct determination of ARA-IIs (candesartan, losartan, irbesartan, valsartan, TLM) in urine and plasma samples by J. Nie et al. [21] Under the optimized extraction condition, the protein component of the biological sample was flushed through the monolithic capillary, while the analytes were successfully trapped. In comparison with existing extraction procedures for the determination of the ARA-IIs in the biological samples, the method established in the present study is simple in preparation procedure, and is relatively easy and accurate with also characters of on-line analysis.

Analytical data for some methods described in the text find in Table 3.

LIQUID CHROMATOGRAPHY– MASS SPECTROMETRY

P. Li et al. [22] describe Q-trap TM LC–MS/MS method for the determination of the TLM, in human plasma using internal standard, diphenhydramine that requires only 50μl of plasma and allows high sample throughput due to a simple sample preparation procedure and short run time. Samples were extracted from plasma using diethyl ether–dichloromethane (60:40, v/v), and separated on a Zorbax extend C18 column using methanol–10mM ammonium acetate (85:15, v/v) adjusted to pH 4.5 after mixing with formic acid as mobile phase. The assay was linear over the range 0.5–600.0 ng/ml with a limit of quantitation of 0.5 ng/ml and a limit of detection of 0.05 ng/ml. Intra- and inter-day precision were <6.7% and <8.1%, respectively, and the accuracy is in the range 88.9–111.0%. Acceptable precision and accuracy is obtained within the standard curve range of 0.5–600.0 ng/ml. The LOD of the method is 0.05 ng/ml.

Singh Saranji et al, [23] described specific SIAM HPLC-MS method under ICH prescribed conditions of hydrolysis (acidic, neutral and basic), photolysis, oxidation and thermal stress. The drug showed lability under only photo-acidic condition by forming a single degradation product. HPLC separation of the drug and the degradation product was achieved on C-8 column using gradient method. Subsequently, the degradation product peak was subjected to LC–MS/TOF and on-line H/D exchange mass studies. Based on these studies, a tentative structure was assigned to the product as 3-((1,7_-dimethyl-2_-propyl-1H,3_H-2,5_-bibenzo(d)imidazol-3_-yl)methyl)-6H-benzo(c)chromen-6-one, which was verified through 1H LC–NMR experiments.

Mixtures

Liquid chromatography–tandem mass spectrometry (LC–MS/MS) has been developed and applied for pharmacokinetic study of TLM and hydrochlorothiazide in human plasma by T. Yan et al. [24]. Sample preparation involved liquid–liquid extraction with diethyl ether–dichloromethane (60:40, v/v). The analytes and internal standard, probenecid, were separated on a Venusil XBP-C8 column using gradient elution with acetonitrile–10mM ammonium acetate–formic acid at a flow rate of 1.2 ml/min. Detection was by electro spray negative ionization mass spectrometry using multiple reaction monitoring.

X. Zhu et al. [25] describe a rapid and sensitive HPLC-ESI–MS/MS detection for the simultaneous determination of multiple angiotensin type 1 receptor antagonists (AT1RAs) WX472, WX581, 1b and TLM in rat plasma for the purpose of high-throughout pharmacokinetic screening. The method was operated under selected reaction monitoring (SRM) mode in the positive ion mode. This method has been successfully applied to the high-throughput pharmacokinetic screening study for both cassette dosing and cassette analysis of four compounds to rats. Significant drug–drug interactions were observed after cassette dosing. The study suggested that cassette analysis of pooled samples would be a better choice for the high-throughput pharmacokinetic screening of angiotensin type 1 receptor antagonists. In spite of the complex matrix, acceptable values of precision and accuracy were obtained by this method. Although the high-throughput method of cassette analysis needed more rats, it could avoid the drug–drug interactions and get the more exact pharmacokinetic data. Therefore, cassette analysis is suitable for the future research of in vitro assay such as Caco-2 permeability, metabolic stability, protein stability and so on.

After developing ELISA technique Uwe Karst [26] presented one another technique LC/APCI-MS/MS with on-line sample clean-up and compare this method to previous method.

The comparison of method is as follows.

LC/MS/MS method provides a linear calibration curve, while the immunoassay calibration typically results in a sigmoidal function. The ratio between concentrations obtained by ELISA and LC/MS (internal or external calibration) are calculated for any of the individual samples. By comparing these results, it can be observed that the deviation between ELISA and LC/MS with internal calibration is usually higher than for ELISA and LC/MS with external calibration.

In case that a high sample throughput for the determination of the TLM concentration of a large number of samples is necessary, the ELISA would be advantageous because of short analysis times and low operating costs.

Table 4: Liquid chromatography– mass Spectrometry methods

Procedure	Analytical data	Samples	Reference
Column: Zorbax extend C18 column, Mobile Phase: Methanol–10mM ammonium acetate (85:15, v/v) adjusted to pH 4.5 Detection was carried out by multiple reaction monitoring on a Q-trapTM LC–MS/MS system with an ESI interface	Linearity: 0.5–600.0 ng/ml LOD:0.05 ng/ml LOQ:0.5 ng/ml Retention Time of TLM: 2.02 min	Human plasma	[22]
Column:C-8 column, Time of flight mass analyzer	Identification of TLM using LC-NMR,LC-MS,LC-MS-TOF	Tablet	[23]
Column: Venusil XBP-C8 column with electrospray negative ionization mass spectrometry detector Mobile Phase: Acetonitrile–10mM ammonium acetate–formic acid at a flow rate of 1.2 mL/min.	The assay was successfully applied to a pharmacokinetic study in 9 healthy volunteers Linearity: 1.00–600 ng/ml Run Time:3.5 min LLOQ: 1.00 ng/ml	Human Plasma	[24]
Column: Gemini analytical column (3μm, 150mm×2.0 mm) Mobile Phase: Acetonitrile and 0.05% aqueous formic acid.	Linearity: 0.5–100 ng/ml for TLM. LLOQ : 0.5 ng/ml for TLM	Rat plasma	[25]
LC/APCI-MS/MS Teachnique:	Linearity:0.9-1000 ng/ml LOD:0.3 ng/ml LOQ:0.9 ng/ml	Human plasma	[26]
Column: Hypurity C18, 5μm, 50mm×4.6mm column using mass spectrometry detector Mobile Phase: ammonium acetate-acetonitrile (20:80)	Internal Standard: Trandolaprilat and hydrochlorothiazide LOQ:2 ng/ml	human plasma	[27]

V.K. Guptaa, et al. [27], established a rapid and sensitive liquid chromatography tandem mass spectrometry method has been developed and validated for the simultaneous determination of ramipril, ramiprilat and TLM in human plasma. The solid-phase extraction technique was used for the extraction of ramipril, ramiprilat and TLM from human plasma. Trandolaprilat and hydrochlorothiazide were used as the internal standards (ISs). Chromatography was performed on a Hypurity C18, 5μm, 50mm×4.6mm column, with the mobile phase consisting of ammonium acetate and acetonitrile (in a 20:80 ratio), followed by detection using mass spectrometry. The method involves a simple reversed isocratic chromatography condition and mass spectrometry detection, which enables detection at sub-nanogram levels. The method was validated and the lower limit of quantification for ramipril, ramiprilat and TLM was found to be 0.1 ng/ml, 0.1 ng/ml and 2 ng/ml, respectively. The mean recovery for ramipril, ramiprilat and TLM ranged from 90.1 to 104.1%. This method increased the sensitivity and selectivity; resulting in high-throughput analysis of ramipril, ramiprilat and TLM using two different ISs in a single experiment for bioequivalence studies, with a chromatographic run time of 1.5 min only.

Analytical data for some methods described in the text find in Table 4.

THIN LAYER CHROMATOGRAPHY

Few methods use this technique for determination of TLM. Also some stability study was performed by researchers. Establishment of a stability indicating assay is mandatory for study of degradation pathways of drug. Chitra Prabhu et al. developed a stability indicating HPTLC for TLM. This method is suitable for quantification for TLM in presence of degradation product. [28]

Sivasubramanian et al. [29]established same method for the quantitative TLM and Ramipril in combination using precoated with silica gel 60F254 on aluminium sheets ,toluene: acetonitrile: formic acid: water (5:5:0.3:1) as a mobile phase. Densiometric analysis of both the drugs was carried out in the absorbance mode at 212 nm. Both the drugs were subjected to acid-alkali hydrolysis, oxidation and photolytic degradation and both of them were found to be susceptible to acid-alkali hydrolysis, oxidation and photolytic degradation. Linearity of TLM was found to be within the range of 500-2500 ng/spot and for Ramipril the range was found to be 250-1250 ng/spot, with significant high values of correlation coefficient for both the drugs.

CAPILLARY ZONE ELECTROPHORESIS (CZE)

As a powerful complementary new technique to HPLC and GC, capillary electrophoresis (CE) has rapidly spread into a wide array of analytical areas due to its excellent separation efficiency, short analysis time, minimal need of samples and solvents and high versatility in terms of separation modes. However, one of the main drawbacks of CE is its low sensitivity in terms of solute concentration compared to other separation techniques, which is due to both the small optical path-length of the capillary used as a detection cell and the small volumes (usually a few nanoliters) that can be injected [30].

M. Zhang et al. describe novel PMME (Polymer monolithic microextraction) with CZE for the determination of several angiotensin II receptor antagonists (TLM, Irbesartan and Losartan) with candesartan as internal standard in human urine. The best separation was realized at 25 kV using a buffer that consisted of 50% acetonitrile and 50% buffer solution (v/v) containing 10mM disodium hydrogen phosphate (adjusted to pH 2.3 with 1M hydrochloric acid). Close correlation coefficients ($R > 0.999$) and excellent method reproducibility were obtained for all the analytes over a linear range of 0.08–3 μg/ml. Use of monolithic capillary increase the extraction capacity and efficiency compared to that obtained from traditional open tubular capillaries and packed capillaries, and the volume of desorption solvent remained at the microliter order of magnitude due to the small caliber of the capillary, indicating greater enrichment of analytes and subsequent higher sensitivity. Moreover, since the desorption was absolutely independent, problems such as peak broadening encountered in on-

line preconcentration could be eliminated. Drawback of offline mode is low automation level and less precision but the latter can be generally eliminated by employing of internal standard as is done in the present work. [31]

CZE and micellar electrokinetic capillary chromatographic (MEKC) methods to simultaneously separate HCT and six angiotensin-II-receptor antagonists: candesartan, eprosartan mesylate, irbesartan, losartan potassium, TLM, and valsartan by S. Hillaert and W. Van den Bossche. Depending on the ARA-II, at least one of the two methods can be used for each combination.The above results demonstrate that CE separation of HCT and one of the six nominated ARAIIs can be achieved using a 60 mM sodium phosphate buffer solution at pH 2.5, or by using a 55 mM sodium phosphate buffer solution at pH 6.5 containing 15 mM SDS, according to the combined ARA-II. Both the CZE and the MEKC methods can be applied successfully to the qualitative and the quantitative determination of the above compounds in pharmaceutical formulations. [32]

OTHERS

ELISA Technique

Uwe Karst [33] develops ELISA technique for determination of TLM in blood plasma and also comparing this technique by new LC-MS. The immunoassay is based on a conversion of 4-(*N*-methylhydrazino)-7-nitro-2, 1, 3-benzooxadiazole (MNBDH) to 4-(*N*-methylamino)-7-nitro- 2, 1, 3-benzooxadiazole (MNBDA), which is detected by fluorescence spectroscopy. The limit of detection was 0.1 ng/ml, the limit of quantification was 0.3 ng/ml and the working range extended from 0.3 ng/ml to 300 ng/ml.

Cell based Assay

Griessner M describe cell-based assay that does not depend on radioactivity or laboratory animals for the detection of ligands of angiotensin II type 1 receptor (AT1R). The assay makes use of stable transfected Chinese hamster ovary cells (CHO-AT1R) expressing the AT1R. A sequential saturation assay principle was used in which receptor binding sites of the CHO-AT1R cells are blocked by the analyte in a concentration-dependent manner. Afterwards, TAMRA-angiotensin II, a fluorescence-labeled ligand, was added to bind to the remaining free binding sites of the receptor. In consequence, the fluorescence signal determined is inversely proportional to the concentration of the analyte. [34]

CONCLUSION

Most of the reported methods are LC-MS and HPLC which require elaborate procedures. Few HPTLC, electrochemical methods and ELISA method are also reported. The electrochemical methods are generally less sensitive. The conventional UV methods suffer from interference due to UV absorbing compounds in the determination of the cited drug. The few reported visible spectrophotometric methods are mainly concerned with charge transfer complexation with different electron acceptors, which give color complex which have high sensitivity compare to conventional UV spectroscopy method. New difference spectroscopy has been used for the analysis of drug in acid and base medium. HPLC and HPTLC methods were well suited for the selective analysis of TLM in pharmaceutical formulations in presence of degradation product. The conclusion is that the ions-pray LC/APCI-MS/MS method has advantages in providing shorter analytical run time, higher selectivity and much lower limit of quantification compared with previous analytical methods.

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