Research Article

A REVIEW ON VARIOUS ANALYTICAL METHODS FOR ANALYSIS OF TELMISARTAN

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A R T I C L E   I N F O

A B S T R A C T

Telmisartan is used alone or together with other medicines to treat high blood pressure (hypertension). Angiotensin II type 1 receptor antagonists were broadly employed to remedy diverse issues along with hypertension, coronary heart failure, myocardial infarction, and diabetic nephropathy. Telmisartan is also used to lower the risk of heart attacks or stroke in patients of 55years of age. Telmisartan is a strong, long- lasting nonpeptide antagonist of the angiotensin II receptor type 1 that's the brand new preference for the remedy of critical hypertension, with its very high lipophilicity, unique telmisartan features, volume of distribution, provides clinical advantages for penetration into target tissues and organs. Various analytical strategies are expanded in each biological fluid and dosage form to estimate the activity of the prescribed drug. This drug has been assigned by various methods according to UV Spectrophotometry, High Performance liquid Chromatography (HPLC) with ultraviolet and force degradation, liquid chromatography and Ultra-performance liquid chromatography (UPLC) methods and Titrimetric methods of analysis.

INTRODUCTION

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR- gamma agonistic properties that could potentially confer beneficial metabolic effects. Telmisartan (TEL) is chemically 4-[[4-Methyl-6-(1-methyl-1Hbenzimidazol- 2-yl)-2-propyl1H- benzimidazol-1-yl] methyl] biphenyl-2-carboxylic acid. It is an angiotensin II receptor antagonist which is used in treatment of hypertension. Angiotensin II receptor blockers bind to angiotensin II type 1 receptors and inhibits its effect on vascular smooth muscle which causes reduction in arterial blood pressure. It is official in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP) and US Pharmacopoeia (USP). It is estimated by Liquid Chromatography as per IP and Potentiometric Titration as per BP and USP. Literature review reveals that HPLC, UV Spectrophotometric and HPTLC methods have been reported for quantification of TEL in pharmaceutical dosage form. Chlorthalidone (CHLO) is chemically a 2-Chloro-5-(1- hydroxy-3- oxo-1- isoindolinyl) benzene sulfonamide is thiazide like diuretic. It inhibits Na+ K + 2Cl co-transport in ascending loop of Henle. It is used in Antihypertensive preparations and other cardiovascular diseases. It is official in

Indian Pharmacopoeia (IP), British Pharmacopoeia (BP) and US Pharmacopoeia (USP). It is estimated by potentiometric titration as per IP and Liquid chromatography as per BP and USP. Literature review reveals that HPLC, UV spectrophotometric methods have been reported for quantification of CHLO in pharmaceutical dosage form. Literature review reveals that HPTLC, HPLC methods have been reported for simultaneous estimation of TEL and CHLO in dosage forms however, so far, no method was reported qualitative estimation of any degradation product with the simultaneous determination of Telmisartan (TEL) and Chlorthalidone (CHLO) in bulk API and FDC. The present developed stability Indicating RP-HPLC method is simple, precise and accurate for simultaneous estimation of both drugs in their Pharmaceutical Dosageform as per ICH guidelines[1].

Chemical Structure of Telmisartan
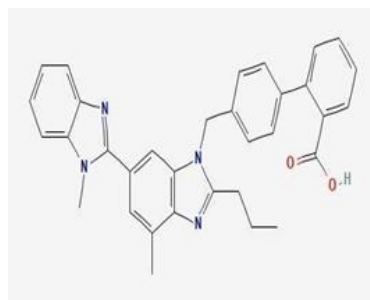
IUPAC name: - 2-[4-[[4-methyl-6-(1-methyl benzimidazol-2-yl)-2-propylbenzimidazol-1-yl]phenyl]benzoic acid.

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Molecular weight: - 514.628g/mlTrade name: - Micardis
Synonyms: - Telmisartan
Dose: - 20mg, 40mg, 80mg
Molecular formula: - $C_{33}H_{30}N_4O_2$

Telmisartan Indication

Used alone or in combination with other classes of antihypertensives for the treatment of hypertension. Also used in the treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes mellitus, as well as the treatment of congestive heart failure (only in patients who cannot tolerate ACE inhibitors).

Pharmacokinetics

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT1 receptor subtype. It has the highest affinity for the AT1 receptor among commercially available ARBS and has minimal affinity for the AT2 receptor. New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects, as PPARγ is a nuclear receptor that regulates specific gene transcription, and whose target genes are involved in the regulation of glucose and lipid metabolism, as well as anti-inflammatory responses. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin- converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin[2].

Side Effects

- Dizziness
- Changes in vision

Previous Studies to Estimate Telmisartan:

Several analytical methods such as UV, HPLC, HPTLC, UPLC and Titrimetric methods have been reported to estimate Telmisartan. The current review is an attempt made to compile all the analytical methods which have been used for the analysis of Telmisartan.

UV- Spectrophotometric Method

Niranjan D. Chivate *et al* reported on the development of a UV estimation and validation method for Telmisartan (TEL). It is simple, fast, accurate and cost efficient and reproducible spectrophotometric method, developed for the estimation of Telmisartan as a pure API. The wavelength (λ_{max}) was found to be 240 nm by using 60% ethanol (95%) and 40% of 0.1 N $NaHCO_3$ as a solvent for the Telmisartan. The linearity for this drug at the selected wavelength ranged between 2-14 µg/ml. Beer's law was obeyed in this concentration range with correlation coefficient of 0.9995. The accuracy and precision of the method were determined and validated according to ICH guidelines. The method has good reproducibility with % RSD less than one. Thus, proposed method can successfully be applied for Telmisartan in routine analysis work[3].

Ajith pandey *et al* developed and validated a simple, precise and accurate UV spectrophotometric method for the estimation of Telmisartan in bulk and tablet dosage form. The zero order spectra of Telmisartan in 0.1N NaOH shows λ_{max} at 234.0 nm and estimation was carried out by A(1% 1cm) and by comparison with standard. Calibration graph was found to be linear (r =0.999) over the concentration range of 4-24 µg/mL. The proposed method was validated for its accuracy, precision, specificity, ruggedness and robustness. The method can be adopted in its routine analysis[4].

Sonali D.Rathod *et al* studied on a simple, precise and accurate UV spectrophotometric method that has been developed and validated for the estimation of Telmisartan in bulk and tablet dosage form. The spectra of Telmisartan in 0.1 N NaOH and distilled water (20:80) shows λ_{max} at 234 nm and estimation was carried out by A (1% 1cm) and by comparison with standard. Calibration graph was found to be linear (r^2 = 0.999) over the concentration range of 2-10 µg/mL. The proposed method was validated for its accuracy, precision, specificity, ruggedness and robustness. The method can be adopted in its routine analysis[5].

Rajesh S. Jadhav *et al* studied an easy, simple, specific, speedy, precise and accurate UV Spectrophotometric method that has been developed and validated for content determination of Telmisartan. Drug Telmisartan demonstrated the absorption maxima at 296.5 nm and linearity was found in the range of 5 µg/ml –25 µg/ml with correlation coefficient of 0.9994. The limit of detection (LOD) of Telmisartan was found to be 1.3 µg/ml and the limit of quantification (LOQ) of Telmisartan was found to be 4.5 µg/ml. The Accuracy percentage recovery on three different levels i.e. 80%, 100% and 120% was found to be 79.6%, 100.7% and 117.9% respectively. The proposed analytical method demonstrated good Intra precision (Repeatability) with relative standard deviation 0.896% and Inter precision with relative standard deviation is 0.671% which is less than 2[6].

HPLC Method

V. P. Kurade *et al* developed and validated a rapid high performance liquid chromatographic method for the estimation of ramipril and telmisartan simultaneously in combined dosage form. A Genesis C18 column having dimensions of 4.6×250 mm and particle size of 5 µm in isocratic mode, with mobile phase containing a mixture of 0.01 M potassium dihydrogen phosphate buffer (adjusted to pH 3.4 using orthophosphoric acid): methanol:acetonitrile (15:15:70 v/v/v) was used. The mobile phase was pumped at a flow rate of 1.0 ml/min and the eluents were monitored at 210 nm. The selected chromatographic conditions were found to effectively separate ramipril (R_t : 3.68 min) and telmisartan (R_t: 4.98 min) having a resolution of 3.84. The method was validated in terms of linearity, accuracy, precision, specificity, limit of detection and limit of quantitation. Linearity for ramipril and telmisartan were found in the range of 3.5-6.5 µg/ml and 28.0-52.0 µg/ml, respectively. The percentage recoveries for ramipril and telmisartan ranged from 99.09-101.64% and 99.45- 100.99%, respectively. The limit of detection and the limit of quantitation for ramipril was found to be 0.5 µg/ml and 1.5 µg/mlrespectively and for telmisartan was found to be 1.5 µg/ml and 3.0 µg/ml, respectively. The method was found to be robust and can be successfully used to determine the drug contentof marketed formulations[7].

Surtirtho Mukhopandhyay *et al* reported that Telmisartan is a potent, long-lasting, nonpeptide antagonist of the angiotensin II type-1 (AT1) receptor that is indicated for the

treatment of essential hypertension. Hydrochlorothiazide is a widely prescribed diuretic and it is indicated for the treatment of edema, control of essential hypertension and management of diabetes insipidus. In the current article a new, accurate, sensitive, precise, rapid, reversed phase high performance liquid chromatography (RP-HPLC) method was developed for determination of related substances of Telmisartan and Hydrochlorothiazide in tablet dosage form. Simultaneous determination of related substances was performed on Chromasil C18 analytical column (250 × 4.6 mm; 5μm particle size) column at 40°C employing a gradient elution. Mobile phase consisting of solvent A (solution containing 2.0 g of potassium dihydrogen phosphate anhydrous and 1.04 g of Sodium 1- Hexane sulphonic acid monohydrate per liter of water, adjusted to pH 3.0 with orthophosphoric acid) and solvent B (mixture of Acetonitrile: Methanol in the ratio 80:20 v/v) was used at a flow rate of 1.0 ml min^{-1}. UV detection was performed at 270 nm. HPLC analytical method is linear, accurate, precise, robust and specific, being able to separate the main drug from its degradation products. It may find application for the routine analysis of the related substances of both Telmisartan and Hydrochlorothiazide in this combination tablets[8].

Majan Naim *et al* studied on development and validation of stability indicating reverse-phase high- performance liquid chromatography (RP-HPLC) method for simultaneous estimation of telmisartan (TEL) and benidipine hydrochloride (BND) in pharmaceutical dosage form. Reverse phase chromatography was selected because of its suggested use for ionic and moderate to non-polar compounds. Reverse phase chromatography is simple, suitable, better regarding efficiency, stability, and reproducibility. C18 column, a 250×4.6 mm column of 5.0 μm particle packing, was selected for separation of TEL and BND. Different solvent systems were tried and optimized in combinations as mobile phase. TEL (40 μg/ml) and BND (4 μg/ml) in buffer, pH 4.0: Methanol (50:50) was developed as it was showing good peak shapes and a significant amount of resolution. The mobile phase was flowed at 1.0 ml/min with detection of both the analytes at 210 nm using photodiode array detector. Development of method was done, and validation was accomplished using specificity, linearity, accuracy, precision, robustness, limit of detection, and limit of quantitation. The method was found linear from 20 to 60 μg/ml and 2–6 μg/ml for TEL and BND individually. The percentage recoveries of TEL and BND were 100.46% and 100.08% respectively. This stability indicating RP-HPLC methods were developed by degradation of sample and compared with standard[9].

Santosh Kumar M, Venkateshwar Rao Jupally developed and validated a new stability indicating reversed phase high-performance liquid chromatographic method for the simultaneous determination of two antihypertensive drugs viz. telmisartan and amlodipine. Chromatography was carried out on a reversed-phase Hypersil BDS C18 Column (100 x 4.6 mm, 5μ.) with mobile phase consisting of a mixture of Buffer (pH was adjusted to 3.6) and Acetonitrile taken in the ratio 60:40, and flow rate of 1 mL/min. The UV detection was performed at 234 nm for telmisartan and amlodipine. The stability-indicating capability of the method was demonstrated through adequate separation of aged and stress degraded telmisartan and amlodipine stability samples. The different analytical performance parameters such as linearity, precision,

accuracy, specificity, limit of detection (LOD), limit of quantification (LOQ) and robustness were determined according to International Conference on Harmonization (ICH Q2B) guidelines. The linearity of the calibration curves for each analyte in the desired concentration range is good (r^2 >0.999). The recovery of the method was between 100.46% and 99.91 % for telmisartan and amlodipine respectively. The proposed stability indicating method is rapid, easy, highly sensitive, precise and accurate and it can be successfully applied to estimate the amount of telmisartan and amlodipine in the formulations by easily available low-cost materials[10].

HPTLC Method

N. J. Shah *et al* developed and validated a simple, precise, accurate and rapid high performance thin layer chromatographic method for the estimation of telmisartan and hydrochlorothiazide simultaneously in combined dosage forms. The stationary phase used was precoated silica gel 60F254. The mobile phase used was a mixture of chloroform: methanol: toluene (2:5:5 v/v/v). The detection of spots was carried out at 272 nm. The method was validated in terms of linearity, accuracy, precision and specificity. The calibration curve was found to be linear between 250 to 500 ng/spot for telmisartan and 200 to 700 ng/spot for hydrochlorothiazide. The limit of detection and the limit of quantification for the telmisartan were found to be 75 and 190 ng/spot, respectively, and for hydrochlorothiazide 55 and 150 ng/spot, respectively. The proposed method can be successfully used to determine the drug content of marketed formulation[11].

Kaliappan Ilango and Pushpangadhan S. Shiji Kumar developed and validated stability indicating HPLC and HPTLC methods for simultaneous estimation of Telmisartan (TLM) and Atorvastatin (ATV) in their combined formulation. The proposed RP-HPLC method utilizes a Phenomenex Luna C18 column using acetonitrile: 0.025 M ammonium acetate (38 : 52%v/v) as mobile phase (pH 3.8), flow rate of 1.0 mL/min. Quantification was achieved with UV detection at 281 nm over concentration range of 12 to 72 μg/mL for TLM and 3 to 18 μg/mL for ATV respectively. In HPTLC, separations were performed on silica gel 60 F254 using toluene- methanol-ethyl acetate-acetic acid (5 : 1 : 1 : 0.3, v/v) as mobile phase. The compact bands of TLM and ATV at 0.37 ± 0.02 and 0.63 ± 0.01 respectively were scanned at 279 nm. Linear regression analysis revealed linearity in the range of 40 to 240 ng/band for TLM and 10 to 60 ng/band for ATV respectively. For both the methods, dosage form was exposed to thermal, photolytic, acid, alkali and oxidative stress. The methods distinctly separated the drugs and degradation products even in actual samples. In conclusion, the proposed HPLC and HPTLC methods were appropriate for routine quantification of TLM and ATV in tablet formulation[12].

R. Maheswari *et al* described a validated HPTLC method for simultaneous estimation of telmisartan and hydrochlorothiazide in tablet formulations. The separation was achieved on pre-coated silica gel plate 60 F254 using ethyl acetate: chloroform: methanol (10:3:1 v/v/v) as mobile phase. Quantification was carried out by the use of densitometer in absorbance mode at 270 nm. Linearity of detector response for telmisartan and hydrochlorothiazide estimated in the average weight of the tablet were found to be 39.58 and 12.48 mg, respectively. The percentage recovery of telmisartan and hydrochlorothiazide estimated in the average weight of the

tablet were found to be 99.61 and 99.49 %, respectively. The proposed method is accurate, precise and reproducible and can be adopted for routine analysis of telmisartan and hydrochlorothiazide in tablet formulation[13].

Tomleshkumar B. Deshmukh *et al* developed and validated a new simple, specific, accurate, precise and robust normal phase high performance thin layer chromatography (HPTLC) method for simultaneous estimation of two antihypertensive drugs Amlodipine Besylate (AMB) and Telmisartan (TEL) in pharmaceutical dosage form. Chromatographic separation of the drugs was performed over aluminum plates precoated with silica gel 60F254 as the stationary phase and solvent system comprised of chloroform: methanol: formic acid (8:2.5:0.5 v/v/v). Densitometric evaluation of the separated zones was performed at 251 nm. Analytical performance of the suggested HPTLC method was validated according to the ICH guidelines with respect to the linearity, accuracy, precision, detection and quantitation limits, robustness and specificity. The two drugs were satisfactory resolve with R_f values 0.57 ± 0.02 and 0.77 ± 0.02 for AMB and TEL, respectively. The linearity was studied in the concentration range 100–600 μg/ml for both AMB and TEL with a correlation coefficient (r^2) >0.9997 and 0.9999, respectively. Statistical analysis showed that the developed method is repeatable and selective for the estimation of AMB and TEL in its pharmaceutical formulations[14].

Santosh R. Butle, Padmanabh B. Deshpande developed and validated a new simple, accurate, precise and selective stability- indicating high performance thin layer chromatographic (HPTLC) method for simultaneous estimation of Telmisartan and Cilnidipine in combined tablet dosage form. The mobile phase selected was Toluene: Methanol: Glacial acetic acid (8: 2: 1, v/v/v) with UV detection at 260 nm. The retention factor for Telmisartan and Cilnidipine were found to be 0.38 ± 0.004 and 0.62 ± 0.007. The method was validated with respect to linearity, accuracy, precision and robustness. The drugs were subjected to stress condition of hydrolysis (acid, base), oxidation, photolysis and thermal degradation. Results found to be linear in the concentration range of 200- 1400ng band-1 and 50-600ng band-1 for Telmisartan and Cilnidipine, respectively. The method has been successfully applied for the analysis of drugs in pharmaceutical formulation. The % assay (Mean ± S.D.) was found to be 100.79 ±1.38 for Telmisartan and 99.55 ± 1.13 for Cilnidipine. The developed and validated stability indicating method can be used for assessing the stability of Telmisartan and Cilnidipine in bulk drug and pharmaceutical dosage form[15].

Aniruddha R. Chabukswar *et al* described an HPTLC method for the simultaneous determination of Telmisartan and Amlodipine Besylate from tablet dosage form. This employes a precoated silica gel 60 F254 (0.2 mm thickness) on aluminium sheets and a mobile phase Ethyl acetate: 1, 4 Dioxane: Methanol: 25% Ammonia in the ratio of 15:1.5:3:1.5 v/v, having chamber saturation for 30 min at room temperature. The developing chamber was run upto 8cm. The R_f values were found to be 0.16 and 0.33 for Telmisartan and Amlodipine respectively. The plate was scanned and quantified at 323nm. The linear detector response was observed between 100 μg/ml to 500 μg/ml and 200 μg/ml to 1000 μg/ml for Telmisartan and Amlodipine respectively. The method so developed was validated for its accuracy and precision. The

LOD and LOQ were found to be 0.025, 0.0747μg/ml and 0.0236, 0.0714μg/ml, respectively for Telmisartan and Amlodipine. The recovery was carried out by standard addition method. The Average recovery was found to be 100.38% and 100.24% for Telmisartan and Amlodipine respectively[16].

Ambadas R. Rote, Poonam R. Sonavane developed a simple, sensitive, rapid and economic high performance thin layer chromatographic method for determination of telmisartan and hydrochlorothiazide in human plasma using paracetamol as an internal standard. The plasma sample was extracted using mixture of methanol-acetonitrile (3.0:0.1,v/v). A concentration ranges from 200, 400, 600, 800, 1000, 1200 ng/spots were used for calibration curve of hydrochlorothiazide and telmisartan respectively. The percent recovery of telmisartan and hydrochlorothiazide was found to be 75.98% and 81.91%. The mobile phase consists of chloroform: methanol: toluene (8:2:4 v/v/v). Densitometric analysis was carried out at wavelength 278 nm. The R_f values for hydrochlorothiazide, paracetamol and telmisartan were 0.28 ± 0.05, 0.50 ± 0.05, 0.66 ± 0.05 respectively. The stability of telmisartan and hydrochlorothiazide in plasma were confirmed during three freeze-thaw cycles ($-20°C$), on bench during 24 hours and post preparative during 48 hours. The proposed method was validated statistically and by performing recovery study for determination of telmisartan and hydrochlorothiazide in human plasma[17].

Vrushali Tambe *et al* proposed a stability indicating HPTLC method for the simultaneous estimation of telmisartan and hydrochlorothiazide in bulk and tablet formulation. Well resolved chromatogram was obtained on TLC plates coated with silica gel 60F254 with densitometric detection at 233 nm. Two drugs were satisfactorily resolved with R_f 0.21± 0.02 and 0.53±0.02 for Telmisartan and Hydrochlorothiazide respectively. Linearity was found in the range of 0.18-5.76 μg / band (r^2 = 0.999) for telmisartan and 0.056- 1.6 μg/ band (r^2 = 0.999) for Hydrochlorothiazide. The % recovery for analytes were in the range of 98.5-101.6 % w/w. Drugs were subjected to stress conditions like acid, base, neutral hydrolysis, oxidative, photolytic and thermal stress[18].

UPLC Method

Reema H Rupareliya *et al* developed and validated a simple, precise and accurate RP-UPLC method for the simultaneous assay of Telmisartan and Cilnidipine in tablets. Isocratic RP-UPLC method was developed on LC system of Waters Acquity UPLC with PDA detector on Water Acquity BEH C18, 2.1 x 100mm, 1.7μm column as stationary phase with binary gradient mode by using mobile phase as ACN: 0.01M sodium phosphates monobasic dehydrate buffer pH 3.0 with phosphoric acid (68:32, v/v), at a flow rate of 0.5 ml/min and the detection was carried out at 245 nm. Forced degradation study was carried out by oxidation, hydrolysis, photolysis and heating the drug. The method was validated for specificity, linearity, precision, accuracy, robustness and solution stability. The method was found to be linear in the concentration range of 40-160 μg/ml with correlation coefficients of 0.9996 for Telmisartan and 10-40 μg/ml with correlation coefficients of 0.9995 for Cilnidipine. Degradation products produced as a result of stress studies did not interfere with the detection of Telmisartan and Cilnidipine: therefore, the assay can be considered to be stability-indicating[19].

V. Bhavani *et al* developed a simple, precise, accurate stability-indicating gradient reverse phase ultra-performance liquid chromatographic (RP-UPLC) method for the quantitative estimation of purity of Telmisartan drug substance and drug products in bulk samples and pharmaceutical dosage forms in the presence of its degradation products and impurities. The present method was developed using Waters Aquity BEH C18 (100 mm x 2.1 mm, 1.7 μ) column with mobile phase containing a gradient time programme of the solvents A and B. The wave length selected for monitoring eluted compounds were monitored at 290 nm, the run time was within 10 min, which Telmisartan and its seven impurities were well separated. Telmisartan was found to degrade significantly in acid stress condition when it was subjected for various stress conditions. The degradation products were well separated from main peak and its impurities, proving the stability-indication of the method. The present method was validated as per international conference on harmonization (ICH) guidelines with respect to precision, specificity, linearity, limit of detection, limit of quantification, accuracy, and robustness[20].

Vani. P and Kalyana seela. K. developed and validated a simple, isocratic rapid stability-indicating ultra- performance liquid chromatography (UPLC) method for the simultaneous quantitative determination of hydrochlorothiazide, ramipril and telmisartan present in tablets. Chromatographic separation achieved isocratically on Waters Acquity BEH Shield RP18 column (100 mm x 2.1, 1.7μm) column. The separation was achieved on simple Isocratic method. The mobile phase consisted of a mixture of 0.1% triethylamine at pH 3.5 with methanol and acetonitrile (3:2:5 v/v) and the flow rate was 0.15 mL/min. The column temperature was maintained at ambient and the detection was carried out at 215 nm. The retention times of Hydrochlorothiazide, Ramipril and Telmisartan are 1.5, 1.9 and 2.9 minutes respectively. The method was validated in terms of system suitability, linearity, precision, limit of detection, limit of quantitation and accuracy. The developed method was linear for hydrochlorothiazide, ramipril, telmisartan in the range of 6.2-18.7 μg/mL, 1.2- 3.7 μg/mL and 20-60 μg/mL respectively. The accuracy of the method was evaluated in the range of 80% to 120% in triplicate and the mean recoveries obtained for hydrochlorothiazide, ramipril, telmisartan were 99.7%, 99.6% and 100.3% respectively. Validation parameters such as specificity and robustness were also determined. The method was found to be rapid and stability-indicating, which can be applied for simultaneous quantitative determination of hydrochlorothiazide, ramipril and telmisartan present in combination tablets[21].

Seema Zargar and Tanveer A Wani developed and validated a simple, rapid, sensitive and specific ultra-performance liquid chromatography-tandem mass spectrometry method for quantification of the angiotensin II receptor antagonist, telmisartan (TMS) and hydrochlorthiazide (HCT) in human plasma. After a simple protein precipitation using methanol and acetonitrile, telmisartan, hydrochlorthiazide and internal standard (IS) irbesartan were separated on Acquity UPLC BEH™ C18 column (50 × 2.1 mm, i.d. 1.7 μm, Waters, USA) using a mobile phase consisted of acetonitrile-methanol-10 mM ammonium acetate-formic acid (50:30:20:0.1% v/v/v/v) pumped at a flow rate of 0.3 mL/min and detected by tandem mass spectrometry with negative ion mode. The ion transitions recorded in multiple reaction monitoring mode were m/z 513.2→287.14 for telmisar-tan, m/z 295.93→268.90 for hydrochlorthiazide and m/z 427.2→193.08 for irbesartan (IS). The assay exhibited a linear dynamic range of 1-500 ng/mL for both telmisartan and hydrochlorothiazide in human plasma with good correlation coefficient of (0.997) and with a limit of quantitation 1 ng/mL for both telmisartan and hydrochlorthiazide. The intra-and inter-assay precisions were satisfactory; the relative standard deviations did not exceed 11.68%. The proposed UPLC-MS/MS method is simple, rapid and highly sensitive, and hence it could be reliable for pharmacokinetic and toxicokinetic study in both animals and humans[22].

Titrimetric Methods

Fajrian Fajrian *et al* reported that Angiotensin II type 1 receptor antagonists were broadly employed to remedy diverse issues along with hypertension, coronary heart failure, myocardial infarction, and diabetic nephropathy. Telmisartan is a strong, long-lasting nonpeptide antagonist of the angiotensin II receptor type 1 that's the brand-new preference for the remedy of critical hypertension, with its very high lipophilicity, unique telmisartan features, plus a high volume of distribution, provides clinical advantages for penetration into target tissues and organs. Various analytical strategies are expanded in each biological fluid and dosage form to estimate the activity of the prescribed drug. This drug has been assigned within biological formulations and fluids by various methods according to spectrophotometry, high-performance liquid activity with ultraviolet and fluorimetry detection, liquid chromatography and tandem mass spectrometry, densitometry, immune test methods, ultra-performance liquid chromatography methods, titrimetric methods of analysis, and electrochemical methods such as voltammetry and polarography[23].

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