Study of Various Methods for the Analysis of Amlodipine and Telmisartan Combination Drug Used In Hypertension

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***Abstract*: In this paper we will study about all the methods which is developed for the analysis of Amlodipine and Telmisartan combination drug which is used in the treatment of hypertension.**

Introduction

Systemic arterial high blood pressure or hypertension (hereafter known as high blood pressure or hypertension) is characterized via way of means of constantly excessive blood strain i.e. Blood Pressure (BP) within side the systemic arteries. BP is generally expressed because the ratio of the systolic BP (that is, the strain that the blood exerts at the arterial partitions whilst the coronary heart contracts) and the diastolic BP (the strain whilst the coronary heart relaxes). The majority (90–95%) of sufferers have an especially heterogeneous 'essential' or primary high blood pressure or hypertension with multifactorial gene-surroundings aetiology. A wonderful own circle of relatives records is a common prevalence in sufferers with high blood pressure, with the heritability (a degree of the way a great deal of the version in a trait is because of version in genetic factors) anticipated among 35% and 50% within side the majority of studies.[1]

For the treatment of hypertension Angiotensin II receptor blockers (ARBs) are effective and well-tolerated antihypertensive agents that inhibit aldosterone production, vasoconstriction and sodium retention by blocking the renin–angiotensin–aldosterone system.[2,3,4] Telmisartan is a extremely selective ARB for the AT1 receptor and, as the withdrawal of this agent is ~24 h, one time in a day administration of telmisartan is resulted to diminish blood pressure (BP) for an entire 24 h.[5,6] Amlodipine, a calcium channel blocker (CCB), is another highly effective and long-acting antihypertensive agent that is widely used for hypertension treatment.[7] The current guidelines recommend that treatment with two or more antihypertensive agents is required to reach optimal BP for most hypertensive patients in order to lower cardiovascular risk.[2, 3]

Today's market is flooded with varieties of combination of drugs for treatment of diseases and simultaneous estimation of such combinations in single dosage form plays a very important role in field of analytical pharmacy. One such combination is Amlodipine and telmisartan, a single dose tablet available in the market for the treatment of Hypertension.

Simultaneous determination of amlodipine and telmisartan is performed by the UV spectrophotometry, RP-HPLC, HPLC, HPTLC, Capillary electrophoresis, TLC-Densitometry, spectrofluorimetry, LC- Tandem mass spectrometery in previous studies.

Various Methods for analysis of Amlodipine and telmisartan is given below in the table

Sr no	Method	Remark
1	RP-HPLC method for simultaneous estimation of telmisartan and amlodipine beslyate in Pharmaceutical dosage form.	The chromatographic analysis was performed by Hypersil BDS C18, 250 x 4.6 mm, 5 u particle size with mobile phase consisting of acetonitrile and phosphate buffer (pH 3.0) in the proportion of 60:40 v/v, at a flow rate of 1.5 ml/min and eluents observed at 237 nm. The retention times of amlodipine besylate and telmisartan were 5.884 and 10.987 min, respectively. The calibration curves of peak area versus concentration, which was linear from 8-48 u*g*/ml for telmisartan and 1-6 ug/ml for amlodipine besylate, had regression coefficient (r) greater than 0.999.[8]
2	Simultaneous spectrophotometric estimation of telmisartan and amlodipine in tablet dosage form.	Four new simple, accurate and precise spectrophotometric methods have been developed for simultaneous determination of telmisartan and amlodipine in pharmaceutical dosage form. Method A involves formation and solving of simultaneous equation using 299nm and 364nm as two wavelengths. Method B involves formation of Q-absorbance equation at 339nm (iso absorptive point) and at 299nm (max of telmisartan). Method C involves first order derivative method for simultaneous estimation of these two drugs. Method D involves the AUC for first order derivative spectrum. Both the drugs obey the Beer's law in the range 5 50pg/mL for amlodipine and 5-40ug/mL for telmisartan. The results of analysis have been validated statistically and by recovery studies.[9]
3	UV-Spectrophotometric Determination for Simultaneous Estimation of Amlodipine Besylate	Two simple spectrophotometric methods have been developed for simultaneous determination of Amlodipine besylate and Telmisartan in tablet formulation. Method 1 is Absorbance correction method that is based on diagnosis of Amlodipine besylate at 362 nm using its absorptivity value and Telmisartan at 292 nm. Method 2 is based on Absorbance ratio in which wavelengths selected were 326 nm, an isoabsorptive point and 292 nm as Amax of Telmisartan.

	and Telmisartan in Combination	Linearity was observed in the concentration range of 0.5-20, 0.5-15.5 ug/ml for AMLB and 3-24, 3-24 ug/ml for TELM by method A and B respectively. The methods can be routinely adopted for quality control of these drugs in tablet.[10]
4	Simultaneous Determination of Telmisartan and Amlodipine in Dog Plasma by LC-MS-MS	A simple, rapid and sensitive method was established for the simultaneous determination of telmisartan and amlodipine in dog plasma by a HPLC-MS-MS analysis. The plasma sample preparation was an easy deproteinization by the insertion of three volumes of methanol/acetonitrile mixture followed by centrifugation. The analytes and internal standard diphenhydramine were separated on a Zorbax SB-C18 column with a mobile phase of acetonitrile: water (45:55, v/v) at a flow rate of 0.2 mU/min with an operating temperature of 25°C. Observation was carried out by electrospray ionization in positive-ion multiple reaction monitoring mode. The calibration plots in dog plasma were linear over the ranges of 0.5–2,000 ng/mL for telmisartan and 0.5-500 ng/mL for amlodipine. The lower limit of quantification was 0.5 ng/mL for two analytes. The intra- and interday precisions (RSD %) were within 9.0%. The average recoveries of analytes were >85.0%.[11]
5	Simultaneous determination of amlodipine and telmisartan from pharmaceutical products by way of capillary electrophoresis	A Fast, easy and sensitive capillary zone electrophoresis method was proposed for the simultaneous determination of amlodipine besylate and telmisartan, in fixed-dose combinations, through the utilization of a UV photodiode array detector. Electrophoretic specification like buffer concentration and pH, system temperature, applied voltage and injection specification were enhanced in order to increase the efficiency of the separation. The best results were obtained when employing fused silica capillary (48 cm length X 50 um ID) and 50 mM phosphate buffer electrolyte at pH 4.50, + 25 kV applied voltage, as well as 25°C system temperature. The separation was achieved in approximately 3 minutes, with a resolution of 4.90, while the order of migration was amlodipine followed by telmisartan.[12]
6	Application of TLC-Densitometry Method for Simultaneous Estimation of Telmisartan and Amlodipine Besylate in Pharmaceutical Dosage form	A fast, particular and stability indicating HPTLC method was proposed and validated for simultaneous estimation of telmisartan and amlodipine besylate in pharmaceutical dosage forms. The method operated TLC aluminum plates precoated with silica gel 60F254 as the stationary phase. The solvent system consisted of tetrahydrofuran: dichloroethane: methanol: ammonia solution (3.0:1.0:0.5:0.2 *v/v*). This system was found to give compact spots for both telmisartan (*Rp* value of 0.22 = 0.02) and amlodipine besylate (*Rf* value of 0.45 = 0.02). Spectrodensitometric scanning-integration was performed at a wavelength of 326 nm. The polynomial regression data for the calibration plots showed good linear relationship with = 0.9993 in the concentration range of 1200 - 7200 ng for telmisartan and 400 - 1400 ng for amlodipine besylate with p = 0.9996.The minimum detectable amounts were found to be 149.41 ng and 53.07 ng for telmisartan and amlodipine besylate, respectively. The limits of quantitation were found to be 452.78 ng for telmisartan and 160.83 ng for amlodipine besylate.[13]
7	RP-HPLC method development and validation for simultaneous estimation of Amlodipine besylate and Telmisartan in tablet dosage form	Simultaneous Estimation of Amlodipine and Telmisartan were carried out by RP-HPLC using Phosphate buffer (PH 4.0): Acetonitrile (42:58) and column Phenomenex Luna C-18 (250*4.6 mm, 5um) as a stationary phase and peak was observed at 236 nm which was selected as a wavelength for quantitative estimation.[14]
8	HPLC Method Development for Telmisartan and Amlodipine	An easy, fast, and specific method is proposed for the quantitative simultaneous estimation of telmisartan and amlodipine in combined pharmaceutical dosage form. A chromatographic separation of the two drugs was attained with a Kromasil C18 (250 mm×4.6 mm, 5um) column using Acetonitrile: Methanol: Triethylamine buffer, PH 5.0 adjusted with O-Phosphoric acid. The instrumental settings are flow rate of 1.5 mL/min, and detector wavelength of 237 nm taking a variable wavelength detector. The resolution between amlodipine and telmisartan were calculated to be more than 5. Theoretical plates of amlodipine and telmisartan were 10547 and 6313. Tailing factor for amlodipine and telmisartan was 1.85 and 1.48 respectively. The described method shows great linearity over a range of 320–480 µg/ml for telmisartan and 50-60 µg/ml for amlodipine. The correlation coefficient for telmisartan and amlodipine are 0.9999. The relative standard deviation for six measurements in two sets of each drug in tablets was always less than 2%.[15]
9	Development and validation of novel HPTLC method for the simultaneous estimation of Amlodipine Besylate and Telmisartan in tablet dosage form using ICH Q2 (R1) directions	An easy, specific, accurate, correct and robust normal phase HPTLC method were proposed and validated 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 achieved at 251 nm. The two drugs were satisfactory resolve with R*f* values 0.57 +0.02 and 0.77 +0.02 *f*or AMB and TEL, respectively. The linearity was studied in the concentration range 100-600 *u*g/ml for both AMB and TEL with a correlation coefficients >0.9997 and 0.9999, respectively.[16]

10	Validated RP-HPLC method for simultaneous estimation of telmisartan and amlodipine	An easy, sensitive and rapid reverse phase HPLC method was proposed for the simultaneous estimation of Telmisartan and Amlodipine. AnHypersil BDS 100mm x 4.6 mm, 5u column was used. The mobile phase contains Phosphate buffer (pH 3.5): Acetonitrile taken in the ratio 57: 43 that was set at a flow rate of 1.0 mL/min, the column temperature was maintained at 30°C and the measurements were made at *237* nm. The retention times of Telmisartan and Amlodipine were found to be 2.560 and 3.148 min, respectively.[17]
11	Simultaneous Estimation of Amlodipine Besylate and Telmisartan by UV-Spectrophotometry	Three different easy, accurate, economic, specific and reproducible spectrophotometric methods are proposed for simultaneous estimation of telmisartan and amlodipine besylate in combined tablet dosage form. First proposed method includes formation and solving of simultaneous equation at 297.0 nm for estimation of telmisartan and amlodipine besylate is estimated from the calibration curve at 362.0 nm. Second developed method makes by using absorbance ratio method at 324.0 nm as isobestic point. Third proposed method is based on first derivative spectroscopy using 236.0 nm as zero crossing point. Methanol and 0.1 N sodium hydroxide in the ratio 5:5 was used as solvent for all above methods. All the proposed methods comply Beer's law in the concentration ranges employed for the respective methods.[18]
12	Simultaneous Estimation of Telmisartan and Amlodipine in Tablet Dosage Form by RP-HPLC	A reverse phase HPLC was proposed for the simultaneous estimation of telmisartan and amlodipine in tablet formulation. The separation was achieved by Luna C_{18} column and phosphate buffer pH 3.0 and acetonitrile (60:40v/v) as mobile phase, at a flow rate of 1.0mL/min. Detection was carried out at 251 nm. Retention time of telmisartan and amlodipine was calculated to be 4.427min and 2.643min respectively. The mean recoveries obtained for telmisartan and amlodipine were 102.4% and 101.6% respectively.[19]
13	Simultaneous Spectrophotometric Estimation of Telmisartan and Amlodipine Besylate in Tablet Dosage Form	Easy, accurate and reproducible spectrophotometric methods have been proposed for the simultaneous estimation of Telmisartan (TEL) and Amlodipine Besylate (AML) in combined tablet dosage forms. The method involves determination using the simultaneous equation method, the sampling wavelengths selected are "TLM = 297nm.and 'AML =238 m., over the concentration ranges of 8-48u g/ml for *TEL and 1-6 ug/ml for AML" respectively.[20]
14	Development and Validation of a Reversed Phase HPLC Method for Simultaneous Determination of Amlodipine and Telmisartan in Pharmaceutical Dosage Form	An easy, accurate and specific method for the simultaneous determination of amlodipine and telmisartan in bulk drug and pharmaceutical dosage has been developed by RP-HPLC method. Separation was performed on a 5um Nucleodur® C18 column (250 4.6mm ID) with acetonitrile: phosphate buffer at pH 4.5 (60:40v/v) in isocratic elution in less than 9 min with a flow rate of 1.3 ml min-1. Good sensitivity for all analytes was observed with UV detection at 238 pm. The method allowed quantification over the 1-11 ug ml-1 range for amlodipine and 8-80 ug ml-1 range for telmisartan.[21]
15	Method development and validation for the simultaneous determination of amlodipine besylate and telmisartan in tablet dosage form by RP-HPLC	An easy, correct and precise method for the simultaneous determination of amlodipine besylate and telmisartan in bulk drug and pharmaceutical dosage has been developed by RP-HPLC method. Separation was performed on a 5um Prontosil C18 column (250 x 4.6mm ID) with methanol: potassium dihydrogen phosphate buffer at pH 4.5 *(*75*:*25*v*/v), flow rate of 1.4 *ml/* min and UV detection wavelength 240 nm. The calibration of the method was performed by concentration range of 2-20ug/ml for amlodipine and 16-160 ug/*m*l for telmisartan.[22]
16	Analytical method development and validation and force degradation studies for simultaneous estimation of amlodipine besylate and telmisartan in tablet dosage form by using RP-HPLC	The chromatographic analysis was performed on Athena C18 column (250x4.6mm, 5 u particle size) with mobile phase consisting of methanol and phosphate buffer (pH 4) in the ratio of 70:30 *v*/v, at a flow rate of 1 mL/min and eluents monitored at 240 nm. The retention times of amlodipine besylate and telmisartan were 2.3 and 3.4 min, respectively. The calibration curves of peak area versus concentration, which was linear from 2.5-15 ug/mL for amlodipine besylate and 20-120 ug/mL for telmisartan, had regression coefficient (12) greater than 0.998.[23]
17	Development and Validation of Multi-Component Mode UV Spectrophotometric Method for the Estimation of Telmisartan and Amlodipine besylate in Combined Dosage Form	An easy, accurate, precise and specific UV spectrophotometric method for Multicomponent Mode of Amlodipine besylate and Telmisartan in combine dosage form has been proposed. The wavelengths 238 nm and 295 nm were selected for estimation of Amlodipine besylate and Telmisartan respectively, where Methanol was used as solvent. Linearity were observed in the concentration range of 2-30 µg/ml (r2=0.9999) and 2-25 µg/ml (r2=0.9994) for Amlodipine besylate and Telmisartan.[24]
18	HPLC Method Development for	An easy, fast and precise method is proposed for the quantitative simultaneous estimation of telmisartan and amlodipine in combined pharmaceutical dosage form. A chromatographic separation of the two drugs was attained with a Kromasil C18 (250 mm×4.6 mm, 5um) column

	Telmisartan and Amlodipine	by using Acetonitrile: Methanol: Triethylamine buffer, PH 5.0 adjusted with O-Phosphoric acid. The instrumental settings are flow rate of 1.5 mL/min, and detector wavelength of 237 nm by using a variable wavelength detector. The resolution between amlodipine and telmisartan were calculated to be more than 5. Theoretical plates for amlodipine and telmisartan were 10547 and 6313 respecitively. Tailing factor for amlodipine and telmisartan was 1.85 and 1.48 respectively. The described method shows great linearity over a range of 320–480 µg/ml for telmisartan and 50-60 µg/ml for amlodipine. The correlation coefficient for telmisartan and amlodipine are 0.9999. The relative standard deviation for six measurements in two sets of each drug in tablets was always less than 2%.[25]

Validation of above various method is done by as per the ICH guideline or by the various validation parameter like accuracy, precision, ruggedness, specificity, robustness, linearity, limit of detection, limit of quantification or by doing statical analysis.

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