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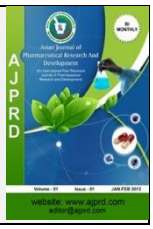

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Review Article

A Review on Simultaneous Determination of Anti-Hypertensive Drug Combinations Containing Amlodipine Besylate using Chromatographic Analysis

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A B S T R A C T

The present review aims to investigate some of the recently reported analytical methods available for the assay of antihypertensive drugs in various combinations of pharmaceutical forms. Several simultaneous RP- HPLC methods have been reported for the determination of antihypertensive drugs. The review familiarizes various reported methods for the simultaneous determination of Amlodipine besylate with other antihypertensive drug formulations which are used in combination treatment protocols.

Keywords: Analytical Methods, RP-HPLC, Anti-hypertensive drugs, Simultaneous determination.

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INTRODUCTION:

Although high blood pressure may be a leading reason for death among elderly population, it is increasingly affecting younger individuals in the recent past due to changing lifestyle and stress of contemporary living [1,2]. Nearly 25% of the world's population suffers from high blood pressure related illness and numbers added to this group is predicted to climb in coming years. The proportion could magnify to 30% by 2025 as per the present estimate [3]. In order to manage or treat this life-threatening condition, various medications are available in a variety of forms. Management of high blood pressure by calcium containing formulations is the most ordinarily prescribed medication. In chronic patients who do not make effective lifestyle changes to alleviate the condition or respond well, monotherapy treatment sometimes fails, and the alternative treatment protocol available is combination therapy. The combination drug therapy using four categories of medication namely angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, diuretics and calcium (Ca) channel blockers can effectively control the hypertension scenarios [4].Using such multiple drug action mechanisms, superior high blood pressure management can be achieved [5].

The long-acting calcium channel blocker vasodilator, Amlodipine (AML) is generally used as Ca channel blocker for the treatment of high blood pressure, coronary failure, and angina. Telmisartan (TEL), Olmesartan (OLM), and Irbesartan (IRB) together with various other alternative medicines and diuretics are other options to treat high blood pressure heart conditions[4,6-7].

For treating high blood pressure, angiotensin-II receptor blocking (ARBs) agents are highly effective and these drug agents are well tolerated with pharmacological effect of inhibiting mineral corticoid production and constriction and retention by blocking the rennin-angiotensin aldosterone system [8-10]. Telmisartan is a very selective binder for the AT1 (angiotensin II type 1) receptor. As the elimination of this agent is approximately 24 h, once in a day administration of telmisartan result to diminish blood pressure (BP) for a whole duration of 24hours [11-12].

Amlodipine, a calcium channel blocker (CCB), is another highly effective and long-acting pharmaceutical agent that is widely used for high blood pressure management [13].In today's market, combination of various active pharmaceutical ingredients is available for the treatment of hypertension condition, and simultaneous estimation of such combos in single- dose type plays a vital role in the field of analytical chemistry and pharmaceutical industry.

The various drug combinations for hypertension management are listed in Table-1. One such combination is Amlodipine and Telmisartan, a one dose pill accessible within the marketplace to treat cardiovascular disease [15]. The various ways of combination therapies available for chronic hypertensive conditions are listed in the table below (Table-1).

Table 1: Classification of Antihypertensive Drugs [14]

Class	Name of Drugs
Angiotensin II receptor blockers	Candesartan, Olmesartan, Telmisartan, Eprosartan, Losartan, Irbesartan, Valsartan
Angiotensin Converting Enzyme inhibitors	Lisinopril, Trandolapril, Captopril, Perindopril, Fosinopril, Enalapril, Ramipril, Quinalapril
Loop diuretics	Furosemide
Thiazide diuretics	Indapamide, Bendroflumethiazide, Chlorthalidone
Calcium channel blockers	Dihydropyridine, Amlodipine, Verapamil, Nor-dihydropyridine, Nisoldipine, Nifedipine, Femodipine, Lercanidipine
Vesodilators	Nitropruside
Renin-inhibitors	Aliskiren
Sympatholytics	Methyldopa, Clonidine
Selective α adrenoreceptor antagonist	Doxazosin, Prazosin
Non-selective α antagonist	Phenoxybenzamine, Phentolamine
β-adrenoreceptor antagonist	Nebivolol, Carvedilol, Labetalol, Propranolol, Bisoprolol, Atenolol, Metoprolol

The information helps to comprehend the pharmacological interventions made with various drug combinations to control the acute high blood pressure scenario. However, few of the combinations are mentioned in the ongoing discussion. The review discusses various analytical methods available for Amlodipine and Telmisartan combination followed by various other Amlodipine combinations.

Simultaneous determinations of Amlodipine and Telmisartan

In a reported method, analysis was carried out by using Hypersil BDS C18, 250 x 4.6 mm,5µ with mobile phase along with acetonitrile and phosphate buffer (pH 3.0) within the proportion of 60:40 v/v, at a flow rate 5 ml/min and eluents determined at 237 nm. The retention time of Norvasc (Amlodipine besylate) and Telmisartan were 5.0 and 1.0min respectively. The standardization curves of concentration against peak space, which was linear from 8-48 ug/ml for Telmisartan and 1-6 ug/ml for Amlodipine besylate, had parametric statistic (r) larger than 0.999[16].

In another investigation, simultaneous estimation of Amlodipine besylate and Telmisartan HCl combination was developed by RP-HPLC under phosphate pH buffer (pH 4.0). Acetonitrile (42:58) and column Phenomenex C-18 (250 x 4.6 mm, 5 µ) as a stationary section and peak determined at 236 nm, which was the selected wavelength for quantitative estimation. The molecules were eluted at retention times of 4.32 and 5.32 minutes for Telmisartan and Amlodipine respectively. Linearity studies showed a relationship in the concentration range 2.5 to 15 µg/ml and 20 to 120 µg/ml for Amlodipine Besylate and Telmisartan, with 0.999 and 0.998 as the value of correlation coefficient for the both drugs respectively [17].

In another study, an easy, sensitive and fast reverse phase HPLC methodology was projected for the synchronic estimation of Telmisartan and Amlodipine besylate. A Hypersil BDS 100mm x 4.6 mm, 5µ column was used successfully for this analysis. The mobile section contains phosphate buffer (pH 3.5): acetonitrile was taken within the quantitative relation of 57:43; set at a flow rate of 1.0 mL/min, the temperature of the column was 30°C and the measurements were recorded at 237 nm. The retention times of Telmisartan and Amlodipine found to be a pair of2.560 and 3.148 min respectively[18].

A reverse phase HPLC was used for the synchronic estimation of Telmisartan and Amlodipine besylate in pill formulation. The sepa ration was brought by Luna C18 column and mobile phase containing phosphate buffer hydrogen ion concentration (60:40v/v), with 1.0mL/min the flow rate maintained. Detection wavelength was set at 251 nm at ambient condition. The retention time achieved for Telmisartan and Amlodipine was at 4.27min and 6.43min respectively. The mean recoveries obtained for Telmisartan and Amlodipine were 102.4% and 101.6% respectively [19].

An accurate, easy and definite method has been developed by RP-HPLC for the synchronic determination of Amlodipine and Telmisartan in bulk drug and pharmaceutical dosage form. Sepa ration performed on a 5µm Nucleodur C18 column (ID being 250 4.6mm) with mobile phase combination of acetonitrile: phosphate buffer with pH stabilized at4.5 (60:40v/v). The methodology was based on isocratic elution with observed retention of Amlodipine at 3.49 min and Telmisartan at 8.40 min with a flow rate maintained at 1.3ml/min[20].

Another reliable method for the determination of Norvasc (Amlodipine) and Telmisartan combination in bulk drug and formulated pharmaceutical dose has been developed by reverse phase-HPLC method. The column used for analytical sepa ration was a 5µm Prontosil C18 column (250 x four.6mm ID) with mobile phase combination of methanol: metal dihydrogen phosphate buffer at pH value of4.5 (75:25v/v), under a flow rate of 1.4 ml/ min and UV detector set at a wavelength of 240 nm[21].

In another method development, Athena C18 column (250x4.6mm, 5µ) was used for analysis with mobile phase consisting of wood spirit and phosphate buffer (pH 4) within the quantitative relation of 70:30 v/v, at a flow of 1mL/min and analytes detected at 240 nm. The retention times of Norvasc and Telmisartan were established at 1.3 and 3.4 min respectively. Linearity was exhibited for a sample volume of5-15 ug/mL for Norvasc and 20-120 ug/mL for Telmisartan with parametric statistic (12) larger than 0.998, when the standardization curves of concentration versus peak area was analyzed[22].

In another reported method development on HPLC, a novel, rapid and accurate isocratic method was developed for the combination tablet of telmisartan and amlodipine. The reverse phase chromatographic method was carried out on Symmetry C18 (250 x 4.6 mm, 5 µm) column with a mobile phase consisting acetonitrile and phosphate buffer of pH 6 in the ratio of 60:40, v/v. The flow rate was maintained at 0.8 ml/min, where the eluents were detected at 243 nm. The retention time for Telmisartan and Amlodipine with a linearity range of 16-48 µg/mlf and 2-6 µg/ml were recorded at 3.209 min and 5.351 min respectively. The correlation coefficient values were found to be 0.999.The developed method showed percentage recoveries of 98.01-101.62% and 99.30-101.40% for Telmisartan and Amlodipone respectively [23].

An HPLC analytical method, which is fast, simple and precise, was developed for Amlodipine besylate and Telmisartan HCl in bulk drug and tablets were developed. The HPLC system used was Younglin HPLC - ACME-9000 loaded with Phenomenix C18 (250 × 4.6 mm, 5 µm) column to bring the needed sepa ration. The sepa ration was effective on a mobile phase combination of 40:35:25 v/v/v, (0.02 M ammonium phosphate buffer: acetonitrile: methanol) with 1 mL/min flow rate maintained. The with UV detector at 254 nm recored Amlodipine besylate at an elution time of 2.65 min and Telmisartan HCl at 4.96 min. The method showed acceptable linearity and recovery values [24].

Other Amlodipine besylate combinations:

Different chromatographic methods were reported for Amlodipine besylate with other drug combinations for the management of hypertension.

In one of the earlier methods reported for Losartan and Norvasc (Amlodipine) estimation, anRP–HPLC technique with Microsorb-MVRP C-18 Column (100-5, 250 x 4.6 mm) was used. The method employed 0.02% triethylamine in water:acetonitrile (60:40) as mobile phase, with pH adjusted to 2.5 with O- phosphoric acid and was maintained at a flow rate of 1.0 ml/min. The analytes were detected at 226 nm wavelength at retention time for Losartan and Norvasc at 2.32 and 10.10 min, respectively. The method exhibited all the required assay acceptance criteria with linearity range for Losartan and Amlodipine determined as 50- 500 µg/ml and 5-50 µg/ml, respectively[25].

A fast and steady HPLC approach was established for the simultaneous estimation of Amlodipine besylate and Valsartan in their mixed combinations during drug dissolution investigation. A C18 column (ODS a pair of, 10 µm, 200 x 4.6 mm) and a mobile phase mixture of acetonitrile: alcohol (46:44:10 v/v/v) with pH stabilized with phosphate buffer (pH 3.6, 0.01/L) was employed for sepa ration and quantitation. Analyses were carried out at 1ml/min flow rate. The injection method used 20µL with UV detector value at 240 nm. Under the above set analytical parameters, Amlodipine eluted at 7.1 min whereas Valsartan eluted at3.4 min [26].

RP-HPLC technique for simultaneous estimation of Norvasc (Amlodipine besylate) and Olmesartan Medoxomil (OLM) from a pill were reported. The best resolution of the two drug molecules were realized with the mobile phase combination of acetonitrile and water with a ratio relation maintained at60:40. The method showed exceptional response for Olmesartan Medoxomil and Amlodipine besylate for an injection volume range of 5-35 µg/ml. Very effective resolution of the two medicines and internal standard was achieved under the optimized condition. For the detection of the drug combinations, 248 nm was chosen as the appropriate wavelength with the needed sensitivity. The analysis results showed excellent recoveries for each medicine molecules starting from 99.75% to 100.62% for Olmesartan Medoxomil and 98.91% to 102.05% for Amlodipine Besylate [27].

For a pill formulation of Amlodipine besylate and Metoprolol tartrate, a quantitative method was established on a reverse phase HPLC. In an isocratic mode, the quantification was performed on a RP stainless-steel column (ODS C18 250 x 4.6 x 5 µL) packing with mobile phase combination of0.03 M phosphate buffer and acetonitrile. The wavelength set for the successful detection of the eluents were at 230 nm. The method exhibited excellent linearity in the range of 8-12µg/ml for drug combination [28].

Mhaske et al. reported simultaneous analysis of quaternary drug Amlodipine Besylate, Valsartan, Telmisartan and diuretics Hydrochlorothiazide and Chlorthalidone which is a commercially available anti-hypertensive drug combination by RP-HPLC method with UV-Visible detector set at 220 nm. The method was developed on a Cosmosil PAQ (150 mm × 4.6 mm) 5 µm column under gradient flow programme containing acetonitrile and 0.05 M sodium dihydrogen phosphate buffer [29].

In another communication, a RP- HPLC method was developed for the assay of Telmisartan, Ramipril, Amlodipine besylate, and Atorvastatin calcium which was precise, rapid and accurate. The method was carried out on a BDS Hypersil C18 (250 × 4.6 mm, 5 µm ID) column with

detection at 205 nm. The mobile phase contained 0.025 M potassium dihydrogen phosphate (pH 6.0): acetonitrile = 60:40, v/v on an isocratic mode which exhibited retention time within 8 minutes. The method offered excellent linear relationship in concentration ranges of 10–60, 16–96, 10–60, 10–60 µg/ml and recovery percentages 100.06, 100.85, 99.54, 100.8% for Ramipril, Telmisartan, Amlodipine besylate, and Atorvastatin calcium respectively [30].

A precise and simple simultaneous analytical reverse phase high performance liquid chromatographic (RP-HPLC) method was developed for Hydrochlorothiazide, Amlodipine besylate and Telmisartan hydrochloride in a tablet dosage form and in biorelevant media. The validated method used Thermosil C18 (4.6 Ã— 100 mm ID, 3.7 µ particle) column with mobile phase combination of 40% (v/v) 20 mM potassium dihydrogen orthophosphate buffer and 60% (v/v) methanol over a flow rate of 1.0 ml/min. At 248 nm UV wave length, the retention times were 1.8, 2.6, and 4.2 min for Hydrochlorothiazide, Amlodipine besylate and Telmisartan hydrochloride respectively. The method showed acceptable linear response for the analytes [31].

Another ICH guideline based method in which reverse phase high performance liquid chromatographic (RP-HPLC) method for simultaneous analysis of Hydrochlorothiazide (HTZ) and Amlodipine besylate (AML) present in combination tablet formulation was developed. The validated method employed Thermosil C18 (4.6 × 100 mm i.d., 3.7 µm particle) column and mobile phase with 35:65 (v/v) 20mM potassium dihydrogen orthophosphate buffer and methanol. The flow rate of 1.0 ml/min was set to obtain elution time 1.823 and 2.639 min for Hydrochlorothiazide and Amlodipine besylate which was detected at UV wave length of 248 nm. Standard calibration graphs were linear over the range of 6.25-100 µg/mL for Hydrochlorothiazide and 2.5-40 µg/mL for Amlodipine besylate. The method afforded the required statistical support during the development and found to be rapid and sensitive [32].

In another investigation, a highly reliable and fast reverse phase high performance liquid chromatographic methodology was developed to analyze Enalapril and Amlodipine in combined pharmaceutical tablet formulation. The method employed C18 column (4.6x250 mm ID., particle size of 5 µm) with the injection volume of 5 µL, and the detection wavelength 215 nm. The mobile phase used was 10% methanol, pH of 2.95 maintained, and flow rate of 1.205 mL/min. The reported retention times for the developed method were 3.8 min and 7.9 min for Enalapril and Amlodipine, respectively over a total run time of 10 min. The method was found to be linear in the range of 0.8-24 µg/mL (R2 >0.999) and 1.6-48 µg/mL (R2 >0.999) for Amlodipine and Enalapril, respectively. Assay values on recovery studies showed the range of 98.6%-101.6% [33].

In another analytical method development of three drug combination, a reliable high-performance thin-layer chromatography was reported for the assay of Telmisartan, Amlodipine and Chlorthalidone in various dosage forms. The analysis was successfully brought about on Merck TLC Aluminum plates, with silica gel 60 F254 of size (20 cm × 10 cm) precoated with a layer of 250 µm thickness. The mobile phase employed was Chloroform: Toluene: Methanol: Glacial Acetic Acid (6:2:2:0.1 % v/v/v/v). Exceptional linearity was achieved for all the three analytes with the detector wavelength at 254 nm [34].

In another analytical work reported for the combination formulation in bulk and dosage form of Amlodipine besylate, Telmisartan and Hydrochlorthiazide, a well resolved sepa ration was obtained with C18 Kinetex column (250 × 4.6 mm, 5 µ). The method used mobile phase of acetonitrile: 20mM phosphate buffer (pH 3.0) (60:40 %, v/v) with flow rate maintained at 1 mL/min with detection wave length at 258 nm. Accepted levels of linearity and recovery was shown by the reported method [35].

An Ultra Performance Liquid Chromatography (UPLC) method has been reported by Bhavin et al. for simultaneous estimation of Amlodipine besylate, Hydrochlorthiazide and Telmisartan formulation used for combination therapy. The successful sepa ration was brought about by using stationary phase of aluminum plates pre-coated with silica gel 60F254 and the mobile phase combination consisting of chloroform: butan-1-ol: ammonia (6: 4: 0.1, v/v/v). The detection method used was spectro-densitometry at 254 nanometers. Excellent linear response was achieved with correlation coefficient r2 = 0.9952, 0.9992 and 0.9979 for Amlodipine besylate, Hydrochlorothiazide and Telmisartan respectively. The range of concentration having 200-1000 ng/band, 500-2500 ng/band and 1600-8000 ng/band was used during the above method development [36].

In another investigation using ICH guideline, highly selective and rapid reverse phase-HPLC technique was reported for the simultaneous analysis of Esidrix (Hydrochlorothiazide), Norvasc (Amlodipine besylate) and Telmisartan in pill formulation. The wavelength for the quantitation was at 239 nm. The mobile phase solvent combination used was acetonitrile, alcohol and water. The mobile phase pH at 3.2 was stabilized with 0.05M dihydrogen ortho-phosphate, acetonitrile and alcohol within the ratio relationship of 45:45:10.The above method could attain efficient sepa ration with the column, Supelco C18 (250 x four.6 mm, 5µ). The flow rate was maintained at 1mL/min for which the retention time for Hydrochlorothiazide, Amlodipine besylate and Telmisartan was recorded at 9.0 min, 5.1min and 8.2min respectively. The method showed excellent linearity response and recovery values[37].

In another investigation for simultaneous estimation, a new technique has been established with Shimadzu HPLC system for Telmisartan and Atorvastatin calcium by reverse phase technique. Method was successfully employed for the estimation of Telmisartan and Atorvastatin calcium by employing Boston ODS C18 column under the mobile phase combination of methanol: acetonitrile: buffer (35:25:40) with flow rate of 1.0 ml/min. The detection wavelength used was 235 nm. The retention values recorded for Atorvastatin calcium and Telmisartan was found to be 2.3 min and 3.4 minutes respectively. The method expressed good acceptance levels [38].

In another analytical estimation, a rapid and reproducible HPLC method was established for the combined solid oral dosage form of Amlodipine, Bisoprolol and Enalapril and validated as per ICH guidelines. The method utilized Agilent 1260 instrument fitted with A C18 column (Phenomenex Polar Synergi, 5 µm, 4.6×50 mm) for sepa ration and quantification. The mobile phase run at flow-rate of 1.0 ml/min and in ambient temperature consisted of methanol: phosphate buffer solution (65:35, v/v). The ultraviolet detector was set at 240 nm. Under these conditions, the elution times were 0.85 min for Bisoprolol fumarate, 1.89 min for Amlodipine and 1.09 min for Enalapril maleate, bringing the overall sepa ration time less than 2.5 min. The method offered good linearity response and assay recoveries [39].

In another communication of analytical method development, which claimed to be green, sensitive, and accurate used fluorescence detection methodology. The validated method was for simultaneous determination of Amlodipine besylate and Celecoxib in one of the recently approved fixed-dose combination tablets. The sepa ration was achieved at at 40°C on reverse-phase C18 column (Thermo ODS Hypersil, 4.6 × 250 mm, particle size 5 µm) using acetonitrile: potassium phosphate buffer (50 mM; pH 5.5, 60:40 v/v) as a mobile phase. The elution rate was 1 mL/min where detection was carried out with excitation and emission wavelengths of 360 and 446 nm for Amlodipine and 265 and 359 nm for Celecoxib, respectively. Sepa ration of the two drugs was successful with retention times 4.41 min and 7.30 min for Amlodipine and Celecoxib, respectively. The method was linear over a concentration range of 0.05-2 and 0.05-10 µg/mL for Amlodipine and Celecoxib, respectively [40].

A reverse phase-high performance liquid chromatography (RP-HPLC) method was developed for the combined tablet form of Amlodipine besylate and Celecoxib. The method developed on Flowrosil C18 analytical column (250 × 4.6 mm, i.d., 5 µm) exhibited accuracy and pecision and speed. The mobile phase was constituted with acetonitrile and water with 80:20 volume ratio which was pumped by isocratic elution at a flow rate of 1 mL/min. Amlodipine besylate and Celecoxib were detected at 250 nm with retention time at 1.98 and 3.15 min respectively. The linear calibration curves were obtained at concentration ranges of 2-12 µg/ml (Amlodipine besylate) and 50-300 µg/ml (Celecoxib). The recoveries were acceptable with the ranges, Amlodipine besylate between 99.46–101.36% and Celecoxib between 99.57–101.42%. The ICH guideline based method showed needed specificity, robustness, limits of detection and quantitation [41].

A fast, precise, simple and simultaneous RP-HPLC method was reported by Ahmad et al. for the analsis of combination drug, Amlodipine and Bisoprolol in its bulk form. The method recorded at 230 nm showed retention time of 3.49 and 6.52 min for Amlodipine and Bisoprolol respectively. The mobile phase was a mixture of a methanol and water (0.1% OPA) in the ratio of 65:35 v/v) on ambient conditions. The method afforded linerity rage over 5-25 µg/ml for both the drug miolecules. The analysis was performed on Agilent instrument mounted with C 18 (250 mm× 4.6 mm) column with packing of particle size 5µm. Standard calibration plots yielded correlation coefficient 2 (r) 0.999 for both drug molecules with a recovery of around 100% [42].

A reverse phase HPLC method has been developed for the simultaneous determination of Candesartan and Amlodipine in bulk and pharmaceutical dosage form which is rapid, specific and sensitive. The method employed isocratic sepa ration using C18(150 x 4.6mm, 5µ) column with mobile phase containing water and methanol (10:90 v/v). The retention time for the analytes, Candesartan was at 3.5min and Amlodipine at 1.17min at a flow rate of 1ml/min and the wavelength was at 355nm. The method exhibited required robustness, specificity, precision, accuracy and linearity. Linearity with the coefficient of correlation for Candesartan and Amlodipine was 0.997 and 0.998 respectively. Assay estimation showed candesartan is 99.5% and amlodipine is 100.3% as recovery values [43].

In a recent report, a rapid and synchronized chromatographic method for the estimation of combination drugs, Hydrochlorothiazide, Amlodipine, Olmesartan, Telmisartan, and Irbesartan, in binary and ternary co formulations was established. The same method could bring about the sepa ration under same parametric conditions. Five analytes were separated with a mobile phase combination of acetonitrile, methanol, and 20 mM phosphate buffer (pH 3.5) in a ratio of 45:20:35% v/v on a Zorbax C18 column using isocratic elution. The flow rate was maintained at 1.5 ml/min where complete elution of analytes occurred within 3.4 min, on a UV wavelength of 230 nm. The percentage assay obtained was in the range of 98% to 102% for all the analytes. The method offered good linearity in the concentration of 2–30 µg/mL for Hydrochlorothiazide, 1–15 µg/mL for Amlodipine, 5–160 µg/mL for Olmesartan and Telmisartan and 10–300 µg/mL for Irbesartan [44].

In another work, Sanap et al developed a novel reverse phase HPLC method was developed for Telmisartan, Amlodipine besylate and Chlorthalidone drug combination. The instrument used was Shiseido Model LC-2030 PLUS(IND) System loaded with Kromasil C8 4.6 mm x 250 cm, 5µ column with mobile phase mixture of potassium dihydrogen orthophosphate and acetonitrile, flow rate maintained at 1.0mL/minute. The detector was set at 228nm.The method showed good response for a linearity range 80 to 280 ppm for Telmisartan, 25 to 87.5 ppm for Chlorthalidone and 10 to 35 ppm for Amlodipine. The accuracy data obtained showed recoveries of 100-101% for Amlodipine, 100.1-100.5% for Telmisartan and 99.6-100% for Chlorthalidone [45].

In another analytical investigation based on ICH guidelines, a RP-HPLC method was developed for accelerated degradation studies for a combination of Atorvastatin and Amlodipine in tablet form. With a mobile phase containing 0.02 M potassium dihydrogen phosphate: acetonitrile: methanol (30:10:60 v/v/v) stabilized at pH 4, well resolved sepa ration was obtained with Octadecylsilane-C18 (5 µm, 25 cm × 4.6mm) column. The retention time reported was 8.32 min and 11.09 min for Amlodipine and Atorvastatin respectively. At the detector wavelength at 244 nm, the authors could

obtain a linearity values between 05 - 30 µg/ml for both drugs with regression coefficient equation 0.995 and 0.999 for Amlodipine and Atorvastatin respectively [46].

An simple and reliable isocratic RP-HPLC method was developed for the simultaneous determination of Hydrochlorothiazide, Amlodipine besylate, and Telmisartan in bulk and tablet dosage form using statistical experimental design. The method was developed on a Shimadzu HPLC having detector wave length set at 237 nm. The mobile phase flow rate maintained at 1.2 ml/min had the combination of acetonitrile: 1% triethylamine buffer (pH 3.0) 47.15:52.85%v/v. The results were linear with the concentration range of 10 to 50 µg/ml for Hydrochlorothiazide, 4 to 20 µg/ml for Amlodipine, and 32 to 160 µg/ml for Telmisartan with the acceptable recovery values [47].

In another novel study, a sensitive, robust, cost-efficient and stable thin layer chromatographic (TLC) technique was established for quantitative estimation of Celecoxib and Amlodipine besylate from a prepared combination using TLC silica gel 60 plates. The detection was performed under fluorescent (FL) detection with 264 nm as wave length. The mobile phase under which effective sepa ration obtained was a combination of alkyl acetate: dimethylamine: 1-propanol (9:1:0.2, V/V). The retention value for drugs were at recorded at 0.80 ± 0.03 and 0.44 ± 0.01 for Celecoxib and Amlodipine besylate respectively[31]. The method could estimate the binary mixture samples and forced degradation samples with required sensitivity [48].

The RP-HPLC method developed by Mistry et al. demonstrated a precise and simple method for the estimation of drug combination Amlodipine Besylate, Telmisartan and Rosuvastatin. The reversed-phase method used Luna C18 100Å column (250 mm × 4.6mm ID, particle size 5 µ) with an isocratic mobile phase combination of methanol and acetonitrile (pH 3.5 adjusted by orthophosphoric acid) (60:40 v/v) maintained at 1.0 ml/min flow rate. At 242 nm UV detection wavelength 7.44, 4.70 and 2.67 min were the retention times exhibited for Amlodipine besylate, Rosuvastatin calcium and Telmisartan respectively. The linearity (correlation coefficient >0.999) obtained from the calibration curve for concentration ranges was 40-200 µg/ml for Telmisartan, 10-50 µg/ml for Rosuvastatin calcium, and 5-25 µg/ml for Amlodipine besylate. Assay from the chromatogram for bulk mixture of combination was 99.24%, 100.21% and 99.98% respectively for Amlodipine besylate, Rosuvastatin calcium and Telmisartan [49].

In a very recent communication, a reverse phase HPLC method was reported for the simultaneous determination of Amlodipine besylate and Olmesartan medoxomil in combination drug available commercially. The simple method which was developed with isocratic run on a mobile phase combination of phosphate buffer:acetone in the ratio 90:10. The estimation was brought about by C-18 column (Inertsil ODS-3 250 x 4.6 mm) and the peaks were identified at 235 nm nm. The retention time recorded for the drug combination was 13.106 (Amlodipine) and 14.243 (Olmesartan medoxomil) mins. During the assay analysis, the method exhibited exceptional linearity and assay recovery of 99% [50].

CONCLUSION:

The review focused on various analytical protocols developed across years to quantify various drug combinations which are used for hypertension treatment and management. Whenever new drug combinations are released for disease management, it become necessary to develop rapid and efficient analytical methods to precisely analyze the drug formulations. The study will give insight to arrive at new analytical methods with the information obtained from the above investigations. This will also help to develop novel methods as and when a new formulation is released by drug companies.

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