IJPSR (2022), Volume 13, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 January 2022; received in revised form, 24 February 2022; accepted, 26 April 2022; published 01 September 2022

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF TERTIARY COMBINATIONS OF ANTIHYPERTENSIVE DRUGS: A REVIEW

Purva Patel and Hiral Dave *

Department of Pharmaceutical Quality Assurance, Parul Institute of Pharmacy, Parul University, P.O Limda, Vadodara - 391760 Gujarat, India.

Keywords:

Analytical method, Hypertension, High-performance liquid chromatography, Liquid chromatography-mass chromatography, High-performance thin layer liquid chromatography, Patent search, Ultraviolet spectroscopy

Correspondence to Author:
Dr. Hiral Dave

Professor,
Department of Pharmaceutical Quality Assurance, Parul Institute of Pharmacy, Parul University, P.O Limda, Vadodara - 391760 Gujarat, India.

E-mail: hiral.dave16194@paruluniversity.ac.in

ABSTRACT: The most important risk factor for cardiovascular disease is high blood pressure, which accounts for around one-third of those who have it. A majority of those who have hypertension are not on antihypertensive medication. It is not a disease, but it is an important risk factor for cardiovascular disease. Hypertension includes the intricate exchange of natural and pathophysiological factors that influence numerous frameworks, just as hereditary inclination. Investigation of patients with hypertension incorporates exact normalized blood pressure (BP) estimation, evaluating patients' anticipated danger of atherosclerotic cardiovascular disease, declaration of target organ harm, location of auxiliary reasons for hypertension, and presence of comorbidities, including cardiovascular disease kidney infection. As a part of many risk factor reduction activities, combination drug therapy is as a well-established option for cardiovascular disease risk reduction. Over the past couple of years, there has been much research done on antihypertensive drugs and there have been many patents that can be beneficial for research purposes. A key element of discovering new drugs, advancing new drugs and assembling pharmaceutical products is the development of analytical methods and their validation. Analytical methods should be used in the Good Manufacturing Practice and Good Laboratory Practice environments and must be developed using the protocol and acceptance criteria in the ICH Q2(R1) guidelines. The following literature surveys reveal that all methods were reported for all tertiary combinations. However, Ultraviolet spectrophotometry Reverse Phase High-Performance Liquid Chromatography, High-Performance Thin-Layer Liquid Chromatography, stability-indicating Reverse Phase High-Performance Liquid Chromatography methods.

INTRODUCTION: Anti-hypertensives drugs are used to treat hypertension (high blood pressure). People with hypertension are very commonly seen to suffer from this chronic condition.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(9).3447-57

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(9).3447-57

Current hypertension treatment guidelines recommend a goal of <140/90 mmHg> for a population with uncomplicated hypertension, and goals are even <130/80mmHg> for patients with diabetes or renal disease.

According to the studies that have been conducted over the long term, the higher the blood pressure reduction, the lower the cardiovascular death risks. Major clinical studies have revealed that most patients require two or more drugs to reach their blood pressure goals.

Evidence suggests that lowering the blood pressure by 5mm Hg can decrease the risk of stroke by 34%, ischemic heart disease by 21% and reduce the likelihood of dementia, heart failure and mortality from cardiovascular disease [2].

Combination therapy should be used as the initial treatment of patients whose probability of achieving monotherapy's BP control is low. As many risk factors as possible can be reduced by using combination drug therapy to reduce cardiovascular disease risk.

Type of Hypertension: There are two types of hypertension. Primary hypertension (Essential). Secondary hypertension.

Primary Hypertension: Primary hypertension is the most common type, affecting between 90-95% of patients diagnosed with essential hypertension. Primary hypertension does not have to be identified clearly. The majority of cases are of essential hypertension *i.e.*, the cause is not known.

Sympathetic and renin-angiotensin systems may or may not be overactive, but they contribute to blood vessels' tone [3]. In this case, hypertension greater than 130 systolic and 80 diastolic has occurred without any diagnosis or treatment.

There can be multiple risk factors contributing to primary hypertension, including excessive salt consumption, abnormalities involving the renin-angiotensin-aldosterone system, and pathogenic disturbances of the CNS such as stress.

Secondary Hypertension: It has been discovered that secondary hypertension causes 5% of all hypertension cases. A medical condition (such as kidney or liver malfunction) or medication can result in high blood pressure.

An abnormality in the arteries supplying blood to the kidneys is the most common cause of hypertension. Additionally, some people suffer from thyroid diseases, hormonal abnormalities, tumors of the adrenal glands, and airway obstructions during sleep if they consume too much salt or alcohol.

Pathophysiology of Hypertension: Hypertension results from irregular physiological regulation of blood pressure resulting from multiple mechanisms. The blood pressure is a product of cardiac output and systemic vascular resistance.

The blood pressure is determined by the interaction of multiple genetic, environmental and demographic factors that influence to hemodynamic variables shown in **Fig. 1**, cardiac output, and total peripheral resistance. Cardiac output is affected by the blood volume, itself greatly dependent on body sodium homeostasis [5].

As the blood vessels contract, humoral factors that cause vasoconstriction (such as angiotensin II) and vasodilators (prostaglandins and nitric oxide) are activated. Resistance vessels also exhibit autoregulation, whereby increased blood flow induced vasoconstriction to fight against tissue hyperperfusion.

Other local factors such as pH and hypoxia and neural interactions (α- and β- adrenergic systems) may be important [4]. The kidneys play a significant role in blood pressure regulation, as follows:

- In the renin-angiotensin system, the kidney influence both peripheral and sodium hemostasis. The juxtaglomerular cells of the kidney produce renin to change plasma angiotensinogen into angiotensin I, which is then converted by angiotensin-converting enzyme (ACE) to angiotensin II [4].
- Angiotensin II increases peripheral resistance and blood volume simultaneously, shown as in **Fig. 2.**
- The kidneys also produce a vasodepressant that counterbalances angiotensin's effects as a vasodepressant.
- In response to volume expansion, heart atria secrete natriuretic factors independent of the glomerular filtration rate, which inhibit sodium reabsorption by distal tubules and cause vasodilation [4].
- When the renal excretory function is impaired, n creased atrial pressure is a compensatory mechanism to restore fluid and electrolyte balance [4].

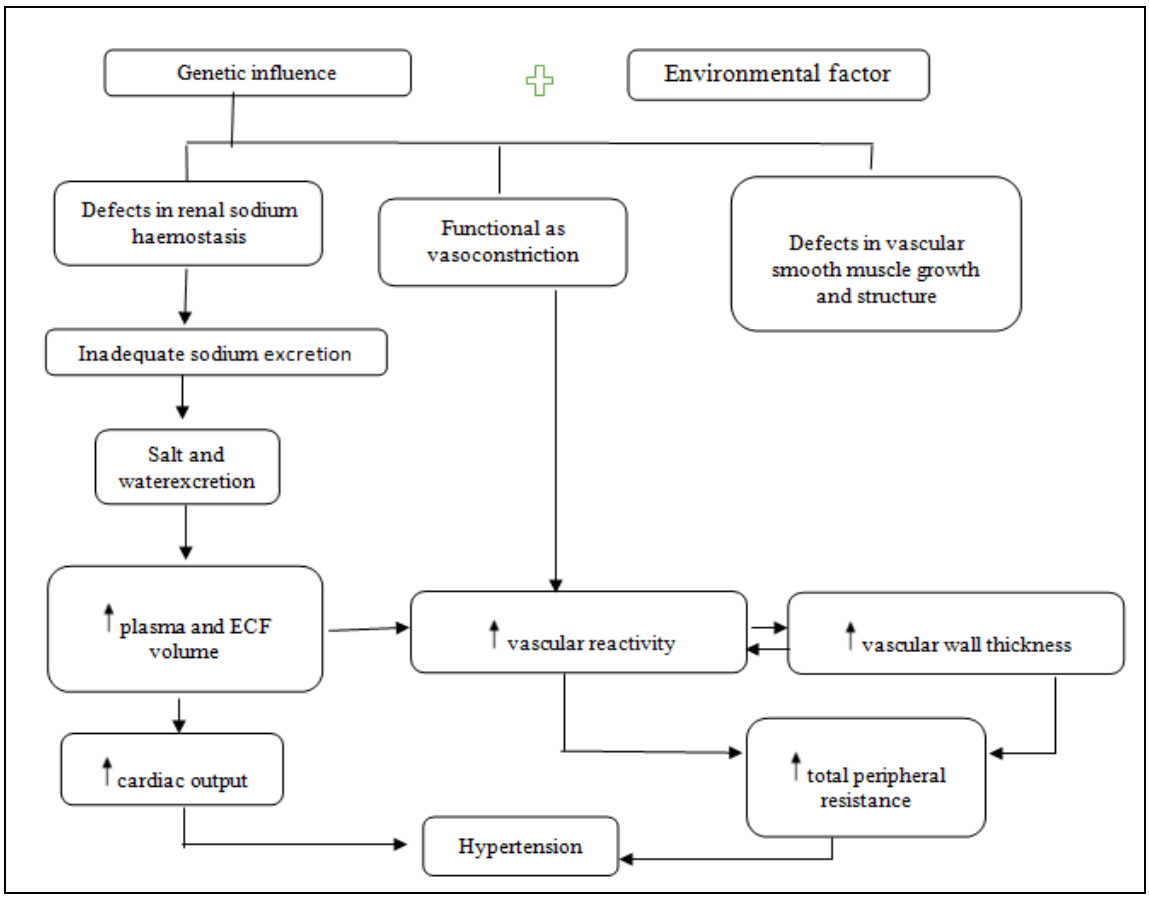

FIG. 1: GENETIC INFLUENCE +ENVIRONMENT FACTOR RELEVANT TO HYPERTENSION

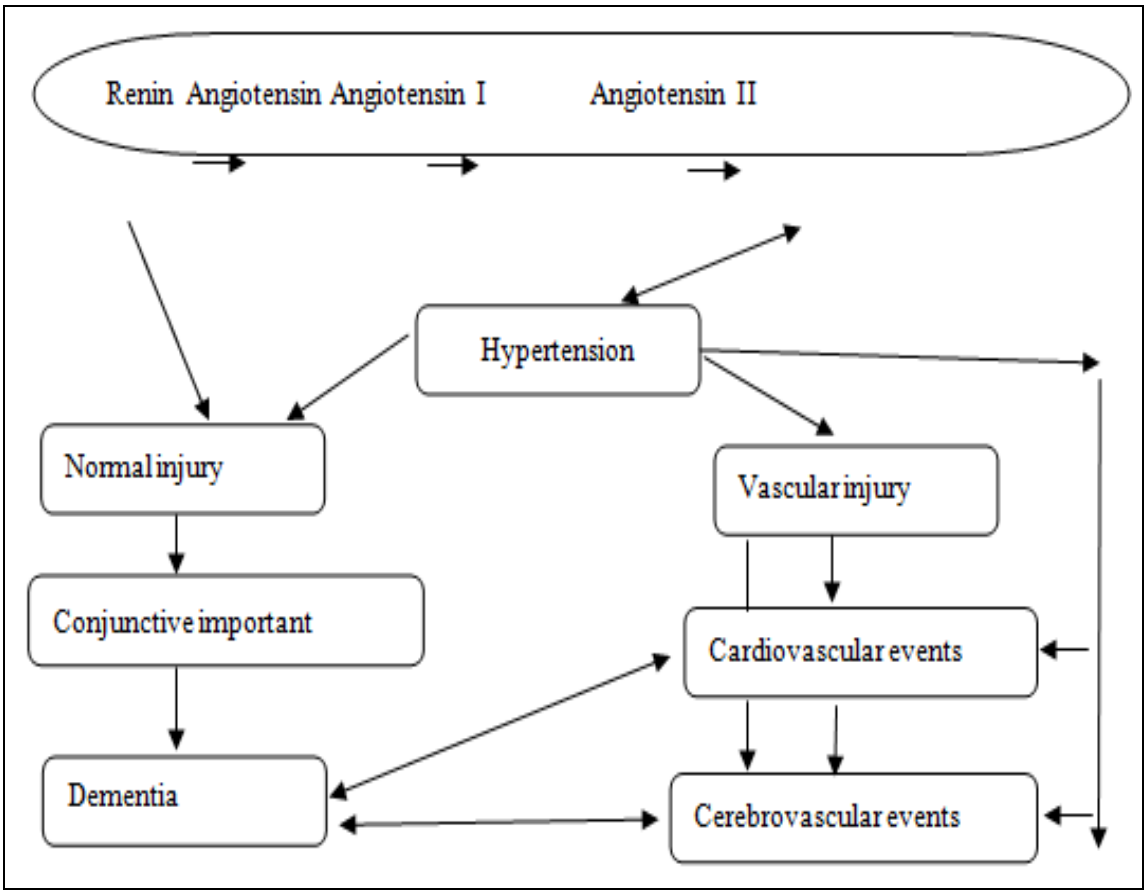

FIG. 2: RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

Proposed Disease Treatment: Controlling and managing high blood pressure can be achieved by changing your lifestyle. In England and Wales, over seven million adults appear on the initial care hypertension registers, which is around 14% of the adult population [5]. By lowering BP to an acceptable level with minimal patient inconvenience, antihypertensive therapy can help prevent morbidity and mortality associated with persistently raised BP. Control technology has an important role to play in this scenario. Currently, 60% of those on hypertensive enrol are controlled [6] and only 50% of those starting on a new antihypertensive remaining taking it after 6 months [7].

Lifestyle Change: Different forms of non-pharmacological treatment to lower blood pressure and prevent hypertension. The most effective interventions are weight loss [8, 9], reduced Na^+ intake [9, 10, 11], increased potassium intake [12, 13], increased physical activity [14], reduced consumption of alcohol [15] and diets like the Dietary Approaches to Stop Hypertension (DASH) diet that includes elements that have favourable effects on blood pressure. The DASH diet is especially successful when combined with other effective BP lowering interventions such as a reduced dietary sodium intake [16]. A lifestyle change is the most effective method of implementing these interventions.

Pharmacological Interventions: Low-dose pharmacological therapy has also been shown to be impressive in lowering BP and preventing hypertension in three randomized controlled trials conducted in adults with high normal BP [17, 18]. The Brazilian multicenter PREVER-Prevention Trial compared treatment with the low-dose long-acting thiazide-like diuretic chlorthalidone in combination with the potassium-sparing agent amiloride with treatment with placebo [19]. Amiloride and chlorthalidone both lower blood pressure and hypertension, including a reduction in left ventricular mass when combined with low dose chlorthalidone.

Management of Hypertension:

Initiation of Antihypertensive Drug Therapy: Importantly, though the diagnosis of hypertension has been confirmed at the 130/80 mm Hg threshold, most patients with stage 1 hypertension (~69%) do not qualify for immediate drug therapy [20]. In first-line therapy for pharmacological treatment of patients with masked hypertension, prescription of drug therapy is four drug classes- thiazide diuretics, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers unless there is comorbidity consideration favoring the use of different class of the drugs.

Combination Therapy: Guidelines from WHO, ISH, and BHS encourage single-drug therapy; however, a second (and third, or even fourth) drug may be prescribed when the primary therapy fails. The hypertension study found that 70% of patients who achieved target blood pressure took two or three drugs. In the management of hypertension, few studies have been conducted on how the different combinations perform. **Table 1** shows a list of recommended and not recommended [21].

A combination of antihypertensive agents is a fixed dose or free combination, including a diuretic. These combinations have been shown to produce greater blood pressure reductions than those seen with monotherapies [24]. Combinations of a calcium antagonist with a renin-angiotensin system inhibitor (RASI), whether an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) [25, 26], have also been shown to be effective and safe in the management of the hypertensive patient [25, 26]. Patients with left ventricular hypertrophy, who are taking ACE inhibitors/ARBs, benefit greatly from this combination.

TABLE: 1 RECOMMENDED AND NOT RECOMMENDED COMBINATIONS

Recommended combinations	Not recommended combinations
Diuretics with angiotensin-renin axis inhibitors or calcium antagonist	Two agents that inhibit the renin–angiotensin axis (derived from a warning published by the Food and Drug Administration, dated 20 April 2012 [22]
Inhibitors of the renin-angiotensin axis with diuretics or with calcium antagonist	Diuretics with beta blockers (greater risk of development of type 2 diabetes, as found in the ASCOT trial [23]
Beta adrenergic blockers with dihydropyridine calcium antagonist	Beta-adrenergic blockers with non-dihydropyridine calcium antagonists (greater risk for bradycardia and/or atrio-ventricular block [22]

Patent Search for Antihypertensive Drugs: Over the past couple of years, there has been much research done on antihypertensive drugs. There have been many patents that can be beneficial for research purposes. **Table 2** shows a list of the patent search for antihypertensive drugs.

TABLE 2: PATENT SEARCH

S. no.	Patent application number	Patent title	Summary
1	EP2255791A1	Extended-release pharmaceutical composition compressing metoprolol succinate [27]	is related to the Extended-release pharmaceutical composition compressing metoprolol succinate [27]
2	CN111517967A	Synthesis method of metoprolol succinate isomer impurities [28]	The invention belongs to the technical field of medicinal chemistry and particularly relates to a synthesis method of metoprolol succinate isomer impurities [28]
3	US2017340583A1	Capsule dosage form of metoprolol succinate [29]	This disclosure provides an extended-release capsule dosage form of metoprolol succinate in the form of coated discrete units, wherein said capsule dosage form is bioequivalent to the marketed Toprol-XL®tablet [29]
4	WO2007141593A2	Improved synthesis and preparation of metoprolol succinate [30]	The invention relates to an improved process for preparing metoprolol and its salts [30]
5	CN102552196A	Spray drying method for preparing metoprolol succinate sustained-release capsule [31]	The invention provides a spray-drying method for preparing metoprolol succinate sustained-release capsule [31]
6	WO2018158777A1	Improved process for the preparation for chlorthalidone [32]	The present invention relates to methods for preparing chlorthalidone. In particular, the disclosed processes are feasible on an industrial scale and provide substantially pure chlorthalidone [32]
7	WO2015153379A1	Fixed-dose combination of angiotensin converting enzyme (ACE) inhibitor and the diuretic chlorthalidone [33]	The invention describes fixed dosage formulations of an angiotensin-converting enzyme (ACE) inhibitor, preferably Lisinopril and the diuretic, preferably Chlorthalidone in the same pharmaceutically acceptable carrier, for example a tablet, capsule [33]
8	US2010204252A1	Method of treating hypertension with at least one AngiotensinII receptor blocker and chlorthalidone [34]	The present invention relates to a method of treating hypertension in a subject or patient needing treatment thereof by administering to said subject or patient at least one angiotensin II receptor blocker in combination with chlorthalidone [34]
9	US2017157094A1	Pharmaceutical formulation comprising losartan potassium and chlorthalidone [35]	The invention is a pharmaceutical tablet formulation comprising between about 12.5 mg and 100mg losartan potassium, between about 6.25mg 50mg chlorthalidone [35]
10	WO2020207355A1	Pharmaceutical composition containing amlodipine, chlorthalidone, amiloride [36]	is related to the Provided is a pharmaceutical composition for treating refractory hypertension. The pharmaceutical composition consists of amlodipine, chlorthalidone, and amiloride [36]
11	CN107966519A	High-performance liquid chromatography analysis method and detection method for impurities in telmisartan medicine [37]	The invention relates to the detection of Telmisartan, and particularly discloses a high-performance liquid chromatography analysis method and a detection method for impurities in a Telmisartan medicine [37]
12	CN110836943A	Analysis method for impurity detection of telmisartan tablet and telmisartan capsule [38]	The invention provides an analysis method for detecting impurities in telmisartan tablets and telmisartan capsules, and belongs to the field of drug detection [38]
13	US2006111417A1	Amorphous telmisartan [39]	Amorphous telmisartan and combination of amorphous telmisartan with one or more pharmaceutical carrier [39]
14	WO2010063997A1	Telmisartan formulation [40]	A telmisartan tablet is formulated with 60 % or more water soluble diluent, avoiding the need for surfactant or a basic amino acid solubilizing agent [40]
15	CN101049305A	Telmisartan pills and	A dripping pill of telmisartan for treating hypertension

		preparation method [41]	is prepared from the telmisartan and the matrix of dripping pill. Its preparation process is also disclosed [41]
16	CN108888593A	Atenolol injection and preparation method thereof [42]	The atenolol injection is prepared from atenolol and sodium chloride, each 100ml of injection contains 30-70mg of atenolol and 0.45-1.8g of sodium chloride [42]
17	CN106176582A	Atenolol emulsifiable paste for testing infant hemangioma and method for preparing atenolol emulsifiable paste [43]	The invention belongs to the field of technologies for preparing medicines, and particularly relates to atenolol emulsifiable paste for treating infant hemangioma and a method for preparing the atenolol emulsifiable paste [43]
18	CN109771497A	Antihypertensive capsule and preparation method [44]	The invention belongs to the technical field of traditional Chinese medicine and discloses an antihypertensive capsule and a preparation method [44]
19	CN109771497A	Cocrystal of telmisartan and hydrochlorothiazide [45]	The present disclosure relates to a cocrystal of telmisartan and hydrochlorothiazide, a preparation method and use thereof [45]
20	CN112641745A	Telmisartan hydrochlorothiazide tablet and preparation method thereof [46]	The invention discloses a telmisartan hydrochlorothiazide tablet and a preparation method thereof [46]
21	CN112516105A	Losartan potassium oral preparation and preparation method thereof [47]	The invention relates a losartan potassium oral preparation [47]
22	CN112274490A	Preparation method of amlodipine losartan potassium compound composition [48]	The invention discloses a preparation method of amlodipine of and losartan potassium compound composition [48]
23	CN112438986A	Application of losartan potassium and dacarbazine combined medicine for treating intestinal cancer [49]	The invention belongs to the field of medicines, and particularly relates to an application of losartan potassium and dacarbazine combined medicine to preparation of a medicine for treating intestinal cancer [49]
24	CN111956624A	Olmesartan medoxomil tablet and preparation method thereof [50]	The invention discloses an Olmesartan medoxomil tablet and a preparation thereof [50]
25	CN111004223A	preparation and separation method of Olmesartan medoxomil dimer impurity [51]	The invention provides a preparation and separation method of an Olmesartan medoxomil dimer impurity [51]
26	CN112315926A	Valsartan oral solid preparation [52]	The invention relates to the technical field of biological medicines, in particular to a valsartan oral solid preparation [52]
27	WO2021022516A1	Valsartan refinement method [53]	Disclosed is a valsartan refinement method comprising firstly, reacting valsartan in water with an alkali or a salt of a strong and a weak acid to generate a valsartan salt [53]

Analytical Method Validation: The development and validation of analytical methods play a crucial role in developing, advancing, and assembling pharmaceutical products. An analysis of drug substances and drug products includes determining their purity and toxicity.

A method of developing analytical methods primarily employed in multicomponent analyses minimizes the time-consuming task of separating interferants and, therefore, reduces time and therefore costs, associated with the analysis of increasingly more analytes. The number of medications introduced to the market has increased in recent years. The steps of method development and validation depend upon type of method being developed; the following steps are common to most types of projects.

- Method development plan definition.
- Background information gathering.
- Laboratory method development.
- Generation to test procedure.
- Method validation protocol definition.
- Laboratory method validation.
- Validated test method generation.
- Validation report.

ICH Q2(R1) guidelines also mention that analyses must adhere to GMP and GLP practices; protocols and acceptance criteria must be followed when developing analytical methods [54].

Development and validation of analytical methods play a critical role in pharmaceutical manufacturing and develop-pmentthe following literature surveys reveal there is all methods were reported for all tertiary combinations. However, UV spectro-photometry, RP- HPLC, HPTLC, and stability indicate RP-HPLC methods. The reported methods are shown in **Table 3**.

TABLE 3: REPORTED METHODS FOR ASSESSMENT OF TERTIARY COMBINATIONS

S. no.	Title / Method	Description
1	Application of an LC-MS/MS method for the analysis of amlodipine, valsartan and hydrochlorothiazide in polypill for bioequivalence study [55]	Extract:100µL human plasma by solid extraction on oasis HLB cartridges, Column: RP_{18e}, Concentration range: VAL:5.00-10,000ng/ml, HCTZ :20-200ng/ml, AML:0.02–20.0 ng/mL
2	Development and validation of analytical method for simultaneous estimation of cilnidipine, chlorthalidone and telmisartan in tablet dosage form [56] (RP HPLC method)	Matrix: Tablet, Mobile phase: 0.025Mpotassium dihydrogen phosphate: ACN (75:25), Flow rate:1.0 mL/min, Detector wavelength :233 nm
3	Comparison of Partial Least Squares Regression and H-Point Standard Addition Method for Simultaneous Spectrophotometric Determination of Losartan Potassium, Hydrochlorothiazide and Amlodipine Besylate in Tablets [57]	Matrix: Tablet, MATLAB software version 7.5 (The MathWorks) and PLS – Toolbox version 5.0 (Eigen Vector Technologies). Solvent:0.1M NaOH: water (20:80), Wavelength: LOS:228.41nm, HCTZ:216.32nm, AML:216.32nm
4	Development and Validation of HPLC Method for Simultaneous Determination of Amlodipine, Valsartan, Hydrochlorothiazide in Dosage Form and Spiked Human Plasma [58]	Matrix: tablet, spiked human plasma, Column: C18, Mobile phase: acetonitrile: phosphate buffer (0.05 M) (40:60), flow rate: 0.8 mL/min, wavelength detection: 227 nm.
5	Development and Validation of HPTLC Method for Simultaneous Estimation of Amlodipine Besylate, Hydrochlorothiazide and Telmisartan in Their Combined Tablet Dosage Form [59]	Matrix: Tablet, Stationary phase: silica gel, Mobile phase: chloroform: butan-1-ol: ammonia (6: 4: 0.1, v/v/v), Detector wavelength :254nm
6	H-point standard addition method for simultaneous spectrophotometric determination of irbesartan, hydrochlorothiazide and telmisartan in tablets [60]	Matrix: Tablet, MATLAB software version 7.5 (The Math Works) and PLS – Toolbox version 5.0 (Eigen Vector Technologies), Solvent:0.1M NaOH: water (20:80 v/v), Wavelength: IRB:228.41nm HCZ:216.32nm, TEL: 295.12nm
7	Simultaneous estimation of hydrochlorothiazide, amlodipine, and losartan in tablet dosage form by RP-HPLC [61]	Matrix: tablet, Column: C18, Mobile phase: acetonitrile: water 0.4% of potassium dihydrogen phosphate (45:35:20), flow rate: 1 mL/min wavelength detection:230 nm
8	Simultaneous spectrophotometric determination of losartan potassium, amlodipine besylate and hydrochlorothiazide in pharmaceuticals by chemometric methods [62]	Matrix: Tablet, MATLAB software version 7 (The Mathworks) and PLS – Toolbox version 5.0 (Eigen Vector Technologies). Solvent: Methanol , Wavelength:230.5–350.4 nm
9	Development and Validation of Stability-indicating Method for the Estimation of Cilnidipine, Olmesartan Medoxomil and Chlorthalidone by Reverse Phase High Performance Liquid Chromatography [63]	Matrix: Tablet, Column: c18, Mobile phase: 0.01 N Potassium dihydrogen phosphate buffer: ACN (60:40), Flow rate: 0.9 mL/min. Detector wavelength: 260 nm
10	Rapid Simultaneous Determination of Telmisartan, Amlodipine Besylate and Hydrochlorothiazide in a Combined Poly Pill Dosage Form by Stability-Indicating Ultra Performance Liquid Chromatography [64]	Column: c18, Mobile phase:sodium perchlorate buffer(0.053M): ACN (90:10 v/v), Flow rate:0.6 mL/min, Column temperature: 55°C Wavelength: HCTZ:271 nm, AMLB:237 nm, TEL:271 nm
11	Related Impurities High-performance Liquid Chromatography Method Development and Validation for drug combinations: Olmesartan Medoxomil, Chlorthalidone and Cilnidipine [65]	Matrix: Tablet, Column: c18, Mobile phase:ammonium acetate: ACN (55:45 v/v) , Flow rate:1.0 mL/min, Detector Wavelength: 260nm
12	RP-HPLC method development & validation for simultaneous estimation of chlorthalidone,	Matrix: Tablet, Column: c18, Mobile phase:0.5M potassium dihydrogen ortho phosphate: methanol (50:50v/v), Flow

	metoprolol succinate and telmisartan in tablets [66]	rate:1.0 mL/min, Detector Wavelength: 215nm
13	RP-HPLC Method Development and Validation for Simultaneous Estimation of Amlodipine besylate, Valsartan and Hydrochlorothiazide in Tablet Dosage Form [67]	Matrix: Tablet, Column: c18, Mobile phase:ACN: Phosphate buffer (55:45 v/v), Flow rate:1.0 mL/min, Detector Wavelength: 237nm
14	Separation of Marketed Formulation containing Hydrochlorothiazide Amlodipine and Losartan through RPHPLC Method [68]	Matrix: Tablet, Column: c18, Mobile phase:Acetonitrile, methanol (65:35), Flow rate:1.5 ml/min., Detector Wavelength: 230nm
15	Simultaneous Analysis of Losartan Potassium, Amlodipine Besylate, and Hydrochlorothiazide in Bulk and in Tablets by High-Performance Thin Layer Chromatography with UV-Absorption Densitometry [69]	Matrix: bulk and Tablet, Stationary phase: silica gel, Mobile phase: chloroform: methanol: acetone: formic acid 7.5:1.3:0.5:0.03 (v/v/v/v), Densitometric scanning: 254nm
16	Simultaneous determination of valsartan, amlodipine besylate and hydrochlorothiazide using capillary zone electrophoresis (CZE) [70]	Matrix: Tablet, Separation: fused silica capillary by applying a potential of 15 Kv, Temperature: capillary cartridge, was kept at 25 ◦C, UV detection: 230 nm
17	Stability-Indicating Method for Simultaneous Estimation of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide by RP-HPLC in Tablet Dosage Form [71]	Matrix: Tablet, Column: c18, Mobile phase:triethylamine: ACN (60:40 v/v), Flow rate:1.4mL/min, Detector Wavelength: 236nm
18	Simultaneous estimation of telmisartan, chlorthalidone and cilnidipine by absorbance correction method using UV spectrophotometry [72]	Matrix: Tablet, Solvent: Methanol, Wavelength: CHL:225nm, TEL:325nm, CIL:350nm
19	UPLCMS Method Development and Validation of Amlodipine, Hydrochlorothiazide and Losartan in Combined Tablet Dosage Form [73]	Matrix: Tablet, Column: c18, Mobile phase: ACN: ammonium acetate (98:2v/v), Flow rate :0.4 ML/min
20	Validated RP-HPLC Method for Simultaneous Estimation of Atenolol, Hydrochlorothiazide and Losartan Potassium in Bulk and Pharmaceutical Dosage Form [74]	Matrix: Tablet, Column: c18, Mobile phase: ACN: Potassium, dihydrogen ortho phosphate (40:60V/V), Flow rate:1.5 mL/min, Wavelength detection :225nm
21	Development and validation of RP HPLC method for simultaneous estimation of metoprolol, telmisartan and cilnidipine in tablet [75]	Matrix: Tablet, Column: c18, Mobile phase: ACN: methanol: phosphate buffer (45:30:25), Flow rate: 1.0 ml/min, Wavelength detection :229nm
22	Determination of losartan, telmisartan, and valsartan by direct injection of human urine into a column-switching liquid chromatographic system with fluorescence detection [76]	Matrix: injection, Column: Chromolith RP-18e monolithic column, Mobile phase: phosphate buffer: ACN: methanol (65:20:15, v/v/v),Flow rate: 3.0 mL/min
23	Spectrophotometric method for simultaneous estimation of atenolol in combination with losartan potassium and hydrochlorothiazide in bulk and tablet formulation [77]	Matrix: Bulk and Tablet, Solvent: methanol, Wavelength: ATE:224.20nm, LOP: 251.60nm, HCTZ: 271.60nm
24	Novel RP-HPLC method for simultaneous determination of Olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide in tablet dosage form [78]	Matrix: Tablet, Column:c18, Mobile phase: phosphate buffer: ACN (50:50 v/v), Flow rate: 3.0 mL/min, Detector wavelength:262nm

CONCLUSIONS: All tertiary combination drugs are shown to be more effective in this article. A literature review is presented to provide information on different methods for determining all combinations of tertiary drugs. Several patents have been published on antihypertensive drugs in the last two or three years that are helpful to researchers.

The different analytical methods are reported for the combinations like UV Spectroscopy, HPLC, LC-MS, HPTLC, stability-indicating, and RP-HPLC. Additionally, this article presents the pharmacological action and solubility of all tertiary combinations. This review will help develop the analytical method for these new combinations and

gives the knowledge about the characteristics of all tertiary combination's drugs.

ACKNOWLEDGEMENT: We wish to acknowledge the Department of Pharmaceutical Quality Assurance at Parul Institute of Pharmacy, Parul University, for his help and support in the compilation of the article.

CONFLICTS OF INTEREST: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES:

1. Tadesse Melaku Abegaz, Abdulla Sheha, Eyob Alemayehu Gebreyohannes, Akshaya Srikanth Bhagavathula and Asim Ahmed Elnour: Nonadherence to antihypertensive drugs a systematic review and meta-analysis. Abegaz Medicine, 2017; 96(4):1-9.
2. Law M and Wald NJ: Morris, lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. Health Technology Assessment 2003; 31: 1–20094.
3. Tripathi KD: Essentials of medical pharmacology. Seventh Edition Jaydeep Brothers Medical Publishers Pvt Ltd 1985; 558-592.
4. Siyad AR: Hypertension. J for Dru and Med 2011; 1: 1-16.
5. ompson AC, Grant S, Greenfield SM, McManus RJ, Fleming S and Heneghan CJ: Patient use of blood pressure self-screening facilities in general practice waiting rooms: a qualitative study in the UK. Br J Gen Pract 2017; 660: 467–73.
6. England NHS. Report of the Review of the Quality and Outcomes Framework in England. NHS England, 2018
7. England Public Health. Health matters: combating high blood pressure. Public Health England 2017. Accessed March 2019.
8. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I JAMA, 1992 267:1213–1220
9. Whelton PK: Efficacy of nonpharmacologic interventions in adults with high-normal blood pressure: results from phase 1 of the Trials of Hypertension Prevention. Trials of Hypertension Prevention Collaborative Research Group. Am. J Clin Nutr 1997; 65: 652–660.
10. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. Arch. Intern Med 1997; 157: 657–670.
11. Sacks FM: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344: 3–10.
12. Whelton PK: Effects of oral potassium on blood pressure. Meta-analysis of randomized controlled clinical trials. JAMA 1997; 277: 1624–1632.
13. Aburto NJ: Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. BMJ 2013; 346: 1378–1378.
14. Whelton SP, Chin A, Xin X & He J: Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann. Intern Med 2002; 136: 493–503.
15. Roerecke M: The effect of a reduction in alcohol consumption on blood pressure: a systematic review and meta-analysis. Lancet Public Heal 2017; 2: 108–120.
16. Sacks FM: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344: 3–10.
17. Julius S: Feasibility of treating prehypertension with an angiotensin-receptor blocker. N Engl J Med 2006; 354: 1685–1697.
18. Lüders S et al. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. J Hypertens 2008; 26: 1487–1496.
19. Fuchs SC: Effectiveness of Chlorthalidone Plus Amiloride for the Prevention of Hypertension: The PREVER-Prevention Randomized Clinical Trial. J Am Heart Assoc 2016; 5: 4248-4259
20. John M Flack: Bemi Adeola, blood pressure and new ACC/AHA hypertension guidelines. Trends in Cardiovascular Medicine 2020; 3: 160-140.
21. Carolina Guerrero-García, MD, Alberto Francisco Rubio-Guerra, PhD, "combination therapy in the treatment of hypertension", drug in contex 2018; 7: 1-9.
22. Task Force for the management of arterial hypertension of the European Society of Hypertension; Task Force for the management of arterial hypertension of the European Society of Cardiology. 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension. Blood Press 2019; 22: 193–278.
23. Poulter NR, Wedel H, Dahlöf B, Sever PS, Beevers DG, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J and Pocock S: ASCOT Investigators. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) Lancet 2005; 366: 907–913.
24. Wald DS, Law M, Morris JK, Bestwick JP and Wald NJ: Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009; 122: 290–300.
25. Burnier M: Antihypertensive combination treatment: state of the art. Curr Hypertens Rep 2019; 17-51.
26. Rubio-Guerra AF, Castro-Serna D, Elizalde-Barrera CI, Ramos-Brizuela LM. Current concepts in combination therapy for the treatment of hypertension: combined calcium channel blockers and RAAS inhibitors. Integr Blood Press Control 2009; 2: 55–62.
27. farmaprojects aamela-navarrojoaquimgual-pujolfranciscoruiz-cordobajoseluis [es]; shah chitraamela-navarro, joaquims; extended release pharmaceutical composition comprising metoprolol succinate EP2255791A1•2010.
28. Handongqidu pharmaceutical co., ltd., a lizhu; feng yu; li zongtao; liusujing; ren zhongqiang; song yingchun; wang meng; yang xueqian; zhai min; zhujiany, synthesis method of metoprolol succinate isomer impurities,CN111517967A•2020.
29. Sun pharmaceutical ind ltd, sun pharmaceutical industries limited mondalbalaram [in]; ramarajukalaiselvan [in]; singhromi barat [in]; vats sandeepkumar [in],

mondalbalaram;,capsule dosage form of metoprolol succinate US2017340583A1•2017.

30. Arnalotaguilar carmen; boschilladojordimedichemsamedichem, s.a.arnalotaguilar carmen, boschilladojordiarnalotaguilar, carmen; "improved synthesis and preparations of metoprolol and its salts" WO2007141593A2•2007.
31. Univchina pharma china pharmaceutical university li song; qineng ping; shengjiang he, he shengjiang; ping qineng; song li, spray-drying method for preparing metoprolol succinate sustained-release capsules. CN102552196A•2012.
32. Mylan laboratories limited, gadakarmaheshkumar, pundednyandeo ,thanasekaranponpandianwaghghanshyam ,wakchaureyogesh, gadakar, maheshkumar; punde, dnyandeo; thanasekaran, ponpandian; wagh, ghanshyam; wakchaure, Yogesh, Improved process for the preparation for chlorthalidoneWO2018158777A1.2018.
33. Ailex pharmaceuticals pvt ltd [us]; rajandorai [us]; sudhimanshu [us], fiixed dosage formulations of angiotensin converting enzyme (ace) inhibitor and the diuretic chlorthalidone WO2015153379A1•2015.
34. Takeda pharmaceuticals northatakeda pharmaceuticals north america, inc. kupferstuart r [us]. Methods of treating hypertension with at least one angiotensin ii receptor blocker and chlorthalidone US2010204252A1•2010.
35. Aldea albert falivene [es]; wijgergangsjan-piet [nl]; zwinkelsjocominusantonius maria [nl]; merck sharp &dohme [us], aldea albert falivene; wijgergangsjan-piet; zwinkelsjocominusantonius maria, pharmaceutical formulation comprising losartan potassium and chlorthalidone, US2017157094a1•2017.
36. shenzhenausa pharmaceutical co ltd [cn]; henzhenausa pharmaceutical co., ltd.; shenzhenausa pharmed co., ltd, bai jie [cnchen ping [cn]; tian minqing [cn]; xu xiping [cn]; yu duo [cn], bai, jie; pharmaceutical composition containing amlodipine, chlorthalidone, and amiloride. WO2020207355A1•2020.
37. weightechhunan pharmaceutical co ltd, he liang, high performance liquidchromatography analysis method and detection method for impurities in telmisartan medicine. CN107966519A•2018.
38. jiangxixinglinbaima pharmaceutical co ltd, li baolin; liu yiping; luoyunhua; zhu qin, analysis method for impurity detection of telmisartan tablet and telmisartan capsule, CN110836943A•2020.
39. Santhi G, China G. mala k [in]; koilkonda purandhar [in]; konda ramesh b [in]; lekkala amarnath r [in], amorphous telmisartan US2006111417a1•2006-05-25.
40. arrow int ltd [mt]; persicaner peter henry robert [au]; sareenrahul [au]; tabatznikanthony s [gb], persicaner peter henry robert [au]; sareenrahul [au] telmisartan formulation. WO2010063997A1•2010.
41. Chen XI [CN], Chen XI, Chen XI Teng [CN], XI Teng Chen, Telmisartan pills, and preparation method. CN101049305A•2007.
42. Jinan kanghe medical tech co ltd,li peng; liuwanlu; xu chunhai; yang jiangyong; zhangying; zhangzuoping, Atenolol injection and preparation method thereof CN108888593A•2018.
43. Univgannan Medical, Huanghaijin; Liuhai; Liuhaijin; Liuqian; ma Jingwen; Pengwei; Tao Chao; xu xianyun; ye xiaoxing, Atenolol emulsifiable paste for testing infant hemangioma and method for preparing atenolol emulsifiable paste, CN106176582A•2016.
44. Nanping people's hospital of fujian province nanping city hospital of fujian province, ji shijian; li xiaoying; shimeili; xu xinyu; xu zhiqin; yutiantai, "antihypertensive capsule and preparation method" CN109771497A•2019.
45. Mei xuefeng [cn]; shanghai instmateria medica cas [cn]; wang jianrong [cn]; yuqihui [cn], meixuefeng [cn]; wang jianrong [cn]; yuqihui [cn], cocrystal of telmisartan and hydrochlorothiazide,US2020181121A1•2020.
46. Suzhou chunghwa chemical & pharmaceutical ind co ltd,li dan, telmisartan hydrochlorothiazide tablet and preparation method thereof,CN112641745A•2021.
47. Chengdu hengrui pharmaceutical,englu; hanpengqin; li xuemei; liu hui; liujiajun; ma yiming; shenhua; wei wen; xiao shiyuan; zhangmao; zhangyu; zhudeqi, losartan potassium oral preparation and preparation method thereof.CN112516105A•2021.
48. Sichuan sunrise biopharm ltd,dai ping; liuqiuhong; pengxianfeng; ren zhijun; tang yan; ye zizheng, preparation method of amlodipine losartan potassium compound composition, CN112274490A•2021.
49. Alphacaithangzhou ai bio tech co ltd, li bin, application of losartan potassium and dacarbazine combined medicine for treating intestinal cancer.CN112438986A•2021.
50. Zhuhai rundu pharmaceutical co ltd,guan doing; li jinqing; shenjilan; xie bin, olmesartan medoxomil tablet and preparation method thereof,CN111956624A•2020.
51. Changsha chenchen pharmaceutical tech co ltd,zhang gen, preparation and separation method of olmesartan medoxomil dimer impurity,CN111004223A•2020.
52. Changzhou pharmaceutical factory co ltd, liuruichao; ren jinfeng; tang lijuan, valsartan oral solid preparation.CN112315926A•2021.
53. Zhejiang huahai pharm co ltd [cn]; zhejianghuahaitiancheng pharmaceutical co ltd [cn]; zhejianghuahaizhicheng pharmaceutical co ltd [cn], wang peng [cn]; wang yifeng [cn]; yan fengfeng [cn]; zhuxiaoren [cn]; zhuyuanxun [cn], valsartan refinement method. WO2021022516A1•2021.
54. International Conferenceon Harmonization, ICHQ2 (R1): Validationof Analytical Procedures: Text and Methodology. Geneva. 2005.
55. Jaivik V. Shaha, Jignesh M. Parekha, Priyanka A. Shaha, Priya V. Shaha, Mallika Sanyal and Pranav S. Shrivastava: Application of an LC–MS/MS method for the analysis of amlodipine,valsartan and hydrochlorothiazide in polypill for a bioequivalence study. JPA 2017; 7: 309–316.
56. Mauly P. Patel, Komal P. Patel and Dhaval B. Patel: Development and validation of analytical method for simultaneous estimation of cilnidipine, chlorthalidone and telmisartan in tablet dosage form. World J of Pharmacy and Pharma Sciences 2017; 5: 1228-1241.
57. Lakshmi Sivasubramanian, K S Lakshmi, Comparison of Partial Least Squares Regression and H-Point Standard Addition Method for Simultaneous Spectrophotometric Determination of Losartan Potassium, Hydrochlorothiazide and Amlodipine Besylate in Tablets. Inventi Rapid: Pharm Analy & Quality Assu 2014; 2: 1-8.
58. Samya M. El-Gizawy, Osama H. Abdelmageed, Mahmoud A. Omar, Sayed M. Deryea and Ahmed M. Abdel-Megied: Development and Validation of HPLC Method for Simultaneous Determination of Amlodipine, Valsartan, Hydrochlorothiazide in Dosage Form and Spiked Human Plasma, American J of Analyti Chemistry 2012; 422-430.
59. Bhavin Pankajbhai Marolia, Kunjan Bharatbhai Bodiwala, Shailesh Amritlal Shah, Pintu Bhagwanbhai Prajapati, Bhavik Himmatbhai Satani and Shailja Alkeshbhai Desa: Development and Validation of HPTLC Method for Simultaneous Estimation of Amlodipine Besylate,

Hydrochlorothiazide and Telmisartan in Their Combined Tablet Dosage Form, Pharm Methods 2016; 7: 48-53.
60. Lakshmi Sivasubramanian and Lakshmi KS: H-point standard addition method for simultaneous spectrophotometric determination of irbesartan, hydrochlorothiazide and telmisartan in tablets. Int J of Res in Pharma and Chem 2014; 4: 373-380.
61. Anandkumar R. Tengli, Gurupadayya BM and Neeraj Soni: Simultaneous estimation of hydrochlorothiazide, amlodipine and losartan in tablet dosage form by RP-HPLC. Int J of Chemical and Analy Sci 2013; 4: 33-38.
62. Nagavalli D, Vaidhyalingam V, Santha A, Sankar ASK and Divya O: "Simultaneous spectrophotometric determination of losartan potassium, amlodipine besilate and hydrochlorothiazide in pharmaceuticals by chemometric methods. Acta Pharm 60 2010; 60: 141–152.
63. Kondeti H. Pavani and Dannana G. Sankar: Development and Validation of Stability-indicating Method for the Estimation of Cilnidipine, Olmesartan Medoxomil and Chlorthalidone by Reverse Phase High Performance Liquid Chromatography. International Journal of Pharmaceutical Quality Assurancen 2021; 2: 53-59.
64. Santajinalwade, Vangalarangareddy, Dantudurgarao and Inabathinakoteswararao: Rapid Simultaneous Determination of Telmisartan, Amlodipine Besylate and Hydrochlorothiazide in a Combined Poly Pill Dosage Form by Stability-Indicating Ultra Performance Liquid Chromatography. Sci Pharm 2011; 69–84.
65. ranavkumar Shah and Bhavin Dhadhuk: Related Impurities High-performance Liquid Chromatography Method Development and Validation for drug combinations: Olmesartan Medoxomil, Chlorthalidone and Cilnidipine. Int J of Pharma Scien and Drug Research 2020; 12: 1-10.
66. Akshay Paliwal, Neha Tiwari and Pragnesh Patani: RP-HPLC method development & validation for simultaneous estimation of chlorthalidone, metoprolol succinate and telmisartan in tablets, Journal of Emerging Technologies and Innovative Research (JETIR) 2021; 8: 804-811.
67. Mohammad Younus, T. Karnaker Reddy, Y. Ravindra Reddy MD and Fasiuddin Arif: RP-HPLC Method Development and Validation for Simultaneous Estimation of Amlodipine besylate, Valsartan and Hydrochlorothiazide in Tablet Dosage Form. Journal of Pharmacy Research 2010; 3: 2647-2650.
68. Rajesh Sharma, Sunil Khanna and Ganesh Prasad Mishra: Separation of Marketed Formulation containing Hydrochlorothiazide Amlodipine and Losartan through RPHPLC Method. IJPLS 2011; 7: 4937-4941.
69. Karunanidhi Santhana Lakshmi and Sivasubramanian Lakshmi: Simultaneous Analysis of Losartan Potassium, Amlodipine Besylate, and Hydrochlorothiazide in Bulk and in Tablets by High-Performance Thin Layer Chromatography with UV-Absorption Densitometry, Journal of Analytical Methods in Chemistry 2012; 1-5.
70. Ebeid W, Salim M, Elkady E, Elzahr A, El-Bagary R and Patonay G: Simultaneous determination of valsartan, amlodipine besylate and hydrochlorothiazide using capillary zone electrophoresis (CZE) Pharmazie 2015; 70: 368–373.
71. Jain PS, Patel MK, Gorle AP, Chaudhari AJ and Surana SJ: Stability-Indicating Method for Simultaneous Estimation of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide by RP-HPLC in Tablet Dosage Form. J of Chromat Science 2012; 50: 680–687.
72. Reddy BH, Spandana B, Mounika D, Sindhu Devi, Anusha Dacha and Prakash KDSI: multaneous estimation of telmisartan, chlorthalidone and cilnidipine by absorbance correction method using uv-spectrophotometry. Indoamerican J of Pharma Sciences 2018; 1998-2003.
73. Anandkumar R. Tengli, Shivakumar G and Gurupadayya BM: UPLCMS Method Development and Validation of Amlodipine, Hydrochlorthiazide and Losartan in Combined Tablet Dosage Form. American Journal of Analytical Chemistry 2015; 6: 228-238.
74. Eswarudu MM, Sakheena P, Lahari K and Srinivasa Babu PM: Chinna Eswaraiah, Validated RP-HPLC Method for Simultaneous Estimation of Atenolol, Hydrochlorothiazide and Losartan Potassium in Bulk and Pharmaceutical Dosage Form. As J of Phar Res and Dev 2021; 9: 60-66.
75. Kalshetti MS and Kankure SS: Development and validation of RP HPLC method for simultaneous estimation of metoprolol, telmisartan and cilnidipine in tablet. International Journal of Pharmaceutical Science and Research 2021; 12: 1651-1657.
76. Brunettoa MDR, Contreras Y, Clavijoa S, Torres D, Delgadoa Y, Ovalles F, Ayalaa C, Gallignani M, José Manuel Estela and Víctor Cerdà Martin: Determination of losartan, telmisartan, and valsartan by direct injection of human urine into a column-switching liquid chromatographic system with fluorescence detection, Journal of Pharmaceutical and Biomedical Analysis 50 2009; 194–199.
77. Bari S, Sathe S, Jain P and Surana S: Spectrophotometric method for simultaneous estimation of atenolol in combination with losartan potassium and hydrochlorothiazide in bulk and tablet formulation, Journal of Pharmacy and Bio allied Sciences 2010; 2: 372-375.
78. Ravisankar P, Swathi J, Kumar KVS and Babu PS: Novel RP-HPLC method for simultaneous determination of Olmesartan medoxomil, amlodipine besylate and hydrochlorothiazide in tablet dosage form. Int J of Biological & Pharmaceutical Research 2014; 5: 927-936.

How to cite this article:
Patel P and Dave H: Analytical method development and validation of tertiary combinations of antihypertensive drugs: a review. Int J Pharm Sci & Res 2022; 13(9): 3447-57. doi: 10.13040/IJPSR.0975-8232.13(9).3447-57.