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Green Analytical Assessment of Methods for the Determination of Amlodipine Besylate, Telmisartan, and Indapamide: A Comprehensive Critical Review

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ABSTRACT

Hypertension, is a common condition that is characterized by abnormally high blood pressure in blood vessel. It is a significant risk factor for cardiovascular mortality and morbidity but is not a disease in and of itself. Amlodipine besylate, Telmisartan, and Indapamide, a more recent combination that has been approved by the National Institutes of Health for a phase 3 clinical trial, is beneficial in reducing hypertension. Amlodipine besylate is a calcium channel blocker, Telmisartan is an angiotensin II receptor antagonist and Indapamide is a thiazide diuretic. Different analytical methods using different techniques such as liquid chromatography, high-performance liquid chromatography, high-performance thin-layer chromatography, gas chromatography, spectrophotometry, spectrofluorimetric methods coupled with ultraviolet, fluorescence, mass, or tandem mass spectrometry for estimation of this individual drug and in combination with other drug have been reported. Therefore, this review summarizes the main analytical aspects reported in literature regarding not only simultaneous estimation but also stability-indicating methods for the analysis of proposed drugs in bulk and pharmaceutical dosage forms. Thus, this review gathers, for the first time, important background information on all analytical methods that have been developed and applied for the determination of Amlodipine Besylate, Telmisartan, and Indapamide. Furthermore, the reported methods have been also evaluated by greenest assessment tools, AGREE providing a comprehensive overview of various feature of analytical methods defining sustainability. Based on AGREE, total 134 methods including UV, HPLC and HPTLC were evaluated.

Keywords: *Amlodipine Besylate, Telmisartan, Indapamide, UV, HPLC, HPTLC, AGREE Tool.*

1. INTRODUCTION

Hypertension, the leading cause of death globally, is characterized by increased blood pressure over 140/90 mm Hg. An estimated 1.28 billion adults aged 30–79 years worldwide have hypertension, most (two-thirds) living in low- and middle-income countries. An estimated 46% of adults with hypertension are unaware that they have the condition. One of the global targets for noncommunicable diseases is to reduce the prevalence of hypertension by 33% between 2010 and 2030. It rises with age and significantly increases the risk of stroke and heart failure. Key antihypertensive medications include ACE inhibitors, calcium channel blockers, ARBs, and thiazide diuretics [1]. Nonpharmacological treatments involve lifestyle changes like reducing salt, increasing fruits and vegetables, regular exercise, and avoiding tobacco and excessive alcohol. Combination therapy often proves more effective than monotherapy, improving blood pressure control and patient compliance with fewer side effects. Effective management aims to reduce cardiovascular disease risk and improve quality of life. Amlodipine besylate, Telmisartan and Indapamide combination is approved by National Institutes of Health for conducting pivotal studies for the treatment of unregulated blood pressure with ischemic heart disorder [2]. This review is mainly focusing on existing analytical methods for quantifying these drugs in pharmaceutical products. This review provides a comprehensive analysis of the analytical methods employed for the determination of these compounds, including spectrophotometric techniques, High-Performance Liquid Chromatography (HPLC), High-Performance Thin-Layer Chromatography (HPTLC), Liquid Chromatography coupled with Tandem Mass Spectrometry (LC-MS/MS), and Liquid

Chromatography with Electrospray Ionization Mass Spectrometry (LC-ESI-MS).Green chemistry principles have become increasingly important in various disciplines of chemistry, including analytical chemistry. This is mainly due to an ongoing awareness of the state of the ecosystem and the negative impacts that analytical procedures can have on the environment. The most important approach developed to address this issue is Green Analytical Chemistry (GAC). GAC is an environmental-friendly approach to analytical chemistry that aims to minimize the negative impact of analytical techniques on the environment and human health. This review provided a comprehensive overview of the history of GAC and the existing greenness assessment metric tools. The various approaches, such as the National Environmental Methods Index (NEMI), Eco-scale Assessment (ESA), Green Analytical Procedure Index (GAPI), and Analytical Greens (AGREE) used to evaluate Green profiles [3]. The assessment criteria are taken from the 12 principles of green analytical chemistry (SIGNIFICANCE) and are transformed into a unified 0–1 scale. The final score is calculated based on the SIGNIFICANCE principles. The result is a pictogram indicating the final score, performance of the analytical procedure in each criterion, and weights assigned by the user. The AGREE tool was analyzed instead of GAPI, BAGI, and RGB models because it provides a comprehensive framework for assessing guideline quality based on rigor, clarity, and applicability. Unlike the other models, it is widely recognized for its structured approach to evaluate reliability and relevance, ensuring a standardized assessment. Additionally, AGREE's criteria are better aligned with quality assurance practices, making it more suitable for detailed evaluations. GREE has the merits of simplicity and automation over GAPI.

2. Drug Profile

2.1 Amlodipine Besylate

Chemically Amlodipine besylate (AMLO) is benzenesulfonic acid;3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. Its molecular formula is C26H31ClN2O8S and its structure is as shown in Fig 1(a). AMLO has a molecular mass of 567.1 g/mol. It is slightly soluble in water and sparingly soluble in methanol. The melting point is 199-201°C. Amlodipine is a well-known antihypertension medication that was first authorized by the FDA in 1987 and is a member of the class of medications known as dihydropyridine calcium channel blocker are linked to a lower incidence of myocardial depression and cardiac conduction problems than other calcium channel blocker because of their selectivity for the peripheral blood vessels. Amlodipine is frequently used to treat angina and excessive blood pressure. Antioxidant qualities and the capacity to increase nitric oxide (NO) synthesis make amlodipine a valuable vasodilator that lowers blood pressure. One appealing aspect of amlodipine is the ability to take it once daily [4].

2.2 Telmisartan

Chemically Telmisartan (TEL) is 2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2 propylbenzimidazol-1-yl]methyl]phenyl]benzoic acid . Its molecular formula is C33H30N4O2 and its structure is as shown in Fig 1(b). TEL has a molecular mass of 514.61 g/mol. It is slightly soluble in water and sparingly soluble in methanol. The melting point is 261-263°C. Telmisartan binds reversibly and selectively to the receptors in the adrenal gland and vascular smooth muscle, interfering with the binding of angiotensin II to the angiotensin II AT1-receptor. Systemic vascular resistance reduces when the effects of angiotensin II, a vasoconstrictor that also promotes the synthesis and release of aldosterone, are blocked. The angiotensin converting enzyme, other hormone receptors, and ion channels are not inhibited by telmisartan. Research indicates that telmisartan functions as a partial agonist of PPARγ, a known target for medications that treat diabetes. This implies that telmisartan can regulate insulin resistance, enhance lipid and carbohydrate metabolism, and avoid the negative effects linked to complete PPARγ activators [5].

2.3 Indapamide

Indapamide is a thiazide diuretic used to treat hypertension as well as edema due to congestive heart failure. Chemically indapamide is known as 4-chloro-N-(2-methyl-2,3-dihydroindol-1-yl)-3-sulfamoylbenzamide. Its molecular formula is $C_{16}H_{16}C_lN_3O_3S$ and its structure is as shown in Fig 1(c). Indapamide molecular mass is 365.835 g/mol. Aqueous solubility in buffer pH 7.4 and the melting point is 161°C. When compared to hydrochlorothiazide (another commonly prescribed diuretic), indapamide has been shown to be superior at lowering systolic blood pressure, reducing left ventricular mass index, lowering oxidative stress, inhibiting platelet aggregation, and reducing microalbuminuria associated with diabetes. Interestingly, unlike thiazide diuretics, several sources suggest that indapamide is not associated with glucose or lipid disturbances [6].

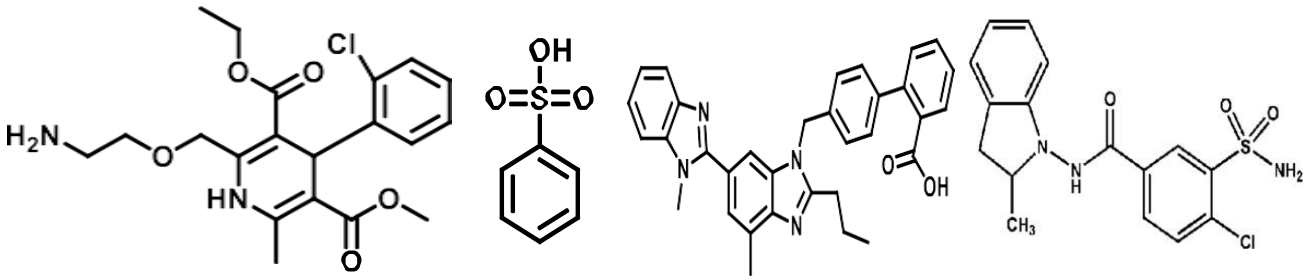


Fig 1: Chemical Structure of (a) AMLO (b) TEL (c) INDA

3. Analytical methods

3.1 Amlodipine Besylate

Compendial method development of Amlodipine besylate (AMLO) as per Indian Pharmacopeia 2018 is liquid chromatographic separation using C18 column (15 cm x 3.9 mm, 5 µm), mobile phase is as (acetonitrile: methanol: pH to 3.0 with orthophosphoric acid 15:35:50%w/v pH 3.5, 1%v/v orthophosphoric acid) flow rate 1 mL/min and detected at 237 nm. Amlodipine Besylate, silica gel GF254 on an aluminum plate as the stationary phase, with a mobile phase of glacial acetic acid:water isobutyl ketone (25:25:50, v/v/v), detection at 254 nm and 365 nm, Rf values 0.18 and 0.22 by HPTLC method [7]. As per British Pharmacopoeia 2022, A liquid chromatography method for the determination of AMLO using column C18 [5 µm], mobile phase [2.3 g/L solution of ammonium acetate R, methanol R (30:70 V/V)], flow rate at 1 mL/min and injection volume 20 µl at detection wavelength 237 nm [8]. As per USP, Chromatographic analysis was performed using a 3.9-mm × 15-cm L1 column. The mobile phase comprised of pH 3.0 buffer, methanol, and acetonitrile (50:35:15), with a flow rate of 1 ml/min with detection at 237 nm, and injection volume of 10 µl [9].

3.2 Telmisartan

For the analysis of Telmisartan as per Pakistan Pharmacopoeia 2018, a stainless steel column (12.5 cm × 4.0 mm) packed with octadecylsilane bonded to porous silica (5 µm), such as Thermoquest, was utilized. The mobile phase consisted of 20 volumes of methanol and 80 volumes of acetonitrile. The flow rate was set at 1 mL/min, with detection at 230 nm. The injection volume was 10 µL. As per IP 2018, Telmisartan is analyzed using a stainless steel column (15 cm × 4.6 mm) packed with octadecylsilane bonded to porous silica (5 µm), such as Inertsil ODS-3. The mobile phase comprises 60 volumes of a buffer solution and 40 volumes of acetonitrile. The flow rate was set to 1 mL/min, detection is at 298 nm, and the injection volume is 20 µL [10]. As per the British Pharmacopoeia 2022, Telmisartan is analyzed using a 0.125 m × 4.0 mm end-capped octadecyl silyl silica gel column. The mobile phase is methanol (20:80), with detection at 230 nm [11]. According to the USP, Telmisartan is analyzed using a 4.0 mm × 12.5 cm column with 5 µm packing. The mobile phase consists of acetonitrile and methanol in 80:20 ratio. The flow rate is set at 1 mL/min, with detection at 230 nm and an injection volume of 2 µL [12]. According to IP 2018, Indapamide is analyzed using a stainless steel column (20 cm × 4.6 mm) packed with octadecylsilane bonded to porous silica (5 µm). The mobile phase consists of 0.1 volumes of glacial acetic acid, 17.5 volumes of methanol, and 65 volumes of a 0.02% w/v sodium edetate solution. The flow rate is 2 mL/min, with detection at 254 nm and an injection volume of 10 µL [13]. As per the British Pharmacopoeia 2022, Indapamide is analyzed using a stainless steel column (20 cm × 4.6 mm) packed with octadecylsilane bonded to porous silica (5 µm). The mobile phase consists of glacial acetic acid:acetonitrile:methanol sodium edetate (0.1:17.5:17.5:65 v/v/v/v). The flow rate is 2 mL/min, with detection at 254 nm and an injection volume of 10 µL [14]. A simple and precise UV method was developed by Ramalingam P *et al.*, [15] for the estimation Amlodipine Besylate, using double distilled water as the solvent. The detection wavelength is 364 nm, with a concentration range of 6-80 µg/mL and an R^2 value of 0.998. Safila Naveed *et al.*, [16] developed the UV method for the determination of AMLO, where water was used as the solvent. The analysis is conducted at a wavelength of 238 nm, with concentrations of 50 ppm, 25 ppm, 12.5 ppm, and 6.25 ppm, and the method shows an R^2 value of 0.998. Priya P *et al.*, [17] developed the UV spectrophotometric method for AMLO, ethanol was used as the solvent. The detection wavelength is 360 nm, with a concentration range of 5-40 µg/mL and an R^2 value of 0.9985. Gidwani B *et al*., [18] developed a simple UV method for Amlodipine in bulk and tablet formulations, methanol was used as the solvent. The detection wavelength is 338 nm, with a concentration range of 10-50 µg/mL and an R^2 value of 0.997. Bernard S *et al*., [19] developed the spectrophotometric analysis of AMLO, a 2M urea solution was used as the hydrotropic solubilizing agent. The detection wavelength was 243 nm, with a concentration range of 5-25 µg/mL and an R^2 value of 0.9986. Reddy K *et al.*, [20] developed the UV method for AMLO, using methanol buffer as the solvent. The detection wavelength is 281 nm, with a concentration range of 5-30 µg/mL and an R^2 value of 0.9985.

Richa S *et al.*, [21] developed a liquid chromatographic method for AMLO using Column (3.9mm x15cm, 10 µl) that contains packing L1 using mobile phase: pH 3.0 Buffer, methanol, and acetonitrile

(50:35:15) with flow rate 1 ml/min and detection wavelength at 237 nm. Pawar HA *et al*., [22] developed RP-HPLC Method for AMLO using cosmosil C18 column (250 mm x 4.6 mm, 5µ) at flow rate 1 ml/min using acetonitrile: potassium dihydrogen orthophosphate buffer: methanol (44:46:10, % v/v/v) as mobile phase and pH adjusted to 3 with orthophosphoric acid with detection wavelength at 239 nm. Vavia PR *et al*., [23] developed HPLC method for Amlodipine Besylate and its related substance in tablet formulation by chiral separation using Zorbax® Eclipse XDB-C18 column (4.6 x 150 mm, 5µm) and buffer (0.7% aqueous triethylamine adjusted to pH 3.0 with orthophosphoric acid): methanol (40:60 v/v) as mobile phase at 1 ml/min flow rate and 239 nm detection wavelength. Quantification of the related substance impurities of AMLO by liquid chromatographic method developed by Chandra D *et al*., [24] reports developed RP-HPLC method using Ultron ES-OVM, C18 column (250mm x 4.6mm, 5 µm) chiral column and Buffer: acetonitrile (78:22, v/v) as mobile phase, at 237 nm detection wavelength and 1ml per minute flow rate. De Borba *et al*., [25] developed HPLC method for AMLO using Zodiac C18 column (250mm x 4.6mm, 5µ) and Methanol: Acetonitrile: 0.01M Phosphoric acid (75:23:2, %v/v/v) as a mobile phase and at 237 and 262 nm detection wavelength using 1 ml/min flow rate was reported.

3.1.1. Amlodipine besylate with Other Drug Combinations

Gholve RB *et al*., [26] developed stability-indicating RP-HPLC method for simultaneous estimation of bisoprolol fumarate and amlodipine besylate using Oyster ODS3 (150 × 4.6 mm, 5 µm) column with 1 ml/min flow rate and 20 mM phosphate buffer with pH 2.5 (adjusted by 5% orthophosphoric acid):methanol:acetonitrile (42:29:29, v/v/v) as eluents at a wavelength of 230 nm. The retention time was found to be 2.543 and 4.883 min for bisoprolol and amlodipine, respectively.

Kumar TH *et al*., [27] developed new validated stability indicating RP-HPLC method for simultaneous estimation of amlodipine besylate and valsartan using a C18 column (250 × 4.6 mm, 0.5 µm). The mobile phase was sodium acetate buffer (pH 5.0) and methanol (35:65 % v/v). Detection was at 234 nm, with a flow rate of 1 ml/min, injection volume of 20 µl, and retention time of 3.146 min for Amlodipine besylate and 6.543 min for Valsartan. Kumar D *et al*., [28] developed stability indicating RP-HPLC method for Amlodipine besylate and olmesartan using a C18 column (4.6 × 150 mm, 5 µm). The mobile phase consisted of varying ratios of triethylamine buffer and acetonitrile. Detection was at 258 nm, with a flow rate of 1 ml/min. Retention time were 2.39 min for Amlodipine besylate and 3.33 min for Olmesartan. Jadhav MP *et al*., [29] developed RP-HPLC method for Amlodipine besylate and celecoxib using a Flowrosil C18 column (250 × 4.6 mm, 5 µm). The mobile phase was acetonitrile and water (80:20 v/v). Detection was at 250 nm, with a flow rate of 1 ml/min, injection volume of 20 µl, and retention time of 1.98 min for Amlodipine besylate and 3.15 min for Celecoxib. Hingde S *et al*., [30] developed RP-HPLC method for Amlodipine besylate, chlorthalidone hydrochloride, and olmesartan medoxomil using a Prontosil C18 column (250 x 4.6 mm, 5 µm). The mobile phase was acetonitrile and 0.02 M potassium dihydrogen phosphate buffer (60:40), pH 3.0. Detection was at 240 nm with a flow rate of 1 ml/min, injection volume of 20 µl, and retention time of 3.017 min for chlorthalidone HCl, 3.313 min for Amlodipine besylate, and 5.010 min for olmesartan medoxomil. Mahant B Das *et al*., [31] developed UV-Spectrophotometric and stability indicating RP-HPLC method for the simultaneous estimation of Amlodipine Besylate and Indapamide using a C18 column (25 cm × 4.6 mm) and mobile phase was methanol and water (95:5 % v/v). Detection was at 238 nm, with a flow rate of 1 ml/min, injection volume of 20 µl, and retention times of 8.780 min for Amlodipine besylate and 2.850 min for indapamide. Dyade GK *et al*., [32] developed RP-HPLC method for Amlodipine besylate, rosuvastatin, and valsartan using a C18 column (25 cm × 4.6 mm, 10 µm). The mobile phase was acetonitrile and water (75:25 % v/v), pH 4.8. Detection was at 245 nm, with a flow rate of 0.8 ml/min, injection volume of 20 µl, and retention times of 2.41 min for Amlodipine besylate, 4.01 min for rosuvastatin, and 5.02 min for valsartan. Sadanand KS [33] reported stability indicating RP-HPLC method for Amlodipine besylate and lisinopril using a C18 COSMOSIL column (150 mm x 4.6 mm, 5 µm). The mobile phase was acetonitrile and phosphate buffer (25:75 % v/v). Detection was at 211 nm, with a flow rate of 1 ml/min, and retention time of 4.41 min for Amlodipine besylate and 5.83 min for lisinopril. Pappula N *et al*., [34] Amlodipine besylate and hydrochlorothiazide were analyzed by HPLC using a Shiseido C18 column (250 × 4.6 mm, 5 µm). The mobile phase was acetonitrile, methanol, and water (30:40:30 % v/v/v), with detection at 227 nm, a flow rate of 1 ml/min, and an injection volume of 10 µl. The retention time was 3.90 min. Patel KP *et al*., [35] developed a new RP–HPLC method for simultaneous quantification of perindopril erbumine, indapamide, and amlodipine besylate using a Phenomenex C18 column, acetonitrile:methanol (30:20:50), 1 mL/min flow rate, 215 nm detection, and 20 µL injection volume. Tamboli AM *et al*., [36] developed HPTLC method for Amlodipine Besylate and Enalapril Maleate, using aluminium-backed silica gel 60F254 plates, mobile phase toluene:isopropanol:GAA (6:2:0.6:0.5), 223 nm detection, Rf values 0.15 and 0.25. Jadhav NB *et al*., [37] developed HPTLC of Amlodipine Besylate and Bisoprolol Fumarate, using aluminium foil plates coated with silica gel 60F254, mobile phase chloroform:ethanol acetic acid (2:8:0.1), 231 nm detection, Rf of Amlodipine besylate and Bisoprolol fumarate were 0.53 and 0.72, respectively.

Mandale TR [38] developed HPTLC method for Amlodipine Besylate and Celecoxib, employing silica gel 60 F254 plates with a mobile phase of toluene: acetate:methanol. ammonia (6:5:1.5:0.3) and detect at 310 nm. Rf values are 0.28 and 0.73. Wankhede SB *et al*., [39] developed HPTLC method Amlodipine Besylate and Lisinopril, using aluminum plates precoated with silica gel 60F254 using a mobile phase of n-butanol:methanol (4:4:1) and detect at 215 nm, with Rf values of 0.62 and 0.27. Ramyasree A *et al*., [40] Stability indicating HPTLC method for Amlodipine and Lisinopril, use 10 × 10 cm 60F254 plates The mobile phase was n-butanol acid (6:2:2), detected at 560 nm, with Rf values 0.69 and 0.31. Solanki T *et al*., [41] developed HPTLC method for Olmesartan Medoxomil, Amlodipine Besylate, and Hydrochlorothiazide, using aluminum plates precoated with silica gel 60F254. The mobile phase consists of toluene: chloroform: methanol formic acid (2:7:1.8:0.8:0.2 %v/v/v/v/v), with detection at 232 nm and Rf values of 0.78, 0.20, and 0.45. Lakshmi S *et al*., [42] developed HPTLC for determination of Losartan Potassium, Amlodipine Besylate, and Hydrochlorothiazide using aluminum plates coated with a 0.2 mm layer of silica gel 60F254 and mobile phase was composed of chloroform: methanol: acetone acid in a ratio of 7.5:1.3:0.5:0.03 (%v/v/v/v). Detection was carried out at 254 nm, with Rf values recorded as 0.74, 0.35, and 0.57, respectively. Saminathan J *et al*., [43] developed HPTLC method for Olmesartan Medoxomil, Amlodipine Besylate, and Hydrochlorothiazide using aluminum plates precoated with silica gel 60F254were used as the stationary phase. The mobile phase comprised chloroform: methanol acid (8.5:1.5:0.25 %v/v/v). Detection was performed at 254 nm, with Rf values of 0.57, 0.36, and 0.21. Swamy GK *et al*., [44] developed HPLC method for Amlodipine Besylate and Valsartan, a C18 column (250 × 4.6 mm, 0.5 µm) was used. The mobile phase consisted of sodium acetate buffer (pH 5.0) and methanol in a ratio of 35:65 (%v/v). The flow rate was 1 ml/min, and detection occurred at 234 nm. The injection volume was 20 µL, with retention times of 3.146 min for Amlodipine Besylate and 6.543 min for Valsartan.

3.2 Telmisartan

Rathod SD *et al*., [45] developed a UV-spectrophotometric method for telmisartan estimation in bulk and tablet forms, using 0.1 N NaOH and water (20:80) at 234 nm, achieving linearity (R^2 = 0.999) within 2-10 µg/ml. Chivate *et al*., [46] evaluated Telmisartan using UV detection at 240 nm with 60% ethanol (95%) and 40% 0.1 N $NaHCO_3$, achieving linearity (R^2= 0.999) within the 2-14 µg/ml concentration range. Patel *et al*., [47] conducted stress degradation studies on Telmisartan, using UV detection at 296 nm with methanol as the solvent, achieving linearity within the concentration range of 4–24 µg/ml. Sonia K *et al*., [48] investigated Telmisartan using UV detection at 295 nm with 0.1 N NaOH as the solvent, achieving linearity (R^2 = 0.999) within the concentration range of 4–24 µg/ml. Waghmare *et al*., [49] assessed telmisartan using UV detection at 292 nm with a pH 6 solvent combination of HCl and water (60:40), achieving linearity (R^2 = 0.997) within the 4–24 µg/ml range. Rajesh S *et al*., [50] developed UV method for telmisartan using UV detection at 296.5 nm with a solvent combination of water, sodium hydroxide, acetic acid, and methanol, achieving linearity (R^2 = 0.9994) within the 5-25 µg/ml range. Kumar M *et al*., [51] developed UV spectroscopy method for Telmisartan with a detection wavelength of 296 nm, a concentration range of 2–12 µg/ml, and an R2 value of 0.999 using 0.1N HCl as the solvent. Tsvetkova DD *et al*., [52] developed UV spectroscopy method for Telmisartan with ethanol as the solvent, a detection wavelength of 298 nm, a range of 60-100 mg/ml, and an R2 value of 0.999. Shaina S *et al*., [53] developed HPLC method for Telimsartan using Hypersil BDS C8 column, a methanol-acetonitrile mobile phase (1:1) with 1.2 ml/min flow rate, a 298 nm detection wavelength, and a 20 µl injection volume. Prajapati P *et al*., [54] developed HPLC method for Telimsartan using C18 column, acetonitrile/0.1% triethylamine (45:55) mobile phase (pH 6.2), 1 ml/min flow rate, 220 nm detection, and 3.442. Upendra B *et al*., [55] developed RP-HPLC method for telmisartan using a C18 column with a mobile phase consign of 0.025M potassium dihydrogen phosphate/acetonitrile/methanol (45:50:5), a flow rate of 1 ml/min, detection at 216 nm, and a 20 µl injection volume. Lakshmi Surekha M *et al*., [56] developed RP-HPLC method for Telmisartan using Phenomenex C18 column (250 × 4.6 mm, 5 µm). The mobile phase comprised 10 mM potassium dihydrogen phosphate buffer and methanol in a 20:80 (v/v) ratio. The flow rate was 0.8 ml/min, detection was at 296 nm and the injection volume was 20 µl. Telmisartan exhibited a retention time of 4.804 min. Prabhu C *et al*., [57] developed a HPTLC method for telmisartan analysis using silica gel G60 F254 plates with a mobile phase of chloroform/methanol/0.1% ammonia (8.6:1.4). Detection was performed at 297 nm, and telmisartan exhibited an Rf value of 0.43. Chandurkar SN *et al*., [58] analyzed telmisartan using HPTLC on silica gel G60 F254 plates, employing a mobile phase of toluene and methanol (7:3 ratio). Detection was carried out at 299 nm, with telmisartan showing an Rf value of 0.46. Vekariya NR *et al*., [59] developed a stability-indicating HPTLC method for telmisartan using silica gel 60 F254 plates. The mobile phase consisted of ethyl acetate, dichloroethane, and methanol in a 6:2:1 ratio. Detection was performed at 295 nm, and the method yielded an Rf value of 0.68.

3.2.1 Telmisartan with other drugs

Lalit Thakare *et al*., [60] developed UV spectroscopy for Telmisartan and Cilnidipine using acetonitrile and water in a 5:5 ratio as the solvent. The detection was carried out at 241 nm, within a concentration range of 2–10 µg/ml, achieving an R^2

value of 0.999. Devi S *et al*., [61] estimated Telmisartan, Chlorthalidone, and Cilnidipine using UV spectroscopy with methanol as the solvent, a detection wavelength of 325 nm, a range of 10-80 µg/ml, and an R2 value of 0.997. Roja P *et al*., [62] developed UV spectroscopy method for simultaneous quantification for Azelnidipine and Telmisartan using methanol as solvent and the detection wavelength was 296 nm. The linearity range was 5-30 µg/ml, and the R2 value was 0.9987. Mohite PB et al. [63] simple, accurate UV method for Ramipril and Telmisartan using 0.2M H2SO4 as the solvent, a detection wavelength of 291 nm, a range of 2-20 µg/ml, and R2 value was found to be 0.9999. Sabhadinde AF *et al*., [64] developed novel RP-HPLC for Chlorthalidone and Telmisartan, The method was developed on the Grace C18 column using acetonitrile/potassium phosphate buffer (45:55, pH 2.5) mobile phase with a flow rate of 0.7 mL/min. This was detected at 203 nm using 20 µl injection volume. Adeshra SD *et al.*, [65] developed HPLC for Efonidipine hydrochloride ethanolate and Telmisartan using a Phenomenex Kinetex® C18 column, acetonitrile/potassium phosphate buffer (45:55, pH 2.5) as a mobile phase with 1 ml/min flow rate. This was detected at 253 nm using 20 µl injection volume. Deshmukh TB *et al*., [66] developed HPLC method for Atorvastatin Calcium and Telmisartan, Chromatography is performed on using a Chemsil C18 column using 0.02 M ammonium acetate buffer/acetonitrile/tetrahydrofuran (400:400:14) as a eluent and carried out at a flow rate of 1.5 ml/min. The analyte was monitored using a PDA detector at 246 nm using 20 µl injection volume. Jawanjal MA *et al*., [67] developed RP-HPLC method for simultaneous estimation of Telmisartan and Azelnidipine using a C8 column and methanol/acetonitrile (50:50, 0.1% formic acid) as mobile phase with 1 ml/min flow rate. This was detected at 257 nm. Kumar M *et al*., [68] developed a stability indicating RP-HPLC method for Azelnidipine and Telmisartan using an Inertsil C18 column and 0.02 M and ammonium acetate buffer/acetonitrile/tetrahydrofuran (400:400:14) as a mobile phase, The flow rate was 1.5 ml/min. This was detected at 254 nm using 10 µl injection volume. Barge VU *et al*., [69] developed RP-HPLC for Bisoprolol Fumarate and Telmisartan using with a Waters X Bridge RP C18 column (4.6 x 250 mm). The mobile phase was 75:25 methanol-water with 1 ml/min flow rate. This was detected at 257 nm and 20 µl injection volume. Gholve R *et al*., [70] developed HPLC method for Telmisartan and Rosuvastatin Calcium using Oyster ODS3 column (150 x 4.6 mm, 5 µm) with 10 mM phosphate buffer (pH 2.5) and acetonitrile (1:1) mobile phase. The flow rate was 1 ml/min using 242 nm detection wavelength with 20 µl injection volume. Kariv S *et al*., [71] developed HPLC method for Benidipine Hydrochloride, Telmisartan, and Chlorthalidone using C18 column (25 cm x 0.46 cm, Hypersil BDS). The mobile phase was 50:50 buffer (pH 3.0) and methanol mobile phase with 1 ml/min flow rate. The detection wavelength was 240 nm using 20 µl injection volume. Tambe V *et al*., [72] developed a stability indicating HPTLC method for Telmisartan and Hydrochlorothiazide using silica gel 60 F254 plates, a 15:1.5:3:1.5 ethyl acetate, 1,4-dioxane, methanol, and ammonia was used as mobile phase with 233 nm detection wavelength. The Rf value of Telmisartan and Hydrochlorothiazide was found to be 0.21 and 0.53. Sivasubramanian L [73] developed HPTLC method for the estimation of Irbesartan, Telmisartan, Hydrochlorothiazide, and Ramipril. The TLC plates used for chromatography as a stationary phase were aluminium plates precoated with silica gel 60F254. The development was done with a mobile phase acetonitrile, toluene, methanol, and formic acid (8:10:2:0.6) The densitometric scanning was done at 210nm and the separation that occurred was found to be at an Rf value of 0.42. Pattanik SK *et al*., [74] developed Stability Indicating HPTLC for Telmisartan and Gallic acid, The stationary-phase used was Aluminium-backed silica gel 60F254 TLC plates (20cm×10cm, thickness-0.2mm). The mobile-phase consisted of ethyl acetate: methanol: chloroform: acetic acid in the ratio of 4:2:2:0.2(v/v/v/v). The wavelengths at which both drugs exhibit substantial absorbance, 280 nm and 296 nm respectively, for the simultaneous assessment of Gallic acid and Telmisartan, the detected Rf values were 0.60 and 0.67, respectively. Maheswari R *et al*., [75] developed HPTLC method for Telmisartan and Hydrochlorothiazide using with pre-coated silica gel plate 60 F254. The mobile phase was ethyl acetate, chloroform, and methanol in a 10:3:1 ratio, and a detection wavelength was 270 nm. Ilango K *et al*., [76] developed HPLC and HPTLC method for Telmisartan and Atorvastatin, The proposed RP-HPLC method utilizes a Phenomenex Luna C18 column using acetonitrile: 0.025 M ammonium acetate (38 : 52%, v/v) as mobile phase (pH 3.8), flow rate of 1.0 ml/min. Quantification was achieved with UV detection at 281 nm over concentration range of 12 to 72 µg/mL for Telmisartan and 3 to 18 µg/mL for Atorvastatin respectively. In HPTLC, separations were performed on silica gel 60 F254 using toluene-methanol-ethyl acetate-acetic acid (5 : 1 : 1 : 0.3, v/v) as mobile phase. The compact bands of Telmisartan and Atorvastatin at 0.37 ± 0.02 and 0.63 ± 0.01 respectively were scanned at 279 nm. Gandu S *et al*., [77] developed an accurate, precise and reproducible RP-HPLC and UV Spectrophotometric method for the simultaneous estimation of Metoprolol and Telmisartan in tablet dosage form. The chromatographic separation was carried out on X-tera C8 column (100mm x 4.6mm,5µ), by using the mobile phase (0.05M Sodium phosphate buffer pH 2.8 and methanol) in the ratio 35:65, at a flow rate 1.2ml/min. The detection was carried out at a wave length of 226nm. The retention time for Metoprolol and Telmisartan was found to be 2.338 and 5.559 respectively. UV method involves solving simultaneous equations based on measurement of absorbance at two wavelengths 223nm and 296nm λmax of Metoprolol and Telmisartan respectively. Beer's law was obeyed in the concentration range of

1.25-6.25µg/ml and 2-10µg/ml for Metoprolol and Telmisartan respectively. Jane J *et al*., [78] developed two methods. A simultaneous estimation of metoprolol and telmisartan by UV spectrophotometry, secondly by RP-HPLC. Method 1 was estimated by three multicomponent analysis procedure, in method 1a the estimation of Metoprolol and Telmisartan was based on Simultaneous equation analysis for metoprolol and telmisartan by UV absorption at 276nm and 296nm respectively and linearity was observed in the concentration range of 20-100 µg/ml for both the drugs. Method 1b, simultaneous estimation by Q-analysis based on isoabsorptive point(269 nm) and at 296 nm. Method 1c, was absorption correction method were the linearity was observed between 20-100 µg/ml at their respective absorption maximas. Method 2 involved an isocratic elution of Metoprolol and Telmisartan in a column of phenomenex C18,250x4.6,5µ using a mobile phase of composition acetonitrile and ammonium acetate buffer of pH 3.5 in the ratio 70:30 v/v at a flow rate of 1ml/min and the analyte was monitored at 269nm. The chromatograms of the standard and dosage forms of metoprolol and telmisartan were recorded and linearity was observed in the concentration range of 30-70 µg/ml and 24-56 µg/ml respectively.

Patel K *et al*., [79] developed a UV spectroscopy method for the simultaneous estimation of Telmisartan and Metoprolol Succinate using methanol as the solvent. The method utilized detection wavelengths of 296 nm and 223 nm, with concentration ranges of 2-16 µg/ml and 3-24 µg/ml, respectively. The method demonstrated high linearity, with R^2 values of 0.9999 and 0.9998 for Telmisartan and Metoprolol Succinate. Mayur Modi *et al*., [80] developed a UV spectroscopy method for the evaluation of Metoprolol Succinate and Telmisartan using methanol as the solvent. The method employed detection wavelengths of 230 nm and 237 nm, with concentration ranges of 3-20 µg/ml and 4-16 µg/ml, respectively, and achieved an R^2 value of 0.999. Suthakaran R *et al*., [81] developed HPLC method for the simultaneous estimation of Telmisartan and Metoprolol using XBridge C18 column. The method utilized a methanol-water mobile phase in a 58:42 ratio with a pH of 3.5, a flow rate of 1 ml/min, and a detection wavelength of 224 nm. Shaikh K *et al*., [82] developed HPLC method for the simultaneous estimation of Telmisartan and Metoprolol using an Inertsil ODS 3V column. The method employed a mobile phase consisting of 0.05 M sodium dihydrogen phosphate buffer and acetonitrile in a 75:25 ratio, with a pH of 3.0, a flow rate of 1 ml/min, and a detection wavelength of 222 nm. Jain Nilesh *et al*., [83] developed HPLC method for Metoprolol Succinate and Telmisartan using Prontosil C18 column. The mobile phase was used acetonitrile, methanol, and phosphate buffer (35:35:30, pH 5) with a 1 ml/min flow rate, and a 225 nm detection wavelength. Nawale PS *et al*., [84] developed HPTLC method for Metoprolol Succinate and Telmisartan using stationary phase (20 cm x 10 cm) HPTLC plates, a toluene-propanol-methanol-triethylamine used as mobile phase (8:1:1:0.5), a 242 nm detection wavelength, and Rf values of 0.45 and 0.70. Patel BS *et al*., [85] developed HPLC method for the simultaneous evaluation of Cilnidipine, Metoprolol Succinate, and Telmisartan. The method utilized methanol as the solvent, with detection wavelengths set at 241 nm, 224 nm, and 296 nm for Cilnidipine, Metoprolol Succinate, and Telmisartan, respectively. The concentration ranges for these analytes were 2-10 µg/ml for Cilnidipine, 5-24 µg/ml for Metoprolol Succinate, and 8-40 µg/ml for Telmisartan. The method exhibited high linearity, with R^2 values of 0.9991 for Cilnidipine, 0.9993 for Metoprolol Succinate, and 0.9989 for Telmisartan.

Sudha ST *et al*., [86] developed a UV spectroscopy method for the simultaneous assessment of Telmisartan, Metoprolol Succinate, and Chlorthalidone using methanol as the solvent. The method utilized detection wavelengths of 315 nm for Telmisartan, 331 nm for Metoprolol Succinate, and 250 nm for Chlorthalidone. The concentration ranges were 16-80 µg/ml for Telmisartan, 9.5-47.5 µg/ml for Metoprolol Succinate, and 2-12.4 µg/ml for Chlorthalidone. The method demonstrated high linearity, with R^2 values of 0.999 for both Telmisartan and Metoprolol Succinate, and 0.998 for Chlorthalidone. Hinge MA *et al*., [87] investigated Metoprolol Succinate, Cilnidipine, and Telmisartan using a UV spectroscopy method with methanol as the solvent. The detection wavelengths were set at 216.50 nm for Metoprolol Succinate, 241.82 nm for Cilnidipine, and 302.18 nm for Telmisartan. The concentration ranges were 2.4-12 µg/ml for Metoprolol Succinate, 1-5 µg/ml for Cilnidipine, and 4-20 µg/ml for Telmisartan. The method exhibited excellent linearity, with R^2 values of 0.9996, 0.9991, and 0.9999, respectively. Kalshetti MS *et al*., [88] evaluated Metoprolol, Cilnidipine, and Telmisartan using HPLC method with a Phenomenex Luna C18 column. The method employed a mobile phase composed of acetonitrile, methanol, and phosphate buffer in a ratio of 45:30:25, with a flow rate of 1 ml/min and a detection wavelength of 229 nm.

3.3 Indapamide

Tarkase K *et al*., [89] conducted an analysis of Indapamide using phosphate buffer at pH 7.4, with detection wavelengths set at 240 nm and 223 nm. The method covered a concentration range of 5-40 µg/ml and achieved R^2 values of 0.996 and 0.998, indicating good linearity. Hegheș SC *et al*., [90] analyzed Indapamide using HPLC with an X-Terra C18 column (250 mm × 4.6 mm, 5 µm), utilizing a mobile phase consisting of aqueous Na_2EDTA, acetonitrile, and methanol, with detection set at 254 nm. Ratnakar BL *et al*., [91] developed HPTLC method for Indapamide using silica gel 60 F254 TLC plates (20 cm × 10 cm, 0.2 mm layer), a mobile phase of ethyl acetate/water/25% ammonia, and detection at 241 nm. The Rf value of

indapamide was found to be 0.62 ± 0.03. Youssef NF [92] developed three sensitive methods for determining indapamide: spectrophotometric, spectrofluorimetric, and densitometric. The first two methods involve an oxidative coupling reaction with 3-methyl-2-benzothiazolinone hydrazone and cerium(IV) ammonium sulfate in an acidic medium, measuring absorbance at 601 nm or quenching fluorescence at 350 nm (emission) and 300 nm (excitation). These methods showed Beer's law compliance for indapamide at 1.2-9.6 µg/mL with mean recoveries around 99.9%. The third, a stability-indicating densitometric assay, used a specific solvent system and scanning at 242 nm, achieving 99.73% recovery.

3.3.1 Indapamide with Other Drug Combinations

Gupta KR *et al*., [93] separated atenolol and indapamide on a silica gel 60G F254 plate using a mobile phase mixture of toluene, ethanol, acetone, and acetic acid (7:2.5:3:0.3 v/v). Quantification was performed using a densitometer in absorbance mode at 266 nm. The Rf values for atenolol and indapamide were found to be 0.21 and 0.74, respectively. Nazareth C *et al*., [94] achieved chromatographic separation on HPTLC aluminum plates coated with silica gel 60F254. The optimized mobile phase for the separation was toluene, chloroform, and ethanol in a 4:4:1 v/v ratio. The Rf values for the separated components were 0.15 for olmesartan medoxomil and 0.47 for indapamide. Vyas N *et al*., [95] developed a HPTLC method for nebivolol and indapamide using silica gel 60 F254 TLC plates using a mobile phase of ethyl acetate, methanol, and dilute ammonia (8.5:0.8:1.0 v/v/v). This system effectively resolved compact bands for nebivolol and indapamide, with Rf values of approximately 0.43 and 0.64, respectively.

Gumieniczek A *et al*., [96] analyzed indapamide and dihydralazine by HPLC/LC-MS using a LiChrospher® CN column (125 × 4.0 mm, 5 µm). The mobile phase consisted of formic acid, ammonium formate, and acetonitrile, with detection at 228 nm. El-Bagary RI *et al*., [97] performed chromatographic separation for Perindopril Arginine, Amlodipine, and Indapamide using BDS Hypersil® C18 column (100 × 3 mm, 5 µm) with a mobile phase of 0.05 M potassium dihydrogen phosphate buffer (pH 2.6) and methanol (50:50 v/v). The column was maintained at 50°C, with a flow rate of 0.6 mL/min using isocratic elution. UV detection was carried out at 215 nm. The retention times were 3.457 minutes for Perindopril Arginine, 6.097 min for Amlodipine, and 2.007 minutes for Indapamide. Babu GR *et al*., [98] used a Waters Alliance HPLC system with an auto-sampler, UV-Visible detector, and a YMC column (150 × 4.6 mm, 3 µm particle size) for drug quantification. Separation was achieved using a mobile phase of potassium dihydrogen phosphate buffer (pH 2.5) and acetonitrile in a 60:40 v/v ratio at a flow rate of 1 mL/min, with detection at 230 nm. The retention time were 2.5 min for indapamide and 4.18 min for perindopril. Valentin I *et al*., [99] developed HPLC method for perindopril and indapamide using a C18 stationary phase (Zorbax Stable Bond 3.5 µm) column under isocratic elution with a flow rate of 1 mL/min. The mobile phase consisted of a mixture of potassium dihydrogen phosphate buffer (5 mM, pH 2.8), acetonitrile, and methanol. Detection was performed at 215 nm, a nonspecific wavelength. The retention times were 1.940 minutes for perindopril and 3.178 minutes for indapamide. Jogia H *et al*., [100] developed HPLC method for Perindopril and Indapamide using an X-Terra C18 column (250 mm × 4.6 mm, 5 µm) with a NaH_2PO_4 buffer (pH 2.0)–acetonitrile mobile phase, and detection at 215 nm.

3.4 Amlodipine and Telmisartan

Shinde SP *et al*., [101] developed a UV spectroscopic method for the analysis of Amlodipine and Telmisartan using 0.1N sodium hydroxide as the solvent. The method involved detection at wavelengths of 242 nm for Amlodipine and 231 nm for Telmisartan, with concentration ranges of 5-30 µg/ml and 2-7 µg/ml, respectively, and achieved R^2 values of 0.999 and 0.998 Dyade GK *et al*., Hirpara KP *et al*., [102] developed a method using 0.1 N HCl as the solvent, with detection at 362 nm for Amlodipine besylate and 292 nm for Telmisartan. The concentration ranges were 0.5-20 µg/ml and 3-24 µg/ml, with R^2 values of 0.999 and 0.998.

Dyade *et al*., [103] employed UV spectroscopy with methanol as the solvent to analyze Amlodipine and Telmisartan. Detection wavelengths were 238 nm for Amlodipine and 296 nm for Telmisartan, with concentration ranges of 5-30 µg/ml and 1-15 µg/ml, achieving R^2 values of 0.999 and 0.998. Maheshwari *et al*., [104] used UV spectroscopy to analyze Telmisartan and Amlodipine Besylate with 0.1N HCl as the solvent. Detection wavelengths were 365 nm for Telmisartan and 291 nm for Amlodipine Besylate. The concentration range for both was 5-40 µg/ml, with R^2 values of 0.9998 and 0.9999, respectively. Kondawar *et al*., [105] utilized UV spectroscopy with methanol to analyze Telmisartan and Amlodipine Besylate. Detection wavelengths were set at 238 nm for Telmisartan and 295 nm for Amlodipine Besylate. The concentration ranges were 2-30 µg/ml and 2-25 µg/ml, with R^2 values of 0.9999 and 0.9994, respectively. Krishnan *et al*., [106] analyzed Amlodipine Besylate and Telmisartan using UV spectroscopy with methanol as the solvent. Detection wavelengths were 360 nm for Amlodipine Besylate and 298 nm for Telmisartan. The concentration ranges were 15-75 µg/ml for Amlodipine Besylate and 1-10 µg/ml for Telmisartan, with R^2 values of 0.999 for both. Patel *et al*., [107] analyzed Telmisartan and Amlodipine Besylate using HPLC with a Hypersil BDS column. The mobile phase consisted of a phosphate buffer (pH 3.5) and acetonitrile in a 57:43 ratio, with a flow rate of 1 ml/min. Detection was carried out at 237 nm, using a 10 µl injection volume.

M. Kranthi *et al*., [108] analyzed Telmisartan and Amlodipine Besylate using HPLC with a Hypersil BDS column. The mobile phase consisted of acetonitrile, water, and triethylamine in a 68:31.8:0.2 v/v ratio at pH 4. The analysis was performed at a flow rate of 1 ml/min with a detection wavelength of 240 nm. The retention times for amlodipine besylate and telmisartan were 2.3 minutes and 3.4 minutes, respectively. Younus M *et al*., [109] developed HPLC method for Amlodipine Besylate and Telmisartan using HPLC with an Athena C18 column, methanol and phosphate buffer (pH 4.0) in a 70:30 ratio as the mobile phase with a 1 ml/min flow rate, and 240 nm detection wavelength. Chabukswar AR *et al*., [110] analyzed Telmisartan and Amlodipine Besylate using HPLC with a Phenomenex Luna C18 column. The mobile phase consisted of a phosphate buffer (pH 4.0) and acetonitrile in a 42:58 ratio. The analysis was carried out at a flow rate of 1 ml/min, with a detection wavelength of 236 nm and an injection volume of 20 µl. Paul RM *et al*., [111] analyzed Telmisartan and Amlodipine Besylate using HPLC with a Kromasil C18 column. The mobile phase consisted of acetonitrile, methanol, and a triethylamine buffer (pH 5.0). The analysis was conducted at a flow rate of 1.5 ml/min, with a detection wavelength of 237 nm and an injection volume of 20 µl. Thomas AB *et al*., [112] developed an HPLC method for analyzing Telmisartan and Amlodipine Besylate using an ODS Symmetry C18 column. The mobile phase consisted of acetonitrile and phosphate buffer (pH 4.0) in a 60:40 ratio. The method utilized a flow rate of 1.2 ml/min and a detection wavelength of 237 nm. Chabukswar AR *et al*., [113] analyzed Telmisartan and Amlodipine Besylate using HPTLC with aluminum-backed silica gel 60F254 plates. The mobile phase comprised ethyl acetate, methanol, ammonia, and glacial acetic acid in a 7.5:1.5:1.0:0.2 ratio. The detection wavelength was set at 226 nm, and the Rf values for Telmisartan and Amlodipine Besylate were 0.34 and 0.60, respectively. Vekariya N *et al*., [114] developed a method using TLC aluminum plates precoated with silica gel 60F254 as the stationary phase. The solvent system consisted of tetrahydrofuran, dichloroethane, methanol, and ammonia solution in a 6.0:2.0:1.0:0.4 v/v ratio. This system produced compact spots for both Telmisartan, with an Rf value of 0.22 ± 0.02, and Amlodipine Besylate, with an Rf value of 0.45 ± 0.02.

3.4.1 Amlodipine and Telmisartan with other drugs

Raskar MA *et al*., [115] developed a UV method for the simultaneous estimation of Telmisartan, Hydrochlorothiazide, and Amlodipine Besylate using methanol as the solvent. The detection wavelengths were set at 222 nm, 227 nm, and 234 nm, with a concentration range of 5-30 µg/ml, achieving an R^2 value of 0.999. Scholar RM *et al*., [116] developed a UV analysis method for Telmisartan, Rosuvastatin calcium, and Amlodipine Besylate, using methanol as the solvent. The detection wavelengths were 242 nm, 296 nm, and 360 nm, with a concentration range of 0.25-6 µg/ml, and the method achieved an R^2 value of 0.999. Bulbule MM *et al*., [117] developed a UV analysis method for Hydrochlorothiazide, Telmisartan, and Amlodipine Besylate using methanol as the solvent. The detection wavelengths were 265 nm for Hydrochlorothiazide, 250 nm for Telmisartan, and 335 nm for Amlodipine Besylate, with concentration ranges of 10-60 µg/ml, 4-20 µg/ml, and 20-100 µg/ml, respectively, and an R^2 value of 0.999. Sasidhar RLC *et al*., [118] conducted an HPLC analysis of Hydrochlorothiazide, Amlodipine Besylate, and Telmisartan using an Agilent ODS UG 5 C18 column. The mobile phase consisted of acetonitrile and acetate buffer (pH 5), with detection carried out at 333 nm, a flow rate of 1 ml/min, and an injection volume of 20 µl. Parmar A *et al*., [119] developed an HPLC method for the analysis of Telmisartan, Amlodipine Besylate, and Hydrochlorothiazide using a C18 Kinetex column. The mobile phase consisted of acetonitrile and phosphate buffer (60:40 v/v, pH 3.0). Detection was performed at 258 nm, with a flow rate of 1 ml/min and an injection volume of 20 µl. Chaudhary BR *et al*., [120] conducted an HPTLC analysis of Telmisartan, Amlodipine, and Chlorthalidone using silica gel 60 F254 plates. The mobile phase comprised chloroform, toluene, methanol, and acetic acid in a ratio of 6:2:2:0.1 v/v. Detection was performed at 254 nm, with Rf values of 0.64, 0.25, and 0.48, respectively. Pinak Patel *et al*., [121] developed a HPTLC method for the analysis of Rosuvastatin calcium, Telmisartan, and Amlodipine Besylate using silica gel G F254 plates. The mobile phase consisted of ethyl acetate, toluene, methanol, and triethylamine in a ratio of 6:2:2:0.1 v/v. Detection was carried out at 238 nm, with Rf values of 0.63, 0.74, and 0.31, respectively. Pankajbhai MB *et al*., [122] developed HPTLC method for analyzing Amlodipine Besylate, Hydrochlorothiazide, and Telmisartan using silica gel 60F254 plates. The mobile phase consisted of chloroform, butan-1-ol, and ammonia in a ratio of 6:4:0.1 v/v/v. Detection was performed at 254 nm, with Rf values of 0.27, 0.43, and 0.14, respectively.

3.5 Amlodipine and Indapamide

Rima NS *et al*., [123] developed an HPLC method for the analysis of Amlodipine besylate and Indapamide using a BDS Hypersil C8 column. The mobile phase comprised methanol and water in a ratio of 40:60% v/v, with a pH of 3. Detection was carried out at 248 nm, with a flow rate of 1 ml/min and an injection volume of 20 µl. Raj MC *et al*., [124] conducted an HPLC assessment of Amlodipine besylate and Indapamide using a C18 column with a methanol-water mobile phase in a ratio of 95:5. Detection was performed at 238 nm, with a flow rate of 1 ml/min and an injection volume of 20 µl. Patel DB *et al*., [125] conducted an HPLC evaluation of Amlodipine besylate and Indapamide using a Brownlee C18 column. The mobile phase consisted of potassium dihydrogen phosphate and methanol in a ratio of 30:70, with a pH of 3. Detection was performed at 242 nm, with a flow rate of 1 ml/min and an injection volume of 20 µl. Gandhi

SV *et al*., [126] developed an HPLC method for analyzing Amlodipine besylate and Indapamide using a Nucleosil C18 column. The mobile phase consisted of potassium dihydrogen phosphate buffer (pH 3) and methanol in a ratio of 30:70 v/v. Detection was performed at 241 nm, with a flow rate of 1 ml/min and an injection volume of 20 µl. Desai AK *et al*., [127] conducted an HPTLC evaluation of Amlodipine besylate and Indapamide using silica gel 60 G F254 plates. The mobile phase comprised dichloromethane, methanol, and ammonia in a ratio of 8.5:1.5:1 v/v/v. Detection was performed at 241 nm, with Rf values of 0.37±0.2 for Amlodipine besylate and 0.81±0.2 for Indapamide. Shah RN *et al*., [128] performed an HPTLC analysis of Amlodipine besylate and Indapamide using a C18 column. The mobile phase consisted of acetonitrile and water in a ratio of 70:30 v/v, with a pH of 4.0. Detection was carried out at 238 nm, with a flow rate of 0.8 ml/min and an injection volume of 20 µl.

3.6 Amlodipine and Indapamide with other drugs

Özsar SA *et al*., [129] performed an HPLC analysis of Perindopril, Indapamide and Amlodipine using a ACE 5 C18 analytical column (12.5 x 4.6 mm). Acetonitril and 50 mM phosphate buffer mixture (40:60 v/v) was used as mobile phase. Measurements were obtained at 215 nm wavelength using UV detector. Thomas S *et al*., [130] performed an HPLC analysis of Perindopril Erbumine, Indapamide, and Amlodipine Besylate using a HypersilC18 column (250mm × 4.6mm, 5µm particle Size). The mobile phase consisted of methanol and phosphate buffer (pH 2.5, strength 0.05M) in the ratio of 65:35, respectively, at a flow rate of 1.1 ml/min. Detection was carried out at 215 nm.

3.7 Telmisartan and Indapamide

Alagar R *et al*., [131] performed an HPLC analysis of Telmisartan and Indapamide using an X Terra column (4.6 x 150 mm, 3.5 µm). The mobile phase consisted of potassium dihydrogen orthophosphate buffer and acetonitrile in a ratio of 43:57 v/v. The flow rate was set at 1 ml/min, with detection at 254 nm and an injection volume of 20 µl. Sureja DK *et al*., [132] conducted an HPTLC analysis of Telmisartan and Indapamide using silica gel 60 G F254 as the stationary phase. The mobile phase consisted of hexane, ethyl acetate, methanol, and glacial acetic acid in a ratio of 14:6:2:1 v/v/v/v. Detection was performed at 249 nm, with Rf values of 0.21 for Telmisartan and 0.36 for Indapamide. Patel NM *et al*., [133] performed an HPTLC analysis of Telmisartan and Indapamide using silica gel 60 G F254 as the stationary phase. The mobile phase was a mixture of toluene, ethyl acetate, acetone, and methanol in a ratio of 7:4:3:1 v/v/v/v. Detection was carried out at 259 nm, with Rf values of 0.61 ± 0.03 for Telmisartan and 0.34 ± 0.03 for Indapamide. Akhtar J *et al*., [134] conducted an HPLC analysis of Telmisartan and Indapamide using a stainless steel C18 column (130 x 4.6 mm, 5 µm). The mobile phase consisted of 50 mM potassium hydrogen phosphate, acetonitrile, and methanol in a ratio of 50:20:30 (v/v/v), with the pH adjusted to 3.0 ± 0.1 using o-phosphoric acid. The flow rate was 1 ml/min, detection was at 280 nm, and the injection volume was 10 µl. All reported methods were shown in Table 1.

3.8 Assessment of greenness profiles

AGREE is a metric system that uses important principles to assess the greenness of analytical techniques. The AGREE pictogram was generated by inputting data for the 12 principles of GAC, and a corresponding score within the range of 0 to 1 was generated. A score of less than 0.50 indicates that the method is undesirable, a score of 0.50–0.75 suggests that it is acceptable, and a score of greater than 0.75 indicates that it is good. A score closer to 1 indicates a more environmentally friendly method. Based on AGREE, total 134 methods including UV, HPLC and HPTLC were evaluated. Four methods revealed a score of greater than 0.75 which is the closer to 1, hence it can be considered eco-friendly method compared to other reported methods whose AGREE score is between 0.5- 0.75.

4. CONCLUSION

Along with methods included in official pharmacopoeia methods, the current review offers information about the various methods accessible in the literature for the estimation of amlodipine besylate, telmisartan, and indapamide. This review revealed that different analytical techniques, such as UV, HPTLC, HPLC have been reported for the determination of amlodipine besylate, Telmisartan, and indapamide alone and in combination with other drugs. As a result, it was found that these methods were simple, accurate, and repeatable. The highest levels of sensitivity, analysis time, reproducibility, and reliability that were possible with these methods were provided. This review will help with the future development of analytical techniques for this novel combination by providing information on the properties of the three drug combinations. In this review, we evaluated the green metric tools, which have been widely applied to assess the greenness of reported analytical methods.

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