WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 11, 804-830. Review Article ISSN 2277–7105

A REVIEW ARTICLE ON ANALYTICAL METHODS FOR COMBINATION OF DRUGS: BENIDIPINE HYDROCHLORIDE AND TELMISARTAN

Rana Yukti*, Tanmay Shah, Nandini Modi, Rumana Dutiya, Dr. Nidhi Chauhan and Dr. Drashti Mandale

Department of Pharmaceutical Quality Assurance, Laxminarayan Dev College of Pharmacy, Bharuch, Gujarat, India.

Article Received on
19 April 2024,

Revised on 09 May 2024,
Accepted on 29 May 2024

DOI: 10.20959/wjpr202411-32673

***Corresponding Author**
Rana Yukti
Department of Pharmaceutical Quality Assurance, Laxminarayan Dev College of Pharmacy, Bharuch, Gujarat, India.

ABSTRACT

High blood pressure, also called hypertension, is a common condition that is characterized by having a higher amount of pressure in blood vessels than normal. Hypertension (HT) is a very common disorder, particularly past middle age. It is not a disease in itself, but is an important risk factor for cardiovascular mortality and morbidity. For improvement activity of hypertension, Benidipine HCl and Telmisartan newer combination in market, which is effective in Hypertension. This combination was developed to improve medication for Stage II Hypertension. Benidipine HCl is dihydropyridine calcium channel blocker and chemically 3-(3R)-1-benzylpiperidin-3-yl 5- methyl (4R)-2, 6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate hydrochloride. Telmisartan is AT1-receptor blocker and Chemically2-{4-[[4-methyl-6-(1-methylbenzimidazol-2yl)-2–propylbenzimidazol-1yl] methyl] biphenyl)- benzoic acid. It provides information about different analytical method development like UV spectrophotometry, HPTLC, HPLC, Stability studies Forced Degradation Study, spectroflourimetry methods reported for Benidipine HCl and Telmisartan for individual and other drug combination. All reported methods found to be simple, accurate, economic, precise and reproducible in nature. This Review focuses on development in analytical method development for Benidipine HCl and Telmisartan, and there were two methods reported for this combination as per our knowledge.

KEYWORDS: Benedipine HCl, Telmisartan, Analytical method, Hypertension, Combination of Drug.

INTRODUCTION[1-3]

The disease known as hypertension, sometimes referred to as high or rising blood pressure, is characterized by a continuously elevated pressure in the blood arteries. Through the vessels, blood is transported from the heart to every area of the body. Blood is pumped into the veins by the heart with each beat. Blood pressure is produced when blood is pushed by the heart and presses up against the walls of blood vessels, or arteries. The heart must pump more forcefully when the pressure is higher. An increased risk of heart, brain, kidney, and other disorders is associated with hypertension, a dangerous medical condition. With up to 1 in 4 men and 1 in 5 women—roughly a billion people—having the illness, it is a leading cause of premature death globally. Due in large part to an increase in risk factors in such populations in recent decades, two thirds of instances of hypertension are found in low- and middle-income nations, where the burden of the disease is disproportionately felt.[1]

The 5 stages of hypertension are[2]

- Normal: Below 120/80.
- Elevated: 120 to 129/Less Than 80.
- Stage 1 High Blood Pressure: 130 to 139/80 to 89.
- Stage 2 High Blood Pressure: 140 and above/90 and above.
- Hypertension Crisis: Higher Than 180/Higher Than 120.

Marketed tablets for combination of Benidipine HCl and telmisartan are: Benistar-TL, Benkair-T, Benidin-T, Benpack-T, Benizex-T, Inzit-TL, Benibuz- Forte, Vitabend, BENIDIN T 4/40MG TABLET is a combination of Benidipine and Telmisartan which belongs to the group of medicines called Calcium channel blockers and Angiotensin II receptor antagonists respectively. It is used to treat high blood pressure. Hypertension is a condition in which the force of the blood against the artery walls is high, generally characterized by symptoms such as severe headache, nose bleeding, weakness, disturbed vision, chest pain and shortness of breath. BENIDIN T 4/40MG TABLET helps in treating high blood pressure, where benidipine works by relaxing the blood vessels and reducing the pressure on the artery wall thus helping the heart to pump blood more easily throughout the body resulting in reduced pressure on the artery walls of the blood vessel and telmisartan blocks the effect of

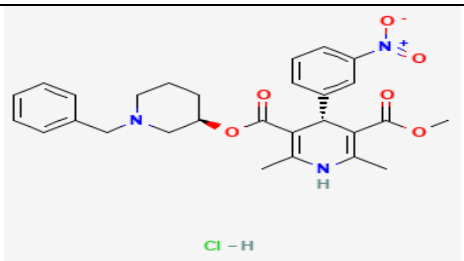
angiotensin II receptors (Chemical structures that transduce the signals to narrow down blood vessels) that causes relaxation and widening of blood vessels, thus lowering the blood pressure.

Precaution should be taken by pregnant women, breastfeeding women, driving and using machines, alcohol, kidney, liver, heart disease person, allergy.[3]

Benidipine HCl[4-6]

Benidipine Hydrochloride is a dihydropyridine calcium channel blocker. It is also commonly used for the small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers. Also used in the long-term treatment of hypertension and angina pectoris.

Table 1: Drug profile of Benedipine HCl.

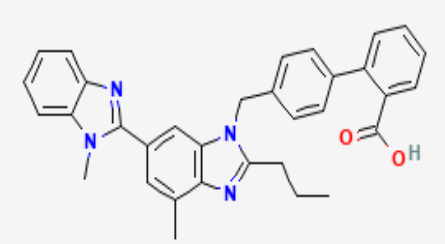
Chemical formula	$C_{28}H_{32}ClN_3O_6$
Category	anti-hypertensive and anti-anginal actions
IUPAC	3-(3R)-1-benzylpiperidin-3-yl 5-methyl (4R)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride
CAS NUMBER	91599-74-5
CDSCO approval	12/08/1996
Chemical structure	
Molecular weight	542.0 g/mol
Appearance	Solid
PKa	pKa (Strongest Acidic) 19.47 pKa (Strongest Basic) 7.89
Solubility	The solubility of benidipine (hydrochloride) in ethanol is approximately 10 mg/ml and approximately 30 mg/ml in DMSO and DMF. ***In vitro:*** **DMSO: 33.33 mg/mL (61.49 mM;** Need ultrasonic) **H_2O : < 0.1 mg/mL** (insoluble)
Mechanism of action	Benidipine is a tripe calcium channel inhibitor by inhibiting L, N and T type calcium channel. It presents a very long-lasting activity that can be explained by its high affinity for cell membranes from the DHP binding site; this characteristic indicated a long-lasting pharmacological activity of benidipine. The additional property of benidipine is the

	vascular selectivity towards peripheral blood vessels.
Melting point	209-215°C
Combination with other drugs	Metoprolol succinate, chlorthalidone, abatacept, telmisartan

Telmisartan[7-10]

Telmisartan is an angiotensin II receptor blocker (ARB). It works by blocking a substance in the body that causes blood vessels to tighten. As a result, telmisartan relaxes the blood vessels. This lowers blood pressure and increases the supply of blood and oxygen to the heart. Telmisartan is used alone or together with other medicines to treat high blood pressure (hypertension). High blood pressure adds to the workload of the heart and arteries. If it continues for a long time, the heart and arteries may not function properly. This can damage the blood vessels of the brain, heart, and kidneys, resulting in a stroke, heart failure, or kidney failure. Lowering blood pressure can reduce the risk of strokes and heart attacks.

Table 2: Drug profile of telmisartan.

Chemical formula	$C_{33}H_{30}N_4O_2$
Category	Angiotensin II receptor blockers
IUPAC	2-[4-[[4-methyl-6-(1-methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] phenyl] benzoic acid
CDSCO approval	25/11/2002
Chemical structure	
Molecular weight	514.6 g/mol
Appearance	Solid
PKa	3.5, 4.1 and 6.0
Solubility	The solubility of benidipine (hydrochloride) in ethanol is approximately 10 mg/ml and approximately 30 mg/ml in DMSO and DMF.
Mechanism of action	Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects. Angiotensin II receptor blocker; inhibits vasoconstrictor and aldosterone-secreting effects of angiotensin II

Melting point	261-263°C
Combination with other drugs	Amlodipine, Hydrochlorothiazide, Chlorthalidone, Metoprolol succinate, rosuvastatin, cilnidipine, Benidipine HCl
Combination of Benidipine HCl and Telmisartan	Fixed drug combination on Benidipine Hydrochloride JP + Telmisartan IP (4mg + 40mg & 4mg + 80mg) 26.02.2021

Official method for estimation of benidipine HCl

Table 3: Official method for Benedipine HCl.

Official in	Method	Description
Japanese Pharmaco poeia (2017)	Liquid Chromato graph	**Stationary phase:** A stainless steel column 4.6 mm in inside diameter and 10 cm in length, packed with octadecyl silanized silica gel for liquid chromatography (3 mm in particle diameter)**Column temperature:** A constant temperature of about 25ºC.**Mobile phase:** A mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 3.0), methanol and tetrahydrofuran (65:27:8) **Flow rate:** Adjust so that the retention time of Benidipine is about 20 minutes Time span of measurement: About 2 times as long as the retention time of Benidipine, beginning after the solvent peak

Reported method for estimation of benidipine HCl[12-31]

Table 4: Reported method for Benedipine HCl.

Sr. no.	Title/ Method	Description	Ref
1.	Development of UV Spectrophotometric method for the determination of benidipine hydrochloride by using quality by design approach.	Model: Shimadzu UV-1800 double beam spectrophotometer; Solvent: Methanol; Wavelength: 236nm; Linearity: 10 µg/ml, 3-18 µg/ml; Scan speed: Fast; Sampling interval: 0.2 nm;	[12]
2.	UV-Visible spectrophotometric method development and validation of assay of Benidipine Hydrochloride tablet formulation	Model:- UV spectrophotometer Shimadzu UV 2450 PC; Solvent:- Methanol; Linearity:- 2-15 µg/ml; Wavelength:- 237	[13]
3.	Multivariate Calibration Techniques aided UV Spectrophotometric method for the estimation of Benidipine Hydrochloride in pharmaceutical dosage forms	Model: UV Spectrophotometer LABINDIA UV 3092 double beam UV –VIS spectrophotometer; λ_{max}: 237 nm; linearity: 7-13 µg mL^{-1}. Wavelength range. i.e., 227, 232, 237, 242, and 247 nm	[14]
4.	Development of new Visible Spectrophotometric methods for determination of	Model: Systronics Double Beam UV/visible spectrophotometer model No.2203; Beer's law limit(µg/ml) (A) 10-30 (B) 0-30 (C) 8-24;	[15]

	Benidipine Hydrochloride in bulk and formulations based on oxidative coupling and diazo coupling reactions	λ_{max} (A) 620 (B) 500 (C) 525; % Range of errors(95% Confidence limits):- 0.05 significance level- (A) 0.665 (B) 0.897 (C) 0.727 0.01 significance level- (A) 1.042 (B) 1.407 (C) 1.14	
5.	Simultaneous Equation Method for the Estimation of Benidipine Hydrochloride and Chlorthalidone by UV Spectrophotometry	Model: double beam UV spectrophotometer (Shimadzu-1800); wavelength of Benidipine hydrochloride and Chlorthalidone at 237 nm and 275 nm respectively; Mobile phase: Methanol: Water (90:10%); Benidipine hydrochloride linearity: 1-5µg/mL and Chlorthalidone linearity: 1.5-7.5µg/mL	[16]
6.	RP-HPLC Method Development and validation for Simultaneous estimation of Benidipine Hydrochloride, Telmisartan and Chlorthalidone in tablet	Stationary Phase- C18 hypersil BDS column (25 cm × 0.46 cm); Mobile Phase-the mixture of buffer (pH 3.0): methanol (50:50)v/v; Flow rate- 1.0 ml / min; Wavelength: 230 nm; Retention Time: CLD, BPH, and TEL were found to be 4.887 min, 6.690 min and 8.813 min, respectively.; Linearity: BPH 2-6 µg/ml, for TEL 20-60 µg/ml and CLD 6.25- 18.75 µg /ml.;	[17]
7.	Method Development and Validation for Simultaneous Estimation of Benidipine Hydrochloride and Metoprolol Succinate in Tablet	Stationary phase: C18 (250 mm x 4.6 mm, 5 µm) Hypersil BDS Column; Mobile Phase: Potassium Dihydrogen Phosphate Buffer (pH 4.0): Methanol (65: 35% v/v); Wavelength: 269 nm; The RT values for Metoprolol succinate and Benidipine Hydrochloride: 3.4 and 5.9 min respectively.; Linearity: 25- 75 µg/ml of Metoprolol Succinate and 4-12 µg/ml of Benidipine Hydrochloride	[18]
8.	First Order Derivative Spectrophotometric Method for the Determination of Benidipine Hydrochloride Pharmaceutical Preparations and Forced Degradation Study	Model: double-beam Shimadzu 2600 UV/Vis Spectrophotometer with a 1.00 cm quartz cells was used under the following operating conditions: scan range 200– 450 nm, slith width 2 nm and derivation interval (Δλ) 2 nm were used; Acid degradation: The acid degradation was performed by refluxing with 0.1 N HC1 at 70°C for 1 h. First order derivative spectrums of 3 µg/mL BEN degraded with acidic degradation and 3 µg/mL BEN (Δλ = 2 nm); Basic degradation. The basic degradation was performed by refluxing with 0.1 N NaOH at 70°C for 1 h. BEN degraded with basic degradation was diluted to 10 µg/mL and it was observed degraded BEN was not decomposition from its first order derivative spectrum; Beer's Law range: 0.2–2 µg/mL	[19]
9.	Spectrofluorimetric determination of benidipine	Model: Hitachi spectrofluorometer (Model U-2900); pH was measures using the WTW pH	[20]

	in pharmaceutical preparation and spiked plasma samples using 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole	526 digital pH meter, sensitivity of the pH meter is: −2.00- 16.00 pH, accuracy: 0.01 at room temperature; Wavelength (nm): $\lambda_{excitation}$: 465 nm, $\lambda_{emission}$:550 nm,; Concentration range (n=5) (µg mL^{-1}): 10-200The 20 µg mL^{-1} of sample solution were added to 10, 100, 150 µg mL^{-1} concentration of the standard solution	
10.	Determination of benidipine hydrochloride in human plasma by capillary column gas chromatography-negative ion chemical ionization mass spectrometry	GC-MS system consisted of a JMS SX-102 coupled to an HP-5890A with a solventless injector (JEOL).; Column was a methyl silicon-coated fused-silica capillary, ULTRA 1; Column oven temperature was maintained at 220°C for 1 min, then increased at 40^0C/min to 300°C; Injector was operated at 270°C and the transfer line at 300°C; Helium was used as the carrier gas at 25 kPa of inlet pressure.; Detection limit was 0.02 ng/ml with 0.5 ml of plasma.; Coefficient of variation of intra-day assay was 17.4% and 12.1% at the 0.02 and 0.1 ng/ml levels, respectively; Relative error was 5.4% at 1 µg/ml, 7.0% at 0.1 µg/ml and 15.0% at 0.02 ng/ml.; T_{max} of 0.60 _+ 0.22 (mean _+ S.D.) h; C_{max} were 2.282 _+ 0.336 µg/ml.; $T_{1/2}$ was 4.51 _+ 2.29 h; $AUC_{0-\infty}$, was 4.09 f 0.84 ng . h/ml.	[21]
11.	Development and Validation of HPLC Method for Determination of Benidipine Hydrochloride in Lipid Vesicles Formulations	ZORBAX Eclipse Plus C18 (4.6mm x 150mm) analytical column with a mobile phase consisting of a mixture of methanol and 50 mM phosphate buffer solution at a ratio of 70:30 (v/v); retention time: 6.045 min; theoretical plates: 5263; tailing factor: 1.33; %RSD: 0.52%; %RSD for LOD: 6.56%; LOQ 4.84%; linear for BEN concentrations between 1 and 400 µg/ml; Entrapment Efficiency % was in ranging from 88.64 ± 1.31 to 93.97 ± 0.31 and the drug content was found to be ranged from 98.34 to 105.87%	[22]
12.	Development and Validation of Analytical RP HPLC Method for Benidipine Hydrochloride	Method development by QBD approach and optimization of chromatographic conditions; Column- Chemsil ODS C18 particle size (5µg); Wavelength-237nm; Mobile phase composition- Ammonium Acetate buffer in the ratio 85:15% v/v; Pump mode-isocratic; Flow rate-1.2 ml/ min; Injection volume-10µl; Run time-15 min; Level of Variables: Low level(-1) Flow rate (ml/min) 1.2 pH 2.8 methanol: buffer 75:25; Level of Variables: Medium level(0) Flow rate (ml/min) 1 pH 3.0 methanol: buffer 85:15; Level of Variables:	[23]

<table>
<tr><td></td><td></td><td>High level(+1) Flow rate (ml/min) 1.4 pH 3.2 methanol: buffer 95:5</td><td></td></tr>
<tr><td>13.</td><td>Development and validation of RP-HPLC method for Benidipine In bulk and tablet dosage form.</td><td>HPLC system (Agilent HPLC) consisted of a pump with manual injection facility; detector consisted of a Photodiode Array UV-VIS spectrophotometer; column used was Agilent C-18 100 mm × 4.6 mm, particle size.2.5µm); Linearity: 10- 50µg/ml for benidipine in triplicate into the HPLC system</td><td>[24]</td></tr>
<tr><td>14.</td><td>Voltammetric and RP-LC assay for determination of benidipine HCl</td><td>XTerra RP-18 column at 25 ◦C with the mobile phase of acetonitrile:water 55:45 (v/v) adjusted to pH 3.0 with 15 mM o-phosphoric acid; flow rate of 1.0 mL min−1; RP-LC method allowed quantitation over the 0.25–15.00 µg/mL range for BEN; range between 3.25 µg/mL and 54.20 µg/mL for GC and 1.08 µg/mL and 54.20 µg/mL for BDD electrodes</td><td>[25]</td></tr>
<tr><td>15.</td><td>Analytical Validation and Stability Indicating Studies for Simultaneous Estimation of Benidipine and Metoprolol by Strong Cation Exchange (SCX) Chromatography</td><td>
<table>
<tr><td>Selective Variable</td><td>Benidipine</td><td>Metoprolol</td></tr>
<tr><td>Theoretical plates (N)</td><td>197</td><td>712</td></tr>
<tr><td>Capacity factor (K’)</td><td>1.84</td><td>9.17</td></tr>
<tr><td>Resolution (R)</td><td>-</td><td>6.27</td></tr>
<tr><td>Selectivity/Separation factor (α)</td><td>-</td><td>4.97</td></tr>
<tr><td>Asymmetry/Tailing factor (T)</td><td>1.91</td><td>1.89</td></tr>
<tr><td>Retention time (tR)</td><td>1.21 min.</td><td>4.34 min.</td></tr>
<tr><td>Wavelength of detection (nm)</td><td>225nm</td><td>225nm</td></tr>
</table>
</td><td>[26]</td></tr>
<tr><td>16.</td><td>RP-HPLC Method Development and Validation for Simultaneous Estimation of Benidipine Hydrochloride and Chlorthalidone in Pharmaceutical Dosage Form</td><td>Agilent 1260 Infinity Quaternary HPLC device equipped with Photodiode array detector; Wavelength: -238 nm; Column: - C-18 Agilent Zorbax Bonus –RP (250 x 4.6 mm, Particle size -5 Micron) and diluent:- Methanol: 0.1% Orthophosphoric acid (50:50); Range: BEN HCl: 32-48 µg/mL Chlorthalidone: 100-150µg/mL Slope BEN HCl: 50184 Chlorthalidone: 37102 Intercept BEN HCl: 30070 Chlorthalidone: 74642; Chlorthalidone: 0.999; Theoretical plates: BEN HCl: 5344 Chlorthalidone: 8346 Tailing Factor: BEN HCl: 1.09 Chlorthalidone: 1.05; Resolution: BEN HCl: 0.00 Chlorthalidone: 9.62; Retention Time BEN HCl: 1.09 Chlorthalidone: 3.5</td><td>[27]</td></tr>
</table>

17.	Identification, synthesis and characterization of process related impurities of benidipine hydrochloride, stress-testing/stability studies and HPLC/UPLC method validations	HPLC system with Waters Alliance 2695 separation module equipped with a Waters 996 photodiode array detector and an Empower-pro data handling system; C18 (100 mm 4.6 mm, 3 mm) column (Hypersil BDS) at 25 °C with phosphate-buffer/methanol/THF (65/27/8) mixture flowing at a rate of 0.75 mL/min (it was adjusted during the analysis so that the retention time of benidipine was about 20 min) during 60 min.; Detection wavelength was fixed at 10 mL and 237 nm; Retention time:- 20.38; Relative Retention time:-1.0	[28]
18.	Stability Indicating Method to Analyse Benidipine and Chlorthalidone Using HPLC Technique: Establishment, Validation and Application to Tablets	Model: Waters Alliance 2695 model HPLC system composed of quaternary pump, autosampler and photodiode array detector; stationary phase: C18 Kromasil column (5 µm particles, 250 mm × 4.6 mm i.d); mobile phase: combination of methanol and 0.1 M dipotassium hydrogen phosphate buffer (adjusted at pH 4.5 with orthophosphoric) in the ratio of 40:60 (v/v); isocratic mode flow rate: 1.0 ml/min; injection volume: 10 µl; range of 2-6 µg/ml (benidipine) and 6.25-18.75 µg/ml (chlorthalidone); wavelength of 260 nm	[29]
19.	Determination of benidipine in human plasma using liquid chromatography–tandem mass spectrometry	Model: Liquid Chromatography–Mass Spectrometry with a PE SCIEX API 3000 LC–MS–MS System equipped with an electrospray ionization interface used to generate positive ions [M+H]+; stationary phase: Reversed-phase column (Luna C18, 2 mm × 100 mm i.e., 3 micrometre particle size); isocratic mobile phase: acetonitrile and 5 mM ammonium acetate buffer (90%:10% (v/v)).; Mobile phase was eluted using an HP 1100 series pump at 0.2 ml/min.	[30]
20.	Analytical method development and validation for the simultaneous estimation of Metoprolol and Benidipine by RP-HPLC in bulk and tablet dosage forms	Model: Younglin (S. K.) gradient system UV detector; stationary phase: C18 column with 250 mm x 4.6 mm i. d. and 5µm particle size Mobile phase: Acetonitrile: OPA water (45: 55v/v) pH 2.5; detection wavelength: 230 nm; flow rate: 1ml/min; retention time: Metoprolol and Benidipine: 2.9833 min and 7.3833 min; RP-HPLC Method: MET %RSD 0.51 BEN %RSD 0.51; range 50-250 µg/ml for MET and 4-20 µg/mL for BEN	[31]

Official method for estimation of telmisartan[32-33]

Table 5: Official method for Temisartan.

Sr.no	Official in	Methods	Description
1.	Indian Pharmacopoeia 2018	Chromatographic method	Stationary phase: Stainless steel column 15cm x 4.6 mm packed with octadecysilane bonded to porous silica. Mobile phase: A mixture of 60 volumes of buffer solution prepared by dissolving 2.72g of potassium dihydrogen phosphate in 1000ml of water; add 2ml of triethylamine and adjust the Ph to 2.4 with orthophosphoric acid and 40 volume of acetonitrile. Wavelength: 298nm Injection volume: 20 µL Flow rate: 1 ml/min
2.	Japanese pharmacopoeia	Chromatographic method	Stationary phase: A stainless steel column 0.4 mm inside diameter and 12.5 cm in length, packed with octadecylsilinized silica gel for liquid chromatography (5 mm in particle diameter). Mobile phase: A) Dissolve 2.0 g of potassium dihydrogen phosphate and 3.4 g of sodium 1-pentanesulfate in 1000 Ml of water, and adjust to ph 3.0 with diluted phosphoric acid (1 in 10). B) A mixture of acetonitrile and methanol (4:1). Wavelength: 230 nm Flow rate: 1 ml/min.

Reported method for estimation of telmisartan[34-77]

Table 6: Reported method for Telmisartan.

Sr. no.	Title/ Method	Description	Ref.
1.	Method development and validation of Simultaneous estimation of Cilostazol and Telmisartan	Shimadzu model 1700 double beam UV-Visible spectrophotometer; Linearity: 4 to 20 µg/ml of CLZ 1 to 5 µg/ml of TLM; Method: UV-Visible Method-1: Wavelength: Cilostazol: 258 nm Telmisartan: 296 nm Method-2: Cilostazol: 237.5nm (Iso Absorptive Point) Telmisartan: 258nm (λ max of Cilostazol) Method-3: Beer's Lambert's Law: Concentration Range: Cilostazol: 1-40 µg/ml Telmisartan: 1-25 µg/ml	[34]
2.	Development of UV spectrophotometric method for estimation and validation of Telmisartan as a pure API	Model: Shimadzu UV1800 UV-Visible double beam spectrophotometer; Solvents: Ethanol (95%), 0.1 N NaHCO3; Wavelength: 240 nm; Linearity: 2-14 µg/ml	[35]
3.	Absorbance correction method for estimation of telmisartan and metoprolol succinate in	Model: UV-Visible double beam spectrophotometer Shimadzu UV1800 Solvent: Methanol Method 1: Absorbance	[36]

	combined tablet dosage forms	correction method Wavelength: Telmisartan: 296 nm Metoprolol: 223 nm Linearity: Metoprolol: 2-16 µg/ml; Telmisartan 3-24 µg/ml	
4.	UV-Spectrophotometric Determination for Simultaneous Estimation of Amlodipine Besylate and Telmisartan in Combination	Model: UVA 1002 E Solvent: 0.1 N HCL Method: 1. Absorbance correction method, 2. Absorbance ratio Method Wavelength: Telmisartan:292 nm, Amlodipine: 326 nm Linearity: Method 1: Absorbance correction method Telmisartan 3-24 µg/ml, Amlodipine:0.5-20 µg/ml Method 2: Absorbance ratio Method Telmisartan:3-24 µg/ml, Amlodipine: :0.5-15.5 µg/ml	[37]
5.	Development and validation of spectrophotometric methods for simultaneous estimation of metoprolol succinate and telmisartan in combined pharmaceutical formulation	Model: Spectrophotometer Shimadzu UV-1700 Double Beam Solvent: Methanol Method: Method A: First derivative simultaneous equation method (Vierodt‟s method) Method B: First derivative Q-Absorbance equation method. Method C: Absorbance correction method Method D: First derivative dual wavelength. Wavelength: Methods of Telmisartan: 1.First derivative simultaneous equation method (Vierodt‟s method): 237nm 2. First derivative Q-Absorbance equation method: 237 nm 3. Absorbance correction method: 296.6 nm 4. First derivative dual wavelength Method: 330 nm Methods of Metoprolol Succinate: 1.First derivative simultaneous equation method (Vierodt‟s method): 230.2 nm 2. First derivative Q-First derivative dual wavelength Method: 282.4 nm,284.6 nm Linearity: Methods of Telmisartan: First derivative simultaneous equation method: 4-16 µg/ml,; First derivative Q-Absorbance equation method: 4-16 µg/ml; First derivative dual wavelength Method: 4-16 µg/ml Methods of Metoprolol Succinate:First derivative simultaneous equation method: 3-20 µg/ml; First derivative Q-Absorbance equation method: 3-20 µg/ml; First derivative dual wavelength Method: 3-20 µg/ml	[38]
6.	UV Spectrophotometric method for estimation of Telmisartan in bulk and tablet dosage form	Model: Shimadzu UV- 1700 Solvent: 0.1 N NaOH, Distilled water Wavelength: 234 nm Linearity: 2-10 µg/ml	[39]
7.	Dissolution Method	Model: Double beam UV Visible	[40]

	Development and Validation for Tablet Dosage form of Telmisartan Using UV Spectrophotometric Method	Spectrophotometer Shimadzu UV 1800 Diluent: Methanol Wavelength:296 nm Linearity: 2-12 µg/ml	
8.	Development and validation of UV- Spectrophotometric method for estimation of Cilnidipine and Telmisartan in bulk and dosage form	Model: Shimadzu UV/Visible double beam spectrophotometer (Model 1700) Solvent: Acetonitrile Wavelength: Telmisartan :241nm Cilnidipine: 203 nm Linearity: Telmisartan: 0.5-2.5 µg/ml Cilnidipine: 2-10 µg/ml	[41]
9.	UV Spectrophotometric analytical method development and validation for determination of Telmisartan in pharmaceutical drug and drug product (tablet dosage form)	Model: UV visible double beam spectrophotometers SL 210 Elico Solvent: Methanol, Acetic Acid Wavelength: 296.5 nm Linearity: 5 -25 µg/ml	[42]
10.	Analytical Method Development and Validation of First Order Derivative Spectrophotometric Method for Simultaneous Estimation of Telmisartan and Metformin Hydrochloride in their Combined Pharmaceutical Dosage Form	Model: Shimadzu model 1700 Diluents: Methanol: Water (50: 50) v/v Method: First Order Derivative Linearity: TEL :6-16 µg/m, MET: 6–16 µg/mL Wavelength: TEL: 251 nm, MET: 217 nm	[43]
11.	Determination of Telmisartan by HPTLC – A Stability Indicating Assay	Model: TLC Plates Mobile Phase: Chloroform: Methanol (8.6:1.4 v/v) Wavelength:297 nm Linearity: 20-160 µg/ml; Accuracy: 80, 100, and 120% additional drug	[44]
12.	Stability Indicating Simultaneous Validation of Telmisartan and Cilnidipine with Forced Degradation Behaviour Study by RP-HPLC in Tablet Dosage Form	Stationary Phase (Column): C18 column (250 x 4.6mm, 5 µm); Mobile Phase: Acetonitrile (ACN): Buffer PH 3.0 With Orthophosphoric Acid (68:32); Flow rate: 1.0 mL/min; Wavelength: 245 nm Telmisartan: Linearity: 40-160 µg/ml; Retention Time: 2min Cilnidipine: Linearity: 10-40 µg/ml; Retention Time: 4 min	[45]
13.	Development and Validation of Stability Indicating HPTLC and HPLC Methods for Simultaneous Determination of Telmisartan and Atorvastatin in Their Formulations	HPTLC: Separation (Silica Gel 60F254) Mobile Phase: Toluene: Methanol: Ethyl Acetate: Acetic Acid (5:1:1:0.3 v/v) Compact Bands: Telmisartan: Rf 0.37 ± 0.02 Atorvastatin 0.63 ± 0.01 Wavelength: 279 nm Linearity: Telmisartan:40-240 ng/band Atorvastatin: 10-60 ng/band RP-HPLC: Column: C18 Mobile phase: Acetonitrile: 0.025 M Ammonium Acetate (38:52% v/v) Flow rate: 1.0 mL/min	[46]

		Wavelength: UV Detection at 281 nm Linearity Range: Telmisartan: 12-72 µg/ml, Atorvastatin: 3-18 µg/ml	
14.	Development and Validation of RP - HPLC method for the estimation of Telmisartan in bulk and tablet dosage Form	Column: Zorbax-SB-18; (ODS), (150 x 4.6 mm; 3.5 µm) Mobile Phase: Buffer: Methanol (40:60 v/v) Flow rate: 1.2 mL/min Wavelength: 230 nm Concentration range: 4-20 µg/ml; Retention Time: 3-4 min; percentage recoveries was found to be 99.55± 0.7211%	[47]
15.	Development and Validation of RP - HPLC Method for the Simultaneous Determination Of Hydrochlorothiazide, Amlodipine Besylate and Telmisartan in Bulk and Pharmaceutical Formulation	Column: RP-C18 Mobile Phase: Acetonitrile: Acetate Buffer (Adjusted to PH5 with Orthophosphoric Acid) (60:40 % V/V) Flow Rate: 1.0 mL/min Wavelength: 333 nm Concentration Range: 20-100 µg/ml Retention Time: Hydrochlorothiazide: 2.9 min Amlodipine Besylate: 5.1 min Telmisartan: 8.2 min; Tailing Factor HCT: 1.42 AMB: 1.35 TEL: 1.34 Number of Theoretical plates HCT: 2725 AMB: 4598 TEL: 6233	[48]
16.	RP-HPLC method development and validation for simultaneous estimation of Benidipine Hydrochloride, Telmisartan and Chlorthalidone in tablet	Column: C18 (25cmx0.46cm) Hypersil BDS Mobile Phase: Buffer (PH3.0): Methanol (50:50 v/v) Flow Rate: 1ml/min Wavelength: 230 nm Retention Time: Benidipine Hydrochloride: 6.690 min Telmisartan: 8.813 min Chlorthalidone: 4.887 min Linearity Range: Benidipine Hydrochloride: 2-6µg/ml Telmisartan: 20-60 µg/ml Chlorthalidone: 6.25-18.75 µg/ml	[49]
17.	RP-HPLC Method Development and Validation for Quantitative Estimation of Metoprolol Succinate and Telmisartan in Bulk Drug and Their Dosage Forms	Column: Prontosil C 18 (5 µm,250 mmx 4.60 mm) Mobile Phase: Acetonitrile: Methanol: Phosphate Buffer PH5 (35:35:30% v/v/v) Flow Rate: 1.0 mL/min Wavelength: UV PDA Detector-225 nm Retention Time: Metoprolol Succinate: (5-25 µg/ml) Telmisartan: (8-40 µg/ml)	[50]
18.	Novel Reverse-phase high performance liquid chromatography method development and validation for estimation of telmisartan and nebivolol hydrochloride in pharmaceutical dosage form	mobile phase composition of acetonitrile: Buffer (potassium dihydrogen orthophosphate pH adjusted 3.1 with orthophosphoric acid) in a ratio of 40:60 v/v at a flow rate of 1.2 ml/min using C18 Shim-pack (150 mm × 4.6 mm, 5 µ) column; The detection was carried out at 280 nm; retention time of telmisartan and nebivolol HCl was 4.8 min and 6.5 min, respectively; concentration range of 24–56 µg/ml for telmisartan and 3–7 µg/ml	[51]

		for nebivolol HCl	
19.	Telmisartan/ RP-HPLC	Column: C18 sun fire column (250 mm x 4.6 mm,5 µm) Mobile Phase: Potassium di-hydrogen Phosphate: Acetonitrile (60:40) v/v Flow Rate: 1 mL/min Wavelength: 243nm Linearity: 50 -150 µg/ml Retention Time: 3.4 min.	[52]
20.	Development and validation of a RP-HPLC method for estimation of telmisartan in human plasma	Column: Hibar C18 (250 mm x 4.6 mm ,5 µm) Mobile Phase: Ammonium format solution (pH 4.0) : Methanol (70:30), v/v Flow Rate: 1 mL/min Wavelength: 275 nm Linearity: 0.1-1.5 (µg/ml) Retention Time: 3.7 min.	[53]
21.	Validated RP-HPLC Method for Simultaneous Determination of Telmisartan and Hydrochlorothiazide in Pharmaceutical Formulation	HPLC system (Shimadzu LC2010HT) with UV- Visible dual absorbance detector (PDA), using Inertsil 250 x 4.6 mm 5- µm packing L11 column; mobile phase consisting of buffer and mixture, acetonitrile and methanol in the ratio of (50:50) [adjust pH to 3.0 with ortho phosphoric acid] and it was flowed at 1.2 ml/min; detection was made at 298 nm for telmisartan and 270 nm for hydrochlorothiazide; linearity range 50–150 µg/ml; retention times of telmisartan and hydrochlorothiazide were found to be 18.43 min and 8.11 min respectively	[54]
22.	QbD Based Development of HPLC Method for Simultaneous Quantification of Telmisartan and Hydrochlorothiazide impurities in Tablets Dosage Form	Column: Kromasil C18(125mm× 4.0 mm, 5 µm), Inertsil ODS 3 V (150 mm 4.6 mm, 3.5 µm) Mobile Phase: Solvent A: Potassium dihydrogen phosphate buffer, (pH 3.5) 1%Ortho phosphoric acid solution Solvent B: Purified water and acetonitrile (100:900) v/v Flow rate: 1.0 mL/min. Wavelength: 230 nm Linearity: TEL :1.5 µg/mL, HCZ: 0.6 µg/mL Retention Time: 3.2 min.	[55]
23.	A Fast and Validated Reversed-Phase HPLC Method for Simultaneous Determination of Simvastatin, Atorvastatin, Telmisartan and Irbesartan in Bulk Drugs and Tablet Formulations	Column: C18 (75 mm × 4.6 mm ,3.5 µ) Mobile Phase: Ammonium acetate buffer (10 mM (pH 4.0): Acetonitrile (40:60) v/v Flow rate: 1 mL/min Linearity: 1–16 µg/mL Wavelength:220 nm Retention Time: IRB: 1.20 min, ATV: 1.82 min. TLM: 2.40 min, SMV: 6.03 min.	[56]
24.	Simultaneous estimation of telmisartan and atorvastatin calcium in API and tablet dosage form	RP-HPLC; SHIMADZU HPLC auto sampler Column: Boston ODS C18 (250mm x 4.6 mm, 5 µ) Mobile Phase: Methanol: Acetonitrile: buffer (35:25:40) v/v Flow rate: 1.0 mL/min. Wavelength: 235 nm Linearity: 60-140 µg/ml Retention	[57]

		Time: TEL: 3.5 min, ATC :2.3 min.	
25.	Development and Validation of HPTLC Method for Simultaneous Estimation of Amlodipine Besylate, Hydrochlorothiazide and Telmisartan In Their Combined Tablet Dosage Form	Stationary phase: pre-coated with silica gel 60F254(10×10 cm) Mobile Phase: Chloroform: Butanol: Ammonia (6: 4: 0.1) v/v/v Flow Rate: 1 mL /min. Wavelength: AML :237.5nm, HCTZ: 270 nm, TLM :297nm Linearity: AML: 200-1000ng/band, HCTZ: 500-2500 ng/band, TLM :1600-8000 ng/band Retention Time: AML: 3.2 min, HCTZ: 3.1 min, TEL :3.5 min.	[58]
26.	RP-HPLC Method development and validation for estimation of telmisartan in bulk and tablet dosage form	Column: RP18 (250mm×4.6mm,5µ) Mobile Phase: 0.025M potassium dihydrogen phosphate: Acetonitrile: Methanol (45:50:5) v/v/v Flow rate: 1 ml/min. Wavelength: 216 nm Linearity: 100 - 500 µg/ml Retention Time: 3.6 min	[59]
27.	Analytical Method Development and Validation for the Simultaneous Estimation of Telmisartan and Atorvastatin in Bulk and Tablet Dosage Form	Column: Inertsil-ODS C18 (250mm×4.6mm,5µ) Mobile Phase: Methanol: water (50:50) v/v Wavelength: 250 nm Flow rate:1 mL/min Linearity: 20 to 80 µg/ml Retention Time: TEL: 2.4 min, ATC: 3 min	[60]
28.	Development and Validation of Bioanalytical HPLC Method For Estimation of Telmisartan In Rat Plasma: Application To Pharmacokinetic Studies	Column: Phenomenex Luna® C8 (300mm× 4.6 mm,5µ) Mobile Phase: Methanol: Acetonitrile (70:30 (v/v) Flow rate: 1 ml/min Wavelength: 190-800 nm Linearity: 10 - 1000 µg/ml Retention Time: 2.3 min.	[61]
29.	Analytical method development and validation for the simultaneous estimation of metformin and telmisartan in bulk and pharmaceutical dosage form using RP-HPLC method	Column: BDS (250mm x 4.6 mm, 5 µm) Mobile Phase: Buffer: Acetonitrile: Methanol (35:55:10) v/v/v Flow rate: 1mL/min Wavelength: 237nm Linearity: MET: 5-30 µg/ml, TEL: 62.5-375µg/ml Retention Time: MET: 2.4 min, TEL: 3.2 min.	[62]
30.	A Validated RP-HPLC Method for Tablets Containing Amlodipine Besylate and Telmisartan HCl as Active Pharmaceutical Ingredient	Column: Phenomenix C18 (250 mm × 4.6 mm, 5 µm) Mobile Phase: 0.02M Ammonium Phosphate buffer: Acetonitrile: Methanol (40:35:25) v/v/v Flow rate: 1.0 mL/min Wavelength:254 nm Linearity: TEL: 0.8 -160 µg/ml, AMLB: 0.1-2 µg/ml Retention Time: TEL: 2.65 min, AMLB: 4.996 min.	[63]
31.	Development and Validation RP-HPLC Method for the estimation of telmisartan in bulk drug using internal standard	Telmisartan using eprosartan mesylate as an internal standard (IS) in bulk and tablet dosage form. Separation was achieved under optimized chromatographic conditions on a phenomenex C-18 column (250 X 4.6 mm, particle size 5µ) with	[64]

		mobile phase consisting of 10mM potassium di hydrogen phosphate buffer:methanol in the ratio 20: 80 v/v, PH adjusted to 5.8 with 10%v/v ortho phosphoric acid at a flow rate of 0.8 ml/ min; detection was carried out at 296 nm using waters UV Visible detector	
32.	Development and Validation RP-HPLC Method for Simultaneous Estimation of Telmisartan and Nifedipine In Synthetic Mixture	Column: Phenomenex Luna C18(250 mm×4.6 mm,5µ) Mobile Phase: ACN: Water: Methanol (10:20:70 v/v/v) pH 3.8 Wavelength: 234 nm Flow rate: 1 ml/min Linearity: TEL: 4-20 µg/ml, NIF: 2-10 µg/ml Retention Time: TEL: 2.563 min NIF: 4.403 min	[65]
33.	Method Development and Validation for Simultaneous Estimation of Telmisartan and Chlorthalidone by RP-HPLC in Pharmaceutical Dosage Form	Column: CAPCELL C18 (250 mm×4.6 mm, 5 µm) Mobile Phase: Potassium di hydrogen ortho phosphate buffer: Acetonitrile: Methanol (35:45:20) v/v/v (pH 3.5) Ortho phosphoric acid Flow Rate: 0.8 mL/min. Wavelength:296nm Linearity: TEL :20- 100µg/mL, CHLT: 6.25-31.25 µg/mL Retention Time: TEL: 4.97 min, CHLT: 3.46 min.	[66]
34.	A New RP-HPLC Method for simultaneous estimation of telmisartan and cilostazol in synthetic mixture	Column: C18G (250 mm × 4.6 mm, 5 µm) Mobile Phase: Potassium di hydrogen phosphate buffer (10mM): Methanol: Acetonitrile (30:10:60) v/v/v (pH 5.8) Flow rate: 1.0 mL/min. Wavelength: 257 nm Linearity: TEL :2-10 µg/ml, CIL :4-20 µg/ml Retention Time: TEL: 9.6 min, CIL: 5.49 min.	[67]
35.	Development and Validation of Analytical Method for Simultaneous Estimation of Bisoprolol Fumarate and Telmisartan by Using RP-HPLC Method	Column: Waters X Bridge RP C18(250mm x 4.6 mm,5µm) Mobile Phase: Methanol and water (75:25 v/v) Flow Rate: 1ml/min. Wavelength: 231nm Linearity: BIS: 5-25 µg/ml TEL: 40-200 µg/ml Retention Time: BIS: 5.7 min, TEL: 7.6 min.	[68]
36.	Stability indicating RP-UHPLC method for determination of telmisartan in drug substance and marketed formulation	Column: Poroshell 120EC-C18 column (4.6 x 50mm, 2.7 µm) Mobile Phase: Acetonitrile: 50 mM ammonium acetate buffer (45: 55) v/v, (pH 4.5) acetic acid. Flow rate: 1mL/min. Wavelength: 290 nm Linearity:100-300 µg/ml	[69]
37.	Development and validation of a stability indicating RP-HPLC method for simultaneous determination of telmisartan and amlodipine in combined dosage form	Column: Hypersil BDS C18 Column (100 mm x 4.6 mm, 5µ.) Mobile Phase: Phosphate Buffer (pH 3.6): Acetonitrile (60:40 v/v) Flow rate: 1 mL/min. Wavelength: 234 nm Linearity: TEL :10–150 µg/ml AMLB :1–20 µg/ml Retention	[70]

		Time: TEL: 4.1 min, AMLB: 2.6 min	
38.	Determination of telmisartan and forced degradation behaviour by RP-HPLC in tablet dosage form	Column: C18 Column (250 x 4.6mm,5 µm) Mobile Phase: 10mM Potassium Dihydrogen Phosphate: Acetonitrile (64:40) Flow Rate: 1.0mL/min Wavelength:230 nm Linearity: 10-50 µg/ml Retention Time: 12 min	[71]
39.	Development and validation of stability indicating HPLC method for the estimation of Telmisartan related substances in tablets formulation	Column :X-Bridge C18 Column (150x4.6mm,3.5µm) Mobile Phase: 25 mM Potassium Dihydrogen Phosphate: Acetonitrile and 10mM of 1- Hexane sulphonic Acid Linearity: 0.08-500 µg/ml	[72]
40.	Impurity profiling of Azelnidipine and Telmisartan in Fixed Dose Combination using Gradient RP-HPLC Method	Column: C18 Column (150x4.6mm,5µm) Mobile Phase: Acetonitrile and Buffer Flow Rate: 1.5mL/min Wavelength:254 nm Retention Time: 40.0 min	[73]
41.	Stability indicating RP-HPLC method for the determination of telmisartan pure and pharmaceutical formulation	Column: C18 Column (4.6x150mm,3.5µm Make: X Terra) Mobile Phase: Buffer: Methanol (40:60 v/v) Flow Rate: 0.5mL/min Wavelength:230 nm Linearity: 20-100 µg/ml Retention Time: 2.6 min	[74]
42.	Stability Indicating RP-HPLC Method Development and Validation for simultaneous estimation of Azelnidipine and Telmisartan in Bulk and Pharmaceutical Dosage Form	Column: C18 Column (150x4.6mm,5µm) Mobile Phase: 0.1. /. OPA: Acetonitrile (60:40 v/v) Flow Rate: 1.0mL/min Wavelength: 242.0 nm Retention Time: 2116-3.188 min; %RSD of the Azelnidipine and Telmisartan System were found to be 1.6% and 1.0% respectively. %Recovery was obtained as 100.15% and 100.20% for Azelnidipine and Telmisartan respectively. LOD and LOQ values obtained from regression equations of Azelnidipine and Telmisartan were 0.04,0.13 and 0.38,1.14 respectively	[75]
43.	Stress degradation studies on Telmisartan and development of a validated method by UV spectrophotometry in bulk and pharmaceutical dosage forms	TELM has the absorbance maxima at 296 nm; methanol: solvent; Linearity: 4-16	[76]
44.	HPLC Method Development and Validation for the Simultaneous Estimation of Pitavastatin and Telmisartan	Wavelength: 250nm; C18, 250 × 4.6 mm, 5µm particle size, Phenomenex with the flow rate of 1.0mL/min.; Mobile phase: Acetonitrile and 10mM Ammonium acetate buffer containing 0.1% formic acid in the ratio of 65:35 v/v; retention time for Pitavastatin 5.408 & Telmisartan was 7.183; range of 10µg/ml to 60µg/ml	[77]

Combination of Benidipine HCl and Telmisartan[78-85]

1. **Sensitivity Enhanced Ecofriendly UV Spectrophotometric Methods for Quality Control of Telmisartan and Benidipine Formulations: Comparison of Whiteness and Greenness with HPLC Methods:** UV-Vis spectrophotometer (Shimadzu 1650, Second Derivative Method (SDM), Ratio Amplitude Difference Method (RAD), Ratio First Derivative Method (RFD), Constant Subtraction Method (CSM).

2. **Validated UV-Spectrophotometric method for simultaneous estimation of Benidipine Hydrochloride and Telmisartan in bulk and pharmaceutical dosage form.** Model: Shimadzu (UV-1780) Double beam UV-Visible spectrophotometer with 1cm matched quartz cells; 1-5 µg/mL and 10-50 µg/mL of Benidipine HCl and Telmisartan; Benidipine HCl and Telmisartan are exhibits maximum absorbance (λ max) at 237 nm and 296 nm with methanol as the solvent; linearity: BPH: 1-5 µg/mL and TEL: 10-50 µg/mL; correlation coefficient (r2) of 0.9992 for Benidipine HCl and 0.9996 Telmisartan

3. **Dual wavelength Spectrophotometric method for estimation of Benidipine Hydrochloride and Telmisartan in pharmaceutical dosage form:** U.V. visible spectrophotometer: A Shimadzu model 1800, Wavelength: BPH: 228.36-245.39 nm TEL: 280.21-315.39 nm, Beer's law limit (µg/ml) BPH: 1-5 TEL: 10-50

4. **Development and validation of RP-HPLC Method for simultaneous estimation of Benidipine hydrochloride and Telmisartan in tablet**: YL 9100 HPLC with PDA detector (YL-Clarity software); Stationary phase (Column): Inertsil ODS C18 column (150 x 4.6 mm, 5 µm); mixture of 0.05M Potassium Dihydrogen Phosphate Buffer (pH - 4.5 adjusted with 1% OPA) and Acetonitrile (40: 60% v/v) as a mobile phase; flow rate: 1 mL/min; Wavelength: 267 nm by used PDA detector; retention times of Benidipine hydrochloride and Telmisartan were found to be 2.977 and 5.167 respectively; Run time : 10 minutes; Linear range 2 - 6 µg/mL and 20 - 60 µg/mL for Benidipine hydrochloride and Telmisartan

5. **Simultaneous estimation of fixed dosage combination of Telmisartan and Benidipine Hydrochloride in human plasma by HPLC-UV:** C18 column 250 x 4.6 mm, 5 µm particle size; pH 4 for 10Mm Acetonitrile: Water (70:30); flow rate: 1 ml per minute.; 20 µl was the injection volume; wavelength: 215 nm; linearity range: 8-40 and 0.5-4 µg/ml

for TEL and BEN; Resolution [Rs]: BEN: 5.001, TEL: 4.653; HETP [cm/plate]: BEN: 0.007 TEL: 0.012; Retention time: BEN: 4.8 TEL: 3.4

6. **Stability indicating HPLC method development and validation for the simultaneous estimation of benidipine HCl and telmisartan in its pharmaceutical dosage form:** Model: LC- 10AT; Column: C18 (25 cm × 0.46 cm) Hypersil BDS; Mobile Phase: Phosphate buffer, pH 4.0: Methanol (50:50); Flow Rate: 1.0 ml/min; Detection Wavelength: 220 nm; Runtime: 8 min; Injection volume: 20.0 µl; Linearity: 20-60µg/ml of Telmisartan and 2-6µg/ml of Benidipine HCl; retention time (RT) 3.273 and 4.807 min for TEL and BEN; Resolution: 7.416

7. **Stability indicating reverse-phase high performance liquid chromatography method development and validation for simultaneous estimation of telmisartan and benidipine HCl in pharmaceutical dosage form:** Stationary Phase-C18 column, (250×4.6 mm), Mobile Phase- buffer: methanol (50:50) pH:4.0 Flow rate- 1.0 ml / min, Wavelength: 210 nm, Linearity: BPH 2-6 µg/ml, TEL 20-60 µg/ml. Retention time* BPH 2.412 TEL 5.021, Tailing factor* BPH 1.13 TEL 1.30, Asymmetrical factor* BPH 1.167 TEL 1.020, Number of Theoretical plates BPH 2879 TEL 15854, Resolution BPH 2.398 TEL 9.323, Flow rate BPH 0.8 ml/min TEL 0.8 ml/min , Run time BPH 8 min TEL 8 min

8. **Stability Indicating Validated RP-HPLC Method Development for Simultaneous Estimation of Benidipine Hydrochloride and Telmisartan from Pharmaceutical Dosage Form:** Shimadzu model UV-VIS 1700 a double beam UV-VIS spectrophotometer; Stationary Phase: Phenomenax C-18 column (250mm×4.6mm,5µm); Mobile Phase: Methanol: Acetonitrile: water (70:20:10); Flow Rate:0.8 ml/min; Wavelength:237 nm; Injection Volume: 20µL; Run Time: 8 min; Linearity:2-10 µg/ml TEL; 5-25 µg/ml BEN; LOD:0.19 µg/ml TEL; 2.94 µg/ml BEN

CONCLUSION

The physico-chemical characteristics, pharmacological actions, and trade names of a few commercially available benidipine HCl and telmisartan formulations are presented in this review article. The review that is being presented provides details on the different approaches that have been documented in the literature for determining the concentrations of benidipine HCl and Telmisartan, including official pharmacopeial assay techniques. This review came to the conclusion that various analytical techniques, such as UV Spectroscopy, HPTLC, and

HPLC, are reported for the estimation of benidipine HCl and Telmisartan separately as well as in combinations. For this reason, every technique discovered has been straightforward, precise, economical, accurate, and repeatable. The majority of the methods used were UV Spectrophotometric methods (11 methods) and RP-HPLC methods (21 methods), as these techniques offered the best available sensitivity, repeatability, analysis time, and reliability. The provided literature review focuses on the two HPLC methods that have been reported for the fixed dose combination of benidipine HCl and Telmisartan. This review provides information about the properties of both medications and will aid in the future development of analytical techniques for this novel combination.

REFERENCES

1. World Health Organization "Hypertension" https://www.who.int/health-topics/hypertension#tab=tab_1
2. George L. Bakris, "High Blood Pressure", 2023. https://www.msdmanuals.com/en-in/home/heart-and-blood-vessel-disorders/high-blood-pressure/high-blood-pressure
3. BENIDIN-T 4/40mg tablets https://www.netmeds.com/prescriptions/848609
4. Benedipine HCl drug profile: https://pubchem.ncbi.nlm.nih.gov/compound/Benidipine-hydrochloride#section=Computed-Descriptors
5. Benedipine HCl drug bank drug profile https://go.drugbank.com/salts/DBSALT001267
6. Benedipine HCl medchem drug profile: https://www.medchemexpress.com/Benidipine-hydrochloride.html
7. Telmisartan description: https://www.mayoclinic.org/drugs-supplements/telmisartan-oral-route/description/drg20067196#:~:text=Telmisartan%20is%20an%20angiotensin%20II,and%20oxygen%20to%20the%20heart.
8. Telmisartan drug profile https://pubchem.ncbi.nlm.nih.gov/compound/Telmisartan#section=Structures
9. Telmisartan drug profile https://reference.medscape.com/drug/micardis-telmisartan-342322#11
10. Telmisartan med chem drug profile: https://www.medchemexpress.com/telmisartan.html
11. Japanese Pharmacopoeia, The Ministry of Health Labour and Welfare, 2017; 18.
12. Manish Kumar et al, "Development of UV Spectrophotometric method for the determination of benidipine hydrochloride by using quality by design approach." International Journal of Applied Pharmaceutics, 2018; 24, 10, 4: 92-97.

13. S.S. Pendhari et al, "UV-Visible spectrophotometric method development and validation of assay of Benidipine Hydrochloride tablet formulation" Indo American Journal of Pharmaceutical Research, 2017; 30, 04: 8159-8168.
14. Vijay P et al, "Multivariate Calibration Techniques aided UV Spectrophotometric method for the estimation of Benidipine Hydrochloride in pharmaceutical dosage forms", International Journal of Biology, Pharmacy and Allied Sciences(IJBPAS), 2022; 1, 11(10): 4501-4511.
15. Buridi Kalyanaramu et al, "Development of new Visible Spectrophotometric methods for determination of Benidipine Hydrochloride in bulk and formulations based on oxidative coupling and diazo coupling reactions" International Journal of Pharmacy and Biological Sciences, 2011; 17, 06: 1-2.
16. Hasan I Shaikhmulani et al, "Simultaneous Equation Method for the Estimation of Benidipine Hydrochloride and Chlorthalidone by UV Spectrophotometry", International Journal of Pharmacy and Pharmaceutical Research(IJPPR), 2022; 30, 24, 3: 406-417.
17. Ms. Bhoomi D. Patel et al, "RP-HPLC Method Development and validation for Simultaneous estimation of Benidipine Hydrochloride, Telmisartan and Chlorthalidone in tablet", Journal of Emerging Technologies and Innovative Research (JETIR), 2019; 6, 3: 110-124.
18. Patel Advaita et al, "Method Development and Validation for Simultaneous Estimation of Benidipine Hydrochloride and Metoprolol Succinate in Tablet", Journal of Drug Delivery and Therapeutics, 2019; 15, 12, 9(6-s): 28-33.
19. Ayça Karasakal, "First Order Derivative Spectrophotometric Method for the Determination of Benidipine Hydrochloride Pharmaceutical Preparations and Forced Degradation Study", GEOMETRICAL AND APPLIED OPTICS, 2015; 118, 6: 1002–1006.
20. Cem ÖNAL et al, "Spectrofluorimetric determination of benidipine in pharmaceutical preparation and spiked plasma samples using 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole", Journal of Research in Pharmacy, 2019; 05, 23(6): 1060-1066.
21. Hiroshi Magara et al, "Determination of benidipine hydrochloride in human plasma by capillary column gas chromatography-negative ion chemical ionization mass spectrometry", Journal of chromatography, April, 1993; 22: 59-63.
22. Khater AL-Japairai et al, "Development and Validation of HPLC Method for Determination of Benidipine Hydrochloride in Lipid Vesicles Formulations", International Journal of Membrane Science and Technology · October, 2022; 9: 40-47.

23. Gadhave Harshada D "Development and Validation of Analytical RP HPLC Method for Benidipine Hydrochloride", International Journal of Advanced Research in Science, Communication and Technology (IJARSCT), 2, 5: 71-76.
24. Development and validation of RP-HPLC method for Benidipine In bulk and tablet dosage form.
25. Nurgul Karadas et al, "Voltammetric and RP-LC assay for determination of benidipine HCl", Journal of Pharmaceutical and Biomedical Analysis, 2012; 23: 116–125.
26. Koshish Babarao Gabhane et al, "Analytical Validation and Stability Indicating Studies for Simultaneous Estimation of Benidipine and Metoprolol by Strong Cation Exchange (SCX) Chromatography", Pharmaceutical Methods, 2020; 11, 1: 6-12.
27. Shaikhmulani HI et al, "RP-HPLC Method Development and Validation for Simultaneous Estimation of Benidipine Hydrochloride and Chlorthalidone in Pharmaceutical Dosage Form", Indian Journal Pharm drug studies, 2022; 28, 3, 2: 6-12.
28. Esen Bellur Atici et al, "Identification, synthesis and characterization of process related impurities of benidipine hydrochloride, stress-testing/stability studies and HPLC/UPLC method validations", Journal of Pharmaceutical Analysis, 2015; 13: 256–268.
29. Kadali Jagadeesh, "Stability Indicating Method to Analyse Benidipine and Chlorthalidone Using HPLC Technique: Establishment, Validation and Application to Tablets", Pharmaceutical Sciences, 2020; 26(1): 75-81.
30. Wonku Kang et al, "Determination of benidipine in human plasma using liquid chromatography–tandem mass spectrometry", Journal of Chromatography B, 2004; 13: 311–314.
31. Mujawar, T. et al, "Analytical method development and validation for the simultaneous estimation of Metoprolol and Benidipine by RP-HPLC in bulk and tablet dosage forms", International Journal of Health Sciences, 6(S6): 8188–8202.
32. The Indian Pharmacopoeia, Government of India, Ministry of Health and Family welfare; The Indian pharmacopeia commission, Ghaziabad, 2018; 7, II: 1304-1305, 3319-3320.
33. Japanese Pharmacopoeia, The Ministry of Health Labour and Welfare, 2016; 17: 704-707.
34. Dharmendra Damor et al, "Method development and validation of Simultaneous estimation of Cilostazol and Telmisartan" Research & Reviews: Journal of Pharmaceutical Analysis, 2015; 01, 09, 4, 3: 41-48.
35. Niranjan D. Chivate et al, "Development of UV spectrophotometric method for estimation and validation of Telmisartan as a pure API" Journal of Pharmacy Research June, 2012; 5, 6: 3331-3333.

36. "Absorbance correction method for estimation of telmisartan and metoprolol succinate in combined tablet dosage forms" https://pubmed.ncbi.nlm.nih.gov/23781489/
37. "UV-Spectrophotometric Determination for Simultaneous Estimation of Amlodipine Besylate and Telmisartan in Combination" https://www.semanticscholar.org/paper/UV-Spectrophotometric-Determination-for-Estimation-Hirpara-Dave/5e56840938a3159f9fc2c7f6995028fbcc6aac73
38. Mayur Modi et al., "Development and validation of spectrophotometric methods for simultaneous estimation of metoprolol succinate and telmisartan in combined pharmaceutical formulation", IJPSR, 2012; 28, 3(5): 1348-1354.
39. Rathod et al., "UV Spectrophotometric method for estimation of Telmisartan in bulk and tablet dosage form" IJPSR, 2012; 26, 3(10): 3936-3939.
40. Manish Kumar et al, "Dissolution Method Development and Validation for Tablet Dosage form of Telmisartan Using UV Spectrophotometric Method", Journal of Chemical and Pharmaceutical Research, 2018; 10(5): 148-156.
41. Lalit Thakare et al, "Development and validation of UV- Spectrophotometric method for estimation of Cilnidipine and Telmisartan in bulk and dosage form", Indo American Journal of Pharmaceutical Research, 2017; 15, 05, 7(04): 8552-8559.
42. Rajesh S. Jadhav "UV Spectrophotometric analytical method development and validation for determination of Telmisartan in pharmaceutical drug and drug product (tablet dosage form)", International Journal of Current Advanced Research, 2018; 7, 6(C): 13292-13296.
43. Avani Khristi et al, "Analytical Method Development and Validation of First Order Derivative Spectrophotometric Method for Simultaneous Estimation of Telmisartan and Metformin Hydrochloride in their Combined Pharmaceutical Dosage Form", IJPQA, 2020; 11, 1: 60-68.
44. Chitra Prabhu et al, "Determination of Telmisartan by HPTLC – A Stability Indicating Assay", Journal of Planar Chromatography, 2007; 20, 6: 477–481.
45. Reema H et al, "Stability Indicating Simultaneous Validation of Telmisartan and Cilnidipine with Forced Degradation Behaviour Study by RP-HPLC in Tablet Dosage Form", ISRN Chromatography, 2013; 25: 1-6.
46. Bhavin Pankajbhai Marolia et al, "Development and Validation of Stability Indicating HPTLC and HPLC Methods for Simultaneous Determination of Telmisartan and Atorvastatin in Their Formulations" Pharmaceutical Methods, 2016; 7, 1: 48-53.

47. M. Lakshmi Surekha et al "Development and Validation of RP - HPLC method for the estimation of Telmisartan in bulk and tablet dosage Form", International Journal of Drug Development & Research, October-December, 2012; 4, 4: 200-205.
48. RLC SASIDHAR et al, "Development and Validation of RP - HPLC Method for the Simultaneous Determination Of Hydrochlorothiazide, Amlodipine Besylate and Telmisartan in Bulk and Pharmaceutical Formulation", ORIENTAL JOURNAL OF CHEMISTRY, September, 2014; 09, 30(4): 1815-1822.
49. Bhoomi D. Patel et al, "RP-HPLC method development and validation for simultaneous estimation of Benidipine Hydrochloride, Telmisartan and Chlorthalidone in tablet" JETIR March, 2019; 6, 3: 110-124.
50. Jain Nilesh et al., "RP-HPLC Method Development and Validation for Quantitative Estimation of Metoprolol Succinate and Telmisartan in Bulk Drug and Their Dosage Forms" Journal Pharmaceutical Biomedical Science, 2012; 24(24): 102-106.
51. VANDANA JAIN et al, "Novel Reverse-phase high performance liquid chromatography method development and validation for estimation of telmisartan and nebivolol hydrochloride in pharmaceutical dosage form", Asian J Pharm Clin Res, 2018; 11, 9, 30: 431-435.
52. Telmisartan/ RP-HPLC Kaur L., Singh G., Kaur, et al. Development and Validation of Rapid RP-HPLC Method for the Detection and Quantification of Telmisartan Incorporated in Dosage Forms and Plasma: J. of Pharmaceutical Research and Therapeutics, 2020; 1(2): 78-83.
53. P. ASHOK et al, "Development and validation of a RP-HPLC method for estimation of telmisartan in human plasma" International Journal of Applied Pharmaceutics, 2019; 11, 1: 237-240.
54. K. Megala et al, "Validated RP-HPLC Method for Simultaneous Determination of Telmisartan and Hydrochlorothiazide in Pharmaceutical Formulation", International Journal of Pharmaceutical Research & Allied Sciences, 2014; 3, 3: 33-40.
55. Ashok K. Palakurthi et al, "QbD Based Development of HPLC Method for Simultaneous Quantification of Telmisartan and Hydrochlorothiazide impurities in Tablets Dosage Form", Journal Pre-proof, 2020; 18(19): 30147-7.
56. Hassan A. Alhazmi et al"A Fast and Validated Reversed-Phase HPLC Method for Simultaneous Determination of Simvastatin, Atorvastatin, Telmisartan and Irbesartan in Bulk Drugs and Tablet Formulations" Scientia Pharmaceutica, 2018; 86: 1.

57. Bangaruthalli J et al "Simultaneous estimation of telmisartan and atorvastatin calcium in API and tablet dosage form" Journal of Drug Delivery and Therapeutics, 2019; 9(1):175-179
58. Bhavin Pankajbhai Marolia et al, "Development and Validation of HPTLC Method for Simultaneous Estimation of Amlodipine Besylate, Hydrochlorothiazide and Telmisartan In Their Combined Tablet Dosage Form", Pharmaceutical Methods, Jun, 2016; 7, 1: 48-53.
59. Bhadoriya Upendra et al, "RP-HPLC Method development and validation for estimation of telmisartan in bulk and tablet dosage form", International Journal of Drug Regulatory Affairs, 2013; 1(2): 61-64.
60. Prashanth Nallavelli et al "Analytical Method Development and Validation for the Simultaneous Estimation of Telmisartan and Atorvastatin in Bulk and Tablet Dosage Form" International Journal of Applied Pharmaceutical Sciences and Research, 2020; 1, 1: 5-1.
61. Jaydeep M. Patel et al, "Development and Validation of Bioanalytical HPLC Method For Estimation of Telmisartan In Rat Plasma: Application To Pharmacokinetic Studies", J. Pharm. Sci, 2012; 11(2): 121-127, (December)
62. P.Gayathri et al, "Analytical method development and validation for the simultaneous estimation of metformin and telmisartan in bulk and pharmaceutical dosage form using RP-HPLC method" WJPPS, 4, 4: 753-762.
63. Shaila Sumaiya et al "A Validated RP-HPLC Method for Tablets Containing Amlodipine Besylate and Telmisartan HCl as Active Pharmaceutical Ingredient" Modern Chemistry & Applications, 2020; 12, 8, l, 8, 3, 276: 1-10.
64. Nagakanyaka Devi et al, "Development and Validation RP-HPLC Method for the estimation of telmisartan in bulk drug using internal standard", INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY, 2013; 3(3): 650-658.
65. Zeel T. Doshi et al, "Development and Validation RP-HPLC Method for Simultaneous Estimation of Telmisartan and Nifedipine In Synthetic Mixture", Asian Journal of Pharmaceutical Technology & Innovation, 2016; 15, 06: 04, (18): 01 -10.
66. N. Vanaja et al, "Method Development and Validation for Simultaneous Estimation of Telmisartan and Chlorthalidone by RP-HPLC in Pharmaceutical Dosage Form" Asian Journal of Pharmaceutical Analysis, 2015; 5, 4: 171-177. https://ajpaonline.com/AbstractView.aspx?PID=2015-5-4-1

67. Manwar et al., "A New RP-HPLC Method for simultaneous estimation of telmisartan and cilostazol in synthetic mixture", IJPPR, 2020; 22, 12, 20, 1: 491-502.
68. Barge V U et al "Development and Validation of Analytical Method for Simultaneous Estimation of Bisoprolol Fumarate and Telmisartan by Using RP-HPLC Method" International Journal of Pharmaceutical and Clinical Research, 2018; 10(8): 219-223.
69. Patra et al "Stability indicating RP-UHPLC method for determination of telmisartan in drug substance and marketed formulation"., IJPSR, 2016; 7(5): 2031-2039.
70. Kumar M et al. "Development and validation of a stability indicating RP-HPLC method for simultaneous determination of telmisartan and amlodipine in combined dosage form" Asian J Pharm Clin Res, 2014; 7, 1: 32-35.
71. M.S. Charde et al "Determination of telmisartan and forced degradation behaviour by RP-HPLC in tablet dosage form" International Journal of Advances in Pharmaceutical Analysis IJAPA, 2011; 1, 2: 38-44.
72. Ch. Phani Kishore et al "Development and validation of stability indicating HPLC method for the estimation of Telmisartan related substances in tablets formulation" Int. J. Res. Pharm. Sci, 2010; 1, 4: 493-501.
73. Manish Kumar et al "Impurity profiling of Azelnidipine and Telmisartan in Fixed Dose Combination using Gradient RP-HPLC Method" Annals of R.S.C.B, 2021; 1, 25, 4: 15050 – 15067.
74. SUJANA K et al, "Stability indicating RP-HPLC method for the determination of telmisartan pure and pharmaceutical formulation", International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3, 2: 164167.
75. Chaitanya and Ajitha, "Stability Indicating RP-HPLC Method Development and Validation for simultaneous estimation of Azelnidipine and Telmisartan in Bulk and Pharmaceutical Dosage Form", 02-01-2022, World Journal Pharmaceutical Science, 10(01): 121-127.
76. Komal Patel et al, "Stress degradation studies on Telmisartan and development of a validated method by UV spectrophotometry in bulk and pharmaceutical dosage forms", Pharmaceutical Methods | October-December, 2011; 2, 4: 253-259.
77. Deepika et al, "Hplc Method Development and Validation for the Simultaneous Estimation of Pitavastatin and Telmisartan", Journal of Pharmaceutical Research & Report, August, 2023; 18, 4(5): 1-11.
78. Muhammad Shahzad Chohan et al, "Sensitivity Enhanced Ecofriendly UV Spectrophotometric Methods for Quality Control of Telmisartan and Benidipine

Formulations: Comparison of Whiteness and Greenness with HPLC Methods", International Journal Environmental Research Public Health 2022, 19, 7260, 1-16

79. M. M. Eswarudu et al, "Validated UV-Spectrophotometric method for simultaneous estimation of Benidipine Hydrochloride and Telmisartan in bulk and pharmaceutical dosage form." European Journal of Biomedical AND Pharmaceutical sciences, 2022; 28, 8, 9, 9: 342-347.
80. Khyati Patel et al, "Dual wavelength Spectrophotometric method for estimation of Benidipine Hydrochloride and Telmisartan in pharmaceutical dosage form" World Journal of Pharmaceutical Research, 2018; 20, 7, 5: 1494-1505.
81. Payal G. Jain et al, "Development and validation of RP-HPLC Method for simultaneous estimation of Benidipine hydrochloride and Telmisartan in tablet", WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES, 2018; 05, 7, 5: 751-762.
82. Deepak Dalal et al, "Simultaneous estimation of fixed dosage combination of Telmisartan and Benidipine Hydrochloride in human plasma by HPLC-UV", Eur. Chem. Bull, 2023; 12(5): 3300 – 3307.
83. Vyas Apexaben Arvindbhai et al "Stability indicating HPLC method development and validation for the simultaneous estimation of benidipine HCl and telmisartan in its pharmaceutical dosage form" PHARMA SCIENCE MONITOR AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES, 2018; 9(2): 143-163.
84. MAJAN NAIM et al, "Stability indicating reverse-phase high performance liquid chromatography method development and validation for simultaneous estimation of telmisartan and benidipine HCl in pharmaceutical dosage form" Asian J Pharm Clin Res, 2018; 11, 5: 342-350.
85. Varsha Chandgude et al, "Stability Indicating Validated RP-HPLC Method Development for Simultaneous Estimation of Benidipine Hydrochloride and Telmisartan from Pharmaceutical Dosage Form", International Journal of Science and Research (IJSR), 2019; 8, 11: 767-773.