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A REVIEW ON COMPARENSIVE ANALYSIS OF AZELNIDIPINE AND TELMISARTAN

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ABSTRACT

Hypertension is a common disease affecting people of all ages, from adults to the elderly. Single-drug therapy often proves insufficient for managing hypertension, prompting the use of drug combinations. Among these combinations, Azelnidipine and Telmisartan stand out as potent and widely utilized options. This article aims to provide comprehensive details regarding Azelnidipine and Telmisartan, including information on manufacturing and marketing companies, official analytical methods, and various analytical techniques such as RP HPLC, HPLC, UPLC, UV, LC, HPTLC, and LC-MS/MS. The article will also elucidate different analytical methods used in recent studies.

KEYWORDS: Azelnidipine, Telmisartan, RP-HPLC, UV, HPTLC, LC-MS/MS Methods.

INTRODUCTION

Hypertension poses a significant global health concern, affecting over 20% of adults worldwide, with developing countries facing escalating challenges due to changing health needs. The prevalence of chronic disease like hypertension is on the rise, creating a public health crisis, especially among women, adolescents, and older adults. In Iraq, according to the 2006 national survey, 40.4% of adults have elevated blood pressure, making hypertension a critical modifiable risk factor for coronary heart diseases, stroke, congestive heart disease, end-stage renal disease, and peripheral vascular diseases.[1]

Azelnidipine, a calcium channel blocker, demonstrates a positive antihypertensive effect in individuals with essential hypertension, induces nitric oxide production, enhances histological processes crucial for diabetic wound healing, and serves as a renoprotective agent in hypertensive patients with mild chronic renal disease, partly due to its antioxidant properties. Azelnidipine, a vasodilator used for hypertension, gradually lowers blood pressure in hypertensive patients without causing reflex tachycardia, distinguishing it from other drugs in the same class.[2]

Telmisartan, also known as TLM, is a type of medication that blocks angiotensin II receptors. This leads to a significant and long-lasting reduction in blood pressure, lasting up to 24 hours. Telmisartan is effective in lowering blood pressure and has additional benefits, including reducing the stiffness of arteries, decreasing left ventricular hypertrophy, preventing the recurrence of atrial fibrillation, and providing protection for the kidneys. Telmisartan, utilized in the management of hypertension as an angiotensin II receptor blocker, exhibits a minimal occurrence of temporary serum aminotransferase elevations; however, there is currently no established association between telmisartan and instances of acute liver injury.[3]

For hypertensive patients unable to achieve sufficient control with single-drug therapy, combination treatment, such as the preferred combination of angiotensin-receptor blocker and calcium channel blocker, is often necessary. In some cases, a triple combination may be required for effective blood pressure control. A newly available product in the market, Azelikem T-40, Telmiwal-AP, Telma-AZ, and Emdip T-40, offers a fixed-dose tablet formulation combining Azelnidipine and Telmisartan, serving as an option for treating hypertension.

Patients with hypertension are prescribed a combination of Azelnidipine and Telmisartan, which helps regulate blood pressure and improve oxygen circulation, reducing the risk of heart-related chest discomfort. The tablets come in two strengths: 80 mg Telmisartan with 8 mg Azelnidipine and 40 mg Telmisartan with 8 mg Azelnidipine.[4]

PHYSICAL AND CHEMICAL PROPERTIES OF DRUGS

Azelnidipine, with the IUPAC name 3-1-Benzhydryl-3-azetidinyl 5-isopropyl 2-amino-6-methyl-4-(m-

nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, is a calcium channel blocker used in the treatment of hypertension. Its molecular formula is $C_{33}H_{34}N_4O_6$, with a molecular weight of 582.6 g/mol and a melting point of 122-123°C. This pale yellow to yellow crystalline powder exhibits insolubility in water, limited solubility in aqueous buffers, and solubility in organic solvents like ethanol, DMSO, and DMF. With a Pka value of 7.89, it is stored at 4°C and functions by inhibiting trans-membrane Ca2+ influx through vascular smooth muscle voltage-dependent channels, thereby relaxing blood vessels and reducing blood pressure.[5,6,7]

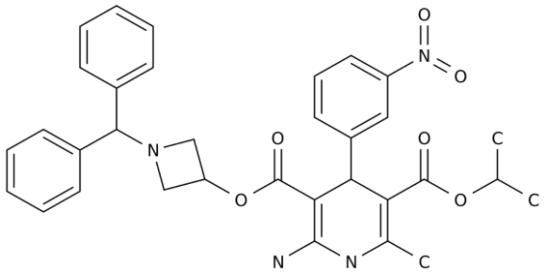

Figure No. 1: Structure of Azelnidipine.[8]

Telmisartan, with the IUPAC name 2-(4-{[4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H- 1,3-benzodiazol-1-yl] methyl} phenyl) benzoic acid, has a molecular formula of $C_{33}H_{30}N_4O_2$ and a molecular weight of 514.629 g/mol. It appears as a white to slightly yellowish solid with a melting point of 261-263°C. Telmisartan exhibits extremely low water solubility but is freely soluble in highly alkalized solutions and organic solvents such as DMSO (dimethyl sulfoxide) and DMF (dimethyl formamide). With a Pka value of 3.5, 4.1, and 6.0, it is stored below 30°C. This compound is categorized for use in the treatment of hypertension, functioning as an angiotensin II receptor blocker. Its mechanism of action involves blocking a substance in the body that causes blood vessels to tighten, leading to the relaxation of blood vessels. Consequently, Telmisartan lowers blood pressure, enhances the supply of blood, and increases oxygen delivery to the heart by inhibiting the action of certain natural substances that constrict blood vessels, allowing for smoother blood flow and improved cardiac efficiency.[9,10,11]

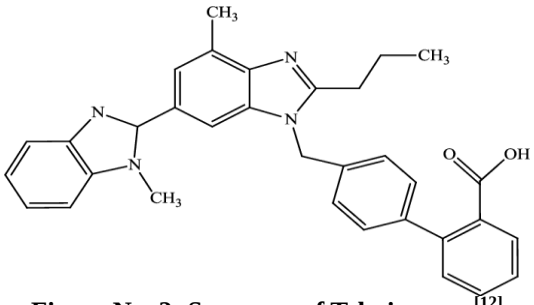

Figure No. 2: Structure of Telmisartan.[12]

Table No. 1: Pharmaceutical manufacturing companies and associated brand information.[13,14]

S.no	Brand name	Dosage form	Manufacturing company	Marketing company
1.	Zeblong T	Azelnidipine 8mg Telmisartan 40mg	Akums drugs and pharmaceuticals	Ipca laboratories ltd
2.	Cortel AZ	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	Corona remedies pvt. Ltd
3.	Telma AZ	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	Glenmark pharmaceuticals
4.	Emdip T	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	Emcure pharmaceuticals ltd
5.	Azovas T	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	JB chemicals and pharmaceuticals ltd
6.	Azusa T	Azelnidipine 8mg Telmisartan 40mg	Ajanta pharmaceuticals	Ajanta pharmaceuticals
7.	Telmed AZ	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	Medley pharmaceuticals.
8.	Azilta T	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	RPG life science ltd
9.	Uniaz T	Azelnidipine 8mg Telmisartan 40mg	Synokem pharmaceuticals	Torrent pharmaceuticals
10.	Telmidoz AZ	Azelnidipine 8mg Telmisartan 40mg	Ausmed life science	Care formulation labs pvt. Ltd
11.	Azelikem –T 40	Azelnidipine 8mg Telmisartan 40mg	Steris healthcare pvt. Ltd – india	Steris healthcare pvt. Ltd – india
12.	Telmiwal-AP	Azelnidipine 8mg Telmisartan 40mg	Intra life india.com – india	Intra life india.com – india
13.	Azedax T 40	Azelnidipine 8mg Telmisartan 40mg	Daxia healthcare pvt ltd	Daxia healthcare pvt ltd

Table No. 2: Official Method of Azelnidipine and Telmisartan.

S.no	Drug and Pharmacopoeia	Method	Description	Reference number
1.	AZELNIDIPINE INDIAN PHARMACOPOEIA (IP) (2022)	LIQUID CHROMATOGRAPHY	✓ Colum: A Stainless-Steel Column 25 Cm X 4.6 Mm, Packed with Octadecylsilane Bonded to Porous Silica (5 Pm), ✓ Column Temperature: 40°C ✓ Mobile Phase: A mixture of 35 Volumes of a Buffer solution Prepared By dissolving 3.0 g of potassium Dihydrogen Orthophosphate In 1000 ml of water. ✓ Adjusted to Ph 5.5 With Orthophosphoric Acid, 45 Volumes of Acetonitrile And 20 Volumes of methanol, ✓ Flow Rate: 1 ml Per minute, ✓ Spectrophotometer: 220 nm, ✓ Injection Volume:10 µL.	[15]
2.	TELMISARTAN INDIAN PHARMACOPOEIA (IP) (2022)	LIQUID CHROMATOGRAPHY	✓ Colum: A Stainless-Steel Column 12.5 Cm X 4.0 Mm, Packed with Octadecylsilane Bonded to Porous Silica (5 Pm) ✓ Column Temperature: 40°C ✓ Mobile Phase: (A). Dissolve 2.0 g of potassium dihydrogen Phosphate And 3.8 g of Sodium Pentane sulphonate Monohydrate in Water, ✓ Adjusted to Ph 3.0 With Orthophosphoric Acid and Dilute to 1000ml with water, ✓ (B). A Mixture of 20 Volumes of methanol and 80 Volumes of Acetonitrile, ✓ Flow Rate: 1 ml per minute ✓ Spectrophotometer: 230 nm ✓ Injection Volume: 10 µL.	[16]

Table No. 3: Analytical Methods for Azelnidipine and Telmisartan in Bulk and Pharmaceutical Dosage Forms.

S.no	Title/method	Method description	Ref.no	Year of published
RP-HPLC Methods				
1.	RP-HPLC method development and validation for simultaneous estimation of azelnidipine and telmisartan in pharmaceutical dosage form by Q by D approach	**Colum:** C-18 250 x 4.6 mm, **Partical size:** 5µ **Mobile phase:** 0.01N Ortho Phosphoric Acid: Acetonitrile ratio of 53.8:46.2V/V **Flow rate:** 0.9 ml/min	17	December 2023
2.	Method development and validation of azelnidipine and telmisartan in human plasma using RP-HPLC	**Colum:** Std Inertsil C-18 (150 x 4.8 mm, 5m) **Mobile phase:** Buffer Disodium Hydrogen Phosphate: Acetonitrile (65:35) **Flow rate:** 1.0 ml/min **Temperature:** 30°C **Wavelength:** 228nm **Retention time:** Azelnidipine 2.139 min and Telmisartan 2.422 min and Internal Standard 3.025 min.	18	March 2023
3.	RP-HPLC Method for Determination of Azelnidipine and Telmisartan in Pharmaceutical Dosage Form	**Colum:** Intersil C-18 column (250 × 4.6mm, 5µm) **Mobile phase:** 70% acetonitrile and 30% 5 millimolar phosphate buffer pH 4.6. **Flow rate:** 1mL/min.	19	February 2023

		Wavelength: 255nm **Linearity:** 10-50µg/ml AZL and 20-100µg/ml TEL		
4.	RP-HPLC–PDA Approach for Concurrent Analysis of Telmisartan and Azelnidipine in Bulk and Commercial Tablets w7	**Colum:** Agilent C-18 column (150 × 4.6 mm, 5) **Mobile phase:** 0.1% V/V ortho phosphoric acid in water and acetonitrile (40:60 v/v) **Flow rate:** 1 ml/min **Wavelength:** 260 nm **Retention times:** Azelnidipine 2.2 min and Telmisartan 2.9 min **Linearity:** Azelnidipine 2–12 µg/mL and Telmisartan 20–120 µg/mL	20	December 2022
5.	Development And Validation of RP-HPLC Method For Simultaneous Estimation of Telmisartan and Azelnidipine in Their Combined Marketed Formulation	**Column:** C-8 150 x 4.6 mm, Zodiac. **Particle size:** 5µ **Mobile phase:** 0.1% Formic Acid buffer Acetonitrile (50:50 v/v) **Flow rate:** 1 ml per minute **Wavelength:**257 nm **Retention time:** Telmisartan 6.16 min and Azelnidipine 8.94 min.	21	August 2022
6.	Advanced forced degradation technique for simultaneous estimation of azelnidipine and telmisartan implementing AQbD approach in its tablet dosage form	**Colum:** Phenomanax Luna C-18 (5 µm, 150 mm × 4.6 mm) **Mobile phase:** water and methanol 50: 50 (v/v) **Wavelength:** 256 nm **Detector:** PDA detector **Linearity:** 4-12 µg mL-1 (r2 = 0.998) Azelnidipine and 20-60 µg mL-1 (r^2 = 0.997) Telmisartan	22	June 2022
7.	Analytical Method Development and Validation of Azelnipidine and Telmisartan by RP HPLC Method	**Colum:** C-18 (4.6 x 150 mm, 5 mm) **Mobile phase:** Buffer 0.01 N KH2PO: Acetonitrile **Flow rate:** 1 ml/min **Wavelength:** 290 nm **Retention time:** Azelnipidine 2.131 min and Telmisartan 2.593 min.	23	March 2022
8.	Development and validation of RP-HPLC method for the simultaneous estimation of azelnidipine and telmisartan in bulk and pharmaceutical dosage form	**Colum:** RP-Purosnosphere C-18 column (5 µm, 4.6mm, 250 mm) **Mobile phase:** methanol: acetonitrile: water (40:30:30) **Flow rate:** 1.0 mL/min **Wavelength:** 225 nm	24	March 2022
9.	Method development & validation of stability indicating RP-HPLC method for simultaneous estimation for Azelnipidine & Telmisartan in bulk & pharmaceutical dosage form	**Colum:** C-18 (100mm x 4.6 mm) **Particle size:** 2.5 µm **Mobile phase:** Methanol 75 ml and 25 ml (pH 4.3 0.1% OPA with TEA) **Flow rate:** 0.8 ml/min **Wavelength:** 249 nm. **Retention time:** Azelnidipine 3.20 min and Telmisartan 6.23 min	25	February 2022
10.	Stability Indicating RP-HPLC Method Development and Validation for simultaneous estimation of Azelnidipine and Telmisartan in Bulk and Pharmaceutical Dosage Form	**Colum:** Std Denali C-18 (150mm x 4.6 mm, 5µ) **Mobile phase:** 0.1% OPA: Acetonitrile in the ratio of 60:40	26	January 2022

		Flow Rate: 1.0 ml/min **Buffer:** 0.1%OPA. **Column temperature:** 30°C **Wavelength:** 242.0nm **Retention time:** Azelnidipine and Telmisartan 2.116 min & 3.188mins		
11.	Method development and validation for the simultaneous determination of azelnidipine and telmisartan in tablet dosage form by RP- HPLC	**Colum:** Hyperchrom ODS C-18 HPLC Column (250mm x 4.6mm) **Buffer:** 0.05M Potassium dihydrogen orthophosphate (KH_2PO_4) **Mobile phase:** Buffer (pH-4.0): Methanol (60:40) **Flow rate:** 1ml/min **Wavelength:** 215 nm	27	October 2021
12.	Investigation of Drug-Excipient Compatibility Studies Using Validated RP-HPLC Method for Azelnidipine and Telmisartan Tablets	**Colum:** inertsil C-18 Column (150 x 4.6mm x 5 µm) **Colum temperature:** 40°C **Flow rate:** 1.5 mL/min **Injection volume:** 10 µL **Run time:** 12.0 minutes. **Wavelength:** 254 nm **Mobile phase:** Acetonitrile and buffer	28	August 2021
13.	A Stability Indicating RP-HPLC Method Validation for Simultaneous Estimation of Azelnidipine and Telmisartan in a Fixed-dose Combination	**Colum:** Inertsil C-18 (150×4.6 mm×5 µm) **Column Oven Temperature:** 40°C **Flow Rate:** 1.5 ml/min **Mobile Phase:** Acetonitrile and Buffer **Volume:** 10 µl **Run Time:** 12.0 Minutes **Wavelength:** 254 nm	29	May 2021
14.	Stability Indicating Rp-HPLC Method Development and Validation for the Simultaneous Estimation of Telmisartan and Azelnidipine in Tablet Dosage Form	**Colum:** Hyperchrom ODS C-18 Column (250mm x 4.6mm) **Buffer:** 0.05M Potassium dihydrogen ortho phosphate **Mobile phase:** Buffer (pH-4.0): Methanol (60:40) **Flow rate:** 1ml/min **Wavelength:** 215nm **Retention time:** Telmisartan 3.440 minutes and Azelnidipine 5.693 minutes	30	May 2021
HPLC Method				
15.	Telmisartan and azelnidipine quantification employing HPLC stratagem; stability investigation on telmisartan and azelnidipine	**Colum:** C-18 Kromasil stationary column (5 µm, 250 mm × 4.6 mm) **Mobile phase:** 0.1M NaH2PO4 solution (pH 3.5) and methanol (50:50) **Flow rate:** 1.0 ml/min **Wavelength:** 256 nm **Detector:** PDA device sensor **Retention time:** TLM 2.225 min and AEL 3.178 min	31	2022
RP-UPLC Method				
16.	Stability indicating RP-UPLC method development and validation for the simultaneous estimation of telmisartan and azelnidipine in	**Colum:** UPLC BEH C-18 column (1.7 µm, 100 × 2.1 mm) **Mobile phase:** Phosphate buffer:	32	October 2023

	their bulk and solid dosage forms	Acetonitrile (70: 30 v/v) **Wavelength:** 240nm **Retention time:** Telmisartan 2.946 and Azelnidipine 5.635		
LIQUID CHROMATOGRAPHY METHOD				
17.	Quantification of Telmisartan and Azelnidipine Combination in Using Liquid Chromatography: Stability studies	**Colum:** Supel cosil C-18 column (250 mm, 4.6 mm, & 5 µm) **Mobile phase:** 0.10M Na2 SO4 (pH 3.6) and acetonitrile (pH 3.6) as 55:45v/v **Flow rate:** 1.00 mL/minute **Wavelength:** 258nm **Injected volume:** 10 µL **Run time:** 8 minutes. **Retention time:** 2.8 and 3.7	33	October 2023
HPTLC Method				
18.	Development and Validation of HPTLC Method for Simultaneous Estimation of Azelnidipine and Telmisartan	**Stationary phase:** Pre coated silica gel G60-F254 aluminum sheet. **Mobile phase:** Toluene: Acetonitrile: Formic acid (5:4.5:0.5 % V/V/V) **Linearity:** 200-700 ng/ band for Azelnidipine and 1000-3500 ng/band for Telmisartan **R^2 value:** 0.9961 Azelnidipine and 0.9971 Telmisartan	34	June 2023
UV- Spectrophotometric Method				
19.	Advanced UV spectrophotometric method development and validation for simultaneous estimation of Azelnidipine and Telmisartan in Pharmaceutical Dosage Form	**Apparatus:** Shimadzu UV-1700 double beam spectrophotometer **Software:** Shimadzu UV-Probe 2.10 **Solvent:** Methanol **Linearity:** 2 µg/ml to 12 µg/ml for AZL and 10 µg/ml to 50 µg/ml for TEL	35	March 2023
20.	Ultraviolet Spectrophotometric Method Development and Validation for Simultaneous Quantification of Azelnidipine and Telmisartan in Pharmaceutical Dosage Form	**Wavelength (λ max):** Azelnidipine 245 nm and Telmisartan 296 nm **Solvent:** methanol **Linearity:** (r^2) 0.9999 Azelnidipine and 0.9987 Telmisartan Concentration rang**e:** 1-6 µg/mL Azelnidipine and 5-30 µg/mL Telmisartan	36	August 2022
21.	First- order derivative and UV-spectrophotometric methods for simultaneous determination of telmisartan and azelnidipine in bulk and tablet dosage form	**(Method A)** Wavelength of telmisartan: 324 nm Wavelength of azelnidipine: 220 nm **(Method B)** Wavelength of telmisartan: 220 nm Wavelength of azelnidipine: 244 nm Linearity: 16-80 µg/ml for TEL and 3.2-16 µg/ml for AZEL	37	April 2021
LC-MS/MS Method				
22.	Development and validation of LCMS/MS method for simultaneous estimation of azelnidipine and telmisartan in tablet and characterization of degradant by LC- MS/MS	**Colum:** Hypersil, BDS, C-18, (150mm x 4.6mm, 5µm) **Mobile phase:** buffer (pH-5): methanol **Ion transitions:** MRM transition of Azelnidipine 583.300→496.200 Da and Telmisartan 515.100→499.500	38	May 2023

		Da. **Linearity:** 0.4-1.2 µg/ml for Azelnidipine and 2.0-6.0 µg/ml Telmisartan. **Run time:** 10 min.		

CONCLUSION

This article has provided a comprehensive exploration and elucidation of the advancements in the combined analysis of azelnidipine and telmisartan up to the present day. The review encompasses an in-depth examination of various analytical methods employed for the simultaneous determination of azelnidipine and telmisartan, shedding light on the diverse approaches and techniques applied in both bulk and pharmaceutical dosage forms. This comprehensive study delves into a detailed review and analysis of various analytical methods encompassing UV, HPLC, RP-HPLC, UPLC, LC, HPTLC, and LC-MS/MS, specifically focusing on their application in the analysis of Azelnidipine and Telmisartan. The research incorporates exhaustive details on manufacturing processes, general assay methods, and drug specifications, providing a comprehensive understanding of the analytical methodologies employed in pharmaceutical analysis.

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