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AN UPDATED REVIEW ON ANALYTICAL METHODS FOR ESTIMATION OF AZELNIDIPINE

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ABSTRACT: Hypertension is a ubiquitous and serious worldwide health concern, having a dramatic influence on individual health outcomes. In light of this rising worry, Azelnidipine, a third generation long-acting dihydropyridine calcium channel blocker, has emerged as a prospective therapeutic treatment. A vast body of research has indicated that Azelnidipine produces a strong antihypertensive impact, especially in individuals diagnosed with essential hypertension, thus validating its therapeutic usefulness in controlling this prevalent illness. This thorough study strives to give an in-depth overview of the numerous analytical techniques applied for the measurement of Azelnidipine. It covers a variety of techniques, including spectroscopic UV analysis, as well as chromatographic methods such as reversed-phase high-performance liquid chromatography (RP-HPLC), high-performance thin-layer chromatography (HPTLC), and ultra-performance liquid chromatography (UPLC), either alone or in combination with other drugs. These methodologies together give useful insights into the reliable measurement of Azelnidipine in pharmaceutical formulations. These techniques are tested for accuracy, precision, and resilience according to ICH criteria. They are excellent for both bulk medication and tablet dose forms because to their simplicity, sensitivity, and reproducibility. This study emphasizes the merits and limits of several analytical approaches for Azelnidipine, giving significant insights for researchers.

INTRODUCTION: Azelnidipine is a dihydro-pyridine calcium channel blocker (CCB) employed in the treatment of hypertension and angina pectoris. Its chemical structure is reported as 3 - [1 - (Benzyldrylazetidin-3-yl)] - 5 - isopropyl - 2 - amino - 6 - methyl - 4 - (3-nitrophenyl) - 1, 4 dihydropyridine-3, 5-dicarboxylate, having a chemical formula of $C_{33}H_{34}N_4O_6$ and a molecular weight of around 583gm/mol [1]. Azelnidipine is classified somewhat soluble in water, demonstrates solubility in methanol, ethyl acetate, acetone, acetic acid, and ethanol.

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Azelnidipine acts by inhibiting transmembrane Ca^{2+} influx via voltage-dependent calcium channels in vascular smooth muscle. Calcium channels are divided into numerous categories, including L-type, T-type, N-type, P/Q-type, and R-type. By blocking L-type calcium channels, which are important for smooth muscle contraction and contribute to hypertension, Azelnidipine causes relaxation of the vascular smooth muscle, hence decreasing blood pressure [2].

Azelnidipine is listed in the Indian Pharmacopoeia, and different analytical techniques have been devised for its detection and quantification, such as spectrophotometry, HPLC, HPTLC and Bio-analytical. It is offered under several brand names, with formulations that may comprise Azelnidipine alone or in combination with other medicinal medicines, as mentioned in following tables.

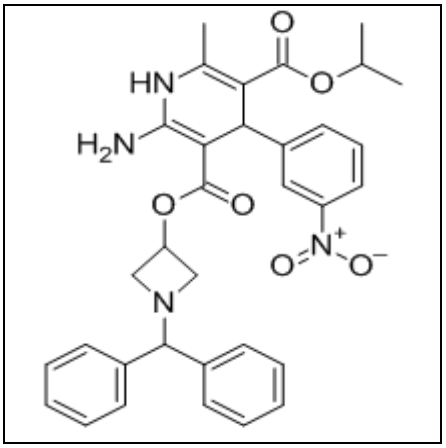

FIG. 1: CHEMICAL STRUCTURES OF AZELNIDIPINE

TABLE 1: PHYSICOCHEMICAL PROPERTIES OF AZELNIDIPINE [3]

Mol. formula	$C_{33}H_{34}N_4O_6$
Mol. Weight	582.657
Description	Yellow powder
Melting point	193-195
Solubility	Insoluble in water
A class of drug	Anti-Hypertensive
Metabolite	No active metabolite product.
Protein Binding	human plasma proteins (90%–91%)
Elimination Clearance	26% in urine and 63% in feces over the 7 days post-dosing.
Half-life [$_{T1/2}$]	16 –28 hours

TABLE 2: LIST OF TRADE NAMES OF AZELNIDIPINE

Sr. no.	Brand Name	Name of the drug and Strength	Manufactured Company
1	Azovas®16	Azelnidipine -16 mg	J.B. Chemicals and Pharmaceuticals Ltd –India
2	Azusa	Azelnidipine -16 mg, Azelnidipine – 8 mg	Ajanta Pharma Ltd – India
3	Azelikem 16Azelikem 8	Azelnidipine -16 mg, Azelnidipine – 8 mg	Steris Healthcare Pvt. Ltd – India
4	Zeblong®16	Azelnidipine -16 mg	IPCA Laboratories Ltd – India
5	Uniaz®16	Azelnidipine -16 mg	Torrent pharmaceuticals Ltd – India
6	Azeldip™16	Azelnidipine -16 mg	Glenmark Pharmaceuticals Ltd –India

Mechanism: Azelnidipine acts by preventing the inflow of calcium ions (Ca^{2+}) *via* voltage-gated channels in the smooth muscle cells of blood vessel walls. These calcium channels contain many varieties such as L-type, T-type, N-type, P/Q-type, and R-type. L-type calcium channels are especially crucial in this process. Typically, calcium ions cause the contraction of smooth muscles, which leads to elevated blood pressure (hypertension). By blocking calcium channels, Azelnidipine stops smooth muscle contraction, resulting to relaxation of the vascular walls and a drop in blood pressure [4].

Pharmacokinetic Profile: Azelnidipine is quickly and dose-dependently absorbed when taken orally. The mean peak plasma concentration (Cmax), which occurred 2.3 to 2.7 hours (tmax) following a single oral dosage of 5–15 mg, varied from 3 to 13.1 ng/mL in healthy adult volunteers who were fasting. From zero to infinity, the mean area under the plasma concentration-time curve (AUC) ranged from 27.5 to 135.8 mg/ml. The mean Cmax and AUC 24 h were 14.7 ng/mL and 81.6 mg/ml, respectively, after 7 days of taking an 8 mg dosage daily. The tmax on day 7 was 2.2 hours. By day two, steady-state concentrations were attained. Azelnidipine has a strong (about 90%) binding to plasma lipoproteins, according to in vitro research. Significant first-pass hepatic metabolism occurs with Azelnidipine, as it does with many calcium channel blockers.

Research on dogs and rats has shown that the parent substance is mostly digested since it is not found in faces or urine. Azelnidipine, as it does with many calcium channel blockers. Research on dogs and rats has shown that the parent substance is mostly digested since it is not found in faces or

urine. Its metabolism is mostly mediated by cytochrome P450 (CYP) 3A4. After a daily dosage of 8 mg for seven days, the terminal elimination half-life of Azelnidipine is about 19.2 hours at steady state, and it is around 14–20 hours after a single oral dose of 5–15 mg in healthy volunteers [4].

The amount of Azelnidipine that is absorbed is increased when taken with meals, but the rate of absorption remains unaffected. When a single 10 mg dose of Azelnidipine was taken after a meal, the mean peak plasma concentration (Cmax) was 2.6 times higher than when taken in a fasted state (18.5 vs. 7.1 ng/mL, $p < 0.05$). Although the mean area under the curve (AUC) was 1.5 times higher after a meal (115.4 vs. 79.4 mg/ml), the difference was not statistically significant. The mean time to peak concentration (tmax) and half-life (t½) were not significantly different between the fed and fasted states (2.3 vs. 2.7 hours and 16.2 vs. 20.9 hours, respectively).

Therefore, the manufacturer recommends taking Azelnidipine with food. The pharmacokinetics of Azelnidipine in hypertensive patients are similar to healthy volunteers. In patients with mild-to-moderate hypertension, a single 8 mg dose resulted in a Cmax of 9.4 ng/mL and an AUC 24 h of 66.5 mg/ml. In elderly hypertensive patients (65-84 years), the same dose after a meal produced a Cmax of 15.8 ng/mL and an AUC24h of 107 mg/ml. After 7 days of 8 mg/day dosing, Cmax and AUC24h increased to 25.7 ng/mL and 242.8 m/ml, with a significant reduction in systemic clearance (640 mL/min vs. 1321 mL/min). ($p < 0.05$) [5, 6].

Pharmacodynamics Profile: Several studies have shown that Azelnidipine effectively lowers blood pressure. In a study of 10 patients with mild essential hypertension, 8 mg/day for 4 weeks reduced BP from 158/97 mm Hg to 145/90 mm Hg, without affecting heart rate, cardiac output, or hormone levels.

During exercise, it lowered BP while maintaining heart rate and vascular resistance, and improved left ventricular function. Azelnidipine (8-16 mg/day) also controlled BP over 24 hours, as shown by ambulatory blood pressure monitoring. In two studies, it significantly reduced both systolic and diastolic BP during daytime ($p < 0.001$) and night-time ($p < 0.01$). In another two studies, systolic BP was reduced at night ($p < 0.05$), with diastolic reductions not significant. Trough-to-peak ratios were 58% and 62%. In a study of 27 hypertensive patients, including those with renal dysfunction, Azelnidipine (8-16 mg/day) reduced BP significantly. In renal dysfunction patients, BP decreased by 24/18 mm Hg, and in those with renal parenchymal disease, by 21/16 mm Hg ($p < 0.01$ and $p < 0.001$, respectively) [7, 8, 9].

Adverse Reaction of Azelnidipine: The administration of teneligliptin is related with numerous undesirable effects, comprising, Headache, Dizziness or light-headedness Edema (swelling), particularly in the ankles or feet, Flushing, Fatigue, and Palpitations. There is less frequent adverse effect such as Hypotension (low blood pressure), gingival hyperplasia, Nausea or vomiting. Some significant response severe allergic responses (anaphylaxis), Liver dysfunction, Arrhythmia. Interaction with other drugs Azelnidipine may interact with other antihypertensive medicines, such as ACE inhibitors, beta-blockers, or diuretics, which may raise the risk of low blood pressure.

Methods for Estimation of the Azelnidipine: The determination of Azelnidipine in a given sample is commonly performed using a range of analytical methods extensively utilized in pharmaceutical research and quality control. Several widely used techniques for measuring Azelnidipine include UV-vis spectrophotometry **Tables 3** and **4**, Reversed-phase high-performance liquid chromatography (RP-HPLC, **Tables 5** and **6**), Ultraperformance liquid chromatography (UPLC, **Table 7**), High-performance thin-layer chromatography (HPTLC, **Table 8**), and Bioanalytical methods (**Table 9**).

Fig. 2 illustrates the articles reported for the estimation of Azelnidipine in percentage. These analytical methods collectively offer accurate and reliable evaluations of the compound's presence and concentration in pharmaceutical formulations, thereby ensuring the quality and efficacy of pharmaceutical products. The accompanying tables provide a summary of the analytical techniques documented in the literature for the determination of Azelnidipine.

TABLE 3: SPECTROPHOTOMETRIC METHODS REPORTED FOR THE ESTIMATION OF AZELNIDIPINE AS SINGLE ENTITY

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	Azelnidipine UV spectrophotometric methods,	Matrices: API Solvent: Acetone λmax (nm): 255 nm Linearity range: 2-14µg/ml LOD (µg /mL): 2.086 LOQ (µg/mL): 8.68	10
2	Azelnidipine by uv-visible spectroscopy methods	Matrices: API & Tablet Solvent: methanol λmax (nm): 257 nm Linearity range: 2-14µg/ml LOD (µg /mL): 0.77 LOQ (µg/mL): 2.36	11
3	Azelnidipine by uv-spectrophotometric method	Matrices: Tablet Solvent: methanol λmax (nm): 255 nm Linearity range: 2-14µg/ml LOD (µg /mL): 0.37 LOQ (µg/mL): 1.12	12
4	Azelnidipine by uv-visible spectroscopy methods	Matrices: API Solvent: methanol λmax (nm): 256 nm Linearity range: 10-50µg/ml	13
5	Azelnidipine by colourimetric methods	Matrices: API Solvent: Ninhydrin, methanol, Glacial acetic acid. λmax (nm): 573 nm Linearity range: 2-14µg/ml LOD (µg /mL): 0.024 LOQ (µg/mL): 0.068	14

TABLE 4: REPORTED SPECTROPHOTOMETRIC METHODS FOR THE ESTIMATION OF AZELNIDIPINE WITH OTHER DRUGS

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	Azelnidipine / Telmisartan UV spectrophotometric methods, simultaneous method, Q-ratio method, and first derivative spectroscopy method.	Matrices: Tablet Solvent: Methanol Detection Wavelength:255nm, TEL: 297nm Linearity: 2-12 µg/ml, TEL:10-50 µg/ml LOD: (µg/ml) simultaneous method- AZL:0.35, TEL:0.73Q-Absorption method- AZL:0.16, TEL:0.77First Derivative method-AZL:1.8, TEL:1.71 LOQ: (µg/ml) simultaneous method- AZL:0.927, TEL:2.16Q-Absorption method- AZL:0.048, TEL:2.34First Derivative method-AZL:5.4, TEL:5.16	15
2	Azelnidipine and Valsartan/UV Spectroscopy, synthetic mixture	Matrices: API Solvent: Methanol Detection Wavelength:240.00 nm, VAL:250.00 nm Linearity: 2-10 µg/ml, TEL:16-80 µg/ml	16
3	Azelnidipine / Metoprolol UV spectrophotometric methods, simultaneous method, q-absorbance ratio method, and first derivative spectroscopy method	Matrices: Tablet Solvent: Methanol: Water Detection Wavelength: 257nm, MET: 223nm Linearity: AZL:1-10 µg/ml, MET:6.25-31.25 µg/ml LOD: (µg/ml) simultaneous method- AZL:0.088, MET:1.875Q-Absorption method- AZL:0.092, MET:1.770First Derivative method-AZL:0.085MET:1.825 LOQ: (µg/ml) simultaneous method- AZL:0.264, MET:5.625Q-Absorption method- AZL:0.276, MET:5.31First Derivative method-AZL:0.255, MET:5.475	17
4	Azelnidipine and Metoprolol	Matrices: Tablet	18

succinate, UV Spectrophotometric Methods	Solvent: Methanol: Distilled water Detection Wavelength: AZL:313nm, MET: 275.40nm

TABLE 5: HPLC METHODS REPRESENTED FOR THE QUANTIFICATION OF AZELNIDIPINE AS SINGLE COMPONENT

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	Azelnidipine By RP-HPLC Methods.	Columns: C18 (250 mm x 4.6 mm i.d.,5 µ) Mobile Phase: Acetonitrile: 0.5% triethyl amine (adjusted to pH 3.5 using orthophosphoric acid) (70:30 v/v). Wavelength: 254 nm Flow Rate: 1.0 ml/min Retention Time: 4.9 min	[19]
2	Azelnidipine By RP-HPLC Methods.	Columns: C8 Column Mobile Phase: methanol: water (85:15 v/v). pH adjusted to 3.0using orthophosphoric acid Wavelength: 257 nm Flow Rate: 1.0 ml/min Retention Time: 9.1 min Linearity:0.5-25µg/ML LOD:0.15 µg/ML LOQ:0.5µg/mL	[20]
3	Azelnidipine By RP-HPLC Methods.	Columns: C8 Column Mobile Phase: Methanol: Water (80: 20%v/v) o-phosphoric acid used for the Ph adjustment (pH-3). Wavelength: 257 nm Flow Rate: 1.0 ml/min Linearity: 20-100µg /ML LOD:0.2826µg/ML LOQ: 0.8566µg /mL	[21]
4	Azelnidipine By RP-HPLCMethods.	Columns: Water's XBridge C18 column of particle size 5µ 250×4.6mm. Mobile Phase: Potassium dihydrogen phosphate and orthophosphoric acid (buffer): Methanol (60:40v/v). Wavelength: 255 nm Flow Rate: 1.0 ml/min Retention Time:4.49min Linearity: 5-30µg /ML LOD: 1.38µg/ML LOQ: 4.17µg/mL	[22]
5	Azelnidipine By RP-HPLCMethods.	Columns: C18 (250×4.6mm.; 5 micron) column Mobile Phase: Sodium dibasic Phosphate Buffer: Acetonitrile: Methanol in the ratio of (10:50:40 v/v/v) pH adjust 4.50 by o-phosphoric acid. Wavelength: 257 nm Flow Rate: 1.0 ml/min Retention Time:4.49min Linearity: 2-10µg /ML LOD: 0.75µg /ML LOQ: 2.75µg /mL	[23]

TABLE 6: HPLC METHODS REPRESENTED FOR THE DETERMINATION OF AZELNIDIPINE IN COMBINED PHARMACEUTICAL PREPARATIONS

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	RP-HPLC Method Azelnidipine and Olmesartan	Columns: Hypersil GOLD C18 column (150 mm × 4.6 mm internal diameter, 5 µm particle size) Mobile Phase: methanol, acetonitrile, and water in the ratio of 40:40:20 (by volume). Detection λ (nm): 257 nm	[24]

		Flow Rate: 0.5 ml/min Retention Time: AZL-8.56min, OLE-3.04min Linearity: AZL-2-48 µg/ML, OLE-2.5-60 µg/ML	
2	RP-HPLC–PDA Telmisartan and Azelnidipine	Columns: Agilent C18 column (150 × 4.6 mm, 5) Mobile Phase: 0.1% V/V ortho phosphoric acid in water and acetonitrile (40:60 v/v) Detection λ (nm): 260 nm Flow Rate: 0.5 ml/min Retention Time: AZL-2.2min, TLM-2.9min Linearity: AZL-2-12 µg/ML, TLM-20-120 µg/ML	[25]
3	RP-HPLC Method Azelnidipine and Telmisartan	Columns: Inertsil C-18 Column with 150×4.6 mm×5 µm at column oven temperature 40°C, Mobile Phase: Acetonitrile and buffer in the ratio of 25: 75 (v/v) Detection λ (nm): 254 nm Flow Rate: 1.5 ml/min Retention Time: AZL-2.2min, TLM-2.9min Linearity: AZL-20.14-60.42µg/ML, TLM-99.91299.73µg/ML LOD: AZL-11.21 µg/ML, TLM-2.75 µg/ML LOQ: AZL-33.96 µg/ML, TLM-8.35 µg/ML	[26]
4	RP-HPLC Method Azelnidipine and Metoprolol Succinate	Columns: Hypersil ODS C185µ column (250 x4.6 mm) Mobile Phase: Acetonitrile: 0.025 M KH_2PO4 Buffer (70:30 v/v, pH adjusted to 3with10% Ortho phosphoric acid. Detection λ (nm): 228 nm Flow Rate: 1 ml/min Retention Time: Azelnidipine-3.281min, Metoprolol Succinate -10.799min Linearity: Azelnidipine-8-40µg/ML, Metoprolol Succinate-25-125µg/ML LOD: AZL-11.21 µg/ML, Metoprolol Succinate -2.75 µg/ML LOQ: AZL-33.96 µg/ML, Metoprolol Succinate -8.35 µg/ML	[27]
5	RP-HPLC Method Azelnidipine and Metoprolol Succinate	Columns: Hibar ODS C185 µ column (250 x 4.6 mm) Mobile Phase: Methanol: water (70:30 v/v) as mobile phase (pH – 3.0) Detection λ (nm): 230nm Flow Rate: 1.0 ml/min Retention Time: AZL-2.2min, Metoprolol Succinate -2.9min Linearity: Azelnidipine-8-40µg/ML,	[28]

		Metoprolol Succinate-25-125µg/ML	
6	HPLC Method Azelnidipine and Telmisartan	Columns: C18 Kromasil stationary column (5 µm, 250 mm × 4.6 mm) Mobile Phase: 0.1M NaH2PO4 solution (pH 3.5) and methanol at a comparative volume ratio of 50% each. Detection λ (nm): 256nm Flow Rate: 1.0 ml/min Retention Time: AZL-4-12µg/ML TEL-20-60µg/ML Linearity: AZL-4-12µg/ML TLM-20-60µg/ML	[29]
7	HPLC Method Azelnidipine and Telmisartan	Columns: 250 mm length C18 column (Supelco, 4.6 mm inner diameter, 5.0 µm particle size) Mobile Phase: 0.1M Na2SO4 (pH 3.6) and acetonitrile (55% volume: 45% volume) Detection λ (nm): 258nm Flow Rate: 1.0 ml/min Retention Time: AZL-3.178min TLM-2.225min Linearity: AZL-4-12µg/ML TLM-20-60µg/ML LOQ: AZL-0.0871 µg/ML, TLM-0.2516µg/ML	[30]
8	RP-HPLC Method Azelnidipine and Olmesartan Medoxomil	Columns: Agilent Eclipse Plus (C18, 250 × 4.6 mm i.d., 5 µm) Mobile Phase: ethanol and 1% v/v aqueous acetic acid in the ratio of 49.5:50.5 Detection λ (nm): 250 nm Flow Rate: 1 ml/min Retention Time: AZL-6.362min, OLM -3.323min Linearity: AZL-6.4-9.6 µg/ML OLM -16-24 µg/ML	[31]
9	RP-HPLC Method Azelnidipine and chlorthalidone	Columns: Phenomenex Luna C8 column (250 × 4.6 mm, 5 µm particle size) Mobile Phase: acetonitrile and water, with the addition of 0.1 percent formic acid,acetonitrile concentration increased linearly from 30% to 55% v/v Detection λ (nm): 256 nm Flow Rate: 1 ml/min Linearity: AZN-16-60 µg/mL CLN -25-100 µg/mL	[32]
10	RP-HPLC Method Azelnidipine and Metoprolol succinate	Columns: Unesphere C18 column Agela Tech., (250 mm x 4.6 mm i.d., 5 µm,) Mobile Phase: Acetonitrile Phosphate Buffer pH 3.5 (40:60%v/v) Detection λ (nm): 275 nm Flow Rate: 1 ml/min Retention Time: Azelnidipine-6.367min, Metoprolol Succinate -2.308min	[33]

		Linearity: Azelnidipine-10.0 - 30.0 µg/mL Metoprolol Succinate-50.0–150.0 µg/mL	
11	RP-HPLC Method Azelnidipine and Telmisartan	Columns: Intersil C18 column (250 × 4.6mm, i.d., 5µm) Mobile Phase: 70 volumes of acetonitrile and 30 volumes of 5 millimolar phosphate buffer pH 4.6. Detection λ (nm): 255 nm Flow Rate: 1 ml/min Retention Time: Azelnidipine-6.367min, Telmisartan-2.308min	[34]
		Linearity: Azelnidipine-10-50 µg/mL Telmesartan-20-100µg/mL	
12	RP-HPLC Method Azelnidipine and Olmesartan Medoxomil	Columns: Agilent Eclipse Plus (C18, 250 × 4.6 mm i.d., 5 µm) Mobile Phase: ethanol and 1% *v/v* aqueous acetic acid in the ratio of 49.5:50.5 Detection λ (nm): 250 nm Flow Rate: 1 ml/min Retention Time: Azelnidipine-6.362min, Olmesartan Medoxomil -3.323min	[35]
		Linearity: Azelnidipine-6.4-9.6 µg/mL Olmesartan Medoxomil -16-24 µg/mL	
13	RP-HPLC Method Azelnidipine and Telmisartan	Columns: Hyperchrom ODS C18 HPLC Column (252×4.6 nm) Mobile Phase: Buffer 0.05M Potassium dihydrogen orthophosphate (KH_2PO_4) Buffer (pH-4.0): Methanol (60:40) Detection λ (nm): 215 nm Flow Rate: 1 ml/min Retention Time: Azelnidipine-5.69 min, Telmisartan -3.39 min	[36]
14	RP-HPLC Method Azelnidipine and Telmisartan	Columns: C18 column (100 × 4.6 mm, 2.5 µm particle size) Mobile Phase: Acetonitrile: pH 3 phosphate buffer (75:25, v/v) Detection λ (nm):237 nm Flow Rate: 0.9 ml/min Retention Time: Azelnidipine – 3.385min, Telmisartan – 6.415min Linearity: Azelnidipine-6.4-32 µg/mL Telmisartan -16-80 µg/mL	[37]

TABLE 7: UPLC METHODS REPRESENTED FOR THE QUANTIFICATION OF AZELNIDIPINE WITH OTHER DRUGS IN PHARMACEUTICAL PREPARATIONS

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	RP-UPLC Telmisartan and Azelnidipine	Columns: Agilent Zorbax Stable Bond (SB) packing C8 (100 mm × 2.1 mm, 2 µm) column Mobile Phase: 0.01 N potassium dihydrogen orthophosphate (pH 4.8) and acetonitrile in 70:30 v/v ratio.	[38]

2	RP-UPLC Telmisartan and Azelnidipine	Detection λ (nm): 257 nm Flow Rate: 0.3ml/min Linearity: Azelnidipine-2-12 µg/mL Telmisartan -20-120 µg/mL Columns: Acquity UPLC BEH C18 column (1.7 µm, 100 × 2.1 mm ID) Mobile Phase: Phosphate buffer: Acetonitrile in the ratio of 70: 30 v/v Detection λ (nm): 240 nm Flow Rate: 0.3ml/min Retention Time: Azelnidipine-5.635 µg/mL Telmisartan -2.946 µg/mL	[39]

TABLE 8: HPTLC METHODS REPRESENTED FOR THE ESTIMATION OF AZELNIDIPINE ALONE AND IN ITS COMBINED PHARMACEUTICAL FORMULATIONS

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	Azelnidipine/HPTLC	HPTLC: Silica gel 60 F254 Mobile Phase: Chloroform: Ethyl Acetate: Methanol in the ratio of 6.5:3.5:0.1 v/v/v Detection λ (nm): 255 nm Rf value: 0.48±0.02 Linearity (ng/spot): 300–800 ng/band LOD: 58.035 ng/band LOQ: 175.86 ng/band	[40]
2	Azelnidipine and Chlorthalidone HPTLC	HPTLC: silica gel 60 F254 TLC plate Mobile Phase: chloroform, ethyl acetate, and methanol in the ratio of 6.5:3.5:0.6 (by volume). Detection λ (nm): 240 nm Rf value: Azelnidipine: 0.67 ± 0.02 Chlorthalidone: 0.24 ± 0.02	[41]
3	Azelnidipine and Telmisartan HPTLC	HPTLC: Silica gel 60 F254 Mobile Phase: Toluene: Acetonitrile: Formic acid (5:4.5:0.5 % V/V/V) Detection λ (nm): 255 nm Linearity (ng/spot): Azelnidipine: 200-700 ng/ band Telmisartan: 1000-3500 ng/band LOD: Azelnidipine-24.71 ng/band LOQ: Azelnidipine- 74.90 ng/band LOD: Telmisartan: 175.04 ng/band LOQ: Telmisartan: 530.44 ng/bank	[42]

TABLE 9: BIOANALYTICAL METHODS REPRESENTED FOR THE QUANTIFICATION OF AZELNIDIPINE ALONE AND IN COMBINED PHARMACEUTICAL FORMULATION

Sr. no.	Drugs /Method	Method characterization	Ref. no.
1	Azelnidipine & Olmesartan Medoxomil in human plasma RP-HPLC	Matrix: human plasma Internal standard: N/A Stationary phase: BDS Hypersil C18, 250 mm X 4.6 mm, 5µ analytical column. mobile phase: Acetonitrile: Water, pH adjusted with ortho-phosphoric acid in the ratio 60:40 Flow rate: 1ml/min. Detection λ (nm): 256nm Linearity: Azelnidipine- 0.5 to 12 µg /ml Olmesartan Medoxomil- 1 to 15 µg/ml	[43]

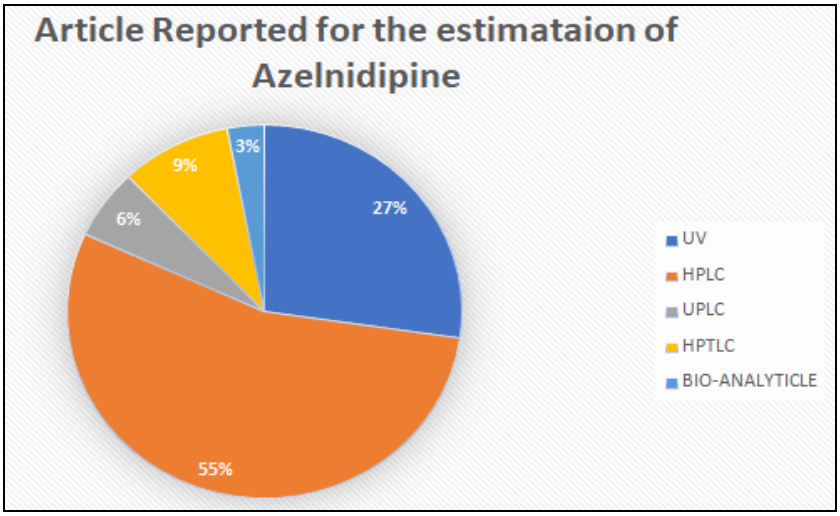

FIG. 2: PERCENTAGE ESTIMATION OF AZELNIDIPINE IN REPORTED STUDIES

Merits and Demerits of the Studies: The method proposed by Panda M *et al.* (2023) is simple, rapid, accurate, precise, and validated, with no interference from excipients and a wide linearity range. However, challenges include method transferability, ongoing regulatory compliance, and potential interference in more complex formulations. The RP-HPLC method introduced by Raimalani J *et al.* (2023) adheres to ICH guidelines for method validation, ensuring rigorous standards for accuracy, precision, specificity, and robustness, which enhances its credibility for regulatory and routine analysis. However, the method faces challenges such as complex development, time-consuming sample preparation, and environmental concerns regarding solvent disposal. The HPTLC method developed by Akshay S. Rane *et al.* (2022) serves as a stability-indicating assay, enabling accurate measurement of Azelnidipine even in the presence of degradation products, thereby ensuring reliable stability testing. Nevertheless, challenges include issues with solvent disposal, limited throughput, potential interference from complex formulations, subjectivity in manual evaluation, and the need for further optimization under various stress conditions.

Challenges: Challenges include complex Mobile phase requirements and potential specificity limitations, with a summary of methods in **Table 10.**

TABLE 10: KEY FEATURES OF ANALYTICAL METHODS FOR AZELNIDIPINE

Study	Most Commonly Used Method	Challenges	Merits
Ahmed A *et al* (2022) [13]	RP-HPLC	Complex mobile phase composition	Precise and accurate estimation, adherence to ICH guidelines
Panda M *et al* (2023) [34]	RP-HPLC	Transferability, maintaining regulatory compliance, and addressing interference from complex formulations.	simple, rapid, accurate, precise, and validated, with no interference from excipients and a wide linearity range
Raimalani J *et al.* (2023) [32]	RP-HPLC	Complex development, lengthy sample preparation, and solvent disposal concerns.	The method complies with ICH validation guidelines, ensuring high standards of accuracy, precision, specificity, and robustness, enhancing its credibility for regulatory and routine use.
Akshay S Rane *et al.* (2022) [40]	HPTLC	Low throughput, interference from complex formulations, subjective manual evaluation, and the need for further optimization.	Stability-indicating, accurately measuring Azelnidipine amid degradation products, ensuring reliable stability testing.

CONCLUSION: In conclusion, Azelnidipine has established itself as a key therapeutic agent in the management of hypertension. This review provides a thorough examination of the drug's

pharmacological properties, pharmacokinetic profile, chemical structure, safety considerations, and mechanism of action. Furthermore, it offers an overview of the various analytical techniques employed for the quantification of Azelnidipine, including UV spectroscopy, HPLC, HPTLC, UPLC and other advanced methodologies. RP-HPLC emerges as the most commonly utilized technique due to its high precision, accuracy, and reliability. However, challenges such as the complexity of mobile phase compositions, stringent method requirements, and potential interference from excipients or other formulation components may limit its broader application in routine analysis. Despite these challenges, the reviewed studies highlight the effectiveness of RP-HPLC and other analytical techniques in providing accurate quantification of Azelnidipine, thus advancing pharmaceutical analysis. Further research and optimization of these methods are essential to address these limitations. Additionally, the current methods have not incorporated a systematic approach, such as Design of Experiments (DoE), particularly for single-drug estimation of Azelnidipine. Future developments should prioritize method validation through a Quality by Design (QbD) approach to ensure a more robust, reliable, cost effective, and efficient process for pharmaceutical analysis.

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REFERENCES:

1. Ram CV: Therapeutic usefulness of a novel calcium channel blocker Azelnidipine in the treatment of hypertension: a narrative review. Cardiology and Therapy 2022; 11(4): 473-89.
2. Tripathi KD: Essentials of Medical Pharmacology; 6th ed., New Delhi, Jaypee Brothers Medical Publishers Ltd. 271-275
3. Jian-Jun Z, Hong-Jian J, Xiao-Hua Z, Yu-Bin Z, Hong-Wei F, Da-Wei X and Qin H: Determination of Azelnidipine by LC–ESI-MS and its application to a pharmacokinetic study in healthy Chinese volunteers. Die Pharmazie-An International Journal of Pharmaceutical Sciences 2008; 63(8): 568-70.
4. Ram CV: Therapeutic usefulness of a novel calcium channel blocker Azelnidipine in the treatment of hypertension: a narrative review. Cardiology and Therapy 2022; 11(4): 473-89.DOI.org/10.1007/s40119-022-00276-4
5. Wellington K and Scott LJ: Azelnidipine. Drugs 2003 Dec; 63:2613-21. Doi.org/10.2165/00003495-200363230-00004
6. Kario K, Sato Y, Shirayama M, Takahashi M, Shiosakai K, Hiramatsu K, Komiya M and Shimada K: Inhibitory effects of Azelnidipine tablets on morning hypertension. Drugs in R&D 2013; 13: 63-73.Doi.org/10.1007/s40268-013-0006-8
7. Chen BL, Zhang YZ, Luo JQ and Zhang W: Clinical use of Azelnidipine in the treatment of hypertension in Chinese patients. Therapeutics and Clinical Risk Management 2015; 309-18. Doi.org/10.2147/TCRM.S64288
8. Kobayashi K: Long-term effects of CS-905 (Azelnidipine) on diurnal blood pressure variation and hemodynamics in patients with essential hypertension. J Clin Ther Med 2000; 16: 269-81. Doi.org/10.1291/hypres.26.201
9. Kuramoto K, Ichikawa S, Hirai A, Kanada S, Nakachi T and Ogihara T: Azelnidipine and amlodipine: a comparison of their pharmacokinetics and effects on ambulatory blood pressure. Hypertension Research 2003; 26(3): 201-8.Doi.org/10.1291/hypres.26.201
10. Richards P, Gowda NS, Khairat K and Shankar PR: Method development and validation of azelnidipine drug by ultraviolet visible double beam spectrophotometer. RGUHS Journal of Pharmaceutical Sciences 2022; 12(1).
11. Muker IH, Kushwaha AK, Neupane NP, Kumar A, Sushant A, Nag A and Malairajan P: Analytical method development and validation of azelnidipine by UV-Visible Spectroscopy. World Journal of Pharmaceutical Research 2021; 10(10): 858-72.
12. Raskapur KD, Patel MM and Captain AD: UV-Spectrophotometric method development and validation for determination of azelnidipine in pharmaceutical dosage form. Toxicology 2010; 106: 135-43.
13. Ahmed A, Majaz Q, Khan GJ, Yaasir A and Imtiyaz LM: Stability indicating analytical method development and validation for determination of azelnidipine in bulk and pharmaceutical dosage form by RP-HPLC and UV-visible spectroscopy. Bull Env Pharmacol Life Sci 2022; 11: 28-36.
14. Suthar P and Mashru R: Advanced Colourimetric Method Development for Estimation of Azelnidipine Using a Smartphone Application 2023; 12(5): 1979-1990.
15. Suthar P and Mashru R: Advanced UV Spectrophotometric Method Development and Validation for Simultaneous Estimation of Azelnidipine and Telmisartan in Pharmaceutical Dosage Form. Indian Journal of Pharmacy & Drug Studies 2023; 2(1): 27-32.
16. Patel HK, Jain VC, Dedania Z, Saiyed NR and Patel RC: Development and validation of spectroscopic simultaneous equation method for simultaneous estimation of azelnidipine valsartan in synthetic mixture. World Journal of Biology Pharmacy and Health Sciences 2023; 13(2): 277-87.
17. Prajapati DM, Kadam A and Mashru R: Analytical Method Development and Validation for Simultaneous Estimation of Azelnidipine and Metoprolol Succinate from the Synthetic Mixture by Three Different UV Spectrophotometric Methods 2022; 11(10): 785-798.
18. Darji H and Dedania Z: Simultaneous estimation of azelnidipine and metoprolol succinate with greenness assessment using HPLC and UV-spectrophotometric methods. Green Analytical Chemistry 2023; 7: 100079.

19. Muralidharan S, Parasuraman S and Venugopal V: Simple validation of azelnidipine By RP-HPLC Method. Rapports De Pharmacie 2015; 1(1): 43-5.
20. Sahoo S and Meyyanathan SN: Development and validation for the estimation of Azelnidipine in its formulation by HPLC. Journal of Pharmaceutical Negative Results 2022; 3801-6.
21. Gore MG and Dabhade PS: RP-HPLC Method Development and Validation of Azelnidipine. International Journal of Pharmaceutical Sciences and Research 2016; 7(12): 5111.
22. Lekhi G, Sreedhar C, Rao TS, Tripathy HK, Kini DD and Manju SV: Analytical method development and validation of RP-HPLC for the determination of azelnidipine in bulk and pharmaceutical dosage Form. World J Pharm Res 2022; 11(15): 567-584.
23. Modi J, Patel SK, Parikh N, Shah SR, Pradhan PK and Upadhyay UM: stability indicating analytical method development and validation for estimation of azelnidipine. World J Pharm Res 2016; 5(2): 831-47.
24. Patel JK and Patel NK: Validated Stability-Indicating RP-HPLC Method for the Simultaneous Determination of Azelnidipine and Olmesartan in Their Combined Dosage Form. Scientia Pharmaceutica 2014; 82(3): 541-54.
25. Godela R, Gummadi S, Pathak S, Pola KK and Yagnambhatla R: RP-HPLC–PDA Approach for concurrent analysis of telmisartan and azelnidipine in bulk and commercial tablets. Chemistry Africa 2023; 6(1): 393-403.
26. Kumar MA, Chandra U, Garg A and Gupta P: A stability indicating rp-hplc method validation for simultaneous estimation of azelnidipine and telmisartan in a fixed-dose combination. International Journal of Pharmaceutical Sciences and Drug Research 2021; 288-94.
27. Goyal PK and Jaimini M: Development and validation of stability indicating RP-HPLC method for quantitative estimation of metoprolol succinate and azelnidipine from synthetic mixture. Journal of Pharmaceutical Negative Results 2023; 772-9.
28. Singh A, Rajput A, Kureshi G, Carpenter G and Vashi J: An RP-HPLC method performance and validation for azelnidipine measurement and metoprolol succinate within a synthetic mixture. Pharmacophore 2023; 14(3-2023): 1-6.
29. Ponnekanti K and Sunitha K: Development of HPLC stability demonstrating methodology for quantifying azelnidipine and telmisartan in tablets and bulk types: validation following ICH Directives. International Journal of Applied Pharmaceutics 2021; 13(5): 298-305.
30. Spandana KV, Subhashini NJ Telmisartan and azelnidipine quantification employing HPLC stratagem; stability investigation on telmisartan and azelnidipine. International Journal of Applied Pharmaceutics 2022; 14(1): 261-5.
31. Dharuman N, Karunanidhi Santhana L and Krishnan M: Eco-Friendly design of experiment based approach for estimation of azelnidipine and olmesartan medoxomil in RP-HPLC: Greenness Appraisal. Journal of Liquid Chromatography & Related Technologies 2023; 46(16-20): 302-15.
32. Raimalani J and Kotadiya R: Gradient reversed-phase HPLC method for the quantitation of azelnidipine and chlorthalidone in a fixed-dose synthetic mixture. Journal of Chemical Metrology 2023; 17(2).
33. Darji H and Dedania Z: Simultaneous estimation of azelnidipine and metoprolol succinate with greenness assessment using HPLC and UV-Spectrophotometric Methods. Green Analytical Chemistry 2023; 7: 100079.
34. Panda M, Dadi V, Yarraguntla SR and Rao VP: RP-HPLC method for determination of azelnidipine and telmisartan in pharmaceutical dosage form. Research Journal of Pharmacy and Technology 2023; 16(2): 509-13.
35. Surendrana SA, Haribabu Y, Kuttya SV, Pavithrana SP and Muralidharan NC: A Novel Stability Indicating UV spectroscopic method for simultaneous estimation of azelnidipine and chlorthalidone in its pure and pharmaceutical dosage form. Indian Drugs 2023; 60(11).
36. Agrawal S and Nizami T: Method development and validation for the simultaneous determination of azelnidipine and telmisartan in tablet dosage form by RP-HPLC. International Journal of Pharmaceutical Sciences and Medicine 2021; 6(10): 26-36.
37. Deore K, Shah U and Jagtap V: Stability-Oriented RP-HPLC method development for simultaneous quantification of azelnidipine and telmisartan in pharmaceutical dosage forms. Library Progress International 2024; 44(3): 10138-48.
38. Swetha A and Ramya KB: New stability indicating RP-UPLC method for simultaneous estimation of telmisartan and azelnidipine in bulk and combined bilayer film-coated tablet dosage form. Pharmaceutical Chemistry Journal 2023; 56(11): 1544-51.
39. Eslawath UR, Kannappan N, Venkateshwarlu L and Smith AA: Stability indicating RP-UPLC method development and validation for the simultaneous estimation of telmisartan and azelnidipine in their bulk and solid dosage forms. Biochemical & Cellular Archives 2023; 23(2).
40. Rane AS and Mahajan SK: Validation and forced stability-indicating hptlc method for determination of azelnidipine. World Journal of Pharmaceutical Research 2016; 5(9): 1053-62.
41. Raimalani J and Kotadiya R: Separation and quantification of azelnidipine and chlorthalidone in a synthetic mixture using optimized HPTLC Method. Inannales Pharmaceutiques Françaises Elsevier Masson 2024; 82(1): 53-63.
42. Kachhiya H, Tandel J, Rupchandani I, Velani A, Patel S, Patel K and Zala N: Development and validation of hptlc method for simultaneous estimation of azelnidipine and telmisartan. Journal of Advances in Drug Discovery and Development 2023; 1(1): 28-38.
43. Bhosale AP and Pingle AP: Bioanalytical RP-HPLC method development and validation for estimation of azelnidipine and Olmesartan Medoxomil in human plasma. J of Medical Pharma and Allied Sign 2022; 11(5): 5235-9.

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