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REVIEW ARTICLE

Definitive Review of Analytical Methods Reported on Estimation of Azelnidipine

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Abstract:
Azelnidipine, classified as a dihydropyridine calcium channel blocker, is utilized in the management of hypertension and angina pectoris. The ongoing tasks across research and development, quality control, and quality assurance departments involve creating and validating analytical methods. These methods play a crucial role in risk management and equivalency assessments, facilitating the establishment of acceptability standards specific to a product and ensuring consistent outcomes. Validation ensures that the analytical process aligns with its intended purpose. Literature review indicates that analytical techniques such as UV spectroscopy, RP-HPLC, and HPTLC can be employed to determine Azelnidipine individually or in combination with other medications. These techniques are assessed for accuracy, precision, robustness, and other parameters according to ICH guidelines. They can be applied to both bulk and tablet dosage form analysis of Azelnidipine due to their simplicity, sensitivity, and repeatability. This comprehensive review not only discusses various analytical methods available for Azelnidipine analysis but also evaluates their suitability and limitations. Researchers focusing on Azelnidipine can gain valuable insights from this study, enhancing their comprehension of the analytical methods for estimation of the drug.

Keywords: Azelnidipine; UV-Spectroscopy; RP- HPLC; HPTLC; Validation; ICH Guidelines

1. Introduction

Azelnidipine, a lipophilic dihydropyridine calcium channel blocker targeting selective L-type calcium channels, has emerged as a therapeutic option for hypertension [1, 2]. It works by reducing systemic vascular resistance and arterial pressure through the inhibition of transmembrane Ca^{2+} influx in smooth muscle cells. As a class II drug in the biopharmaceutical classification systems (BCS), it is employed in the treatment of essential hypertension and angina pectoris [3]. Chemically known as 3-(1-benzhydrylazetidine-3-yl) 5-isopropyl 2-amino-6-methyl-4-(nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate [4], Azelnidipine exhibits a molecular formula of $C_{33}H_{34}N_4O_6$ and a molecular weight of 582.6g/mol. It exists as a light-yellow solid powder, soluble in organic solvents like dimethyl sulfoxide, methanol, acetone, and ethanol, but sparingly soluble in water, with dosage options ranging from 8mg to 16mg. [5]. The structure of Azelnidipine is shown in Figure 1. This review aims to critically evaluate past analytical methods reported on estimation of Azelnidipine.

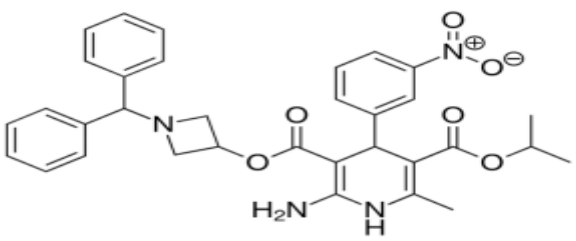

Figure 1. Structure of Azelnidipine

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2. Analytical methods reported for estimation of Azelnidipine in bulk and dosage forms

Kunti D raskapur et al. (2011) developed a straightforward and reproducible UV spectrophotometric method to ensure the presence of Azelnidipine in tablet form. They utilized a SHIMADZU 1800 UV-VISIBLE spectrophotometer with 1.0cm quartz cells for absorbance measurements, recording UV spectra from 200 to 400nm. Azelnidipine exhibited maximum absorbance at 255nm in methanol, with linearity observed in the concentration range of 2-14µg/ml and a mean correlation coefficient of 0.999. The assay remained unaffected by excipients in commercial tablet preparations. The devised UV spectrophotometer method proved accurate, sensitive, and precise, successfully applied to quantitatively estimate Azelnidipine in pharmaceutical tablet formulations, thus offering a viable option for routine analysis without interference. [5]

Dhruvin M. Prajapati et al. (2022) developed and validated three distinct UV spectrophotometric methods – simultaneous equation, Q-absorbance ratio, and first derivative (zero-crossing) spectroscopic methods – for simultaneous estimation of Azelnidipine and metoprolol succinate in tablet formulations. Each method utilized specific wavelengths for absorbance measurements and demonstrated linearity in concentration ranges compliant with ICH guidelines. The simultaneous equation method showed an iso-absorptive point at 233nm, while the Q-absorbance ratio method utilized 257nm as the second wavelength. The first derivative method relied on signal measurements at 241nm for Azelnidipine and 234nm for metoprolol succinate. These methods exhibited linear responses and can be deemed suitable for accurate estimation of both drugs in pharmaceutical formulations. [6]

Pallavi sutar et al. (2022) validated three advanced UV spectrophotometric methods – simultaneous, Q-ratio, and first derivative spectroscopy – for concurrent estimation of Azelnidipine (AZL) and telmisartan (TEL). Utilizing methanol as the solvent, absorbance was measured at 273nm, with linearity extending from 2µg/ml to 12µg/ml for Azelnidipine and 10µg/ml to 50µg/ml for telmisartan. Correlation coefficients indicated high precision for simultaneous estimation and the first derivative method. Notably, the simultaneous estimation method exhibited lower LOD values, emphasizing its heightened sensitivity. Robustness and ruggedness studies confirmed the methods' reliability and sensitivity, highlighting their potential for accurate quantification of Azelnidipine and telmisartan in pharmaceutical formulations. [7]

Pranali V. Dhasade et al. (2022) proposed a UV spectrophotometric method for precise quantification of Azelnidipine and chlorthalidone in fixed-dose combinations. This method, known for its simplicity, speed, sensitivity, accuracy, and precision, involved absorbance measurements at 260nm for Azelnidipine and 227nm for chlorthalidone in methanol. Linearity was observed for Azelnidipine within the range of 64µg/ml to 75µg/ml, with a recovery study confirming method accuracy. Validation based on ICH guidelines underscored the suitability of this UV method for routine measurement of Azelnidipine and chlorthalidone in fixed-dose formulations. [8]

Mahesh Attimarad et al. (2022) pioneered the development of four eco-conscious analytical methods, overseen by [Author's Name], focusing on enhanced selectivity through mathematical processing of UV absorption spectra to simultaneously quantify chlorthalidone (CTL) and azelnidipine (AZL). Utilizing 10% v/v ethanol as a solvent for UV absorption spectra, the team utilized two methods based on peak amplitude determination from zero-crossing point first derivative spectra and ratio first derivative spectra. These methods involved measurements at specific wavelengths for CTL and AZL. Additionally, they calculated peak amplitude differences from ratio spectra and further refined the data through transformation into zero-order spectra. Validation of these methods highlighted their accuracy and precision, with remarkable recovery rates ranging from 98.37% to 100.34% and low percentage relative standard deviations between 0.397% and 1.758%. The methods demonstrated excellent linearity in the concentration range of 1–15µg/mL for both analytes, with a quantification limit below 1µg/ml. [9]

Manisha Panda et al. (2022) employed a reverse phase-high performance liquid chromatography (RP-HPLC) method to quantitatively determine azelnidipine (AZL) and telmisartan (TEL) levels in pharmaceutical dosage forms. They utilized an Intersil C18 column with isocratic elution and a mobile phase comprising acetonitrile and phosphate buffer. Detection at 255nm exhibited linearity within specific concentration ranges for AZL and TEL, with recoveries ranging from 99.48–100.22% for AZL and 99.62–99.88% for TEL. Importantly, no interference from excipients was observed, affirming the method's reliability for pharmaceutical analysis. [10]

Jayvadan K Patel et al. (2014) meticulously developed a rapid and selective reversed-phase high-performance liquid chromatography (RP-HPLC) method for simultaneous determination of azelnidipine (AZL) and olmesartan (OLM) in fixed dosage strengths. Utilizing a Hypersil GOLD C18 column and a gradient HPLC system, they achieved effective chromatographic separation with a precise mobile phase ratio. The method exhibited linearity in specific concentration ranges for both analytes and showcased selectivity and stability-indicating characteristics, ensuring robustness and reliability in pharmaceutical analysis. [11]

Anuja Prabhakar Bhosale et al. developed a precise and rapid bioanalytical method utilizing reversed-phase high-performance liquid chromatography (RP-HPLC) to accurately estimate azelnidipine (AZL) and olmesartan medoxomil (OLM) levels in human plasma. Their method involved liquid-liquid extraction and chromatographic separation using a BDS Hypersil C18 column, with a mobile phase of acetonitrile and water. The method demonstrated a linearity range for both AZL and OLM, confirming its applicability for quantifying these compounds in biological samples [12]

D Basava Chaitanya et al. (2022) introduced a novel and dependable RP-HPLC method for simultaneous determination of azelnidipine and telmisartan in both active pharmaceutical ingredient and pharmaceutical dosage forms. Chromatographic separation was achieved using a Std Denali C18 column with a mobile phase comprising 0.1% orthophosphoric acid (OPA) and acetonitrile in a 60:40 ratio, maintained at a flow rate of 1.0 ml/min. A column temperature of 30 degrees Celsius was maintained, and detection wavelength was optimized at 242.0 nm. Retention times for azelnidipine and telmisartan were determined as 2.116 and 3.188 minutes, respectively. The method demonstrated precision with %RSD values of 1.6% for azelnidipine and 1.0% for telmisartan, and accuracy with % recovery values of 100.15% and 100.20%, respectively. Limit of detection (LOD) and limit of quantification (LOQ) values were found to be sensitive, indicating the method's capability to detect low analyte concentrations. Importantly, optimization led to decreased retention times and overall run time, enhancing analytical efficiency and effectiveness. [13]

Silky Agarval et al. (2021) innovatively applied RP-HPLC methodology for concurrent determination of azelnidipine and telmisartan in bulk drug and pharmaceutical dosage forms. Utilizing a Hyperchromic ODS C18 HPLC column, separation was achieved with a mobile phase comprising 0.05M potassium dihydrogen orthophosphate (KH_2PO_4) Buffer (pH-4.0) and methanol in a 60:40 ratio, at a flow rate of 1 ml/min, with UV detection at 215nm. Concentration ranges of 20-60µg/ml for telmisartan and 40-120µg/ml for azelnidipine were calibrated. [14]

Anamika Singh et al. (2023) designed an innovative RP-HPLC method for determination of azelnidipine and metoprolol succinate from a synthetic mixture. Employing the Shimadzu HPLC LC2010 platform with a UV-VIS detector and binary gradient system, separation was performed on a hyper ODS C18 5µ column at ambient temperature, using an isocratic mode with a mobile phase composed of methanol: water (70:30 v/v) at pH 3.0 and a flow rate of 1.0 ml/min. UV detection at 230nm was utilized, exhibiting a linear response within concentration ranges of 8-40µg/ml for azelnidipine and 25-125µg/ml for metoprolol succinate, thus meeting validation criteria outlined in ICH Q2 R1. [15]

Jenisha Modi et al. (2016) introduced a simplified and robust approach for estimating azelnidipine, employing critical spectrophotometric methods in line with the Quality by Design (QbD) principle following ICH Q8 (R2) guidelines. Their RP-HPLC method utilized an isocratic separation mode with an Enable C18 column, featuring a mobile phase consisting of sodium dibasic phosphate buffer, acetonitrile, and methanol in specific proportions, pH adjusted to 4.50. The flow rate was set at 1 ml/min, and detection occurred at 257nm using a UV detector. Additionally, they employed zero-order and first-order derivative spectrophotometric methods, each with distinct parameters and detection wavelengths. The developed HPLC method exhibited linearity within the concentration range of 2-10µg/ml for azelnidipine. [16]

V. Dinakaran et al. (2023) introduced a novel RP-HPLC method for precise and accurate estimation of azelnidipine (AZL) and telmisartan (TEL) in both bulk and pharmaceutical dosage forms. This method utilized a reverse-phase chromatography C18 column with a unique mobile phase comprising 0.2% triethylamine: acetonitrile, adjusted to pH 3.0 using orthophosphoric acid. Monitoring at 226nm, a flow rate of 1.0 mL/min revealed distinct retention times for azelnidipine and telmisartan. Linearity of the drugs was established over specific ranges, indicating the method's precision and applicability across varying concentrations. The study adhered to validation standards outlined in ICH guidelines, ensuring the robustness and reliability of the analytical results. [17]

Akshay S Rane et al. (2022) conducted a forced degradation study on azelnidipine, leading to the development of a stability-indicating HPTLC method for quantification. This method employed silica gel 60 F254-coated plates with a mobile phase comprising chloroform, ethyl acetate, and methanol. Absorbance maxima were observed at 255nm. The HPTLC method exhibited specificity, as demonstrated by the absence of interference between azelnidipine peak and degradation products. Linearity data revealed a strong relationship across concentrations ranging from 300 to 800 ng/band. Under diverse stress conditions, azelnidipine exhibited degradation solely during acidic hydrolysis, highlighting the method's robustness in selectively determining azelnidipine even in the presence of degradation by-products [18]

3. Key highlights of the analytical methods reported so far

Following are the key highlights of the analytical methods used for estimation of Azelnidipine.

3.1. Most commonly used method

RP-HPLC emerged as the predominant method in the literature for the estimation of azelnidipine and other compounds. It offers high precision and accuracy, along with flexibility in adjusting mobile phase composition and detection parameters.

3.2. Merits and demerits of the studies

The simplified approach and adherence to Quality by Design (QbD) principles are notable merits of the RP-HPLC method proposed by Jenisha Modi et al. (2016). However, challenges such as specific mobile phase requirements may limit its applicability. The RP-HPLC method introduced by V. Dinakaran et al. (2023) offers precise and accurate estimation, along with adherence to International Council for Harmonization (ICH) guidelines. However, specific mobile phase requirements may pose challenges in method implementation. The HPTLC method developed by Akshay S Rane et al. (2022) provides stability-indicating characteristics and high sensitivity. However, it may exhibit limited specificity under certain conditions, warranting careful consideration during method validation and application.

3.3. Challenges

Complex mobile phase compositions, specific requirements for the mobile phase, and potential limitations in specificity under certain conditions pose challenges in the analytical methods described. Summary of the reported analytical methods on Azelnidipine are enlisted in Table 1.

Table 1. Key aspects of analytical methods on Azelnidipine

Study	Most Commonly Used Method	Challenges	Merits/Demerits
Jenisha Modi et al., (2016) [16]	RP-HPLC	Complex mobile phase composition	Simplified approach, adherence to QbD principles
V. Dinakaran et al., (2023) [17]	RP-HPLC	Specific mobile phase requirements	Precise and accurate estimation, adherence to ICH guidelines
Akshay S Rane et al., (2022) [18]	HPTLC	Limited specificity in certain conditions	Stability-indicating method, high sensitivity

4. Conclusion

In conclusion, the literature review highlights the diverse analytical methods employed for the estimation of azelnidipine and related compounds. RP-HPLC emerges as the most commonly used method, offering high precision and accuracy. However, challenges such as complex mobile phase compositions and specific requirements may limit its applicability. Despite these challenges, the reviewed studies demonstrate the potential of RP-HPLC and other methods in providing precise and accurate estimations of azelnidipine, contributing to the advancement of pharmaceutical analysis. Further research and method development are warranted to address challenges and enhance the robustness and applicability of these analytical techniques in pharmaceutical quality control and research.

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Author's short biography

Sahana K M

Sahana K M is a determined and accomplished individual holding a Bachelor of Pharmacy (B. Pharm) degree and currently pursuing Master of Pharmacy (M. Pharm). Academic journey reflects a deep-rooted passion for pharmaceutical sciences, marked by her unwavering commitment to the field.

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Naveen Kumar, an accomplished professional with an PhD, currently serves as an HOD in the Department of Pharmaceutical Analysis at Bharathi College of Pharmacy, Bharathi Nagar, Karnataka. Beyond teaching, Naveen Kumar actively contributes to the academic landscape through the publication of articles, showcasing a dedication to advancing pharmaceutical knowledge. Simultaneously, as a mentor, Naveen Kumar provides guidance to students, fostering their academic and research growth. This tri-fold role, encompassing teaching, publication, and guidance, exemplifies Naveen Kumar's commitment to both imparting knowledge and nurturing the next generation of pharmacists at Bharathi College

Suresh D N

Suresh, a dedicated professional, holds an M. Pharm degree and currently serves as an Assistant Professor in the Department of Pharmaceutical Analysis at Bharathi College of Pharmacy, Bharathi Nagar, Karnataka. With a passion for pharmaceutical education, Suresh's contributes to shaping aspiring pharmacists' futures. The role involves imparting theoretical and practical insights, fostering a dynamic learning environment. Suresh's commitment to continuous learning and research makes a significant impact, positioning them as a valued member of the faculty at Bharathi College