Acta Scientific Biotechnology

Volume 1 Issue 4 April 2020

Review Article

In Depth Investigation of Analytical Methods for the Determination of Azelnidipine in Biological Fluid and Pharmaceutical Dosage Forms: A Review

Kajal Patel*, Prasanna K Pradhan, Ritu Sapra and Dhananjay Meshram

Department of Quality Assurance, Pioneer Pharmacy Degree College, Sayajipura, Vadodara, Gujarat, India

***Corresponding Author:** Kajal Patel, Department of Quality Assurance, Pioneer Pharmacy Degree College, Sayajipura, Vadodara, Gujarat, India.

Received: February 25, 2020

Published: March 16, 2020

Abstract

Hypertension is the most common regulating risk factor for cardiovascular disease (CVD) and death; the increased risk associated with blood pressure (BP) elevation can be greatly reduced by treatment with antihypertensive drugs that lower both BP and related target organ damage. Azelnidipine has also been confirmed to have cardio-protective, neuroprotective, and anti-atherosclerotic properties, and has also been found to prevent insulin resistance. Azelnidipine is dihydropyridine derivative with calcium antagonistic activity. Azelnidipine is inhibits trans membrane Ca^{+2} influx through the voltage dependent channels of smooth muscle in vascular walls. They enter the cells through cell membrane and is used for treatment of essential hypertension and angina pectoris. This review covers most recent analytical methods such as various spectroscopic methods, chromatographic methods and other methods for determination of Azelnidipine in various pharmaceutical dosage forms and biological matrix were reported.

Keywords: Azelnidipine; Analytical Methods; Antihypertensive Drug; Matrices; Estimation

Introduction

Hypertension is a condition where blood pressure is elevated to an extent that clinical benefit is obtained from BP lowering. Hypertension is one of the most important risk factor for both coronary artery disease and cardiovascular disease [1]. Azelnidipine was synthesized by Ube Industries, Ltd. and developed by Sankyo Co., Ltd. (currently known as Daiichi Sankyo Co., Ltd., Tokyo, Japan) and was launched into the market as CALBLOCK® in Japan in 2003. The drug has renoprotective effects (such as reducing proteinuria by dilating efferent arterioles), as well as cardioprotective, insulin resistance-improving, cerebroprotective, and antiatherosclerotic effects. Azelnidipine occurs as two enantiomers due to an asymmetric carbon at the 4-position of the 1,4 dihydropyridine ring [2].

Azelnidipine (AZEL) (3-[1-(diphenylmethyl)azetidin-3-yl] 5-propan-2-yl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) is a new dihydropyridine derivative with calcium antagonistic activity. Azelnidipine is inhibits trans membrane Ca^{+2} influx through the voltage dependent channels of smooth muscle in vascular walls. They enter the cells through cell membrane, lower peripheral vascular resistance and arterial pressure. It is used for treatment of essential hypertension and angina pectoris [3].

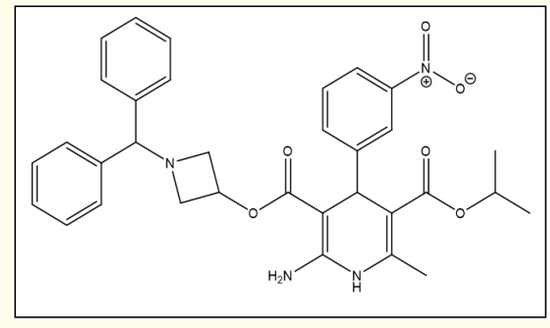

Figure 1: Chemical structure of AZEL.

Drug profile [4,5]

Sr no.	Parameters	Azelnidipine
1.	Molecular weight	582.646 g/mol
2.	Molecular formula	$C_{33}H_{34}N_4O_6$
3.	CAS no.	123524-52-7
4.	Melting point	122 - 123°C
5.	pKa	7.89
6.	Solubility	Slightly soluble in methanol, freely soluble in acetone , soluble in ethyl acetate, sparingly soluble in water
7.	Storage	Stored in tightly closed container in cool, dry and well maintained area.

Table 1: Chemical Profile of AZEL.

Parameters	Azelnidipine
Absorption	Orally absorbed
Metabolism	Metabolized by cytochrome P450 (CYP) 3A4 in the liver and has no active metabolite
Bioavailability	Less than 50%
Half life	16 - 24 hrs
C_{max}	3.0 - 13.1 ng/ml
Plasma protein binding	≈90%

Table 2: Pharmacokinetic Profile of AZEL.

Mechanism of action of Azelnidipine (AZEL) [6]:

Azelnidipine is Ca^{+2} channel blocker inhibits trans membrane Ca^{+2} influx through the voltage dependent channels of smooth muscle in vascular walls. Ca^{+2} channels are classified into various categories including L-type, T-type, N-type, P/Q- type, R-type Ca^{+2} channels. Normally, calcium induces smooth muscle contraction, contributing to hypertension. When calcium channels are blocked, the vascular smooth muscle does not contract, resulting in relaxation of vascular smooth muscle walls and decreased BP.

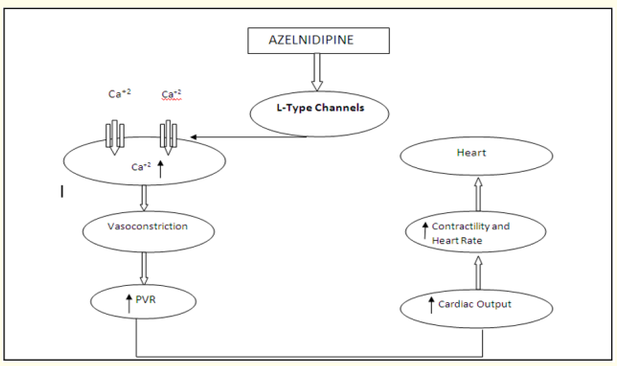

Figure 2: Mechanism of Action of Azelnidipine [6].

Marketed formulations of Azelnidipine

Sr no.	Brand name	Company name	Formulation	Dose (mg)
1	Azovas	JB Chemicals and Pharmaceuticals Ltd	Tablet	8, 16
2	Calblock®	Daiichi Sankyo healthcare co ltd.	Tablet	8,16

Table 3: Marketed formulation of Azelnidipine.

Analytical Methods

This all are the methods which are used for the determination of Azelnidipinein marketed formulation and in biological fluids. This all analytical methods are reported which are seen during the literature survey. Various U.V. spectroscopic, HPLC, HPTLC and other analytical methods for simultaneous determination of Azelnidipine and its combination with Olmesartan medoxomil have been reported. Below describes the various methods with the method description and condition which are reported on review literature.

Compendial method

Azelnidipineis is official in Indian pharmacopoeia (IP-2018) described chromatographic method, Japanese pharmacopoeia (2016) described potentiometric titration.

Reported method

UV spectroscopic methods

Various U.V. spectroscopic methods for simultaneous determination of Azelnidipine and its combination with Olmesartan medoxomil have been reported:

- Rele RV., *et al*. specifies UV- spectrophotometric methods, first order derivative and area under curve [AUC], have been developed and validated for the estimation of Azelnidipine in bulk drug and its tablet formulation. The methanol is used as a solvent. It was estimated at 242.6 nm for the first order derivative UV-spectrophotometric method (A) while in area under curve (AUC) method (B) the zero order spectrum of Azelnidipine was measured in between 250.5 nm to 258.8 nm. Beer's law was obeyed in the concentration range of 1 to 20 µg/ml. Similarly in AUC method, Beer's law was obeyed in the concentration range of 1 to 20 µg/ml with coefficient of correlation value 0.9991 [7].
- Rele RV., *et al*. specifies second order derivative have been developed and validated for the estimation of Azelnidipine in bulk drug and its tablet formulation. The methanol was used as a solvent. It was estimated at 233.8 nm for the second order derivative UV-spectrophotometric method. Beer's law was obeyed in the concentration range of 1 to 20 µg/ml with coefficient of correlation value 0.9993 [8].
- Shah SR., *et al*. specifies the Simple Spectrophotometric methods was developed according to Quality by design (QbD) approach as per ICH Q8 (R2) guidelines for estimation of Azelnidipine. QbD approach was carried out by varying various parameters and these variable parameters was designed into Ishikawa diagram. RP-HPLC method was developed for estimation of AZEL utilizing isocratic separation mode with Enable C_{18} column, optimum mobile phase consist of Sodium diabasic Phosphate Buffer: Acetonitrile: Methanol in the ratio of (10:50:40 v/v/v) pH adjust 4.50 by o-phosphoric acid. The flow rate was set at a 1 ml/min and detecting wavelength at 257 nm in UV detector. Parameters in zero order Spectrophotometric method were solvent (methanol + water), sample preparation API, Wavelength 257 nm. And for first order derivative Spectrophotometric method it was sacling factor: 10 and delta lambda 4. Linearity was observed in the concentration range of 20 - 100 µg/ml [9].

- Patel N., *et al*. specifies the First Derivative Spectrophotometric method for the simultaneous estimation of Azelnidipine and Olmesartan medoxomil in synthetic mixture. Quantitative determination of the drugs was performed at 239.4 nm and at 217 nm for Azelnidipine and Olmesartan medoxomil, respectively. Quantification was achieved over the concentration range of 4 - 32 µg/ml for Azelnidipine and Olmesartan medoxomil disoproxil fumarate. The AR grade methanol is used as a solvent [10].
- Raskapur KD., *et al*. specifies the simple UV spectroscopic method for the assay of Azelnidipine from tablet formulation. Azelnidipine shows the maximum absorbance at 255 nm and the linearity was observed in the concentration range of 2 - 14 µg/ml The AR grade methanol is used as a solvent [11].

Chromatographic methods

Various chromatographic methods for simultaneous determination of Azelnidipine and its combination with Olmesartan medoxomil have been reported

- Prabhakar D., *et al*. specifies the RP-HPLC method for the estimation of azelnidipine in the plasma of rat animal model studies for transdermal drug delivery. The chromatographic method was standardized for azelnidipine using Shimadzu HPLC model reverse phase analytical inspire C18 column with LC10AD pump and SPD-10A UV Detector, The mobile phase consists of methanol: water and 0.1%glacial (75:25) acetic acid, with flow rate of 1ml/min. The retention time of azelnidipine found to be 6.130 min.The HPLC detector was set to the wavelength of 254 nm [12].

- Amin AA., *et al*. specifies the RP-UFLC method for simultaneous determination of azelnidipine and olmesartan medoxomil in Pharmaceutical Dosage form. The chromatographic separation was achieved by using Phenomenex, Prodigy, ODS3, 5 µm, 100 Å, (250 x 4.6 mm) analytical column with a mobile phase consisting of methanol and water at the ratio of (85:15% v/v). The flow rate was set at a 1.5 ml/min, and detector wavelength of 255 nm using a PDA detector [13].

- Gore MG., *et al*. specifies the a simple method for the assay of azelnidipine from tablet formulation. Azelnidipine shows the maximum absorbance at 257 nm Chromatographic separation was performed on a reverse phase Hexon C8 shield The mobile phase was a mixture of methanol and water (80:20% (v/v)). The flow rate was adjusted to 1.0 ml/min. Linearity was observed in the concentration range of 20 - 100 µg/ml [14].

- Muralidharan S., *et al.* specifies the RP-HPLC method for estimation of Azelnidipine from pharmaceutical Tablet dosage form. The method was carried out on a C18 (250 mm x 4.6 mm i.d., 5 µ) column with a mobile phase consisting of acetonitrile: 0.5% triethyl amine (adjusted to pH 3.5 using orthophosphoric acid) (70:30 v/v) at a flow rate of 1.0 ml/min. Detection was carried out at 254 nm. The retention time of Azelnidipine was 4.9 min [15].

- Ganduri RB., *et al.* specifies a stability indicating RP-HPLC method for the simultaneous determination of olmesartan medoxomil (OLM) and azelnidipine from combined tablet dosage form was developed. The separation was achieved on Inertsil 3V column using a mobile phase consisting of potassium dihydrogen phosphate buffer and acetonitrile(80:20). The analytes were monitored by a PDA detector set at 255 nm and the flow rate was kept at 2.0 ml/min. The retention time for olmesartan medoxomil and azelnidipine were 3.148 and 3.704 respectively. Linearity was observed in the concentration range of 10 - 60 µg/mL for olmesartan medoxomil and 4 - 24 µg/mL azelnidipine [16].

- Patel NK., *et al.* specifies a RP-HPLC method for the simultaneous determination of Azelnidipine (AZL) and Olmesartan (OLM). The chromatographic separation was achieved using a Hypersil GOLD C18 (150 mm × 4.6 mm internal diameter, 5 µm particle size)column with a mobile phase composed of methanol, acetonitrile, and water in the ratio of 40:40:20 (v/v/v). The flow rate was set at a 0.5 ml/min, and quantification of the analytes was based on measuring their peak areas at 260 nm. The retention times for Azelnidipine and Olmesartan were about 8.56 and 3.04 min, respectively. The linearity was observed in the ranges of 2 - 48 µg/ml for Azelnidipine and 2.5 - 60 µg/ml for Olmesartan [17].

- Rane AS., *et al.* specifies the stability indicating HPTLC method for the estimation of Azelnidipine on the plates precoated with silica gel 60 F254. The mobile phase used was Chloroform: Ethyl Acetate: Methanol in the ratio of 6.5:3.5:0.1 v/v/v. The drug showed absorbance maxima at 255 nm. The data of linearity indicated a good linear relationship over the range of 300 - 800 ng/band concentrations [18].

Other methods

- Lou H., *et al*. specifies a HPLC-tandem mass spectrometric (HPLC-MS/MS) assay for the high throughput quantification of the azelnidipine in human plasma was developed and validated azelnidipine were extracted from human plasma by precipitation protein and separated on a C18 column using acetonitrile- methanol-ammonium format with 0.1% formic acid as mobile phase. The method has a wide analytical measuring range from 0.0125 to 25 ng/ml [19].

- Suneetha G., *et al.* specifies the method for analysis of azelnidipine in human plasma by ultra-performance liquid chromatography tandem mass spectrometry. azelnidipine was analyzed by the system with a C18 column. The linearity of calibration curve in the range of 0.01 - 10 ng/ml or quality control samples spiked with azelnidipine. The detection limit was as low as 1 pg/ml [20].

- Pallapothu LMK., *et al.* specifies the LCMS/MS method for the simultaneous determination of Azelnidipine and Olmesartan in K2EDTA human plasma. The method involves simple, solid phase extraction procedure and separation with an C18 column with mobile phase Acetonitrile/5 mM Ammonium Formate pH - 3.00 (80/20, V/V), at a flow-rate of 1.0 ml/min with a total run time of 3.0 minutes. The method was developed and validated using 200 µl of plasma, over a concentration range of 0.100 - 40.070 ng/ml for Azelnidipine and 3.001 - 1200.340 ng/ml for Olmesartan [21].

Discussion

The presented review highlights on various analytical methods reported for estimation of Azelnidipine in alone or in combination with Olmesartan medoxomil in marketed formulation and biological matrix like human plasma. RP-HPLC and UV methods were found to be most widely used methods. These methods are found to be rapid, accurate, sensitive, economical and reproducible for determination of Azelnidipine in various marketed formulations and biological matrix.

Conclusion

So, from all above information it should be concluded that various spectroscopic methods, chromatographic methods and other methods were used for determination of Azelnidipine alone or in combination which has been successfully used on a routine basis and allows the quantification of the drug in various pharmaceutical dosage form and in biological matrix in short analytical time.

Bibliography

1. Walker R and Whittlesea C. Clinical Pharmacy and Therapeutics; 5thEdn; Elsevier (2007): 295-307.

2. Shewale VU., *et al*. "Azelnidipine: A Review on Therapeutic Role in Hypertension". *Journal of Drug Delivery and Therapeutics* 9 (2019): 1002-1005.

3. Chen B., *et al*. "Clinical use of azelnidipine in the treatment of hypertension in Chinese patients". *Therapeutics and Clinical Risk Management* 11 (2015): 309-318.

4. Drug profile of "Azelnidipine" (2019).

5. "Azelnidipine" (2019).

6. Tamargo J and Ruilope LM. "Investigational calcium channel blockers for the treatment of hypertension". *Expert Opinion on Investigational Drug* (2016): 1-51.

7. Rele RV. "Spectrophotometric Estimation of Azelnidipine in Bulk drug and Pharmaceutical Dosage form by First Order Derivative and Area Under Curve Methods". *American Journal of PharmTech Research* 4.2 (2014): 126-135.

8. Rele RV. "Spectrophotometric estimation of azelnidipine in bulk and pharmaceutical dosage form by second order derivative method". *Journal of Chemical and Pharmaceutical Research* 6.8 (2014): 198-202.

9. Modi J., *et al*. "Stability Indicating Analytical Method Development and Validation for Estimation of Azelnidipine". *World Journal of Pharmaceutical Research* (2016): 831-847.

10. Patel N and Patel JK. "Simultaneous Determination of Azelnidipine and Olmesartan medoxomil by First Derivative Spectrophotometric Method". *Scholar Research Library* 4.4 (2012): 1080-1084.

11. Raskapur KD., *et al*. "UV-Spectrophotometric Method Development and Validation for Determinaton Of Azelnidipine In Pharmaceutical Dosage Form". *International Journal of Pharmacy and Pharmaceutical Sciences* (2011): 238-240.

12. C Prabhakar., *et al*. "Method Development and Validation of Azelnidipine by RP-HPLC". *International Journal of Chem Tech Research* 10.10 (2017): 418-423.

13. Amin AA., *et al*. "Simultaneous Determination of Azelnidipine and Olmesartan Medoxomil in Pharmaceutical Dosage Forms by UFLC Method". *Journal of Pharma SciTech* (2016): 69-74.

14. Gore MG and Dabhade PS. "Rp-Hplc Method Development and Validation of Azelnidipine". *IJPSR* (2016): 5111-5114.

15. Muralidharan S., *et al*. "Simple Validation of Azelnidipine By Rp-HPLC Method". *Rapports De Pharmacie* 1.1 (2015): 43-45.

16. Ganduri RB., *et al*. "Stability Indicating Liquid Chromatographic Method for the Simultaneous Determination of Olmesartan Medoxomil and Azelnidipine in Combined Tablet Dosage Form". *IJPSR* (2014): 275-282.

17. Patel NK and Patel JK. "Validated Stability-Indicating RP-HPLC Method for the Simultaneous Determination of Azelnidipine and Olmesartan in Their Combined Dosage Form". *Scientia Pharmaceutica* 82 (2014): 541-554.

18. Rane AS and Mahajan SK. "Validation and Forced Stability-Indicating Hptlc Method for Determination of Azelnidipine". *World Journal of Pharmaceutical Research* (2016): 1053-1056.

19. Gao Y., *et al*. "A liquid chromatography- tandem mass spectrometric assay for the antihypertensive agent azelnidipine in human plasma with application to clinical pharmacokinetics studies". *Biomedical Chromatography* 29 (2015): 970-974.

20. Suneetha G., *et al*. "Sensitive Analysis of Azelnidipine and Related Derivative in Human Plasma by Ultra-Performance Liquid Chromatography-Tandam Mass Spectrometry". *Asian Journal of Chemistry* 25.18 (2013): 10319-10321.

21. Adepu R., *et al*. "A novel method for the simultaneous determination of Azelnidipine and Olmesartan in Human plasma by using liquid chromatography-electro spray Ionization tandem mass spectrometry and application to a pharmacokinetic study". *International Journal of Pharmaceutics* 7.3 (2017): 111-124.