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A REVIEW ON BIO ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF AZELNIDIPINE IN BIOLOGICAL MATRICES

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ABSTRACT
Bioanalysis is related to the analysis of analytes (drugs, metabolites, biomarkers) in biological samples.Blood pressure (BP) can be notably decreased by using therapy the use of antihypertensive which reduce bp and the associated target organ damage. quantification of the drug in various pharmaceutical dosage form and in biological matrix in short analytical time this overview includes most latest strategies consisting of various spectroscopy,potentiometry, chromatography [High-Pressure Liquid Chromatography, Liquid Chromatography-Electron Spray Ionization-Tandem Mass Spectrometry, Ultra-Performance Liquid Chromatography, Ultra-Fast Liquid Chromatography] and different azelnidipine techniques for numerous prescription drugs and organic matrix.

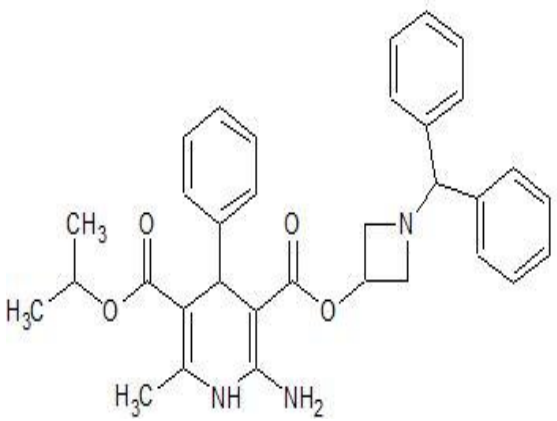
KEYWORDS: Bioanalytical methods; azelinidipine; mechanism of action; pharmacodynamic-pharmacokinetic, estimation.

BIOANALYSIS CONCEPT

The bioanalytical method plays an important role in the concerns In order to perform toxicokinetic (TK), pharmacokinetic (PK) and pharmacodynamic (PD) studies of new drugs, bioanalysis has an important significance. Two main sections, sample preparation and sample separation and detection, are associated with the development of bioanalytical methods.[1]

INTRODUCTION: (AZLENIDIPINE)

Hypertension (BP) is a major risk factor for both coronary heart disease and cardiovascular.[2] Nilvadipine, CCB, acting of CBF and cerebral hemodynamic. It caused by antihypertensive treatment through the reduction in CBF. Azelinidipine it's comes under the class of calcium channel blockers in third generation. It is used for angina pectoris and hypertension treatment.[2] Azelinidipine (8-16 mg) such as every morning for 2-months reduced BP over 24 hours in 60 young patients with essential hypertension ($p<0.05$),as demonstrated with 24- hour ABPM.[3] Long-acting calcium channel blockers are widely used for the treatment of hypertension as a first-line drug and short-acting calcium channel blockers are stimulation of the renin-angiotensin system due to an excess and rapid decrease BP[4].



Structure for AZELNIDIPINE.

structure have two methyl groups located at the 2- and 6-positions of the di-hydropyridine ring, one methyl group at the 2-position is substituted by an amino group in the azelnidipine molecule.[5]

The pharmacological action of AZEL resides in the (R)-enantiomer. This is in marked contrast to other CCBs in which the (S)-enantiomer is responsible for the biological activity. The clinical study protocol was reviewed and approved.[6]

Table: 1 DRUG PROFILE.

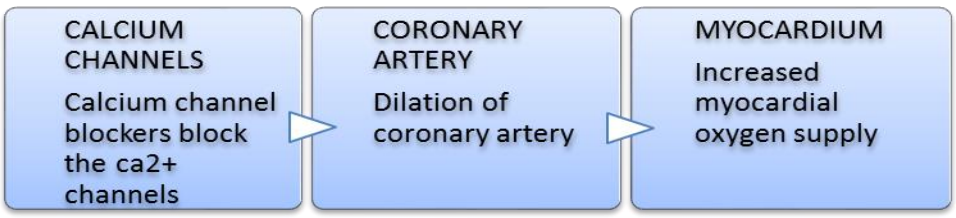
Sr.no	parameters	Azelnidipine	Sr.no	parameters
1	Molecular weight	582.646g/mol	1	Molecular weight
2	Molecular formula	$C_{33}H_{34}N_4O_6$	2	Molecular formula
3	IUPAC name	(3-(1-diphenylmethyl) azetidine 3-yl)5-propane 2-yl 2-amino-6-methyl-4-(3-nitrophenyl)1,4-dihyropyridine -3,5-dicarboxylate)	3	IUPAC name
4	CAS no.	123524-52-7	4	CAS no.
5	Melting point	122-123^{0}C	5	Melting point
6	p^{K}a	7.89	6	p^{K}a
7	Solubility	Slightly soluble in methanol, freely soluble in acetone, soluble in ethyl acetate, sparingly soluble in water.	7	Solubility
8	Storage	Stored in tightly cooled container in cool, dry & well maintained area.	8	Storage
9	Absorption	Orally absorbed	9	Absorption
10	Metabolism	Metabolized by cytochrome P_{450}(CYP) 34A in the liver and has no active metabolite.	10	Metabolism
11	Bioavailability	Less than 50%	11	Bioavailability
12	Half-Life	16 – 24 hrs	12	Half-Life
13	C max	3.0 – 13.1 ng/ml	13	C max
14	Plasma Protein Binding	≈90%	14	Plasma Protein Binding
15	Chemically Purity	99.77%	15	Chemically Purity
16	Elimination	Single 4mg oral dose of 14C- labelled azelnidipine in humans, about 26% of the drug was thought to be excreted in the urine and 63% in the feces during the 1 week period post administration.	16	Elimination

Table: 2 FORMULATION.

Sr.no	Brand name	Company name	Formulation	Dose
1	AZOVAS	JP chemicals and pharmaceuticals Ltd	Tablet (AZL)	8,16mg
2	AZEL	Cadila healthcare name	Tablet (AZL)	8mg
3	CALBLOCK	Daiichi sankyo Healthcare co. Ltd	Tablet (AZL)	8,16mg
5	REZALTAS	Sankyo co. Ltd	Tablet (Olmesaratan medoxomil & (AZL)	10/8mg 20/16mg
6	AIZANT	Drug research solutions	Tablet (AZL)	8mg
7	UNIAZ	Torrent pharmaceuticals Ltd.	Tablet(AZL)	16mg
8	AZELDIP	Glenmark pharmaceutical Ltd.	Tablet(AZL)	16mg
9	AZUSA	Ajanta pharma Ltd	Tablet(AZL)	16mg

MECHANISM OF ACTION

Azelnidipine is a channel blocker are inhibits Ca^{+2} trans membrane flux by the voltage-based smooth muscle channels in vascular walls. Ca^{+2} groups including L-type, T-type, N-type, P/Q and R-type, Ca^{+2}. Channels of Ca^{+2} are known as L-type. The calcium channels are blocked, which induces vascular smooth muscle wall relaxation and decreased PB.[6]



T-type their sequence of aldosterone, and N expressed to the release of neurotransmitter. Azelnidipine (L-type), cilnidipine, benidipine and efonidipine (L-/T-type CCB)[6]. Types L/N- and L/T CCBs also called secondgeneration.[7]

PHARMACODYNAMICS

This azelnidipine does not cause bar-receptor reflex reaction tachycardia to inhibit a sympathetic nerve activity.[8] In vitro studies showed that azelnidipine competitively inhibits the binding of radiolabelled nitrendipine.In compared to, amlodipine and nicardipine had IC50s of vitro studies in isolated rat aortic strips consistent with its high lipophilicity, azelnidipine has a long duration of action.[9]

PHARMACOKINETICS

(1) average parameter values, (2) a quantitative relation to human physiology (e.g., body height, liver, pulse, renal, etc) and (3) diversity across patient classes. All three pharmacokinetic parameters are delivered and eliminated.[10] Azelnidipine, a new calcium antagonist, differs from amlodipine with respect to its pharmacokinetic profile.[11]

SAMPLE EXTRACTION TECHNIQUES

The main aim of extraction is to Sample clean-up before analysis is mainly a step before the injection into analytical instruments of complex matrices, such as plasma, blood, urine and tissue. To enriched the analyte from biological matrices, done by extraction techniques are protein precipitation,solid-phase extraction,liquid-liquid extraction.

Instruments used for estimation of azelnidipine in biological samples

To quantify the amount of analyte azelnidipine present in the biological samples researcher has used the following instrument are HPLC-UV, HPLC-MS, LC-MS/MS, UPLC-MS/,MS and SFC-MS/MS.

Liquid chromatography-UV (LC-UV) are HPLC-UV detector is competitive, but it can only be used for a high analyte level (M range).[13]

High performance liquid chromatography (HPLC) is used for the separation of the compound that is dissolved in the mixtures of a solution are separated by injecting a sample mixture into the column.

Liquid chromatography-Tandem mass spectrometry (LC–MS/MS)it has led to reduced analysis times, improved selectivity and increased throughput in drug bio analysis. Researcher has chosen the instrument because of its high sensitivity, selectivity and ruggedness.[14]

Ultra-performance liquid chromatography-Tandem mass spectrometry (UPLC–MS/MS) a rapid chromatography with faster gradient curves, higher flow rates, reduced ion suppression [15].

Supercritical fluid chromatography-Tandem mass spectrometry (SFC-MS/MS) it consists for faster research, higher flow rates and higher sample capacity are eluent is higher than the hplc technique.

RESULT AND DISCUSSION

The presented review highlights on various analytical and bio-analytical methods reported for estimation of zelnidipine in alone or combination in marketed formulation and biological matrix like human plasma, RP-HPLC,UV methods were found to be most widely used methods.

According to this review, the most common used mobile phase for the estimation of the analyte is methanol, acetonitrile, ammonium acetate and formic acid to becomes a good resolution peak. Due to bu UV the limit of detection and linearity was found to be were around in the range of 0.3 µg/ml and 1-20 µg/ml.

LITERAT RUREEVIEW: [UV[18-21], POTENTIOMETRY,[22] HPLC,[23-27] UPLC,[29] UFLC[30]

AUTHOR	ELUENT	WAVELENGTH	ACCURACY	PRECISION		RUGGEDNESS	LINEARITY	LOD	LOQ
Rele RV. et.al	Methanol	method(A) 1st order: 246.6nm method(B) AUC: 250.5258.8 nm	1st order: 0.7449 AUC: 0.2859	Intra-day precision 1st order: 0.24847 AUC: 0.03446	: 0.13607 AUC: 0.00768	1st order: 3.8641 AUC: 0.00812	1-20µg/ml	0.17891 to 0.07093 µg/ml	1st order derivative: 0.54216 µg/ml AUC : 0.21496 µg/ml
Rele RV. et.al	Methanol	233.8nm	0.1850	Intra-day precision 0.2576	Inter-day precision 0.4532	0.3412	1-20µg/ml	0.0338 µg/ml	0.1024µg/ml
Raskapur et.al	Methanol	255 nm	98.33-99.16	0.416	Inter-day precision: 0.211	3.7321	2-14µg/ml	0.37 µg/ml	1.12µg/ml

AUTHOR	CHROMATOGRAPHIC CONDITIONS					VALIDATION PARAMETERS					
	COLUMN	ELUENT	WAVELENTH	RETENTION TIME	FLOW RATE	ACCURACY	PRECISION		LINEARITY	LOD	LOQ	CONCLUSION
Prabhakar et al	C18 Column (250mm ×4.5mm× 5µm)	75:25 methanol:H_2O 0.1%glacial acetic acid	UV- Detector 254nm	6.13min	1 ml/min	98.08%	Intra day 0.47%	Inter day 0.78%	1-50µg/ml	0.1935 µg/ml	0.5866µg/ml	Validation of HPLC method is suitable for intented use.
J. K. Patel and N. K. Patel	Hypersilic Gold C18 Column (50mm× 4.6mm×5µm)	Methanol: ACN:H_2O [40:40:20 v/v/v]	UV- Detector 260nm	8.5min(AZL) 3.0min(OLM)	0.5 ml/min	AZL: 101.07% ± 0.35. OLM: 100.61%± 0.98	Intra day 0.33-0.52 %	Inter day 0.76-1.54.%	AZL: 2-48µg/ml OLM: 2.5-60µg/ml	AZL: OLM-1.24 &0.89 µg/ml	AZL:OLM-1.24 &0.89 µg/ml	Data for acceptance, Release,stability Are reliable method.
Gore and Dabhade	hexonC8 (250mm ×4.5mm× 5µm)	80:20v/v, methanol: H_2O	UV- Detector 257nm	Not reported	1 ml/min	100.17-100.56%	Intra day 0.51 %	Inter day 0.61%	20-100µg/ml	0.2826 µg/ml	0.8566 µg/ml	Testing revealed the method was specific and selective
RaveendaBabuGanduri et al	Inertsil C18 (250mm ×4.6mm,3µm)	Solvent A – Buffer pH 3.0, ACN [80:20] Solvent B - Buffer pH 3.0, ACN [20:80]	Diode Array Detector. 255nm	3.1 min[OLM] 3.7min[AZL]	2 ml/min	98.0-102.0%	OLM and AZL. 26 and 0.3%		4-24µg/ml	Not reported	Not reported	Method as routine testing for stability analysis of OLM and AZL in synthetic mixtures and combined dosage form.

SelvaduriMuralidharan	C18 (250mm ×4.6mm,5µm)	ACN 0.5%Triethyl amine [adjusted pH 3.5 ortho-Phosphoric acid], 70:30v/v	PDA- Detector 254 nm	4.9min	1 ml/min	81.52%	Intra day 5.57%	Inter day 8.85%	5.0 to 30.0 µg/ml	5 µg/ml	11µg/ml	Method developed for the analysis of AZL in their pharmaceutical preparations is simple and accurate.

AUTHOR	Quantitative determination					Determination				
	METHOD	TEMP	TITRATE	DISSOLVED	END POINT	ACCURACY	PRECISION	LINEARITY	%RECOVERY	CONCLUSION
Rajan. V. Rele et al	(VEEGO-MATIC)	120ºC for 2 hours)	0.1 N perchloric acid	anhydrous glacial acetic acid.	violet colour changes to emerald green	99.42 to 101.85 %.	<1 (n = 6). 0.7908	r^2 > 0.9989	100.03 % to 101.85 %.	non-aqueous otentiometric titration,quality control method of azelnidipine.

AUTHOR	CHROMATOGRAPHIC CONDITIONS						VALIDATION PARAMETERS				
	COLUMN	ELUENT	EXTRACTION	RETENTION TIME	FLOW RATE	MRM	ACCURACY	PRECISION	LINEARITY	DETECTION LIMIT	CONCLUSION
Suneetha et al	C18 Column [50mm×2.1 mm× 1.7µm]	A: (20Mm ammonium acetate) B: (0.1% formic acid in ACN)	SPE 1 mL plasma	3min	0.15 ml/min	m/z 580 → 168	86.9-103 %	5.5 %	0.01-10ng/ml	0.25 ng/mL.	No significant interferences caused by endogenous compounds were observed,(C_{max}), (t_{max}),(k_{el}),($t_{1/2}$)

AUTHOR	CHROMATOGRAPHIC CONDITIONS					VALIDATION PARAMETERS					
	COLUMN	ELUENT	λmax	RETENTION TIME	FLOW RATE	RUN TIME	ACCURACY	PRECISION	LINEARITY	LOD/ LOQ	CONCLUSION
Amin et al	C18 Column (250mm× 4.6mm× 5µm)	Methanol and water, (85:15)v/v	225nm PDA detector	6min (AZL), 1.72min(OLM)	1.5ml/min	8.0 min.	86.9-103 %	Inter-day[AZL] 0.63 %Intra-day [OLM] 0.47 %	1 -60 ng/ml	[AZL]: 0.17 µg/ml [OLM]: 0.51 µg/ml	No significant interferences caused by endogenous compounds were observed,(C_{max}), (t_{max}),(k_{el}),($t_{1/2}$)

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. It showed satisfactory data for all the parameters of validation This method enables simultaneous determination of azelnidipine and olmesartan medoxomil because of good separation and resolution of the chromatographic peaks. The derivatives of UV spectra give applicable information in elucidating compounds in pharmaceutical formulation. This present article provides complete understanding about derivative spectrophotometry technique & its applications. This makes easy to analyst in obtaining useful information from spectra of respective compounds.

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