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Review Article

A Review: Analytical Methods for Determination of Cilnidipine in Biological Fluid and Pharmaceutical Dosage Forms

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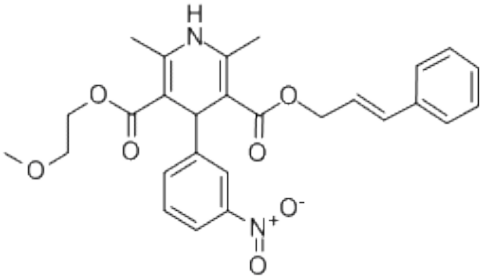
ABSTRACT

Cilnidipine is act as a dual blocker by blocking L- type of calcium channel present in vascular smooth muscles and N- type of calcium channel present in sympathetic nerve terminal that supply blood vessels. Cilnidipine used in treatment of mostly in hypertension and various cardiovascular diseases except in Angina. Cilnidipine used alone or in combination. This review covers most recent analytical methods such as various spectroscopic methods, chromatographic methods and other methods for determination of cilnidipine in various pharmaceutical dosage forms and biological matrix were reported.

Keywords: Cilnidipine, L/N type calcium channel blocker, Anti- hypertensive drug, analytical method

INTRODUCTION

Cilnidipine (CIL) 1,4- Dihydro- 2,6- dimethyl- 4-(3-nitrophenyl)-3,5-pyridinecarboxylic acid 2-methoxyethyl(2E)-3-phenyl-propenyl ester is a novel and unique dihydropyridine calcium channel blocker that possesses a slow-onset, long-lasting vasodilating effect.[1]



Chemical Structure of Cilnidipine

Table No: 1 Drug Profile [2-5]

PARAMETERS	DESCRIPTION
Category	Calcium channel antagonist
Molecular Formula	$C_{27}H_{28}N_2O_7$
Molecular Weight	492.52 gm/mol
Characteristics	Yellow crystalline solid
Solubility	Soluble in DMSO (> 25 mg/ml), ethanol (20 mg/ml), water (≤ 2 mg/ml), and methanol.

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Dose	Adult: 5-10 mg once daily, increase to 20 mg once daily if necessary.

MECHANISM OF ACTION: [6-7]

Cilnidipine is a dual blocker of L-type voltage-gated Ca^{2+} channels in vascular smooth muscle and N-type Ca2+ channels in sympathetic nerve terminals that supply blood vessels. The inhibition of N-type Ca^{2+} channels may provide a new strategy for the treatment of cardiovascular diseases. L-type calcium channels are the main targets of the CCB. N-type calcium is distributed along the nerve and in the brain, cilnidipine is anticipated to exert specific action on nerve activity, such as inhibition of the sympathetic nervous system. It inhibits the Ca^{2+} influx in both in vessel & in the nerve. So causes the Vasodilation & inhibits the release of nor epinephrine, which causes the Vasodilation and decreases the heart rate & also decreases cardiac contraction in heart. So, used in treatment of hypertension

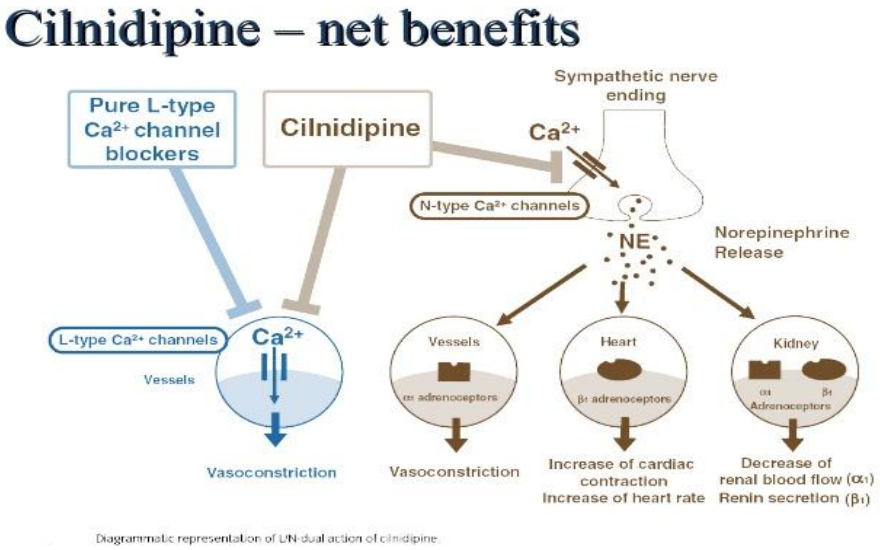

Fig 1: Diagrammatic representations of Dual Action of Cilnidipine [7]

PHARMACOKINETIC PARAMETERS:

Table No: 2 Pharmacokinetic Parameters of Cilnidipine

PARAMETERS	DESCRIPTION
Absorption	Orally absorbed
Metabolism	Hepatic. Metabolised extensively (90%) to inactive metabolites via the cytrochrome P_{450} 3a4 iso enzyme.
Excretion	Urine
Peak Plasma Concentration	6-12 hour following oral administration. Bioavailability is 64-90%.

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SIDE EFFECTS[8]

Dizziness; flushing; headache; hypotension; peripheral oedema; tachycardia; palpitations; GI disturbances; increased micturition frequency; lethargy; eye pain; depression; ischaemic chest pain; cerebral or myocardial ischaemia; transient blindness; rashes; fever; abnormal liver function; gingival hyperplasia; myalgia; tremor; impotence.

COMBINATION OF CILNIDIPINE:

Cilnidipine + Telmisartan
Cilnidipine + Olmesartan medoxomil
Cilnidipine + Metoprolol Succinate

MARKETED FORMULATION OF CILNIDIPINE:

Table No: 3 Marketed Formulation of Cilnidipine[9]

Sr. No.	Brand Name	Company Name	Formulation	Dose (mg)
1	Cilcar	United pharmacies	Tablet	5,10
2	Cilnidipine tablet	Actza pharmaceutical	Tablet	250
3	Cilcar	J.B. Chemicals & Pharmaceuticals Ltd.	Tablet	5,10,20

ANALYTICAL METHOD

This all are the methods which are used for the determination of Cilnidipine in marketed formulation and in biological fluids. This all analytical methods are reported which are seen during the literature survey. This article describes the review on the all reported analytical methods with specific conditions.

A. COMPENDIALMETHOD:

Cilnidipine is not official in any pharmacopeia.

B. REPORTED METHOD:

1. CHROMATOGRAPHIC METHODS:

Various chromatographic methods are used for the determination of the Cilnidipine alone or combination with other drugs in various marketed formulation and in biological fluids like human plasma. Chromatographic methods like Reverse phase High performance liquid chromatography (RP-HPLC) & High performance thin layer chromatography (HPTLC) are used for determination of Cilnidipine. Below in table describes the summary of the various chromatographic methods are used with the method description.

Table No.4: Summary of Chromatographic Methods of Cilnidipine

Title	Method	Mobile Phase	Stationary Phase	Wavelength (nm)	Ref.
Simultaneous estimation of telmisartan and cilnidipine in bulk and in tablet formulation using RP-HPLC	RP-HPLC	Buffer: methanol: Acetonitrile (30:40:30 v/v/v)	INERTSIL ODS C18 (250 x 4.6 mm, 5 µ, Make: GL Sciences) pre packed column.	232	10
Simultaneous RP-HPLC estimation of cilnidipine and telmisartan in combined tablet dosage form	RP-HPLC	Methanol: 40 mM Potassium dihydrogen ortho phosphate buffer (pH 3) (90:10 v/v))	HiQ sil C18 HS column (250 × 4.6 mm i.d.) and PDA detector	245	11
Development and validation of analytical	RP-HPLC	Methanol: 40 mM Potassium	HiQ sil C18 column (250 × 4.6	252	12

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method for simultaneous estimation of Cilnidipine and Olmesartan Medoxomil in bulk and tablet dosage form by RP-HPLC		dihydrogen ortho phosphate buffer (90:10 v/v)	mm i.d.) and PDA detector		
	RP-HPLC	Acetonitrile: Water (90:10 v/v)	Shimandzu Phenomenex-luna C18 (250 x 4.6mm, 5 µ)	231	13
Development and validation of high performance thin layer chromatographic Method for Cilnidipine and Metoprolol S Succinate in their combined Pharmaceutical dosage form	HPTLC	Chloroform: Ethyl acetate: Methanol: Triethylamine 9:2:0.5:0.5 v/v/v/v.	Silica gel F254 TLC plates	280 -	14

2. UV SPECTROSCOPIC METHOD

Spectrophotometric method is versatile and economical particularly for developing countries. Spectrophotometric method has several advantages such as being easy, less expensive and less time consuming compared with most of the other methods. A simple, precise and economical Spectrophotometric method for the estimation of Cilnidipine in pharmaceutical bulk and tablet dosage form was developed and validated. Various methods like Q-absorption ratio, Simultaneous equation, dual wavelength & derivative methods are used for determination of Cilnidipine alone or in combination with other drugs in marketed formulation. Below in table describes the various Spectroscopic methods with the method description and condition which are reported on review literature.

Table No.5: Summary of UV spectroscopic methods of Cilnidipine

Title	Method	Wavelength for Cilnidipine	Wavelength for other drug	Solvent	REF.
Spectrophotometric Method for the Estimation of Cilnidipine in Bulk and Pharmaceutical Dosage forms	simple and sensitive Spectrophotometric Method	240nm	-	Ethanol	15
Method validation Spectrophotometric estimation of cilnidipine	Spectrophotometric Method	240nm	-	Methanol	16

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Development and validation of UV Spectrophotometric method for the simultaneous estimation of cilnidipine and telmisartan in tablet dosage form utilising simultaneous equation and absorbance ratio method	Simultaneous equation method	240nm	297nm	Methanol	17
	Q- absorption ratio method	Iso- Absorptive point-270nm			
Dual Wavelength Spectrophotometric Method for Estimation of Cilnidipine and Telmisartan in Their Combined Dosage Form.	Dual Wavelength Spectrophotometric Method	264 nm and 297.4 nm	229 nm and 246.8 nm	Methanol	18
Development and Validation of Dual Wavelength UV Spectrophotometric Method for simultaneous estimation of Cilnidipine and Olmesartan Medoxomil in Tablet dosage form	Dual Wavelength Spectrophotometric Method	352.92nm	282.99nm	Methanol	19
Development and validation of Q-absorbance ratio Spectrophotometric method for simultaneous estimation of Cilnidipine and Metoprolol succinate in bulk and combined dosage form	Q- absorbance ratio Spectrophotometric method	240nm	224nm	Methanol	20
		Iso- absorptive point-231nm			

3. STABILITY INDICATING METHOD

Stability indicating method is used to check out the stability of drug in various conditions like in acidic, basic, oxidative, photolytic & thermal Degradation. Below in table describes the various Stability indicating methods with the method description and condition which are reported on review literature.

Table No: 6 Summary of Stability Indicating methods of Cilnidipine

Title	Method	Mobile phase	Stationary phase	Wave length	Ref.

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Development and validation of a Rapid Stability Indicating chromatographic determination of Cilnidipine in Bulk and Dosage form.	Stability indicating RP HPLC	Methanol and 0.05 M Phosphate Buffer at pH 3.0 (80:20 v/v)	C18 column	254nm	21
Stability Indicating Simultaneous Validation of Telmisartan and Cilnidipine with Forced Degradation Behaviour Study by RP-HPLC in Tablet Dosage Form	Force degradation study by RP-HPLC	Acetonitrile (ACN): buffer pH 3.0 with orthophosphoric acid (68 : 32v/v)	Waters C18 250 × 4.6 mm, 5 μm	245nm	22

4. OTHER ANALYTICAL METHOD FOR CILNIDIPINE

Table No. 7 : other method for determination of Cilnidipine

TITLE	Method	Internal Standard	Mobile Phase	REFERENCE
Quantification of Cilnidipine In Human Plasma By Liquid Chromatography-Mass Spectrometry	LC-MS Method(ESI positive ion mode)	Nimodipine	0.1M Ammonium acetate (pH 7.0) : Acetonitrile (80:20, v/v)	23
Development of a liquid chromatography/negative-ion electro spray tandem mass spectrometry assay for the determination of cilnidipine in human plasma and its application to a bioequivalence study	LC-MS Method(ESI negative ion mode)	Benidipine	10 mM Ammonium acetate buffer: Methanol (30:70, v/v; adjusted with acetic acid to pH 5.0).	24

DISCUSSION

The presented review highlights on various analytical methods reported for estimation of Cilnidipine in alone or in combination with other drugs in marketed formulation and biological matrix like human plasma. RP-HPLC & UV methods were found to be most widely used methods. Various chromatographic & Spectroscopic conditions are presented in under Table. These methods are found to be rapid, accurate, sensitive, economical and reproducible for determination of Cilnidipine in various marketed formulations & biological matrix.

CONCLUSION

So, from all above information it should be concluded that various spectroscopic methods, chromatographic methods & other methods were used for determination of Cilnidipine 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 & in biological

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matrix in short analytical time. These all methods are sensitive, simple, fast, accurate, reproducible & posses excellent linearity & precision characteristic.These observations make it possible to anticipate the use of these methods as an official procedure.

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