



Analytical Methods of Some Calcium Channel Blockers: A Brief Review

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Abstract

Calcium channel blockers (CCBs) are a class of pharmaceutical compounds frequently used to treat a variety of cardiovascular and neurological problems. For such drugs to be therapeutically effective and patient-safe, their exact and accurate determination is essential. A detailed description of the analytical methods used to determine three of the calcium channel blockers, namely, lercanidipine, Nimodipine and Nifedipine is provided in a brief review article with 100 references. It includes a thorough review of research articles published up to September 2023. High-performance liquid chromatography, gas chromatography, electrochemical, capillary electrophoresis and spectroscopic techniques including UV-Visible and spectrofluorometry are only a few of the analytical methods covered in the paper. These techniques provide excellent CCB quantification in a variety of matrices with high sensitivity, specificity, and reproducibility. In order to perform precise and reliable analysis of these CCBs, the research emphasizes the significance of sample preparation procedures, extraction methodologies, and validation criteria. Additionally, it explores current developments in analytical instrumentation and how they can be used to analyze lercanidipine, nimodipine, and nifedipine.

Keywords: Lercanidipine, nimodipine, nifedipine, calcium channel blockers.

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1. Introduction

A major risk factor for the emergence of cardiovascular illnesses, hypertension is becoming more common. Despite advances in knowledge and treatment, The leading factor in morbidity and mortality is hypertension., accounting for the most years lost to premature death and years spent living with a disabilities(Fay and Cohen 2021).

Hypertension is treated using a group of drugs known as calcium channel blockers (CCBs)(Zhu, Chen et al. 2021). By influencing the transport of calcium ions in cells, especially in the heart and blood arteries, calcium

channel blockers (CCBs) are a class of drugs used to treat numerous cardiovascular disorders (Scholz 1997). They are divided into many subclasses according to the unique mechanisms and therapeutic applications of each(Elliott and Ram 2011). We'll concentrate on three distinct CCBs in this introduction: lercanidipine, nimodipine, and nifedipine.

A calcium channel blocker called lercanidipine is generally used to treat hypertension, or high blood pressure. It is a member of the CCB subclass that primarily targets smooth muscle cells in perivascular blood vessels(Scriabine and Van den Kerckhoff 1988).

Lercanidipine relaxes and dilates the blood arteries, reducing vascular resistance and lowering blood pressure by inhibiting calcium input into these cells. Lercanidipine is well-known for its selectivity and negligible effect on the electrical activity of the heart, when compared to several other CCBs. It is frequently recommended as part of a complete approach for managing hypertension and lowering the risk of cardiovascular problems (Bang, Chapman et al. 2003). Another dihydropyridine CCB with a more specialized use is nimodipine (Carlson, Hänggi et al. 2020). It is mostly used to treat subarachnoid haemorrhage, a kind of brain bleeding that can result from a ruptured cerebral artery by stimulating blood flow to the brain, nimodipine prevents the occurrence of cerebral vasospasm, a potentially fatal consequence following subarachnoid haemorrhage. It is typically delivered orally or through a nasogastric tube due to its specific application, which makes it essential drugs in neurocritical care (Van Geijn, Lenglet et al. 2005). One of the first dihydropyridine CCBs developed, nifedipine is used to treat a number of cardiovascular diseases. By relaxing arterial smooth muscle cells, which causes vasodilation and a decrease in cardiac effort, it effectively decreases blood pressure (Kumari, Subhasish et al. 2010). For the treatment of disorders including hypertension and angina (chest discomfort), nifedipine is frequently recommended. It is available in a variety of formulations, including immediate-release and extended-release varieties, each with a unique dose regimen and intended medical use. In a hospital context, immediate-release nifedipine is occasionally used to treat acute hypertension because of its rapid start of effect (Sarker and Rafe 2021).

For evaluating CCBs in different pharmaceutical dosage forms for quality control assays and method optimization, a variety of approaches have been used. There are now other methods for analyzing drugs and their metabolites in bodily fluids.

2. Reported Methods of analysis:

2.1. For Lercanidipine:

Numerous analytical techniques have been described for the determination of lercanidipine in pure form, dosage form, and biological fluids.

Spectroscopic methods:

Several spectrophotometric techniques have been published for LER determination in biological fluids or pharmaceutical preparations: these are illustrated in table 1.

2.1.2. Electrochemical Methods:

To measure LER in tablets, a differentiable pulse

voltametric method was developed (Álvarez-Lueje, Pujol et al. 2019). To evaluate the voltametric behavior of LER in tablets, differential pulse polarography was developed (Álvarez-Lueje, Núñez-Vergara et al. 2002). Using the anodic adsorptive stripping voltametric approach, the voltametric behavior of LER in pharmacological dosage forms and biological fluids was evaluated (Ozturk, Zeybek et al. 2014).

For the analysis of the LER in dosage form and biological fluids, electroanalytical methods, particularly voltametric approaches, produce accurate results (Ağın 2019). A method for examining the redox behavior of LER utilizing cyclic, square-wave, and differential pulse voltammetry at various carbon electrode materials and over a wide pH range had been presented (Fernandes, Chiorcea-Paquim et al. 2020). The electrochemical behavior and adsorption-diffusion properties of LER on a glassy carbon electrode in an ethanol-Britton Robinson buffer solution were investigated using voltammetry. (Ozturk, Tasdemir et al. 2011).

Voltametric methods were used to examine the electro-oxidative behavior of LER in an aqueous acetonitrile solution at a boron-doped diamond electrode (Altun, Uslu et al. 2010).

2.1.3. Chromatographic Methods:

Table 2 provides a summary of the many techniques published for the HPLC analysis of LER and its metabolites in bulk, pharmacological formulations, or biological fluids.

2.1.4. Capillary electrophoresis:

An enantioselective method based on capillary electrophoresis was created and confirmed to identify the chiral enantiomers of LER (17).

2.2. For Nimodipine:

Nimodipine is official drug in British and united states pharmacopeia (Convention 1916, Cartwright 2016).

For the purpose of determining NIM in pure form, dose form, and different biological fluids, a variety of analytical approaches have been described.

Analytical profiles of NIM provides a thorough monograph that provides a comprehensive overview of the research that has been published up to 2005 (Al-Omar 2005). The more recent studies that analyze this drug can be divided into the following categories:

Table 1: Reported spectrophotometric methods for determination of LER.

Sample matrix	Principle	Detection wavelength	Ref
LER in bulk and pharmaceutical formulations.	Bromothymol blue and bromocresol green produce colored chloroform extractable ion pairs in an acidic solution.	416 nm	(Erk 2003)
LER in tablets.	Reduced LER is diazotized using nitrous acid, then coupled with -naphthol in an alkaline media to produce a red color ..	553 nm	(Mubeen, Rao et al. 2009)
labetalol HCl and LER HCl in tablets.	Labetalol HCl and LER HCl are oxidized with Fe^{+3} and the amount of Fe^{+2} that is generated is measured using 1,10-phenanthroline.	510 nm	(El-Enin, El-Wasseef et al. 2009)
LER hydrochloride and Atenolol in tablets.	Absorbance Ratio Method and Simultaneous Equation Method.	261 nm 273 nm	(Jain, Jain et al. 2011)
Betrixaban and LER HCl in tablets.	measurement of the first-derivative amplitude.	304 and 229 nm	(El-Masry, El-Wasseef et al. 2022)
Enalapril Maleate and LER HCl	Q value analysis based on measurement of absorptivity at iso-absorptive point	238 nm	(Shah, Patel et al. 2011)
LER hydrochloride in dosage forms.	first order, second order, third order and fourth order derivative	238 nm	(Kumari, Subhasish et al. 2010)
LER in bulk and tablets.	reduced LER is diazotized after which ammonia solution is added.	445 nm	(Saradhi, Himabindu et al. 2006)

Table 2: HPLC techniques reported for determining LER.

Matrix	Column	Mobile phase	Detection	Ref.
LER in human plasma samples.	C18 Column	70% acetonitrile in water containing 0.2% v/v formic acid	ESI in positive ion mode	(Kalovidouris, Michalea et al. 2006)
LER and its synthetic impurities.	C18 Column	Acetonitrile-water-triethylamine 55:44.8:0.2 (v/v/v)	UV detection was set at 240 nm	(Mihaljica, Radulović et al. 2005)
LER in bulk and in its formulations.	C 18 Column	sodium perchlorate buffer pH 3.0 adjusted using 5 % phosphoric acid and acetonitrile in the ratio of 40:60	UV detection at 220 nm	(Vijaya Kumar and Muley 2004)

Cont. Table 3: HPLC techniques reported for determining LER.

Matrix	Column	Mobile phase	Detection	Ref.
LER hydrochloride in tablets	C 8 Column	0.02 M ammonium dihydrogen phosphate buffer: methanol (35:65, v/v) with pH 3.5 adjusted with phosphoric acid.	UV detection at 240 nm	(Kaila, Ambasana et al. 2010)
LER in tablets	C 18 Column	methanol/TEA buffer (0.01 M) 60:40 (v/v), adjusted to pH 4	UV detection at 265 nm	(Fiori, Gotti et al. 2006)
LER in human samples plasma.	ODS-2 column	methanol and 5 mM ammonium acetate buffer containing 0.1% formic acid	MS/MS	(Li, Shi et al. 2016)
LER hydrochloride in pharmaceutical tablets and spiked human breast milk	C 18 Column	acetonitrile and phosphate buffer (pH=4) (55:45, v/v)	UV detection at 237 nm	(Tekkeli, GAZİOĞLU et al. 2019)
LER in human plasma samples.	C 18 Column	water (pH 2.5, adjusted with formic acid) and acetonitrile (10:90, v/v)	MS/MS	(Chaudhary, Patel et al. 2016)
LER hydrochloride in rabbit serum samples	C18 Column	Aqueous phase (10 mM potassium dihydrogen phosphate buffer, pH 4) and acetonitrile (40:60 v/v).	UV detection at 240 nm	(Charde, Kumar et al. 2007)
LER HCl in dosage forms.	C 18 Column	Dihydrogen phosphate Buffer: Methanol: ACN (40 :40 : 20)	UV detection at 256nm	(Mondal, Pushpalatha et al. 2020)
LER and valsartan in human plasma samples.	C 18 Column	acetonitrile and 10 mmol/L ammonium acetate containing 0.5% formic acid (53:47, v/v)	MS/MS	(Sabi-Mouka, Agbokponto et al. 2016)
LER, in pharmaceutical formulations and biological fluids.	Cyano column	acetonitrile: methanol: water (35:35:30, v/v/v) containing 0.2% orthophosphoric acid adjusted to pH 3.2 by triethylamine,	UV detection at 240 nm	(El-Masry, El-Wasseef et al. 2021)
LER and Atenolol in dosage forms.	C 18 Column	Acetonitrile: Buffer pH-3.4 with OPA (40:60)	UV detection at 330 nm	(AHMED and AYMAN)

2.2.1. Spectroscopic Methods:

For the purpose of determining NIM, two spectrofluorimetric techniques were created. The first technique involved detecting the NIM's native

fluorescence at 426 nm following excitation at 385 nm. The second method involved calculating the fluorescence intensity in micellar medium with 0.3% Tween-80 at excitation wavelengths of 385 nm and 423 nm (Mohamed, Omar et al. 2015).

The table 3 provides examples of various spectrophotometric techniques for determining NIM in

pharmaceutical formulations and biological fluids.

Table 3: Examples of various spectrophotometric techniques for determining NIM in pharmaceutical formulations and biological fluids.

Sample matrix	Principle	Detection wavelength	Reference
NIM in tablet formulations.	reduction of NIM containing an aromatic nitro group by heating them with cadmium metal in 0.05 N HCl	234 nm	(Canlica and Islimyeli 2005)
NIM in its dosage forms.	direct spectrophotometric measurement in tablet dosage forms	238.5 nm	(Reddy, Sowjanya et al. 2012)
NIM in bulk drug, tablets, and injections	Reduced NIM is diazotized using nitrous acid, then coupled with phloroglucinol to produce colorful azo dye .	410 nm	(Deepakumari and Revanasiddappa 2013)
NIM in dosage forms.	Reduced NIM is diazotized using nitrous acid, then coupled with - naphthol in an alkaline media to produce an orange-red colored chromogen.	555 nm	(Revanasiddappa 2011)
NIM and nitrazepamin pure form and in pharmaceutical formulations	Reduced NIM are diazotized using nitrous acid, then coupled with resorcinol to produce colored azo-dye in an alkaline media.	480 nm	(Revanasiddappa, Deepakumari et al. 2011)
NIM in formulations	Direct spectrophotometric measurement in ethanol.	239.0 nm	(Jadhav and Jagdish 2018)
NIM in pharmaceutical formulations	Reduction of NIM and bromothymol blue results in the production of a yellow ion-pair complex in an acidic media.	414.5 nm	(Nguyen, Le et al. 2022)
NIM in pure form and in pharmaceutical formulations	Direct spectrophotometric measurement in dimethyl sulphoxide.	238.50 nm	(Raghunath, Hemamalini et al.)
NIM in tablets and biological fluids	Oxidation and coupling reaction of nimodipine with 4-aminoantipyrine using KIO ₃ as an oxidizing agent.	464 nm	(Rashid, M. A., M. Bilani et al)

2.2.2. Electrochemical Methods:

The electrochemical properties of NIM at the nitrogen-doped graphene modified electrode were investigated using cyclic voltammetry (Lei, Si et al. 2015). In the cyclic voltammograms, a glassy carbon electrode modified with multiwall carbon nanotubes displayed a sharp anodic peak potential at roughly 0.5 V for amlodipine and NIM, and 0.4 V for felodipine (Sikkander, Vedhi et al. 2012).

Homogeneous polyacrylonitrile superstructures can be converted into 3D hierarchical porous carbon superstructures. It was utilized as an electrode material to investigate the electrochemical sensing of NIM (Mutharani, Rajakumaran et al. 2021).

The development of an improved electrochemical technique for NIM sensing using sodium montmorillonite clay (Sikkander, Vedhi et al. 2014). For NIM sensing, a carbon nanofiber screen printed electrode connected to a flow injection system was established (Salgado-Figueroa, Gutiérrez et al. 2015).

NIM was estimated using differential pulse voltammetry for the manufacture of electrochemical sensors utilizing a reduced graphene oxide composite modified with -cyclodextrin (Ma and Ou 2023). Adsorptive stripping square-wave voltammetry and differential-pulse voltammetry methods were developed for the assay of NIM in therapeutic

formulations (Gupta, Jain et al. 2011). It was intended to investigate the pharmacokinetic interaction of avanafil with NIM in real human serum using square-wave voltammetry and a hybrid NiO nanostructured/sulfanilamide polymeric film (Ali, Abdel-aal et al. 2022).

2.2.3. Chromatographic Methods:

With a capillary column and a FID detector, Headspace Gas Chromatography was designed to determine the amount of residual organic solvents in NIM Liposomes. The injector and detector were both 250°C, and the carrier gas was nitrogen (Xiang, Zhang et al. 2014).

To determine NIM in beagle plasma, a supercritical fluid chromatography tandem mass spectrometry technique was applied (Wang, Li et al. 2019).

A supercritical fluid chromatography-ESI-MS/MS technique had been developed to identify NIM and 3-n-butylphthalide in the plasma of beagles. It employed an isocratic elution method using a mobile phase of CO₂ and methanol (along with 0.3% formic acid and 2 mM ammonium acetate) (Wang, Li et al. 2020).

The following table provides examples of the many procedures that have been published for HPLC determination of NIM in pharmaceutical formulations or biological fluids.

Table 4: HPLC techniques reported for determining NIM

Matrix	Column	Mobile phase	Detection	Ref.
NIM in human plasma samples.	C18 Column	0.03% formic acid/acetonitrile (20/80, v/v)	Electrospray tandem mass spectrometric	(Nirogi, Kandikere et al. 2006)
NIM in plasma samples.	C18 Column	water and acetonitrile (both containing 0.1% formic acid)	MS/MS	(Qin, Ma et al. 2008)
NIM concentration in human plasma samples.	C18 Column	methanol and water (75:25, v/v)	electrospray ionization mass spectrometric	(Zhao, Zhai et al. 2010)
NIM in sustained release tablets.	C18 Column	methanol-acetonitrile-water (35: 38: 27, v/v)	UV detection at 237 nm	(Shang, Ma et al. 2013)
NIM in plasma samples	C18 Column	acetonitrile–water (70:30, v/v)	UV detection at 238nm	(Wang, Chen et al. 2016)

NIM impurity in formulations.	C18 Column	methanol: acetonitrile: water in proportion of (35:40:25v/v)	UV detection at 234 nm	(Shaikh, Pande et al. 2015)
NIM in the presence of its degradation products	C18 Column	Acetonitrile:methanol:water (55:11:34, v/v/v)	UV detection at 234 nm	(Riekes, Rauber et al. 2013)
NIM and its metabolites.	C18 Column	acetonitrile and water (70:30 v/v)	UV detection at 236 nm	(Sotoudegan, Amini et al. 2017)
NIM in formulations and spiked serum samples	C18 Column	methanol: water (pH 3.5 maintained by o-phosphoric acid), (80:20, v/v)	UV detection at 355 nm	(Panda, Ravi Kumar et al. 2020)
NIM in dosage forms	C18 Column	methanol: acetonitrile: water (35v:38v:27v)	UV detection at nm	(Lahamage, Dhamak Vikrant et al. 2020)
NIM in dosage forms.	C18 Column	Methanol: water (60:40 v/v).	UV detection at nm	(Sri, Sri et al. 2021)

2.3. For Nifedipine:

NIF is official drug in British and united states pharmacopeia (Convention 1916, Cartwright 2016). For the purpose of determining NIF in pharmacological preparations or different biological fluids, a number of analytical approaches have been reported. Up till 2018, various analytical techniques had been enclosed in the literature(Tayade, Patil et al. 2019). Other techniques range under the following categories:

2.3.1. Spectroscopic Methods:

Based on the inner filter effect theory, NIF might be measured spectrophotometrically through its reaction with a high-quantum-yield sulfur quantum dot probe(Sheng, Huang et al. 2022). The following table provides various spectrophotometric techniques for detecting NIF in biological fluids and dosage forms.

Table 5: Reported spectrophotometric methods for determination of NIF

Sample matrix	Principle	Detection wavelength	Ref
NIF in topical formulations	Analyze the topical NIF cream's photostability against UVA light.	365 nm	(Wasan, Zhao et al. 2019)
NIF in pharmaceutical forms	utilizing an oxidative coupling reaction between reduced NIF and pyrocatechol that has been oxidized by MnO ₂	235 nm	(Alsaeedi and Abed 2019)
NIF in pure and pharmaceutical forms.	NIF and p-nitro aniline undergo a diazotization coupling process in the presence of an alkaline media.	509 nm	(Alsaeedi, Abed et al. 2019)

NIF and Candesartan cilexetil	Simultaneous Equation Method	235nm	(DHOBI 2018)
NIF in pure and pharmaceutical forms.	Red colored product is produced by an oxidative coupling reaction between reduced NIF and 4-aminoantipyrine.	554 nm	(Abed 2020)
NIF in pure and pharmaceutical forms.	While standing, proton transfer occurs between the NIF and three to five dinitro salicylic acid reagents in a basic solution to produce colorful product.	359 nm	(Abed 2020)

2.3.2. Chromatographic Methods:

Inverse gas chromatography was used to assess the crystallization activity on the surface of NIF solid dispersion powder (Miyanishi, Nemoto et al. 2013). Acute NIF overdose conditions were identified using

gas chromatography-mass spectrometry (Melnikov, Belova et al. 2014).

For the HPLC determination of NIF in pure form, pharmaceutical forms, or biological fluids, several approaches have been reported. The table below provides examples of various techniques

Table 6: HPLC techniques reported for determining NIF:

Matrix	Column	Mobile phase	Detection	Ref.
Hydrochlorothiazide and NIF in tablets.	C18 Column	methanol containing 0.1% (v/v) formic acid and 5mM aqueous ammonium format pH 6.0	electrospray ionization mass spectrometry	(Ongas, Kokwaro et al. 2018)
Atenolol and NIF in formulations.	C18 Column	acetonitrile and phosphate buffer (pH=4.6) (53.2:46.8 % v/v)	Diode Array detector	(Ahmed, Alqurshi et al. 2018)
Lidocaine and NIF in its topical dosage forms.	C18 Column	20 mM ammonium acetate buffer (pH-4.8 adjusted with glacial acetic acid): Acetonitrile 65:35)	UV detection at 231 nm	(Meshram, Mehta et al. 2018)
NIF in Human Plasma samples.	C18 Column	gradient mode (acetonitrile – water – formic acid)	MS/MS	(Logoyda 2020)
NIF and its degradants.	C18 Column	ACN to MeOH ratio of 2.06	UV detection at 254 nm	(Choiri, Ainurofiq et al. 2018)
NIF in dosage forms.	C18 Column	Methanol-0.1% formic acid aqueous solution (65:35, v/v).	mass spectrometer	(Guo, Tan et al. 2022)
NIF in dosage forms.	C18 Column	Gradient mode (eluent A (acetonitrile – water – formic acid, 5: 95: 0.1 v/v), eluent B (acetonitrile – formic acid, 100: 0.1 v/v)).	mass spectrometer	(Logoyda 2020)
NIF and valsartan	C6-phenyl column	acetonitrile, methanol and ammonium format in the ratios of (15:45:40% v/v)	UV detection at 236 nm	(Rashid, Bilani et al. 2022)
NIF, bisoprolol and captopril.	C18 Column	methanol–0.1% formic acid (95:5, v/v)	MS/MS	(Abdel-Megied, Kovalenko et al. 2023)

2.3.3. Electrochemical Methods:

The surface of a modified electrode created by immobilizing Ag nanoparticles at the surface of a glassy carbon electrode was used to study the catalytic activity of NIF (Baghayeri, Namadchian et al. 2013).

The determination of NIF and atenolol was created utilizing an anodically pretreated boron-doped diamond electrode coupled to differential pulse voltammetry (Scremin and Sartori 2018). For the purpose of detecting NIF at a glassy carbon electrode constructed with zinc oxide nanoparticles implanted on functionalized multi-walled carbon nanotubes, a novel method had been used (Agrawal, Savalia et al. 2021). At the unmodified and modified glassy carbon electrodes, cyclic voltammetry was used to explore the electrochemistry of NIF and its primary metabolite dehydro-NIF (Mokhtari, Nematollahi et al. 2018). Barium stannate, a needle-shaped perovskite, was created using a co-precipitation method for the electrochemical measurement of nitrofurantoin and the pericardial medication NIF simultaneously (Balamurugan, Alagumalai et al. 2021). To avoid or minimize the problems associated with overdosages, an electroanalytical approach serving as an electrochemical sensor for the detection of NIF was absolutely necessary. Bi_3NbO_7 , a bismuth niobium oxide, was created using a one-pot hydrothermal synthesis method (Babulal, Chen et al. 2022).

Ultrasound-Assisted and Stirring-Assisted Synthesis were used to create strontium cerate nanoparticles, which were then used as an electrocatalyst for the sensitive and specific electrochemical detection of the calcium channel blocker NIF (Sundaresan P 2019). Utilizing an electro-oxidation technique and a mixed metal oxide electrode with a titanium composition, NIF degradation was carried out. By employing Britton-Robinson buffer and differential pulse voltammetry at a hanging mercury drop electrode, NIF was determined (Wirzal MD 2021).

Electrochemical Sensor based on phthalocyanine was developed for Detection of NIF (Liu, Peng et al. 2022). In order to provide an active electrode surface for the oxidation of the NIF molecule, an electrochemical sensor based on a glassy carbon electrode modified with carbon nanofibers and gold nanoparticles in a Nafion® layer was carried out. This was used for its examination in biological and environmental samples together with a voltametric approach. (Santos, Wong et al. 2023).

2.3.4. Capillary electrophoresis:

Micellar electrokinetic capillary chromatography was used to examine NIF and the product of its degradation. Using an applied voltage of 30 kV and a buffer comprising 100 mM borate, pH 9.0, 15 mM sodium dodecyl sulfate, and 25% acetonitrile, the compounds were separated (Özaltın, Nemutlu et al. 2003).

3. Conclusion:

The review article underlines the importance of using a variety of analytical techniques to determine calcium channel blockers. To select the best appropriate method, researchers and analysts must carefully analyze the particular conditions and aims of their investigation. The continual development of analytical techniques in this field promises continuous increases in the accuracy and precision of CCB determination, enhancing their clinical and pharmaceutical applications. This review is a valuable reference for scientists, analysts, and researchers who are interested in calcium channel blockers.

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