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A review on analytical methods of cilnidipine and its combinations

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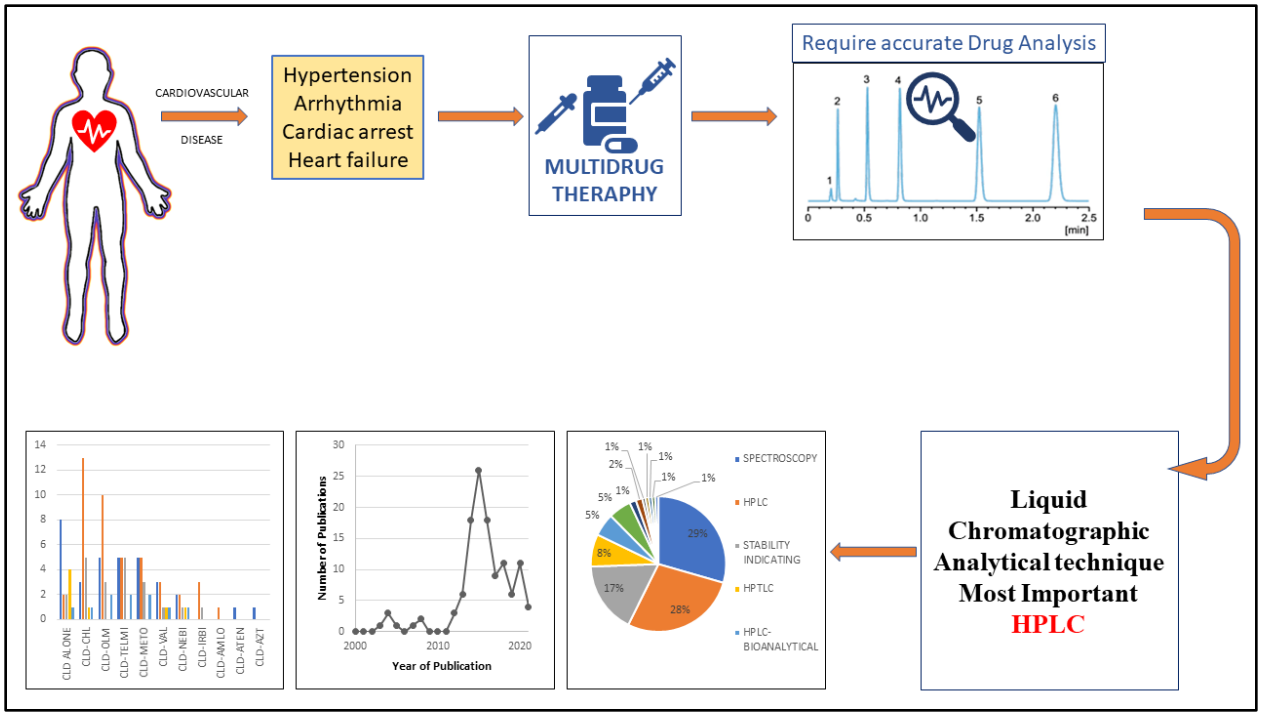
Abstract

Background - The chase to improve the quality of life has stimulated desirable changes in research to design and develop a new drug and enhance its safety and effectiveness. Thus, there is a gradual rise in demand to develop susceptible and specific analytical techniques for newly developed drugs. Thus, analysts are striving very hard to develop new and efficient analytical methods to achieve these targets.

Main body of abstract - Analytical methods that analyze drug compounds in a given matrix need to be optimized and validated to ensure excellent selectivity, sensitivity, ease of use, speed of analysis, less expensive, and efficient analytical procedures. Developing a new analytical method should be considered critical, based on availability and accurate handling of different instruments. This review is a genuine venture of compiled literature of earlier and recent trends in the method developments for Cilnidipine (CLD) analysis alone and in combination with other drugs. It provides an in-depth assortment of practical aspects of various analytical techniques published for CLD.

Conclusion - High-performance liquid chromatography and ultraviolet spectroscopy have been found the most acceptable for the analysis of CLD. Stability indicating studies and impurity profiling of CLD also prevailed in the assembled literature. Scanty work was observed with capillary electrophoresis, Fourier transform-infrared spectroscopy, and electroanalytical methods to analyze CLD. Applications mentioned for CLD are significant in their particular field and contribute to analytical assay in future endeavos.

Keywords- Cilnidipine, Bioanalytical method, Stability indicating method, HPLC, Spectrophotometry.



Graphical Abstract

INTRODUCTION

Hypertension is one of the most significant observed public health challenges contributing to cardiac disease and death globally. Hence, to lower the risk for cardiovascular disease, it is admissible to control blood pressure strictly. Combining two or more antihypertensive agents with different action mechanisms can be used reliably to achieve the aforementioned condition. This combination therapy has proved beneficial in preventing major cardiovascular diseases, reducing the risk for adverse effects, and maximizing drug compliance [1,2].

Calcium channel blockers (CCB) are first-line drugs in the treatment of hypertension. However, CCB alone was insufficient in lowering blood pressure. Hence, CCBs have been widely co-administered to treat hypertension. These drugs act by inhibiting calcium (Ca)-channels in the myocardium and vascular smooth muscle cells, which lowers the myocardial contractions, decrease pulse conduction, and causes vasodilation. Thus, they are found to be effective in the treatment of essential hypertension. Furthermore, among the three main classes of CCBs, 1,4-dihydropyridines (DHP) have contributed to a widely used hypotensive drug class [3,4].

Among various 1,4-dihydropyridine CCBs, Cilnidipine (CLD) shows unique action on sympathetic N-type Ca-channels, besides acting on L-type Ca-channels, as with most Ca-channel antagonists. Their action is performed through vasodilatation, decreased heart rate, and increased renal blood flow [5]. CLD has opted as CCB of choice in hypertensive patients with diabetes, chronic kidney disease, and patients developing edema. It is a novel 4^{th} generation CCB [6]. It is found to dilate both efferent and afferent arterioles resulting in decrease in pressure in the capillary bed. Hence, the accumulated fluid of tissues flows back to veins, thus skipping pedal edema incidence [7]. It shows a slow onset but long-lasting hypotensive effect by inhibiting sympathetic neurotransmission and norepinephrine release. It shows excellent selectivity for vascular smooth muscle. CLD has also emerged as a good candidate for combination therapy [8,9].

CLD is chemically described [Figure 1] as 2-Methoxyethyl (2E)-3-Phenyl-2-propen-1-yl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate [10,11]. The development of CLD can be credited jointly to Fuji Viscera Pharmaceutical Company, Japan, and Ajinomoto, Japan which was approved in 1995. Countries like China, Japan, Korea, India, and several countries in the European Union have approved this drug [12]. CLD is a light yellow-coloured crystalline powder. It is insoluble in water. The molecular weight of CLD is 492.528 g/mol, and the molecular formula is $C_{27}H_{28}N_2O_7$. Absorption of CLD is rapid; maximum peak concentration is achieved in 2 hours. Distribution in kidneys, liver, plasma and other tissues is high. Even after repeated oral administration, accumulation of CLD is not observed. It has a large volume of distribution. It shows low bioavailability due to low aqueous solubility and high permeability [13]. Microsomal enzymes highly metabolize it with a dehydrogenation process in both the liver and kidney. Elimination is 20% through the urine and 80% through feces. The half-life of the hypotensive effect for CLD is about 20.4 min. It shows cardioprotective, renoprotective, and neuroprotective effects. Administration of CLD has been shown to decrease blood pressure safely and effectively, without excessive blood pressure reduction or tachycardia [14].

Methods of analysis

Various analytical methods for the determination of CLD are presented here as compendial and reported methods. Compendial methods are official methods.

Compendial method

Japanese Pharmacopeia and Indian Pharmacopeia approved CLD in 2018 in 2016, respectively. The identification method for CLD includes Ultraviolet (UV)/ Visible (Vis)-spectrophotometry and infrared spectrophotometry. In the Japanese Pharmacopeia, chromatographic separation was achieved on stainless steel column with dimensions 25 cm x 4.6 mm and particle size of 5 µm, and the mobile phase reported is a mixture of sodium acetate buffer and methanol. The detection wavelength is 240 nm using a UV detector. The column temperature mentioned is 25°C [15].

The Indian Pharmacopeia also mentioned chromatographic separation using Phenomenex-Prodigy ODS 3V column of dimension 25 cm x 4.6 mm and particle size of 5 µm. The mobile phase reported is a mixture of acetonitrile (ACN): 0.01M sodium acetate buffer (70:30% v/v). The flow rate is

reported to be 1.0 mL/min. The injection volume is 20 µL, and the detection wavelength was 240 nm using a UV detector [16].

Reported methods of analysis

The rapid progress of science and technology has led to the development of numerous newly synthetic drugs prompting the development of analytical methods for determining these drugs in the manufacturing phase of the pharmaceutical formulations and their determination in the human body. Thus, the analysis of pharmaceuticals has gained progressive importance in the overall drug development process. This study aimed to comprehensively review the literature and collect the evidence concerning the analysis of CLD and its combinations of dosage forms. Data was assembled by search on Google Scholar, Pubmed, and Elsevier's Science Direct. The keywords included "estimation of cilnidipine", "analytical method development of cilnidipine," "pharmaceutical preparations of cilnidipine," "cilnidipine in biological fluids." Figure 2 provides chronological reported methods for estimation of CLD. The results show that CLD can be estimated by spectrophotometry, High-performance liquid chromatography (HPLC), Liquid chromatography-mass spectroscopy (LC-MS), High-performance thin layer chromatography (HPTLC), voltammetry, capillary electrophoresis, and spectrofluorimetry, either in the form of raw materials or pharmaceutical preparations. Different analytical methods for estimating CLD as reported in the literature are comparatively provided in Figure 3. This review provides a complete insight for the analysis of CLD, alone or in combination in pharmaceutical preparations or biological fluids. Figure 4 provides comparative data of estimation methods for CLD alone and in combination with other drugs.

Spectrophotometry methods

Spectrophotometry is concerned with the quantitative measurement of a material's reflecting or transmitting properties as its function of wavelength. It represents several advantages: simple, fast, easy to perform, less expensive, and accurate for the routine analysis of an analyte in bulk or pharmaceutical preparations in a quality control laboratory [17]. Literature reveals numerous methods for the analysis of CLD through UV/Vis-spectrophotometry [18-54]. Methanol was mainly used as a choice of solvent for analysis. Various spectrophotometric methods employed were simultaneous equation method, absorbance ratio method, first and second derivative spectroscopic method, Vierodt's method, and dual-wavelength method. UV/Vis-spectrophotometric method reported for estimating CLD as alone or combined with other drugs is represented in Table 1.

In a special method, El Hamd MA and his coworkers developed an indirect method, using N-bromo succinimide (NBS) and indigo carmine (INC) dye to quantify five different drugs of the 1,4-DHP category [54]. They followed a fascinating mechanism, wherein they added the acidic solution of 1,4-DHP drugs with an excess amount of NBS. They calculated the excess amount of unreacted NBS bleached with the dye from the drug corresponding to reacted NBS. They reported obeying the Beer-Lambert law in the concentration range of 1.25–13.00 µg/mL. They found excellent correlation coefficient values and percent recoveries. Detections limits ranged between 0.141 to 0.5 µg/mL. The method found successful application for the analysis of different dosage forms.

Liquid chromatography

Chromatography refers to the separation of analyte as an individual component from a mixture and assessing it thoroughly. It is the most extensively used technique in pharmaceutical analysis. Among chromatographical techniques, special attention is gained by HPLC and emerging ultra-performance liquid chromatography (UPLC), which mainly enhance "speed, resolution, and sensitivity" to separate, identify, and quantify each component in a mixture [55,56]. In reported methods, [20,46,57-90] separation is mainly achieved on the C18 column, and the mobile phase consists mainly of ACN and a buffer of potassium phosphate, pH ranges between 3-5. The flow rate observed mainly was 1 mL/min. The chromatography method reported for estimating CLD as alone or in combination with other drugs, i.e., Telmisartan (TELMI), Olmesartan (OLM), Metoprolol succinate (METO), Amlodipine mesylate (AMLO), Bisoprolol fumarate (BF), Chlorthalidone (CHL), Nebivolol HCl (NEBI), Valsartan (VAL), Atenolol (ATEN) and Irbesartan (IRB) is represented in Table 2.

Analytical eco-scale and quality by design-oriented liquid chromatography

In a single reported method, Panda SS et al. developed an RP- HPLC method to estimate CLD, TELMI, and METO, employing an eco-scale and quality-by-design approach [90]. They separated drugs on the C18 column using a mobile phase consisting of a mixture of methanol and 0.01 M KH_2PO_4 buffer of pH 3.0 at a ratio of 70:30% v/v with a flow rate of 1.0 mL/min. They quantified the drugs with a diode array detector at 240 nm. They assessed method variables using the Box-Behnken design. Well-separated peaks, with a resolution greater than 2.0, of all the three analytes were obtained. They observed linearity between 2.5-80 µg/mL, accuracy was >99%, and precision was <1%. The eco-scale analysis showed an excellent green score for the present all three drugs. The optimized method quantified the analytes from pharmaceutical dosage forms and showed excellent and acceptable results for a limit of detection (LOD), the limit of quantitation (LOQ), system suitability, and solution stability. The green analytical method can be successfully applied for simultaneous estimation of combined pharmaceutical formulations.

Stability indicating estimation of CLD

The stability-indicating assay method is a validated quantitative analytical method that detects chemical, physical or microbiological change with time. These assays generally include forced degradation/stress testing to produce specific drug products in which active ingredients and degradation products can be measured accurately without interference. The HPLC method is widely used as a research tool in analytical techniques to estimate degradation impurities in drug substances and products.

Common stress-induced conditions include acid, base, oxidative, photolytic, thermal, and humidity stresses [91,92].

A thorough literature search revealed that various assay procedures such as RP-HPLC, HPTLC, and LC/MS/MS are available for the stability study of CLD [72,93-110]. In all the studies reviewed, separation was achieved on a C18 column, and the mobile phase consisted mainly of ACN, methanol, and buffers such as potassium monophosphate, orthophosphoric acid and acetate buffers. The flow rate was between 0.8-1.2 mL/min. Generally, the detectors used were photodiode array (PDA) detectors and mass spectrometry (MS). Estimations were carried out at room temperature. The stability-indicating method was reported to estimate CLD as alone or in combination with other drugs like METO, TELMI, VAL, NEBI, OLM, CHL, and IRB and the results are represented in Table 3.

In a special method, Ch KR et al. worked with liquid chromatography coupled with quadrupole time of flight mass spectrometry (HPLC-QTO/MS). They developed an analytical method to study stress degradation studies of seven degradation products as per the International Conference on Harmonization (ICH) Q1A (R2) guidelines, characterized using high-resolution mass spectrometry [110]. Three oxidative degradation products, CD1, CD2, and CD3, were separated from the analyte's mixture with the HPLC C18 column. Structure elucidation was performed by a high-resolution mass spectrometer, nuclear magnetic resonance, and spectroscopic techniques. Degradation showed the formation of racemic mixtures for two degradative products, which chiral HPLC verified. They used ROESY data for fixing stereocenters for CD1 and its enantiomer and CD2 and its enantiomer. They observed novel structures of CD1 and CD2.

Stability indicating estimation of CLD with UPLC

UPLC provides better separation capabilities than HPLC with added benefits such as increased resolution, sensitivity, and speed of analysis with shorter run time and lower solvent consumption. Due to its benefits, this technique has gained considerable attention to analyze pharmaceutical and biomedical compounds of interest [111]. Only two methods were reported in the literature under stability-indicating estimation of CLD with UPLC.

Alagar RM et al. have developed and validated the UPLC method as per the ICH/FDA regulatory requirements for estimating CLD and OLM in its pharmaceutical dosage form [112]. Chromatographic separation using BEH C18 column (100 × 2.1 mm, 1.7 µm), and pH 3.5 buffer: methanol in ratio 35:65% v/v as mobile phase with a flow rate of 0.3 mL/min was achieved. The detection wavelength was selected to be 254 nm. Different stress conditions for CLD and OLM implemented were thermal stress, photolytic stress, acid media, alkali media, and oxidative media. Retention time values obtained for degradation products were significantly different from those of pure drugs. Linearity was found in the

concentration range of 0.2-0.3 µg/mL. Good precision and smaller relative standard deviations were seen. Analyte recovery was acceptably between 99.04-101.58%. The proposed method can find application in quality control industry laboratories for various pharmaceutical dosage forms.

Shah PK et al. have developed a validated stability-indicating RP-HPLC method to estimate OLM medoxomil, CHL, and CLD and their impurities [72]. Analytes were separated on Hypersil-BDS Thermo-Scientific, C18 (12.5 cm x 4.6 mm, 5µm) using mobile phase ammonium acetate solution (pH 5): ACN in gradient mode at 25°C. The flow rate was 1mL/min, and the detection wavelength was 260 nm. CHL impurity and OLM impurity showed retention at 2.7 and 7.2 minutes, respectively. The retention time of OLM was found at 3.3 min. The stress degradation products showed acceptable separation from analytes and impurities. The developed method was accurate, sensitive, specific, linear, and with less run-time. Hence it can be successfully applied for routine quality control and stability analysis of pharmaceutical dosage form.

Bioanalytical methods

Bioanalytical methods are the quantitative assessment of the concentration of the drug, its metabolite, and biomarker in biological fluids, such as blood, plasma, serum, urine, saliva, or tissue extracts. This method is characterized by speedy analysis, sensitivity, and robustness, which are imperative to fulfill the validation guidelines requirements, including accuracy, precision, sensitivity, selectivity, reproducibility, and stability [113]. These methods enable the separation, identification, and determination of many biologically active compounds [114]. The literature revealed many reliable bioanalytical methods, which can be applied successfully and conveniently for the intended research purpose [115-121]. It was observed that in most bioanalytical methods, sample preparation was performed using protein precipitation (PPT), liquid-liquid extraction (LLE), or solid-phase extraction (SPE) method. Separation was mainly achieved on the C18 column, and the mobile phase consisted mainly of ACN, methanol, and buffers. Commonly used detectors were PAD, MS, and fluorometric. The bioanalytical method reported for estimating CLD as alone or in combination with other drugs like VAL, CHL, NEBI, and AMLO is represented in Table 4.

HPTLC Methods

HPTLC is the separation and identification method having universal expectance for various chemical and biological mixtures [122]. This method uses various solvents as mobile phases and a variety of solids as stationary phases. In HPTLC, mobile phases can be used in various manners, such as isocratic or mixed solvents. The addition of various modifiers can alter the nature of mobile phases. HPTLC offers several advantages, including better resolution, lesser sample size, smaller volumes of mobile phases, etc. The literature survey on HPTLC of CLD with other drugs has been summarized in Table 5 [123-132].

Estimation of CLD with impurities

Impurity profiling of drugs in pharmaceutical research is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity as per the guidelines published by the ICH. It is designed to detect, identify or elucidate the structure and quantify organic and inorganic impurities in bulk drugs and pharmaceutical formulations. Few methods are found through literature surveys that reported various impurities present in CLD [133,134]. Subsequent methods are summarized here.

Kasimala BB et al. developed a validated stability-indicating RP- HPLC method to quantify CLD and its related impurities in pharmaceutical formulations [135]. The column employed for separation was an X Terra (250 × 4.6 mm; 5 µm) C18 column. The mobile phase used was methanol and phosphate buffer of pH-5.8 (10:90% v/v) with isocratic elution at a 1.0 mL/min flow rate. UV detector at 229 nm wavelength was used to detect the eluents. Linearity was found to be in the range of 2-12 µg/mL. The recovery rate was more than 98% for each analyte. They found stress degradation studies showed that UV light exposure degraded the analyte up to 9.967% and base hydrolysis showed the analyte degradation up to 6.223%. Conditions like acidic stress (5.347%), oxidative stress (4.916%), and thermal stress (4.319%) conditions showed no interference of both known impurities with CLD. The developed method was precise, robust, selective, specific, and suitable for quantifying and determining CLD impurities in pharmaceutical formulations.

Masada S et al. developed an HPLC method to detect N-nitroso dimethylamine (NDMA) contaminated VAL and CLD tablets [136]. They initially assayed a standard solution for the quantitative estimation, followed by quantitative estimation in gradient elution mode with mobile phase water-ACN and 0.1% formic acid to detect components simultaneously. The retention times of NDMA, VAL, and CLD were acceptably separated at 7.8, 16.3, and 17.1 min, respectively. They found linearity in the range of 0.0111–7.4 µg/mL and a correlation coefficient of 0.999. The LODs and LOQs were 0.0085 µg/mL and 0.0285 µg/mL, respectively. They also reported a GC-MS method for detecting NDMA in VAL & CLD combination, successfully with much lower LOD. The method used was in the isotopic mode and required multiple extraction steps. They concluded that the developed HPLC method was low-cost and more suitable for rapidly screening NDMA contaminated VAL CLD combination with sufficient sensitivity.

Zeng H et al. developed a liquid chromatography/Q-Orbitrap mass spectrometry (LC/Q-Orbitrap MS) method to investigate the structural information photodegradation impurities of CLD [137]. Boston Group C18 column (250 × 4.6 mm, 5µm) was employed for chromatographic separation, whereas ACN: H2O in the ratio of 75:25% v/v was used as mobile phase. Detection was carried out using a Thermo LC system coupled with a Q-Orbitrap high-resolution mass spectrometer with both positive and negative ion modes. To carry out a systematic forced degradation study, CLD underwent photolysis. The structural information of the detected five photodegraded impurities of cilnidipine was determined by LC/MS/MS analysis. Structure elucidation was performed with 1H-NMR and 13C-NMR data. Two photodegradation pathways to produce different photodegradation impurities were also revealed in the study. The optimized method provided good results and can be successfully applied to investigate separated and characterized drug substances.

Hu CC & Gu X developed an HPLC-QTO/MS method to identify the light degradation impurity of CLD [138]. Chromatographic separation was performed on the C18 column (250 × 4.6 mm, 5µm). The impurity was initially synthesized, and then the structure was identified by the full scan with NMR. Comparative analysis of UV spectra, the mass spectra, and retention time of this impurity of synthesized impurity was performed. The chemical structure of light degradation impurity was a Z-isomer of CLD in tablet and capsule. The method provides valuable scientific data for studying the preparations, the photodegradation behavior, and the quality control of degradation impurities of CLD.

Wang SG & Gu P developed an RP-HPLC method to estimate CLD related substances using a C18 chemical column at 40°C column temperature [139]. The mobile phase employed was ACN and 0.025 mol/L ammonium dihydrogen phosphate solution and cyclohexane ratio 60:39:1 at a 1.5 mL/min flow rate. Detection was accomplished at 240 nm with a UV detector. The drug peak and impurity peak were well separated. Linearity was found in the range of 1-16 mg/L. RSD was found as 0.42%. The developed method showed suitability and sensitivity for the determination of CLD related substances.

Zeng H et al. performed an impurity profiling study of CLD tablets and capsules by HPLC-QTO/MS and evaluation of packaging materials [140]. The source of the impurities was investigated. HPLC was used to analyze impurities produced on photodegradation; the method showed significant results for separating and identifying impurities in cilnidipine tablets and capsules. They compared four different pharmaceutical packaging materials for impurities. Impurity II was produced by direct exposure to light, and impurity III was produced from the ethanol solution of CLD. UV-vis spectrophotometer detected the shading effect of the four packaging materials, which showed a remarkable difference in the formation of photodegradation products. HPLC-QTO/MS/MS elucidated the structure of five impurities in commercial cilnidipine tablets and capsules. High-resolution MS/MS data successfully separated and identified the impurities. Thus, the method can find application for the successful identification of impurities in CLD in pharmaceutical preparations. An animal study was also performed with the impurities and found that impurity II and impurity III were cytotoxic. Based on the result, methods suggested modification of packaging material for CLD tablets.

Capillary electrophoresis and enantio-separation of cilnidipine

Du Y & Di B developed a rapid and straightforward capillary electrophoresis method with high separation efficiency using a synthetic polysaccharide, desulphated chondroitin sulfate C, as a novel chiral selector [141]. It was applied to the enantiomer separation of the racemic mixture of CLD. The chiral separation was investigated for studying the effects of concentration of pH, buffer, and applied voltage. The optimum resolution conditions showed pH 2.50, concentration to be 30 g/L, and voltage applied to be 10 kV. The successfully resolved CLD enantiomers showed a good resolution factor of 2.01.

Supercritical Fluid chromatography (SFC)

Zhang L et al. developed a rapid, environmentally friendly, and potential SFC coupled with two-phase hollow fibre-based liquid-phase microextraction for chiral separation of seven most commonly used 1,4-DHP [142]. Separation was achieved on immobilized polysaccharide chiral selectors coated with cellulose-tris (3,5-dichlorophenylcarbamate). Isopropanol was used to modify resolution; as such maximum resolution of 13.38 was obtained. Within optimal conditions, nimodipine enantiomers showed the LOD as 0.3 and 0.5 μg cm^{-3}. A total of 80.0–99.8% recoveries were observed. Additionally, the developed SFC technique was found to be an effective and environment-friendly method that can successfully find its application for separating and quantifying 1,4-DHP enantiomers and other pharmaceutical drugs.

Fourier transform infrared (FT-IR)

One of the reliable analytical methods is infrared (IR) spectroscopy which provides rapid, label-free, and objective analysis for the active pharmaceutical ingredients in the pharmaceutical industry. It is more considered as an attractive and promising analytical tool regarding process analytical technology and green chemistry. IR spectroscopy has gained wide industrial acceptance for routine analysis [143].

Literature survey reveals that Patel A et al. have developed and validated the FT-IR spectrometric analytical method for quantitative estimation of a single dosage of CLD in tablet form [144]. Absorbance was measured for carbonyl group (C=O) peak at 1697 cm^{-1} and plotted against concentration to obtain a calibration curve and calculate all the regression parameters. Linearity was obtained by overlaying the spectra of all individual concentrations. For CLD calibration curve was plotted over a concentration range of 5-25 μg/mg. Recoveries were found to be 99.8-102.5, and 99.8- 101.4% RSD was observed to be less than 2. The detection limit was 0.22 and 0.050 μg/mg; the LOQ was 0.60 and 0.17 μg/mg. The developed method suggested that FT-IR is a simple, rapid, reproducible, and less time-consuming analytical method that can find its application for the direct determination of CLD in pharmaceutical formulations.

Voltametric Detection of Calcium Antagonist Cilnidipine

Jain R has developed a susceptible and selective sensor voltammetric detection method to estimate CLD [145]. They characterize the fabricated sensor by cyclic voltammetry, chrono-coulometry, electrochemical impedance spectroscopy, square wave voltammetry, and scanning electron microscopy. They enhanced the sensor's sensitivity by fabricating hybrid film by increasing the surface area and active electron transfer sites. Thus, it showed high sensitivity and selectivity in performance as compared to bare glassy carbon, zinc oxide nanoparticle modified, and multi-walled carbon nanotubes modified electrodes. The linearity of CLD was found to be in the range of 5 ng/mL to 5 μg/mL. The proposed electrochemical method was helpful in the electroanalytical determination of CLD in its pharmaceutical formulation and will find application for the routine analysis of other pharmaceutical formulations.

Fluorescence probe for CLD assay

Tan S et al. carried out a fluorescence assay for CLD. A fluorescence probe was encapsulated 1-naphthaleneboronic acid (NBA), with an emulsion polymerization technique, using Triton-X 100, EDMA, butyl methacrylate, and potassium persulfate [146]. The average diameter was 764.1 nm for the resultant polymer particles in the phosphate buffer solution. It showed high sensitivity and was used for CLD assay based on fluorescence quenching. Linearity of CLD was observed over the concentration range of 2.0×10^{-7} to 1.1×10^{-5} mols/L. The NBA-encapsulated probe showed a significantly improved response to that of free NBA. The proposed method can find application for analysis of other calcium blockers in bulk and pharmaceutical formulations.

CONCLUSIONS

An insight of the present work comprehensively serves as a systematic review of the current analytical methods for determining CLD and its combination in pharmaceutical and biological samples like serum and plasma. The past and present scenario of widely accepted analytical methods for analyzing CLD has been systematically presented. These methods include spectrophotometry,

spectrofluorimetry, liquid chromatography, electroanalytical methods, and FT-IR. Figure 5 provides distinguished estimation methods for various combinations of CLD. From the literature, it is observed that due to its advantages such as sensitivity, specificity, and better separation efficiency, over other analytical techniques, HPLC has been found as the most acceptable application for the analysis of CLD. It has been observed that other analytical methods too showed prominent utilization for its determination. Although there are numerous well-defined and validated methods for the quantification analysis of CLD, these methods lack the principles of “green chemistry.” Henceforth, there is a rise in demand to develop eco-friendly methods that will diminish toxic organic effluents, hazardous to the environment. The presented systematic information is a rapidly developing subject that can be anticipated for its utility in the near future to researchers involved in formulation development and quality control of CLD.

List of Abbreviations –

1,4-dihydropyridines	DHP
1-Naphthaleneboronic acid	NBA
Acetonitrile	ACN
Amlodipine mesylate	AMLO
Ammonium acetate buffer	NH_4Ac
Atenolol	ATEN
Azilsartan	AZT
Bisoprolol fumarate	BF
Calcium	Ca
Calcium channel blockers	CCB
Centimeter	cm
Chloroform	$CHCl_3$
Chlorthalidone	CHL
Cilnidipine	CLD
Ethanol	EtOH
Fourier transform infrared	FT-IR
Glacial acetic acid	GAA
High-performance liquid chromatography	HPLC
Indigo carmine	INC
International Conference on Harmonization	ICH
Irbesartan	IRB
Limit of detection	LOD
Limit of quantitation	LOQ
Liquid chromatography coupled with quadrupole time of flight mass spectrometry	HPLC-QTO/MS
Liquid chromatography-mass spectroscopy	LC-MS
Liquid-liquid extraction	LLE
Methanol	MeOH
Metoprolol succinate	METO
Microgram/Milliliter	µg/mL
Millimeter	mm
Nanometer	nm
N-Bromo succinimide	NBS
Nebivolol HCl	NEBI
Nifedipine	NIF
N-nitroso dimethylamine	NDMA
Normal phase	NP
Olmesartan medoxomil	OLM
Orthophosphoric acid	OPA
Performed using protein precipitation	PPT
Photodiode array	PDA
Potassium dihydrogen orthophosphate buffer	KH_2PO_4
Reverse phase	RP
Sodium hydrogen phosphate	Na_2HPO_4
Sodium hydroxide	NaOH
Solid-phase extraction	SPE
Telmisartan	TELMI
Triethylacetic acid	TEA
Ultra violet	UV
Ultra-performance liquid chromatography	UPLC
Valsartan	VAL
Visible	Vis
Volume/Volume	v/v

Table1 Spectrophotometric specifications and results for determination of CLD alone and with other drugs in the bulk drugs and pharmaceutical dosage forms

S. No.	Method	Matrices	Solvent/reagent	λ max(nm)	Linearity range (µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	Refs
1.	a) Spectrophotometric and b) Spectrofluorimetric	CLD (Bulk/Tablet)	ACN	a) 510 b) Excitation - 254; Emission - 350	a) 2.0 - 25.0 b) 0.25 - 11.2	a) 1.050 b) 0.130	a) 3.17 b) 0.41	[18]
2.	Spectrophotometric method	CLD (Bulk/Tablet)	EtOH	240	2-14	0.0638	0.193	[19]
3.	Spectrophotometric method	CLD (Bulk/Tablet)	MeOH	242	2-10	0.1509	0.4574	[20]
4.	Spectrophotometric method	CLD (Bulk/Tablet)	MeOH	242	5-25	2.3	7.6	[21]
5.	Colorimetry Method	CLD (Bulk/Tablet)	MeOH	425	1-9	0.7122	2.1582	[22]
6.	Spectrophotometric Method	CLD (Bulk/Tablet)	EtOH	240	02 - 30	0.0255	0.0772	[23]
7.	Spectrophotometric Method	CLD (Bulk/Tablet)	MeOH	240	3-18	-	-	[24]
8.	Spectrophotometric area under the curve method	CLD BF (Bulk/Tablet)	MeOH: Water (80:20)	CLD- 231-254.80; BF- 222.20 to 322.40	CLD-10-30; BF-5-15	CLD-0.8674; BF-0.4521	CLD-2.6287; BF-1.3700	[25]
9.	a) Simultaneous equation method b) Q- Absorption ratio method	CLD TELMI	MeOH	240; 297 Iso-Absorptive point-270nm	CLD-4-10; TELMI-6-18	-	-	[26]
10.	Spectrophotometric Method	CLD TELMI (Bulk/Tablet)	ACN: Water; (1:9)	CLD-203; TELMI-241	CLD-0.5-2.5; TELMI-2-10	CLD-0.317; TELMI-0.67	CLD-096; TELMI-5.086	[27]
11.	Dual Wavelength Spectrophotometric Method	CLD TELMI	MeOH	CLD- 264 & 297.4; TELMI-229 & 246.8	CLD- 2-6 TELMI-3-15	CLD-0.050 TELMI-0.088	CLD -0.16 TELMI - 0.266	[28]
12.	Vierodt's method	CLD TELMI (Bulk/Tablet)	MeOH	CLD- 350 TELMI- 294	CLD – 1-25 TELMI – 1-24	CLD- 0.020; TELMI-0.087	CLD-0.062; TELMI-0.265	[29]
13.	Spectrophotometric method	CLD TELMI (Bulk/Tablet)	MeOH: 0.01M NH_4Ac (8:2)	CLD- 357 TELMI- 297	CLD-1-30 TELMI –1-80	CLD-3.92 TELMI – 1.12	CLD-1.91 TELMI – 0.57	[30]
14.	a) Simultaneous equation method b) Q- Absorption ratio method	CLD TELMI (Bulk/Tablet)	MeOH: Water (80:20)	CLD-241; TELMI-297 Iso-Absorptive point-270nm	CLD-1-10; TELMI-2-18	-	-	[31]
15.	First-order derivative spectroscopic method.	CLD METO TELMI (Bulk/Tablet)	MeOH	CLD-252; TELMI-243; METO-216	CLD-5-25; TELMI-11.8-59; METO-20-100	CLD-0.0307; TELMI-0.4184; METO-0.0349	CLD-0.0932; TELMI-1.268; METO-0.106	[32]
16.	Dual Wavelength Spectrophotometric Method	CLD OLM (Tablet)	MeOH	CLD- 352.92 OLM-282.99, 337.85	CLD-10-60 OLM -20-120	CLD-0.2828 TELMI-0.4554	CLD-0.8571 TELMI-1.3800	[33]
17.	Simultaneous Equation method	CLD OLM (Bulk/Laboratory mixture)	MeOH	CLD - 253 OLM - 241	CLD - 2-10 OLM - 4-20	CLD-0.363 OLM-0.245	CLD- 1.102 OLM-0.745	[34]
18.	Simultaneous Equation method	CLD OLM (Tablet)	MeOH	CLD-256; OLM-240	CLD-2-20 OLM-2-20	CLD-0.067, 0.100	CLD-0.204,0.304	[35]

						OLM-0.210, 0.192	OLM-0.638, 0.583	
19.	First-order derivative spectroscopic method.	CLD OLM (Tablet)	MeOH	256 220	CLD-2-10 OLM-4-20	CLD-0.067; OLM-1.90	CLD-2.04, OLM-5.77	[36]
20.	a) Simultaneous Equation method; b) Q- absorption ratio method	CLD OLM (Bulk/Tablet)	MeOH	a) CLD - 240; OLM - 210 b) Isoabsorptive point - 285	CLD-1-5; OLM-2-10	CLD-0.0349; OLM-0.05	CLD-0.106; OLM-0.151	[37]
21.	First order-UV derivative spectroscopy	CLD CHL (Tablet)	MeOH	CLD-240 CHL-268	CLD -2-10 CHL-2-10	CLD -0.13 CHL-0.12	CLD -0.39 CHL-0.32	[38]
22.	Dual-wavelength spectrophotometric method	CLD CHL (Tablet)	MeOH	CLD-271.83, 278.34 CHL-233.83, 250.0	CLD-2-10 CHL-2.5-12.5	CLD-0.4174 CHL-0.068	CLD-1.264 CHL-0.206	[39]
23.	Absorption correction Method	CLD, CHL TELMI (Tablet)	MeOH	CLD-350 CHL-225 TELMI-325	CLD-5-40 CHL-3.12-25 TELMI-10-80	-	-	[40]
24.	Ratio spectra derivative spectroscopic method	CLD, CHL METO (Tablet)	MeOH	CLD- 241.62 CHL- 239.72 METO- 342.11	CLD-2-6 CHL-2.5-7.5 METO -10-30	CLD-0.0478 CHL-0.0270 METO - 0.6576	CLD-0.1451; CHL-0.0819; METO - 1.9928	[41]
25.	Simultaneous equation method	CLD VAL Synthetic mixture	MeOH	CLD-240 VAL-250	CLD-2-10 VAL-16-80	CLD-0.07 VAL-0.266	CLD-0.22 VAL-0.808	[42]
26.	Second Order Derivative spectrophotometric method	CLD VAL (Tablet)	MeOH	CLD-219 VAL-227	CLD-2-10 VAL-5-25	CLD-0.33 VAL=1.01	CLD-0.18 VAL-0.55	[43]
27.	First-order derivative UV spectroscopic method.	CLD VAL (Tablet)	MeOH	CLD-248 VAL-240	CLD-1-6 VAL-8-48	CLD-0.0279; VAL- 0.083	CLD-0.0846; VAL-0.253	[44]
28.	Q - absorbance ratio method	CLD METO (Tablet)	MeOH	CLD-230.60 METO-223.40	CLD- 2-10 METO-10-50	CLD-0.0529; 0.0909 METO-0.1647; 0.1281	CLD-0.160; 0.275 METO-0.499; 0.388	[45]
29.	Q- absorbance ratio Method	CLD METO (Tablet)	MeOH	CLD-240; Isosbestic point -230	CLD- 4-8; METO-20-40	-	-	[46]
30.	Spectrophotometric Method	CLD METO (Bulk/Tablet)	MeOH	CLD-240; METO-223	CLD-1-12; METO-3-50	-	-	[47]
31.	Q- absorbance ratio Method	CLN METO (Tablet)	MeOH	CLD-240 METO-224 Isoabsorptive point-231	CLD- 2-10 METO-10-50	CLD-0.040 METO-0.23	CLD-0.121 METO-0.72	[48]
32.	Simultaneous equations method	CLD AZT Synthetic mixture	MeOH	CLD-240 AZT–212	CLD- 2-14 AZT- 2-14	CLD-0.12, 0.08 AZT-0.05, 0.07	CLD-0.38, 0.24 AZT-0.17, 0.20	[49]
33.	Simultaneous equation method	CLD BF (Tablet)	MeOH & water	CLD-233.4, BF- 360	-	-	-	[50]
34.	Simultaneous equation method	CLD BF (Tablet)	MeOH	CLD-241 nm BF-224 nm	CLD-4-12 BF-2-6	CLD-0.959 BF-0.507	CLD-2.908 BF-1.538	[51]
35.	First-order derivative spectroscopy	CLD NEBI (Tablet)	MeOH	CLD-249 NEBI-221.6,	CLD-5-25; NEBI-4-20	CLD-0.17; NEBI-0.17	CLD-0.52; NEBI-0.52	[52]
36.	First-order derivative spectroscopy	CLD NEBI (Bulk/Tablet)	MeOH	NEBI -269.15 nm; CLD-281.85 nm	CLD-4-20; NEBI - 2-10	CLD-0.003; NEBI - 1.782	CLD-0.01; NEBI-5.4	[53]

CLD-Cilnidipine; BF-Bisoprolol Fumarate; TELMI-Telmisartan; OLM-Olmesartan medoxomil; METO-Metoprolol succinate; BF-Bisoprolol; CHL-Chlorthalidone; NEBI-Nebivolol HCl; VAL-Valsartan; AZT-Azilsartan; ACN-Acetonitrile; EtOH-Ethanol; MeOH-Methanol; LOD-Limit of detection; LOQ-Limit of quantitation. NH_4Ac-Ammonium acetate buffer; --Not provided.

Table 2 Chromatographic specifications and analytical specifications of HPLC methods for determination of CLD alone and with other drugs in the bulk and pharmaceutical dosage forms

Sr no	Analytes	Column	Mobile phase	Detection wavelength (nm)	Flow rate (mL/min)	Rt Min	Mode of analysis	Linearity range(µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	Refs
1.	CLD (Bulk/ Tablet)	Thermo scientific model C18 (250x4.6 mm, 5µm)	ACN: MeOH (50:50 v/v)	242	1.0	3.067 ± 0.0012	Gradient	2-10	0.003	0.009	20]
2.	CLD(Bulk/Tablet)	Hexon C18 (250x4.6 mm, 5µm)	MeOH: Water (85:15 v/v; pH-3.5 OPA)	243	1.0	4.658 ± 0.001	Isocratic	10-50	1.56	4.74	57]
3.	CLD VAL (Bulk drug /synthetic mixture)	Luna C18 100A◦ (250x4.6 mm, 5µm)	ACN: water (85:15 v/v)	240	1.0	CLD-2.083; VAL-5.458	Gradient	CLD- 5-25; VAL- 40-200	CLD-0.037; VAL-0.31	CLD-0.206 VAL-0.62	58]
4.	CLD, VAL (Pharmaceutical formulation)	ODS C18 (250x4.6 mm, 5µm)	MeOH: Water (85:15 v/v; pH 3 OPA)	245	1.0	CLD-7.064; VAL-3.962	Isocratic	CLD-1-5; VAL-8-40	-	-	59]
5.	CLD, VAL (Pharmaceutical formulation)	Symmetry C18 (250x4.6 mm, 5 µm)	ACN: NH4Ac Buffer pH-5.0 (75:25 v/v) with TEA	240	1.0	CLD-8.43; VAL-2.45	Isocratic	CLD-4-20; VAL-24-120	-	-	60]
6.	CLD, TELMI (Tablet)	Inertsil ODS C18 (250x4.6 mm, 5µm)	KH_2PO_4 Buffer: MeOH: ACN (30:40:30 v/v/v, pH-4)	UV detector 232	1.0	RT CLD-4.958; TELMI-2.735	Isocratic	CLD-12-28; TELMI-48-112	CLD-9.14; TELMI-3.01	CLD-1.59 TELMI-0.53	61]
7.	CLD TELMI (Bulk/Tablet)	HiQ sil C18 HS (250x4.6 mm; 5µm)	MeOH: 40 mM KH_2PO_4 (90:10 v/v; pH 3)	PDA at 245	1.0	CLD-5.720; TELMI-2.587	-	CLD-1-10; TELMI-5-30	CLD-0.28; TELMI - 0.60	CLD-0.86; TELMI - 1.81	62]
8.	CLD TELMI (Bulk/Tablet)	Hi Q Sil C 18 (250x4.6 mm, 5µm)	MeOH: water (80:20 v/v; pH 3.0 OPA)	UV detector at 264	1.0	CLD-4; TELMI-2	Gradient	CLD-10-35; TELMI-20-120	CLD-0.034; TELMI-0.225	CLD-0.104; TELMI-0.683	63]
9.	CDL TELMI (Tablet)	Younglin C18 (250x4.6 mm, 5µm)	ACN:0.05 % OPA (60:40 v/v)	UV detector at 236	0.7	CLD-4.70; TELMI-8.01	Gradient	CLD- 1-10; TELMI- 10-40	-	-	64]
10.	CLD OLM (Bulk/Tablet)	Enable C18 (250x4.6 mm, 5µm)	ACN: MeOH (40:60 v/v)	UV detector 260	1.0	CLD-3.351; OLM-1.833	Isocratic	CLD-5-25; OLM-10-50	CLD-0.021; OLM-0.031	CLD-0.066; OLM-0.094	65]
11.	CLD OLM (Bulk/Tablet)	HiQ sil C18 (250x4.6 mm, 5µm)	MeOH: 40 mM KH_2PO_4 (90:10 v/v, pH 3 OPA)	PDA detector at 254	1.0	CLD-6.32; OLM-2.47	Isocratic	CLD- 5-30; OLM - 10-50	CLD-2.00; OLM - 2.24	CLD-6.009; OLM-6.69	66]
12.	CLD OLM (Bulk/Tablet)	Symmetry C18 (250x4.6 mm, 5µm)	ACN: Buffer (75:25 v/v, pH 6.5 TEA)	Dual wavelength absorbance	1.0	CLD-2.655; OLM-4.720	Isocratic	CLD- 10-90; OLM -20-180	CLD-0.130; OLM 0.790	CLD-0.395; OLM - 2.397	67]

				detector at 265							
13.	CLD OLM (Tablet)	Hypersil C18 (250x4.6 mm, 5µm)	ACN: Phosphate buffer (70:30 v/v, pH 3.6)	UV detector at 270 nm	1.0	CLD-7.79; OLM - 4.14	Isocratic	CLD- 10 – 50; OLM - 40-200	CLD-0.117; OLM - 0.130	CLD-0.355; OLM - 0.395	68]
14.	CLD OLM (Bulk/Tablet)	Inertsil C18 (250x4.6 mm, 5µm)	buffer: ACN (55:45 v/v)	PDA detector at 225 nm	1.0	CLD-3.7; OLM-2.2	Isocratic	CLD- 5-30; OLM-10-60	CLD-0.0017; OLM-0.0146	CLD-0.0051; OLM-0.0443	69]
15.	CLD, AMLO, OLM, (Tablet)	Symmetry C18 (75x4.6 mm, 5µm)	0.05 M NH_4Ac: ACN: MeOH (30:50:20 v/v pH 7.3)	UV detector 240	0.3	CLD-4.513; AMLO-3.060; OLM-2.209	Isocratic	CLD-10-100; AMLO-5-50; OLM-10-100	CLD-0.22; AMLO-0.5; OLM-0.22	CLD-0.67; AMLO-0.14; OLM-0.79	70]
16.	CLD, CHL, OLM (Synthetic Mix)	Sheisedo C18 (250x4.6 mm, 5µm)	ACN: MeOH: Water (40:20:20 v/v/v)	UV detector 226nm	1.0	CLD-5.366; CHL-3.760; OLM-2.693	Isocratic	CLD-50-300; CHL-60-360; OLM- 100-600	CLD-15.609; CHL-18.33; OLM-31.57	CLD-45.63; CHL-55.55; OLM-95.69	71]
17.	CLD, OLM, CHL (Bulk/Tablet)	Hypersil-BDS C18 (125x4.6 mm,5µm)	NH_4Ac buffer (pH 5): ACN (55:45 v/v)	PDA detector at 261 nm	1.0	-	Gradient CHL-2.7; OLM-7.2; CLD-	CHL-3.6-60; OLM-; CLD-	OLM-3.6	-	72]
18.	CLD, CHL, OLM, (Bulk/Tablet)	Inertsil ODS C18 (150x4.6m m, 5µm)	0.5 M KH_2PO_4: ACN: TEA (80:20:0.1 v/v/v, pH 3.5)	PDA detector at 248 nm	1.0	CLD-6.887; CHL-4.667; OLM-3.807	Isocratic	CLD-5-15; CHL-6.25-18.75; OLM-20-60	CLD-0.184; CHL-0.144; OLM-0.082	CLD-0.275; CHL-0.556; OLM-0.437	73]
19.	CLD, CHL, OLM (Bulk/Tablet)	Merck Chromolith RP-18e (50x4.6 mm, 5µm)	0.1% Formic acid: MeOH	PDA detector at 265nm	0.6	CLD-15.23; CHL-6.77; OLM-2.95	Gradient	CLD-5-20; CHL-5-20; OLM-10-60	CLD-0.1; CHL-0.3; OLM-0.8	CLD-0.4; CHL-0.9; OLM-2	74]
20.	CLD, CHL, TELMI (Tablet)	Zorbax Eclipse XDB C8 (150x4.6m m, 5 µm)	0.025M KH_2PO_4 (pH-2.5 10% OPA): ACN (75:25 v/v)	PDA detector at 233 nm	1.0	CLD-6.773; CHL-3.867; TELMI-2.033	Isocratic	CLD-5-30; CHL-6.25-37.50; TELMI-20-120	CLD-0.132; CHL-0.415; TELMI - 1.09	CLD-0.402; CHL-1.25; TELMI - 3.32	75]
21.	CLD, CHL (Bulk/Tablet)	Inertsil ODS 3V (250x4.6 mm, 5µm)	0.025 M KH_2PO_4: ACN (pH-2.5 OPA)	Variable PDA detector at 240	1.0	CLD-7.668; CHL-3.872	Gradient	CLD-160-480; CHL-200-600	CLD-0.40 CHL-0.50	CLD-1.20 CHL-1.50	76]
22.	CLD, CHL (Tablet)	HIQ SII C18 (250x4.6 mm, 5µm)	MeOH: water (80:20 v/v)	UV-Visible detector at 231.6	1.0	CLD-4.23; CHL-1.84	Isocratic	CLD-10-70; CHL-10-70	CLD-1.5611; CHL-5.1516	CLD-1.7442; CHL-5.7559	77]

23.	CLD, CHL (Tablet)	Zorbax Bonus RP (250x4.6 mm, 5µm)	0.05 M KH_2PO_4: MeOH (50:50 v/v, pH 6.5 with 1% OPA)	PDA detector 225	1.0	CLD-4.337; CHL-8.107	Isocratic	CLD-50-150; CHL-50-150	CLD-2.490 CHL-2.295	CLD-7.547; CHL-6.955	78]
24.	CLD, IRB, CHL (Tablet)	C18 (250x4.6 mm, 5µm)	KH_2PO_4 0.05M: ACN: TEA (80:20:0.1 %v/v/v, pH 3.5)	UV detector. 222	1.0	CLD-6.887; IRB-3.807; CHL-4.667	Isocratic	CLD-1-3; IRB-30-90; CHL-1.25-3.75	CLD-0.028 IRB-0.862 CHL-0.036	CLD-0.085; IRB-2.612; CHL-0.111	79]
25.	CLD, IRB, CHL (Tablet)	Hypersil BDS C18 (250x4.6 mm, 5µm)	0.05 M NH_4Ac: ACN (60:40 v/v, pH-3)	UV detector 226	1.0	CLD-6.923, IRB-2.967, CHL-4.097	Isocratic	CLD-0.5-1.5; IRB-15-45, CHL-0.625-1.875	CLD-0.142, IRB-4.402, CHL-0.156	CLD-0.432; IRB-13.340; CHL-0.473	80]
26.	CLD, IRB (Tablet)	Inertsil ODS C18 (150x4.6 mm, 5µm)	ACN: Phosphate buffer (70:30 v/v, pH-3)	PDA detector at 225	1.0	CLD-2.507; IRB-3.233	Isocratic	CLD-20-100; IRB-20-100	-	-	81]
27.	CLD, ATN, CHL (Bulk)	Hypersil-keystone C18 (250x4.6 mm, 5µm)	MeOH: water (80:20, v/v, pH 7)	UV detector 225	1.0	CLD-3.25; ATEN-5.366; CHL-9.025	Isocratic	CLD-10-50; ATEN-10-50; CHL-6-30	-	-	82]
28.	CLD, METO, CHL (Bulk)	ODS (250x4.6 mm, 5µm)	MeOH: ACN: 0.05 M Phosphate buffer (10: 80: 10 v/v/v pH 6.5 with NaOH)	PDA detector at 224	1.0	CLD-8.29; METO-6.10; CHL-3.01	Isocratic	CLD-2-10; METO-10-50; CHL-2.5-12.5	CLD-0.165; METO-3.263; CHL-0.205	CLD-0.499; METO-9.888; CHL-0.621	83]
29.	CLD, METO (Tablet)	Enable C18G (250x4.6 mm, 5µm)	MeOH: water (80:20 v/v, pH-3.5 with OPA)	UV Detector 231	1.0	CLD-4.092; METO-2.913	Isocratic	CLD-2-10; METO - 10-50	CLD-0.053; METO-0.161	CLD-0.226; METO-0.685	84]
30.	CLD METO (Bulk/Tablet)	Shimadzu Phenomenex-luna C18 (250x4.6 mm, 5µm)	ACN: Water (90:10 v/v)	PDA detector 231	1.0	-	-	CLD-1-11; METO - 5-55	CLD-0.040; METO-0.23	CLD-0.121; METO-0.72	85]
31.	CLD, METO (Tablet)	Altima (150x4.6 mm, 5µm)	0.1% OPA: MeOH (45:55 v/v, pH-3)	PDA detector at 225	1.0	CLD-3.062; METO-2.249	Isocratic	CLD-5-30; METO - 12.5-75	CLD-0.03; METO-0.08	CLD-0.08; METO-0.25	86]
32.	CLD METO (Bulk/Tablet)	C18 (250x4.6 mm, 5µm)	MeOH: Buffer (87:13 v/v, pH-6.9)	UV detector at 240 & 223	1.0	CLD-6.4; METO – 4.3	Isocratic	CLD-1-12; METO-3-50	-	-	46]
33.	CLD, NEBI (Tablet)	Grace smart C18 (250x4.6 mm, 5µm)	0.05 M KH_2PO_4 Methanol (30:70 v/v pH-5)	PDA detector at 225	1.0	CLD-6.470; NEBI-4.057	Isocratic	CLD-10-30; NEBI-5-15	CLD-0.992; NEBI-0.494	CLD-3.006; NEBI-1.496	87]

34.	CLD, NEBI (Bulk/Tablet)	C8 (250x4.6 mm, 5µm)	Water: ACN (50:50 v/v, pH-3.5 with 0.2% OPA)	UV detector 290	1.5	CLD-6.915; NEBHI-4.645	Isocratic	CLD- 320-480; NEBI-160-240	CLD - 4.6; NEBI-4.93	CLD-14.51; NEBI-14.94	88]
35.	CLD BF (Tablet)	Shiseido C18 (250x4.6 mm, 5µm)	Phosphate buffer: MeOH (60:40) v/v, pH-3.5)	225	1.0	CLD-4.053; BF-5.730		CLD-10-30; BF-5-15	CLD-1.419; BF-0.570	CLD-4.300; BF-1.729	89]

CLD-Cilnidipine; TELMI-Telmisartan; OLM-Olmesartan medoxomil; METO-Metoprolol succinate; AMLO-Amlodipine mesylate; BF-Bisoprolol fumarate; CHL-Chlorthalidone; NEBI-Nebivolol HCl; VAL-Valsartan; ATEN-Atenolol; IRB-Irbesartan; UV-Ultra violet; ACN-Acetonitrile; EtOH-Ethanol; MeOH-Methanol; KH_2PO_4-Potassium dihydrogen orthophosphate buffer; TEA-Triethylacetic acid; OPA-Orthophosphoric acid; NaOH-Sodium hydroxide; PDA-Photodiode array; LOD-Limit of detection; LOQ-Limit of quantitation; NH_4Ac-Ammonium acetate buffer; --Not provided.

Table 3 Chromatographic specifications and results of Stability indicating studies method for determination of CLD alone and with other drugs in the bulk drugs and pharmaceutical dosage forms

Sr No.	Analytes	Degradation conditions	Column	Mobile phase	Detection wavelength (nm)	Flow rate mL/min	Rt (min)	Mode of analysis	Linearity range(µg/mL)	LOD (µg/mL)	LOQ (µg/mL)	Refs
1.	CLD	-	Cosmosil (250x4.6 mm, 5µm)	MeOH: KH_2PO_4 (50:50 v/v)	UV detector at 241	1.0	4.8165	Gradient	100-500	0.00471	0.01427	93]
2.	CLD (Tablet)	Acidic, basic, oxidative & photo	Grace C18 (250x4.6 mm, 5µm)	MeOH: 0.05 M Phosphate Buffer (80:20 v/v pH 3.0)	UV detector at 254	1.0	8.189	Isocratic	5-30	0.179	0.544	94]
3.	CLD METO (Bulk/Tablet)	Acidic, basic, oxidative, thermal & photolytic	STD Kromasil C18 (150x4.6 mm, 5µm)	ACN: Phosphate Buffer (65:35 v/v, pH-5 with 10% OPA)	UV detector at 230	0.8	CLD-3.26; METO-2.27	-	CLD-12.5-75; METO-62.5-375	CLD-1.10; METO-0.41	CLD-3.33; METO-1.24	95]
4.	CLD METO (Bulk/Tablet)	Acidic, basic, oxidative, thermal & photolytic	Cosmocil C18 (250x4.6 mm, 5µm)	0.05M KH_2PO_4: MeOH (70:30 v/v, pH-3.5 with OPA)	UV detector at 230	1.0	CLD-3.493; METO-5.960	Isocratic	CLD-12.5-37.5; METO-2.5-7.5	-	-	96]
5.	CLD METO (Bulk/Tablet)	Acidic, basic, oxidative, thermal & photolytic	BDS (150x4.6 mm, 5µm)	Phosphate buffer: ACN (60:40, v/v)	UV detector at 237	1.0	CLD-4.026; METO-2.679	Isocratic	CLD-5-30; METO-12.5-75	CLD-0.03; METO-0.03	CLD-0.09; METO-0.10	97]
6.	CLD TELMI (Tablet)	Acidic, basic, oxidative, thermal & photolytic	Waters C18 (250x4.6 mm, 5µm)	ACN: 0.01M Na_2HPO_4 (68:32 v/v, pH 3.0 with H_3PO_3)	PDA detector at 245	1.0	CLD-10.5; TELMI-3.2	Isocratic	CLD-10-40; TELMI-40-160	CLD-0.09; TELMI-0.01	CLD-0.4; TELMI-0.06	98]
7.	CLD VAL	Acidic, basic, oxidative, thermal & photolytic	Inertsil ODS C18 (150x4.6 mm, 5µm)	ACN: water- (70:30 v/v with 0.1 mL GAA)	UV detector at 230	1.0	CLD-5.500; VAL-2.367	Isocratic	CLD-5-30; VAL-40-240	CLD-0.45; VAL-2.55	CLD-1.39; VAL-7.72	99]
8.	CLD, NEBI (Tablet)	Acidic, basic, oxidative, thermal & photolytic	Spheri-5-RP-C18 (250x4.6 mm, 5µm)	MeOH: 20 mM NH4Ac (85:15, v/v, pH with formic acid 4.0)	UV detector at 240 nm	1.0	CLD-8.4; NEBI - 3.4	Isocratic	CLD-10-60; NEBI -5-30	CLD-1.73; NEBI - 0.80	CLD-5.26; NEBI - 2.43	100]
9.	CLD OLM (Tablet)	Acidic, basic, neutral, oxidative, thermal & photolytic	ODS C18 (250x4.6 mm, 5µm)	0 .1% OPA buffer: ACN (42:58 v/v)	UV detector at 240	1.0	CLD-3.763; OLM-2.317	Isocratic	CLD-25-150; OLM-50-300	CLD-1.17; OLM-0.43	CLD-3.53; OLM-1.13	101]
10.	CLD CHL (Tablet)	Acidic, basic, oxidative &	waters C18, (100x4.6	A. 0.1 % Formic acid in MeOH:	PDA detector at 240	1.0	CLD-12.642 ±0.2; CHL-	Gradient	CLD- 2 - 400; CHL- 2.5 - 500	-	-	102]

		photolytic	mm, 2.5µm)	ACN (80:20 v/v) B. 10 mM NH4Ac			6.047± 0.2					
11.	CLD CHL TELMI (Tablet)	Acidic, basic, neutral, oxidative, thermal & photolytic	Kromasil C18 (250x4.6 mm, 5µm)	0.1% OPA buffer: ACN (57:43 v/v)	PDA detector 238	1.2	CLD- 3.924; CHL- 2.573; TELMI-3.106	Isocratic	CLD-5-30; CHL-3-20; TELMI-20-110	CLD-0.13; CHL-0.03; TELMI-0.80	CLD-0.40; CHL-0.10; TELMI-2.42	103]
12.	CLD, CHL, OLM (Bulk/Tablet)	Acidic, basic, neutral, oxidative, thermal & photolytic	Kromosil (250x4.6 mm, 5µm)	0.1% perchloric acid: ACN: MeOH (45:50:5v/v, pH2.5)	PDA detector at 240	1.0	CLD-3.722; CHL-2.838; OLM-3.357	Isocratic	CLD5-30; CHL-6.25-37.5; OLM-20-120	CLD-0.02; CHL-0.05; OLM-0.03	CLD-0.07; CHL-0.16; OLM-0.08	104]
13.	CLD, TELMI, CHL (Tablet)	Acidic, basic, oxidative, thermal & photolytic	BDS Hypersil C18 (250x4.6 mm, 5µm)	MeOH: 0.05 M NH_4Ac buffer (40:60 v/v, pH-5 with OPA)	Absorbance detector at 270	1.0	CLD-11.467 TELMI-3.390 CHL-4.167	Isocratic	CLD-6.25-18.75 TELMI-20-60 CHL-5-15	CLD-0.699 TELMI-1.263 CHL-0.429	CLD-2.118 TELMI-3.827 CHL-1.300	105]
14.	CLD, TELMI, CHL (Tablet)	Acidic, basic, oxidative, thermal & photolytic	Agilent C18 (150x4.6 mm, 5µm)	0.1% OPA: ACN- (55:45 v/v pH-2.5)	UV detector 238 nm	1.0	Isocratic	CLD-2.105; TELMI-3.505; CHL-2.813	CLD-5-30; TELMI-20-120; CHL-6.25-37.5	-	-	106]
15.	CLD OLM (Bulk/Tablet)	Acidic, basic, oxidative, thermal & photolytic	Phenomenex, C8 (250x4.6 mm, 5µm)	MeOH: ACN: Water (30:55:15 v/v/v)	UV detector at 256	1.0	-	Isocratic	CLD- 10-60; OLM-20-120	-	-	107]
16.	CLD IRB (Tablet)	Acidic, basic, oxidative, thermal & photolytic	Hypersil BDS C18 (250x4.6 mm, 5µm)	Phosphate buffer: ACN (40:60 v/v, pH 5.5 with 0.1 N NaOH)	UV Detector at 240	1.0	CLD-6.040; IRB-3.730	Isocratic	CLD-1-3; IRB-30-90	CLD-0.094; IRB-1.428	CLD-0.287; IRB-4.327	108]
17.	CLD TELMI (Tablet)	Acidic, basic, oxidative, thermal & photolytic	Water acquity BEH C18 (100x2.1 mm, 1.7µm)	ACN: 0.01M Na_2HPO_4 (68:32 v/v pH -3 with phosphoric acid	PDA detector at 245	0.5	CLD-9.33; 4.22	Gradient	CLD – 10-40 TELMI – 40-160	-	-	109]

CLD-Cilnidipine; TELMI-Telmisartan; OLM-Olmesartan medoxomil; METO-Metoprolol succinate; CHL-Chlorthalidone; NEBI-Nebivolol HCl; VAL-Valsartan; ATEN-Atenolol; IRB-Irbesartan; UV-Ultra violet; ACN-Acetonitrile; EtOH-Ethanol; MeOH-Methanol; KH_2PO_4-Potassium dihydrogen orthophosphate buffer; OPA-Orthophosphoric acid; Na_2HPO_4-Sodium hydrogen phosphate; NaOH-Sodium hydroxide; PDA-Photodiode array; LOD-Limit of detection; LOQ-Limit of quantitation; NH_4Ac-Ammonium acetate buffer; GAA- Glacial acetic acid; --Not provided.

Table 4 Chromatographic specifications and results of Bioanalytical method for determination of CLD alone and with other drugs in the bulk drugs and pharmaceutical dosage forms

Sr No.	Analytes	Extraction Technique	Extraction t solvent	Column	Mobile phase	Detection wavelength (nm)	IS	Rt (min)	Flow rate (mL/min)	Linearity range (ng/mL)	LOD (ng/mL)	LOQ (ng/mL)	Refs
1.	CLD (Human Plasma) LC-MS	LLE	ACN	Gemini C6-Phenyl 110A HPLC (250x4.6 mm, 5µm) Gemini Gard (4x3 mm)	0.1M Ammonium acetate: ACN (80:20, v/v, pH 7.0)	MS detector (ESI positive ion mode) with selected ion monitoring	NIMO	CLD-10.5; NIMO-9.25	0.3	CLD- 0.5-50	-	CLD-0.5	115]
2.	CLD (Human plasma) LC-MS	LLE	MTBE	Capcell PakUG 120 CN (50x2 mm, 5µm)	MeOH: 10mM NH4Ac buffer (70:30 v/v, pH-5 with acetic acid) Isocratic	MS/MS (ESI-negative ion mode)	Benidipine	CLD-2.06; Benidipin-2.35	0.2	CLD-0.1–20	-	CLD- 0.1	116]
3.	CLD (Human plasma)	PPT	ACN	C18 (250x4.6 mm, 5µm)	ACN: 5mM KH_2PO_4 (60:40 v/v, pH 4.5)	UV detector at 260	NIF	-	1	CLD-10-125	-	-	117]
4.	CLD (Human plasma) LC-MS/MS	PPT	ACN	Agilent Eclipse C18 column (150x4.6 mm, 5µm)	MeOH: NH_4Ac (96:4 v/v, pH 7) Isocratic	Triple quadrupole mass spectrometric detector)	NIMO	CLD-2.04; NIMO-1.8	1	CLD 0.1-10	0.02	-	118]
5.	CLD VAL (Rat plasma) HPLC	LLE	ACN	RP-18, Inertsil ODS (250x4.6 mm, 5µm)	MeOH: water (85:15 v/v, pH 3.0 with OPA)	UV detector at 254	-	CLD-6.6; VAL-4.3	1.1	CLD-1–5; VAL-8–40	CLD-0.023 VAL-0.069	CLD_ 0.078 VAL-0.235	119]
6.	CLD CHL (Human plasma) HPLC	PPT	ACN	Inertsil C18, (150x4.6 mm, 5µm)	ACN: 0.1% OPA (35:65 v/v)	PDA detector at 248	AZT	CLD-3.518; CHL-3.516; AZT-2.308	1	CLD-0.025-2.5; VAL-0.05-5.0	-	(LLOQ)CLD-0.0259 VAL 0.0482	120]
7.	CLD NEBI (Human plasma) HPLC	PPT	ACN	BDSC18 (250x4.6 mm, 5µm)	OPA 0.1%: ACN (45:55 v/v) Isocratic	PDA detector at 260	AMLO	CLD-3.943; NEBI-4.719; AMLO-5.972	1	CLD-0.20-20; NEBI-0.02-2	-	CLD-200; NEBI-20	121]

CLD-Cilnidipine; CHL-Chlorthalidone; NEBI-Nebivolol HCl; VAL-Valsartan; AZT-Azilsartan; NIF- Nifedipine; NIMO-Nimodipine; AMLO-Amlodipine; UV-Ultra violet; ACN-Acetonitrile; EtOH-Ethanol; MeOH-Methanol; KH_2PO_4-Potassium dihydrogen orthophosphate buffer; OPA-Orthophosphoric acid; Na_2HPO_4-Sodium hydrogen phosphate; NaOH-Sodium hydroxide; PDA-Photodiode array; LOD-Limit of detection; LOQ-Limit of quantitation; NH_4Ac-Ammonium acetate buffer; GAA- Glacial acetic acid; MS-Mass spectrophotometer; ESI-Electron spray ionization; LLE-Liquid liquid extraction; PPT- protein precipitation technique; methyl-t-butyl ether (MTBE)

Table 5 Chromatographic specifications and results of HPTLC method for determination of CLD alone and with other drugs in the bulk drugs and pharmaceutical dosage forms

Sr. No.	Analytes	Stationary phase	Mobile phase	Chamber saturation (min)	Scanner & Detection (nm)	Migration distance (cm)	Rf	Linearity range(ng/spot)	LOD (ng/spot)	LOQ (ng/spot)	Refs
1.	CLD	Silica gel G 60F254 plates (20x10 cm, 250µm)	Toluene: ethyl acetate (6:4 v/v)	8	TLC Scanner II at 238	8	CLD-0.6	CLD- 5-45	3	5	123]
2.	CLD, OLM (Tablet)	Silica gel G 60F254 plates (10x10 cm, 250µm)	MeOH: Toluene: Ethyl acetate: Acetic acid (2.5: 5.5: 2.0: 0.1 v/v/v/v)	15	Camag TLC Scanner IV at 254	-	CLD-0.66, OLM-0.43	CLD-100-200 OLM-200-400	CLD-23.05, OLM-39.18	CLD-69.86; OLM-118.75	124]
3.	CLD, OLM (Tablet)	Silica gel G 60F254 plates (10x10 cm, 250µm)	Toluene: MeOH: $CHCl_3$ (6: 3:2 v/v/v)	30	TLC Scanner IV at 257	7.5	CLD-0.67; OLM-0.26	CLD-200-600 OLM-400-1200	CLD-13.31; OLM-34.71	CLD-40.36; OLM-105.20	125]
4.	CLD METO (Tablet)	Silica gel F254 TLC Plates (10x10 cm, 250µm)	$CHCl_3$: Ethyl acetate: MeOH: TEA (9:2:0.5:0.5 v/v/v/v)	20	TLC scanner III at 280	7	CLD-0.58; METO-0.37	CLD- 200 - 1200; METO-1000-6000	CLD-1.19; METO-0.82	CLD-3.62; METO-2.48	126]
5.	CLD, METO (Tablet)	Silica gel G 60F254 (10x10 cm, 250µm)	Toluene: $CHCl_3$: MeOH: GAA (45:25:25:5 v/v/v/v)	30	TLC Scanner IV at 231	9	CLD-0.70; METO - 0.34	CLD-100-500; METO-500-2500	CLD-4.9360 METO-4.9360	CLD-27.182 METO-82.370	127]
6.	CLD, TELMI (Tablet)	Silica gel G 60F254 (20x20 cm, 250µm)	Toluene: MeOH: ethyl acetate (8:2:1 v/v/v)	15	TLC Scanner III at 260	9	CLD-0.51; TELMI-0.71	CLD- 200 - 1200; METO-800-4800	CLD-36.48; TELMI-188.28	CLD-110.56; TELMI-570.54	128]
7.	CLD, TELMI (Tablet)	Silica gel G 60F254 plates (10x10 cm, 250µm)	Toluene: MeOH: GAA (8: 2: 1, v/v/v)	20	TLC Scanner III at 260	9	CLD-0.62 TELMI-0.38	CLD-50-600; TELMI-200-1400	CLD-15; TELMI-97	CLD-47; TELMI-115	129]
8.	CLD, VAL (Tablet)	Silica gel G 60F254 plates (10x10 cm, 250µm)	Toluene: MeOH: ethyl acetate: GAA (8: 1:1: 0.1 v/v/v/v)	15	TLC Scanner IV at 240		CLD-0.29 VAL-0.56	CLD-1000-6000; VAL-8-48 (µg/mL)	CLD-0.00083; VAL-1.324	CLD-0.00757; VAL-3.678	130]
9.	CLD, CHL (Bulk/ Tablet)	1. NP-Silica gel G 60F254 plates (20x10 cm, 250µm) 2. RP-18 Silica gel G F254S plates	1. Toluene: ethyl acetate: MeOH (3.2:1.3: 0.5 v/v/v) 2. MeOH: water	20	TLC Scanner III at 275	8	1. CLD-0.79 CHL-0.34; 2. CLD-0.81 CHL-0.24	CLD-200-1200; CHL-250-1500 ng/band	CLD-0.32; CHL-0.46 2. CLD-3.33 CHL-14.07;	CLD-0.71; CHL-1.39 2. CLD-10.10 CHL-42.64	131]

		(10x10 cm, 200µm)	(3.2: 1.8 v/v								
10.	CLD, NEBI (Bulk/ tablet	Silica gel G 60F254 plates (10x10 cm, 250µm)	$CHCl_3$: GAA: MeOH; (8.5:1:0.5 v/v/v)	20	TLC Scanner III at 270	8	CLD-0.69; NEBI-0.29	CLD- 50-500; NEBI-100-1000	CLD-31.788; NEBI-16.395	CHL-96.328 ; NRBI-49.681	132]

NP-Normal phase; RP-Reverse phase; HPTLC: High-Performance Thin Layer Chromatography; $CHCl_3$-Chloroform; MeOH-Methanol; NIF-Nifedipine; CLD-Cilnidipine; TELMI-Telmisartan; OLM-Olmesartan medoxomil; METO-Metoprolol succinate; AMLO-Amlodipine mesylate; BF-Bisoprolol fumarate; CHL-Chlorthalidone; NEBI-Nebivolol HCl; VAL-Valsartan; AZT-Azilsartan; ATEN-Atenolol; IRB-Irbesartan; UV-Ultra violet; ACN-Acetonitrile; EtOH-Ethanol; MeOH-Methanol; KH_2PO_4-Potassium dihydrogen orthophosphate buffer; TEA-Triethylacetic acid; OPA-Orthophosphoric acid; Na_2HPO_4-Sodium hydrogen phosphate; NaOH-Sodium hydroxide; PDA-Photodiode array; LOD-Limit of detection; LOQ-Limit of quantitation; NH_4Ac-Ammonium acetate buffer; GAA- Glacial acetic acid.

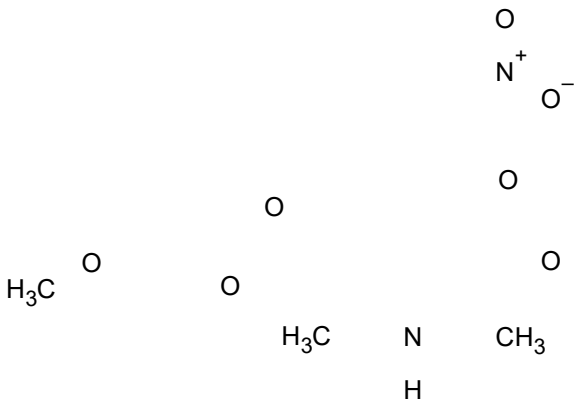


Figure 1. Chemical structure of Cilnidipine

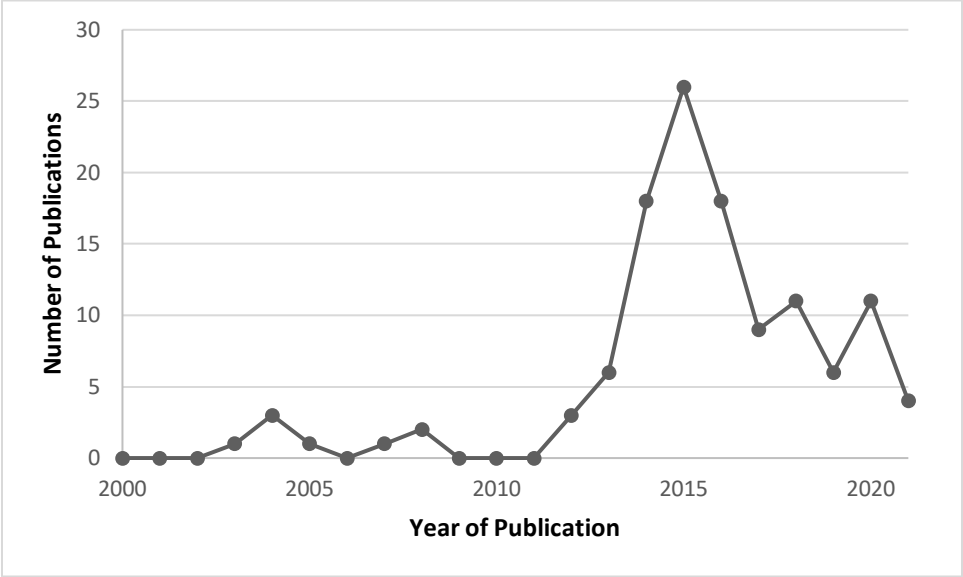


Figure 2. Chronological reported methods for estimation of Cilnidipine

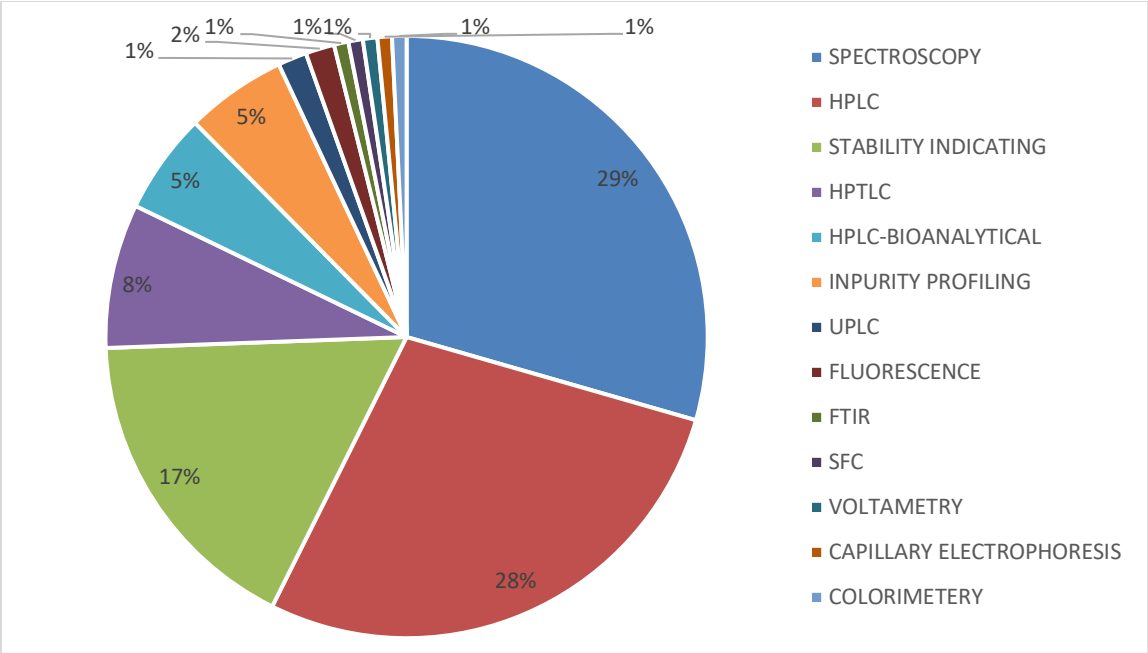


Figure 3. Various analytical methods reported for analysis of Cilnidipine

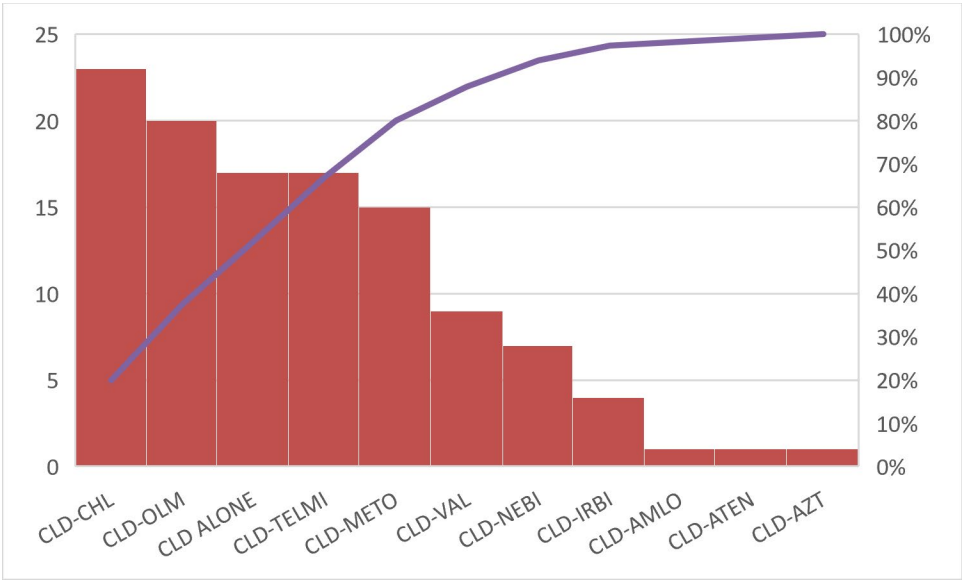


Figure 4. Reported analytical methods of Cilnidipine alone and in combinations with other drugs

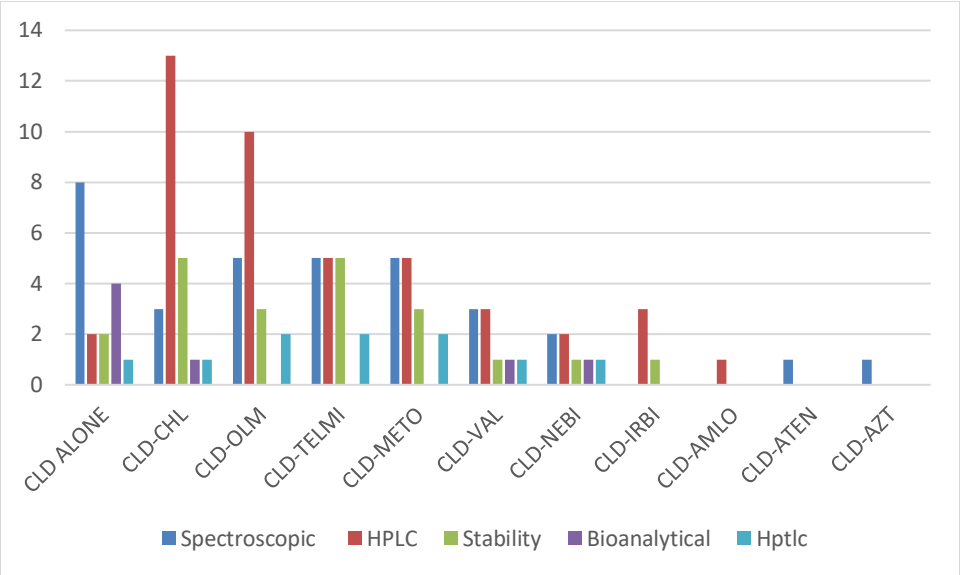


Figure 5. Distinguish estimation methods reported for various combinations of Cilnidipine.

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