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Overview of the Determination of Captopril Levels in Pharmaceutical Preparations and Biological Matrices

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Abstract
Captopril is the most commonly prescribed ACE-Inhibitor class of drugs because it is easily accessible and affordable. Therefore, to ensure drug quality, captopril levels were determined. This review article aims to provide an overview of the various analytical techniques that have been carried out in selecting the groups of captopril in both pharmaceutical dosage forms and biological matrices. Some of these analytical methods include the UV-Visible spectrophotometric method, high-performance liquid chromatography (HPLC), voltammetry, and flow injection. The data collection process in this review article is to collect research journals through trusted sites in the last ten years (2011-2021) with the search keywords "Determination of Captopril," "Analysis of Captopril on Pharmaceutical Preparations," and Analysis of Captopril on Biological Matrices." From the data that has been collected, the voltammetric method is the most widely used analytical technique in determining captopril for both pharmaceutical preparations and biological matrices in the last ten years.

Keywords: Captopril; spectrophotometric determination; HPLC; voltammetry; flow injection; pharmaceutical preparations; biological matrices

1. Introduction
Captopril is an antihypertensive and heart failure drug classified into the ACE-Inhibitor class. The mechanism of action of ACE-Inhibitors is to inhibit the conversion of angiotensin I to angiotensin II by ACE so that aldosterone decreases. This reduction in angiotensin II and aldosterone attenuates many of the effects of neurohormones that cause vasoconstriction, norepinephrine release, and sodium and water retention. ACE inhibitors can prevent bradykinin's degradation and stimulate the synthesis of other vasodilator compounds, including prostaglandin E2 [1].

Captopril is the most widely prescribed antihypertensive drug. In 2013, Tarigan conducted a study that showed the dominant use of captopril, which was 60.1% of the total prescription [2]. Other studies have also suggested that the most commonly used antihypertensive drugs ACE-Inhibitor and ARB, are captopril and valsartan. ACE-Inhibitor antihypertensives were more effective in reducing patients' urine protein levels than ARBs [3]. Therefore, to ensure the drug's quality under the dosage, the drug's active substance must be calculated. This review article will provide an overview of the analytical techniques that have been carried out in determining the levels of captopril in pharmaceutical preparations. Besides, this review article also provides information about the analytical methods that have been carried out in selecting the groups of captopril in biological matrices.

Captopril has the chemical name 1 - [(2S) -3-mercapto-2-methylpropionyl] -Lprolina with a molecular weight of 217.28. Captopril is a white or almost white crystalline powder that has a slight sulfuric odor. Captopril is soluble in water (about 160 mg / mL), methanol, and ethanol and is slightly soluble in chloroform and ethyl acetate. Captopril has a melting point of 104 ° -110 ° C [4]. The chemical structure formula of captopril can be seen in Figure 1.

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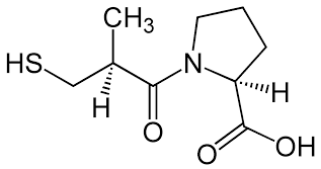

Figure 1: Chemical structure formula of captopril [4]

Based on the pharmacokinetic data obtained, captopril contains sulfhydryl groups easily bound to albumin and other plasma proteins. The drug also forms mixed disulfides with endogenous thiols (cysteine glutathione) and disulfide dimers as parent compounds [5].

In healthy subjects given intravenous captopril, the clearance and volume of captopril distribution at stable conditions were about 0.7 L/hr/kg and 0.8 L/kg, respectively. About 70 to 75% of the oral dose is absorbed, and the bioavailability of captopril is about 65%. Peak blood concentration reaches approximately 45 to 60 minutes after oral administration. In various doses of oral (10 to 150 mg) and intravenous (2.5 to 10 mg), captopril has linear kinetics in healthy volunteers [5].

The determination of captopril in pharmaceutical preparations has been carried out by various methods such as titrimetric, high-performance liquid chromatography, kinetic spectrophotometric, and reverse-phase high-performance liquid chromatography (RP - HPLC) with ultra-violet (UV) [6]. Many analytical methods have been developed for the quantitative determination of captopril levels, summarized from the last ten years' data (2011-2021).

2. Method of collecting data

The data in this review article was collected from sources and literature from pharmaceutical books and online research journals on the internet through trusted sites such as Google Scholar, NCBI, Researchgate, and ScienceDirect with the search keywords "Determination of Captopril," "Analysis of Captopril on Pharmaceutical Preparations" and "Captopril Analysis on Biological Matrices." The primary data were obtained from journals with inclusion criteria, journals published from 2011 to 2021, discussing the analytical method to determine the level of captopril drug used during the last ten years.

3. Method of analysis of captopril

3.1 UV-Vis Spectrophotometric Analysis

Several UV-Vis spectrophotometric methods have been carried out in determining the quantitative level of captopril in pharmaceutical preparations (Table 1).

Table 1: Captopril analysis using UV-Vis spectrophotometry

No.	Samples	Solvent	Wavelength	Range of Concentration	Ref
1.	Tablet (pharmaceutical preparation)	Distilled water	400-800 nm λ_{max} : 600,5 nm	20-60 µg/mL	[6]
2	Tablet (pharmaceutical preparation)	NaOH 1N	200-400 nm $\lambda_{max:}$ 265 nm	10 µg/mL	[7]
3	Tablet (pharmaceutical preparation)	Method I: Distilled water and some reagents (Bromo Pyrogallol red, 1,10	460-700 nm λ_{max}: 635 nm	2-10 µg/mL	[8]

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		phenanthroline, Gelatin solution, Silver nitrate solution, and Ammonium acetate 20%) Method II: Distilled water and some reagents (Copper quinoline-8-olate (CuQ2) and buffer acetate)	340-500 nm λ_{max}: 410 nm	30-90 µg/mL	

This study develops and validates the captopril tablet analysis method with the absorbance method and the broad method under the curve with UV-Vis spectrophotometry. The principle of this research is the calculation of the absorbance and area under the curve obtained from the measurement of the analytical solution using a UV-Vis spectrophotometer and distilled water as a solvent with several reagents. Reagents are used to oxidize captopril compounds with a thiol group (-SH) in their structure. Captopril linearity was obtained in the concentration range of 20-60 µg/mL. The value of the correlation coefficient by the absorbance method and the area under the curve method are 0.9998 and 0.9994, respectively. The results showed that the sample rate obtained by the absorbance method and the area under the curve method were 104.55% ± 0.433 and 92.22% ± 0.351 for patent tablets; 93.42% ± 1.306 and 91.09% ± 0.093 for generic tablets. The mean percent recovery obtained by the absorbance method and the curve area method were 95.62% ± 14.444 and 101.55% ± 15.989 for patent tablets; 95.33% ± 14,278 and 100.96% ± 15,655 for generic tablets [6].

This research is a simple, fast, and accurate analytical method developed to estimate captopril in bulk dosage forms and tablets using a UV spectrophotometer. It validated with various parameters such as linearity, accuracy, system precision, intra-day precision, inter-day precision. medium precision/roughness, robustness, detection limit (LOD), and quantification limitation (LOQ) as per the ICH Guidelines. 1N sodium hydroxide (NaOH) was chosen as the solvent. A 10 µg / ml captopril solution was prepared and scanned in the UV region from the 265 nm spectrum selected as the analysis wavelength. Optical characteristics such as maximum absorption (nm), Beer's legal limit (2-12 µg/mL), and correlation coefficient (r = 0.999566813) were calculated for this method. The results obtained in the recovery study will show that there is no interference from the excipient used in the formulation. Thus it is proposed that this method can be applied successfully for captopril estimation in pure dosage form and tablets [7].

This research develops two spectrophotometric methods based on the combination of the redox-ligand exchange reaction to determine captopril and penicillamine in its pure form and its dosage form. The first method is based on attenuating the ternary complex's absorbance: silver (I) - bromopyrogallol red - phenanthroline in a pH6-8 buffer solution. This method has a concentration range of 2-10 µg mL^{-1} and 0.5-1.75 µg mL^{-1} for captopril and penicillamine, respectively, and detection limits of 7.1×10^{-2} and 5.7×10^{-2}. µg mL^{-1} for captopril and penicillamine, respectively. The second method is based on decreasing the absorbance of the chloroformic copper (II) solution - chelate oxin when shaken with the drug solution in pH 8 buffer media. The drug is determined at concentrations of 30-90 µg mL^{-1} and 30 - 100 µg mL^{-1}, respectively, for captopril, penicillamine, and detection limits of 0.94 and 1.76 µg mL^{-1}, respectively, for captopril and penicillamine. The proposed method is applied in the analysis of both compounds in pharmaceutical preparations, and the results are better than the reference spectrophotometric method regarding accuracy and precision [8].

3.2 High-Performance Liquid Chromatography Analysis

The high-performance liquid chromatography method that has been widely used as a quantitative method for analyzing captopril levels is as follows (Table 2).

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Table 2: Captopril analysis using High-Performance Liquid Chromatography Analysis

No.	Sample	Column	Mobile phase	Detector	Chromatographic Condition	Ref
1	Tablet (pharmaceutical preparation) and human serum	Column Purospher Start C18 (250 mm x 4.6 mm, 5 µm) dan Hypersil ODS C18 (150 × 4.6mm, 5 micron)	Methanol: water (70:30 v/v)	UV detector (225 nm)	Flow rate: 1,0 mL/min	[9]
2	Human serum (biological matrices)	column C18 (5 µm, 150 mm x 4.6 mm)	Methanol:buffer (3:1)	UV detector (290 nm)		[10]
3	Urine (biological matrices)	Reverse phase Hypersil ODS column (100 mm × 4.6 mm)	MeOH:buffer fosfat (15:85)	UV detector (285 nm)	Flow rate: 0,5 mL/min	[11]
4	Tablet (pharmaceutical preparation)	Fused-Core® column Ascentis Express C18 (4.6 × 150 mm)	Methanol: 0.1% trifluoroacetic acid solution (40/60, v / v)	UV detector (220 nm)	Flow rate 1,2 mL/min	[12]
5	Tablet (pharmaceutical preparation)	Phenomenex® Luna 5 µm (C18)	buffer fosfat: asetonitril (70:30)	Full scan multi-channel ESA coulometric detector	Flow rate 1.0 mL/min	[13]
6	Tablet (pharmaceutical preparation)	Phenomenex Synergi Fusion 4 µm C18 stainless steel column (250 mm × 4.6 mm ID)	buffer methanol/trietilamonium (TEA) fosfat (pH 3; 0,05 mol/L) 75:25 (v/v)	UV detector (300 nm)	Flow rate 0,6 mL/min	[14]
7	Tablet (pharmaceutical preparation)	Xterra RP8 column 250 × 4.6 mm, particle size 5 µm	26 mM mixture of pentane-1-sulfonic acid sodium salt in 30 mM potassium dihydrogen	UV detector 210 nm	Flow rate 2.0 mL/min	[15]

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			phosphate (pH 2.8, adjusted for phosphoric acid): methanol: acetonitrile (6: 2: 2)			
8	Human plasm	Column C18 (250 × 4.6 m, with a particle size of 10 µ)	acetonitrile: water (60:40 v / v)	UV detector (225 nm)	Not available	[16]
9	Human serum (biological matrices)	Nucleosil C18 column (250 mm x 4.6 mm, particle size 5 µ)	Acetonitrile: water (50:50 v/v) plus a supporting electrolyte (NaNO3)	Electrogenerated Chemilumine scence	1 mL/min	[17]

The isocratic reverse-phase high-performance liquid chromatography (RP-HPLC) method has been developed for the simultaneous determination of captopril and diuretics (furosemide and hydrochlorothiazide) in API, dosage and serum formulations. Chromatographic separation was achieved on Purospher Start C18 (250 mm x 4.6 mm, 5 µm). Hypersil ODS C18 (150 × 4.6 mm, 5 microns) columns using a mobile phase, methanol: water (70:30 v / v) adjusted to pH 3 .0 through 85% phosphoric acid has a flow rate of 1.0 mL min $^{-1}$ at room temperature with the detector set at 225 nm. The calibration curve is linear in the range 5-25 µg mL^{-1} with a correlation coefficient of ± 0.999. LOD and LOQ were in the range 0.4-2.3 µg mL^{-1}. Intra- and inter-run precision and yield accuracy of 98.0 to 102% [9].

In this study, a simple, sensitive, and reliable HPLC- UV method that applies a rapid sample preparation technique for the determination of captopril in human plasma has been developed and validated. This method is based on the pre-column derivatization of captopril and 2-propene-1-thiol (internal standard) with the new reagent 2-naphthyl propiolate. Sample cleaning, derivatization, and extraction were carried out in two steps, totaling less than 30 minutes. The extract was chromatographed on column C18 (5 µm, 150 mm x 4.6 mm i.d.). The mobile phase consists of methanol (75%, v / v) and phosphate buffer (25%, pH = 8, 0.01 M). UV detection was carried out at 290 nm. To get the best reaction results, factors that can influence the derivatization process, including the concentration of derivatization reagents, the pH of the sample solution, and the temperature, are studied in detail and optimized using the Box - Behnken response surface methodology. Under optimal conditions, the average extraction yield of captopril and internal standards was> 86%. The lower limit of quantification (LLOQ) achieved was 3 ng / mL; The test shows a linear dynamic range of 3–2000 ng / mL with a correlation coefficient (r2) ≥of 0.99. Satisfactory precision throughout the calibration range with RSD 5.9-12.4% (accuracy: from 97.5% to 93.6%) and 6.4-12.8% (accuracy: from 97.3% to 95, 2%) for intra and inter-test, respectively. The method's stability was confirmed in a series of experiments, including freeze-thaw, short and long-term stability testing. Finally, the developed method was successfully applied to the bioequivalence study of captopril given as a single oral dose (50 mg) to 12 healthy male volunteers [10].

This study reports a new liquid chromatography (HPLC) method to determine the antihypertensive drug captopril (CAP) in human urine. After separation from the sample matrix in the reverse phase HPLC column, CAP reacted with the thiol ethyl-propiolate (EP) selective reagent in the post-column configuration, and the formed thioacrylate derivative was detected at 285 nm. Automatic 4-fold preconcentration of analytes before analysis was achieved by a solid-phase extraction (SPE) step using a sequential injection (SI) manifold. The Oasis HLB SPE cartridge offers quantitative recovery and effective sample cleaning by applying a simple SPE protocol. The detection and quantitation limits were 10 µgL^{-1} and 35 µgL^{-1}, respectively. The percentage

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recovery for the analysis of human urine samples ranged between 90 and 96% and 95 and 104%, respectively, using matrix-appropriate calibration curves and water. [11].

This study aims to develop a more straightforward, sensitive, accurate, and less expensive analytical method for determining captopril in pharmaceuticals by high-performance liquid chromatography. Captopril chromatography analysis was performed on liquid chromatography of the Agilent 1290 Infinity II LC System. Chromatography in pharmaceutical and single-drug dosage forms in combination with hydrochlorothiazide without prior separation. A satisfactory resolution was achieved using Fused-Core® technology Ascentis Express C18 column (4.6 × 150 mm) and a mobile phase consisting of methanol and 0.1% trifluoroacetic acid solution (40/60, v / v) at the flow rate is 1.2 mL/min and a detection wavelength of 220 nm. Ascentis Column express, based on Fused-core column technology, delivers more than twice the speed and efficiency of traditional columns at half the back pressure of sub-2-µm columns. The retention time of captopril was 1.345 minutes. The validation of this method is based on the ICH and USP guidelines. The results obtained in this research work clearly show that the assay is rapid, sensitive, and successfully applied to the determination of both drugs in the pharmaceutical dosage form without tablet excipients' interference: Captopril, Hydrochlorothiazide, Ultra high-performance liquid chromatography, Pharmaceutical dosage forms [12].

In this research, an accurate, sensitive, and specific high-performance liquid chromatography-detection electrochemical (HPLC-ECD) method has been developed and validated to determine captopril. Separation was achieved using a Phenomenex® Luna 5 µm (C18) column and a mobile phase consisting of a phosphate buffer (adjusted to pH 3.0): acetonitrile with a ratio of 70:30 (v / v). Detection was performed using a full-scan multi-channel ESA coulometric detector in "oxidative screen" mode with the upstream electrode (E1) set at +600 mV and the downstream electrode (analytical) (E2) set at +950 mV. In comparison, the guard cell potential was maintained at +1050 mV. The system was found to produce sharp and well-resolved peaks for CPT and CYC with retention times of 3.08 and 7.56 minutes, respectively. Linear regression analysis for the calibration curve shows a good linear relationship with a regression coefficient of 0.978 over a 2-70 µg / mL concentration range. The linear regression equation is y = 0.0131x + 0.0275. The detection limits (LOD) and quantitation (LOQ) were found to be 2.27 and 0.6 µg / mL, respectively. This method is used to analyze CPT in tablets. The wide range of linearity, accuracy, sensitivity, short retention time, and mobile phase composition suggests that this method is better for calculating CPT than the pharmacopoeial method [13].

In this study, 1,4-anthraquinone (ANQ) was proposed as a new pre-column reagent for high-performance liquid chromatography (HPLC) for the determination of N-acetylcysteine (NAC) and captopril (CAP) in pharmaceutical formulations. The derivatization reaction was carried out at room temperature: NAC at pH 8 for 1 minute, while CAP at pH 7.5 for 20 minutes. Both reactions achieve completion at a reagent to thiol molar ratio of about 2.5. The1H NMR and IR characterized the synthesized derivatives chromatographic separation was performed on a C18 Phenomenex Synergi Fusion 4 µm (250 mm × 4.6 mm ID) stainless steel column with detection at λ = 300 nm. The mobile phase consists of a buffer of methanol / triethylammonium (TEA) phosphate (pH 3; 0.05 mol / L) 75:25 (v / v) with a flow rate of 0.4 mL / minute for NAC and 88:12 (v / v))), with a flow rate of 0.6 mL / min for CAP. The validation parameters (linearity, sensitivity, accuracy, precision, specificity, and stability) are very satisfactory. A linear response was observed (coefficient of determination ≥0.9996). The detection limits were about 8 and 18 ng / mL for NAC and CAP, respectively. The intra-day precision (relative standard deviation, RSD) was ≤1.58%, for the ratio of the internal standardized peak area (IS) of thiol and ≤0.33%, for thiol retention time and IS (tR), with no significant difference between intra- and inter-intra. Data of the day. A satisfactory (99.50%) thiol recovery study with RSD. ≤0.56%. The results highlighted the high method sensitivity, reactivity, and excellent selectivity of the thiol function reagents. The method developed is suitable for quality control of both thiols in commercial products. The method can be applied in any analytical laboratory which does not require sophisticated instrumentation [14].

A validated HPLC method demonstrating stability has been developed for the simultaneous determination of Captopril (CP), Indapamide (ID), and related compounds in tablets using a 250 × 4.6 mm RP8 Xterra column, 5 µm particle size with UV detection at 210 nm. Isocratic elution was carried out using a mobile phase consisting of a mixture of 26 mM sodium salt of pentane-1-sulfonic acid in 30 mM potassium dihydrogen phosphate (pH 2.8, adjusted for phosphoric acid): methanol: acetonitrile (6: 2: 2) v / v / v. The method

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described was linear in the range 0.25–150 µg / mL with (r = 0.9999) for CP and 0.2–100 µg / mL with (r = 0.9999) for ID. The stability of CP and ID was studied under accelerated acid, alkaline, and oxidative conditions. The proposed method was used to investigate the kinetics of the acid and base degradation processes of CP and ID at different temperatures. The pseudo-first-order rate constants, half-lives, and activation energies were calculated. The pH level profile of CP and ID degradation in the Britton-Robinson buffer solution in the pH range 1.8-12.0 was studied. The method developed is validated by taking into account linearity, accuracy, precision, selectivity, and durability. The forced degradation study proved its stability showing the strength of the method developed [15].

This study proposes a high-performance liquid chromatography (HPLC) - UV method for the simultaneous determination of lisinopril, enalapril, captopril, and fosinopril in human plasma. Good analyte separation was achieved by RP-HPLC gradient with the mobile phase prepared as acetonitrile: water (60:40 v / v) adjusted to pH 3.0 by orthophosphoric acid. Lisinopril, enalapril, captopril, and fosinopril were eluted from Purospher STAR RP- and Hypersil ODS columns in 1.8, 2.9, 3.2, and 5.4 minutes, respectively. A good linear relationship was observed for all analytes (R2 was higher than 0.995). The intra- and inter-day precision and accuracy results were 98.0 to 102%. The recommended application of the procedure was successfully applied to the determination of this compound in active pharmaceutical preparations, dosage formulations, and human serum with high cure rates, good accuracy, and precision (no interference except), and this method can be applied to routine clinical analysis [16].

Captopril shows electrogenerated chemiluminescence (ECL) in NaNO3 solution when a constant current is applied. Based on these observations, the direct ECL method coupled with high-performance liquid chromatography (HPLC) separation was developed to determine captopril in human serum. Factors affecting ECL emissions were investigated. Under optimal conditions, the ECL intensity has a linear relationship with the captopril concentration in the range 4.0×10^{-6} –2.0×10^{-3} g mL^{-1}, and the detection limit is 2×10^{-6} g mL^{-1} (S / N = 3). Compared with electrically generated chemiluminescence experiments, the method developed does not require other fluorescence additives [17].

3.3 Voltammetry analysis

Manganese supported on an organo-modified SiO_2/Al_2O_3 skeleton is a novel mediator for captopril selective voltammetric determination (CAP) in actual samples such as drug urine. The redox response and electrocatalytic activity of the sensors were studied using the cyclic voltammetry (CV) method, the double-step potential chronoamperometry (CA), and the linear swept voltammetry (LSV) method. Under optimal conditions (pH 6.0), the anodic peak current of LSV shows a linear relationship to the concentration of CAP in the range 3.0×10^{-7}–300×10^{-4} mol/dm^3, with a detection limit of 9.0×10^{-8} mol/dm^3 [18].

Electrocatalytic oxidation of captopril (CAP) has been studied by ZnO/CNT (N-HPDB/ZnO/CNTs/CPE) nanocomposite carbon paste electrodes modified by N-(4-hydroxyphenyl)-3,5-dinitrobenzamide (N-HPDB). Cyclic voltammetry (CV), electrochemical impedance spectroscopy (EIS), and chronoamperometry were used to investigate the suitability of N-HPDB as a mediator for electrocatalytic oxidation of CAP in aqueous solutions. The catalytic reaction rate constant, k_h, was calculated (2.28×10^3 $M^{-1}s^{-1}$) using chronoamperometry. The peak square wave voltammetric current (SWV) from the electrodes increases linearly with the corresponding CAP concentration in the range 5.0×10^{-8} M - 8.0×10^{-4} M with a detection limit of 1.0×10^{-8} M [19].

A new catechol-derived compound, N-(3,4-dihydroxyphenethyl) -3,5-dinitrobenzamide, was synthesized and used to build modified carbon nanotube paste electrodes. The electro-oxidation of captopril on the modified electrode surface was studied using cyclic voltammetry, chronoamperometry, and electrochemical impedance spectroscopy. Under optimal conditions, the captopril differential pulse voltammetric current increases linearly with the captopril concentration in the range 6.4×10^{-8} to 3.2×10^{-48} mol L^{-1}. The detection limit is 3.4×10^{-8} mol L^{-1} captopril. Diffusion coefficients and kinetic parameters (such as electron transfer coefficients and heterogeneous rate constants) for the captopril oxidation are also determined. The % RSD for 0.5 and 10.0 µmol L^{-1} captopril were 2.1% and 1.6%, respectively. The proposed sensor was successfully applied for captopril determination in urine samples and human patients' tablets [20].

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This study aims to synthesize gold nanoparticles/biphenol-biphenoquinone (AuNPs - BOH - BQ). The study also aims to study its application as a heterogeneous electron transfer mediator to modify carbon paste electrodes (CPE/Au NPs - BOH - BQ) for ultra-trace determination of captopril (CP). The characterization results showed that the Au NPs were well spread with sizes in the range of 8.0-10.5 nm. Under the optimized conditions, the linear calibration plots from 1 to 5×10^4 nM (two segments, 1-150 nM and 0.15-50.0 µM) and the detection limit is calculated to be 0.4 AnM (S / N = 3) . Finally, the suggested sensors show a stable and reliable CP response in CP pharmaceutical tablets and urine samples [21].

Chlorpromazine is used as a homogeneous electrocatalyst in captopril oxidation. The anodic peak currents of chlorpromazine were substantially increased in the presence of low captopril concentrations (pH 4). Cyclic voltammetry and chronoamperometry are used to study the kinetics of the catalytic electron transfer reaction. The electron transfer coefficient (α) values and the catalytic rate constant (k_{cat}) was estimated at 0.34 and respectively. Linear swept voltammetry was used for the determination of captopril in the presence of chlorpromazine. The linear calibration curve was obtained in the range of captopril concentrations of 10.0–300.0 µM, with a detection limit of 3.65 µM. The relative standard deviation (RSD%) for five repeat captopril measurements (100 µM) was 1.96%. The captopril determination method was applied in pharmaceutical formulations and blood serum samples with satisfactory results [22].

In this research, a modified carbon paste electrode with carbon nanotubes and benzoylferrocene (BF) was made. The electrochemical studies of the modified electrodes and their efficiency for the electrocatalytic oxidation of captopril (CAP) have been described. The electrodes were used to study electrocatalytic oxidation of CAP using cyclic voltammetry (CV), chronoamperometry (CHA), and square wave voltammetry (SWV) as diagnostic techniques. It found that oxidation of CAP on the surface of the modified electrodes occurs at a potential of about 85 mV, which is less positive than that of the unmodified CPE. SWV represents a linear dynamic range from 1.0×10^{-7} to 3.5×10^{-4} M and a detection limit of 3.0×10^{-8} M for CAP. Finally, a modified electrode was used for CAP determination in CAP tablets and urine samples [23].

New modified carbon paste electrode (CPE) based on a new compound synthesized from (E) -3 - ((2- (2,4-dinitrophenyl) hydrazone) methyl) benzene-1,2-diol (DHB) and carbon nanotubes (CNT) prepared. Initially, the redox properties of the modified electrodes were studied by cyclic voltammetry (CV). Then the modified electrode was used as an electrochemical sensor for captopril oxidation (CAP). Below optimum pH 7.0, the overpotential of CAP oxidation is reduced by about 500 mV at the modified electrode than for the unmodified CPE. Differential pulse voltammetry (DPV) CAP on the electrochemical sensor shows two linear dynamic ranges with a detection limit (3σ) of 70 nM. Also, DPV is used for selective and simultaneous determination of CAP, acetaminophen (AC), and tryptophan (Trp) by electrochemical sensors. The proposed electrochemical sensor was used to determine these substances in real samples [24]

In this study, the synthesis and application of NiO (NiO / NPS) and (9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboximide)-4-ethylbenzene-1,2-diol (DED) nanoparticles as High sensitive sensor for captopril voltammetry (CAP) determination using carbon paste electrodes. The synthesized nanoparticles were characterized by different methods such as TEM and XRD. Electrochemical oxidation of CAP on new NiO / NP carbon paste electrodes (9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboximide)-4-ethylbenzene-1, 2-diol carbon paste electrode (NiO/NPS/DED/CPE) has been carefully studied. Under the best selected experimental conditions, a calibration curve for linear CAP in the concentration range from 0.035 to 550 µmol L-1 and a detection limit of 0.007 µmol L-1 was obtained. The effect of pH and potential confounders on CAP determination was studied. Electrochemical impedance spectroscopy (EIS) is used to study the charge transfer properties at the electrode-solution interface. Finally, the sensor is examined as a new, selective, simple, and precise electrochemical sensor for determining CAP in real samples, such as drugs and urine [25].

Carbon electrodes modified with the ionic liquid octylpyridinium hexafluorophosphate and copper hydroxide nanoparticles were used in the electrochemical test for the simultaneous determination of captopril (CPT) and hydrochlorothiazide (HCT). The electrodes showed two well-defined oxidation peaks for CPT (at 0.22 V) and HCT (at 0.73 V, both vs. Ag/AgCl) at pH 8.0 using square wave voltammetry. The calibration plots were linear in the concentration ranges of 0.7-70 µM (CPT) and 3-600 µM (HCT), with detection limits of 12 and 60 nM. The electrodes were repeatedly applied to determine CPT and HCT simultaneously in pharmaceutical formulations without showing any fouling. Graphic abstract The application of a liquid ionic carbon (CILE)

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electrode modified with Cu (OH) 2 ($Cu(OH)_2$NP/CILE) nanoparticles for the simultaneous determination of captopril (CPT) and hydrochlorothiazide (HCT) in a pharmaceutical formulation is presented [26].
The electrocatalytic oxidation of captopril (CAP) was studied with a modified carbon nanotube paste electrode in the presence of isoproterenol (ISPT) using cyclic voltammetry (CV) chronoamperometry and square wave voltammetry (SWV). The catalytic rate constant (k) and the electron transfer coefficient (α) for CAP are calculated. The mechanism of the electrochemical behavior of CA on the modified electrode surface was analyzed by various electrochemical methods in the presence of a mediator. The prepared modified electrode exhibits a high sensitivity voltammetric response for CAP, making it particularly suitable for detecting CAP at trace levels. Under the optimized conditions, the peak currents were linear with the concentration CAP over a concentration range of 0.3 to 90 µmol L^{-1} using SWV. The detection limit is 0.1 µmol L^{-1}. The proposed method was successfully applied to determine CAP in urine samples, tablets, and urine of patients [27].

3.4 Flow Injection system analysis
This paper describes a new technique for captopril determination in pharmaceutical preparations implemented using multicommuted flow analysis. The analytical procedure is based on the reaction between hypochlorite and captopril. The remaining hypochlorite oxidized luminol which produces electromagnetic radiation, is detected using a homemade luminometer. According to the authors, this is the first time this reaction has been exploited for captopril determination in a pharmaceutical product, offering a clean analytical procedure with minimal reagent use. The effectiveness of the proposed procedure is confirmed by analyzing a set of pharmaceutical formulations. The application of the paired t-test showed that there were no significant differences between the data sets at the 95% confidence level. Useful features of the new analytical procedure include linear response to captopril concentrations in the range 20.0–150.0 µmol / L (r = 0.997), detection limit (3σ) 2.0 µmol / L, sample throughput 164 determinations per hour, reagent consumption of 9 µg luminol and 42 µg of hypochlorite per determination and 0.63 mL of waste generation. A relative standard deviation of 1% (n = 6) for the standard solution containing 80 µmol / L captopril was also obtained [28].
In this study, a simple, versatile, and automatic analytical methodology has been proposed for the chemiluminometric determination of captopril - an inhibitor of the angiotensin II converting enzyme (ACE) - in pharmaceutical preparations. The method developed was based on the increased chemiluminescence emission of tris (2,2'-bipyridyl) ruthenium (II) by captopril. The system developed uses three micro solenoid pumps as the only active component of the flow type. It ensures insertion, propulsion, and passage of all solutions. The solenoid micro-pumps automatic actuation provides an analytical flow system that is easy to program, operate, and control, demonstrating high versatility, efficiency, and compactness at low cost. Under optimized experimental conditions, the proposed method allows the determination of captopril for concentrations between 2×10^{-3} and 1.5×10^{-1} mmol L^{-1} (r = 0.9996, n = 6) and a sampling frequency of about 58 determinations per hour, yielding 620 µL of waste per determination. The results obtained for the pharmaceutical formulations were statistically comparable to those provided by the reference procedure, with a relative deviation of between -2.32 and 1.39%. The possible mechanisms of chemiluminescence reactions are also discussed in this work [29].
A new flow injection procedure for the determination of N-acetylcysteine and captopril in pharmaceutical formulations is proposed. The developed flow procedure is based on the oxidation of the analyte by Fe (III) in an acidic medium and the subsequent reaction of the resulting Fe (II) with excess hexacyanoferrate (III) to produce soluble Prussian blue (KFe [Fe (CN) 6]) measured at 700 nm. Detection limits of 1.0×10^{-5} mol L^{-1} and 3.0×10^{-5} mol L^{-1} were found for N-acetylcysteine and captopril. The sample throughput was 70 h^{-1} for both analytes, and the results obtained correspond to the 95% confidence level with those obtained using the reference method [30].

4. Conclusion
Overall, various analytical methods have been carried out and developed to determine captopril in both pharmaceutical dosage form and biological matrix from 2011 to 2021. Spectrophotometry, HPLC, voltammetry, and flow injection are precise, accurate, and exact methods in determining captopril. From the

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data that has been obtained, the methods used to determine levels in pharmaceutical preparations are UV-Vis spectrophotometry, HPLC, voltammetry, and flow injection spectrophotometric methods. The methods used to assess captopril levels in the biological matrix are voltammetry and HPLC. Voltammetry is the method most widely used in determining the levels of pharmaceutical preparations and biological matrices because it is the easiest method to modify and develop so that it advances to more specific, sensitive, accurate, and efficient analytical methods.

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A Brief Author Biography

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