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Review Article

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COMPREHENSIVE CONTEMPLATIONS FOR ADVANCED EXPLANATORY STRATEGIES: LISINOPRIL AND HYDROCHLOROTHIAZIDE

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ABSTRACT

The most used combination in the treatment of hypertension is hydrochlorothiazide and lisinopril. For efficacy and safety in treating hypertension, precise measurement of lisinopril (LIS) and hydrochlorothiazide (HCTZ) in pharmaceutical formulations is required. Different analytical methods are investigated in this research for their simultaneous estimation, such as spectroscopic (UV-Vis), fluorimetric, and chromatographic (HPLC, RP-HPLC, and HPTLC) methods. For everyday analysis, more affordable UV-Vis spectrophotometry is a better choice, although RP-HPLC is the best method due to its high sensitivity and precision. The greater sensitivity of fluorimetric methods makes them useful for the determination of trace levels of drugs. Green analytical methods and LC-MS are future opportunities that may enhance pharmaceutical quality control and provide accurate and long-term medication analysis.

KEYWORDS

- Lisinopril
- Hydrochlorothiazide
- RP-HPLC
- UV- spectrophotometry
- HPTLC
- Fluorimetry.

INTRODUCTION

Most of the significant high blood pressure diseases of the heart are included under the category of hypertensive heart disease. Even though the "hypertensive heart disease" term has many different meanings in medical literature, the term is applied most generally in the Worldwide Classification of Diseases (ICD) scoring systems of classification.[1] With direct or implicit links between hypertension and heart disease on the death certificate, cardiac complications, and heart failure are part of the definition. There were 630,000 deaths in 1990 from hypertensive heart disease and 1.07 million deaths in 2013.[2,3,4]

Antihypertensive drugs are a category of medications used to manage high blood pressure. They come in various forms and work through different mechanisms to help lower blood pressure. Some medications help the body get rid of excess fluid and salt, while others work by relaxing the blood vessels or slowing the heart rate. The effectiveness and side effects of these medications can vary from person to person, so some individuals may need to take multiple antihypertensive drugs to achieve their blood pressure goals.[5]

One fixed-dose combination drug for treating hypertension is lisinopril and hydrochlorothiazide, commonly known by various brand names, including Zestoretic. This medication combines the ACE inhibitor lisinopril with the diuretic hydrochlorothiazide, and it is typically prescribed when a patient responds well to each component individually.

Besides its use in managing acute myocardial infarction (heart attack), lisinopril is frequently prescribed for high blood pressure, congestive heart failure, and diabetic nephropathy. As part of the ACE inhibitor class, lisinopril is effective in treating cardiovascular diseases and hypertension. When used together, lisinopril and hydrochlorothiazide help control high blood pressure.

Lisinopril works by reducing certain substances that narrow blood vessels, thereby improving blood flow.[6]

DRUG PROFILE

a) Lisinopril

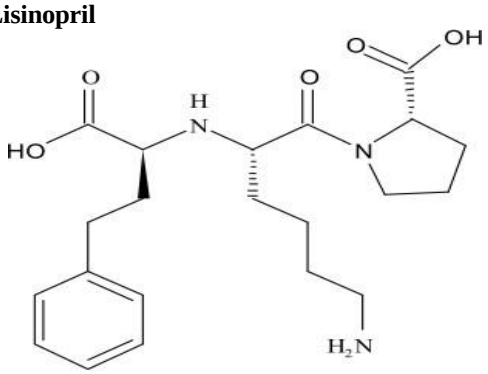

Fig: 1 Lisinopril.

IUPAC Name: (S)-1-[N2-[(S-1- Carboxy-3-phenylpropyl]-l-lysyl-l-proline dihydrate

Molecular Formula: $C_{21}H_{31}N_3O_5 \cdot 2H_2O$

Molar Mass: 405.488 g/mol

Melting Point: 160°C

pKa: 3.85

Bioavailability: 6-60%

Drug Category: ACE (angiotensin-converting enzymes) inhibitors

Solubility: Soluble in Water and Methanol.

Mechanism of Action: Lisinopril is an ACE inhibitor that helps lower blood pressure by preventing the conversion of angiotensin I to angiotensin II, which is a substance that narrows blood vessels. By relaxing and widening the blood vessels, it reduces vascular resistance and lowers blood pressure. Additionally, Lisinopril decreases the secretion of aldosterone, which aids in the excretion of sodium and water, making it effective for managing hypertension and heart failure. It also offers protective benefits for the kidneys in patients with diabetes.

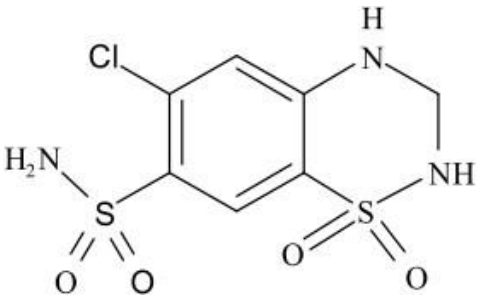

Fig:2 Hydrochlorothiazide.

IUPAC Name: 3,4-dihydro-2H-1,2,4-benzothiadiazole 1,1-dioxide

Molecular Formula: $C_7H_8ClN_3O_4S_2$

Bioavailability: 65-75% **Molar Mass:** 297.741 g/mol **pKa value:** 7.7 & 9.2

Drug Category: Thiazide-type diuretic

Solubility: Soluble in Water, Methanol, Sodium Hydroxide, n-butylamine, dimethylformamide.

Mechanism of Action: Hydrochlorothiazide is a thiazide diuretic that is commonly prescribed to manage high blood pressure and reduce edema. It works by blocking the sodium chloride symporter in the distal convoluted tubule of the kidneys. This action decreases the reabsorption of sodium and chloride, which results in increased excretion of these ions along with water in the urine. The resulting diuresis helps to lower blood volume, thereby reducing blood pressure. Moreover, hydrochlorothiazide also leads to the loss of potassium and bicarbonate, which adds to its diuretic effects. This decrease in blood volume and vascular resistance is beneficial for controlling hypertension and alleviating fluid retention in conditions such as heart failure and edema.

ANALYTICAL METHODS

Chromatography is a technique where the different components of a mixture are separated using an adsorbent column in a flowing system, as described in Tswett's early works from 1906. Since Tswett's time, chromatography has evolved considerably and now includes various modifications to the basic separation process. Consequently, chromatography encompasses a wide range of techniques, many of which have distinct names.[7]

a) Hydrochlorothiazide

Table 1: Chromatographic method for simultaneous estimation of Hydrochlorothiazide and Lisinopril.

SI. No	Title	Method	Column	Mobile phase [M.P], Flow rate [F.R] & Injection Volume [I.V]	Retention time [RT] & Wavelength [W]
1	Mohammed NS et al 2016[8]	RP-HPLC	C_{18}Inertsil ODS-3 (4.6 × 250 mm, 5 μm) and C_{18}Zorbax Eclipse Plus (4.6 × 250 mm, 5 μm)	**MP:** acetonitrile: w ater [50:50 (v/v)] **FR:** 1ml/min **IV:** 20 µL	**RT:** 11.041 minutes **W:** 272 nm
2	Bhagwate S et al., 2013 Feb	HPLC	Column Thermo Hypersil	**MP:** Methanol: Buffer pH-	**RT:** 11.041

	27[9]		ODS 5 µ C18 (250 x 4.6mm)	3.2 (60:40 v/v) **FR:** 1ml/min **IV:** 20 µL	minutes **W:** 270nm
3	Raju VB et al., 2012[10]	HPLC	Analytical column Spherisorb RP–18, ODS 2,	**MP:** Phosphate buffer and methanol in the ratio of 35:65v/v. **FR::** 0.8 ml/min **IV:** 20 µL	**W:** 215nm
4.	Tzvetkova D et al., 2005[11]	HPLC	Column SpherisorbR P – 18, ODS 2, 4.6 mm / 250.0 mm, particle diameter: dp = 5 µm; column oven CTO - 10 Asvp Shimadzu	**MP:** 0.125 % solution of sodium 1 hexane sulfonate in Phosphate solution (pH = 2): acetonitrile = 800: 200 **FR:** 1.5 ml/min **IV:** 20 µL	**W:** 215nm
5.	Chander V et al.,2012 jan 1[12]	RP-HPLC	Buffer (pH 2.0) Nucleosil (125 x 4.0mm, 5mm)	**MP:** isopropyl alcohol and triethylamine (95:5:0.1) **FR:** 1 mL/min **IV:** 20 µL	**W:** 239 nm
7.	Maslarska V et al., 2013[14]	RP-HPLC	LiChrosorb C 18 column (250 x 4.6 mm, particle size 10 µm)	**MP:** Acetonitrile: Phosphate buffer (70:30 %v/v) **FR:** 1.5 ml/min. **IV:** 20 µl	**RT:** 3.4 min (LIS) and 6.9 min (HCTZ) **W:** 215nm
8.	Padmini VL et al., 2013[15]	RP-HPLC	Inertsil ODS 3 column (250 x 4.6mm, 5µm)	**MP:** Ammonium acetate: Acetonitrile (80:20% v/v) **FR:** 1.0 mL/min **IV:** 10 µL	**RT**: 3.7min (LIS) and 7.6min (HCTZ) **W:** 220nm

Table 2: HPTLC method for simultaneous estimation of hydrochlorothiazide and lisinopril.

SI. No	Title	Method	Column	Mobile phase [M.P], Flow rate [F.R] & Injection Volume [I.V]	Retention time [RT] & Wavelength [W]
1.	Patel RB et al., 2022 jun 1[16]	HPTLC	Silica gel 60F254 plates (10 × 10 cm, layer thickness 0.2 mm; E. Merck KGaA, Darmstadt, Germany)	**MP:** chloroform: methanol: ethyl acetate: acetic acid (7:2:1:0.2; V/V/V/V) **Concentration Range:** 200–1200ng/band [HCTZ] and 250-1500 ng/band [LIS] **LINEARITY:** 0.9990 [HCTZ] and 0.9992 [LIS]	**W:** 218nm

SPECTROSCOPIC ESTIMATION

UV spectroscopy plays a crucial role in the quantitative analysis of substances such as lisinopril and hydrochlorothiazide, both of which are antihypertensive medications. Researchers frequently utilize UV spectroscopy to investigate these drugs in both bulk and dosage forms. By examining the absorbance, transmittance, and reflectance properties of these medications at various concentrations, it becomes possible to establish their linearity and other important characteristics.

Table 3: UV Spectroscopic method for simultaneous estimation of hydrochlorothiazide and lisinopril.

S. No	Title	Instrumental model	Materials & Description
1.	Basavaiah K et al., 2009[17]	A Systronics model 106 digital spectrophotometer	**Wavelength:** 420nm **Solvent:** Methanol **Concentration Range:** 10-50 µg/mL **Linearity (R2):** 0.9979
2.	Patel N et al., 2015 jun 30[18]	Shimadzu UV 1700 double beam UV-visible	**Wavelength:** 269.8nm [HCTZ] and 209.4nm [LIS] **Solvent:** HCl buffer **Concentration Range:** 10 µg/ml

		spectrophotometer	**Linearity (R2):** 0.9995[HCTZ] and 0.9996 [LIS]
3.	Mohammed FF et al., 2019 Apr 1[19]	Spectronic Genesis 2PC UV/visible (Milton Roy Co, USA)	**Wavelength:** 270 nm [HCTZ], 211nm [LIS] **Solvent:** Methanol **Concentration Range:** 2.5 - 30.0 µg mL-1[HCTZ], 1.0 - 30.0 µg mL-1[LIS]
4.	Dinc S et al., 2013[20]	Agilent 8453 UV-VIS spectrophotometer	**Wavelength:** 213 nm **Concentration Range:** e 4-20 µg mL-1 [LIS] and 3-11 µg mL-1 [HCTZ]

Table 4: Fluorimetry method for simultaneous estimation of hydrochlorothiazide and lisinopril.

S. No	Title	Instrumental model	Materials & Description
5.	CM Jamakhandi et al., 2010[21]	Elico Fluorimeter, model CL-53	**Wavelength:** fluorescence intensity excitation wavelength of 366 nm and emission wavelength of 475 nm. **Solvent:** Methanol **Concentration Range:** 0.03 µg-0.15 µg **Linearity (R2):** 0.03 – 0.15 µg ml-1
6.	Derayea SM et al., 2018 Jun 5[22]	Perkin Elmer LS 45 Luminescence spectrometer (UK) that is coupled to an IBM PC with the FL WINLAB™ software. MLW	**Wavelength:** fluorescence intensity emission wavelength at 438 nm after excitation wavelength at 350 nm **Solvent:** Distilled water **Concentration Range:** 0.5 – 4.5 µg/mL **Linearity (R2):** 0.9981

CONCLUSION

Various analytical techniques, such as chromatographic, spectroscopic, and fluorimetric methods, have been employed to simultaneously estimate lisinopril (LIS) and hydrochlorothiazide (HCTZ). Each of these methods offers unique advantages in terms of sensitivity, precision, accuracy, and applicability in pharmaceutical analysis.

Chromatographic techniques like HPLC, RP-HPLC, and HPTLC enable highly effective separation and quantification of HCTZ and LIS, with performance enhanced by adjusting the mobile phase composition, column type, and flow rate. The reliability, repeatability, and ability to analyze complex pharmaceutical formulations have made these techniques widely adopted. Notably, RP-HPLC remains the most commonly used method due to its superior accuracy and sensitivity. Future research may focus on innovative techniques such as LC-MS and eco- friendly analytical methods to further enhance sensitivity and sustainability.

Spectroscopic techniques, particularly UV-visible spectrophotometry, offer a fast, simple, and cost-effective alternative for drug quantification. Due to their excellent linearity and accuracy, these methods are well-suited for routine quality control in the pharmaceutical industry. However, they may exhibit lower selectivity compared to chromatographic methods. Fluorimetric techniques are also being explored due to their enhanced sensitivity and specificity, thanks to fluorescence-based detection. These methods are particularly important in forensic and pharmaceutical research, as they are effective for analyzing trace amounts of drugs. Ultimately, the choice of analytical technique is influenced by the specific requirements of pharmaceutical quality control, including sensitivity, cost-effectiveness, and adherence to regulations. Continuous advancements in the accuracy and reliability of these analytical methods will lead to improved drug formulation analysis and quality assurance in the pharmaceutical industry.

ABBREVIATION

RP-HPLC: Reversed-Phase High-Performance Liquid Chromatography, **UV**: Ultraviolet, **HPLC**: High-Performance Liquid Chromatography, **HPTLC**: High-Performance Thin-Layer Chromatography, **MP**: Mobile Phase, **RT**: Retention Time, **IV**: Injection Volume, **W**: Wavelength, **pH**: Potential of Hydrogen, **R2:** Linearity**, HCTZ:** Hydrochlorothiazide**, LIS:** Lisinopril.

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