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A Comprehensive Review: Simultaneous Analytical Determination of Nebivolol HCl and Ramipril in Combined Dosage Forms

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Abstract: Managing heart health often requires a strategic combination of medications, and Nebivolol hydrochloride and Ramipril are two of the most effective tools in that kit. Nebivolol works as a selective beta-blocker, essentially helping the heart beat more calmly and efficiently to lower blood pressure. Ramipril, on the other hand, is an ACE inhibitor that does double duty: it treats high blood pressure and heart failure while providing a vital layer of protection for the kidneys, particularly for those living with diabetes. Research suggests that finding the "sweet spot" for a patient's dosage can significantly reduce the risk of major cardiovascular events and slow the progression of kidney disease. Because these medications are so frequently used together, scientists rely on advanced analytical techniques like UV spectrometry, HPLC, and HPTLC to ensure each dose is precise and pure. These methods allow researchers to detect and measure both drugs simultaneously, even when they are mixed with other substances. By refining these detection methods, the medical community ensures that these life-saving treatments remain consistent, safe, and effective for the patients who depend on them.

Keyword: Nebivolol hydrochloride, Ramipril, UV spectrometric, HPLC, HPTLC

I. INTRODUCTION

1.1 NEBIVOLOL

Effective heart health management often relies on medications like Nebivolol hydrochloride, a specialized cardiovascular drug known as a selective beta-blocker. Unlike general beta-blockers, Nebivolol focuses its action specifically on the cardiovascular system to prevent an excessive heart rate and manage the heart's overall pumping power. Beyond just regulating the heartbeat, it also helps dilate blood vessels, which directly assists in lowering blood pressure and reducing the workload on the heart. Because this medication is so vital for treating high blood pressure and heart failure, the ability to analyze it quickly and accurately is essential for both patient care and manufacturing. In a clinical setting, reliable testing allows doctors to fine-tune dosages to meet a patient's specific needs. Meanwhile, in pharmaceutical production, having fast and economical quality control methods ensures that every tablet produced is safe,

consistent, and effective, allowing for immediate adjustments during the manufacturing process to maintain high standards.

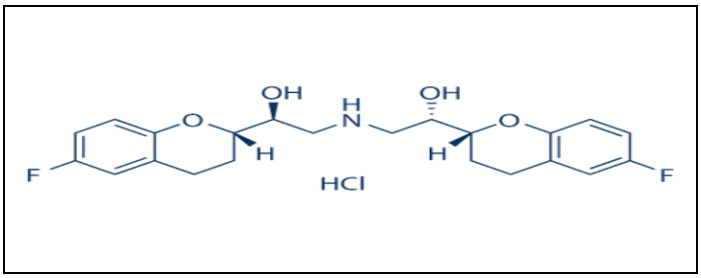

Fig 1. Structure of Nebivolol Hydrochloride

1.2 RAMIPRIL

Ramipril acts as a versatile protector for the cardiovascular system, primarily serving as an ACE inhibitor that helps manage high blood pressure and heart failure. By blocking a specific substance in the body that causes blood vessels to constrict, it allows the vessels to relax and widen. This physical relaxation not only lowers blood pressure but also significantly improves the flow of oxygen-rich blood to the heart. Because of its effectiveness and reliability, it is often a go-to choice for doctors when first starting a patient on blood pressure treatment. Beyond its role in daily maintenance, this medication serves as a powerful preventative tool, particularly for patients over the age of 55 who have vascular disease. For these individuals, it helps lower the risk of severe events like heart attacks or strokes. Additionally, it plays a critical role in managing diabetic kidney disease, offering a layer of protection that helps preserve long-term organ health. By improving circulation and reducing the heart's workload, it provides a comprehensive approach to both treating existing conditions and preventing future complications

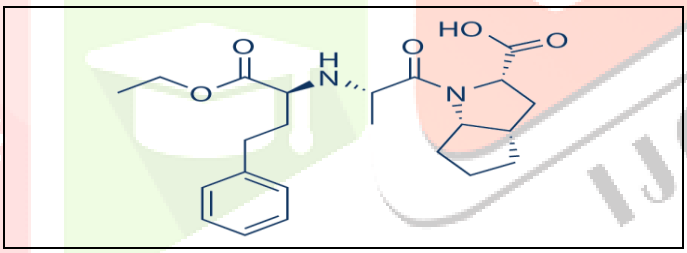

Fig 2. Structure of Ramipril

The combination of Nebivolol hydrochloride and Ramipril is frequently prescribed in Europe, but single pill combination could enhance treatment adherence and streamline regimens, potentially leading to significant benefits.

II. LITERATURE REVIEW

Sr. No.	Author name	Journal name	Title name	Summary
1	Lakshmana Rao Atmakuri et al.	Journal of Chemistry	Spectrophotometric Method for the Determination of Nebivolol hydrochloride in Bulk and Pharmaceutical Formulations	The analytical method was optimized using methanol as the solvent, exhibiting a maximum absorption wavelength of 281 nm and a linear range of 4–60 µg/ml.
2	Kamila, M. M et al.	An International	A validated UV spectrophotometric	Using methanol as a solvent, the compound showed a peak absorbance

		Journal of Pharmaceutical Sciences	method for estimation of Nebivolol hydrochloride in bulk and pharmaceutical formulation	at 282 nm and demonstrated linearity within the concentration limits of 5 to 50 µg/ml
3	Mishra kamal et al.	J. Indian Chem, Soc.	UV and extractive spectrophotometric methods for the determination of Nebivolol hydrochloride in tablets	Spectrophotometric analysis in distilled water revealed a λmax at 283.5 nm, with the Beer-Lambert law obeyed over a concentration range of 10–65 µg/ml
4	Kamila M.M. et al.	Pharmazie	UV Spectrophotometric method for the estimation of Nebivolol HCl in bulk and pharmaceutical formulations	The UV-visible spectrum of the sample in Methanol: phosphate buffer pH 6.8(10:90) displayed a characteristic absorption peak at 282 nm, maintaining a linear response across concentrations ranging from 10 to 50 µg/ml
5	Voors AA et al.	Aging Health	Stability Indicating RP-HPLC Estimation of Nebivolol hydrochloride in Pharmaceutical Formulations	The analysis was performed using a 250 x 4.6 mm C-18 column detected by a UV/Vis detector at a λmax of 280nm, achieving a retention time of 2.6 min using a mobile phase of methanol:acetonitrile:0.02 M potassium dihydrogen phosphate (60:30:10, v/v/v) adjusted to pH 4 .
6	Shirkhedkar AA et al.	The Pharma Review	Reverse phase HPLC method for determination of Nebivolol hydrochloride in pharmaceutical preparation.	The analysis was performed using a C-18 column (250 x 4.6 mm) and a UV/Vis detector set at a λmax of 282 nm, utilizing a mobile phase of methanol and water (70:30 v/v) which resulted in a retention time of 3.3 minutes.
7	Sean C Sweetman et al.	The Complete Drug Reference	RP-HPLC Method for the Estimation of Nebivolol hydrochloride in Tablet Dosage Form	The chromatographic analysis was conducted using a C-18 column 250 x 4.6mm) and a UV/Vis detector set at a λmax of 282 nm, where a mobile phase of methanol and water (80:20 v/v) yielded a retention time of 3.175 minutes.
8	Pankaj K Kachhadia et al.	Journal of AOAC International	Development and Validation of a Stability-Indicating Column High Performance Liquid Chromatographic Assay Method for Determination of Nebivolol hydrochloride in Tablet Formulation	Chromatographic separation was achieved using a C-8 column (250 mm × 4.6 mm) with a mobile phase consisting of acetonitrile and pH 3.5 phosphate buffer (35:65, v/v), resulting in a retention time of 1 minute

9	K.D.Tripathi et al.	Essentials of medical pharmacology	Analytical method development and validation of Nebivolol HCl in tablet dosage form by RP-HPLC method.	The analyte showed a retention time of 5.67 minutes using a UV/Vis detector set at a λmax of 210 nm, facilitated by an isocratic elution of acetonitrile and tetrabutylammonium hydrogen sulphate buffer (350:650, v/v) on a C-8 column.
10	J. Cockcroft et al.	Expert Opin. Pharmacother	Validated HPLC method for determination of Nebivolol hydrochloride in pharmaceutical dosage form and in vitro dissolution studies	Using a UV/Vis detector set at a λmax of 281 nm, the analyte was successfully eluted at 4 minutes on a 150 x 4.0 mm C-18 column using an isocratic mixture of trifluoroacetic acid in water and acetonitrile (60:40, v/v).
11	Van de Water et al.	Eur. J Pharmacol	Development & validation of stability indicating method for quantification of Nebivolol hydrochloride & their related substances by HPLC-UV-PDA detection in its pharmaceutical drug product	Analytes were monitored at 220 nm using a C-18 (250 mm x 4.6 mm) column; the mobile phase consisted of buffer/acetonitrile (80:20, v/v), resulting in a retention time of 0.56 minutes.
12	YANG, Le-ting et al.	Chinese Journal of Pharmaceutical Analysis,	HPLC-MS/MS determination of Nebivolol hydrochloride in human plasma and its application in pharmacokinetic study	Chromatographic separation was achieved on a C-18 column (100 mm × 2.00 mm) using a mobile phase composed of methanol, water, and formic acid (70:30:0.1, v/v/v), with detection monitored at 220 nm.
13	N.V.S. Ramakrishna et al.	Pharm. Biomed. Analysis.	Validation of a high performance thin layer chromatographic method, with densitometric detection, for quantitative Analysis of Nebivolol hydrochloride in tablet formulations.	A mixture of toluene, ethyl acetate, methanol, and formic acid (8:6:4:1, v/v/v/v) was employed as the developing solvent on silica gel 60 F 254 plates, followed by spectrophotometric evaluation at 285 nm.
14	Salem H et al.	Pharm. Journal	UV spectrophotometric methods for estimation of Ramipril in pharmaceutical dosage form by Absorption maxima Method and Area under Curve	Calibration curves were constructed in methanol at an analytical wavelength of 210 nm, exhibiting a linear response within the limits of 0.1–3.5 µg/ml.

15	H.E. Abdellatef et al.	J. Pharm. Biomed. Anal.	Spectrophotometric and spectrofluorimetric methods for the determination of Ramipril in its pure and dosage form	The spectrophotometric analysis was conducted using methylcellulose as the solvent, exhibiting a maximum absorption wavelength of 310 nm and a linear range of 15–50 µg/ml.
16	Yadav V. et al	Indian J Pharm Biol Research	Method development and validation of fast dissolving tablet of Ramipril by HPLC method	Analytical detection was performed at 210 nm on a C-18 (250 mm × 4.60 mm) stationary phase; the mobile phase comprised 40% methanol and 60% acetonitrile, yielding a retention time of 2.910 minutes.
17	Aboul-Enein HY et al	Anal. Lett	Determination of Ramipril and Its Precursors by Reverse Phase High Performance Liquid Chromatography	A C18 (250 mm × 4.60 mm) column was employed for the analysis; the mobile phase comprised acetonitrile/5% phosphoric acid (30:70) with detection set at 220 nm.
18	Kapoor, G, et al	Journal of chromatography and separation techniques	Stability indicating HPTLC method for Ramipril and its degradation products	The chromatographic separation was conducted on silica gel 60 F 254 stationary phase using a mobile phase of chloroform and methanol (9:1, v/v), with the resulting chromatogram monitored at a wavelength of 210 nm.
19	Jain, D. et al	Biomedical chromatography	HPTLC method for the quantification of Ramipril in plasma	Analytical evaluation was conducted at 220 nm following separation on silica gel 60 F 254 plates, utilizing a 7:2:0.5 (v/v/v) mobile phase of toluene/methanol/formic acid.
20	Bhusari , K .P., et al	Indian journal of pharmaceutical sceiences	HPTLC method for determination of Ramipril in bulk and pharmaceutical dosage forms	Using a UV/Vis detector set at a λmax of 220 nm, the sample was resolved on silica gel 60 F 254 plates; the development was carried out in a solvent system of ethyl acetate:acetone:ammonia (8:2:0.1, v/v/v).
21	Akabari, A. H et al	Journal of Chromatographic Science,	Analytical Method Development And Validation For Simultaneous Estimation Of Nebivolol hydrochloride And Ramipril In Synthetic Mixture By HPLC Method	The dual analysis of Nebivolol hydrochloride (RT: 4.7 min) and Ramipril (RT: 3.36 min) utilized a C-18 stationary phase and an isocratic mobile phase of buffer/methanol/acetonitrile (20:60:20), exhibiting linearity over a concentration range of 25–200 µg/ml at 212 nm.
22	Birajdar A. S.	Indian J.Pharm. Educ. Res.	Simultaneous Estimation of Nebivolol Hydrochloride and Valsartan and Nebivolol Hydrochloride and	The spectrophotometric analysis was conducted in methanol, with the maximum absorption wavelengths identified at 270.4 nm for Nebivolol hydrochloride and 280.2 nm for Hydrochlorothiazide. The method demonstrated linearity over the

			Hydrochlorothiazide in Pharmaceutical Formulations by UV Spectrophotometric Methods	concentration ranges of 0.5–2.5 µg/ml and 1.0–20 µg/ml, respectively.
23	SHAH K. V.	International Journal of Pharmaceutical Science & Research	Simultaneous quantification of Nebivolol hydrochloride and hydrochlorothiazide by first derivative UV-Spectroscopy	Using methanol as the solvent, the calibration curves for Nebivolol hydrochloride and Hydrochlorothiazide were found to be linear across the ranges of 4–24 µg/mL and 2–32 µg/mL. The analytes were monitored at their respective λmax values of 280 nm and 272 nm.
24	Patil P. R.	Arch Pharm Sci & Research	Spectrophotometric methods for simultaneous estimation of Nebivolol hydrochloride and amlodipine besylate in tablets	Simultaneous estimation of Nebivolol (280 nm) and Amlodipine besylate (360 nm) in methanol exhibited validated linearity ranges of 10–65 µg/ml and 5–45 µg/ml, adhering to the Beer-Lambert law.
25	Patel LJ	Indian J Pharm Science	A New RP-HPLC Method for Simultaneous Estimation of Nebivolol hydrochloride and Hydrochlorthiazide in Dosage Forms	Using a 250 mm C-18 stationary phase and a 1.2 ml/min flow rate, Hydrochlorothiazide (RT: 3.57 min) and Nebivolol hydrochloride (RT: 6.66 min) were successfully separated. The isocratic mobile phase comprised acetonitrile and pH 3.2 phosphate buffer (50:50), with detection monitored at 282 nm.
26	Arunadevi	International Journal of Pharmaceutical Sciences and Research.	RP-HPLC Method for the Simultaneous Estimation of Nebivolol hydrochloride and Valsartan	Using a 25 cm C-18 stationary phase and a 1.2 ml/min flow rate, Nebivolol hydrochloride (RT: 3.93 min) and Valsartan (RT: 4.78 min) were successfully separated. The mobile phase comprised a 15:50:35 (v/v/v) mixture of phosphate buffer, acetonitrile, and methanol, with detection monitored at 273 nm
27	Vyas Niraj	Asian Journal of Pharmaceutical Analysis	Development and validation of RP – HPLC method for the simultaneous estimation of Nebivolol hydrochloride and Indapamide in pharmaceutical dosage form	The chromatographic separation was performed on a C-18 column (150 x 4.6 mm) utilizing a mobile phase of buffer and acetonitrile (60:40, v/v) at a flow rate of 1 ml/min. Effluent monitoring was conducted at a wavelength of 282 nm using a UV/Vis detector
28	Parambi GT	Int J Pharm Sci Review Research	Development and validation of reversed phase high performance liquid chromatography method for simultaneous	Using a 25 cm C-18 column and a 1 ml/min flow rate, Nebivolol HCl (RT: 4.057 min) and Cilnidipine (RT: 6.47 min) were successfully resolved. The mobile phase comprised a 30:70 (v/v) mixture of phosphate buffer (pH 5.0) and methanol, with detection

			estimation of Nebivolol HCl and Cilnidipine in combined tablet dosage form	monitored at 282 nm using a PDA detector.
29	Damle MC	Eur. J of Anal. Chem	A Validated HPTLC Method for Simultaneous Quantification of Nebivolol hydrochloride and Hydrochlorothiazide in Bulk and Tablet Formulation	Using a UV/Vis detector set at 281 nm, the analytes were resolved on silica gel 60 F 254 plates. The development was carried out using a solvent system of 1,4-dioxane:toluene:triethylamine in a volume ratio of 5:3:0.1
30	Chandrashekar TG	J. Planar. Chromatography	HPTLC Method Development and Validation for the Simultaneous Estimation of Amlodipine Besylate and Nebivolol Hydrochloride in tablet dosage form	Chromatographic separation was performed on silica gel 60 F 254 stationary phase using a mobile phase consisting of methylene chloride, methanol, and ammonia (8.5:1:0.5, v/v/v), with densitometric detection carried out at 285 nm.
31		Indian Pharmacopoeia	Development and Validation of High-Performance Thin-Layer Chromatography Method for Determination of Nebivolol hydrochloride and Amlodipine besylate in Combined Dosage Forms	Evaluation was conducted at 273 nm following separation on silica gel 60 F 254 stationary phase, utilizing a chloroform/methanol/toluene/ammonia (8:1.8:1:0.3) solvent system as the mobile phase.
32	Sahoo MK	E-Journal of Chemistry	A validated HPTLC method for simultaneous estimation of Nebivolol hydrochloride and Indapamide in solid dosage form	The analyte was resolved on silica gel 60 F 254 plates utilizing a solvent system of ethyl acetate:methanol:dilute ammonia (8.5:0.8:1, v/v/v); detection and quantification were performed using a UV/Vis detector set at a λmax of 274 nm.
33	Khaled Attala	Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy	Smart UV spectrophotometric methods based on simple mathematical filtration for the simultaneous determination of Celecoxib and Ramipril in their pharmaceutical mixtures with amlodipine: A	Simultaneous estimation of Ramipril (222 nm) and Celecoxib (253 nm) in methanol exhibited validated linearity ranges of 5–60 µg/ml and 5–30 µg/ml, ensuring high sensitivity for both active pharmaceutical ingredients.

			comparative statistical study	
34	Popat B. Mohitea	Eurasian J. Anal. Chem	Simultaneous Estimation of Ramipril and Telmisartan in Tablet Dosage Form by Spectrophotometry	Using methanol as the primary solvent, calibration curves for Ramipril and Telmisartan were established at their respective λmax values of 205 nm and 291 nm. The established linearity was found to be 5–40 µg/ml for Ramipril and 2–20 µg/ml for Telmisartan, following the Beer-Lambert law.
35	Anjan De	Indo American Journal Of Pharmaceutical Research	UV spectrophotometric methods for estimation of Ramipril and hydrochlorothiazide by absorbance correction method	The spectrophotometric analysis was conducted in methanol, with the maximum absorption wavelengths identified at 209 nm for Ramipril and 270 nm for Hydrochlorothiazide. The method demonstrated linearity over the concentration ranges of 0.25–1.25 µg/ml and 0.5–10 µg/ml, respectively.
36	Sunil Jawla	International Journal of PharmTech Research	Development and Validation of Simultaneous HPLC method for Estimation of Telmisartan and Ramipril in Pharmaceutical Formulations	Using a 250 mm C-18 column and a 1.5 ml/min flow rate, Ramipril (RT: 5.7 min) and Telmisartan (RT: 10.8 min) were successfully separated. The isocratic mobile phase comprised a 60:40 (v/v) mixture of phosphate buffer and acetonitrile, with detection monitored at 210 nm via a PDA detector
37	K. Srinivasa Rao	Indian J Pharm Sci	RP-HPLC Method for the Determination of Losartan Potassium and Ramipril in Combined Dosage Form	Chromatographic separation was achieved on a C-18 column (250 mm × 4.6 mm) using a ternary mobile phase of acetonitrile, methanol, and 10 mM tetrabutylammonium hydrogen sulphate (30:30:40, v/v/v). At a flow rate of 1.0 ml/min and detection wavelength of 210 nm, the retention times were 3.3 minutes for Ramipril and 4.7 minutes for Losartan potassium.
38	Maste M.M	Asian Journal of Research in Chemistry	Development of RP-HPLC method for simultaneous estimation of Amlodipine and Ramipril in tablet dosage form.	Using a 245 mm C-18 column and a 1.0 ml/min flow rate, Ramipril (RT: 3.41 min) and Amlodipine (RT: 6.10 min) were successfully separated. The isocratic mobile phase comprised a 60:40 (v/v) mixture of acetonitrile and phosphate buffer, with detection monitored at 222 nm via a PDA detector.
39	Praveen S.Rajput	Journal of applied Pharmaceutical Science	Simultaneous Estimation of Ramipril and Amlodipine in Bulk and tablet Dosage form by RP-HPLC Method	The simultaneous estimation of Ramipril and Amlodipine was conducted using a PDA detector set at 210 nm. The method demonstrated linearity over concentration ranges of 1–16 µg/ml and 0.2–3.2 µg/ml, respectively, with well-resolved

				peaks appearing at 2.64 and 7.45 minutes using an isocratic elution system
40	K. S. Lakshmi	Journal of the Chilean Chemical Society	A stability indicating HPLC method for the simultaneous determination of Valsartan and Ramipril in binary combination	Chromatographic separation was achieved on a C-18 column (250 x 4.6 mm) using an isocratic mobile phase of acetonitrile and water (55:45, v/v). At a flow rate of 1.0 ml/min and a detection wavelength of 215 nm, the retention times were found to be 1.91 minutes for Ramipril and 4.82 minutes for Valsartan.
41	Gaikwad A Va	Indo-Global Journal of Pharmaceutical Sciences	Development and Validation of HPTLC Method for the Simultaneous Estimation of Telmisartan and Ramipril in Combined Dosage Form	The analytes were resolved on silica gel 60 F 254 plates developed in a solvent system of acetone:benzene:ethyl acetate:glacial acetic acid (5:3:2:0.03, v/v/v/v). Quantification was achieved using a UV/Vis detector, with Ramipril monitored at 210 nm and Telmisartan at 296 nm.
42	Connors, K.A	A Text Book of Pharmaceutical Analysis	Simultaneous Estimation of Ramipril & Valsartan in Tablets by HPTLC	Evaluation was conducted at 220 nm following separation on silica gel 60 F 254 plates, utilizing an 8:2:0.2 (v/v/v) mixture of ethyl acetate, chloroform, and glacial acetic acid as the developing solvent

III. CONCLUSION

The current study shows that several analytical approaches, including spectrophotometric, chromatography techniques are used to determine Nebivolol hydrochloride and Ramipril. The current review will be very beneficial to researchers in analytical method development and validation method for Nebivolol Hydrochloride and Ramipril.

IV. Summary

The review and survey of a UV/Vis spectrophotometric method for the simultaneous estimation of Nebivolol hydrochloride and Ramipril from a combined drug formulation. In addition, High-Performance Liquid Chromatography (HPLC) and High-Performance Thin Layer Chromatography (HPTLC).

Table No. 1 summary

Method	Nebivolol Hydrochloride	Ramipril	Combination drug
UV-Vis Spectrophotometric Method	✓	✓	Not found
HPLC Method	✓	✓	✓
HPTLC Method	✓	✓	Not found

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