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A Systematic Review of Method Development and Validation for Ramipril Analysis Using HPLC in Cardiovascular Research

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Abstract

The field of analytical chemistry encompasses a variety of methods that are crucial in determining the chemical composition of different substances. UV-visible spectroscopy and high-performance liquid chromatography (HPLC) are two widely utilized methods that are the subject of this article. UV-visible spectroscopy uses the Beer-Lambert law to quantify light absorption, which can provide information about the concentration of absorbing species. The method is based on how light and matter interact, with absorption occurring due to molecular electronic transitions. Conversely, high pressure is used in HPLC to separate mixture components according to how well they bind to a stationary phase. Its versatility stems from a variety of separation techniques, such as size exclusion chromatography, ion exchange, partition, and adsorption. Method development and validation are crucial to guaranteeing the dependability of analytical procedures. It is necessary to assess validation variables including specificity, accuracy, precision, linearity, and robustness to make sure a method is appropriate for the task at hand. Various HPLC techniques for the analysis of ramipril, an angiotensin-converting enzyme (ACE) inhibitor used to treat hypertension and heart failure, have been explored in the literature. These studies investigated different mobile phases and columns, demonstrating the flexibility of HPLC in pharmaceutical analysis. Ramipril works by blocking the renin-angiotensin-aldosterone system (RAAS), which reduces inflammation and vasoconstriction. This abstract provides an extensive review of analytical chemistry techniques, with special emphasis on their importance in pharmaceutical analysis and drug development.

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INTRODUCTION

The study of techniques for ascertaining the chemical makeup of material samples. Information regarding the atomic or molecular species or functional groups of a material can be obtained using a qualitative method. In contrast, a quantitative approach provides numerical data on the proportion of one or more of these components [1]. Analytical chemistry is characterized by a set of powerful concepts and procedures that apply to all fields of research and medicine. There is a constant search for better ways to determine the chemical composition of both natural and synthetic materials.

While an analytical method is a specific application of a technique to address an analytical problem, this chemistry discipline is carried out in a large number of laboratories using various methods [2]. Analytical techniques are regularly developed, enhanced, verified, cooperatively researched, and used. Both qualitative and quantitative analyses are part of the field of analytical chemistry [3–4].

Introduction of UV

The physical use of Optical spectroscopy using visible, ultraviolet, and near-infrared light is known as UV spectroscopy. It is predicated on the Beer-Lambert law, which argues that the route length and concentration of the absorbing species in a solution are directly correlated with the absorbance of the solution. Consequently, it can be applied to determine the absorber concentration in a solution for a given path length. Knowing how fast the absorbance changes with concentration is important [5].

Principle of UV

Spectroscopy is based on the creation of different spectra that occur when chemical compounds absorb ultraviolet or visible light. The relationship between light and matter forms the foundation for spectroscopy. A spectrum is created when matter absorbs light and undergoes excitation and deexcitation. When an electromagnetic wave hits a medium, various processes can occur including transmission, absorption, reflection, and scattering. The measured spectrum demonstrates the interactions of discrete-dimensional objects, such as molecules, macromolecules, and atoms, at different wavelengths. Absorption occurs when a molecule's excited and ground states have an energy difference equal to the frequency of incoming light. The process by which an electron changes from its ground state to its excited state is known as electronic transition [6].

High-Performance Liquid Chromatography

One type of liquid chromatography is high-performance liquid chromatography (HPLC), which is also known as high-pressure liquid chromatography. This method is widely used in analysis to identify, measure, and separate the constituent parts of a mixture. HPLC is an advanced type of column liquid chromatography. Gravity normally drives the solvent through the column, but the high pressure of the HPLC process compresses the solvent to 400 atm, enabling the sample to be divided into different constituents according to variations in relative affinities [7].

The HPLC Principle

involves injecting the sample solution into a porous material column (stationary phase) and then pumping the liquid phase (mobile phase) through the column at a higher pressure. The separation principle states that the solute is adsorbed onto the stationary phase in accordance with its affinity for the stationary phase [8].

Depending on the characteristics of the stationary phase, the separation process can take one of four different forms.

1. In adsorption chromatography, separation is accomplished through repeated adsorption-desorption processes.
2. Partition chromatography involves dividing the mobile and stationary phases to achieve separation.
3. Anionic surfaces with charges opposite to those of the sample comprise the separation phase in ion-exchange chromatography.
4. Size exclusion chromatography separates samples based on their molecular size using a column packed with a substance with a precisely controlled pore size [9].

HPLC METHOD DEVELOPMENT

Method Validation

The analytical method must be validated before a chemical evaluation can be performed. Method validation involves performing a series of tests to confirm that an analytical test system is suitable for

its intended use and can deliver relevant and reliable analytical data. A validation examination tests multiple features of a procedure to determine whether accurate information can be obtained when applied automatically. To effectively evaluate the method parameters, the validation test should include typical test conditions, such as product excipients. Consequently, technique validation analysis is product-specific (Figures 1–3) [10].

Specificity

The term 'specificity' describes the capacity of an analytical method to identify and measure analytes in complicated mixtures. When identifying contaminants and validating identification tests, specific inquiries must be conducted. The ability of HPLC to provide signals free from interference is an important property. The ability to conclusively assess the analyte in the presence of other compounds is known as the specificity, as per ICH recommendations. These are frequently substances such as pollutants, degradants, and matrices [11].

Accuracy

The accuracy of an analytical method is defined as the degree to which the test results obtained using this method are close to actual values. Accuracy is sometimes expressed as a percentage of recovery by assessing additional amounts of the analyte. Applying this methodology to analyze samples with known analyte addition levels allows one to assess the accuracy of an analytical method. The accuracy of the test results was determined using the percentage of analyte recovered by the assay [12].

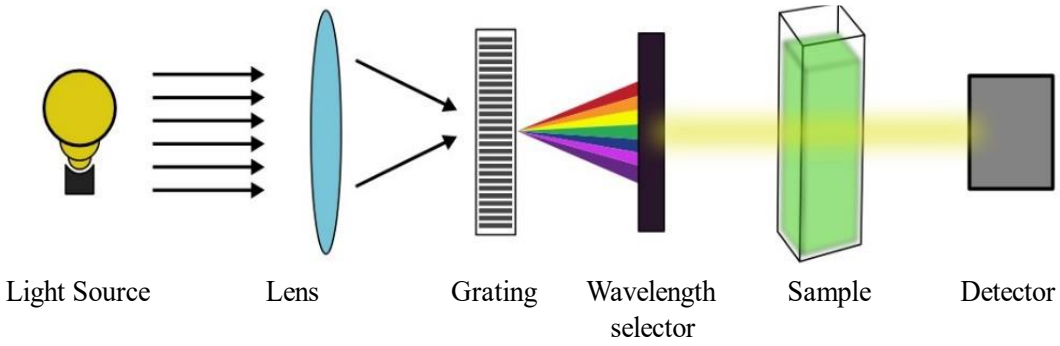

Figure 1. UV-Visible spectroscopy.

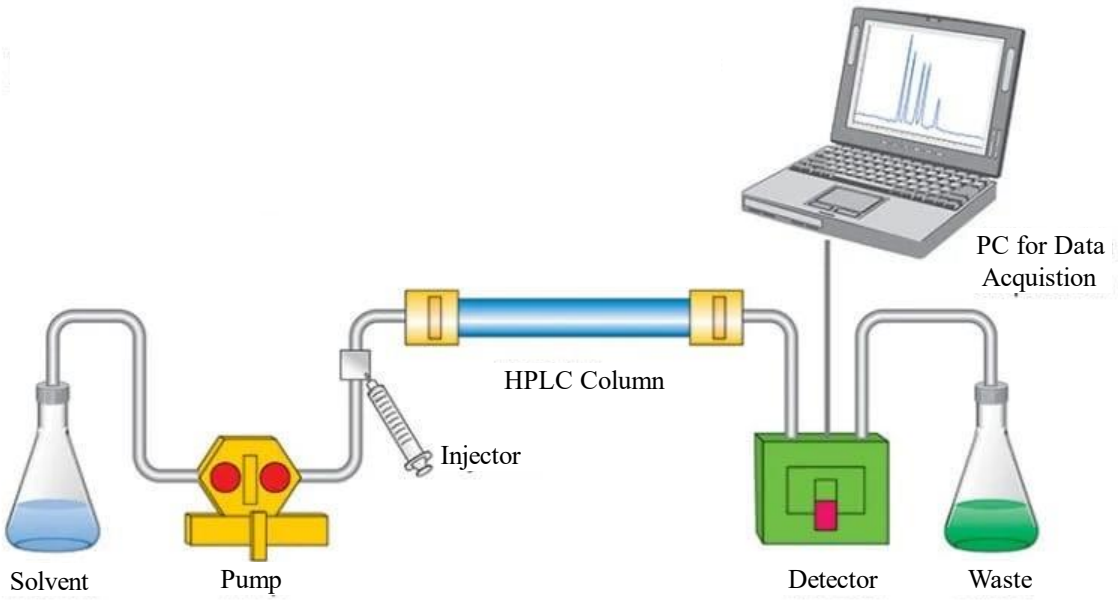

Figure 2. HPLC (high-performance liquid chromatography).

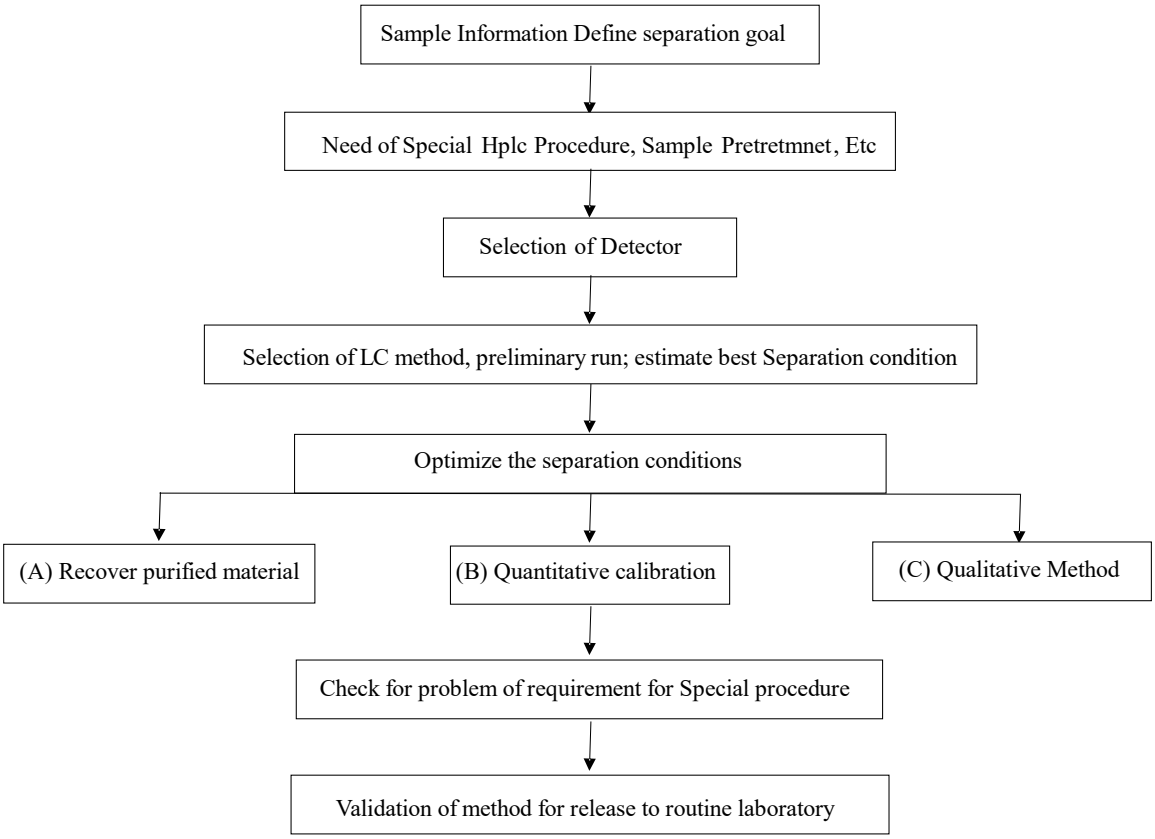

Figure 3. HPLC Procedure in laboratory using different methods.

Precision

"Closeness of agreement between a series of measurements obtained from multiple sampling of the same standardized sample under the prescribed conditions" is one definition of accuracy in analytical processes [13].

Repeatability

It conveys accuracy over a short time span under the same operational circumstances. That is the analysis of duplicates by the analyst using the same methods and instruments.

Intermediate Precision

It conveys the accuracy of laboratory variances, such as various days, analysts, and equipment, among others. Studying affects one at a time is not necessary.

Reproducibility

It expresses laboratory precision to add procedures to pharmacopoeias (two-way studies, often applied to the standardization of methods). i.e., Precision was examined as part of the validation procedure for tests used in the assay and quantitative impurity testing.

Linearity

The capacity of an analytical process to produce a result that is precisely proportional to the quantity or concentration of the analyte in the sample is known as linearity [14].

Range

The difference between the highest and lowest analyte concentrations in an analytical technique with an appropriate degree of linearity, accuracy, and precision is known as the range of the analytical procedure [15].

Limit of Detection

The LOD is the smallest amount of analyte that can be found in the specified experimental conditions.5 It can be calculated using either the 3:1 signal-to-noise ratio or the 3.3:1.5 ratio obtained by dividing the standard deviation of the y-intercepts by the slope of the calibration curve acquired in the linearity test.

Limit of Quantification

A lower-order quantitative quantity, or LOQ, is the smallest quantity of analyte that may be precisely and accurately quantified within the confines of the experiment. Five

This parameter can be evaluated in the same manner as the LOD, but at a 10:1 ratio for each instance [16].

Robustness

Small adjustments to the optimized technique parameters, such as the mobile phase ratio, flow rate, and detection wavelength, were made to conduct a robustness investigation. The retention time and tailing factor were significantly unaffected [17].

LITERATURE REVIEW

A systematic review of method development and validation highlights the critical steps involved in ensuring the reliability, accuracy, and reproducibility of scientific methods across various fields. These reviews emphasize the importance of rigorous validation protocols, including statistical analysis, calibration, and verification, to meet regulatory and research standards. They contribute to enhancing the robustness of methodologies, particularly in fields like climate science and pharmaceutical research, where precision is paramount Table 1.

Table 1. Summary of Analytical Methods for Drug Combinations using High-Performance Liquid Chromatography (HPLC).

	Drug	**Authors**	**Details**	**Ref. No.**
1	Ramipril	Bilal Yilmaz	*Mobile Phase:* 20 mM phosphate buffer (pH 2.5) containing 0.1% trifluoroacetic acid (TFA)-acetonitrile (50:50, v/v) *Column:* ACE C18 column (5 µm, 250×4.6 mm)	[18]
2	Ramipril	Vaibhav Rajoriya, Amrita Soni, Varsha Kashaw et al.	*Mobile Phase:* acetonitrile: methanol (60:40 v/v) *Column:* ODS C-18 Kromacil (250 mm × 4.60 mm)	[19]
3	Aspirin + Atorvastatin + Ramipril	*Nora A.* Abdallah, Amina M. El-Brashy, Fawzia A. Ibrahim1 and Mohamed I. El-Awad, et al.	*Mobile Phase:* 0.3% triethylamine (TEA) in 90: 10 an aqueous solution of 0.12 M sodium dodecyl sulfate (SDS): n-propanol, (v/v). The pH was adjusted to 2.5 *Column:* Monolithic column	[20]
4	Ramipril + Amlodipine	Praveen S. Rajput, Amanjot Kaur, Navdeep Kaur Gill, Karan Mittal, and Ganti Subrahmanya Sarma et al.	*Mobile Phase:* Acetonitrile, Sodium phosphate buffer, and Methanol in the ratio of 50: 20:25 v/v/v, pH= 6.8 (pH adjusted with OPA). Column: C18 Column (250 × 4.6 mm, i.e., 5 µm particle size),	[21]
5	Ramipril + Olmesartan Medoxomil	Deepthi Yada, Divya Yada, T. Rajeshwari, M. Madhavilatha, G. Tulja Rani et al.	*Mobile Phase:* acetonitrile: 0.05 M KH2PO4 pH 3.0 (60:40) *Column:* Hypersil C18 (4.6 mm × 250 mm, 5 µm)	[22]
6	Ramipril + Olmesartan	M. Prasada Rao, M. Srikanth, K. Umamaheswari et al.	Mobile Phase: buffer (pH 2.0), methanol and acetonitrile (30:20:50% v/v/v)	[23]

	Drug	Authors	Details	Ref. No.
	Medoxomil		*Column:* ODS C18 column (150 mm × 4.8 mm, i.e., particle size 5 µm	
7	Ramipril + Aspirin + Atorvastatin	Rajesh Sharma, Sunil Khanna, and Ganesh P. Mishra et al.	Mobile Phase: (A) acetonitrile methanol (65:35) and (B) 10 mM Sodium dihydrogen phosphate monohydrate ($NaH_2PO_4.H_2O$) buffer and mixture of A: B (60:40 v/v) adjusted to pH 3.0 *Column:* 25 cm × 4.6 mm, i.e., 5 µm particle, C18 column	[24]

Drug Profile

Ramipril

Category: Angiotensin-converting enzyme (ACE) inhibitors

Molecular formula: $C_{23}H_{32}N_2O_5$

Chemical name: 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid

Molecular weight: 416.5 g/mol

Description: White crystalline substance

Melting point: 105°C and 112°C.

Solubility: Organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF).

Structure:

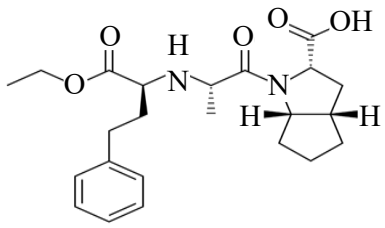

Figure 4. Chemical Structure of a Cyclopeptide Derivative.

Mechanism of Action

Ramipril binds to ACE, which inhibits the RAAS system and prevents the conversion of angiotensin I to angiotensin II. When plasma levels of angiotensin II decrease, two G-protein coupled receptors, angiotensin receptor I (AT1R) and angiotensin receptor II (AT2R), become less active.AT1R mediates oxidative damage, fibrosis, inflammation, and vasoconstriction through a variety of signaling pathways. MAP kinases Gi and G12/13, as well as Ca2+-dependent phospholipases C, A2, and D that support the synthesis of eicosanoid compounds, are among them. Activation of the JAK/STAT pathway, which stimulates cell growth and synthesis of extracellular matrix components, is the final pathway. Go coupling with the inositol triphosphate pathway is another mechanism. The increased activity of membrane-bound NADH/NADPH oxidase and AT1R activation results in ROS production of reactive oxygen species. The renoprotective, antihypertensive, and cardioprotective actions of ramipril are mediated by decreased activation of this receptor, which also lowers inflammation and vasoconstriction. By activating phosphotyrosine phosphatases that inhibit MAP kinases, block Ca2+ channel opening, and promote the synthesis of cGMP and nitric oxide, which results in vasodilation, AT2R counteracts the actions of AT1R. Similar opposing effects are seen in the activation of the Mas receptor by Ang(1–7), a subtype of angiotensin produced by plasma esterases from AngI or by ACE2 from AngII produced through a secondary pathway by tonin and cathepsin G. Ang (1–7) also activates AT2R, but most of its actions are mediated by MasR (Figure 4).

CONCLUSION

In conclusion, this review provides information on the importance of method development and validation in analytical chemistry, particularly focusing on the HPLC method for ramipril analysis. This review also includes a literature review of ramipril, which will help in the optimization of chromatographic conditions. It also highlights the importance of validation factors such as specificity, accuracy, and precision. These parameters are vital to guarantee the trustworthiness and efficiency of the analytical approach.

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