International Journal of Research and Development in Pharmacy & Life Sciences

Review Article Open Access

Surveying Progress: A Comprehensive Review of Analytical Methods for Cardiovascular Drugs in Formulated Dosage Forms and Bulk Compositions

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Abstract

High-Performance Liquid Chromatography (HPLC) has transformed pharmaceutical analysis by enabling precise and efficient simultaneous estimation of multiple drugs in complex mixtures, offering advantages such as time efficiency and high precision. However, challenges like ensuring selectivity and rigorous method validation persist. Meanwhile, cardiovascular diseases remain a global health concern, necessitating optimized analytical methods for cardiovascular drugs. This study aims to develop advanced techniques tailored to cardiovascular drug complexities, addressing challenges like formulation variations and regulatory compliance. By optimizing methods and ensuring regulatory adherence, this research contributes to enhancing pharmaceutical analysis in cardiovascular care. Through rigorous method development and validation, this study seeks to advance the field, ultimately improving patient outcomes in cardiovascular disease management.

Introduction

High-Performance Liquid Chromatography (HPLC) has revolutionized pharmaceutical analysis by enabling the simultaneous estimation of multiple drugs in complex mixtures. This analytical technique has become indispensable in various domains, including pharmaceutical research, quality control, and clinical studies, owing to its remarkable sensitivity, precision, and efficiency.

Simultaneous drug estimation is particularly crucial in pharmaceutical analysis, especially when dealing with formulations containing multiple active ingredients. HPLC, a chromatographic technique, facilitates the separation of components within a mixture based on their interactions with both a stationary phase and a mobile phase. In HPLC, the sample mixture is injected into a column, where the components are separated according to their affinity for the stationary and mobile phases [1].

The stationary phase, typically a material with specific properties, interacts with the components of the sample mixture differently, causing them to move at different rates through the column. Meanwhile, the mobile phase, a liquid that flows through the column, aids in carrying the sample components along and facilitating their separation. This differential partitioning between the stationary and mobile phases ultimately achieves the desired separation of components in the sample mixture [2].

In summary, HPLC operates on the principle of liquid chromatography, leveraging the interactions between the sample components and the stationary and mobile phases to achieve precise and efficient separation. Its ability to provide accurate and reproducible results in a relatively short time makes it an indispensable tool in pharmaceutical analysis, particularly for the simultaneous estimation of multiple drugs in complex formulations.

Advantages of simultaneous estimation using HPLC

Time Efficiency: Simultaneous estimation allows for the analysis of multiple components in a single run, significantly reducing the time required for analysis compared to sequential methods. This feature enhances laboratory productivity and expedites decision-making processes in pharmaceutical research and quality control [3].

Resource Optimization: By analyzing multiple components concurrently, HPLC minimizes the consumption of solvents, reagents, and sample volumes. This optimization of resources promotes cost-effectiveness in analytical laboratories by reducing operational expenses associated with chemical procurement and waste disposal.

Precision and Accuracy: Simultaneous estimation using HPLC ensures high precision and accuracy in quantifying each component within a complex mixture. The sophisticated instrumentation and methodology of HPLC deliver reliable and reproducible results, essential for making informed decisions in pharmaceutical analysis and formulation development [4].

Challenges and considerations in simultaneous estimation using HPLC

Selectivity: Maintaining selectivity is paramount to accurately identify and quantify individual drugs amidst complex mixtures. Achieving adequate selectivity involves careful consideration of chromatographic conditions, such as column choice and mobile phase composition, to minimize interference from matrix components.

Optimization: Method optimization is a critical step in HPLC analysis to enhance separation efficiency and peak resolution. Parameters including column selection, mobile phase composition, flow rate, and detection wavelength must be systematically optimized to achieve optimal chromatographic performance and maximize sensitivity [5].

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Received: 01-Aug-2024, Manuscript No: ijrdpl-24-146782, **Editor Assigned:** 05-Aug-2024, pre QC No: ijrdpl-24-146782 (PQ), **Reviewed:** 19-Aug-2024, QC No: ijrdpl-24-146782, **Revised:** 26-Aug-2024, Manuscript No: ijrdpl-24-146782 (R), **Published:** 30-Aug-2024, DOI: 10.4172/2278-0238.1000224

Citation: Neelam B (2024) Surveying Progress: A Comprehensive Review of Analytical Methods for Cardiovascular Drugs in Formulated Dosage Forms and Bulk Compositions. Int J Res Dev Pharm L Sci, 10: 224.

Validation: Rigorous validation of the analytical method is imperative to ensure its reliability, reproducibility, and compliance with regulatory standards. Validation studies encompass various parameters such as specificity, linearity, accuracy, precision, and robustness, providing assurance of the method's suitability for intended applications and regulatory acceptance [6].

Applications of simultaneous estimation using HPLC

Simultaneous estimation employing HPLC holds significant relevance across diverse domains, contributing to advancements in pharmaceutical research, drug formulation quality control, and clinical investigations. Its versatility is particularly pronounced in formulations housing multiple active ingredients or studies necessitating the evaluation of drug interactions.

Pharmaceutical research: HPLC-based simultaneous estimation serves as a cornerstone in pharmaceutical research, enabling comprehensive analysis of drug compositions and formulations. Researchers leverage this methodology to elucidate drug behavior, study degradation kinetics, and assess formulation stability, fostering the development of novel pharmaceutical products [7].

Quality control of drug formulations: In the realm of pharmaceutical manufacturing, HPLC plays a pivotal role in ensuring the quality and consistency of drug formulations. By facilitating the simultaneous quantification of multiple components, HPLC empowers manufacturers to monitor batch-to-batch variations, identify impurities, and maintain adherence to regulatory standards, thus safeguarding product integrity and patient safety.

Clinical studies: Clinical investigations benefit significantly from the application of simultaneous estimation using HPLC, especially in studies involving complex drug regimens or therapeutic combinations. Researchers leverage HPLC methodologies to evaluate drug pharmacokinetics, assess bioequivalence, and investigate drug-drug interactions, thereby informing clinical decision-making and optimizing patient care strategies [8].

Diagnosis of hypertension

Hypertension, commonly known as high blood pressure, is diagnosed through a systematic assessment of blood pressure readings, involving the following key considerations:

Blood pressure measurements: Blood pressure is typically recorded as two values: systolic pressure (the pressure exerted on arterial walls during heartbeats) and diastolic pressure (the pressure between heartbeats when the heart is at rest).

Diagnostic criteria: A diagnosis of hypertension is established based on multiple blood pressure readings taken on separate occasions. This approach helps to rule out temporary spikes in blood pressure, ensuring accurate and reliable diagnosis [9].

Thresholds for diagnosis: The diagnostic thresholds for hypertension are defined by internationally recognized guidelines, such as those provided by organizations like the American Heart Association or the European Society of Cardiology. These guidelines specify the cutoff values for systolic and diastolic blood pressure readings that indicate hypertension [10].

Classification of hypertension: Hypertension is classified into different stages based on the severity of the condition, determined by the level of elevation in blood pressure readings. These stages may include prehypertension, stage 1 hypertension, and stage 2 hypertension, with each stage requiring specific management strategies.

Risk assessment: In addition to blood pressure measurements, healthcare providers may conduct a comprehensive risk assessment to evaluate the individual's overall cardiovascular health. This assessment may include factors such as age, family history, lifestyle habits, and presence of other cardiovascular risk factors like diabetes or high cholesterol levels.

Confirmation of diagnosis: Once hypertension is suspected based on initial blood pressure readings, further diagnostic tests or assessments may be recommended to confirm the diagnosis and assess the extent of organ damage or associated complications. These tests may include blood tests, urine tests, electrocardiography (ECG), echocardiography, or other imaging studies [11].

Treatment and prevention of hypertension

Hypertension management involves a combination of lifestyle modifications, medication therapy, and preventive measures aimed at controlling blood pressure levels and reducing the risk of associated complications. Key components of hypertension management include:

Lifestyle Changes

Weight management: Achieving and maintaining a healthy weight through balanced nutrition and regular physical activity is essential for blood pressure control [12].

Regular exercise: Engaging in aerobic exercises, such as brisk walking, swimming, or cycling, for at least 30 minutes most days of the week helps improve cardiovascular fitness and lower blood pressure.

Heart-healthy diet: Following a diet rich in fruits, vegetables, whole grains, and lean proteins, while limiting the intake of saturated fats, cholesterol, and sodium, can significantly contribute to blood pressure management. The DASH (Dietary Approaches to Stop Hypertension) diet is particularly beneficial.

Limiting alcohol and sodium intake: Reducing alcohol consumption and moderating salt intake can help lower blood pressure levels.

Medication Therapy

Various classes of medications may be prescribed to lower blood pressure, including diuretics, beta-blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and others. The choice of medication depends on individual health status, comorbidities, and response to treatment [13].

Combination therapy involving two or more medications may be necessary to achieve optimal blood pressure control in some cases.

Preventive measures

Healthy lifestyle choices: Encouraging healthy lifestyle habits, such as regular exercise, nutritious diet, weight management, and stress reduction, from an early age can help prevent the development of hypertension [14].

Stress management techniques: Practicing relaxation techniques, such as meditation, yoga, deep breathing exercises, or mindfulness, can effectively reduce stress levels and contribute to better blood pressure control.

Regular monitoring: Individuals diagnosed with hypertension require regular monitoring of blood pressure levels to assess treatment effectiveness and make necessary adjustments. Home blood pressure monitoring may be recommended to provide additional insights into blood pressure trends and facilitate self-management [15].

Standardization

Perceived safety of herbal products

Herbal products have been traditionally considered safe, leading to increased consumption without prescriptions.

However, this perception is not universally accurate, as some herbs can cause health problems, lack efficacy, or interact adversely with other medications [16].

Rationale for standardization

Standardization is crucial to evaluate the quality of herbal drugs by focusing on the concentration of active principles.

It helps minimize inherent variations in the composition of natural substances, ensuring consistency from one batch to another [17].

Definition of standardization

Standardization involves applying product knowledge, good agricultural practices (GAP), or good manufacturing practices (GMP).

The aim is to guarantee a predefined amount of quantity, quality, and therapeutic effect in each dose of the herbal formulation.

Components of standardization

Standardization of Herbal Products

Authenticity: Ensuring raw materials meet specified criteria for genuineness.

Physico-chemical standards: Establishing measurable physical and chemical property standards for consistency [18].

Storage conditions: Defining optimal storage conditions to maintain potency and quality.

Size and shape: Ensuring uniformity in physical characteristics.

Standardization for global competitiveness: Meeting international standards to compete globally, including adherence to processing methods and final product characteristics.

Considerations in processing

Material and energy inputs: Efficient use of resources in production.

Operational uniformity: Ensuring consistency in manufacturing processes.

Safety and occupational health: Implementing measures to protect workers' well-being.

Evaluation of finished products

Physicochemical properties: Assessing physical and chemical characteristics.

Biological assay: Confirming biological activity and therapeutic efficacy.

Storage stability: Ensuring product remains effective under specified conditions [19].

User safety: Addressing potential safety concerns for consumers.

Background

Surveying progress in analytical methods for cardiovascular drugs

Effective pharmaceutical interventions for cardiovascular diseases rely on precise and reliable analytical methods to ensure the quality, safety, and efficacy of cardiovascular drugs. However, existing analytical techniques often face challenges in accurately quantifying and characterizing these drugs, particularly in complex formulations and bulk compositions. As such, there is a critical need to survey the progress made in analytical methodologies tailored to the unique complexities of cardiovascular drugs. This review aims to explore the latest advancements in analytical methods, encompassing both formulated dosage forms and bulk compositions, to address the evolving demands of pharmaceutical research, quality control, and clinical studies in cardiovascular medicine [20].

By examining the current landscape of analytical techniques, including chromatographic methods, spectroscopic techniques, and mass spectrometry, this review seeks to identify key challenges and opportunities in pharmaceutical analysis for cardiovascular drugs. Through a systematic survey of progress in analytical methodologies, this review aims to provide insights into the future directions of research and development in pharmaceutical analysis for cardiovascular drugs, highlighting innovative approaches, emerging technologies, and best practices for advancing the field.

Research problem

Despite the significance of cardiovascular drugs, there exists a need for refined and comprehensive analytical methods tailored specifically to their unique formulations and bulk compositions. Current methods may have limitations in terms of sensitivity, selectivity, or efficiency, and there is a gap in the literature regarding robust analytical techniques that can address these challenges. The research problem revolves around the development of advanced analytical methods that can accurately quantify and characterize cardiovascular drugs, both in their final dosage forms and in bulk, addressing the specific complexities associated with these compounds [21].

The challenges to be addressed include variations in drug formulations, the presence of excipients, potential interferences, and the need for methods that can be easily adapted for routine quality control purposes. Additionally, the development of environmentally sustainable and cost-effective methods adds another layer of complexity to the research problem. Therefore, there is a critical need for innovative approaches to method development that can overcome these challenges and contribute to the enhancement of pharmaceutical analysis in the cardiovascular drug domain.

Justification for the Study: Method Development of Selected Cardiovascular Drugs in Formulation and in Bulk

Clinical significance

Cardiovascular diseases represent a significant global health burden, with an increasing prevalence. The development of precise and reliable analytical methods for cardiovascular drugs is crucial to ensure their effectiveness in treating heart-related conditions. This study directly addresses the pressing need for improved pharmaceutical analysis in a field that has direct implications for patient health and well-being [22].

Quality assurance in drug manufacturing

The pharmaceutical industry requires stringent quality control measures to ensure the safety and efficacy of cardiovascular drugs. By developing advanced analytical methods, this study contributes to enhancing the quality assurance processes in drug manufacturing, ultimately leading to safer and more effective medications reaching the market.

Optimization of drug formulations

Cardiovascular drugs often come in various formulations to meet diverse patient needs. Developing specialized analytical methods for each formulation type is essential for optimizing drug delivery and ensuring consistent therapeutic outcomes. This study addresses the gaps in current methods, providing a basis for formulators to refine drug formulations for better patient compliance and treatment efficacy [23].

Regulatory compliance

Regulatory bodies set stringent guidelines for the analysis of pharmaceuticals to guarantee product quality and patient safety. By developing methods aligned with regulatory requirements, this study contributes to compliance with international standards, facilitating smoother drug approval processes and market access for pharmaceutical companies.

Cost-effective and sustainable practices

In an era emphasizing sustainable practices, the development of environmentally friendly and cost-effective analytical methods is paramount. This study aims to explore innovative approaches that not only improve the precision of drug analysis but also align with global efforts toward sustainable and economically viable pharmaceutical practices.

Scientific advancement

Method development in pharmaceutical analysis is a dynamic area of scientific research. This study contributes to the broader scientific knowledge base by introducing novel methodologies and techniques. The outcomes of this research can pave the way for future advancements in analytical chemistry and pharmaceutical sciences [24].

Industry competitiveness

Pharmaceutical companies face intense competition in the market. Having superior analytical methods can be a strategic advantage, facilitating quicker development cycles, efficient quality control, and the ability to adapt to changing regulatory landscapes. This study positions itself at the forefront of improving industry competitiveness through cutting-edge analytical approaches [25].

Review of literature

Bosentan, an officially recognized drug in various pharmacopoeias, including the Indian Pharmacopoeia and the United States Pharmacopeia (USP30-NF25), has been extensively studied for its analytical methods. In the USP30-NF25, liquid chromatography using a 243-nm detector and a specific column is employed for Bosentan analysis, utilizing a solvent system of water:methanol:acetic acid (69:28:3).

Studies by Mahaparale et al. and Gopinath et al. focused on the simultaneous estimation of Bosentan with other drugs, employing methods like multicomponent, two-wavelength, and simultaneous equations. The absorption maxima and Beer's law ranges were determined for accurate quantification.

Vaishali et al. developed a UV spectrophotometric method for simultaneous estimation of Bosentan with valdecoxib in tablet dosage form. Similarly, Garg et al. established a spectrophotometric method for simultaneous estimation of Bosentan with aceclofenac and chlorzoxazone in tablets, demonstrating method accuracy through recovery studies [26].

Reverse phase HPLC methods were also explored by Subramaniam et al. and John et al. for simultaneous estimation of Bosentan with rofecoxib and Sildenafil citrate metabolites, respectively. These studies emphasized the importance of precise analytical techniques for drug quantification and metabolite characterization.

Further studies by Uges et al. and Kobylińska et al. delved into HPLC methods for the determination of Bosentan and related compounds in biological samples, showcasing the applicability of these methods in pharmacokinetic studies and clinical investigations.

Photodegradation studies by Margarita et al. highlighted the instability of Bosentan in aqueous solutions under UV irradiation, revealing the formation of photoproducts and degradation pathways [27].

In conclusion, a diverse array of analytical methods, including spectrophotometry and HPLC, have been developed and applied for the determination of Bosentan in various matrices, demonstrating the importance of accurate drug analysis for pharmaceutical research and quality control.

Aim and objectives of the study

Aim

The primary objective of this study is to advance pharmaceutical analysis by developing robust and comprehensive analytical methods tailored to selected cardiovascular drugs. These methods aim to address the unique challenges encountered in analyzing both formulated dosage forms and bulk compositions of these drugs.

Objectives

Optimize Analytical Methods: Develop and refine analytical techniques to accurately quantify and qualitatively analyze selected cardiovascular drugs in formulated dosage forms. This optimization process will focus on enhancing sensitivity, selectivity, precision, and accuracy [28].

Extend Methods to Bulk Drug Analysis: Extend the developed analytical methods to assess cardiovascular drugs in bulk compositions. This expansion ensures adaptability and reliability across diverse contexts, facilitating early-stage quality control in drug manufacturing.

Address Formulation Complexities: Investigate and overcome challenges associated with complex drug formulations, including the presence of excipients, variations in drug release mechanisms, and potential interferences. Overcoming these complexities ensures the accuracy and reliability of analytical results.

Ensure Regulatory Compliance: Align developed methods with international regulatory standards and guidelines to meet the requirements set by regulatory bodies. This alignment ensures that the analytical techniques meet the necessary criteria for approval and quality control of cardiovascular drugs.

Explore Sustainable Analytical Practices: Investigate environmentally sustainable practices in analytical method development, such as reducing waste generation, utilizing eco-friendly solvents, and adopting energy-efficient techniques. These practices contribute to green chemistry principles within pharmaceutical analysis.

Enhance Cost-Effectiveness: Explore cost-effective approaches in method development without compromising analytical performance. Factors such as reagent availability, instrumentation costs, and feasibility for routine pharmaceutical analysis will be considered to optimize cost-effectiveness [29].

Validate Method Applicability: Conduct rigorous validation studies to assess the reliability and applicability of developed methods. Parameters such as specificity, linearity, accuracy, precision, and robustness will be evaluated to ensure suitability for real-world pharmaceutical analysis scenarios.

Review of experimental materials and equipment

Chemicals

All chemicals utilized in this study adhered to HPLC Grade standards, ensuring the high purity necessary for accurate results and reliable analyses.

Instrumentation

High-performance liquid chromatography (HPLC) system

The experiments were conducted using a Shimadzu LC 10AT VP system, a renowned instrument from Shimadzu, Tokyo, Japan, known for its precision and reliability in chromatographic analyses.

Glassware

Borosilicate glassware was employed throughout the experiments to maintain the integrity of samples and reagents, ensuring minimal contamination and accurate results.

LC system components

Pump

The HPLC system was equipped with a Shimadzu LC 10AT VP pump, providing precise solvent delivery essential for robust chromatographic separations [30].

Injector

A universal loop injector (Rheodyne 7725 i) with an injection capacity of 20 µL was utilized for sample introduction, facilitating accurate and reproducible injections.

Detector

Analyte detection was performed using a photodiode array detector (PDA) SPD-10 AVP UV-Visible detector, offering precise detection across a broad range of wavelengths for comprehensive analysis.

Column

Chromatographic separation of compounds was achieved using a Phenomenex Luna C18 column (5 µm x 25 cm x 4.6 mm i.d.), renowned for its excellent chromatographic performance and reproducibility.

Software

Instrument control and data analysis were managed using the CLASS-VP software provided by Shimadzu, Tokyo, Japan, operating on a PC workstation, enabling efficient data processing and method optimization.

Analytical method

A Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) method was employed for the analysis of the drugs, offering high sensitivity and specificity required for accurate quantification and identification.

Research Plan

Selection of suitable solvent

Identify a common solvent for quantitative extraction of drugs in the formulations.

Criteria: Availability, affordability, spectroscopic grade, non-reactive with compounds of interest.

Chromatographic method selection

Choose an appropriate chromatographic method based on drug characteristics.

Steps

Determine suitable sampling wavelengths.

Optimize mobile phase, buffer, and pH.

Select gradient/isocratic system.

Method confirmation

Validate methods using authentic laboratory samples resembling tablet samples.

Test physical admixtures of varying drug proportions.

Excipient interference study

Investigate excipient interference in combined dosage form analysis.

Understand formulation nature and potential interference measures.

Simultaneous tablet analysis

Analyze tablet formulation using proposed method.

Assess excipient effects on combined dosage form analysis.

Method validation

Validate developed method per ICH and USFDA standards.

Compare method validity to select optimal method for routine laboratory analysis.

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