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RP-HPLC Method Development and Validation for Simultaneous Estimation of Dextromethorphan Hydrobromide, Bilastine, and Phenylephrine Hydrochloride in Pharmaceutical Dosage Forms

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Abstract

Upper respiratory tract infections (URTIs) and allergic conditions represent a significant global health burden, accounting for frequent outpatient visits and extensive use of combination pharmaceutical products. Fixed-dose combinations containing dextromethorphan hydrobromide, bilastine, and phenylephrine hydrochloride provide comprehensive symptomatic relief by simultaneously addressing cough, allergic manifestations, and nasal congestion. Accurate and reliable analytical techniques are essential to ensure the quality, safety, and therapeutic efficacy of such multicomponent formulations. Reverse-phase high-performance liquid chromatography (RP-HPLC) has emerged as the most widely accepted analytical tool due to its sensitivity, precision, selectivity, and regulatory acceptance. This review critically examines the disease background, pharmacological relevance of the selected drug combination, fundamentals of RP-HPLC, analytical method development strategies, and validation parameters as per ICH Q2(R2) guidelines. Additionally, reported chromatographic methods for individual drugs and combination products are systematically evaluated, highlighting existing analytical gaps. The review strongly supports the need for a simple, robust, and validated RP-HPLC method for simultaneous estimation of dextromethorphan hydrobromide, bilastine, and phenylephrine hydrochloride in pharmaceutical dosage forms.

1. Introduction

Upper respiratory tract infections (URTIs) are among the most prevalent infectious diseases worldwide, affecting individuals across all age groups and contributing significantly to healthcare utilization and economic burden [1]. These infections are primarily viral in origin and are characterized by symptoms such as nasal congestion, rhinorrhea, sneezing, sore throat, cough, mild fever, headache, and malaise [2]. Although URTIs are generally self-limiting, symptomatic management remains essential to improve patient comfort and prevent complications.

Combination pharmacotherapy plays a crucial role in the management of URTIs and allergic conditions. The rational combination of an antitussive, an antihistamine, and a nasal decongestant offers synergistic therapeutic benefits. Dextromethorphan hydrobromide suppresses the cough reflex, bilastine alleviates histamine-mediated allergic symptoms, and phenylephrine hydrochloride reduces nasal congestion via vasoconstriction [3–5].

The increasing use of such fixed-dose combinations necessitates the development of reliable analytical methods capable of simultaneous estimation of all active components. Regulatory agencies emphasize validated analytical procedures to ensure batch-to-batch consistency, stability, and patient safety. RP-HPLC has become the analytical technique of choice for multicomponent pharmaceutical analysis due to its versatility, reproducibility, and compatibility with regulatory standards [6].

2. Upper Respiratory Tract Infections: Disease Overview

2.1 Pathophysiology

The pathophysiology of URTIs depends on the causative viral or bacterial pathogen. Influenza viruses cause extensive cytopathic effects on respiratory epithelial cells, whereas rhinoviruses primarily induce host-mediated inflammatory responses without significant epithelial destruction [7]. The release of inflammatory mediators such as histamine, bradykinin, and cytokines leads to vasodilation, increased vascular permeability, and mucus secretion, resulting in nasal obstruction, discharge, and throat irritation.

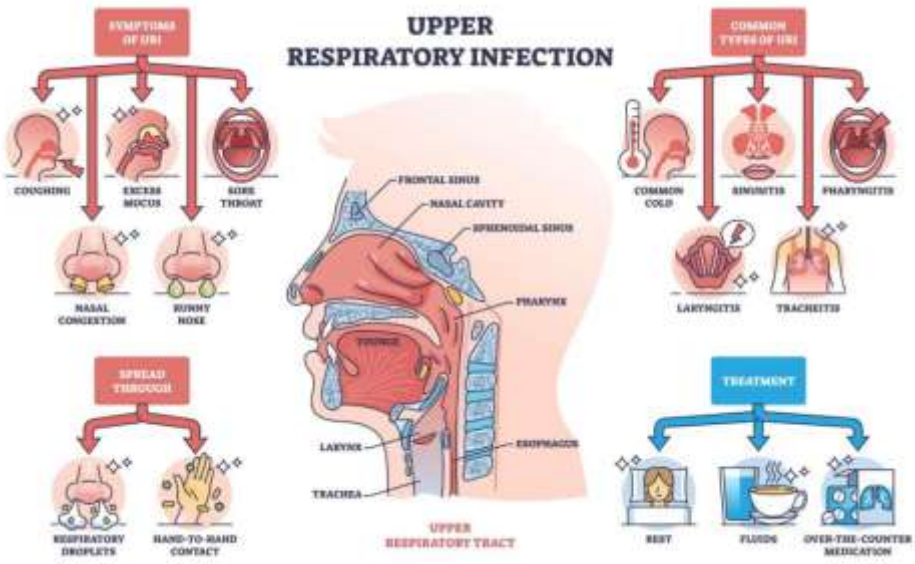

Fig.no.1: Overview of Upper Respiratory Infection

2.2 Epidemiology and Global Burden

Respiratory infections display strong seasonal trends, particularly in temperate climates, with peak incidence during colder months [8]. Children under five years of age experience the

highest frequency of infections, while elderly individuals and patients with comorbid conditions are more prone to severe disease and complications [9]. Rhinovirus and respiratory syncytial virus remain the most frequently detected pathogens worldwide.

Table 1. Causes and Clinical Manifestations of URTIs

Category	Details
Viral agents	Rhinovirus (30–50%), Coronavirus (10–15%), Influenza virus (5–15%), RSV, Adenovirus
Bacterial agents	Streptococcus pyogenes, Haemophilus influenzae, Moraxella catarrhalis
Predisposing factors	Poor immunity, smoking, air pollution, overcrowding
Common symptoms	Nasal congestion, rhinorrhea, sneezing, sore throat, cough
Systemic symptoms	Mild fever, fatigue, headache, malaise
Complications	Sinusitis, otitis media, bronchitis

3. Pharmacological Significance of Selected Drugs

3.1 Dextromethorphan Hydrobromide

Dextromethorphan hydrobromide is a widely used non-opioid antitussive agent that acts centrally on the medullary cough center to elevate the cough threshold [10]. In addition to its antitussive action, it exhibits NMDA receptor antagonism and sigma-1 receptor agonism, contributing to its neuromodulatory effects. Its favorable safety profile and non-addictive nature make it suitable for use in cough and cold formulations.

3.2 Phenylephrine Hydrochloride

Phenylephrine hydrochloride is a selective α1-adrenergic receptor agonist that produces vasoconstriction of nasal blood vessels, thereby reducing mucosal edema and nasal congestion [11]. At therapeutic doses, it exhibits minimal β-adrenergic activity, reducing the risk of cardiovascular adverse effects. It is commonly included in oral and nasal decongestant preparations.

3.3 Bilastine

Bilastine is a second-generation, non-sedating H1-antihistamine approved for the treatment of allergic rhinitis and chronic urticaria [12]. It demonstrates high selectivity for peripheral H1 receptors with negligible central nervous system penetration, minimizing sedation and cognitive impairment. Its long duration of action and excellent safety profile make it an ideal candidate for combination therapy.

4. Reverse-Phase High-Performance Liquid Chromatography

4.1 Principle of RP-HPLC

RP-HPLC is based on the differential partitioning of analytes between a non-polar stationary phase (commonly C18 or C8) and a polar mobile phase consisting of aqueous buffers and organic solvents such as methanol or acetonitrile [13]. Separation occurs due to hydrophobic interactions, enabling efficient resolution of compounds with varying polarity.

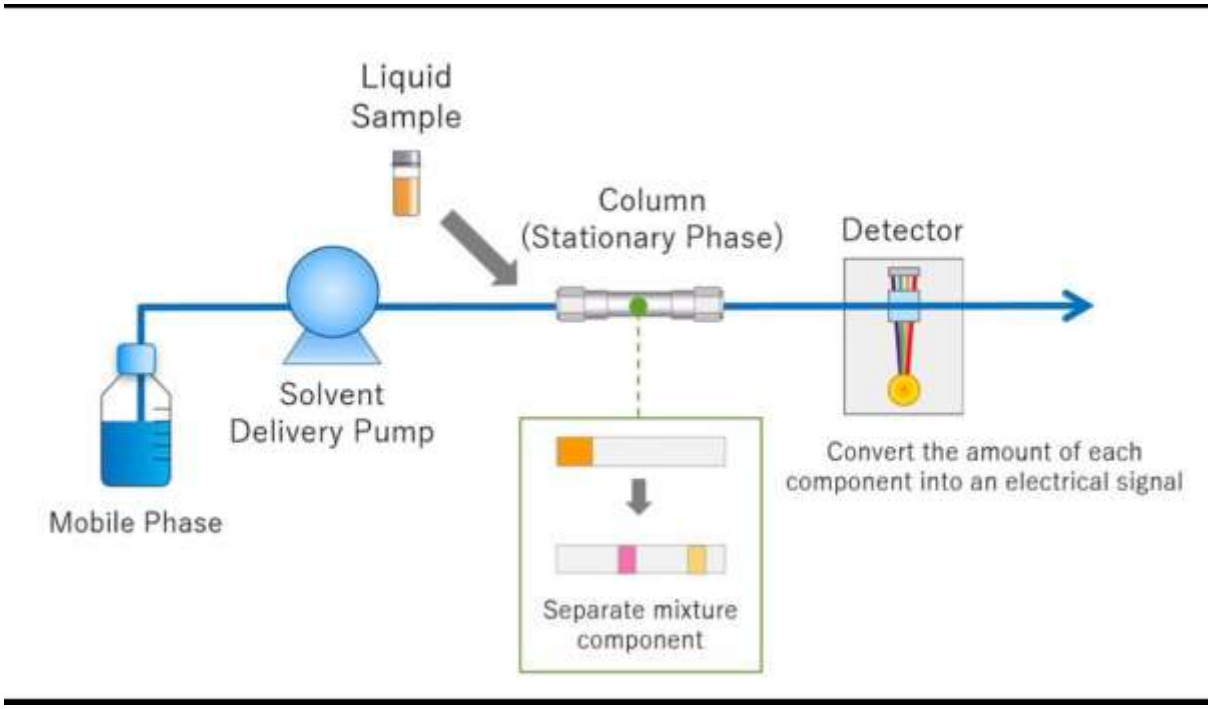

Fig. No. 2: Principle and Instrumentation of RP-HPLC

4.2 Applications in Pharmaceutical Analysis

RP-HPLC is extensively employed in pharmaceutical quality control for assay determination, impurity profiling, stability studies, dissolution testing, and bioequivalence evaluation [14]. Its adaptability to different detectors further enhances its analytical utility.

Table 2. Key RP-HPLC Method Development Parameters

Parameter	Role in Method Optimization
Mobile phase composition	Controls resolution and elution
pH of buffer	Influences ionization of analytes

Flow rate	Affects analysis time and resolution
Column chemistry	Determines Selectivity
Detection wavelength	Ensures sensitivity

5. Analytical Method Development Strategy

Analytical method development involves systematic optimization of chromatographic parameters to achieve acceptable resolution, peak symmetry, sensitivity, and reproducibility. Key variables include mobile phase composition, pH, flow rate, column chemistry, and detection wavelength [15]. Proper method development ensures robustness and reliability during routine analysis.

6. Analytical Method Validation as per ICH Q2(R2)

Method validation confirms that an analytical procedure is suitable for its intended purpose. Validation parameters include accuracy, precision, specificity, linearity, range, robustness, limit of detection (LOD), limit of quantitation (LOQ), and system suitability [16]. Compliance with ICH guidelines is mandatory for regulatory acceptance.

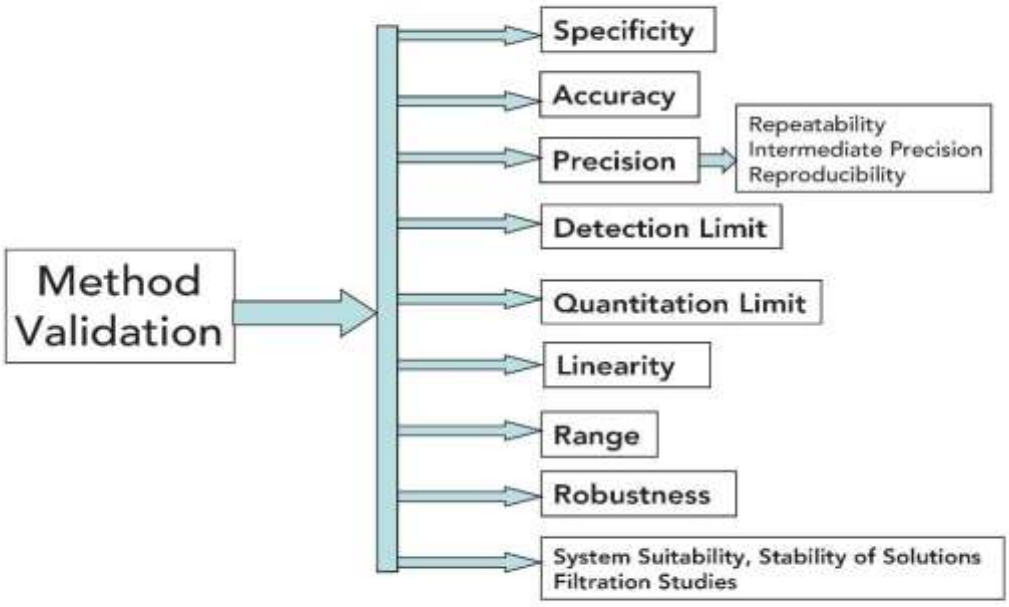

Fig. No. 3 : Analytical Method Validation (ICH Q2 (R2))

7. Review of Reported RP-HPLC Methods

Numerous RP-HPLC methods have been reported for the estimation of dextromethorphan hydrobromide, phenylephrine hydrochloride, and bilastine individually [17–24]. Limited methods are available for their simultaneous determination in combination products, with some employing complex mobile phases or longer run times [25–28]. These limitations highlight the need for a simplified, validated method suitable for routine quality control

8. Rationale for Simultaneous Estimation

The absence of a universally accepted RP-HPLC method for simultaneous estimation of dextromethorphan hydrobromide, bilastine, and phenylephrine hydrochloride necessitates further analytical research. A validated simultaneous method would reduce analysis time, solvent consumption, and cost while improving efficiency and reproducibility.

9. Conclusion

This expanded review emphasizes the pharmaceutical relevance of RP-HPLC in the simultaneous estimation of multicomponent formulations. The literature survey clearly indicates a gap in simple, robust, and validated methods for the combined analysis of dextromethorphan hydrobromide, bilastine, and phenylephrine hydrochloride. Development of such a method would be highly beneficial for routine quality control, stability testing, and regulatory compliance.

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