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Review

High-performance liquid chromatography-based analytical techniques for simultaneous determination of Naltrexone hydrochloride (NTX) and Bupropion hydrochloride (BUP): a comprehensive review

Sehrish Zehra[1] · Muhammad Asad Saeed[1] · M. Zaman[1] · Sadia Hassan[2] · Fazal-Ur-Rehman[3]

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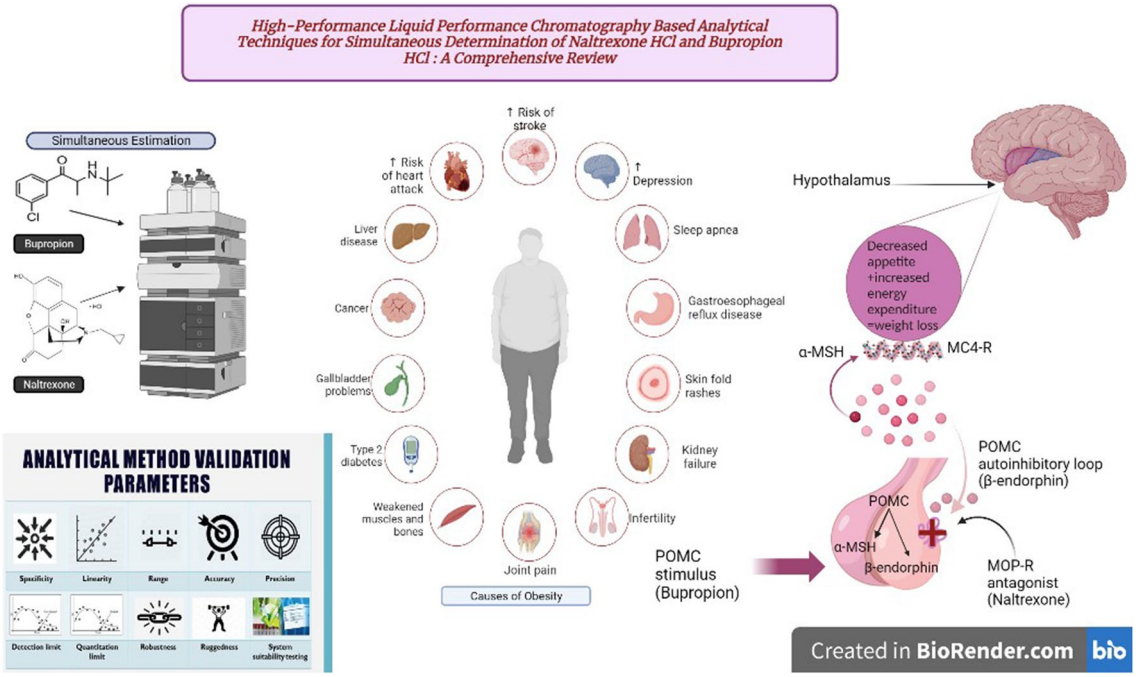
Abstract
The confluence of Bupropion Hydrochloride and Naltrexone Hydrochloride within a composite pharmaceutical formulation has garnered the prestigious endorsement of the U.S. Food and Drug Administration (FDA) for its targeted application in addressing the pervasive issue of obesity. Naltrexone hydrochloride, a semi-synthetic opioid compound, exerts its therapeutic influence through competitive antagonism of the mu receptors, while Bupropion hydrochloride, a tricyclic antidepressant, operates by impeding the reuptake of dopamine, thus amplifying its activity in distinctive cerebral domains. Notably, Naltrexone's impact is modulated through the intricate manipulation of pro-opiomelanocortin neurons within the hypothalamus, underscoring the amalgamated efficacy of this unique tandem in the protracted management of obesity. This scholarly exposition focalizes on the meticulous delineation of high-performance liquid chromatography (HPLC)-based analytical methodologies, meticulously tailored for the concurrent quantification of naltrexone hydrochloride (NTX) and bupropion hydrochloride (BUP). This comprehensive review scrutinizes an array of analytical strategies, traversing from archetypal HPLC (high performance liquid chromatography) methodologies to the burgeoning realm of environmentally conscious chromatographic approaches. Each method undergoes scrupulous examination, elucidating the nuanced applications, from the constitution of the mobile phase and judicious column selection to the refinement of optimal flow rates. Moreover, the review orchestrates a comprehensive evaluation of the validation parameters intrinsic to these analytical approaches, fortifying the reliability and precision of their findings. This erudite exploration not only encapsulates the diversity of chromatographic techniques but also expounds on the methodological robustness that underpins the determination of these pharmacologically significant compounds. In doing so, it elevates the pursuit of scientific excellence in pharmaceutical analysis, contributing significantly to the ongoing discourse in this critical field.

✉ Sehrish Zehra, sehrishzehra151@gmail.com | [1]Department of Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan. [2]Department of Biomedical Engineering and Sciences, School of Mechanical and Manufacturing Engineering, National University of Sciences and Technology, Islamabad, Pakistan. [3]Department of Chemistry, Lahore Garrison University, Lahore, Pakistan.

Graphical abstract



Article Highlights

1. Explores wide range of HPLC based analytical procedures for simultaneous estimation of Naltrexone HCl and Bupropion HCl.
2. Comprehensive evaluation of validation parameters to increase reliability and precision of methods.
3. Simultaneous estimation of different API's is advantageous in terms of saving cost, time, energy and resources
4. Validates HPLC as an accurate, robust and technique of choice as an analytical tool.

Keywords Estimation · Naltrexone HCl · Bupropion HCl · Simultaneous · HPLC

1 Introduction

According to the World Health Organization, obesity has emerged as a profound challenge of the twenty-first century, with over 1 billion individuals classified as obese. This global concern transcends age, affecting not only adults but also a staggering 390 million children. Distressingly, every fifth woman grapples with obesity, with these numbers exhibiting an upward trajectory. Simultaneously, a significant segment of the populace is embroiled in an opioid crisis. The American Medical Association reports that up to 19% of the human population encounters opioids due to medical conditions or addiction. Consequently, obesity and opioid dependence have surged due to lifestyle choices, medical predispositions, and dietary habits. Varied therapeutic modalities, encompassing lifestyle modifications and exercise regimens, are recommended for these conditions. Yet, medical interventions, including medications such as Naltrexone HCl and Bupropion, are also prescribed by healthcare practitioners. These drugs, recognized for their efficacy in addressing obesity and opioid dependence respectively, have gained widespread acceptance globally. However, stringent regulatory guidelines governing their prescription and distribution stem from their potential for abuse and dependency. Accurate quantification of these drugs in their formulations becomes imperative to comply with these regulations [13, 18, 22, 26, 27].

An array of analytical techniques exists for precise drug estimation, notably chromatography and spectrometry-based methodologies. Chromatography stands as a robust tool for separating and identifying components within mixtures,

finding application across diverse domains from food and drugs to environmental analysis. Its utility extends to diagnosing diseases, monitoring treatment progress, and even identifying novel pharmaceuticals. Conversely, spectrometry-based techniques rely on interactions between electromagnetic radiation and materials, furnishing detailed insights into atomic and molecular energy levels and transitions, facilitating identification and quantification of compounds. Techniques such as UV–Vis, IR, NMR, and mass spectrometry fall under this category, finding myriad applications in scientific disciplines. The choice between chromatography and spectrometry hinges upon specific analysis requisites, with chromatography primarily used for purification and separation, while spectrometry aids in identification, structural elucidation, and quantitative analysis. Often, these techniques complement each other, synergizing for comprehensive outcomes.

In the pharmaceutical sphere, chromatography-based techniques assume paramount importance, pivotal in drug development, product analysis, impurity detection, pharmacokinetics, and bioavailability studies. High-performance liquid chromatography (HPLC) emerges as a cornerstone analytical method, facilitating the precise quantification and separation of compounds within pharmaceutical formulations. Renowned for its high sensitivity, specificity, and selectivity, HPLC has gained prominence as the method of choice for simultaneous determination of multiple drugs in pharmaceutical formulations in recent years [4, 12, 14, 15, 29].

Given the widespread use of bupropion hydrochloride and naltrexone hydrochloride, their analytical methodologies have been extensively explored in literature. This paper presents a comprehensive survey of HPLC techniques documented in literature for the concurrent quantification of these compounds in pharmaceutical formulations. The review aims to intricately analyze reported HPLC methods in this context, delving into aspects such as stationary and mobile phases, and detection methods. Furthermore, the validation of these methods, encompassing development, optimization, and validation parameters, is thoroughly discussed [6, 20]. The paper navigates through the nuances of method development using HPLC, elucidating the factors influencing it. Subsequently, it explores the chemical compositions of both drugs and their specifics. The examination extends to detection methods for these compounds, culminating in a comprehensive analysis and conclusion.

2 Method development using HPLC

The development of analytical methods through High-Performance Liquid Chromatography (HPLC) is an intricate process that entails the systematic refinement and validation of techniques for the precise separation, identification, and quantification of specific compounds. This study focuses exclusively on the application of HPLC for the simultaneous determination of naltrexone hydrochloride (NTX) and bupropion hydrochloride (BUP), delving into the efficacy and feasibility of HPLC methodologies in accurately quantifying these compounds concurrently. The steps involved in the method development are demonstrated in Fig. 1.

Numerous indispensable factors underpin the method development process utilizing HPLC which are explained below.

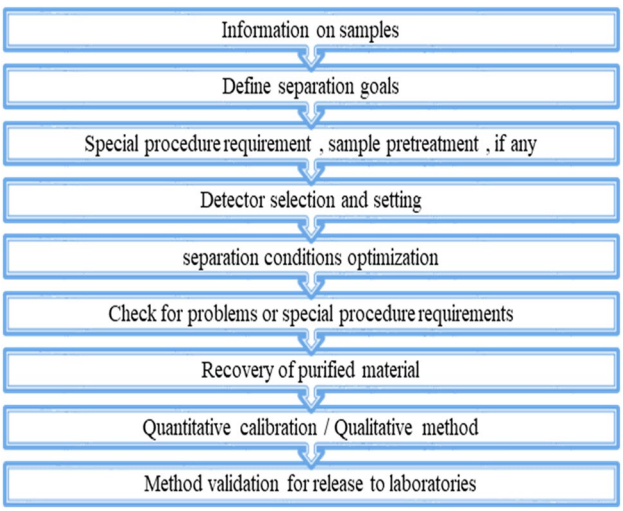


Fig. 1 Steps for method development using HPLC

2.1 Selection of stationary phase

The selection of a suitable stationary phase in HPLC stands as a pivotal juncture in method development, exerting direct influence on compound separation and resolution. It significantly impacts analyte selectivity and retention during chromatography. Stationary phases encompass diverse categories such as Reversed-Phase (C18, phenyl, C8, C4), Normal-Phase (Silica, Cyano), Size Exclusion, and Ion-Exchange. The choice hinges on analyte properties and the requisite separation criteria. For instance, in the context of BUP HCl and NTX HCl, commonly utilized stationary phases are C18 and C8 columns [1, 8, 16, 40].

2.2 Selection of mobile phase

Equally critical is the selection of the mobile phase, pivotal in determining elution time and analyte separation. Comprising solvents like Methanol, Acetonitrile, and Water, with or without ion-pairing agents, the mobile phase facilitates analyte movement. These solvents have proven effective in the separation of Naltrexone HCl and Bupropion HCl. Addition of ion-pairing agents, such as tetrabutylammonium bromide, has been reported to enhance analyte retention and separation [1, 3, 7, 16].

2.3 Selection of detection method

The choice of detection method holds significant weight, defining the sensitivity and specificity of the approach. Common methods for estimating Bupropion HCl and Naltrexone HCl include UV–Visible spectroscopy for its simplicity and widespread availability, while mass spectrometry offers heightened sensitivity, specificity, and selectivity, particularly beneficial for analyzing these compounds in complex matrices [1, 7].

2.4 Method optimization

Optimization constitutes a meticulous process aimed at fine-tuning various parameters to achieve desired separation, resolution, and sensitivity. Wavelength, mobile phase composition, pH, flow rate, column temperature, and injection volume undergo optimization. This critical step is essential for enhancing method performance, minimizing analysis time, refining peak shape, and maximizing compound separation. Once the method has been developed and optimized, it must be validated to ensure that it is accurate, precise, and robust. There are multiple factors studied and considered for the validation of the HPLC methods [5, 19, 20, 28, 39] as shown in Fig. 2 below:

2.5 Method validation

Method validation is an important step for pharmaceutical product development to check the suitability of the test for its intended purpose. Through method validation, quality, reliability and consistency of analytical results is confirmed. Different types of tests are performed in method validation. The details are explained in the following sections.

2.5.1 Linearity

Linearity in analytical methods is the measure of how well a method can reflect changes in substance concentration. It is like tuning an instrument to make sure it hits the right notes across a wide range. Imagine it as a musical scale where each note corresponds precisely to its place, allowing us to accurately measure substances in different amounts. This is done by experimenting with different standard solutions at varying concentrations and plotting what we call a calibration curve—a visual guide that helps ensure our measurements stay accurate, no matter the concentration we are dealing with.

Fig. 2 Details of method validation in HPLC

2.5.2 Range

The concentration range pivotal to an analytical method's precision and accuracy is a fundamental parameter in its characterization. This range, established through meticulous assessment, involves the systematic analysis of standard solutions across a gradient of concentrations. Subsequent determination of the limits of detection (LOD) and quantitation (LOQ) is imperative in this process. These metrics delineate the lower boundaries of reliably detectable analyte concentrations (LOD) and the minimum levels accurately quantifiable (LOQ). Therefore, the scope of the method is meticulously defined by these critical thresholds, ensuring its competence in effectively and precisely measuring analytes within a specified concentration range [6].

2.5.3 Accuracy

Accuracy stands as a pivotal measure in assessing the fidelity of measured values to the actual values within analytical methodologies. In the context of analytical methods, accuracy delineates the proximity of acquired results to the true quantity being measured. The evaluation of accuracy typically involves the utilization of spiked samples, a method wherein a known quantity of the analyte is deliberately introduced into a sample. Subsequently, the percentage recovery, elucidating the degree of successful analyte retrieval, undergoes assessment. An accurate method is characterized by a percentage recovery falling within predefined acceptable bounds, affirming the close alignment of measured values with the true concentrations of the analyte [5].

2.5.4 Precision

Precision, a critical aspect of method evaluation, is used to assess the analytical method's reproducibility**.** This assessment involves examining spiked samples and subsequently computing the percentage relative standard deviation (%RSD). Through this metric, researchers can precisely quantify the extent of variability or dispersion within results obtained from multiple measurements of the same sample. Analyzing precision in this manner offers crucial insights into the method's uniformity and trustworthiness, providing researchers with a means to gauge its reproducibility and consistency [6].

2.5.5 Selectivity

Selectivity, a crucial parameter in analytical methodology, serves to discriminate between target analytes and interfering substances. It embodies the method's capacity to precisely measure the desired analyte even when amidst other compounds or potential interferences. The essence lies in the method's adeptness to accurately detect and quantify the intended analyte while mitigating the influence of extraneous factors. High selectivity guarantees the analytical method's proficiency in distinguishing and quantifying the desired analyte with minimal disruption from other constituents, thereby elevating the dependability and accuracy of the measurements [23, 31].

2.5.6 Robustness

This parameter is used for producing consistent results under varying method conditions. "Robustness" within an analytical context refers to the capacity of a method to maintain consistent and dependable results despite encountering variations in experimental conditions. It delves into the method's resilience when faced with alterations in factors like temperature, pH, and other environmental variables. Robustness evaluations involve deliberately introducing controlled changes to these conditions and observing their effects on the method's performance. By systematically assessing how different conditions influence the outcomes, researchers ascertain the method's ability to uphold accuracy and precision across diverse settings. This exploration aims to validate the method's reliability and applicability under realistic and fluctuating conditions, enhancing confidence in its utility within analytical practice [6, 43].

3 Details of drugs

High-performance liquid chromatography (HPLC) stands as a widely utilized method within the pharmaceutical sector, serving as the primary analytical tool for scrutinizing numerous drugs and Active Pharmaceutical Ingredients (APIs). This investigation specifically targets the examination of Naltrexone hydrochloride and bupropion hydrochloride. Detailed information regarding both substances is outlined subsequently.

3.1 Naltrexone hydrochloride

As an FDA-approved medication, Naltrexone hydrochloride falls within the class of opioid receptor antagonists, as shown in Fig. 3 [37], finding primary application in the treatment of alcohol and opioid dependence. This compound, formulated as the salt derivative of naltrexone, demonstrates augmented solubility and stability properties. Its presence is notable across various generic products like RiVia, Vivitrol, and Depade, where the Naltrexone hydrochloride salt is a key constituent. Beyond its role as an opioid antagonist, its utilization extends to appetite suppression, aimed at mitigating food cravings [38, 41, 44].

3.2 Bupropion hydrochloride

In the realm of pharmaceuticals, Bupropion stands as a multifaceted antidepressant known for its auxiliary benefits in curbing cravings and supporting smoking cessation efforts. Its mechanism of action revolves around modulating specific neurotransmitter levels in the brain, particularly norepinephrine and dopamine. The hydrochloride formulation of Bupropion, known as Bupropion hydrochloride, represents the salt variant of the compound. The structure of bupropion

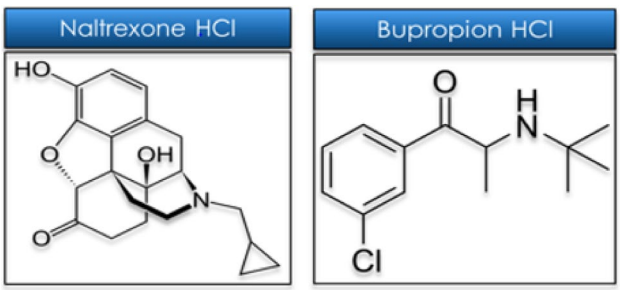


Fig. 3 Structure of Naltrexone HCl and Bupropion HCl

HCl is provided in Fig. 3 [37]. Functionally, Bupropion hydrochloride operates as a dopamine and norepinephrine reuptake inhibitor, fostering a sense of satiety. This compound falls within the aminoketone classification, characterized by its high lipophilicity, and manifests its effects through the blockade of nicotine receptors by impeding epinephrine and norepinephrine reuptake [8]. Commercially, it is accessible under varied brand names like Wellbutrin, Zyban, and Forfivo X.

3.3 Combination of Naltrexone hydrochloride and Bupropion hydrochloride

In a quest to harness potential synergies and leverage complementary mechanisms of action, the combination of Naltrexone hydrochloride and Bupropion hydrochloride salts has been formulated into a singular dosage form. This union aims to capitalize on the distinct therapeutic properties of both active pharmaceutical ingredients (APIs), envisaging enhanced weight loss outcomes. The disparate mechanisms underlying each compound's action serve as a foundation for their constructive collaboration in the realm of weight management. Naltrexone operates as an antagonist to opioid receptors, impeding the effects of opioids within the body and curbing cravings for food and potentially addictive substances. Conversely, Bupropion influences the equilibrium of specific neurotransmitters, such as norepinephrine and dopamine, crucial in appetite control and reducing food consumption. The amalgamation of these medications capitalizes on their individual merits, fostering a collaborative effect to bolster endeavors aimed at weight reduction [17, 24, 35].

Commercially available as Contrave, this medication represents the convergence of Naltrexone hydrochloride and Bupropion hydrochloride salts, duly sanctioned by the FDA for chronic weight management among overweight or obese adults grappling with weight-associated comorbidities like hypertension or type 2 diabetes. Despite the precise mechanism of action for weight loss facilitated by Contraves remaining partially elucidated, conjecture suggests its involvement in regulating appetite, mitigating food cravings, and modulating energy equilibrium.

4 Analytical methods for Naltrexone hydrochloride and Bupropion hydrochloride

Naltrexone hydrochloride and Bupropion hydrochloride can be analyzed and quantified by using HPLC and spectrometry-based analysis. The details of all the methods are given below.

4.1 HPLC based methods for Naltrexone hydrochloride and Bupropion hydrochloride

High-Performance Liquid Chromatography (HPLC) methods have long been established for the individual analysis of Naltrexone hydrochloride and Bupropion hydrochloride, key constituents in pharmaceutical production. With the advent of their combination in pharmaceutical formulations, the necessity arises to develop a simultaneous detection method.

The concurrent quantification of these compounds is paramount in ensuring the quality and consistency of combination drug formulations incorporating Naltrexone hydrochloride and Bupropion hydrochloride. This paper underscores the pivotal role of accurate and reliable simultaneous estimation techniques in upholding stringent standards of product quality. A myriad of analytical techniques exists in literature and industrial applications for this purpose, spanning bulk drugs and single pharmaceutical dosage forms. Notably, High-Performance Liquid Chromatography (HPLC)-based methods have gained prominence due to their exceptional sensitivity, selectivity, and efficiency in handling multiple samples. This review focuses on delineating various available analytical methods, spotlighting the significance and advantages of employing HPLC-based techniques for the concurrent estimation of these medications [1, 5, 7, 25, 39].

The primary aim of this literature review is to comprehensively outline the High-Performance Liquid Chromatography (HPLC) methodologies established and validated for the simultaneous quantification of Naltrexone hydrochloride and Bupropion hydrochloride across diverse pharmaceutical dosage forms. The paper aims to offer an extensive analysis of HPLC techniques, encompassing their development, validation, and practicality in accurately determining drug concentrations within pharmaceutical formulations [1, 5, 9].

Recognized as a widely employed analytical method, High-Performance Liquid Chromatography (HPLC) has seen numerous methodologies devised and validated for the effective and precise simultaneous detection of Naltrexone hydrochloride (NTX) and Bupropion hydrochloride (BUP) in varied pharmaceutical formulations [8, 36]. Table 1 presents a comprehensive account of these methodologies, elucidating their intricacies and specific approaches utilized.

Table 1 Summary of HPLC-based methods for simultaneous estimation of naltrexone hydrochloride and bupropion hydrochloride

Sr no.	Method	Mobile phase	Column	UV detection (nm)	Flow rate (mL/min)
1	RP-HPLC	ACN:TEA(55:45)	C-18	215	1.2
2	RP-HPLC	ACN:KH2PO4 (70:30)	Nuceosil C-18	214	1.35
3	RP-HPLC	ACN:methanol:water (20:60:20)	Chromosil C-18	254	1
4	RP-HPLC	Triethanolamine:SLS:propanol	RP-C18	210	1.2
5	RP-HPLC	Buffer:CAN (60:40)	C-18	224	1
6	RP-HPLC	*N*,*N*-Diisopropylethylamine:water (25:75)	C-18	251 281	1.2

4.2 RP-HPLC (reversed-phase high-performance liquid chromatography based methods

RP-HPLC commonly employs stationary phases like octadecylsilane (C18) or octyl silane (C8) in their compositions, paired with a blend of water (as the aqueous phase) and an organic solvent like acetonitrile or methanol (as the organic phase). These identical stationary and mobile phase combinations were employed for the analysis of Naltrexone hydrochloride (NTX) and Bupropion hydrochloride (BPU). Numerous studies detailed in the literature have elaborated on these methodologies extensively.

4.2.1 Study 1

In their 2013 research, Srikalyani and colleagues meticulously outlined a validated reversed-phase high-performance liquid chromatography (RP-HPLC) technique. This method aimed to simultaneously detect naltrexone hydrochloride (NTX) and bupropion hydrochloride (BUP) within bulk and pharmaceutical dosage forms. The analytical process utilized a C18 column and a precisely optimized mobile phase consisting of acetonitrile and 0.05% triethylamine (pH 6.5) (55:45) using isocratic mode at a consistent flow rate of 1.2 mL/min. Detection of the target compounds relied on UV spectroscopy at a specific wavelength of 215 nm. Notably, this method exhibited good linearity and correlation coefficient of 0.999 for naltrexone and 0.998 for bupropion. The study's analytical findings underscored the efficiency and reliability of this HPLC approach, displaying its potential significance in pharmaceutical quality control and drug formulation evaluation [40].

4.2.2 Study 2

Apostilidi et al. investigated introducing an alternative RP-HPLC methodology using a Nucleosil C18 column paired with a mobile phase composed of acetonitrile and potassium dihydrogen phosphate (70:30). The UV detection was set at 214 nm with pump flow rate of 1.35 mL/min highlighting a noteworthy Limit of Quantification (LOQ) of 0.500 µg/mL for naltrexone HCl and 1 µg/mL for bupropion HCl. This research significantly contributes to the existing knowledge repository concerning the concurrent determination of these two drugs, offering an additional avenue for their analysis within pharmaceutical dosage forms. The study emphasizes the adaptability of the C18 column and the specific mobile phase formulation in achieving effective separation and detection of naltrexone hydrochloride (NTX) and bupropion hydrochloride (BUP). The disclosed UV detection wavelength and LOQ values offer crucial insights beneficial for researchers and analysts engaged in pharmaceutical analysis, propelling advancements in analytical techniques vital for drug development and quality control [2].

4.2.3 Study 3

Numerous strides have been taken to augment the effectiveness and user accessibility of these methodologies. An illustrative instance is evidenced in the research conducted by Phani et al., where they refined an RP-HPLC technique employing a phenomex chromosil C18 column. The mobile phase consisted of a blend of acetonitrile, methanol and water at a proportion of 20:60:20 (pH 4.8), with detection executed at a wavelength of 254 nm. The detection and quantitation limits for Naltrexone HCl and Bupropion HCl were determined to be 0.5 µg/mL and 1.7 µg/mL,

respectively. The commercial product claimed 99.5% and 99.7% for bupropion HCl and naltrexone HCl, respectively and method explained in this study was effective to quantify both APIs and the results fell well within the specified range which affirmed the reliability and robustness of the method. Such discoveries significantly enrich the landscape of analytical approaches in pharmaceutical studies, furnishing scientists and analysts with a sensitive and resilient RP-HPLC protocol essential for precise quantification in drug development, quality assurance, and formulation evaluation.

4.2.4 Study 4

In their research, Gawad et al. introduced an innovative method to simultaneously detect Bupropion HCl and Naltrexone HCl in human urine samples. As stationary phase they employed a RP-C18 column (150 mm × 4.6 mm, 5-µm particle size) combined with a mixture of mobile phase, comprising of 3 components stated as 0.3% triethanolamine, 0.175 M sodium dodecyl sulphate and 12% *n*-propanol in 0.02 M phosphoric acid. Flow rate of the pump was adjusted to 1.2 mL/min. The pH of the developing system was adjusted at 3.5. The detection wavelength was set at 210 nm, establishing a Limit of Quantification (LOQ) for both substances at 0.30–0.93 µg/mL. Comparative analysis against existing methods underscored notable improvements in Linearity and detection limits using this approach. By strategically using a C18 column alongside the modified mobile phase, they effectively identified the targeted compounds simultaneously, offering valuable insights for researchers and analysts in pharmaceutical analysis. These findings significantly advance analytical methodologies, especially in ensuring reliable quantification in drug-related investigations, particularly concerning human samples [1].

4.2.5 Study 5

In 2015, Haritha et al. conducted a study that introduced a reversed-phase high-performance liquid chromatography (RP-HPLC) technique for concurrently assessing naltrexone hydrochloride (NTX) and bupropion hydrochloride (BUP) in tablet dosage forms. Their method involved utilizing a C18 column (4.6 × 250 mm, 5 µm) coupled with a mobile phase composed of buffer and acetonitrile in a specific proportion of 60:40 (v/v). They operated the system at a flow rate of 1.0 mL/min and employed UV detection at a wavelength of 224 nm. The retention time of Naltrexone HCl and Bupropion HCl was 2.5 and 4.6 min, respectively. Notably, they achieved a percentage purity of 99.63% for naltrexone HCl and 99.20% for bupropion HCl. These results present a highly effective and sensitive RP-HPLC methodology for the simultaneous determination of NTX and BUP in oral formulations. This method's encouraging feature was that it remained robust even when the mobile phase changed by ± 5% at lower flow conditions. The precise mobile phase composition and optimized detection parameters significantly enhance the method's precision and reliability, offering researchers and analysts a robust means to accurately quantify these compounds across diverse analytical contexts [21].

4.2.6 Study 6

Trivedi et al. introduced a comprehensive High-Performance Liquid Chromatography (HPLC) technique utilizing a C18 column and green mobile phase consisting of *N*,*N*-Diisopropylethylamine (pH 6.5) and water. The composition of mobile phase used was (25:75 v/v). For elution of components isocratic pump was used and temperature was maintained at 20 °C. Detection wavelength of 251 and 281 nm was employed to monitor the eluents. The retention time of Bupropion HCl was 2.692 min and Naltrexone HCl was 4.56 min. The percentage recoveries for both the eluents were found to be 99%. This method was validated as per ICH Guidelines and it complied with all validation parameters such as linearity, accuracy, precision, limit of quantitation limit of detention and system suitability [42].

Reversed-phase high-performance liquid chromatography (RP-HPLC) has emerged as the predominant technique for concurrently estimating bupropion hydrochloride and naltrexone hydrochloride due to its extensive utilization and inherent adaptability. RP-HPLC offers a versatile and comprehensive analytical methodology capable of handling diverse compound types encountered in pharmaceutical analysis. Its user-friendly operation further bolsters its practicality, establishing it as a preferred choice among researchers. Moreover, the method demonstrates exceptional accuracy and sensitivity, furnishing robust and reliable data for pharmaceutical product analysis. Hence, RP-HPLC stands as an invaluable analytical tool ideally suited for pharmaceutical quality control and characterization [10, 33, 34].

4.3 Spectrophotometric method

4.3.1 Study 7

Dighe et al. undertook an innovative investigation aiming to develop a spectrophotometric approach for simultaneously determining two drugs within their respective dosage forms. This novel method utilized a distinctive combination of concentrated sulfuric acid and acetic acid as a composite solution. Remarkably, this method highlighted exceptional precision and sensitivity, facilitating accurate quantification of both drugs across a range of pharmaceutical dosage forms. These outcomes offer significant insights into the realm of spectrophotometry by introducing a dependable and sensitive technique for simultaneous drug analysis. Its precision and sensitivity render it highly applicable in pharmaceutical contexts, particularly in the realms of formulation assessment and quality assurance [11].

4.3.2 Study 8

In a similar vein, Patel et al. engineered an innovative UV–Vis spectrophotometric method to concurrently estimate Naltrexone HCl and Bupropion HCl using a precisely formulated mixture of methanol and hydrochloric acid. This method exhibited outstanding sensitivity, simplicity, and precision, enabling the accurate quantification of both compounds. This study contributes to UV-Visible spectrophotometry by introducing a reliable and straightforward approach for simultaneous estimation of Naltrexone HCl and Bupropion HCl. Its sensitivity, simplicity, and precision make it universally applicable in pharmaceutical arenas, particularly in quality control and formulation analysis [30].

4.3.3 Study 9

Sai datri et al. also performed an analysis on 1800 double beam UV–visible spectrophotometer—Schimadzu. The absorption spectrum of reference and sample solutions were obtained using 1 cm quartz cells over the range of 200–400 nm. Linearity range for both naltrexone HCl and Bupropion Hcl was 2–10 µg/mL. recovery studies were also performed and the results of analysis were statistically validated. The method proved to be simple, rapid and practically useful in quality control laboratories [32].

5 Discussion

In the pursuit of simultaneous determination of Bupropion HCl and Naltrexone HCl, alternative analytical approaches have been explored, including spectrophotometric methods. While these methods offer simplicity and cost-effectiveness, it is imperative to acknowledge certain inherent limitations in terms of their sensitivity and selectivity when compared to chromatographic techniques. In this regard, a detailed comparison of these analytical techniques is discussed below in Table 2.

The spectrophotometric methods, albeit straightforward and economically viable, may encounter challenges in attaining the desired level of sensitivity required for accurate quantification of Bupropion HCl and Naltrexone HCl. Additionally, their ability to discern and differentiate between the target analytes and potential interfering substances may be comparatively limited when compared to the discriminating power offered by chromatographic methods. Nevertheless, it is worth acknowledging that spectrophotometric methods present valuable alternatives for preliminary analyses and screening purposes, where the demand for high sensitivity and selectivity may be less critical. Their simplicity and cost-effectiveness make them particularly suitable for rapid routine analyses or situations where extensive sample throughput is required. As the field of pharmaceutical analysis progresses, it is imperative to consider the specific analytical requirements of each study, weighing the benefits and limitations of the available techniques. While spectrophotometric methods offer practicality and cost-efficiency, the choice between these methods and chromatographic techniques should be made based on the specific objectives of the study, considering factors such as sensitivity, selectivity, precision, and accuracy. Spectrophotometric methods offer simplicity and cost-effectiveness in the simultaneous determination of Bupropion HCl and Naltrexone HCl. However, their utility may be limited by

Table 2 A detailed comparison of different analytical techniques for estimation of drugs

	UV–VIS	HPLC
Mechanism	Absorbance of 1 component at a time is measured	Separation of more than one component take place at a time
Accuracy and precision	Less precise and accurate	High accuracy and precision
Cost of analysis	Very low	High
Reagents/mobile phase/diluents	Polar solvents mostly	Multiple combinations of Buffers, Organic and polar solvents (HPLC Grade)
Instrument operation	Easy operation	complex
Parameters	Qualitative	Quantitative
Run time	Compared to HPLC, analysis is complete in less time	High run time—(depends upon elution of the component)
Resolution	Low resolution	Higher resolution
Sensitivity and selectivity	Limited sensitivity and selectivity	Highly sensitive and selective
Solvent consumption	Depends on cut-off value	Low
Injection volume	2.5–4 mL	2 µL
Advantages	• Quick and accurate • Non-destructive	• Quick and precise quantitative analysis • Extremely precise, fast and automated technique
Disadvantages	• Only for solutions • Not for solid/gaseous samples	• Expensive as it requires large electric supply and organic solvents • Difficulty in trouble shooting

their comparatively reduced sensitivity and selectivity when compared to chromatographic techniques. Therefore, the selection of the most appropriate analytical approach should be guided by the specific requirements and objectives of the study, ensuring that the chosen method aligns with the desired level of analytical performance [39].

6 Conclusion

The concurrent assessment of active drug ingredients proves advantageous in the simultaneous analysis of two medications, offering efficiency in method usage while economizing time, expenses, and resources. This study provides comprehensive insights into Naltrexone hydrochloride and Bupropion hydrochloride, outlining diverse approaches for their simultaneous estimation, with a specific focus on High-Performance Liquid Chromatography (HPLC) techniques.

Detailed exploration within this paper emphasizes various methodologies encompassing distinct stationary phases, mobile phase compositions, optimal detection wavelengths, and essential validation parameters. Remarkably, the utilization of Acetonitrile and water-based mobile phases demonstrated superior outcomes in analysis. Among the range of stationary phases evaluated, the octyldecylsilane-based C18 column emerged as most suitable for the precise detection of these two drugs.

Moreover, the paper delves into alternative methods incorporating acids and other chemical agents, elucidating associated challenges and considerations. The findings underscore the efficacy of HPLC-based methodologies as robust and accurate analytical tools for the simultaneous determination of diverse Active Pharmaceutical Ingredients (APIs), particularly Naltrexone hydrochloride and Bupropion hydrochloride, within pharmaceutical formulations.

7 Future recommendations

To broaden the horizons of these methodologies, future endeavors might delve into exploring their effectiveness in ascertaining drug concentrations within tissues and biological fluids. Such inquiries would yield invaluable insights into the pharmacokinetics and distribution of naltrexone hydrochloride and bupropion hydrochloride, fostering a more comprehensive comprehension of their therapeutic characteristics [19]. Later investigations are warranted to assess the feasibility of formulating analytical techniques employing environmentally friendly polar solvents, as this approach can deliver cost-effective and highly efficient methodologies. Embracing such solvents enables researchers to tackle sustainability concerns and curtail the environmental impact associated with analytical processes. These initiatives hold substantial promise in propelling the field of simultaneous estimation of naltrexone hydrochloride and bupropion hydrochloride forward, presenting innovative and eco-conscious alternatives to conventional solvent systems.

Author contributions SZ conceived the idea, collected the data and prepared the main manuscript. FR provided assistance in data collection. SH helped in data collection and final drafting of manuscript. MAS and MZ supervised the study and reviewed the final manuscript.

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Data availability The authors declare that the data supporting the findings of this study are available within the paper and its supporting supplementary files. The figures and tables are prepared by authors themselves after thorough study of available data.

Declarations

Competing interests The authors declare no competing interests.

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