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Review Article

Advancing Analytical Insights: A review Estimation Techniques for Acebrophylline and Erdostaine Acebrophylline, Erdosteine, Ultra Violet, HPLC High Performance Liquid Chromatography, Ultra Performance Liquid Chromatography

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ABSTRACT

The present review provides a comprehensive overview of the various analytical techniques used for the estimation of Acebrophylline and Erdosteine, two therapeutic agents primarily used in the management of respiratory disorders. Acebrophylline, a bronchodilator and anti-inflammatory agent, and Erdosteine, a mucolytic, have gained prominence in respiratory care. Accurate quantification of these drugs in bulk, pharmaceutical formulations, and biological matrices is crucial for quality control and pharmacokinetic studies. This review explores diverse analytical methods, including spectroscopic techniques (UV) chromatographic methods (HPLC, UPLC, TLC), and, highlighting their advantages, limitations, and applications. Special emphasis is placed on recent advancements such as green analytical chemistry approaches and stability-indicating methods. The review also discusses method validation parameters in accordance with ICH guidelines, including precision, accuracy, sensitivity, and specificity. This paper aims to serve as a reference guide for researchers and pharmaceutical analysts in developing robust methods for the routine analysis of Acebrophylline and Erdosteine.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disorder characterized by declining respiratory function and accompanied by various mental and physical comorbidities. It pose a major global health challenge, significantly impacting populations worldwide [1]. The

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condition significantly contributes to both illness and death, particularly in developing countries, while also placing a heavy strain on healthcare systems and leading to substantial global healthcare expenditures [2]. Chronic obstructive pulmonary disease (COPD) is a major global health concern, affecting more than 300 million individuals worldwide and causing approximately 2.9 million deaths annually. By 2040, COPD-related deaths are projected to increase by 32% to 4.4 million per year, elevating It from the ninth to the fourth leading cause of mortalité, following ischemic heart Disease, stroke and pneumonia[3].The world Health Organization (WHO) reports that ambient air pollution is responsible for 4.2 million deaths annually, while 3.8 million deaths are attributed to exposure to biomass fuel and inefficient stoves. Alarmingly, WHO estimates that 91% of the global population resides in regions where air quality fails to meet acceptable health standards [4].The primary objective of pharmacologic Therapy for COPD are to alleviate symptoms, enhance overall health status and exercise capacity, and prevent exacerbations. Although treatment plans are individualized based on each patient's needs, most maintenance therapies can be categorized into three main group inhaled corticosteroids, long-acting muscarinic antagonists (LAMA), and long-acting β_2 –agonists [5].

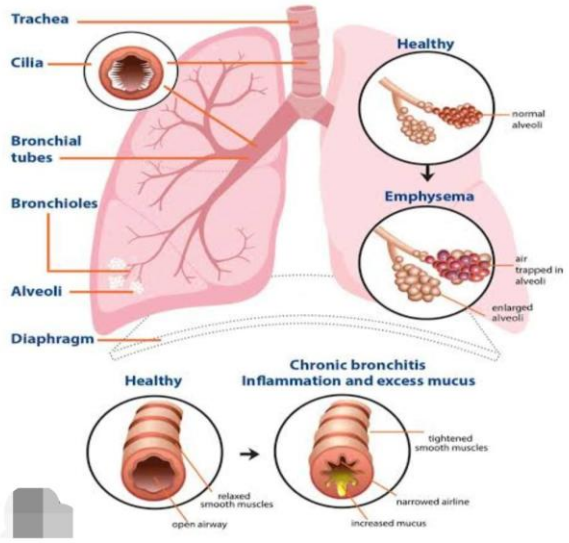

Figure1. The Lungs and Chronic Obstructive pulmonary Disease (COPD)[6].

Classification of (COPD): Major 3 type

Centriacinar COPD: Centriacinar COPD is the most common type of pulmonary COPD, primarly affecting the second and third respiratory bronchioles. The degree of lung tissue destruction varies between lobules. This form of COPD is strongly linked to cigarette smoking and dust inhalation, as evidenced by research dating back to the mid-20th century. Notably, the majority of COPD cases in heavy smokers are of the centriacinar type [7].

Panacinar COPD: In panacinar COPD, two type of disease distribution have been identified. a) Localized from- This type of COPD exhibits a multilobular distribution, indicating that the disease related changes are present in multiple lobules. However, the areas of lung damage remain relatively localized within specific regions

of the lung. b) Diffuse form- This form of the disease is not restricted to specific zones of the lung's anatomy and can manifest more uniformly across the lung. Unlike localized forms, it dose not show a preference for particular lung regions. This distinction is crucial in understanding the severity and extent of lung damage inn panacinar COPD. While the localized form involves discrete areas of damage [8].

Distal acinar COPD: It is a subtype of COPD, The Disease characterized by the enlargement of airspaces at the periphery of the acini. It is typically localized and most frequently observed along the dorsal surface of the upper lungs. This condition is often linked to fibrosis and may coexist with other COPD types. Although usually asymptomatic, distal acinar COPD is recognized as a potential cause of spontaneous pneumothorax, particularly in young adults, as demonstrated in studies by peters et al, (1978) and Lesur etc. al (1990)[9].

Pathophysiology of COPD: The development of COPD involves various process, with a key factor being the imbalance between protease and antiprotease activity, which results in the breakdown of alveolar walls. The details of this mechanism are outlined below.

Protease-Antiprotease Imbalance: Proteases are enzyme responsible for breaking down proteins, while antiprotease serve as their inhibitors. Maintaining a balance is between these two is essential for preserving lung tissue integrity. In COPD, this equilibrium is disrupted, leading to increased protease activity. The excessive protease activity causes damage to the alveoli, contributing to the disease's progression**.**

Reduced antiprotease activity: One of the most crucial antiproteases in the lung is alpha-1 antitrypsin (AAT), which inhibits elastase a protease that degrades elastin, a vital component of alveolar walls. The pathogenesis of COPD is driven by various process, with a key factor being the imbalance between protease and antiprotease activity. The imbalance ultimately results in the destruction of alveolar walls [10]. Repeated exposure of the lungs to harmful substances like tobacco triggers an inflammatory response. While initially protective, prolonged exposure leads to chronic inflammation, causing lung damage such as emphysema and fibrosis. This results in air trapping, reduced airflow, and conditions like COPD. Reducing exposure to harmful substance is crucial for lung health [11].

Parenchymal Destruction and Emphysema: In emphysema the breakdown of alveolar walls causes parenchymal destruction and loss of lung elastic recoil, hindering full exhalation. Combined with airway inflammation, this airflow limitation makes efficient breathing increasingly difficult [12].

Air Trapping and Hyperinflation: Narrow airways and lost elasticity trap air during exhalation, causing lung hyperinflation. This limits fresh air intake, especially during exercise when oxygen demand increases.

Dyspnea and Exercise Limitation: This sequence of events illustrates why COPD patients often develop worsening breathlessness over time, making it increasingly difficult to perform daily activities as the disease advances. Hypoxic vasoconstriction in small pulmonary arteries results in intimal hyperplasia and smooth muscle hypertrophy, which contribute to pulmonary hypertension. The progression of pulmonary

hypertension leads to right ventricular hypertrophy and ultimately causes right-sided heart failure [13].

COPD Diagnosis-Symptoms: It is recommended to universally measure COPD symptoms using tools like the COPD Assessment Test (CAT) and the modified Medical Research council (mMRC) dyspnea scale, alongside assessing airflow limitation and exacerbation history.

a) **CAT:** An 8 item questionnaire assessing the impact of COPD on health, including cough, phlegm, chest tightness and breathlessness.
b) **mMRC Dyspnea Scale:** Measures breathlessness severity, from exertion to interference with daily activities [14].
Category A: Patients with mild symptoms and low exacerbation risk. Early lifestyle changes, like smoking cessation, can improve outcomes significantly.
Category B: Patients with more symptoms but low exacerbation risk.
Category C: Patients with fewer symptoms but higher exacerbation risk.
Category D: Patients with severe symptoms and high exacerbation.

The categories help clinical tailor treatment to each group's needs, improving prognosis and reducing the burden of COPD [15].

Treatment: The true prevalence of COPD is likely higher than reported, as many case go undiagnosed due to early symptoms being mistaken for aging factor. This underreporting and under treatment pose major public health challenges**.**

Table 1: Treatment of COPD

Drug name	Class of drug	Therapeutic use
Salbutamol	Bronchodilator	Asthma, COPD, Bronchitis, Cystic fibrosis
Formoterol	Long-acting β_2 Adrenergic Receptor	Increase air flow, Reducing cough
Theophylline	Methylxanthines	Anti-inflammatory Effect
Oral steroids[16]	Corticoids	Respiratory, Immunosuppressive
Ampicillin	Betalactum antibiotic	Respiratory, Urinary tract, Gastrointestinal
Amoxicillin	Betalactum antibiotic	Respiratory, Urinary tract, Skin, Dental
Azithromycin	Macrolide antibiotic	Acute bronchitis
Benzyl Penicillin	Natural penicillin	COPD, Bronchitis
Cefotaxime	Cephalosporin	Respiratory, Skin, Urinary Tract
Gentamicin[17]	Aminoglycoside	COPD, Bacterial infection

Acebrophylline, a bronchodilator with anti-inflammatory and mucoregulating properties, combines ambroxol and theophylline-7 acetic acid. It is used to treat respiratory disorders like asthma and COPD. Ambroxol, a mucolytic agent, enhances lung function by promoting pulmonary surfactant production, reducing alveolar surface tension. Theophylline-7-acetic acid relaxes airway smooth muscles, improving airflow [18].The bronchodilator effect of Theophylline-7-acetate stems from its inhibition of intracellular phosphodiesterases, which raises cyclic adenosine breathing in respiratory conditions [19]. Ambroxol enhances mucociliary clearance by stimulating cilia motility, aiding in effective mucus stimulating cilia motility, aiding in effective

mucus removal. This dual action reduces congestion and alleviates respiratory symptoms [20]. Acebrophylline inhibits phospholipase A and phosphatidylcholine, key enzymes in producing pro-inflammatory substances like leukotrienes and tumor necrosis factor. By reducing these mediators, it minimizes airway inflammation, a primary cause of obstruction in conditions like asthma and COPD. This anti-inflammatory effect improves airflow and helps manage chronic symptoms [21].

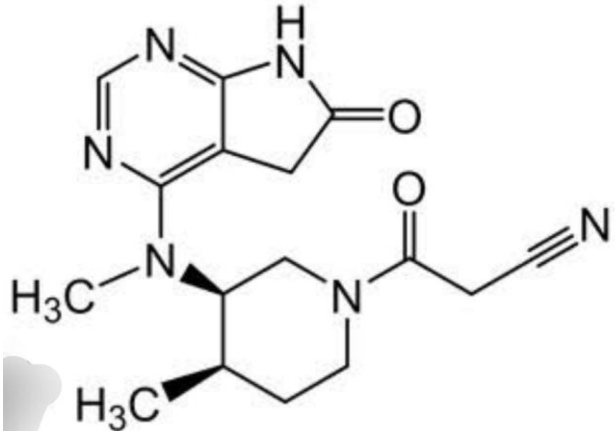

Figure 2: Structure of Acebrophylline [22]

Mechanism of action: Acebrophylline, containing ambroxol and theophylline-7 acetic acid, works together to support pulmonary surfactant production, regulate mucus and improve mucokinetics for clearing excess mucus. Its anti-inflammatory and antireactive effects help reduce bronchial obstruction, benefiting patients [23].

Mucoregulating action: a) Direct activity (Mucoregulation): The ambroxol in acebrophylline normalizes the viscosity of abnormal bronchial secretions. It works not on the already secreted mucus but by regulating glandular function. Ambroxol helps restore normal mucus production by allowing mucosal cysts to regress and activating serous glands to produce higher Quality mucus, improving overall mucus clearance[24].b) Indirect activity (Surfactant stimulation): Acebrophylline reduces mucus viscosity indirectly by stimulating alveolar surfactant production. The interaction between mucus and surfactant molecules, particularly bronchial phospholipids, contributes to the formation of the fibrillary structure of mucus. For mucus to form the supracillary colloidal gel, it must pass through the sol layer and the phospholipid layer [25].

Mucosecretory activity: The results showed that acebrophylline was more effective than ambroxol alone in stimulating mucus secretion. This was confirmed by comparing the 50% effective dose (ED50), which represents the amount needed to achieve half of the maximum effect. Acebrophylline had a significantly lower ED50 of 0.278 Mm/kg, compared to ambroxol's 0.498 mM/kg. This suggests that acebrophylline is more potent in eanhancing mucus production at lower oral doses [26].

Anti-inflammatory-antireactive activity: Acebrophylline inhibits phospholipase A_2 in the lung parenchyma, preserving phosphatidylcholine for surfactant resynthesis by type ii pneumocytes

Scaglione. Demonstrated in cultured human type ii pneumocytes that acebrophylline significantly reduces LTB_4 leukotriene production, promoting surfactant synthesis. In vivo rat studies further showed reduced LTC_4 and LTB_4 levels after acebrophylline pretreatment and bronchial lavage, with a notable decrease in LTB_4 compared to controls [27].

Pharmacokinetic of Acebrophylline: This passage outline the pharmacokinetics of acebrophylline in healthy volunteers after a 200mg oral dose. The drug contains two components ambroxol and theophylline-7 acetic acid. Following ingestion, both components are released in the stomach and absorbed through the stomach and intestine [28].the low blood levels of theophylline-7 acetic acid in acebrophylline suggest that it is unlikely to cause the adverse effects typically associated with theophylline, which occur within a therapeutic window of 10-20 mcg/ml. this indicates that acebrophylline presents a significantly lower risk for such side effects compared to theophylline [29]. Erdostaine, a mucolytic drug (N-(carboxymethylthioacetyl)-homocysteine thiolacetone), improves sputum viscosity, relieves cough symptoms in COPD, and enhances antibiotic penetration, increasing their effectiveness [30]. Erdostaine lacks a free thiol group in its original form. However, upon metabolism in vivo. It produce active metabolism containing thiol groups. These metabolites can break disulphide bones in mucins, reducing sputum viscosity and enhancing mucociliary clearance in the airways. Further more, they neutralize anti-inflammatory properties [31]. A novel ultra-high performance liquid chromatography (UHPLC) method has been development to quantify erdosteine and its five impurities, including HCT, N – thiodiglycolyl homocysteine, bis –N-(2-oxo-3-tetrahydrothienylthiodiglycolylamide, and two oxidative degradation products (ox1 and ox2) specifically in newly formulated efferevescent tablets[32].Two acid degradation products of Erdostaine ,HCT and 2,2 sulfanediyldiacetic acid have been identification. Various analytical techniques, including HPLC, are reported for determining erdosteine in bulk drugs, formulation and biological sample [33].

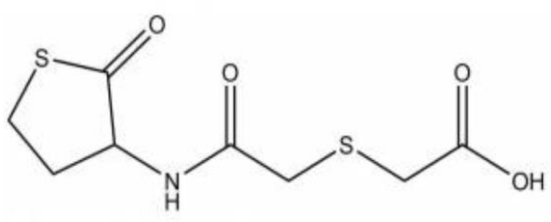

Figure 3: Structure of Erdostaine

Mechanism of action: Erdostaine, a mucolytic prodrug, aids in breaking down mucus for easier expulsion from the respiratory tract. It became active after metabolism, releasing two sulphur atoms one from thio-ether in the side chain and another from the thiolacetone ring. These free sulphur atoms provide antioxidant effects. Reduce bacterial adhesion, and improve mucociliary clearance. The drug is stable in dry and acidic environments, protecting it during oral administration. Upon reaching the alkaline intestines, its thiolactone ring pens, forming the active metabolite N-thiodiglycolylhomocysteine with a free thiol group. This group breaks disulfide bonds in mucins, reducing mucus viscosity, improving clearance and aiding in respiratory conditions with mucus build up [34].

Pharmacokinetic of Erdosteine: Erdosteine is a mucolytic used in COPD and bronchitis. Its pharmacokinetics include absorption, metabolism, distribution and elimination.

Absorbance: Rapidly absorbed orally, with low bioavailability in its original form. It is metabolized in to the active metabolite, which is pharmacology active.

Metabolism: Undergoes extensive first-pass metabolism in the liver, producing active metabolites. Peak plasma levels are reached 1-2 hours post-administration**.**

Distribution: Erdosteine and its metabolites are widely distributed in tissues, with 64-70%protein binding to plasma proteins.

Elimination: The active metabolite has a half-life of 1.5-2 hours. About 60-80% is excreted in urine, with a smaller portion in faces [35].

Table 2: Physiochemical Properties of Acebrophylline and Erdostaine

Parameters	**Description**	
Drug name	**Acebrophylline**	**Erdostaine**
Category of drug	FDC	FDC
Class of drug	Bronchodilator (β-2 adrenergic)	Mucolytic agent (β-2 adrenergic)
CAS Number	96989-76-3	84611-23-4
Physical Appearance	White to off white	White or Slightly yellowish
Chemical Formula	$C_{22}H_{28}Br_2N_6O_5$	$C_8H_{11}NO_4S_2$
Dosage form of drug	Film coated tablet	Film coated tablet
IUPAC Name of drug	4-[(2-amino-3,dibromophenyl)methylamino]cyclohexan-1-ol;2-(1,3-dimethyl-2,6-dioxopurin-7-yl)acetis	2-({[(2-oxothiolan-3yl)carbamoyl]methyl}sulfanyl)acetic
Use of drug	COPD, Chronic bronchitis	COPD, Respiratory
Half-life of drug	4-9hr	3-4hr
Side effect of drug	Nausea, Vomiting, Headache	Skin reaction, allergy

Table 3: The Analytical Method Development & Validation of Acebrophylline

Drug Name	**Analytical Method**	**Description**	**Ref.**
Acebrophylline	UV Spectroscopy	**Linearity:** Range 2-18 µg/ml **Solvent:** Methanol **Wavelength:** 270nm	36
Acebrophylline	UV Spectroscopy	**Linearity:** Rang 2-20 µg/ml **Solvent:** Ethanol **Wavelength:** 274nm	37
Acebrophylline	RP-HPLC	**Stationary Phase:** C18column **Mobile Phase:** Acetate buffer (4.7pH) Methanol **Flow Rate:** 0.85 ml **Detection:** 274nm **Concentration Range**: 0.5-200µg/ml	38
Acebrophylline	HPTLC	**Mobile Phase:** Toluene and Methanol 5:5v/v **Wavelength:** 248nm	39

		Concentration Rang: 500-2500 µg/ml	

Table 4: The Analytical Method Development & Validation of Acebrophylline with Other Drug

Acebrophylline+ Acetylcysteine (Table)	RP-HPLC	**Stationary Phase:** Hypersil, BDS,C18 **Mobile Phase:** Buffer solution(pH:7),acetonitrile(90:10) **Flow Rate:** 1.0 ml/min **Detection:** 260nm(PDA) **Concentration Rang:** Acebrophylline (200µg/mg) Acetylcysteine (600µg/mg)	40
Acebrophylline+ Acetylcysteine	RP-HPLC	**Stationary Phase:** Hypersil BDS,C18,100×4.6mm,5µ **MobilePhase:**BufferPhosphate(pH:6) Acetonitrile (90:10%v/v) **Flow Rate:** 0.9ml/min **Detector:** 260nm(PDA) **ConcentrationRange:**Acebrophylline (25-150µg/ml), Acetylcysteine (150-900µg/ml)	41
Acebrophylline+ Levocetirizine+ Pranlukast	HPLC	**StationaryPhase:**C18Kinetexcolumn (250mm×4.6mm×5µg) **Mobile Phase:** Methanol and Acetone (14:86**)** **Flow Rate:** 1.0ml/min **Concentration Rang:** (100-1600µg/ml)	42
Acebrophylline+ Doxofylline (Tablet)	HPTLC	**Mobile Phase:** Toluene, Methanol, Glacial acetic acid(6:2:2v/v**)** **Wavelength:** 232nm **Concentration Range:** Acebrophylline(100-600µg/ml)	43
Acebrophylline+ Montelukast sodium	HPTLC	**Mobile Phase:** Chloroform, Ethyalacetate, Methanol, Tryethylamine(6:4.5:2.5:0.8,v/v/v/v) **Wavelength:** 272nm **Concentration Rang:** Acebrophylline(600to1000µg/ml), Montelukast sodium(12000-20000µg)	44
Acebrophylline+ Montelukast sodium	HPLC	**StationaryPhase:**C18Column(Hibar Lichrospher 100, RP- 18e, 5µm, 250mm L ×4.6mm diameter in size **MobilePhase:**Acetonitrile,Methanol, (60:40%v/v,pH3.2) **Flow Rate:** 0.8 ml/min **Detector:** 260nm(UV) **ConcentrationRang:**Acebrophylline (25µg/ml), Montelukast sodium(100-500µg/ml)	45
Acebrophylline+ Montelukast+ Fexofenadine	RP-HPLC	**Stationary Phase:** Hyper clone 5µ BDS C18 130A (250×4.6mm) **MobilePhase:**Methanol,Ammonium, Ortho phosphoric acid (70:30) **Flow Rate:** 1.0ml/min **Detector:** 268nm(PDA) **ConcentrationRang:**Acebrophylline	46

		(100-200µg/ml),Montelukast (10µg/ml), Fexofenadine (180µg/ml)	

Table 5: The Analytical Method Development & Validation of Erdosteine

Drug Name	Analytical Method	Description	Reference
Erdosteine	HPLC	**Stationary Phase:**C18column(250mm ×4.6nm,5µm) **Mobile phase:** Acetonitrile(0.01 mol/L),Citric acid solution (13:87v) **Floe Rate:** 1.ml/min **Detector:** 254nm (PDA) **Concentration Rang:** 10-80µg/ml	47
Erdosteine	HPLC	**StationaryPhase:**Ace5-C18 (250×4.6mm) **Mobile Phase:** Acetonitrile, Phosphate buffer (pH: 7.2**)** **Flow Rate:** 0.5ml/min **Detector:** 236nm(PDA) **Concentration Rang:**100µg/ml	48
Erdosteine	UPLC	**Stationary Phase:** C18-UPLC column 95Å, 2.1×50mm, 1.8µm **Mobile Phase:** 0.1% Formicacid, Acetonitrile (25:75v/v**)** **Flow Rate:** 0.15ml/min **Detector:** 249nm **Concentration Rang:** 1-5000µg/ml	49
Erdosteine	UPLC	**Stationary Phase:** UPLC HSS T3, 1.8µg/ml (2.1mm×150mm) **MobilePhase:**0.1%TFAWater,Methanol **Flow Rate:**0.29ml/min **Concentration Range:** 100µg/ml	50
Erdosteine	UV spectroscopy	**Linearity:** rang 10-15 µg/ml **Solvent:** Ethanol **Wavelength:** 235nm	51

Table 6: The Analytical Method Development & Validation of Erdosteine with Other Drugs

Erdosteine+ Cefixime Trihydrate	HPTLC	**Stationary Phase:** TLC aluminium plates, silica gel 60F254 **Mobile Phase:** Ethyl acetate, Acetone Methanol, Water(7.5:2.5:2.5:1.5) **Flow Rate:** 1.5ml/min **Detector:** 235nm (UV) **Concentration Rang:** Erdosteine (100-500µg/ml), Cefixime Trihydrate (150-750µg/ml)	52
Erdosteine+ Cefixime	UPLC	**Stationary Phase:** Sunfire C18,5µ, 46mm×150mm **MobilePhase:**Buffer (pH:7), Methanol (65:35%v/v) **Flow Rate:** 1.0 ml/min **Detector:** 254nm(PDA)	53

		Concentration Rang: Erdosteine (20-200µg/ml), Cefixime (30-300µg/ml)	
Erdosteine+ Cefixime	UV Spectrophotometetry	**Linearity:** Rang 10-15µg/ml **Solvent:** Ethanol **Wavelength:** 227.5nm	54
Erdosteine+ Guaiphenesin+ Terbutaline sulphate	HPTLC	**Stationary Phase:** Aluminium plates, Silica gel 60F254 **MobilePhase:**Toluene,Dichloromethane, Methanol, Glacialacetic acid (4:4:1.8:0.2%v/v/v/v/) **Flow Rate:** 2.0nm **Detector:** 225nm **Concentration Rang:** Erdosteine(500-300µg/ml), Guaiphenesin(200-1200µg/ml), Terbutaline sulphate (25-150µg/ml)	55

CONCLUSION:

In the review the conclusion highlights that several analytical method, including Spectrophotometry, chromatography (HPLC, UPLC), have been development and validation for the quantitative analysis of Acebrophylline and Erdosteine individually in perform. These methods are reliable, sensitive, and can be applied for the estimation of these drug in both pure forms and pharmaceutical formulations. The review emphasizes the importance of selecting appropriate methods based on the specific requirements of accuracy, sensitivity, and cost-effectiveness. Future advancements in analytical techniques are perform to combination for (RP-HPLC, HPTLC, UV Spectroscopy and Stability Testing).

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Abbreviations:

COPD- Chronic Obstructive Pulmonary Disease
UV- Ultra Violet
HPLC- High Performance Liquid Chromatography
TLC- Thin Layer Chromatography
RP-HPLC- Reversed phase High Performance Liquid Chromatography
HPTLC- High Performance Thin Layer Chromatography
cAMP- Cyclic Adenosine Monophosphate
mMRC- Modified Medical Research Council

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