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Review Article

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AN IN-DEPTH REVIEW OF THE ANALYTICAL METHODS FOR LUMACAFTOR AND IVACAFTOR

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ABSTRACT

Cystic fibrosis (CF) is a genetic condition resulting from mutations in the CFTR gene, which leads to dysfunctional chloride channels that impact several organs, particularly the lungs and pancreas. Ivacaftor and lumacaftor are new modulators of the cystic fibrosis transmembrane conductance regulator (CFTR) aimed at enhancing chloride transport in patients with certain CFTR mutations. Ivacaftor serves as a potentiator, boosting the function of the CFTR protein, while lumacaftor aids in the proper folding and movement of the CFTR protein to the cell surface. This review examines the profiles of lumacaftor and ivacaftor, concentrating on their mechanisms of action, structural features, and therapeutic roles in CF management. Furthermore, it discusses various analytical methods, including chromatographic techniques like HPLC and spectroscopic methods such as UV spectroscopy, used for the estimation and quality control of these medications. These techniques are essential for accurately assessing drug purity, dosage, and stability, which are vital for ensuring effective treatment. The continuous development and refinement of these analytical methods play a significant role in improving care for cystic fibrosis patients.

KEYWORDS

- Lumacaftor
- Ivacaftor
- RP-HPLC
- UV Spectrophotometry

INTRODUCTION

This disease is marked by issues with absorbing fats and proteins, leading to symptoms like steatorrhea, growth failure, and frequent lung infections. Damage to the pancreas and insufficient secretion of pancreatic enzymes result in nutritional deficiencies, which are thought to increase the risk of lung infections, often culminating in severe outcomes. The presence of thick, sticky mucus obstructing the ducts of mucus glands throughout the body has led to the alternative name “mucoviscidosis.” Cystic fibrosis (CF) is a genetic disorder caused by mutations in the CFTR gene located on chromosome 7. It presents in a complex and highly variable manner. The condition affects various systems, including the airways, pancreas, male reproductive system, intestines, liver, bones, and kidneys. The absence or malfunction of CFTR leads to difficulties in fat absorption and chronic lung infections, which can result in bronchiectasis and progressive damage to the lungs.[1]

IVACAFTOR

Cystic fibrosis results from various defects in a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR). This protein plays a crucial role in regulating fluid flow within cells, impacting sweat, digestive fluids, and mucus. The defects arise from mutations in an individual's DNA, which can occur at different sites along the protein, each affecting its function in unique ways. For instance, the G551D mutation allows the CFTR protein to reach the surface of epithelial cells but prevents it from effectively transporting chloride through the ion channel. Ivacaftor acts as a potentiator for the CFTR protein, enhancing chloride transport by increasing the likelihood that the G551D-CFTR protein will open its channel. The CFTR protein is a chloride channel located on the surface of epithelial cells across various organs.[2]

LUMACAFTOR

Lumacaftor, marketed as Orkambi, is a combination of lumacaftor and ivacaftor, both of which are oral modulators of the cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR protein functions as a chloride channel located on the surface of epithelial cells in various tissues. Ivacaftor is currently approved for use alongside Lumacaftor in the

combination product Orkambi for treating chronic cystic fibrosis.[3]

DRUG PROFILE

a) LUMACAFTOR

Structure

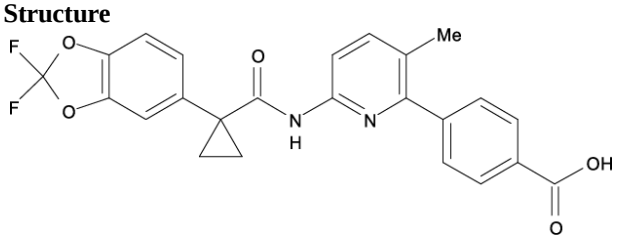

Fig 1: Molecular structure of Lumacaftor.

IUPAC Name: 3-{6-{[1-(2,2-Difluoro-1,3-benzodioxol-5 yl)cyclopropanecarbonyl]amino}-3- methylpyridin-2-yl}benzoic acid.[4]

Molecular formula: $C_{24}H_{18}F_2N_2O_5$.

Molar Mass: 452.41 g·mol−1.

Boiling Point: 653.0±55.0 °C (Predicted).

Storage Condition: -20° C Freezer.

Pka: 3.95±0.10 (Predicted).

Drug Category: It is a cystic fibrosis transmembrane conductance regulator [CFTR].

Solubility: DMSO (Slightly), Methanol (Slightly).[4]

Mechanism of action: lumacaftor acts as a chaperone during protein folding and increases the number of CFTR proteins that are trafficked to the cell surface.[5]

b) IVACAFTOR

Structure

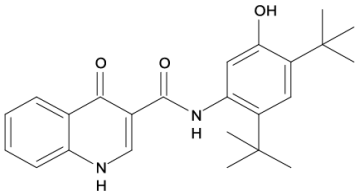

Fig 2: Molecular structure of Ivacaftor.

IUPAC Name: N-(2,4-tert-butyl-5-hydrophenyl)-4-oxo-,4 dihydroquinoline-3-carboxamide.
Molecular formula: $C_{24}H_{28}N_2O_3$ **Molar Mass:** 392.499 g.mol-1 **Boiling Point:** 550.4^{0}C.
Storage Condition: -20°C Freezer.
Pka: 11.08.[6]
Drug Category: It is a cystic fibrosis transmembrane regulator [CFTR] potentiators.
Solubility: in ethanol is approximately 0.1 mg/ml and approximately 25 mg/ml in DMSO and DMF.[7]
Mechanism of action: Ivacaftor, a CFTR potentiator, improves the transport of chloride through the ion channel by binding to the channels directly to induce a non-conventional mode of gating which in turn increases the probability that the channel is open.[8]

ANALYTICAL METHODS

Analytical methods can be used to estimate and independently identify unknown compounds. To analyze these mystifying chemicals, a variety of methods are available, such as TLC, HPLC, HPTLC, NMR spectroscopy, mass spectroscopy, UV spectroscopy, and IR spectroscopy.

Table 1: Chromatographic estimation in RP-HPLC on lumacaftor and ivacaftor.

SI. No	Author's Name	Column	Mobile phase [M.P], Flow rate [F.R] & Injection Volume[I.V]	Retention time & Wavelength
1.	Akram NM et al., (2017)[9]	Ineertsil ODS column (4.6×250 mm)5µ,	**MP:** (30:10:60v/v) ACN, Methanol **FR:** 1ml/min **IV:** 20 µL	**RT:** 3.101 mins(LUMA)4. 205mins(IVA) **W:** 254 nm
2.	Gorantla N et al., (2019)[10]	C18 4.6×150mm, 5µ	**MP:** Methanol: Water in the ratio of 65:35 v/v **FR:** 1ml/min **IV:** 10 µL	**RT:**2.460 mins (LUMA) and 4.312min (IVA) **W:** 270 nm
3.	Praveena A et al., (2017)[11]	(250mm ×4.6 mm)	**MP:** Acetonitrile**:** OPA Phosphate buffer (40:60%v/v) **FR:**1ml/min **IV:**10ml	**RT:**2.579(LUMA) and 3.877mins(IVA) **W:** 255nm
4.	Nataraj KS et al., (2020)[12]	Inertsil ODS column (4.6×250m m) 5µm,	**MP**: ACN, Methanol, OPA(30:10:60v/v) **FR:** 1 ml/min **IV**: 20 µL	**RT:** 3.10 mins (IVA)and 4.229 mins(LUMA) **W:** 255nm
5.	Bhagya Kumar Tatavarti et al.,(2023) [13]	Hyper clone 5µ BDS C18 130°A column of dimensions 250X4.6mm, 5µm	**MP:** OPA: acetonitrile (60:40 v/v) **FR:** 1.0 mL/min **IV:** 10 µL	**RT**: 3.152 min(IVA) and 6.932 min(LUMA) **W:** 260nm
6.	Özcan S et al., (2023) [14]	C18-bonded monolithic	**MP:** 30 mM phosphate buffer	**RT**: 2.5(LUMA) and

		silica column (Chromolith High Resolution RP-18e, 100 mm × 4.6 mm i.d., Merck KGaA, Darmstadt, Germany)	with a pH of 3.5: acetonitrile (3:97v/v) **FR:** 1 mL/ min **IV:** 5 µL	4.2(IVA) **W:** 220nm

Spectroscopic Estimation

The quantitative estimation of compounds like and Ivacaftor, which are cystic fibrosis medications, depends heavily on UV spectroscopy. To examine these medications in bulk and dosage forms, researchers have made considerable use of UV spectroscopy technique. Through the analysis of their absorbance, transmittance, and reflectance characteristics at different doses, UV spectroscopy makes it possible to demonstrate linearity and charateristics of these drugs.

Table 2: UV Spectroscopic method for estimation of ivacaftor

S. No	Title	Method	Materials & Description
1.	Yasa GD et al., (2024)[15]	UV spectroscopy method	**Wavelength:** 310 nm **Solvent:** Ethanol **Concentration Range:** 5-25 µg/mL **Linearity (R2):** 0.9989

CONCLUSION

In conclusion, lumacaftor and ivacaftor are essential therapies for cystic fibrosis, focusing on correcting CFTR protein defects to enhance chloride transport and reduce disease symptoms. Analytical techniques such as HPLC and UV spectroscopy are critical for verifying the quality, precision, and safety of these medications. Ongoing improvements in these methods will aid in advancing drug development and tailoring treatments for cystic fibrosis, ultimately leading to better outcomes for patients.

ABBREVIATION

RP-HPLC: Reversed-Phase High-Performance Liquid Chromatography, **UV**: Ultraviolet, **HPLC**: High-Performance Liquid Chromatography, **HPTLC**: High-Performance Thin-Layer Chromatography, **MP:** Mobile Phase, **RT**: Retention Time, **IV**: Injection Volume, **W**: Wavelength, **pH**: Potential of Hydrogen, **R2**: Linearity, **LUMA**:Lumacaftor, **IVA**: Ivacaftor.

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