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Analytical Method Development and Validation for the Simultaneous Estimation of Bempedoic Acid and Ezetimibe in Pure and Pharmaceutical Dosage Form- An Overview

Aakash Suresh*, Anbarasi Balakrishnan, Vijayamirtharaj Ramaswamy and Senthilkumar Natesan

Department of Pharmaceutical Analysis, Annai JKK Sampoorani Ammal College of Pharmacy, India

Abstract

Adenosine triphosphate citrate lyase (ACL) inhibitors of the highest Caliber include Bempedoic acid and Ezetimibe. In individuals who are resistant to statins, Bempedoic acid is used to reduce LDL cholesterol levels. When taken alone or in conjunction with other medications that decrease cholesterol, Ezetimibe is used to treat hyperlipidemia. The combination medicine NEXLIZET, which contains Bempedoic acid and Ezetimibe, was authorized on February 26, 2020. The combo drug is used to treat elevated cholesterol. To treat elevated blood levels of triglycerides and cholesterol, the combination is taken in conjunction with a healthy diet. In the present study methods developed and used for determination as single and combination in bulk medicines, pharmaceutical formulation, and biological fluids have been examined, along with a scan of literature and reviews published in major analytical and pharmaceutical publications. The analytical techniques include liquid chromatography-tandem mass spectroscopy, spectrophotometric techniques, and chromatographic techniques like HPLC, RP-HPLC, HPTLC and etc.

Keywords: Ezetimibe; Bempedoic acid; Hyperlipidaemia; UV; HPLC; Method Development; Validation

Introduction

Bempedoic acid, which was developed by Espersion Therapeutics Inc1, is a first-in-class adenosine triphosphate citrate lyase (ACL) inhibitor that is used once daily to decrease LDL cholesterol levels in individuals who are resistant to statins2,3 NEXLIZET, a medication that combines Bempedoic acid and Ezetimibe, received approval on February 26, 20204. The combo drug lowers cholesterol levels. IUPAC name for Bempedoic acid is 8-hydroxy-2, 2, 14, 14-tetramethyl Penta decanedioic acid. It is a prodrug that requires liver activation5. Its conversion to the pharmacologically active metabolite ETC-1002-CoA is carried out by the enzyme very-long-chain acyl-CoA synthetase-1 (ACSVL1). For cholesterol production to occur, the enzyme ATP lyase, sometimes referred to as ATP synthase, must function [1-5]. Coenzyme A (CoA) initiates the liver's response to the parent medication, while ETC-1002-CoA directly inhibits CoA6, 7; Ezetimibe is a lipid-lowering substance that prevents the absorption of phytosterol and cholesterol via the intestines8, 9. The early 1990s saw the discovery and investigation of this medication. The structure of Ezetimibe is composed of (3R, 4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl) azetidin-2-one10, Ezetimibe is used to decrease cholesterol levels in patients with primary hyperlipidemia, mixed hyperlipidemia, homozygous familial hypercholesterolemia, and phytosterolaemia. By specifically blocking the small intestine's ability to absorb cholesterol and phytosterol, Ezetimibe lowers blood cholesterol levels without affecting the absorption of fat-soluble vitamins and minerals. The extensive literature review revealed that various methods have been published for the estimation of Bempedoic acid and Ezetimibe single or in combination with other drugs. Methods have been developed for simultaneous estimation of Bempedoic acid and Ezetimibe in combined dosage form were RP-HPLC techniques [6-10].

Physical and chemical properties

Powdered Bempedoic acid is white to off-white in color. 8-hydroxy-2, 2, 14, 14-tetramethylpentadecanedioic acid is its IUPAC name. Bempedoic acid's molecular formula is C19H36O5. The weight of a mole is 344.5 g/mol. 87°C to 92°C is the melting point. It is insoluble in water and aqueous solutions with a pH lower than 5, although it is extremely soluble in ethanol, isopropanol, and pH 8 phosphate buffer.

Ezetimibe is a solid white color. The IUPAC is (3R, 4S).1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl) 3-4-(4-hydroxyphenyl) Azetidin-2-1. Ezetimibe's molecular formula is C24H21F2NO3. The weight of a mole is 409.4 g/mol. One can melt at 163°C. Ezetimibe is insoluble in aqueous solutions that are acceptable for injection, so it is impossible to ascertain the precise bioavailability [11-13].

Analytical method development

The development and validation of analytical methods play a crucial role in drug discovery, drug progression, and pharmaceutical product assembly. It involves determining a pharmacological substance's toxicity and purity. The process of choosing a precise assay approach to ascertain a formulation's composition is known as analytical method development. It involves demonstrating that an analytical technique is appropriate for use in a lab setting to determine the concentration of ensuing samples. The ICH guidelines Q2 (R1) require that analytical techniques be established under the procedures and acceptance standards set forth. Pharmaceuticals are discovered, developed, and manufactured in part via the use of analytical methods and validation. According to the Literature Review that follows, a few approaches for the combination of Bempedoic acid and Ezetimibe have been described. Also, Ezetimibe with other medications have been recorded using RP–HPLC, HPTLC, HPLC, Stability indicating RP–

***Corresponding author:** Aakash Suresh, Department of Pharmaceutical Analysis, Annai JKK Sampoorani Ammal College of Pharmacy, India, Email: sakashsureshh@gmail.com

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HPLC techniques, liquid chromatography-tandem mass spectroscopy, and spectrophotometric techniques [14-16].

Mechanism of action of bempedoic acid

LDL cholesterol normally circulates in the blood and is created in the liver. Excess LDL accumulates in blood vessels, notably the coronary arteries, as the blood gets saturated, raising the risk of cardiovascular events. As a prodrug, Bempedoic acid has to be activated in the liver. The enzyme known as very-long-chain acyl-CoA synthetase-1 (ACSVL1) is in charge of activating it into the pharmacologically active metabolite ETC-1002-CoA. The enzyme ATP lyase, sometimes referred to as ATP synthase, is crucial to the creation of cholesterol. Once coenzyme A (CoA) has activated the parent drug in the liver, BETC-1002-CoA directly inhibits this enzyme [17-20].

Mechanism of action of ezetimibe

By specifically blocking the small intestine's ability to absorb cholesterol and phytosterol, Ezetimibe lowers blood cholesterol levels without affecting the absorption of fat-soluble vitamins and other minerals. Niemann-Pick C1-Like 1 (NPC1L1) protein, a cholesterol transport protein, is the main target of Ezetimibe. In combination with the adaptor protein 2 (AP2) complexes and clathrin, NPC1L1 plays a function in enabling the internalization of free cholesterol into the enterocyte [21-23]. It is expressed on enterocytes/gut lumen (apical) as well as the hepatobiliary (canalicular) interface. After entering enterocytes through the gut lumen or bile, cholesterol attaches to the sterol-sensing domain of NPC1L1 to create an NPC1L1/cholesterol complex. After attaching to AP2 clathrin, the complex is internalized or endocytosed and forms a vesicle complex that is translocated to the endocytic recycling compartment for storage [24-26].

Literature Review

- RP-HPLC Method Development and Validation for the Simultaneous Estimation of Bempedoic Acid and Ezetimibe in Pharmaceutical Dosage Form Column: Agilent 150mm x 4.6 mm, 5µm, Mobile phase: 55% Acetonitrile: 45% KH2, Flow rate: 1.0 mL/min, Wavelength: 230nm, Retention time: 6 mins.

- Development and Validation of a RP-HPLC Method for the Simultaneous Determination of Bempedoic Acid & Ezetimibe in Pure and Pharmaceutical Dosage Form Mobile phase: 30% HSA: 70% Acetonitrile, Flow rate: 1.0mL/min, Wavelength: 225nm, Retention time: 3.246 and 3.865.

- Development and Validation of Novel RP-HPLC Method for the Simultaneous Estimation of Ezetimibe and Bempedoic Acid in a Tablet dosage Form Column: Prontosil C18 (250 x 4.6mm, 5µm), Mobile phase: 60% Acetonitrile: 40% Water, Flow rate: 1.0 mL/min, Wavelength: 225 nm, Retention time: 4.7 and 5.7mins.

- Validated method for the simultaneous estimation of Bempedoic acid and Ezetimibe in bulk and tablet formulation by RP-HPLC method Column: Kromosil C18 150×4.6mm, Mobile phase: 55% $KH2PO_4$: 45% Acetonitrile, Flow rate: 0.9mL/min, Wavelength: 246nm, Retention time: 2.240 and 2.956mins.

- Stability indicating RP-UPLC method for simultaneous quantification of Bempedoic acid and Ezetimibe in bulk and pharmaceutical formulations Column: Waters Acquity C18 [50×2.1mm, 1.7µm], Mobile phase: 50% Methanol: 30% Acetonitrile: 20% Water, Flow rate: 0.5mL/min, Wavelength: 260nm, Retention time: 1.827 and 3.577mins [27].

- Characterization of novel stress degradation products of Bempedoic acid and Ezetimibe using UPLC–MS/MS: development and validation of stability-indicating UPLC method Column: C18 (150 mm×4.6mm, 3.5µm).Mobile phase: 50% Orthophosphoric acid: 50% Acetonitrile , Flow rate: 1mL/min, Wavelength: 230nm.

- Synchronized analysis of Bempedoic acid and Ezetimibe in pure binary mixture and their combined tablets by a new stability indicating RP-UPLC method Column: Phenyl XBD (100×2.1mm, 1.7µm), Mobile phase: 60% TFA: 40% Water, Flow rate: 0.4mL/min, Wavelength: 236nm, Retention time: 0.43 and 0.86mins.

- RP HPLC Method Development and Validation for Simultaneous Estimation of Bempedoic Acid, Ezetimibe and Atorvastatin in Synthetic Mixture Column: C 18 (250 mm - 4.6 mm), 5 µm, Mobile phase: 30% Potassium Dihydrogen Phosphate: 60% Methanol: 10% Acetonitrile, Flow rate: 1mL/min, Wavelength: 262nm, Retention time: 3.76, 5.49 and 6.85 mins.

- Development and validation of a reversed-phase HPLC method for the determination of Ezetimibe in pharmaceutical dosage forms Column: Kromasil 100 (250×4mm, 5µm), Mobile phase: 30% Water: 60% Acetonitrile, Flow rate: 0.5mL/min, Wavelength: 232nm, Retention time: 2.6mins.

- High performance liquid chromatographic method for determination of Ezetimibe in pharmaceutical formulation tablets Column: C18 analytical column (250mm×4.6mm, particle size - 5µm Mobile phase: 75% Acetonitrile: 25% Ammonium Acetate, Flow rate: 1mL/min, Wavelength: 240nm, Retention time: 5.083 mins [28].

- A stability indicating RP-HPLC method development for determination of Ezetimibe in tablet dosage form Column: Zorbax SB C18 (250mm×4.6mm), 5µm, Mobile phase: 20% Orthophosphoric acid: 80% Acetonitrile, Flow rate: 1mL/min, Wavelength: 232nm, Retention time: 3.5mins.

- RP-HPLC Method Development and Validation for the Simultaneous Estimation of Atorvastatin and Ezetimibe in Pharmaceutical Dosage Form Column: C18 (250×4.6 mm, 5mm), Mobile phase: 35% Phosphate Buffer: 65% Acetonitrile, Flow rate: 1mL/min, Wavelength: 228nm, Retention time: 2.36 and 3.43mins.

- LC-MS-MS Simultaneous Determination of Atorvastatin and Ezetimibe in Human Plasma Column: C18 (100×4.6mm, 3.5µm), Mobile phase: 30% Formic acid: 70% Acetonitrile, Flow rate: 0.6mL/min, Retention time: 3.0 mins.

- Development and Validation of a Method for Simultaneous Densitometric Estimation of Atorvastatin Calcium and Ezetimibe as the Bulk Drug and in Tablet Dosage Forms Stationary phase: - Precoated Silica gels F254 aluminium, Mobile phase: - Toluene: methanol (8:2; v/v) Detection wavelength: - 240nm.

- HPTLC Method Development, Validation and Stress Degradation Studies for Atorvastatin and Ezetimibe in Multicomponent Tablet Dosage Form Stationary phase: - Precoated Silica gels F254 aluminium, Mobile phase: - Toluene: ethyl acetate: methanol (12:5:3; v/v/v), wavelength: - 254nm.

- High Performance Liquid Chromatographic Method for Estimation of Ezetimibe in Pharmaceutical Formulation Tablets Column: C18 (250×4.6 mm, 5µm), Mobile phase: Acetonitrile: ammonium acetate (75:25, v/v), pH = 3.0, Wavelength: 240nm, Flow rate: 1.0mL/min, Retention time: 3.6mins.

- Validated RP-HPLC Method for Estimation of Ezetimibe

in Different Tablet Dosage Form Column: C18 (250×4.6 mm, 5µm), Mobile phase: 50% Acetonitrile: 50% Methanol, Wavelength: 245nm, Flow rate: 1.0mL/min, Retention time: 4.959mins [29].

- A Stability Indicating RP-HPLC Method Development for Determination of Ezetimibe in Tablet Dosage Form Column: Zorbax SB C18 (250×4.6 mm, 5µm), Mobile phase: 0.02N ortho phosphoric acid: acetonitrile (20:80, v/v), pH = 3.0, Wavelength: 232nm, Flow rate: 1.0mL/min, Retention time: 3.5mins.

- Development and Validation of a Reversed Phase HPLC Method for the Determination of Ezetimibe in Pharmaceutical Dosage Forms Column: Kromasil 100 C18 (250×4.6mm, 5µm), Mobile phase: Water: Acetonitrile: ammonium acetate (30:70 v/v), Wavelength: 232nm, Flow rate: 0.5mL/min, Retention time: 6 mins.

- HPLC Analysis for Simultaneous Determination of Atorvastatin and Ezetimibe in Pharmaceutical Formulations Column: Inertsil ODS- 3V (250 x 4.6 mm, 5 µm), Mobile phase: - 0.01M ammonium acetate buffer: acetonitrile (50:50, v/v), Wavelength: 254nm, Flow rate: 1.0mL/min, Retention time: 15.5 and 19.3 mins [30].

- A RP-HPLC Method for Simultaneous Estimation of Atorvastatin and Ezetimibe in Pharmaceutical Formulations Column: Phenomenex C18 (250×4.6 mm, 5 µm), Mobile phase: Water and 0.4%(v/v) TFA: acetonitrile (50:50, v/v); pH = 6.5, adjusted suing orthophosphoric acid, Wavelength: 248 nm, Flow rate: 1.0 mL/min, Retention time: 3.42 and 6.90 mins.

- A Validated Stability Indicating RP-HPLC Method for the Simultaneous determination of Atorvastatin Calcium and Ezetimibe Hydrochloride in Bulk and Tablet Dosage Form Column: X- terra C8 (150×4.6mm, 3.5µm), Mobile phase: Phosphate buffer: acetonitrile, (pH = 3.5) pH adjusted with orthophosphoric acid; (55:45, v/v), Wavelength: 232nm, Flow rate: 1.2mL/min, Retention time: 6.81 and 4.96mins.

- Application of a Stability Indicating HPTLC Method for the Quantitative determination of Ezetimibe in Pharmaceutical Dosage Form Stationary phase: - Precoated Silica gels F254 aluminium, Mobile phase: - Toluene: ethyl acetate (7:3; v/v), Detection wavelength: - 254nm.

- Development and Validation of a Liquid Chromatography-Tandem Mass Spectrometry Method for the determination of Ezetimibe in Human Plasma and Pharmaceutical Formulations
Ion transition for atorvastatin (m/z): - 392/161 Ion transition for fluvastatin (m/z): - 359.3/280 Column: - Phenomenex (Torrance, USA) Luna C18 column (150 x4.5mm, 4µm), Mobile phase: - 0.02M phosphate buffer (pH=7): acetonitrile: methanol (40:55:5, v/v/v), Flow rate: - 1.0ml/min.

- LC-MS/MS Simultaneous Determination of Atorvastatin and Ezetimibe in Human Plasma Ion transition for atorvastatin (m/z): - 422.0/290.0, Ion transition for fluvastatin (m/z): - 408.0/271.0, Column: - Zorbax Eclipse plus (USA) C18 column (4.6*100mm, 3.5µm), Mobile phase: - 0.2% formic acid in water: acetonitrile (30:70, v/v), Flow rate: - 0.6ml/min,Retention time: - 2.680 & 3.361 min [30].

Conclusion

This review article represents with Physio-chemical properties and Pharmacological actions of Bempedoic acid and Ezetimibe. The presented review depicts the information about the various methods available in the literature for the determination of Bempedoic acid and Ezetimibe including official pharmacopeial assay methods. According to this review, it was concluded that different analytical methods are reported for the estimation of Bempedoic acid and Ezetimibe. Individual and other combinations like UV Spectroscopy, HPTLC, HPLC, and LC-MS. Hence all methods are found to be simple, accurate, economical, precise and reproducible in nature. Most of the methods were RP-HPLC and UV Spectrophotometric methods because these methods provided with best available reliability, repeatability, analysis time and sensitivity. A selection of buffer and mobile phase composition plays a substantial role on the separation selectivity. Final modification can be performed by changing the gradient slope, temperature and flow rate as well as the type and concentration of mobile-phase moderate. Optimized method is validated with various parameters (e.g. specificity, precision, accuracy, detection limit, linearity, etc.) as per ICH guidelines. The given Literature review focuses that there are few methods reported for Bempedoic acid and Ezetimibe in fixed-dose combination. This review will help in the future to develop the analytical methods for this new combination and also give knowledge about the characteristics of both drugs.

Conflict of Interest

There are no conflicts of interest pertaining to this review article for the writers.

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