IJBPAS, October, 2022, 11(10): 4825-4833

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

# ANALYSIS OF EZETIMIBE: A REVIEW

**R.GANDHIMATHI*, M.VIJEY AANANDHI AND K.VENMATHY**

Department of Pharmaceutical Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600117, Tamil Nadu, India

***Corresponding Author: Dr. R. Gandhimathi; E Mail: drgmathipharm2017@gmail.com**

**Received 18th Jan. 2022; Revised 25th March. 2022; Accepted 18th April. 2022; Available online 1st Oct. 2022**

https://doi.org/10.31032/IJBPAS/2022/11.10.6507

## ABSTRACT

The Ezetimibe (EZE) drug has a good ambiance in lowering blood cholesterol and is most advanced and useful for the pharmaceutical formulations, and also in the method validation which is validated according to ICH guidelines, very simple different estimation techniques were used to analyze for routine use of analysis for quality control, and for the tablet dosage form. Ezetimibe well interacts with all analytical techniques and also with the combined dosage form. In LCMS, the liquid extraction is removed, the analyte and inner standard were isolated, and the concentrations were analysed accurately in human plasma. In HPLC, the crude samples contain impurities and ezetimibe were hydrolytic for degradation products, In UV, the absorption spectra of the peak concentration stays constant. The experiments prove that all the accurate values in all analytical techniques were achieved for the successful use of the pharmaceutical dosage form. Therefore, the ezetimibe (EZE) drug is affiliated to all kinds of analytical techniques with an accurate range of concentrations.

**Keywords: ezetimibe, analytical method, pharmaceutical formulations**

## INTRODUCTION:

Cholesterol is a kind of fat found in the human body. It travels through the bloodstream by attaching itself to proteins and forming lipoprotein molecules.

Cholesterol is divided into 2 types:

- low-density lipoprotein (LDL) and
- high-density lipoprotein (HDL).

Cholesterol is a crucial chemical in humans, and both excess and deficiency can lead to disease. Most doctors are aware

of its involvement in cellular plasma membrane stabilization but are unaware of its many additional roles. Cholesterol is essential for healthy growth and development throughout life, yet it may also act as an anticancer catalyst. Because humans have a limited ability to catabolize cholesterol, when there is an overabundance in the food or a genetic defect, it rapidly accumulates in the body **[1]**. Cholesterol homeostasis is critical for cell and systemic function. Cardiovascular infirmity, similarly as an expanding number of various sicknesses like neurological contamination and illness, is achieved by an unsettling influence in cholesterol homeostasis. The cell cholesterol level reflects the unique harmony between biosynthesis, uptake, export, and esterification -an interaction in which cholesterol is converted to nonpartisan cholesteryl esters for capacity in lipid drops or excretion as constituents of lipoproteins is reflected in the cell cholesterol level **[2]**. Cholesterol is primarily transported in plasma as low-density lipoproteins (LDL), with high-density lipoproteins (HDL) serving as the primary pathway from tissues to the liver, with bile excretion following. Cholesterol levels in healthy adults are fewer than 200 mg/dL. Blood pressure that is borderline high is measured in 240mg/dL Cardiovascular diseases, heart attacks, strokes, peripheral artery disease, type 2 diabetes, and high blood pressure are all considered biomarkers. Although there are various methods for detecting cholesterol, the majority of them are time-consuming, need sample pre-treatment, are expensive to set up, and require expert personnel to use. Biosensing overcomes these limitations because it is very specific, rapid, simple, cost-effective, and sensitive **[3]**.

**Ezetimibe:**

Ezetimibe is a medication that requires a prescription. It comes in the form of an oral tablet and is used to treat excessive blood cholesterol. When taken as the only treatment for high blood cholesterol, it is less effective than statins. If a statin alone isn't enough, it can be used in tandem with one. Ezetimibe works by preventing cholesterol from being absorbed in the intestines. Upper respiratory tract infections, joint discomfort, diarrhea, and exhaustion are the most commonly reported side effects. Anaphylaxis, liver issues, depression, and muscular disintegration are all possible serious side effects. The safety of using it during pregnancy and breastfeeding is unknown. The schematic structure of the ezetimibe drug is shown in **(Figure 1)**.

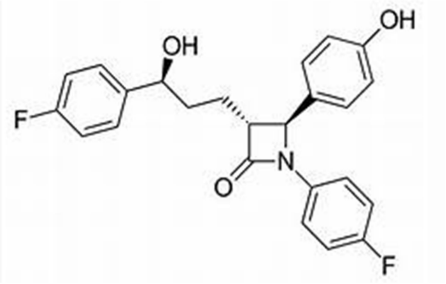


**Figure 1: Structure of ezetimibe**

**Mechanism of action:**

Ezetimibe blocks the sterol transporter at the brush border, which reduces cholesterol absorption in the intestine, lowering cholesterol conveyance down to the liver and bringing down hepatic cholesterol storage. The Niemann–Pick C1–Like 1 (NPC1L1) protein, which is found on the brush-line film of jejunal enterocytes, is the molecular target of ezetimibe. Ordinary NPC1L1 action is needed for the vehicle of cholesterol and phytosterols from the digestive lumen to the intracellular compartments of enterocytes.

**Pharmacokinetic**

Through inhibition of a membrane transporter, Ezetimibe and its active glucuronide metabolite limit the ingestion of food and hepatically made biliary cholesterol in the gastrointestinal package. Following oral association, ezetimibe is immediately ingested and is unaffected by the production of the supper. Human plasma proteins are inextricably linked to ezetimibe and its active metabolites (90%)

Absorption Bioavailability: Variable Time to reach peak plasma: 4-12 hours (parent drug) 1-2 hours (metabolite)

- Distribution: >90% of the protein is bound.
- Metabolism: Glucuronide conjugation is used to metabolise it. Ezitimibe-glucuronide is a metabolite (80-90 percent )
- Elimination: 22-hour half-life Urine (78%) and bile (78%) are the two most common excretions (11 percent )

**Analytical methods:**

An analytical method is a method for determining the grouping of a synthetic or chemical product. Examining procedures come in a variety of shapes and sizes. The following are some of the most widely used analytical techniques:

The advancement of sound Analytical methods is of incomparable significance during the course of drug revelation, delivery to market, and improvement, coming full circle in an advertising endorsement. The goal of this paper is to overview the technique improvement, advance, and approval of the method for the drug item from the formative phase of the definition to the business cluster of the item. The method advancement for the intrigued part concerning the completed thing or in-process tests and to give practical methods of overseeing choosing

in selectivity, sensitivity, linearity, range, accuracy, precision, recuperation steadiness, roughness and life of liquid chromatographic techniques to help the Routine, in-interaction and sufficiency investigation **[4]**.

**Quantitative analytical method for ezetimibe:**

Analytical technique for quantitative analysis helps to accurately decide the concentration of individual parts present in the sample.

**LCMS method**

In this analytical chemistry approach, the physical division powers of liquid chromatography (or HPLC) are joined with the mass analysis skills of mass spectrometry (MS). While liquid chromatography isolates complex mixtures, mass spectrometry reveals the underlying personality of individual components thanks to its great molecular specificity and detection sensitivity.

The analyte and internal wide were eliminated using liquid extraction with methyl tert-butyl ether (13C6-ezetimibe). After pivoted segment chromatographic separation on a Capcell C18 portion, Gao J and partners **[5]**, proposed that the plasma eliminate be eluted with a slant of acetonitrile and 5 mM ammonium acidic acid determination. The analyte was found using negative ionization and a grouping of response actually looking at modalities. The action revealed straight levels of 0.02 to 20 ng/ml without a hint of charge ezetimibe and 0.25 to 250 ng/ml inside sight out hard and fast ezetimibe in human plasma. The arrangement obsessions were inclined in the direction of, and remarkable organization was done ith the best exactness and accuracy possible.

The analytes and an inside broad, atorvastatin (ATO), were disengaged using a RP-C18 fragment with an isocratic cell section of 0.1 percent (v/v). (20+80, v/v), formic acid methanol. A mass spectrometer is used to recognize them using explicit molecule following and their connected changes. Varghese, S.J and team **[6]**, analysed that For both analytes, the method changed to straight in the extent of 0.1 to 10 ng/mL. Astounding exactness and accuracy had been cultivated for centers outside of the standard twist range. Since it gives a high LOD, LC/MS with ESI in the horrendous mode was utilized to test ROS and EZE simultaneously. To authoritatively evaluate the proportions of analytes in plasma Furthermore, The latest structure uses a lone development, strong LLE strategy to isolate analytes from plasma tests. Since no bioanalytical LC/MS methodologies for simultaneous examination of the two meds have been circulated, this way of thinking can be used for pharmacokinetic, bioavailability, or

bioequivalent examinations of ROS and EZE in human plasma.

Liquid extraction was performed using methyl-tert butyl ether following acidifying 300L of human plasma. The analytes and their deuterated internal guidelines (ISs) were recovered in an extent of 95.7-99.8%, according to Bhadoriya, A, and coworkers **[7]**. The column portion was used to isolate rosuvastatin and ezetimibe on a Symmetry C18 segment using an acetonitrile and ammonium formate support (pH 30:70, v/v). The analytes were especially settled, with a decision part of 3.8. Under various reaction following, ESI (+) for rosuvastatin (m/z 482.0 258.1) and ESI(-) for ezetimibe (m/z 407.9 271.1) were utilized for acknowledgment and evalution. In the thought degrees of 0.05-50.0 ng/mL and 001-10.0 ng/mL, an immediate reaction was made for rosuvastatin and ezetimibe, exclusively. IS-normalized network components of the analytes.

Hypercholesterolemia is treated with lipid-decreasing down drugs like atorvastatin and ezetimibe. By assessing how much atorvastatin and ezetimibe in human plasma using pitavastatin as an inside standard, El-Bagary, R. I., and colleagues **[8]** set up and exhibited the capacities of a LC-MS-MS approach. The liquid extraction approach was used to cleanse and pre-concentrate analytes from the human plasma structure. The chromatographic parcel was done in a brief time frame using an isocratic cell segment including zero.2% formic acid in water-acetonitrile (30:70, v/v) and spilling down an Agilent Eclipse notwithstanding C18, 144.06 mm, three. Five second astute area with a float cost of 0.6 mL. (-1). Various response following changes for atorvastatin and the inside standard were seen in fantastic molecule mode; regardless, Ezetimibe was evaluated in terrible molecule mode. A standard C18 area was sufficient for first in class division of ATO and EZE when taken care of at 408C. ATO and EZE sizes just zero might be distinguished using pair mass spectrometry.

**HPLC method:**

HPLC is reliable quantification for the method, that is used for active pharmaceutical dosage form, the solvents and detectors are successfully used to fulfill for the automatic instrument. HPLC is the most suitable method for several drugs to meet up for separations, absorption depending on the components.

As shown by Luo, Z., and partners **[9]**, the unpleasant models certainly contained 11 structure pollutions (beginning materials, (3S, 4S, three'S)- isomer, degradants, and secondary effects). The starter developments of all unfamiliar substances not permanently set up generally speaking at their support periods and mass spectrometric data to those of nearby

necessities and references. Ezetimibe was presented to hydrolytic, acid, principal, oxidative, and pressure conditions, as demonstrated by the ICH, to extend the degradation things that might be used as a most critical result possible to evaluate the logical system's overall execution. Under heat, acid, oxidative, base, and hydrolytic strain conditions, the supportive substance separated basically, but photolytic debasement had no effect. Ezetimibe and its associated combines have changed affinities with the ultimate objective of this concentrate. hromatographic composing material is a sort of paper used to make chromatograms. It's essential to observe a HPLC portion fit for binding a wide extent of tops in a sensible time period. First section screening studies were finished with the help of trusted in providers' C18 and Phenyl-Hexyl workspace bound characteristics to show up at this target.

"AL-Hashimi, N. N., and partners proposed **[10]** that the improvement of a new cetyl-alcohol strengthened opening fiber strong/liquid piece smaller than expected extraction (CA-HFSLPME) followed by HPLC-DAD [method for simultaneous acknowledgment of ezetimibe and simvastatin in human plasma and pee tests. The CA-HFSLPME contraption is made by immobilizing acetyl alcohol in the pores of a 2. 5cm opening fiber scaled down chamber, filling the lumen with 1-octanol, and fixing the two terminations. Starting there ahead, 10 mL of analyte-containing plan course of action is agitated with the as of late formed instrument. The change twists for (ezetimibe/simvastatin) and (0.193-25 g L1/0.312-25 g L1) in plasma and are immediate in the ranges and for (ezetimibe/simvastatin) are straight in the reaches.

A LiChrospher **[11]**, and team proposed that,100 C18, five microns, 250 x 4.0 mm id column at ambient temperature; a most pleasant cell section of acetonitrile-water-methanol (60 + 25 + 15, v/v/v) with an obvious pH of 4.0 +/- 0.1; a cell phase drift cost of one. 5 mL/min; and ultraviolet detection at 238 nm," adds Chau. The confused samples were subjected to thermal, photolytic, and oxidative pressure with SIM, EZE, and their blended medicinal product to test the use of the recommended approach. There were no correlated, interfering peaks from excipients, contaminants, or degradation products due to the various pressure settings, and the approach is exact for computing SIM and EZE in the presence of degrading items.

**UV Spectroscopic technique:**

This UV spectrophotometry might be used to analyze in bulk and pharmaceutical formulations. The proposed technique gave appropriate validation outcomes and statistical analysis proved that the

technique is accurate, and reproducible and could be used for routine analysis

**UV method**

Because of the absorption spectra of ATV and EZE overlap significantly, conventional UV spectrophotometry cannot be used to decide their simultaneous willpower in a binary mixture."Belal, T. S and co-workers **[12]** proposed that it have an impact on the diluting solvent at the depth of measurements became explored in terms of technique optimization. Due to EZE insolubility or b-lactam ring instability, aqueous solvents inclusive of water, 0.1 M sodium hydroxide (NaOH), and 0.1 M hydrochloric acid (HCl) were not noted, and methanol was hired for dilution instead. They have an impact on divisor concentration at the ratio spectra of ATV and EZE became investigated in an examination. When the divisor concentration is expanded or reduced, the absorbance ratio values lower or growth consequently; but, the positions of the peaks and troughs live constant.

**CONCLUSION:**

The ezetimibe has a really positive vibe in every drug plan and, additionally, with technological advancement. These approaches are simple and reasonable to measure, and they are frequently used for great manipulation evaluation. It is more advanced in terms of the assessment procedure. This strategy has been around for a long time and is used to execute an analytical technique. The ezetimibe medicine has viable rules for the confirmation in human plasma for the characterization of every analytical procedure. Using the ICH guidelines, the techniques are approved for use.

**ACKNOWLEDGEMENT**

The authors are very much thankful to Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science, Technology and Advanced Studies (VISTAS), Pallavaram, Chennai-600 117, Tamil Nadu, India for providing the facilities to complete this work

**CONFLICT OF INTEREST**

The authors declare that no conflict of interest among us

**REFERENCES**

**[1]** Schade, D. S., Shey, L., & Eaton, R. P. (2020). Cholesterol Review: A Metabolically Important Molecule, Endocrine Practice, 26(12), 1514–1523.

**[2]** Luo, J., Yang, H. & Song, BL. Mechanisms and regulation of cholesterol homeostasis. Nat Rev Mol Cell Biol 21, 225–245 (2020)

**[3]** Narwal, V., Deswal, R., Batra, B., Kalra, V., Hooda, R., Sharma, M., & Rana, J. S. (2019). Cholesterol biosensors: A review. Steroids, 143, 6–17.

**[4]** G. Geetha, Karanam Naga Ganika Raju, B. Vignesh Kumar and M. Gnana Raja, Analytical Method Validation: An Updated Review, IJAPBC – Vol. 1(1), Jan- Mar, 2012

**[5]** Gao J, Zhong D, Duan X, Chen X, Liquid chromatography–negative ion electrospray tandem mass spectrometry method for the quantification of ezetimibe in human plasma. Journal of Pharmaceutical and Biomedical Analysis, 2006 Mar 3; 40(4): 987-92

**[6]** Varghese, S. J., & Thengungal Kochupappy, R, Development and Validation of a Liquid Chromatography/Mass Spectrometry Method for the Simultaneous Quantitation of Rosuvastatin and Ezetimibe in Human Plasma, Journal of AOAC International, Mar-Apr 2013; 96(2): 307-12.

**[7]** Bhadoriya, A., Sanyal, M., Shah, P. A., & Shrivastav, P. S, Simultaneous quantitation of rosuvastatin and ezetimibe in human plasma by LC-MS/MS: Pharmacokinetic study of fixed-dose formulation and separate tablets. Biomedical Chromatography, 2018Oct; 32(10): e4291.

**[8]** El-Bagary, R. I., Elkady, E. F., El-Sherif, Z. A., & Kadry, A. M, LC-MS-MS Simultaneous Determination of Atorvastatin and Ezetimibe in Human Plasma. Journal of Chromatographic Science, 2014 Sep; 52(8): 773-80

**[9]** Luo, Z., Deng, Z., Liu, Y., Wang, G., Yang, W., Hou, C., Zhou, H., Development and validation of a novel stability-indicating HPLC method for the quantitative determination of eleven related substances in ezetimibe drug substance and drug product. Talanta, 2015 Jul 1; 139: 67-74.

**[10]** AL-Hashimi, N. N., Shahin, R. O., AL-Hashimi, A. N., Al Ajeal M., Tahtamouni, L. H., & Basheer, C.,Cetyl-alcohol-reinforced hollow fiber solid/liquid phase microextraction and HPLC-DAD analysis of ezetimibe and simvastatin in human plasma and urine. Biomedical Chromatography, 2019 Feb; 33(2):e4410.

**[11]** Chaudhari BG, Patel NM, Shah PB. Stability-indicating reversed-phase liquid chromatographic method for simultaneous determination of simvastatin and ezetimibe from their combination

drug products. J AOAC Int. 2007 Sep-Oct; 90(5): 1242-9.

**[12]** Belal, T. S., Daabees, H. G., Abdel-Khalek, M. M., Mahrous, M. S., & Khamis, M. M.. New simple spectrophotometric method for determination of the binary mixtures (atorvastatin calcium and ezetimibe; candesartan cilexetil and hydrochlorothiazide) in tablets. Journal of Pharmaceutical Analysis, 2013 Apr; 3(2): 118-126.