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Simultaneous Determination of Atorvastatin and Ezetimibe: A Comprehensive Review of Analytical Methods

Suhani Barot[1], Dr.Pruthviraj Chaudhary[2], Dr.Khushbu Patel[3] and Dr. C. N. Patel[4]

[1]*Department of Pharmaceutical Quality Assurance, Shri Sharvajanik Pharmacy College, Gujarat Technological University, Arvind Bag Mehsana-384001, Gujarat, India.*

[2]*Assistant Professor, Department of Pharmaceutical Quality Assurance and Pharmaceutical Chemistry, Shri Sharvajanik Pharmacy College, Gujarat Technological University, Arvind Bag Mehsana-384001, Gujarat, India.*

[3]*Associated Professor, Department of Pharmaceutical Quality Assurance and Pharmaceutical Chemistry, Shri Sharvajanik Pharmacy College, Gujarat Technological University, Arvind Bag Mehsana-384001, Gujarat, India.*

[4]*Principal and Professor, Department of Pharmaceutical Quality Assurance and Pharmaceutical Chemistry, Shri Sharvajanik Pharmacy College, Gujarat Technological University, Arvind Bag Mehsana-384001, Gujarat, India.*

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ABSTRACT:

The combination of atorvastatin and ezetimibe is a highly effective therapy for managing hyperlipidemia and reducing the risk of cardiovascular diseases. Atorvastatin, a HMG-CoA reductase inhibitor, lowers LDL-C (bad cholesterol) and increases HDL-C (good cholesterol), while ezetimibe inhibits cholesterol absorption in the small intestine, further lowering overall cholesterol levels. Together, they provide a dual mechanism to significantly reduce LDL-C, total cholesterol, and triglyceride levels, improving cardiovascular outcomes. This combination is particularly beneficial for patients with familial hypercholesterolemia and mixed dyslipidemia.

Given the widespread use of atorvastatin and ezetimibe in combination therapy, accurate and reliable methods for their simultaneous estimation in tablet formulations are essential for ensuring therapeutic efficacy and product quality. Traditional methods, such as HPLC and UV spectrophotometry, have been used, but more advanced, efficient, and cost-effective techniques are necessary to meet the challenges posed by modern pharmaceutical formulations. This review explores the latest advancements in analytical methods for the simultaneous estimation of these drugs, providing insights into the key challenges and recent developments in the field.

I. INTRODUCTION:[1-3]

The **combination therapy** of **atorvastatin** and **ezetimibe** is widely used to manage **hyperlipidemia** and reduce the risk of **cardiovascular diseases**. **Atorvastatin**, a**HMG-CoA reductase inhibitor**, lowers **LDL-C** (bad cholesterol) by inhibiting the enzyme responsible for cholesterol production in the liver, while also increasing **HDL-C** (good cholesterol). This makes atorvastatin effective in preventing **atherosclerotic cardiovascular diseases** like heart attacks and strokes.

On the other hand, **ezetimibe** works by inhibiting the **NPC1L1 protein** in the **small intestine**, preventing the absorption of cholesterol from dietary sources and bile. This results in reduced cholesterol levels in the bloodstream, and when combined with statins like atorvastatin, it provides an enhanced cholesterol-lowering effect, especially for patients who do not achieve sufficient LDL-C reduction with statins alone.

This combination provides a **dual mechanism** for managing **dyslipidemia**, significantly reducing **LDL-C**, total cholesterol, and triglyceride levels, while improving cardiovascular outcomes. This is especially beneficial for patients with **familial hypercholesterolemia** and **mixed dyslipidemia**.

Given the increasing use of atorvastatin and ezetimibe in combination, accurate and reliable methods for their **simultaneous estimation** in tablet formulations are essential for ensuring

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therapeutic efficacy and **product quality**. Traditional techniques like **HPLC** and **UV spectrophotometry** have been employed, but there is a need for more **advanced and efficient** methods to address the growing complexity of pharmaceutical formulations. This review will discuss the latest **analytical methods** for simultaneous estimation and highlight the challenges and advancements in the field.

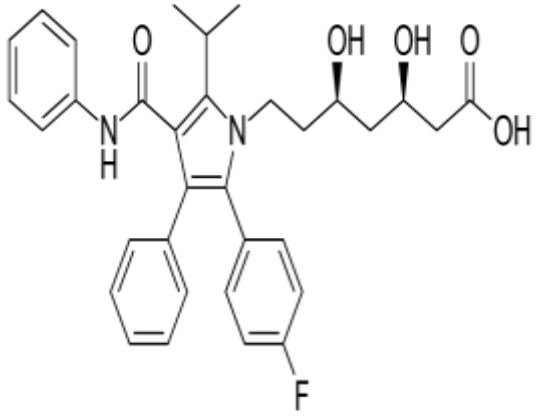

Figure:1 Structure of Atorvastatin

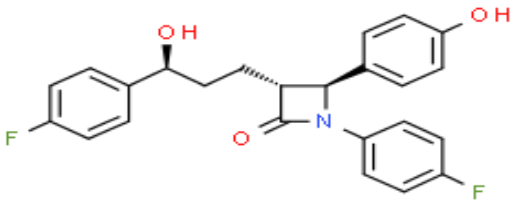

Figure:2 Structure of Ezetimibe

DETAIL LITERATURE SURVEY OF ATORVASTATIN AND EZETIMIBE:

Table 1: Official methods for assessment of Atorvastatin:

Sr. No.	Official	Method	Description	Ref No.
1	Indian Pharmacopoeia (2022)	Liquid Chromatography (API)	**Stationary phase:** A stainless-steel column (250 mm x 4.6 mm, 5µm) packed with octadecylsilane bonded to porous silica **Mobile phase:** A Mixture of 92.5 volumes of acetonitrile and 7.5 volumes tetrahydrofuran **Flow rate:** 1.8 mL/min **Wavelength:** 246 nm **Injection Volume:** 20 µl	4
2	Indian Pharmacopoeia (2022)	Liquid Chromatography (Tablet)	**Stationary phase:** A stainless-steel column (250 mm x 4.6 mm, 5µm) packed with octadecylsilane bonded to porous silica **Mobile phase:** Acetonitrile: Tetrahydrofuran (92.5:7.5 % v/v) **Flow rate:** 2.0 mL/min **Wavelength:** 246 nm **Injection Volume:** 20 µL	4

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Table: 2 Official methods for assessment of Ezetimibe:

Sr No.	Official	Method	Description	Ref No.
1	Indian Pharmacopoeia (2022)	Liquid Chromatography (API)	**Stationary phase:** A stainless-steel Column (250 × 4.6 mm), packed with octadecyl silane bonded to porous silica (5 µm) **Mobile phase:** Ammonium acetate buffer: Water (pH:4.5) (50:50 % v/v) **Flow rate:** 1 mL/min. **Wavelength:** 210 nm **Injection Volume:** 20 µl	5
2	Indian Pharmacopoeia (2022)	Liquid Chromatography (Tablet)	**Stationary phase:** A stainless-steel Column (150 × 4.6 mm, 5 µm) packed with octadecyl silane bonded to porous silica **Mobile phase:** Ammonium acetate buffer: Acetonitrile (50:50 % v/v) **Flow rate:** 1.5 mL/min **Wavelength:** 230 nm	5

Table:3 Reported methods for assessment of Atorvastatin:

Sr. No.	Title	Description	Ref No.
UV-VISIBLE SPECTROSCOPY			
1	Simple **UV Spectrophotometric Assay** of Atorvastatin API Formulation and their Comparative Study	**Solvent:** Methanol **Wavelength:** 244 nm	6
2	Development and Validation of **UV-Spectrophotometric Method** for the Determination of **Atorvastatin** Calcium Using **Sodium Citrate** as Hydrotropic Agent.	**Solvent:** 0.01M Sodium citrate **Wavelength:** 241 nm **Linearity:** 2 – 20 µg/mL. **R^2:** 0.999	7
3	Development And Validation of New Analytical Method for The Estimation of Atorvastatin Calcium Hydrate Residue by Using **UV Spectrophotometric**	**Solvent:**Methanol: Water (90:10%v/v) **Wavelength:**245 nm **Linearity:** 1-10 µg/ml	**8**
4	Determination Of Atorvastatin Calcium in Pure and Its Pharmaceutical Formulation Using Iodine in Acetonitrile By **UV-Visible Spectrophotometric Method**	**Solvent:** Iodine in acetonitrile **Wavelength:** 291 and 360 nm **Linearity:** 0.5586-11.173 µg/mL.	9
5	Development and validation method for the determination of Atorvastatin calcium tablets drugs by using **UV-spectrophotometer** in pharmaceutical formulation	**Solvent:** Anhydrous methanol **Wavelength:** 291nm **Linearity:** 5 to 35 µg/mL	10
6	Method Development and Validation of Atorvastatin Calcium by **UV-Visible Spectroscopy**	**Solvent:** Water:Methanol (90:10% v/v) **Wavelength:** 241 nm **Linearity:** 4 to 32 µg/mL	11
7	**Validated Spectrophotometric** Method for Simultaneous Estimation of Fenofibrate AndAtorvastatin In Synthetic Mixture and in Bulk Tablet Dosage Form	**Wavelength:** 249 nm **Linearity:** 5-30 µg/mL for both Fenofibrate and atorvastatin.	12
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
8	Development and Validation of RP-HPLC	**Stationary phase:** Luna C_{18} column	13

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	Method for Simultaneous Estimation of Atorvastatin Calcium and Fenofibrate in Tablet Dosage Forms	**Mobile phase:** Methanol: Acetate buffer pH 3.7 (82:18 % v/v) **Flow rate:** 1.5 mL/min **Wavelength:** 248 nm.	
9	Development and validation of reversed-phase **HPLC** method for Simultaneous Estimation of **Atorvastatin calcium** and **Telmisartan** in Tablet dosage form	**Stationary phase:** Waters symmetry C_{18}, (250mm x 4.6mm, 5µ) **Mobile phase:** Ammonium acetate (0.02M): Acetonitrile (40:60% v/v) (pH 4.0 adjusted with glacial acetic acid) **Flow rate:** 1.0 mL/min **Wavelength:** 254 nm	14
10	Analytical **Quality by Design** Approach of **Reverse-Phase High-Performance Liquid Chromatography** of Atorvastatin: Method Development, Optimization, Validation, and the Stability-Indicated Method	**Stationary phase**: C_{18} column (Acclaim120C_{18}, 4.6 mm 2.2 µm) **Mobile phase:**Acetonitrile:Water (50:50%v/v) **Flow rate:** 0.68 ml/min **Wavelength:** 235 nm **Linearity:** 5–30 µg/mL	15
11	Development and validation of **RP-HPLC** method for determination of **Atorvastatin calcium** and **Nicotinic acid** in combined tablet dosage form	**Stationary phase:** Agilent ZORBAX SB-C_{18} (150 × 4.6 mm, 3.5 µm) **Mobile phase:** Acetonitrile: distilled water (85:15 % v/v) at pH 4.5 (adjusted with phosphoric acid) **Flow rate:** 1.0 ml/min **Wavelength:** 261 nm **Linearity:** 2–12 µg/mL and 0–80 µg/mL for Atorvastatin calcium and Nicotinic acid respectively	16
12	Development and Validation of **RP-HPLC** Method for Simultaneous Estimation of **Ramipril, Aspirin and Atorvastatin** in Pharmaceutical Preparations	**Stationary phase:**C_{18} column (250 ×4.6 mm, 5µm) **Mobile phase:** (A) acetonitrile methanol (65:35% v/v) and (B) 10 mM sodium dihydrogen phosphate monohydrate ($NaH_2PO_4.H_2O$) buffer and mixture of A: B (60:40 % v/v) adjusted to pH 3.0 with o-phosphoric acid (5%v/v) **Flow rate:** 1.5 mL min **Wavelength:** 230 nm **Linearity:** 02-20 µg mL for Atorvastatin	17
13	Method Development and Validation for The Simultaneous determinationOf Metoprolol andAtorvastatinby**Reversed-Phase High-PerformanceLiquidChromatography**In Its Bulk AndPharmaceutical Tablet Dosage Form Using Biorelevant Dissolution Media (Fasted State Small Intestinal Fluid)	**Stationary phase:** Inertial ODS-C_{18} (150 × 4.6 mm, 5 µm) **Mobile phase:** Phosphate buffer 4.8 pH: Acetonitrile (35:65% v/v) **Flow rate:** 1 mL/min **Wavelength:** 244 nm **Linearity:** 50–250 µg/mL and 10–50 µg/mL for Metoprolol and Atorvastatin respectively	18
HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
14	Validated **HPTLC Method** for Estimation of Atorvastatin Calcium and Fenofibrate in Bulk Drug and In Tablets According to ICH Guidelines	**Stationary phase**: Silica gel 60F_{254} plates **Mobile phase:** Dichloromethane:Toluene:Methanol (2:6:2% v/v/v) **Wavelength:** 287 nm	19

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Table:4 Reported methods for assessment of Ezetimibe:

Sr. No.	Title	Description	Ref No.
UV-VISIBLE SPECTRSCOPY			
1	Development Of **UVSpectrophotometric** Method for the Estimation of **Ezetimibe**from Tablet Formulation	**Solvent:** Acetate buffer (pH 4.5) **Wavelength:** 232 nm **Linearity:** 5-30 µg/mL	20
2	**UV** and **ThreeDerivativeSpectrophotometric** Methods for Determination of **Ezetimibe** in Tablet Formulation	**Method A:** Quantitative determination of the drug **Solvent:** Methanol **Wavelength:** 233 nm **Linearity:** 6-16 µg/ml **Method B:** First, second and third derivative spectrophotometric methods **Wavelength**: 259.5 nm, 269 nm and 248 nm **Linearity:**4-14 µg/mL, 4-14 µg/mL and 4-16 µg/mL	21
3	**UV Spectrophotometric** Method Development and Validation of **Ezetimibe** and **Simvastatin** in Bulk and Pharmaceutical Dosage Form	**Solvent:** 0.1 N NaOH **Wavelength:** 244nm **Linearity:** 0.5 to 30 µg /mL (Atorvastatin) 1.0 to 40 µg /mL (simvastatin)	22
4	Spectrophotometric Method for the Determination of **Ezetimibe** in Pharmaceutical Formulations	**Solvent:** Ethanol **Wavelength:** 234nm **Linearity:** 5-20 µg/mL	23
5	Development and Validation of UV Spectrophotometric Method for The Simultaneous Estimation of **Rosuvastatin** and **Ezetimibe** in Pharmaceutical Dosage Form	**Solvent:** Distilled water **Wavelength:** 223nm (Rosuvastatin) and 229nm(Ezetimibe) **Linearity:** 4-32 µg/mL for both the drugs	24
6	**UVSpectrophotometric** estimation of **Ezetimibe** and **Fenofibrate** in Bulk drug and Dosage form using Simultaneous Equation Method	**Solvent:** Methanol **Wavelength:** 286.6 nm and 232.6 nm for Fenofibrate and Ezetimibe respectively **Linearity:** 2 – 20 µg/mL	25
7	Analytical Method Development and Validation of **Ezetimibe** by Using **UV-Spectrophotometric** Method	**Solvent:** Ethanol **Wavelength:** 234 nm **Linearity:** 2-12 µg/mL	26
8	Simple novel UV-spectroscopic method for estimation of Ezetimibe in tablet dosage form	**Solvent:** Ethanol**:** Acetic acid (90:10 % V/V) **Wavelength:** 252 nm **Linearity:** 2- 20 µg/mL	27
9	First derivative UV-spectrophotometric method for simultaneous determination of simvastatin and ezetimibe in tablet dosage form	**Solvent:** Methanol **Wavelength**: 235 nm and 266 nm of Simvastatin and Ezetimibe, respectively **Linearity:** 2-20 µg/mL	28
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY			
10	Validated **RP- HPLC** Method For Estimation of Ezetimibe in Different Tablet Dosage Form	**Stationary phase:** Phenomenex, (250x4.6mm) LunaC-$_{18}$ column **Mobile phase:** Acetonitrile**:** Methanol (50:50 % v/v) **Flow rate:** 1.0 mL/min **Wavelength:** 245 nm	29
11	Development and validation of a	**Stationary phase:** Kromasil 100 C_{18}	30

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	reversed-phase **HPLC** method for the determination of ezetimibe in pharmaceutical dosage forms	column **Mobile phase:** Water (pH 6.8, 0.05%, v/v 1-heptane sulfonic acid) and Acetonitrile (30:70 % v/v) **Flow rate:** 0.5 mL/min **Wavelength:** 232 nm	
12	Development and validation Of Novel **RP-HPLC** Method for the Simultaneous Estimation of **Ezetimibe** and Bempedoic acid In a Tablet Dosage Form	**Stationary phase:** Prontosil C_{18} (250 x 4.6 mm, 5 µm) column **Mobile phase:** Acetonitrile: Water (60:40 % v/v) **Flow rate:** 1.0 mL/min **Wavelength:** 225 nm **Linearity:** 20-60 µg/mL	31
13	Development and validation of RP-HPLC method for simultaneous estimation of **Ezetimibe** and glimepiride in tablet dosage form	**Stationary phase:** Phenomenex C_{18} column (250 × 4.6 mm, 5 µm) **Mobile phase:** Methanol: 20 mM potassium phosphate buffer (pH 3.00) (80: 20 % v/v) **Flow rate:** 1 mL/min **Wavelength:** 230 nm **Linearity:** 2-10 µg/mL(Glimepiride) 20-100 µg/mL (Ezetimibe)	32
HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY			
14	HPTLC method for determination of **Ezetimibe** in tablets	**Stationary phase:** Silica gel 60GF_{254} **Mobile phase:** Toluene: Acetone (6:4 % v/v) **Wavelength:** 233 nm **Linearity:** 300-2100 ng/spot	33

Table:5 Reported method for combination of Atorvastatin and Ezetimibe:

Sr. no	Title/method	Description	Ref No.
1	Development and Validation of an **RP-HPLC Method** for Simultaneous Estimation of **Atorvastatin** and **Ezetimibe** in pharmaceutical dosage forms	**Stationary phase:** Isocratic elution with Phenomenex ODS C_{18}column **Mobile phase:** Methanol: Acetonitrile: 0.1M KH_2PO_4(60:30:10%v/v) **Flow rate:** 0.9 mL/min **Wavelength:** 232 nm **Linearity:** 10-100 µg/ml for both the drugs	34
2	**RP -HPLC Method**Development and Validationfor Simultaneous Estimation of **Atorvastatin** and **Ezetimibe** in Pharmaceutical Dosage Form	**Stationary phase:** Hypersil BDS C18 column (250 × 4.6 mm, 5 µm) **Mobile phase:** Phosphate buffer (pH-4.5): Acetonitrile (35:65 % v/v) **Flow rate:** 1 mL/min **Wavelength:** 228 nm **Linearity:** 12.5-75 µg/mL for both Atorvastatin and Ezetimibe	35
3	New Validated stability **RP-HPLC Method** for the Simultaneous Estimation of **Atorvastatin** and **Ezetimibe**in Human Plasma by Using PDA Detector	**Stationary phase**: X-Terra C_8 (4.6 x 150 mm, 3.5 µm) **Mobile phase**: Phosphate buffer (pH 3.5 with Ortho Phosphoric Acid)–Acetonitrile (40:60 % v/v) **Flow rate:** 1.2 mL/min	36

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		Wavelength: 235 nm **Linearity:**5-25 µg/mL for both Atorvastatin calcium and Ezetimibe	
4	Method development and validation of **Atorvastatin**, **Ezetimibe** and **Fenofibrate** using **RP-HPLC** along with their forced degradation studies and **greenness profiling**.	**Stationary phase**: Inertsil ODS (250 x 4.6 mm, 5 µm) **Mobile phase**: (0.1% triethanolamine buffer in water): Ethanol (10:90 % v/v) **Wavelength:** 256 nm **Linearity:** 12–28 µg/mL for ATR, EZB, and 192- 448 µg/mL for FNF.	37
5	**RP- HPLC** Method Development and Validation For SimultaneousEstimation Of **Bempedoic Acid,Ezetimibe** And **Atorvastatin** In **SyntheticMixture**	**Stationary phase**: C_{18} (250 mm x 4.6 mm, 5 µm) column **Mobile phase**: Potassium dihydrogen phosphate buffer (pH=5.8): Methanol: Acetonitrile (30:60:10 % v/v/v) **Wavelength:**262 nm **Flow rate:** 1 mL/min **Linearity:**90-540 µg/ml (Bempedoic acid), 5- 30 µg/ml (Ezetimibe) and10 – 60 µg/ml (Atorvastatin)	38
6	RP-HPLC Method for simultaneous estimation of Atorvastatin calcium-Ezetimibe in pharmaceutical formulation	**Stationary phase**: Hypersil BDS (250 X 4.6mm ,5 µm) column **Mobile phase**: Acetonitrile: Water: Methanol (35:55:10 % v/v) (pH to 4.0) with Orthophosphoric acid **Wavelength**: 250 nm **Flow rate:** 2.0 mL/min	39
7	Simultaneous assessment of Atorvastatin-ezetimibe combination in tablets by An **Ion-pair RP-HPLC**	**Stationary phase**: Standard C_{18}-type column **Mobile phase**: 35% of cetyltrimethylammonium bromide (cetrimide) 10 M as the ion-pairing agent and 65% acetonitrile **Flow rate:** 1.5 mL/min	40
8	Development of a **RP-HPLC** method for separation of ezetimibe in presence of atorvastatin calcium and simvastatin and its application for quantitation of tablet dosage forms	**Stationary phase:** C_{18} column (250 × 4.6 mm, 5 µm) column **Mobile Phase**: Acetonitrile: Water (70:30 % v/v) **Wavelength:** 242 nm **Flow rate:**1.2 mL/min	41
HIGH PERFORMANCE THIN LAYAR CHROMATOGRAPHY			
9	Development and Validation of **HPTLC** method for the simultaneous estimation of **Atorvastatin** Calcium and **Ezetimibe**.	**Stationary phase:** Precoated silica gel 60F_{254} **Mobile phase**: Chloroform: Benzene: Methanol: Acetic acid (6.0:3.0:1.0:0.1 % v/v/v/v). **Wavelength**: 250 nm **Linearity:** 0.8 and 4.0 µg/spot (Atorvastatin calcium) 0.1 and 1.0 µg/spot (Ezetimibe**)**	42

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II. CONCLUSION:

The combination of atorvastatin and ezetimibe offers a potent and effective solution for managing dyslipidemia and reducing the risk of cardiovascular events. Their complementary mechanisms of action allow for enhanced cholesterol-lowering effects, benefiting patients who do not achieve adequate results with statins alone. As the use of this combination therapy grows, the demand for accurate, efficient, and reliable methods for the simultaneous estimation of atorvastatin and ezetimibe in pharmaceutical formulations becomes increasingly important. While traditional techniques like HPLC and UV spectrophotometry are still in use, the development of more advanced analytical methods is crucial to ensure the consistent quality, efficacy, and safety of these combination products. Future research and advancements in analytical methodologies will be vital to address the complexities of modern pharmaceutical formulations and enhance patient outcomes in hyperlipidemia treatment.

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