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# REVIEW ARTICLE ON IMPURITY PROFILE OF LOVASTATIN

***Arunima Aravind V. P., Shahana T. S.**

Malik deenar college of Pharmacy ,Seethangoli, Bela, Kasaragod.

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***Corresponding Author: Arunima Aravind V. P.**

Malik deenar college of Pharmacy ,Seethangoli, Bela, Kasaragod.

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## ABSTRACT

A crucial drug for lowering cholesterol and cardiovascular problems, lovastatin is frequently recommended. The stability, safety, and effectiveness of the pharmaceutical product may be impacted by a variety of contaminants that develop throughout the manufacturing, storage, and degrading processes. In order to identify, detect, characterize, and quantify these undesirable chemicals in pharmaceutical formulations, impurity profiling is essential. This study looks at the impurity profile of lovastatin using analytical methods such mass spectrometry, UV spectroscopy, FTIR spectroscopy, and High-Performance Liquid Chromatography. To assess the stability behaviors of lovastatin and its associated impurities, stress degradation tests were conducted under acidic, alkaline, oxidative, thermal, and hydrolytic environments. Excellent precision, accuracy, robustness, and sensitivity for impurity identification were shown by the devised analytical approach.

**KEYWORDS:** Lovastatin; Impurity profiling; HPLC; Forced degradation studies; Method validation; Pharmaceutical analysis; Stability studies; FTIR spectroscopy; UV spectroscopy; Mass spectrometry.

## INTRODUCTION

The methodical detection, identification, structural characterization, and quantification of impurities found in active medicinal substances and formulations is known as impurity profiling. To guarantee medication safety and effectiveness, regulatory bodies like the International Council for Harmonization (ICH) have set stringent requirements for impurity monitoring and reporting.

Because of their sensitivity and dependability, analytical methods like mass spectrometry, Fourier Transform Infrared Spectroscopy (FTIR), UV spectroscopy, and High-Performance

Liquid Chromatography (HPLC) are frequently used for impurity analysis. Furthermore, forced degradation studies are frequently carried out to assess the stability profile of pharmaceutical compounds under a variety of stress conditions, including oxidation, heat, light exposure, acid hydrolysis, and base hydrolysis.

In order to identify degradation products, evaluate method performance, and guarantee compliance with pharmaceutical quality standards, the current work focuses on the impurity profiling and stability evaluation of lovastatin using validated analytical methods. Impurities are defined as foreign particles that compromise the purity of a substance; they are the undesired chemicals present alongside active pharmaceutical ingredients (APIs) or in drug product formulations.

## CLASSIFICATION OF IMPURITIES IN DRUG SUBSTANCE OR API, NEW DRUG PRODUCTS

Impurities can be categorized into the following groups:

### 1. Organic impurities

Organic contaminants may develop when the new medicinal material is being manufactured or stored. Starting materials, byproducts, intermediates, degradation products, reagents, and ligands are examples of substances that can be identified or not, volatile or non-volatile. catalyst.

### 2. Inorganic impurities

The industrial procedure may result in inorganic contaminants. Usually, they are identified and acknowledged.

Reagents, ligands, catalysts, heavy metals or other residual metals, inorganic salts, and other materials like charcoal and filter aids are among them.

### 3. RESIDUAL SOLVENTS

Organic volatile chemicals used or produced during the manufacturing of medicinal ingredients are referred to as residual solvents in the pharmaceutical industry. ICH standards Q3C define the allowable quantities of residual solvents in pharmaceutical products, which fall into three classifications.

## RATIONALE FOR REPORTING AND CONTROL OF DEGRADATION PRODUCTS

For a number of reasons that are all related to guaranteeing the medication's safety, effectiveness, and quality, controlling and reporting contaminants in a pharmacological product

is essential. The main justifications are as follows:

Safety: Drug product impurities may result in negative reactions or detrimental effects. They may interact with the medicine or other ingredients, or they may be dangerous in and of themselves.

Efficacy: A drug's pharmacokinetic or pharmacodynamic properties may be impacted by the presence of contaminants.

Regulatory compliance: Strict adherence to impurity standards is required by regulatory bodies like the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the United States**.**

## WHO AND ICH GUIDELINES FOR IMPURITY PROFILING

**WHO TRS 943 Annex 3:** The World Health Organization (WHO) offers impurity profiling recommendations mainly to guarantee the efficacy, safety, and quality of pharmaceutical products. The ideas and methods for detecting, describing, and managing contaminants in pharmaceutical substances and products are described in these guidelines.

refers to the World Health Organization's (WHO) 2007 Technical Report Series No. 943, which included general principles for the creation, upkeep, and distribution of chemical reference substances. Goal: By using reference standards, this paper offers a thorough framework for guaranteeing the quality, accuracy, and repeatability of pharmaceutical analysis.

**ICH Impurity Guidelines:**

- Organic, inorganic, and process-related impurities are the main topics of ICH Q3A (R2), Impurities in New Drug Substances.
- ICH Q3B (R2): Impurities in New Drug Products: This section addresses reaction and degradation products involving excipients and container systems.• ICH Q3C (R9)- Residual Solvents: Establishes stringent concentration limits and classifies solvents according to toxicity (Class 1, 2, 3).
- ICH Q3D (R1) - Elemental Impurities: Determines PDE limits based on toxicity for metal impurities (such as Pb, Hg, and As).
- ICH M7 (R1) - Mutagenic/Genotoxic Impurities: Uses the Threshold of Toxicological Concern (TTC) to evaluate and regulate DNA-reactive contaminants.

## ANALYTICAL TECHNIQUES FOR IMPURITY PROFILING

Analytical techniques are used to find, identify, or clarify the structure and amount of organic

and inorganic contaminants as well as leftover solvents found in active pharmaceutical substances and their corresponding formulations.

These fall into four main categories: hyphenated methods, spectroscopy, isolation, and separation.

Radiation method is given by:

E=hv

Where E= energy (in joules)

h=plank's constant, v=frequency (in seconds)

**ANALYTICAL TECHNIQUES**

**1. SPECTROSCOPIC TECHNIQUES**

PRINCIPLE: It is the detection and interpretation of electromagnetic radiation that is either emitted or absorbed when a sample's molecules, atoms, or ions change energy states. It gauges how much UV or visible light is absorbed between 200 and 400 nm or 400 and 800 nm.

**2. FTIR(FOURIER TRANSFORM INFRARED SPECTROSCOPY)**

PRINCIPLE : when the natural frequency of vibration and the frequency of infrared radiation are equal .A peak is absorbed when the molecule absorbs infrared energy. For absorption, each link, part of a molecule, or functional group needs a separate frequency.

**3. MASS SPECTROSCOPY**

It is the most accurate method to determine molecular mass of compound and elemental composition.

PRINCIPLE: This method involves subjecting molecules to an intense electron beam. Ionization causes the molecules to split into numerous pieces, some of which are positive ions.

**4. NMR (NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY)**

It is used to characterize organic molecules by identifying carbon hydrogen framework within molecule.

PRINCIPLE: NMR is based on the idea that a nucleus's spin creates a magnetic field. The directions of the nuclear spins are random in the absence of an external magnetic field.

**2.SEPARATION TECHNIQUE**

**1. HPLC (HIGH PERFORMANCE LIQUID CHROMATOGRAPHY)**

PRINCIPLE : Its foundation is the division of the analyte into a mobile phase and a stationary phase.

The component that has a higher affinity for the adsorbent moves more slowly. The component

that is less attracted to the stationary phase moves more quickly. The components are divided because no two of them have the same affinity for the stationary phase.

**2. TLC (THIN LAYER CHROMATOGRAPHY)**

Principle: Depending on the adsorbent, how it is treated, and the type of solvents used, either adsorption or partition may cause the separation. The components that have a stronger affinity for the immobile phase move more slowly. Components that have a lower affinity for the immobile phase move more quickly.

**3. COLUMN CHROMATOGRAPHY**

In this separation takes place on the basis of adsorption with an aid of Column.

Principle: When the sample to be separated and a combination of mobile phase are added from the top of the column.

**GAS CHROMATOGRAPHY**

It is a process of separating components from crude drug by using gaseous mobile phase.

Principle: Partition (Gas Liquid Chromatography) or adsorption (Gas Solid Chromatography) are the methods of separation.

**STUDY ON VARIOUS HYPHENATED TECHNIQUES THEIR APPLICATION IN IMPURITY**

**HYPHENATED TECHNIQUES:**

In the realm of analytical science, the hyphenated technique is a relatively new method that combines two or more techniques with the aid of an interface.

**TYPES OF HYPHENATED TECHNIQUES**

1. Double hyphenated techniques.

- Gas Chromatography–Mass Spectroscopy (GC-MS).
- Liquid Chromatography–Mass Spectroscopy (LC-MS).
- Liquid Chromatography–NMR Spectroscopy (LC-NMR).
- Gas Chromatography–NMR Spectroscopy (GC-NMR).

2. Triple hyphenated techniques.

- Liquid Chromatography–Mass Spectroscopy–Mass Spectroscopy (LC-MS-MS).
- Gas Chromatography–Mass Spectroscopy–Mass Spectroscopy (GC-MS-MS).

Advantages of hyphenated techniques

- Fast and accurate analysis.
- Higher degree of automation and Higher sample throughput.
- Higher sample throughput

## IMPURITY PROFILING OF LOVASTATIN

Lovastatin is a member of the class of medications known as statins or HMG-COA reductase inhibitors. By inhibiting the rate-limiting enzyme for cholesterol manufacture, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, it lowers blood cholesterol levels.

In August 1987, the US Food and Drug Administration authorized lovastatin as a hypocholesterolemic medication, making it the first statin.

It is a 24-carbon molecule having three rings, two ester functions (one of which is a lactone), two conjugated carbon-carbon double bonds, and a hydroxyl group.

Lovastatin's empirical formula is **$C_{24}H_{36}O_5$.**

## STABILITY STUDY USING HPLC METHOD CHEMICALS AND REAGENTS

The medication lovastatin was made available in bulk by Merck Ltd. in India.

## SAMPLE SOLUTION

100 ppm of lovastatin in a 100 ml calibrated flask with a 1:1 combination of acetonitrile and water. Accurate dilution was used to get the medication at the required concentration.

## PREPARING OF STANDARD STOCK SOLUTION

In a volumetric flask, standard stock solutions containing 100 ppm of lovastatin in acetonitrile and water (1:1) were made.

## CHROMATOGRAPHIC CONDITION

An auto-injector, column oven, UV detector, degasser, and quaternary solvent delivery pump make up the Systronic chromatographic system. Octadecyl silane Inertsil ODS C18 is loaded into a chromatographic column that is 250 mm long and has an internal diameter of 4.6 mm. The injection volume was 20 µl, the wavelength was 230 nm, and the instrumental parameters were 1 ml/min.

## METHOD VALIDATION

**1. Linearity**

Plotting the lovastatin calibration curve for the six-concentration level between 80% and 120% of the desired level of lovastatin assay concentration allowed for the determination of linearity.

**2. Precision**

By measuring the amounts of the medication lovastatin in the pill six times, the method's accuracy was investigated.

**3. Accuracy (Recovery test)**

The degree of agreement between the value that is recognized as either a conventional true value or an approved reference value and the value discovered is expressed by the accuracy of an analytical method.

**4. Robustness**

The resolution between lovastatin and the acid-degraded product was assessed, and experimental settings were purposefully changed to ascertain the robustness of the suggested approach

**5. Limit of Detection (LOD)**

LOD was calculated by using the following formula, LOD = 3.3σ / S

Where σ is the standard deviation of the response and S is the slope of the calibration curve.

**6. Limit of Quantitation (LOQ)**

LOQ was calculated by using the following formula, LOQ = 10σ / S

Where σ is the standard deviation of the response and S is the slope of the calibration curve.

## IMPURITY PROFILING OF LOVASTATIN

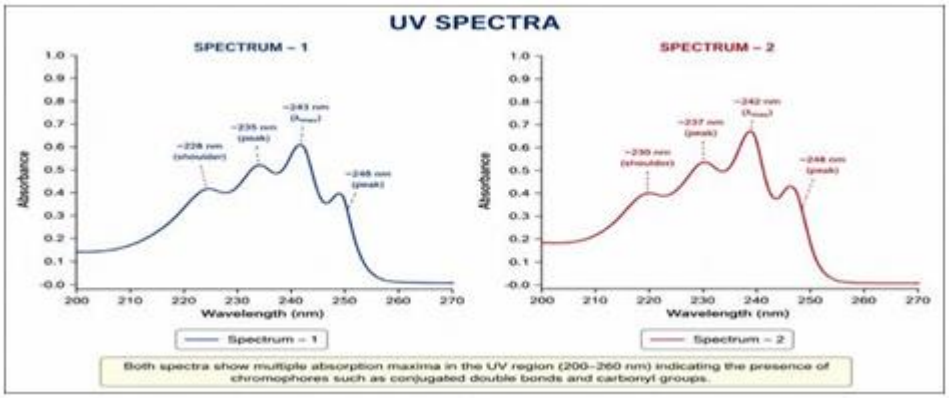
Frequently observed impurities include:

8-[2-(3-hydroxy-5-oxotetrahydro-2H-pyran-2-yl)ethyl]-3,7-dimethyl-1,2,3,7,8,8a-hexahydro 9-naphthalen-1-yl-2-methyl-3-oxobutanoate. Dehydro Lovastatin with Monacolin-X.

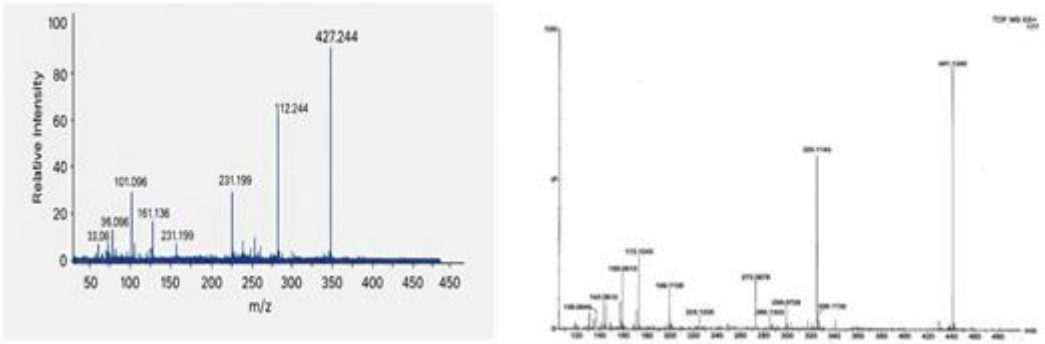
## LOVASTATIN'S UV SPECTRUM AND IMPURE LOVASTATIN

A Perkin Elmer device was used to examine the UV spectra of the impurity at 0.52 RRT and lovastatin in acetonitrile. Both lovastatin and the isolated impurity showed peaks at 238.2 nm.

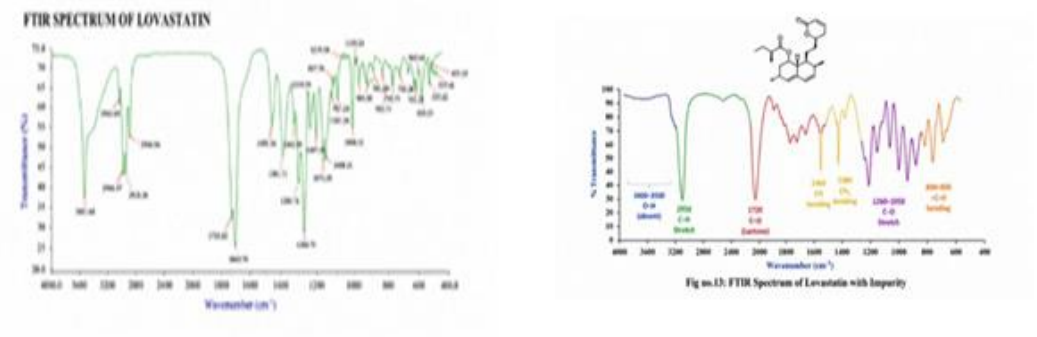
Uv spectrum of lovastatin with and without impurity




Mass spectrum of lovastatin with and without impurity




Ftir spectrum of lovastatin with and without impurity




**VIBRATIONAL MODE of Ftir**

- 1073 – (lactone C–O–C asymmetric bend)
- 1055 – (ester C–O–C symmetric bend)
- 970 – (alcohol C–OH stretch)
- 870 – (trisubstituted olefinic C–H) Spectral Analysis of Lovastatin

**1. UV–Visible Spectrum of Lovastatin** Parameter Observation λmax (Methanol) 238–240 nm

Electronic Transition π → π* transition FTIR Spectrum of Lovastatin

Wavenumber ($cm^{-1}$) | Functional Group | Stretching / Vibrational Mode 3540–3450 :–OH group O–H stretching

2960–2870 : Alkyl group C–H stretching 1725–1705 :

Ester carbonyl C=O stretching 1660–1640 :

Lactone carbonyl C=O stretching 1460–1380 :

Methyl / methylene C–H bending 1270–1160 :

Ester linkage C–O stretching 1100–1050 :

Alcohol group C–O stretching 970–890 :

Alkene group =C–H bending

**2. Mass Spectrum (MS) of Lovastatin** Parameter & Observation Molecular Formula: $C_{24}H_{36}O_5$ Molecular Weight: 404.54 g/mol Molecular Ion Peak: m/z 405 $[M+H]^+$

Major Fragment Ions: m/z 387, 285, 199, 159

**FORCED DEGRADATION STUDIES**

All drug substances were subjected to drastic condition of stress studies involving,

1. Acid hydrolysis
2. Base hydrolysis
3. Oxidation
4. Thermal degradation
5. Photolytic degradation

**1. Acid hydrolysis**

The aqueous solution of lovastatin was mixed with 0.5 N hydrochloric acid (HCL) and allowed to hydrolyse for approximately 48 hours.

**2. Base hydrolysis**

After two hours, the lovastatin aqueous solution was treated with 0.025N NaOH and base hydrolysis was monitored.

**3. Oxidation**

For 48 hours, heat the sample solution with 30% H2O2. The sample was examined for signs of deterioration.

**4. Thermal degradation**

The sample solution lovastatin was heated to 80°C for seven days.

**5. Photolytic degradation**

After lovastatin was exposed to light for 1.2 Lux million hours, photolytic deterioration occurred.

## RESULT OF FORCED DEGRADATION

Under stressful conditions as acid heat stress, Lovastatin bulk samples did not show significant deterioration. Under stress conditions like base, lovastatin was found to degrade significantly, and oxidative hydrolysis results in the development of some unidentified degradation peaks.

## RESULTS

Several analytical methods, including High Performance Liquid Chromatography (HPLC), UV spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), Mass Spectrometry (MS), and Nuclear Magnetic Resonance (NMR), were used to profile the impurities of lovastatin. The results showed that these analytical techniques were appropriate for identifying, separating, and characterizing lovastatin and its associated contaminants.

It was determined that the method validation parameters—linearity, precision, accuracy, robustness, and specificity—were sufficient. The analytical method's accuracy was confirmed by the percentage Relative Standard Deviation (%RSD) being less than 2%.

To assess the stability behavior of lovastatin, forced degradation tests were conducted under a variety of stress conditions, such as acid hydrolysis, base hydrolysis, oxidative degradation, thermal degradation, and photolytic degradation.

## DISCUSSION

Lovastatin is extremely vulnerable to hydrolytic breakdown, particularly in acidic and alkaline environments, as the impurity profile investigations showed. Base hydrolysis caused the most deterioration under all stress levels, while photolytic degradation displayed relatively less degradation. The established analytical techniques were able to successfully separate and identify lovastatin as well as its contaminants and degradation products.

HPLC paired with spectral methods such as FTIR, UV, MS, and NMR offered extensive evaluation of lovastatin impurities. The acquired results demonstrated the significance of forced degradation studies in pharmaceutical quality control and regulatory compliance and validated the stability-indicating character of the analytical approach.

## CONCLUSION

The existence of contaminants in drug substances and drug products is discussed in this article. Drug safety is an increasing topic in the literature, and the significance of impurity profiling in pharmaceuticals is expanding. Standardized criteria for contaminants are desperately needed. The types and classifications of impurities, their origins, the WHO and ICH guidelines, and the analytical techniques utilized for their detection are all crucial details that can be obtained by conducting impurity profiling research.

The linearity, accuracy, precision, and limits of detection and quantitation of the HPLC method for lovastatin were validated. Statistical analyses showed that the technique made it possible to measure these medications both in bulk and in pharmaceutical goods in a repeatable and targeted manner. The approach is appropriate for stability-indicating applications since it can successfully separate the medicines from their degradation byproducts. FTIR, mass, and NMR spectroscopy were used to analyse impurities. Lovastatin is susceptible to degradation under basic conditions, according to a forced degradation research.

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