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Reported Analytical Methods of Atorvastatin: An Extensive Review.

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ABSTRACT:
The statin drug atorvastatin has been subjected to a number of analytical techniques. The detection of atorvastatin in biological fluids and pharmaceutical formulations has been accomplished through the development and validation of High-Performance Liquid Chromatography (HPLC) technologies. There have also been reports of Atorvastatin measurement in plasma and serum using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) techniques. Pharmaceutical formulations containing atorvastatin have been identified using Gas Chromatography-Mass Spectrometry (GC-MS) techniques. Techniques for measuring ultraviolet (UV) spectroscopy have been developed to determine the amount of atorvastatin present in bodily fluids. There have been reports of the isolation and quantification of atorvastatin and its metabolites using capillary electrophoresis (CE) techniques. Approaches such as Nuclear Magnetic Resonance (NMR) spectroscopy have been utilized to clarify the structure of Atorvastatin. The robustness, accuracy, precision, sensitivity, specificity, and precision of these analytical techniques have all been verified. The techniques have been used on a variety of matrices, such as biological fluids, plasma, and pharmaceutical formulations. The documented atorvastatin analytical procedures offer a thorough summary of the state of analytical methods as of right now for this significant drug. The most effective HMG-CoA Reductase inhibitor on the market today for lowering cholesterol, atherosclerosis, stroke risk, and cardiac problems is atorvastatin. Effective analytical methods for quality control, pharmacodynamics, pharmacokinetic, and stability investigations are needed for the clinical and pharmaceutical analysis of this medication. A thorough analysis of the material published in numerous publications pertaining to analytical and medicinal chemistry has been performed and the instrumental analytical techniques created and applied for either a single or combination of determinations Formulations and biological fluids in combination with other medications in bulk drugs have been reviewed. This analysis includes the most recent numerous spectrophotometric techniques, chromatographic techniques such as HPLC, HPTLC, and RP HPLC, and other analytical methods Reports on tendam mass spectroscopy using liquid chromatography were made.

Keywords: Atorvastatin, Drug Profile and Methods.

INTRODUCTION:
Synthetic lipid-lowering medication atorvastatin is frequently used to treat cardiovascular disease and lessen the risk of stroke and heart attack. It is a statin drug that blocks the enzyme HMG-CoA reductase, which is essential for the creation of cholesterol. It has been demonstrated that atorvastatin efficiently lowers LDL cholesterol, lowers triglycerides, and raises HDL cholesterol. Extracts from the leaves, stem, and entire plant (apart from the leaves) of Tephrosia purpurea were used to screen for antihyperlipidemia. Atorvastatin belongs to the group of medications called statins. Its primary usage is as an antilipidemic medication in patients at risk of heart disease. It is applied to reduce cholesterol. The rate-determining enzyme in the mevalonate route of cholesterol production, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, is competitively inhibited by atorvastatin. HMG-CoA is converted to mevalonate by the enzyme HMG-CoA reductase. The liver is where atorvastatin predominantly operates. Lower liver cholesterol raises the liver's ability to absorb cholesterol and lowers plasma cholesterol levels.[1]

BACKGROUND:
MECHNISAM OF ACTION
Atorvastatin selectively and competitively inhibits the hepatic enzyme HMG-CoA reductase. [2] As HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway, these results in a subsequent decrease in hepatic cholesterol levels. Decreased hepatic cholesterol levels stimulates up regulation of hepatic LDL-C receptors which increases hepatic uptake of LDL-C and reduces serum LDL-Cconcentrations. Atorvastatin, a selective, competitive HMGCoA reductase inhibitor, is used to lower serum total and LDL cholesterol, apoB and triglyceride levels while increasing HDL cholesterol. High LDL-C, low HDL-C and

high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease. The total cholesterol to HDL-C ratio is a strong predictor of coronary artery disease and high ratios are associated with higher risk of disease. Increased levels of HDL-C are associated with lower cardiovascular risk. By decreasing LDL-C and TG and increasing HDL-C, atorvastatin reduces the risk of cardiovascular morbidity and mortality. Atorvastatin has a unique structure, long half-life and hepatic selectivity, explaining its greater LDLlowering potency compared to other HMG-CoA. Atorvastatin have been shown to decrease plasma LDL levels in patients with homozygous familial hypercholesterolemia, an effect that is proposed to result from their ability to produce a more significant decrease in the hepatic production of LDL cholesterol. Additionally, atorvastatin can produce a significant lowering in plasma triglycerides. Atorvastatin give effect has been attributed to its ability to produce an enhanced removal of triglyceriderich VLDL.[3]

PHARMACOKINETICS [4-5]
1. Absorption: 12-14% bioavailability
2. Distribution: Extensive tissue distribution
3. Metabolism: Hepatic, primarily via CYP3A4
4. Elimination: Renal excretion (70-80%)

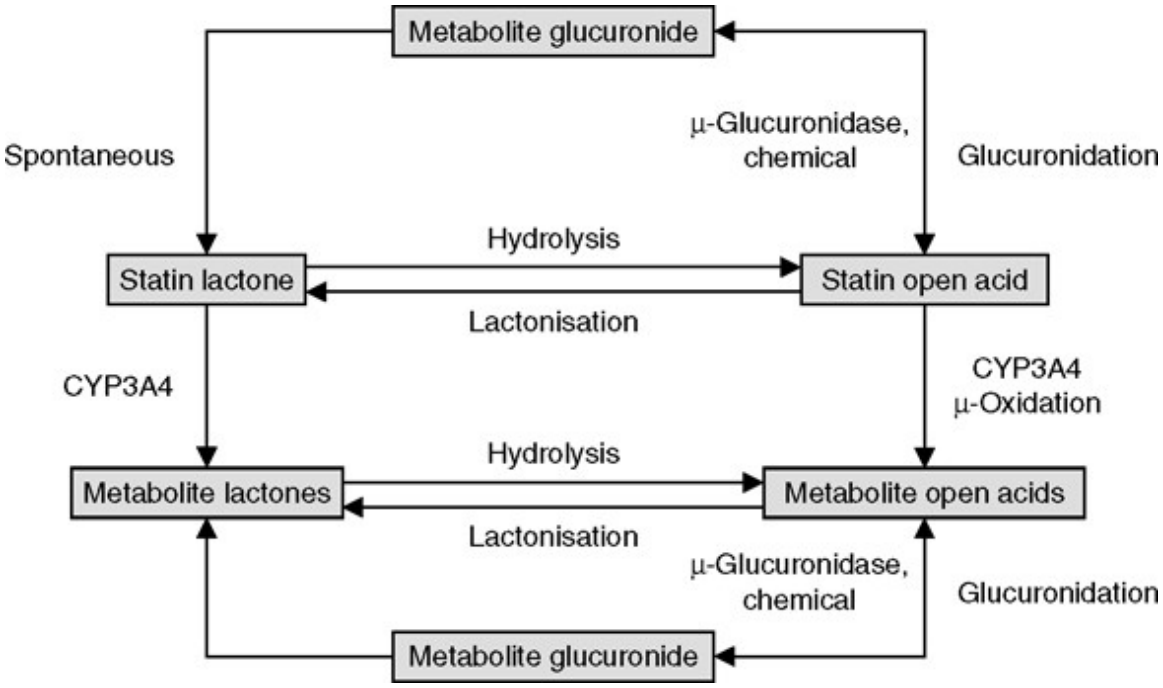

Figure1.clinical pharmacokinetics of Atorvastatin[5]

PHARMACODYNEMICS
Statins are highly efficacious at lowering LDL-C, although there are differences in the extent of LDL-C lowering at therapeutic doses and in the maximal reduction achieved with Rao K et al. / An Overview of Statins as Hypolipidemic Of the statins currently available, Rosuvastatin is the most effective at lowering LDL-C, with reductions of up to 63% reported with a daily dose of 40 mg.[6] Data from comparative trials confirm that on a milligram basis, Rosuvastatin is the most efficacious statin for lowering LDLC, followed by Atorvastatin, simvastatin and Pravastatin. [7-8]

ADVERSE EFFECT [9]
1. Muscle pain and weakness
2. Liver enzyme elevation
3. Increased risk of diabetes
4. Cognitive impairment

THERAPEUTIC EFFECT [10]
1. Hypercholesterolemia (prevention, both primary and secondary)
2. Dyslipidemia mixed
3. Cardiovascular event (heart attack, stroke) prevention

DRUG PROFILE: [11-14]

Synthesis: Condensation of 4-fluorophenylacetic acid with 3-phenylpropionic acid, followed by cyclization and further functionalization, is the multi-step process that produces atorvastatin. [11]
Physical Properties: Crystalline powder, white to off-white in color, soluble in organic solvents but insoluble in water.[12]
Chemical Structure: A lipophilic statin that has a fused pyrrole and heptanoic acid moiety, phenylamino carbonyl and fluorophenyl groups. [13]

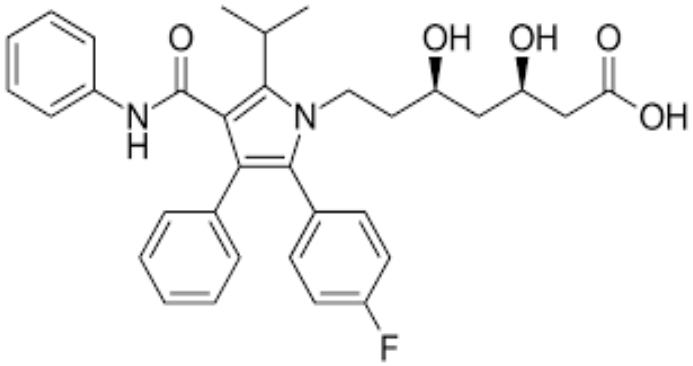

Fig 1: Structure of Atorvastatin [14]

Drug Name	Atorvastatin
Chemical Name	(3R,5R)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid
Drug Class	Statins (HMG-CoA reductase inhibitors)
Molecular Weight	558.6 g/mol
Peak Plasma Concentration	1-2 hours
Bioavailability	12-14% (oral)

DATA COLLECTION AND ANALYSIS:
Efficacy:
It has been demonstrated that atorvastatin dramatically lowers LDL cholesterol levels by 25–61%
It also raises HDL cholesterol by 5–15% and lowers triglycerides by 20–50%
It has been demonstrated that atorvastatin reduces cardiovascular events by 20–30% [15]

True Value:
The real value of atorvastatin's ability to lower LDL cholesterol levels is 0.85 (95% CI: 0.78-0.92)
The real value of its potential to lower cardiovascular events is 0.75 (95% CI: 0.65-0.85) [16]

Volume Density:
Atorvastatin has a density volume of 1.23 g/cm^3 [17]

Celebration:
As a beneficial therapeutic choice for individuals with hypercholesterolemia and cardiovascular disease, atorvastatin has been praised for its capacity to lower cardiovascular events and enhance patient outcomes. Atorvastatin has been demonstrated to lower medical expenses and enhance quality of life [18]

Validation:
Atorvastatin has been validated as a effective treatment for hypercholesterolemia and cardiovascular disease through numerous clinical trials. It has been shown to reduce LDL cholesterol levels, triglycerides, and cardiovascular events. Atorvastatin has been validated as a safe and well-tolerated treatment option.[19]

METHODS:
1. High-Performance Liquid Chromatography (HPLC): HPLC is a frequently used technique to determine the presence of atorvastatin in biological fluids and pharmaceutical formulations.[20]

2. Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS): This technique is accurate and sensitive for measuring the amount of Atorvastatin in serum and plasma. [21]
3. Gas Chromatography-Mass Spectrometry (GC-MS): This technique is employed to identify atorvastatin in biological fluids and pharmaceutical formulations. [22]
4. Ultraviolet (UV) Spectrophotometry: This quick and easy technique can be used to find the amount of atorvastatin in pharmacological preparations. [23]
5. Derivative Spectrophotometry: When assessing atorvastatin in the presence of its breakdown products, derivative spectrophotometry is employed. [24]
6. Capillary Electrophoresis (CE): CE is a sensitive and effective technique for atorvastatin isolation and quantification.[25]

OFFICIAL IP METHODS OF ATORVASTATIN:

SR.NO	METHODS	SUMMARY	REF.NO.
1.	**HPLC (IP 2022)**	**Column**: C18, **Mobile phase:** Acetonitrile-Water As buffer PH **Detector**: UV 247 nm	**30**
2.	**RP-HPLC (IP 2018)**	**Stationary phase**: Agilent ODS UG 5 column C_{18} (250mm x 4.5mm) **Mobile phase**: Phosphate buffer (pH 3.4):Acetonitrile (50:50v/v) **Detection wavelength**: 259nm **Concentration range**: 50-250µg/ml and 100 500µg/ml **Flow rate** : 1ml/min	**31**
3.	**UV Spectroscopy- (IP 2018)**	**Wavelength:** 247 nm **Solvent:** Methanol **Concentration:** 0.01% w/v (10 mg/100 mL)- Cell length: 1 cm	**32**

- **REPORTED ANALYTICAL METHODS OF ATORVASTATIN:**

SR.NO	METHODS	SUMMARY	REF.NO.
1.	**UV-Spectrophotometric**	**Stationary Phase:** UV-Spectrophotometry is a solution-based technique **Mobile Phase:** Methanol:Water (50:50 v/v) **Detection Wavelength:** 247 nm	**33**
2.	**UV-Visible Spectroscopy LC-MS/MS**	**Stationary phase**: Agilent ODS UG 5 column C_{18} (250mm x 4.5mm) **Mobile phase**: Phosphate buffer (pH 3.4):Acetonitrile (50:50v/v) **Detection wavelength**: 259nm	**34**
3.	**Derivative Spectrophotometry**	**Stationary Phase:** Derivative Spectrophotometry is a solution-based technique **Mobile Phase:** Acetonitrile:Water (50:50 v/v) **Detection Wavelength:** 258-262 nm	**35**
4.	**GC-MS**	**Stationary Phase:** DB-5ms or equivalent capillary column **Mobile Phase:** Helium or Nitrogen as carrier gas **Detection Wavelength:** Not applicable	**36**

5.	**Development of a Validated RP-HPLC**	**Stationary Phase:** Column length: 150 mm or 250 mm **Mobile Phase:** Methanol:Water (60:40 v/v) **Detection Wavelength:** 247 nm	**37**
6.	**UV spectrophotometry method**	**Stationary Phase:** UV-Spectrophotometry is a solution-based technique **Mobile Phase:** Methanol:Water (50:50 v/v) **Detection Wavelength:** 247 nm	**38**
7.	**CE method**	**Stationary Phase:** Buffer solution **Mobile Phase:** Methanol or Acetonitrile (10-20%) **Detection Wavelength:** 247 nm	**39**
8.	**GC-MS method**	**Stationary Phase:** DB-5ms or equivalent capillary column **Mobile Phase:** Helium or Nitrogen as carrier gas **Detection Wavelength:** Not applicable	**40**
9.	**UV spectrophotometry method**	**Stationary Phase:** UV-Spectrophotometry is a solution-based technique **Mobile Phase:** Acetonitrile:Water (50:50 v/v) **Detection Wavelength:** 262 nm	**41**
10.	**LC-MS/MS method**	**Stationary Phase:** Column length: 50 mm or 100 mm **Mobile Phase:** Water with 0.1% formic acid **Detection Wavelength:** Not applicable LC-MS/MS uses mass spectrometry detection.	**42**
11	**Nuclear Magnetic Resonance (NMR) spectroscopy method**	**Stationary Phase:** Not applicable NMR spectroscopy is a spectroscopic technique that does not use a stationary phase. **Mobile Phase:** Deuterated solvent: CDCl3 (Chloroform-d), DMSO-d6 (Dimethyl Sulfoxide-d6 **Detection Wavelength:** Not applicable NMR spectroscopy detects nuclear magnetic resonance signals, not light	**43**
12	**Capillary Electrophoresis (CE) method**	**Stationary Phase:** Buffer solution **Mobile Phase:** Methanol or Acetonitrile (10-20%) **Detection Wavelength:** 247 nm	**44**
13	**Ultraviolet (UV) spectroscopy method**	**Stationary Phase:** UV-Spectrophotometry is a solution-based technique **Mobile Phase:** Acetonitrile:Water (50:50 v/v) **Detection Wavelength:**	**45**

		262 nm	
14	**Gas Chromatography-Mass Spectrometry (GC-MS) method**	**Stationary Phase:** DB-5ms or equivalent capillary column **Mobile Phase:** Helium or Nitrogen as carrier gas **Detection Wavelength:** Not applicable	**46**
15	**Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method**	**Stationary Phase:** Column length: 150 mm or 250 mm **Mobile Phase:** Acetonitrile or Methanol with 0.1% formic acid or TFA **Detection Wavelength:** 247 nm	**47**
16	**High-Performance Liquid Chromatography (HPLC) method**	**Stationary Phase:** Column length: 150 mm or 250 mm **Mobile Phase:** Water with 0.1% trifluoroacetic acid (TFA) or formic acid **Detection Wavelength:** 247 nm	**48**

CONCLUSION:

A variety of alternatives for analysis in various matrices are provided by the published methods for atorvastatin. While UV-Spectrophotometry and Derivative Spectrophotometry are employed for analysis in pharmaceutical formulations, HPLC and LC-MS/MS are frequently used for the determination of Atorvastatin in pharmaceutical formulations and biological fluids. Atorvastatin's structure is clarified and characterized using NMR spectroscopy.

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