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# ANALYTICAL AND BIOANALYTICAL PROFILE FOR ATORVASTATIN: AN EXPLORATORY REVIEW

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## ABSTRACT

Statins are exceptional in lowering total cholesterol and low- density lipoproteins present in the human body. These are inhibitors of HMG CoA reductase; which are rate the limiting enzymes in Cholesterol biosynthesis. Atorvastatins used in the treatment of atherosclerosis and cardiac risks. Atorvastatin calcium is calcium salt of atorvastatin and a trihydrate. The atorvastatin is a medicine used to cure high cholesterol and marketed as calcium salt with the name Lipitor. Atorvastatin is generally combined with pharmaceutical formulations because they block the Niemann-Pick C1-Like protein cholesterol transporter and inhibit the absorption of cholesterol. The present review critically assesses various methods for the analysis of atorvastatin as well as atorvastatin calcium as bulk drug and pharmaceutical dosage forms and or in the biological fluid. This exhaustive review displays the assortment, correlation and assimilation of more than 80 analytical and bioanalytical approaches. These reported investigations are not limited to sophisticated chromatographic, spectrophotometric techniques but also literates about hyphenated stability-indicating analyses and its precise applications towards pharmaceutical estimation. The exhaustive tabular presentation of essential analytical information would be of great significance to pharmaceutical analysts. The compilation therefore explores the scope for comparison of the existing methods at once for better utility and effective future estimation.

**KEYWORDS:** Atorvastatin Calcium, analytical, bioanalytical, statins.

## INTRODUCTION

Statins are highly effective in lowering total cholesterol and low density lipoproteins (LDL) in the human body.[1] Statins inhibits HMG-CoA reductase (3- hydroxyl-3-methylglutaryl coenzyme A) which are rate limiting enzymes in cholesterol biosynthesis to mevalonate. Statins are effective in reducing both cholesterol and triglycerides.[2] Statins are frequently used to treat several types of hypercholesterolemia, atherosclerosis and cardiac risks. A preparatory cause of the ischemic disease is related to dyslipidemia. Dyslipidemia is a disorder of the metabolism of lipoproteins, which also includes lipoprotein overproduction and deficiency.[3] They reduce morbidity and mortality related to CHD proved by various clinical trials. Statins reform endothelial function, improve the stability of atherosclerotic plaques, reduces oxidative stress and inhibit the thrombogenic responses.[4] Statins are derivatives of Nicotinic acid, probucol and omega-3 marine triglycerides.[5] Statins are classified as Natural (Lovastatin), Semisynthetic (Simvastatin and Pravastatin) and Synthetic (Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin, and Pitvastatin).[6] The drug has two known and eight unknown process impurities are called DSAT and DFAT.[7]

### Historical overview about ATOCa

Atorvastatin calcium (ATOCa) is the most often used drug and commercially available pharmaceutical formulations used for the clinical treatment of hypercholesterolemia. The atorvastatin was first synthesized by an American Scientist, Bruce D. Roth in 1985 as a senior scientist while working with Parke-Davis of Warner-Lambert Company.[8] The atorvastatin (ATO) is a medicine used to cure high cholesterol and marketed as calcium salt with the name Lipitor.[9] Atorvastatin is generally combined with pharmaceutical formulations because they block the Niemann-Pick C1-Like protein cholesterol transporter and inhibit the absorption of cholesterol.[10]

### ATOCa and its therapeutic applicability

ATOCa is calcium salt and a trihydrate which stabilizes plaque and inhibit strokes through anti-inflammatory action. Atorvastatin calcium chemically (3R,5R)-7-[2-(4-Fluoro-phenyl) -5-isopropyl-3-phenyl-4-phenyl carbamo yl-pyrrol-1-yl]3,5dihydroxyheptanoic acid calcium salt is shown in **Figure 1**, is an established drug under the category of cardiovascular therapeutic use.[11]

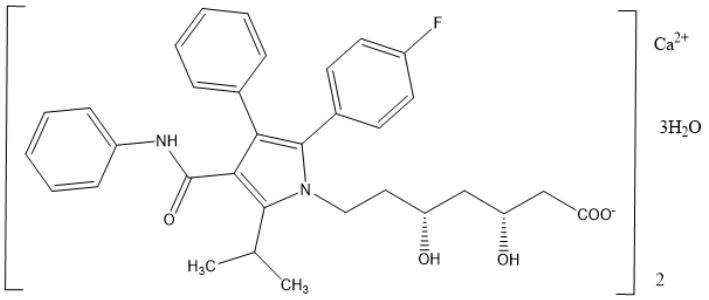


**Fig. 1: Chemical structure of Atorvastatin Calcium.**

Graphically, represented the different percentages of various methods used for the analysis of Atorvastatin calcium, the HPLC technique was mostly used in the described method, as HPLC is a quick, precise, reproducible and efficient method. Some of the articles are based on the Reverse Phase HPLC method. Many methods use acetonitrile (ACN) or methanol as a mobile phase which is toxic organic solvents, therefore buffers are used. But it also has some disadvantages like it reduces the life of the column as well as instruments. Solvents used as mobile phases are selected based on solvent viscosity, solvent miscibility parameters. Most of the methods described in this review have used methanol, phosphate buffer and ACN as mobile phase either in isocratic mode or in gradient mode. Methanol is a green solvent therefore, it is the most frequently used solvent **[Figure 2]**.

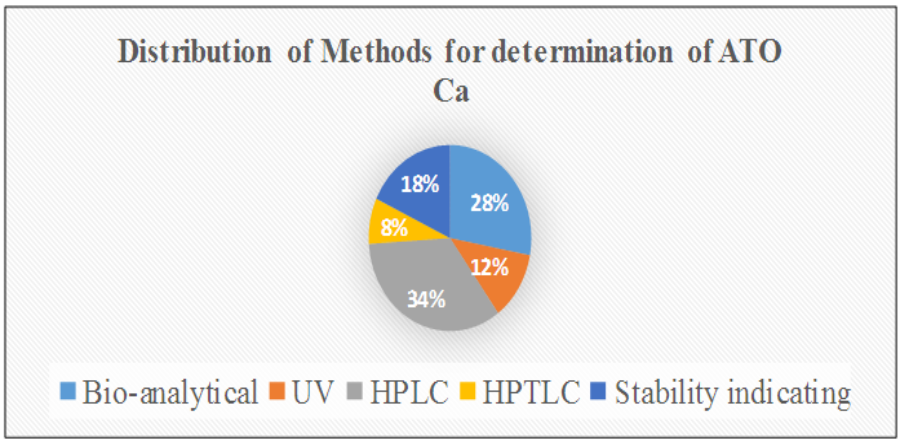


**Fig. 2: Distribution of Methods for Determination of ATO Ca.**

The graphical data of the published articles based on the bio-analytical and analytical techniques developed for the determination of ATO as bulk drug and with its pharmaceutical dosage form. As per the literature survey, the maximum papers published for ATO is in the year of 2011-2015 **[Figure 3]**.

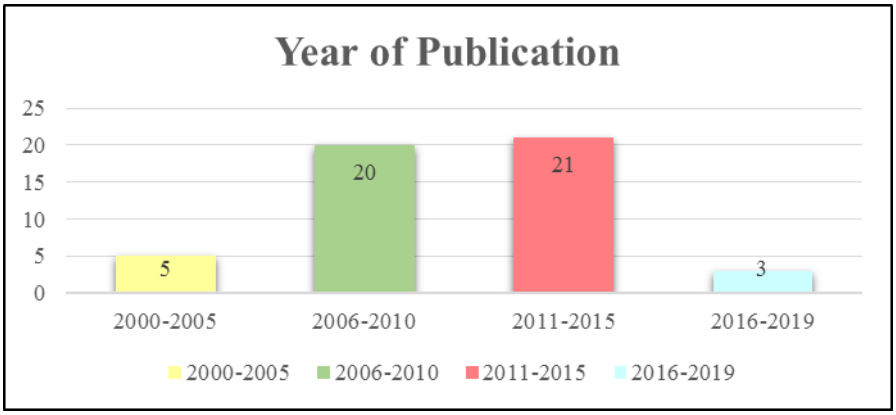


**Fig. 3: Annual publication chronology for pharmaceutical analysis of ATO and ATOCa.**

**Functional properties**

Atorvastatin (ATO), cerivastatin, fluvastatin (FLU), rosuvastatin (ROS) and, pitavastatin are synthetic compounds while pravastatin (PRA), lovastatin (LOV), simvastatin (SIM) are fungal derived inhibitors of HMG-CoA reductase.[12] The major difference between natural and synthetic Statins depends on their potency to interact and inhibit the HMG-CoA reductase and also on their lipophilicity. Atorvastatin, fluvastatin, simvastatin are lipophilic compounds while rosuvastatin and pravastatin are hydrophilic due to the presence of methane sulphonamide group and polar hydroxyl groups respectively.[13-15] The structures show that statins act by binding to the active site of HMG-CoA prevents the substrate from binding. The molecule ATO is a substrate analogue of the enzyme. It depicts a complex hydrophobic ring structure covalently linked to the substrate and involved in binding of the statin to the reductase enzyme. The side groups on the rings that define the solubility properties of the drugs and therefore many of their pharmacokinetic properties.[16]

**Comprehensive upbeat pharmaceutical analysis of ATOCa**

The analytical methods for ATOCa were researched in the literature through scientific articles, as well as in official compendium United State Pharmacopoeia, Indian Pharmacopoeia 2007, Indian Pharmacopoeia 2018, Japanese Pharmacopoeia (17$^{th}$ edition). Nearly 14 papers are compiled for bio-analytical and 36 papers for analytical method development for bulk as well as pharmaceutical dosage forms.

**Bio-analytical methods for determination of ATOCa**

Bio-analytical methods for the quantitative determination of drugs and metabolites generates consistent and reproducible data; used to evaluate the pharmacokinetics, bioequivalence and bioavailability studies.[17] The extensive literature survey revealed that several bioanalytical techniques *viz* LC-MS/MS, ESI- LC-MS/MS, HPLC- MS/MS, RP-HPLC, Tandem MS, HPLC. UHPLC MS/MS was used in Human Plasma for the determination of Atorvastatin or Atorvastatin Calcium along with various drugs. **Table 1** describes the bio-analytical methods developed for the determination of ATO and ATOCa in Human Plasma.

In bio-analytical techniques, the most frequently used method is LC/MS-MS and HPLC. For example, Hotha et al. and coworkers have reported an LC/MS-MS based method for the determination of ATO and GLI in human plasma. The liquid-liquid extraction method is used for sample preparation. Less volume of plasma was used to reduce the bleeding in human volunteers.[20]

**Analytical Methods for Determination of ATOCa**

Apart from bioanalytical methods, many analytical methods were reported for the determination of ATO and ATO Ca along with its pharmaceutical formulations. The development of an analytical method for analysis of ATO is very appropriate, to assist bioavailability, bioequivalence, pharmacokinetic as well as monitoring the quality of the marketed dosage form.[18] For performing the analytical methods ICH guidelines are referred. The quality of analytical data is a major factor in the success of drug development.[19] Analytical methods such as UV- Spectrometry, HPLC, HPTLC and Stability-Indicating are illustrated. **Table 2, 3, 4 and 5** describes all the analytical methods developed for determination for ATO and ATOCa. Other methods like HPTLC, capillary electrophoresis fluorimetric methods are rarely used.

**UV- Spectrophotometric Method for Determination of ATOCa**

UV Spectrophotometry is the most common method used for the analysis of samples. Various methods are developed by UV spectroscopy for the determination of ATOCa as the bulk and pharmaceutical dosage form.

Singh et al. and co-workers developed a UV spectroscopy method for the determination of ATO, CLOP, and ASP in capsule dosage form by using first-order derivative and multicomponent spectrophotometry. Quantitative determination was performed and the percent recovery was between the ranges of 98% to 101%.[34] Various methods like zero order derivative, Q-analysis including first-order derivative and multicomponent analysis were performed by using UV spectrophotometry.

**Table 1: Bioanalytical Pharmaceutical methods for estimation of ATOCa.**

| Drug(S) | Biological fluid | Technique | Stationary Phase | Detection (m/z) | Internal Standard | Ref. |
|---|---|---|---|---|---|---|
| ATO, GLI | Human serum | LC-MS/MS | C18 (50 × 4.6 mm) | 559.4 | ATO, GLI | [20] |
| ATO, AML, RAM, BEN | Human serum | LC-MS/MS | C18 | 560.4, 409.3, 417.2, 425.1 | Nevirapine | [21] |
| ATO, p-HATO, o-HATO | Human serum | ESI-LC-MS/MS | C8, C-18, 75 × 4.6mm ID, 3.5 µ, | 559.2-440.2 575.3-440.4, 575.0-440.4, 377.1-234.2 | Enalapril | [22] |
| ATO, AML | Human Plasma | HPLC–MS–MS | C18, 2.1×100 mm, 3.5 µm column | 409.1-237.9, 559.3 - 440.2 | Nitrendipine | [23] |
| ATO, ROS | Human serum | RP-HPLC/UV | C18,(150×4.6mm,5µm),C8(150mm×4.6mm, 5µm),RP18 (30×4.6mm, 10µm) | - | Naproxen Sodium, (Paracetamol, Diclofenac Sodium and Simvastatin) | [24] |
| ATO, p-HATO, o-HATO | Human Plasma | LC–tandem MS | C18 (3 µm, 30×2 mm) | 540 - 578 | Methaqualone | [25] |
| GLQ, PIO HCl, ATO | Human Serum | RP-LC | RP-18 end-cap (250 mm x 4.6 mm,5 µm) | - | | [26] |
| ATO, 2-HATO | Human Plasma | HPLC–MS–MS | C18, (10 mm×3.0 mm, 3µm particles) | 559, 575, 426 | Clindamycin Hydrochloride | [27] |
| ATO | Human Serum | RP-HPLC | C18(150mm×4.6mm I.D.) 5µm particles,(1cm×4.0mm I.D., 5µm) | - | Diclofenac Sodium | [28] |
| ATO | Human Plasma | HPLC | C8, (5µm particle size) | - | Diltiazem | [29] |
| ATO | Human Plasma | HPLC | C18 (5µm, 150 ×4.6 mm) | - | Ibuprofen | [30] |
| ATO, O- HATO, P- HATO | Human Plasma | LC-MS/MS | C18 column (5.0 µm, 100 × 4.6 mm i.d.) | 559-440, 575-466, 575-440 | Rosuvastatin | [31] |
| MET, AML, GLBN and ATO | Human Plasma | HPLC-UV | Water's Novapack Phenyl (150mm×4.6 mm, i.d., 5.0 µm) | - | Ranitidine, Rosiglitazone | [32] |
| ATO Ca | Human Plasma | UHPLC-MS/MS | C18 reversed-phase column (100×2.1mm, 2.7µm) | 557.0-453.0, 480.0-418.0 | Rosuvastatin Calcium | [33] |

**Table 2: Spectrophotometric Methods for Pharmaceutical estimation of ATOCa.**

| Drug(S) | UV Method | Solvent | Detection (nm) | LOD (µg) | LOQ (µg) | Application | Ref. |
|---|---|---|---|---|---|---|---|
| ATO, CLOP, ASP | First Order Derivative spectrometry | Methanol | 276, 226 and 222 | 0.55, 0.74, 0.69 | 1.69, 2.27, 2.1 | Capsule | [34] |
| | Multicomponent Analysis | | 247, 220 and 235 | 0.12 0.67 0.67 | 0.37 2.09 2.01 | | |
| ATO, TELM | First Order Derivative spectrometry | Methanol | 272, 223 | 0.40, 0.37 | 2.12, 2.07 | Tablet | [35] |
| | Q- Analysis | | 296.0, 280.9 | 0.30,0.13 | 2.71, 1.81 | | |
| | Multicomponent Analysis | | 296.0, 246.9 | 0.35,0.19 | 2.65, 1.76 | | |
| ATOCa, NifedipineHCl | Zero Order UV | Methanol | 237 and 297 | 0.1028 and 0.1214 | 4.464 and 0.3678 | Bulk, Tablet | [36] |
| ATO Ca, RAM | First Order UV | Water: Methanol | 294 and 229 | 0.0147 and 0.056 | 0.041 and 0.18 | Capsule | [37] |
| ATO, AML | Zero Order UV | ACN: water | 242 | 0.025, 0.024 | 0.076, 0.070 | Tablet | [38] |
| ATO Ca | Zero Order UV | Iodine with ACN | 291, 360 | 0.056 | 0.17 | Tablet | [39] |
| ATOCa, EZE | Zero Order UV | Methanol | 232.5 and 246.0 | - | - | Tablet | [40] |
| ATOCa, EZE | Zero Order UV | Methanol | 235.5 and 246.0 | - | - | Tablet | [41] |

**Table 3: HPLC Methods for Pharmaceutical estimation of ATO.**

| Drug(S) | Stationary Phase | Mobile Phase (*v/v*) | Detection (nm) | Application | Ref |
|---|---|---|---|---|---|
| ATOCa, EZE | RP C18, (5 µm, 25 cm X 4.6 mm i.d.) | Amm. Acetate Buffer pH 5.0: ACN: Triethylamine (50:50:0.2, v/v) | 240 | Tablet | [41] |
| ATO | Luna C18 (250 ×/4.6mm i.d.) 5 µm, guard (4×/3 mm i.d.) | ACN: Ammo. Acetate Buffer pH 4.0: 4-Tetrahydrofuran (25:70:5 v/v/v) | 248 | Tablet | [42] |
| ATO, EZE | Inertsil ODS-3V (250mm × 4.6mm,5µ) | 0.01 M ammo. Acetate Buffer (pH:3.0): ACN (50:50 v/v) | 254 | Tablet | [43] |
| ATO,LOV, PRA, ROS, SIM | Intertisl ODS 3V column (4.6 × 250 mm,5 µm) | 0.01 M Ammo. Acetate(pH 5.0): ACN : Methanol | 237 | Tablet | [44] |
| ATO | C-18 column | Methanol: Water (50:50 v/v) | 245 | Tablet | [45] |
| ATO, FENO | C18, 100 × 4.6, 5µm | Methanol: Water (40:60 v/v) | 274 | Tablet | [46] |
| B-group vitamins, ATO | C-18, (250 x4.6mm, 5µ) | Methanol | 254 265 | Tablet | [47] |
| ATO, TEL | C18, (4.6x150mm, 3.5 µm) | Phosphate Buffer (pH 3.0): ACN (40:60v/v) | 276 | Tablet | [48] |
| ATO, LOS | C18, (250mmx 4.6mm id) | Methanol : Phosphate Buffer (pH 6.8) (80:20) | 238 | Tablet | [49] |
| ATO, ATE | C-18**,** (25mm× 4.6mm i.d. 5-µm) | ACN: Phosphate Buffer (pH 4.5) (72:28 v/v) | 238 | Tablet | [50] |
| ATO Ca, Nicotinic Acid | C18, (150 · 4.6 mm, 3.5 µm) | ACN: water (85:15) pH 4.5 | 261 | Tablet | [51] |
| ATO Ca, RAM, ASP | C-18, (250 mm x 4.6 mm) | Methanol and Acetate buffer (pH 3.1) (70:30 v/v) | 210, 245 254 | Capsule | [52] |
| ATO Ca, LOS-K | C18, (250×4.6mm i.d), | ACN : 0.02M PDP Buffer (pH 3.4) | 236 | Tablet | [53] |

| | | | | | |
|---|---|---|---|---|---|
| ATE, ASP | 5 µm | (70:30 % v/v) | | | |
| ASP, ATO Ca, CLOP-BIS | Inertsil ODS (150 × 4.6mm; 5 µm) | ACN : Phosphate Buffer pH 3.0 (50:50 v/v) | 235 | Capsules | [54] |
| ATO Ca, ASP | C-18,(5µm,250×4.6 mm i.d) | 0.02M PDP: Methanol (20:80) (pH4) | 240 | Capsule | [55] |
| ATO Ca, FENO | Luna C18 column | Methanol: Acetate buffer (pH 3.7) (82:18 v/v) | 248 | Tablet | [56] |
| ATO Ca | C-18, (250 mm×4.6 mm, 3.5 µm) | Phosphate Buffer (pH5.4), ACN: Tetrahydrofuran (90:10 v/v). | 220 | Pure Drug | [57] |
| ATO Ca, EZE | C18, (150 mm × 4.6 mm, 5 µm) | 20 mM Ammonium Acetate Buffer pH 5.0:ACN:TEA (50:50:02 v/v/v) | 240 | Tablet | [58] |
| PRA, FLU, ATO, ROS | C18, (125×4 mm,5 mm) | Methanol: water (70:30 v/v) | 238 | Tablet | [59] |
| AML BES, LOS K, VAL, ATOCa | RP18, (250 mm × 4.6 mm, 5 µm) | Amm. Acetate (pH 5.5, 0.01M) :ACN (45:55, v/v) | 240 | Tablet | [60] |

**HPLC Method for Determination of ATOCa**

HPLC is a technique used for the identification, quantification, and separation of the individuals as well as in mixture forms. Instrumentation of HPLC has a sampler, pump, and a detector. There are four types of HPLC methods based on its separation technique like normal phase, reverse phase, size exclusion, ion exchange HPLC method. Nearly 20 papers are reported in this review in which the HPLC method is preferred for the determination of ATOCa in bulk as well as in pharmaceutical dosage form as a single entity or in combination. In HPLC methods the most common mobile phase used is ACN, methanol, water, and buffer. In almost all articles C18 column was used as a stationary phase. Ertuk et al. reported an HPLC method for the determination of ATO and its impurities in bulk as well as in tablets dosage form. The drugs were having 8 unknown and 2 known impurities called as DFAT and DSAT. Until now there was none of the paper for resolution and determination of impurities in bulk drug and pharmaceutical dosage form. The limit of impurity and total impurity in bulk was within the range of 0.5 and 1.5 %. Required validation parameters like linearity, accuracy, precision, and selectivity were performed.[42]

**Table 4: HPTLC Methods for Pharmaceutical estimation of ATOCa.**

| Drug(S) | Stationary Phase | Mobile Phase (v/v) | Detection | LOD (ng) | LOQ (ng) | Ref. |
|---|---|---|---|---|---|---|
| ATO | Silica gel 60F254 | Toluene: Methanol, (70:30) | 280 | 30.3 | 101 | [61] |
| ATO Ca, FENO | Aluminium foil silica gel 60 F254 plates | Toluene: Methanol: Triethylamine (7:3:0.2) | 258 | 25.41, 292.40 | 77.02, 886.09 | [62] |
| ATO Ca, LOS-K | Silica gel 60 F254 plates | ACN: chloroform: Methanol: Conc. Ammonia (7:2:0.9:0.1) | 241 | - | - | [63] |
| ATOCa, METO SUC | Silica gel 60 F254 plates | Toluene : Methanol: Ethyl Acetate: Glacial :Acetic Acid (7:1.5:1:0.5) | 276 | 15.001, 45.457 | 78.736, 238.595 | [64] |
| ATOCa | Silica gel 60 RP18F254S plates | Methanol : Water (3.5 : 1.5) | 246 | | | [65] |
| ATOCa, EZE | Silica gel 60 F254 plates | Chloroform : Benzene : Methanol : Acetic Acid (6.0:3.0:1.0:0.1) | 250 | 170, 20 | 570, 70 | [66] |
| ATOCa, EZE | Silica gel 60 F254 plates | Toluene : Methanol (8:2) | 240 | - | - | [67] |

**Table 5: Stability Indicating Methods for Pharmaceutical Estimation of ATOCa.**

| Drug(S) | Method | Stationary Phase | Mobile Phase | Detection | LOD (µg) | LOQ (µg) | Ref |
|---|---|---|---|---|---|---|---|
| ATO, AML | HPLC | Target ODS-3, 5 µm, (250mm×4.6mm i.d.) | ACN:0.025M $NaH_2PO_4$ Buffer (pH 4.5) (55:45, v/v) | 237 | 0.65, 0.35 | 2,1 | [68] |
| ATO,AML | RP-HPLC | C18,5mm, (250mm×4.0 mm i.d) | ACN: 50mM PDP buffer (60 : 40, v/v) | 254 | 0.4,0.6 | 1.0,1.0 | [69] |
| METO,ATO,RAM | RP-UPLC | C18, (4.6 mm x 50 mm, 1.8 µm) | 0.06% Ortho Phosphoric Acid : 0.0045 M SLS as Buffer:ACN (50:50 v/v) | 210 | - | - | [70] |
| ATO Ca | HPLC | C18, (250 x 4.6 mm), 5 µ | Methanol: ACN: Phosphate Buffer (45:45:10) | 246 | - | - | [71] |
| ATO Ca, EZE | RP-HPLC | C-18,125 mm × 4.6 mm i.d 5 µm | ACN: 0.4% v/v Triethylamine (pH 5.5) (55:45, v/v) | 231 | 0.44,0.52 | 1.34,1.57 | [72] |
| EZE, ATO | RP-HPLC | C18 (5 mm, 250×4.6 mm) | 0.02 M PDP: ACN: Methanol (10:40:50 v/v/v) | 236 | - | - | [73] |
| ATO Ca, AML-BES | RP-HPLC | C-18,5µm (250×4.6mm i.d.) | 0.02M PDP : ACN : Methanol (30:10:60,v/v/v) (pH 4) | 240 | 0.04,0.03 | 0.1,0.08 | [74] |
| ATO Ca, ATO, impurities | LC | RP-Zorbax Bonus (150 × 4.6 mm and 3.5 µm as particle size) | Water: ACN: Trifluoroacetic acid | 245 | 0.011 | 0.035 | [75] |
| ATO | HPLC | Agilent Zorbax XDB C18 | ACN:0.02 M Sodium Acetate, pH 4.2 (45:55 v/v) | 282 247 | - | 2.0 | [76] |
| ATO, AML | HPLC | Agilent Zorbax ODS column (5 µm, 4.6 x 250 mm) | ACN: Methanol: Phosphate Buffer, pH 3.0 (45:30:25 v/v/v) | 254 | 0.31, 0.29 | 1.00, 0.98 | [77] |
| ATO | HPLC | XTerra RP,18 column (25× 4.6 mm), Luna C8 (250 × 4.6 mm) | Methanol: ACN : Phosphate Buffer | 246 | - | - | [78] |

**Table 6: Capillary Electrophoresis for Pharmaceutical Estimation of ATO.**

| Drug(S) | Method | Capillary | Electrolyte Solution | Detection | Internal Standard | Ref |
|---|---|---|---|---|---|---|
| LIS, HCT, ASP, ATO | MEKC | Fused Silica Capillary (58 cm × 75 mm ID) | Borax Buffer (20 mM, pH 9.5):30mM SLS | 210 | Paracetamol | [79] |
| ATO | MEKC | Fused Silica Capillary | 10 mM sodium tetraborate buffer pH 9.5: 50 mM, SDS and 20% (v/v) methanol | 214 | Pravastatin sodium | [80] |
| ATOCa | CE (MCE) | Fused Silica Capillary (33cm× 650 mm ID) | 25mM Sodium Acetate Buffer(pH 6) | 214 | Diclofenac sodium | [81] |
| AML, ATO | CE | Fused Silica Capillary (50 cm×75 mm ID) | Phosphate Buffer (pH 6.5, 25 Mm): Methanol (80:20, v/v) | 210 | Losartan | [82] |
| EZE, ATO | CE | Fused Silica Capillary (58 cm× 75 mm ID) | Phosphate Buffer (2.5 mM, pH 6.7) : Methanol (70:30 v/v) | 210 | Losartan | [83] |

**HPTLC Method for Determination of ATOCa**

High-Performance Thin-Layer Chromatography is an advanced technique of Thin-Layer Chromatography. HPTLC is advantageous in many ways as it is a flexible technique, requires a short period for analyses and simple to handle.[84] There are very few articles published for the determination of ATOCa in bulk as well as pharmaceutical dosage form by HPTLC method.

**Atypical Methods for Determination of ATOCa**

**Capillary Electrophoresis for Determination of ATOCa**

Capillary electrophoresis is the most meticulous method to be utilized in the pharmaceutical analysis due to its lower cost, less organic solvent consumption and faster resolution in comparison with HPLC Method.[83] Separation takes place due to the migration of solutes in

an electric field, electrophoresis is performed when narrow bore capillaries are filled with background electrolytes. Several different types of capillary electrophoresis are used for the determination of ATOCa like Micellar electrokinetic capillary chromatography (MEKC).[85]

**Voltammetric Techniques for Determination of ATOCa**

The voltammetric analysis is a technique in which a small portion of the material is electroanalytical reduced or less commonly oxidized. Electrochemical techniques are very effective and manifold techniques that have high sensitivity, accuracy, precision with large dynamic range. Various types of voltammetric techniques are available such as polarography, square wave voltammetry, cyclic voltammetry, Differential, and normal pulse, stripping analysis, linear sweep voltammetry. Various papers are published for the determination of ATOCa in bulk as well as in pharmaceutical dosage form by the Voltammetric technique.[86-92] This review is the detailed study of the paper published since 2000-2019 of the ATO in various Bio-analytical and Analytical techniques. This is a comprehensive study for the researchers to revise concepts within a very short period.

## CONCLUSIONS

Right now, we have accumulated the published bioanalytical and analytical methods for the quantification ATOCa in biological matrices and pharmaceutical dosage forms. Atorvastatin is an older synthetic drug, synthesized in 1985, and therefore there are sufficient articles available for quantification. Spectrophotometric method *viz* HPLC is the most commonly applied method for the determination of ATOCa in pharmaceutical formulations. A stability study revealed that ATOCa is a stable drug in various solvents. From this article, we can conclude that HPLC is the technique of choice for atorvastatin and biological matrices LC-MS/MS methods are suitable as it gives selective and sensitive results. Several other methods like voltammetric and electrophoresis techniques are also applied for the determination of ATOCa in bulk as well as in pharmaceutical dosage form. There are very few articles for the determination of ATOCa in Urine analysis. This comprehensive review revealed that more research in urine is yet to be studied.

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**Abbreviations**

- Ammo. : Ammonium
- AML: Amlodipine
- AML-BES: Amlodipine Besylate
- ASP: Aspirin
- ATE: Atenolol
- BEN: Benazepril
- CLOP: Clopidogrel
- CLOP-BIS: Clopidogrel Bisulphate
- DFAT: Desfluoro-atorvastatin
- DSAT: Diastereomer-atorvastatin
- ESI-LC-MS/MS: Electrospray ionization- Liquid Chromatography Mass Spectroscopy
- EZE: Ezetimibe
- FENO: Fenofibrate
- GLBN: Glibenclamide
- GLI: Glimepiride
- GLQ: Gliquidone
- HCT: Hydrochlorothiazide
- InGaAs: Indium–gallium arsenide
- LIS: Lisinopril
- LOS-K: Losartan Potassium
- MET: Metformin
- METO: Metoprolol
- o- HATO: Ortho- hydroxy Atorvastatin
- PDP: Potassium dihydrogen phosphate
- p- HATO: Para- hydroxy Atorvastatin
- PIO HCl : Pioglitazone Hydrochloride
- RAM: Ramipril
- SLS: Sodium Lauryl Sulphate
- TEL: Telmisartan
- VAL: Valsartan

**Caption**

**Figure 1:** Chemical structure of Atorvastatin Calcium

**Figure 2:** Distribution of Methods for Determination of ATO Ca

**Figure 3:** Annual publication chronology for pharmaceutical analysis of ATO and ATOCa

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