State-of-the-Art Analytical Approaches for the Characterization and Quantification of Atorvastatin: A Critical Appraisal

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Abstract

The abnormally raised level of lipids in the blood that results in hyperlipidemia is a major risk factor for numerous heart disorders, including atherosclerosis and stroke. In humans, lipids have been linked to the emergence of atherosclerosis. Both LDL and triglyceride levels are higher in hyperlipidemia. Statin therapy for hyperlipidemia has become a crucial component of vascular disease care. The first-line treatment for reducing lipid levels is statin medication. The most potent and readily accessible antihyperlipidemic medication at the moment is atorvastatin, one of the statins. For the production of endogenous cholesterol, an enzyme called 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is essential. Atorvastatin is an HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitor that also raises HDL (high-density lipoprotein) levels while considerably lowering lipid levels (low-density lipoprotein, triglycerides, and very low-density lipoprotein). Numerous analytical techniques have been reported for the determination of atorvastatin both alone and in combination with other medications, including capillary electrophoresis (CE), spectrophotometric methods, high performance thin layer chromatography (HPTLC), liquid chromatography tendam mass spectroscopy, near infrared spectroscopy, and thin layer chromatography (TLC). An effort has been made in this review to cover all of the most recent analytical techniques used to analyse atorvastatin.

Key words: Atrovastatin, RP-HPLC, Estimation, HPTLC, UV Spectrophotometery

Introduction

The progression of atherosclerotic lesions and the development of coronary artery disease are both known to be significantly influenced by hyperlipidemia. For the treatment of hyperlipidemia, which aims to (1) stop the growth of atherosclerotic plaque, (2) cause its regression, and (3) lower the risk of acute coronary events in patients with pre-existing coronary or peripheral vascular disease, dietary therapy in conjunction with lipid-lowering medications is crucial [1, 2]. The goal of treatment in patients with hypertriglyceridemia is to prevent the onset of hepatomegaly, splenomegaly, and pancreatitis, whereas the goal of treatment in patients with high risk of coronary artery disease but without evidence of atherosclerosis is to prevent the premature development of coronary artery disease. In the United States, 650000 new cases of myocardial infarction and approximately 215000 deaths each year are caused by cardiovascular disease [3, 4].

The most popular medications for treating hyperlipidemias in primary and secondary prevention are statins, which lower levels of plasma lipoproteins that are high in cholesterol and lessen the risk of coronary disease. These effects come from statins' inhibition of the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase), an enzyme that can the ability to prevent the conversion of the HMG-CoA substrate into mevalonic acid, hence preventing the initial stages of cholesterol manufacture. These imitating compounds, which can be classified as natural or synthetic, differ significantly in terms of their potency, pharmacokinetic profile, pharmacological interaction, and unfavorable myotoxic effect [5].

The first HMG-CoA reductase inhibitor was mevastatin, also known as compactin, which was first isolated as a metabolic byproduct from cultures of Penicillium citrinium. It has a 10000 times stronger affinity for the enzyme site than the HMG-CoA substrate. Later, lovastatin or mevinolin with a structure similar to mevastatin (added 6′-methyl group) but higher efficacy was discovered in cultures of Aspergillus terreus and Monascus ruber [6].

With the release of atorvastatin in 1996 [7], a new class of synthetic statin derivatives was first introduced; this drug was later given U.S. Food and Drug Administration approval in 2003.

The most popular medication worldwide in 2002 was atorvastatin [8, 9, 10].

In order to offer the people with high-quality medications, quality control of this pharmaceutical product is essential.

In this work, available analytical techniques for atorvastatin evaluation were reviewed from the literature and from official compendia.

Atorvastatin

The medication is an odourless, white, crystalline powder that is soluble in methanol but practically insoluble in water. It is also slightly soluble in methylene chloride [11]. With a maximum daily dose of 80 mg, atorvastatin is more powerful and appears to have the highest LDL-CH reducing efficacy. If the same was raised at baseline, a larger reduction in TGs is observed at this dose. Compared to other statins, atorvastatin has a plasma half-life of 18 to 24 hours and extra antioxidant properties [12]. Runny nose, sneezing, coughing, and gas are Atorvastatin side symptoms that are most frequently reported.

Severe adverse effects include upper stomach pain, liver issues, and muscle and appetite loss [13]. It is not recommended to take atorvastatin when pregnant or while nursing. Teenagers and youngsters shouldn't use it [14]. Niacin and gemfibrozil increase the reduction in LDL levels but raise the risk of myopathy with statins; ketoconazole, cyclosporine, and erythromycin have an elevated effect and risk of myopathy [15].

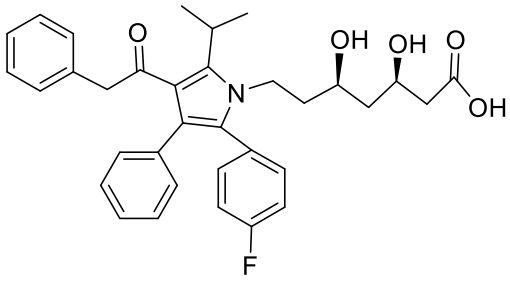

Figure 1- Chemical structure of Atorvastatin

Atorvastatin Calcium

The commercial form of atorvastatin is calcium salt (2+1) trihydrate. It has the chemical formula C66H68CaF2N4O10, a molecular weight of 1209.41 g/mol, and the characteristics of a white crystalline powder [16]. In addition to being extensively soluble in acetonitrile, distilled water, and phosphate buffer, atorvastatin calcium is also readily soluble in methanol, only marginally soluble in ethanol, and insoluble in solutions of pH ≤4 [17].

Mechanism of Action

Low density lipoprotein (LDL)-C, apo-B, very low density lipoprotein (VLDL)-C, and triglycerides are among the hazardous fractions whose levels are decreased by atorvastatin calcium, while the levels of good cholesterol HDL-C; [18–20] are increased. Atorvastatin calcium

reduces the amount of LDL (bad) cholesterol that is produced by the liver and increases LDL (bad) cholesterol absorption and elimination by 40–60% [16,21].

Analytical methods

Numerous analytical techniques, including HPLC, HPTLC, TLC, Spectrophotometric methods, Capillary electrophoresis, UPLC, and LC/MS methods, have been reported for the estimation of atorvastatin in pharmaceutical dosage forms and in human plasma. HPLC is the most significant analytical technique that has been widely used for the quantitative analysis of atorvastatin. An effort has been made to include all of the analytical techniques lately employed for the study of atorvastatin in this review.

HPLC Methods

Attia, K. A. *et al.* (2025) High-sensitivity HPLC methods are now made with the fluorescence detection option which qualifies atorvastatin in human plasma using a green method. Isocratic elution is used on a Thermo Hypersil BDS C18-column (150 × 4.6mm, 5µm), ethanol-potassium phosphate buffer (pH 5.2, 40:60, flow rate 0.6 mL/ min) as a mobile phase. Chromatographic separation was achieved within 10 minutes. Separation was confirmed with UV detection (210-260nm), while FLD settings (ATV at 274/378nm) enhanced specificity. Validation of the method was carried out as per ICH guidelines with linearity ranges of 10-200 ng/mL for ATV, demonstrating high accuracy and precision using efficient liquid-liquid extraction sample preparation. Thus making it an economical and durable choice for the concurrent monitoring of cardiovascular drugs in plasma. [22].

Tomikj, M. *et al.* (2024) A newly validated RP-HPLC method was developed for the simultaneous assay of amlodipine and atorvastatin in film-coated tablets. The assay method employed a C8 column with ethanol-phosphate buffer (pH 3.0, 63:37 v/v) separation, which achieved separation in under 5 minutes and found its validation per ICH guidelines evaluated for robustness by Plackett-Burman design, while high greenness and whiteness with scores of 93.5 via Eco-scale, SMGS, and AGREE tools. Methods such as HPLC-UV and LC-MS/MS methods specifically developed to quantify amlodipine in human plasma have concurrently been validated. As with most UV-detection protocols, the objective is to precipitate the proteins using acetonitrile, use a

Nucleosil C8 column, sodium phosphate-acetonitrile (60:40, pH 5.5) mobile phase, and UV detection at 245nm, with 20-800ng/ml as linear range, LOD 1 ng/mL full recovery, and inter-/intra-day CV <7%. There are also highly sensitive LC-MS/MS assays that can quantify atorvastatin and metabolites down to 0.02 ng/mL with excellent precision (RSD <8%) and are highly applicable for pharmacokinetics [23].

Dangre *et al.* (2022) A new, straightforward, precise, and reversed phase high performance liquid chromatographic approach was used to simultaneously quantify the drugs atorvastatin calcium (ATOR) and clopidogrel bisulphate (CLOP) in a combination capsule dosage form. Reversed phase liquid chromatography served as the basis for the procedure, and a Eurosphere 100-5 was used to achieve separation. Using acetonitrile and 0.01M potassium dihydrogen phosphate at a ratio of 75:25 (v/v) at pH 6.1 with a flow rate of 1.0 ml/min, the eluent's absorbance at wavelength 240 nm was measured. In the concentration ranges of 60-140 g mL-1 and 294-686 g mL-1 for ATOR and CLOP, respectively, calibration curves were discovered to be linear. The suggested method was successfully used for the quick, accurate, and simultaneous quantitative detection of atorvastatin calcium and clopidogrel bisulphate in capsules after passing tests for linearity, recovery, and repeatability [24].

Sandhu *et al.* (2022) In this study, liquid chromatography and spectroscopy were used to construct and test a dissolve technique for tablets containing atorvastatin and ezetimibe.

The analysis was performed using Waters HPLC, which features a UV-Vis detector and robust software.

Initially, a number of mobile phase combinations were utilised to separate atorvastatin and ezetimibe using the C18 column. The amount of pharmaceuticals was calculated using the Waters X-Bridge C18 column, which has dimensions of (250 m x 4.6 mm internal diameter, 5 m). The 233 nm was selected as detecting wavelength. The injection volume was 20 L, and the run time was 6.5 minutes. The isocratic mobile phase is composed of acetonitrile, water, and methanol in a ratio of 60:30:10 v/v/v at pH 3.0. To change the pH of the mobile phase, orthophosphoric acid was diluted and utilised; flow rates of 1.0 ml/min occurred at 2589–2595 psi. [25].

Bangaruthalli *et al.* (2019) established HPLC technique for calcium atorvastatin and telmisartan estimation together. On an ODS C18 column at a flow rate of 1.0 ml/min, the separation was achieved.

The mobile phase was detected at 235 nm and is composed of methanol, acetonitrile, and buffer in the following ratio: 35:25:40. The SHIMADZU HPLC auto sampler was the device used. Telmisartan and atorvastatin calcium were shown to have retention times of 2.350 and 3.490 minutes, respectively.

With telmisartan and atorvastatin calcium, the correlation coefficient (r2) was found to be 0.997 and 0.999, respectively, and the percentage mean recovery was found to be 100.943% and 100.576%, respectively [26].

Chaudhari *et al.* (2018) worked on developing and validating RP-HPLC methods for atorvastatin, aspirin, ramipril, and metaprolol succinate simultaneous estimation in tablet dose form. Using a (250 cm. 4.6 mm,) C18 column with a 5 m particle size, all the medicines were separated. The mobile phase, which was tuned by an experimental design, was pumped at a flow rate of 1 ml/min and contained a 90:10 (v/v) mixture of phosphate buffer (pH 4) and acetonitrile. At 210 nm, UV detection was carried out. Atorvastatin, aspirin, ramipril, and metoprolol succinate all had retention times that were discovered to be 8.013 minutes, 4.497 minutes, 7.240 minutes, and 3.403 minutes, respectively. The concentration ranges used to validate the approach were 3–9 g/ml for atorvastatin, 22.5–9 g/ml, 67.59 g/ml for aspirin, 1.54–49 g/ml for ramipril, and 15–45 g/ml for metoprolol succinate. The LOD values for atorvastatin, aspirin, ramipril, and metoprolol succinate were 0.3489 g/ml, 2.6739 g/ml, 0.2369 g/ml, and 1.6279 g/ml, while the LOQ values were 1.056 g/ml, 8.100 g/ml, 0.716 g/ml, and 4.931 g/ml [27].

Pratiksha *et al.* (2018) For the measurement of atorvastatin and clopidogrel in pharmaceutical dosage form, the stated stability points to the RP-HPLC method. On a C18 column, phosphate buffer (pH 3.0): acetonitrile (40:60) was used as the mobile phase to achieve the chromatographic separation, and UV detection of the analyte was done at 242 nm. Retention times for atorvastatin and clopidogrel were 6.90 and 10.05, respectively. According to ICH criteria, the current method's precision, accuracy, linearity, and robustness have all been validated. Stress conditions were

applied to the combination medication product of atorvastatin and clopidogrel (acid, base, oxidation, thermal, humidity and photolysis).

While photolysis only caused a minimal amount of degradation, temperature and humidity stress conditions revealed significant degradation [28].

Hassan *et al.* (2018) provide a quick and reliable RP-HPLC method for measuring simvastatin, atorvastatin, telmisartan, and irbesartan simultaneously in bulk medications and tablet formulations.

In this investigation, the chromatographic separation was carried out using a symmetric C18 column (75 mm 4.6 mm; 3.5 m) and a mobile phase made up of acetonitrile and ammonium acetate buffer in a 40:60 v/v ratio. Until 3.5 minutes, the flow rate was kept at 1 ml/min; after that, it abruptly increased to 2 ml/min until the end of the run (7.5min). The information was gathered using a UV detector tuned to 220 nm. The method's linearity, precision, accuracy, and specificity were all validated. Across the concentration range of 1-16 g/ml, the proposed technique has demonstrated high linearity (r 2 > 0.999).

The limits of quantification (LOQ) and detection (LODs) were 0.603-0.630 g/ml and 0.189-0.190, respectively [29].

Tomlesh *et al.* (2018) worked on developing and validating the RP-HPLC technology for atorvastatin calcium and telmisartan tablet dosage. The mobile phase was used as a buffer (0.02 M ammonium acetate buffer pH 4.0 by glacial acetic acid), along with acetonitrile and tetrahydrofuran in the ratio (400:400:14 v/v/v), to achieve the HPLC separation on the Chemsil C18 column (150 mm x 4.6 mm id, 5 particle size) under isocratic conditions at room temperature. 1.5 ml/min of flow was used for the analysis. UV detection at 246 nm allowed for quantification. Telmisartan and atorvastatin calcium were shown to have retention times of 5.70 0.20 and 6.72 0.20 minutes, respectively. For atorvastatin calcium and telmisartan, the linearity was examined in the concentration ranges of 10–60 g/ml and 402–40 g/ml, respectively [30].

Yugatama *et al.* (2017) By using RP-HPLC, you may find atorvastatin in the tablet. In this investigation, the experiment was run on a Cosmosil C18 column (150 cm x 4.6 mm, 5 m) for stationary reverse phase chromatography. The mobile phase was a solution of methanol and water

at pH 3 (80:20 v/v), and the UV detection was done at a wavelength of 245 nm. The devised method shown good linearity in the concentration range of 20 to 120 g/ml, and LOD and LOQ were found to be 0.2 and 0.7 g/ml, respectively [31].

Porwal *et al.* (2017) For the simultaneous measurement of metformin, amlodipine, glibenclamide, and atorvastatin in human plasma and application to protein binding experiments, a validated HPLC-UV approach has been published. The Water's Novapack Phenyl column (150 mm 4.6 mm, i.d., 5.0 m) was used to achieve the best separation conditions. The mobile phase consisted of 0.1% phosphoric acid (pH 3.0) and acetonitrile (ACN) in gradient mode, and the column oven temperature was kept at 30°C. Elution was observed by a UV detector at 227 nm. We used protein precipitation to remove the chosen analyte from human plasma. For all analytes in cold aqueous 10% trichloroacetic acid (TCA) and acetonitrile, the recoveries were found to be greater than 90%. Six replicate readings were accurate enough to meet the LLOQ (Lower limit of quantification) standard [32].

Sangshetti *et al.* (2016) developed and validated an RP-HPLC method using an Agilent ZORBAX SB-C18 (150 4.6 mm, 3.5 um) column and an acetonitrile:distilled water (85:15) mobile phase with a pH of 4.5 (phosphoric acid adjusted) for the measurement of atorvastatin calcium and nicotinic acid in combination tablet dosage form. The detection was carried out at a wavelength of 261 nm at a flow rate of 1.0 ml/min. It was shown that the atorvastatin calcium and nicotinic acid retention times were 6.092 and 3.125 min, respectively [33].

A appropriate dissolve method using the RP-LC method was developed by **Cansel *et al.* (2016)** for the combination tablet formulation of atorvastatin and ezetimibe. In this proposed method, the effects of pH and surfactant on the dissolution of a weakly water-soluble combination drug therapy with different pKa values in an in vitro environment were investigated. Using USP apparatus 2 and 900 ml of 0.01 M acetate buffer (pH 6.8) with 0.45% SDS as a dissolving media at a paddle rotation speed of 75 rpm, the optimal test conditions were achieved. Data from the dissolution sample were quantified with a new, fully validated RP-LC method using UV detection at 242 nm [34].

Bkhaitan *et al.* (2015) measured atorvastatin, irbesartan, and amlodipine simultaneously in bulk and pharmaceutical formulations using the stability-indicating HPLC-DAD method. A gradient mobile phase system with acetonitrile and orthophosphoric acid buffer (pH 2.2) was used to separate the samples on a Waters XBrigde C18 column (5 m, 25 0.46 cm), with UV detection at 240 nm. The method's linearity was evaluated for each drug in the 5-30 g/ml range, and the correlation coefficients (r 2) for atorvastatin, irbesartan, and amlodipine were, respectively, 0.9982, 0.9973, and 0.9986 [35].

Kumar *et al.* (2014) used a novel, validated RP-HPLC analytical method for the simultaneous measurement of atorvastatin and ezetimibe in bulk samples as well as tablet dosage forms. The chromatographic separation was performed on an X Terra C8 (4.6 x 250 mm; 5 m) using acetonitrile and phosphate buffer (pH 3.5) in a 40:60 (v/v) ratio as the mobile phase. The detection was completed at 240 nm. The accuracy was determined to be 99.59% for atorvastatin and 98.98% for ezetimibe, respectively. The linearity was 5- 25 g/ml for both drugs. The intra-day RSD for atorvastatin calcium was 0.57%, the inter-day RSD was 0.13%, and the intra-day RSD for ezetimibe was 0.56%, the inter-day RSD was 0.09%. [36].

In order to evaluate atorvastatin, **Kurakula *et al.* (2014**) created and validated an RP-HPLC procedure. They then applied it to dissolving tests on thermosensitive hydrogel-based nanocrystals. Chromatographic identification was carried out on a C18 (5 m) column using acetonitrile as the mobile phase and 0.025 M potassium dihydrogen ortho-phosphate buffer pH 5 (45:55 v/v). A photo diode array detector (PDA) was used to detect at 246 nm. In accordance with ICH Q2(R1) recommendations, the developed HPLC technique was validated using Lipitor® as a reference and applied to dissolution experiments on atorvastatin thermosensitive hydrogel-based nanocrystal formulation. With a correlation coefficient of 0.9995, atorvastatin showed a 4.5-minute retention time and linear effects in the 0.1-0.5 g/ml range. Precision was observed to range from 0.16 to 0.61 percent relative standard deviation (% RSD) for the samples under examination. The quantification and detection cutoffs were set at 35.6 and 71.2 ng/ml, respectively. The recovery rates for Lipitor® and atorvastatin nanocrystal were 99.37 and 99.12%, respectively, in the assay findings. The sustained release of atorvastatin from Lipitor® and thermosensitive hydrogel nanocrystal

formulation was 40 and 65%, respectively, at 40 minutes, according to dissolution experiments. [37].

When under stress, **Oliveira *et al.* (2013**) looked into the kinetics of atorvastatin degradation. Chromatographic separation was carried out on a C18 column (ODS, 250 4 mm, 5 m, SunFire) using an acetonitrile/phosphoric acid mobile phase that was 0.1% v/v (65:35). The flow rate was maintained at 1.5 ml/min throughout the entire research. The maximal UV DAD detection wavelength was 238 nm at 303 K, and the injection volume was 10 l. The linear correlation coefficient (r2) was found to be more than 0.99 in the concentration range of 14 to 26 g/ml. A detection limit of 0.45 g/ml and a quantification limit of 1.36 g/ml were found. [38].

In a combination capsule dosage form, atorvastatin calcium (AST) and aspirin (ASP) were estimated and validated by RP HPLC by **Suma *et al.* (2012).** Chromatographic separation was carried out using a mobile phase of acetonitrile and ammonium acetate buffer 0.02M (68:32), pH 4.5, on a 5-micron C-18 column (250 x 4.6mm). At 0.8 ml per minute, the flow was maintained. The components of AST and ASP were found using a UV detector at 245 nm. Retention times for AST and ASP were found to be 4.5915 and 3.282 minutes, respectively [39].

Bhinge *et al.* (2012) released a new technique for measuring atorvastatin calcium and fenofibrate simultaneously in pharmaceutical dose forms. Atorvastatin calcium, fenofibrate, and diclofenac (internal standard) were successfully separated using a reversed phase column and a mobile phase made of acetonitrile: potassium di hydrogen phosphate (50 mm) (72:28 v/v) (pH 4.1). While the mobile phase was being pumped at a flow rate of 1.0 ml/min, uv-vis detection at 260 nm was used to detect atorvastatin calcium and fenofibrate. Retention times for the internal standard, fenofibrate, and calcium atorvastatin were 4.34, 5.35, and 12.05 min, respectively. The LOD and LOQ for atorvastatin calcium and fenofibrate, respectively, were determined to be 1.95 and 4.80 g/ml and 1.73 and 3.98 g/ml [40].

The synchronised separation of the antihyperlipidemic medication atorvastatin with the antihypertensive, antidiabetic, and antithrombotic medicines by RP LC for determination in mixed formulations was studied by **Talluri *et al.* (2012).** When performing a gradient elution mode

chromatographic separation using acetonitrile as the organic modifier and 0.1% triethylamine acetate (TEAA) buffer pH 5 at a flow rate of 1 ml/min, the analytes were detected using a diode array detector with a wavelength of 230 nm. The calibration curves were linear in the 5-150 mg/ml range and had correlation coefficients of determination (r2 values) of 0.999 for all of the drugs. The LOQ and LOD were 0.1 to 0.27 mg/ml and 0.3 to 0.89 mg/ml, respectively. The investigation of intraday and interday precision employed three concentration levels (20, 60, and 100 mg/ml). The intra-day and inter-day RSD was less than 2.0% for all compounds. For all compounds, the accuracy was said to vary from 98% to 102% [41].

J.N. Sangshetti *et al.* (2012) developed a simple, exact, and accurate reverse phase liquid chromatographic method for the simultaneous detection of atorvastatin calcium and nicotinic acid in tablet dosage forms. The analysis was carried out using Agilent ZORBAX SB-C18 (150 X4.6 mm, 3.5 µm) and mobile phase with acetonitrile:distilled water (85:15) at pH 4.5 (adjusted with phosphoric acid).

The detection was carried out at a wavelength of 261 nm at a flow rate of 1.0 ml/min.

The retention times for nicotinic acid and calcium atorvastatin were 6.092 and 3.125 minutes, respectively. Both atorvastatin calcium and nicotinic acid demonstrated linearities ranging from 2 to 12 and 10 to 80 µg/ml, respectively. The recovery rates for nicotinic acid and atorvastatin calcium were found to be 99.031% and 99.744%, respectively. The proposed method, which was validated and utilized satisfactorily, was used to determine the estimated quantities of atorvastatin calcium and nicotinic acid in the combined tablet formulation [42].

N. Kannappan *et al.* (2011) developed a reverse phase high performance liquid chromatographic method for simultaneous detection of atorvastatin calcium and ubidecarenone in tablet formulation. The separation was accomplished using a 250x4.6 mm, 5, L-7 pack (peerless C-8) column with an 80:20 methanol: acetonitrile mobile phase and a flow rate of 1.5 ml/min was employed. In order to demonstrate that the drug Atorvastatin Calcium and Ubidecarenone is suitable for its intended use, an analytical method is being validated. The retention time for individual peaks of Atorvastatin calcium and Ubidecarenone were found to be around 1.692 and 10.709. Visual inspection of the plot of peak area as a function of analyte concentration was used

to assess the linearity for both atorvastatin calcium and ubidecarenone. In quantitative work, a retention value of more than 2 denotes satisfactory findings, while a high resolution value denotes complete drug separation. The obtained RSD values are under 2%, demonstrating the accuracy of the used approach. Injecting the placebo and the placebo spiked standard and observing that there was no interface due to placebo served as a good indicator of accuracy, and the specificity of the method was confirmed. The percentage recovery was found to be within 99 to 100% w/w for Atorvastatin calcium and 100.2 to 101.5% w/w for Ubidecarenone. Precision studies helped to further validate the suggested method's validity.System precision and method precision were used to do this, and it was discovered that the percentage RSD values for both were within the allowable range [43].

Nagaraju *et al.* (2011) developed and validated the RP-HPLC method for the detection of atorvastatin calcium in bulk and pharmaceutical formulations. The separation was carried out using a mobile phase that included acetonitrile, orthophosphoric acid (0.1%), and tetrahydrofuran (48:0.04:52) on a Phenomenex C18 (250 4.6 mm, 5) column. The effluent was observed using a 244 nm laser. Recovery studies and statistical data validation have confirmed that the suggested technique is correct. [44].

Hirave *et al.* (2010) estimated atorvastatin calcium and fenofibrate in tablet dosage form simultaneously using RP-HPLC. The best separation was generated by the HiQ sil C8 (4.6x250mm) column. employing a mobile phase made up of the following components: The drugs were found at 260 nm with a flow rate of 1 ml/min of methanol: water pH 3.2 (90:10 v/v) [45].

Jena *et al.* (2010) reported on a simultaneous detection of atorvastatin calcium and amlodipine besylate in tablet dosage by RP-HPLC. The chromatographic resolution of pharmaceuticals was achieved using a Grace Smart RP C18 column (250 x 4.6, 5 m) in a mobile phase made up of phosphate buffer (1 ml ortho phosphoric acid in 1000 ml of water), acetonitrile, and methanol in the proportion 53:43:4. A photo dine array detector with a UV detection wavelength of 246 nm was utilised to detect the samples as they were eluted at a rate of 1 ml/min [46].

For the simultaneous measurement of atorvastatin calcium and telmisartan in tablet dosage form, **Kumar *et al.* (2010**) suggested a new RP-HPLC approach. A few medicines were separated using chromatography on a Waters symmetrical C18 (250mm x 4.6mm, 5) column. The mobile phase was maintained at a 40:60 v/v ratio of acetonitrile and ammonium acetate (0.02M, pH 4.0 adjusted with glacial acetic acid). The detection wavelength was 254 nm, and the flow rate was kept constant at 1.0 ml/min [47].

Shetty *et al.* (2010) worked on a quantitative application to a polypill by developing a stability indicating LC method for the simultaneous estimation of aspirin, atorvastatin, atenolol, and losartan potassium. On a C18 stationary phase, efficient chromatographic separation was achieved using only buffer and acetonitrile as the mobile phase. The buffer is provided in a gradient method, includes 0.1% orthophosphoric acid (pH 2.9), and is quantitated using UV detection at 230 nm with a flow rate of 1.0 ml/min. Retention times for atorvastatin, atenolol, aspirin, and losartan potassium were 3.3, 7.6, 10.7, and 12.9 min, respectively [48].

Jena Antaryami *et al.* (2010) A combination pharmaceutical tablet dosage form containing atorvastatin calcium and amlodipine besilate was simultaneously separated and analysed using a high performance liquid chromatography technology. A mobile phase composed of phosphate buffer (1 ml orthophosphoric acid in 1000 ml of water), acetonitrile, and methanol (53:43:4, v/v), was used to carry out the chromatographic estimation. UV light with a wavelength of 246 nanometers was detected using a photodiode array detector. With the help of a Grace Smart RP C-18 column, the decision was made (250 X 4.6 mm, 5 m). Amlodipine besilate and atorvastatin calcium had retention durations of 3.337 and 6.067, respectively. Throughout concentration ranges of 40–60 g/ml and 80–120 g/ml, respectively, the amlodipine besilate and atorvastatin calcium calibration curves were linear with correlation values of 0.9989 and 0.9981, respectively. AML and ATV had recovery rates of 99.60 to 100.02 and 99.05 to 100.52%, respectively [49].

A stability-indicating RP-HPLC technique for the simultaneous detection of atorvastatin (ATR) and nicotinic acid (NTA) was proposed by **Gupta *et al.* (2009).** The Phenomenex® C18, 5m, 250mm X 4.6mm i.d. column was utilised in the suggested RP-HPLC method, and it had an ideal mobile phase made of acetonitrile and 50mM potassium dihydrogen phosphate buffer (68:32, v/v)

with an effluent flow rate of 0.8 ml/min and UV detection at 247 nm. Conditions of oxidative, thermal, humidity, acid/base hydrolysis, and thermal stress were applied to the combination pharmaceutical product. The suggested technique was used to evaluate the stressed samples. The reported method was linear for ATR and NTA over the ranges of 2–10 g/ml and 20–100 g/ml, respectively. The average recoveries for ATR and NTA were 100.99 and 102.6, respectively [50].

The study by **Zaheer *et al.* (2008)** focused on the stability-indicating high-performance liquid chromatographic detection of atorvastatin calcium in pharmaceutical dosage form. A reversed-phase C18 column of 250 x 4.6 mm, 5 m, and a mobile phase consisting of a 45:45:10 ratio of methanol, acetonitrile, and phosphate buffer solution made up the chromatographic setup. The flow rate was 1 ml/min. 246 nm was the detecting wavelength. The retention time for atorvastatin was 6.98 minutes. The oxidation, thermal, photochemical, and acid and alkali hydrolysis reactions all contributed to the atorvastatin calcium's deterioration. In the concentration range of 52.20 to 156.60 g/ml, the calibration plots' linear regression analysis results showed a strong linear association. 0.9999, 36.02, and 26.45 were the values for the correlation coefficient, slope, and intercept, respectively. The medication deteriorated in settings of acidic, basic, photochemical, and thermal deterioration. The active pharmaceutical ingredient was able to repair all of the degraded product peaks with noticeably different retention durations [51].

Another RP-HPLC approach for the simultaneous detection of ezetimibe and atorvastatin calcium in pharmaceutical formulations was developed, according to **Qutab *et al.* (2007).** A 250 x 4.6 mm, 5 Hypersil phenyl-2 column was used to achieve the best separation of the selected medications. Eluent was measured at 242 nm using a solvent system of 0.1 M ammonium acetate (pH 6.5) and acetonitrile in a ratio of 28:72 (v/v) [52].

Shah *et al.* (2007) created and published their findings about the determination of atorvastatin calcium and nicotinic acid in combination tablet dose form . A Phenomenex Luna C18 column measuring 5 mm, 250 x 4.6mm in diameter was used for chromatographic separation. Isocratic separation was achieved using a mobile phase containing 0.02 M potassium dihydrogen phosphate, methanol, and acetonitrile (20:40:40, pH 4). After samples were eluted at a flow rate of 1 ml/min, effluents were seen at 240 nm [53].

Shah *et al.* (2007) looked at the stability of atorvastatin calcium and amlodipine besylate in pharmaceutical formulations. The best separation was found in the Phenomenex Gemini C18 column in isocratic mode (250 4.6 mm i.d., 5 m). The mobile phase was MeOH (20: 80, pH 4.0) containing 0.02 M potassium dihydrogen phosphate. The flow rate was held constant at 1 ml/min while the drugs were measured at 240 nm [54].

Mohammadi *et al.* (2007) carried out a stability-indicating high-performance liquid chromatographic (HPLC) assay for the simultaneous detection of atorvastatin (AT) and amlodipine (AM) in commercial tablets. The separation was carried out using a mobile phase consisting of acetonitrile and 0.025 M NaH2PO4 buffer (55:45, v/v, pH 4.5) on a Perfectsil Target ODS-3 (250 4.6 mm i.d., 5 m) column. The flow rate was maintained at 1 ml/min, and UV detection was carried out at 237 nm. The drugs were subjected to oxidation, hydrolysis, photolysis, and heat to simulate stress conditions. Due to the fact that stress-related degradation products did not prevent the detection of AT and AM, the assay can be regarded as stability-indicating [55].

Alla (2007) suggested a stability-indicating LC technique for the simultaneous assessment of metoprolol (ME), atorvastatin (AT), and ramipril (RA) in mixed pharmaceutical dose form. Using a Hypersil C8, 15-cm analytical column, buffer, and acetonitrile (55:45 v/v), the three medications were separated chromatographically. 0.02 M sodium perchlorate is used as a buffer in the mobile phase of double-distilled water. The flow rate was held at 1.0 ml/min for ME, AT, and RA, and a 210 nm UV detector was used for detection. Methanol was used as a diluent [56].

Using stability-indicating reversed-phase liquid chromatographic methods, **Chaudhari *et al.* (2007)** measured atorvastatin and ezetimibe simultaneously from their combination drug preparations. ATV and EZE were separated using an acetonitrile water-methanol (45+ 40+ 15, v/v/v) mobile phase with a pH of 4.0 0.1 on a Li Chrospher 100 C18, 5-micron, 250 cm x 4.0 mm id column at room temperature. UV detection was carried out at 250 nm with a 1 ml/min flow rate [57].

Raja *et al.* (2006) developed an RP-HPLC method for the simultaneous assessment of atorvastatin and amlodipine in tablet dose form. The mobile phase consisted of acetonitrile and 0.03 M

phosphate buffer (55:45 v/v, pH 2.9). A dual-absorbance detector was used to find atorvastatin and amlodipine at 240 nm and 362 nm, respectively [58].

The HPLC method for atorvastatin tablet determination and solid phase stability monitoring was validated by **Stanisz *et al.* (2006).** With the pH set at 2.0 with 80% orthophosphoric acid, atorvastatin was successfully separated on a C18 column using water and acetonitrile at a volumetric ratio of 48:52. The detecting wavelength was 245 nm. The technique was confirmed to be valid, and the response was discovered to be linear in the drug concentration range of 0.04 mg/ml and 0.4 mg/ml. The slope's average RSD and correlation coefficient were 8.192, 0.260, and 0.999, respectively [59].

Pasha *et al.* (2006) looked studied the five HMG-CoA reductase inhibitors: atorvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Additionally, they created a brand-new technique for analysing pharmaceutical formulations and in vitro metabolism research. On an Intertisl ODS 3V column (4.6 x 250 mm, 5 microm) operating at room temperature with a flow rate of 1 ml/min, drug separation was accomplished using ternary gradient elution. Acetonitrile, methanol, and 0.01 m ammonium acetate (pH 5.0) made comprised the mobile phase. There was an internal standard (IS), and it was theophylline. The HMG-CoA reductase inhibitors and their metabolites were visible at a wavelength of 237 nm. Drugs were determined to be 89.6–105.6% of what was claimed on their labels in the pharmaceutical formulations [60].

Reversed-phase high performance liquid chromatography with UV detection was utilised by **Bahrami *et al.* (2005**) to measure the amount of atorvastatin in human serum. Chromatographic separation was performed using a C18 analytical column and a mobile phase composed of sodium phosphate buffer (0.05 M, pH 4.0) and methanol (33:67, v/v). Using UV absorbance at 247 nm, the internal standard and atorvastatin were identified. The internal standard and drug recoveries were, respectively, 95 and 80%. Twelve healthy people participated in a randomized cross-over bioequivalence investigation of two different atorvastatin preparations, and the analytical performance was assessed using the method specified on the labels [61].

Manoj *et al.* (2004) reported utilising RP HPLC to detect atorvastatin and aspirin simultaneously in a capsule formulation. The maximum resolution was achieved using mobile phase acetonitrile, 0.05 M potassium dihydrogen phosphate buffer, and methanol in the ratio (50:30:20, v/v/v) at pH 3.0. At 1.5 ml/min flow rate and 240 nm detection wavelength, it was found that this mixture was appropriate, enabling acceptable component separation. Under these conditions, atorvastatin calcium and aspirin were eluted in 4.7 and 2.2 minutes, respectively [62].

Erturk *et al.* (2003) measured atorvastatin and its impurities in bulk medication and tablet form using a gradient RP-HPLC test with UV detection. A Luna C18 column and an acetonitrile ammonium acetate buffer mobile phase with a pH of 4-THF were used to achieve the best resolution. The samples were eluted with the mobile phase at a flow rate of 1.0 ml/min. the event was discovered at 248 nm [63].

UV Spectrometric Methods

Almutairi, F. M (2025) recently advances in UV spectrophotometric approaches for Atorvastatin determination emphasize both simplicity and sustainability. A macro green UV-PLS method developed in this case called Firefly Algorithm-PLS (FFA-PLS) allows for simultaneous quantitation of rosuvastatin, pravastatin, and atorvastatin in pharmaceutical formulation. The FFA-PLS model reportedly brought down the prediction error of atorvastatin to 1.63% (compared to 3.20% when the normal PLS was relied on), simplified the model into three latent variables, and required searching through fewer wavelengths. The average recoveries ranged from 99.23 to 99.90% with RSD <2%; the method passed full ICH validation and enforced green chemistry (AGREE score of 0.78; RGB12 whiteness = 91.4%), thus outperforming HPLC-UV methods (AGREE = 0.64; whiteness = 75.8%). Earlier, very simple UV-visible spectrophotometric methods were validated for Atorvastatin in pure drug and tablet forms. One such method was a rapid and economical assay, wherein methanol was employed as solvent and the absorbance measured at $\lambda_{max} \approx 244$ nm for linearity and accuracy, making the method suitable for assay for the wholesale release of the product. Another method applied routinely in the UV runs a water-methanol (90:10) procedure with detection at 241 nm and is linear from 4-32 µg/Ml with high molar absorptivity

value (~2289), acceptable sensitivity (Sandell's ~ 0.125) and it meets all the ICH validation criteria [64].

Haque, S. M. (2025) Atorvastatin, widely used in the treatment of hyperlipidemia, has been quantified by one or more techniques among UV spectrophotometry, HPLC, UHPLC, LC MS, etc. Analyses have been performed on different dosage forms and biological samples. These were measured using various green analytical chemistry tools: Analytical Eco Scale (79-91), AGREE (0.54-0.86), and BAGI (practicality scores of 75-82.5) as well as RGB 12 whiteness index (77.6-91) testing to indicate whether those protocols were sufficiently reliable and environmentally friendly. The cumulatively applied metric provides additional knowledge with respect to ecology, analytical parameters and practical approach, directing the researcher more meaningfully toward greener method development for atorvastatin as a single drug concerning pharmaceuticals and biological fluids [65].

Hamache, T. *et al.* (2024) atorvastatin has been widely quantified via UV spectrophotometry for both bulk drug and tablet dosage forms. It can provide a simple yet cost-effective alternative to chromatographic techniques for analysis. The validated method using anhydrous methanol solvent showed maximum absorbance at 244-250nm and has linearity between 2-10 µg/mL, more than 99% accuracy, and LOD and LOQ that comply with ICH criteria. Another method employed a hydrotropic agent, 0.01M sodium citrate, and absorbance measured at 241nm, exhibited excellent linearity ($R^2 = 0.999$). Recovery was between 100 and 10.4%, RSD < 2%, LOD ~0.64 µg/mL, and LOQ ~1.9 µg/mL and all validated per ICH requirements across three commercial tablet brands. A third method developed by conventional UV spectroscopic measurement reported linearity in the range of 20-120µg/Ml (R^2= 0.9996), LOD ~0.20µg/mL, LOQ ~ 0.65 µg/mL, intra/inter day RSDs below 0.3%, and specificity verified in the presence of common excipients. All these methods showed consistently high molar absorptivity (~2289 $L \cdot mol^{-1} \cdot cm^{-1}$) and Sandell's sensitivity (~0.125 µg/cm2), with very good statistical validation and practical application to marketed products, enabling accurate, precise, and interference-free quantitation and thus suitable for routine quality control [66].

Kashyap, P. *et al.* (2024) a new simple yet effective RP-HPLC method has been developed and validated comprehensively for a simultaneous qualitative and quantitative estimation of atorvastatin and aspirin in bulk and in finished pharmaceutical dosage form. The selected method wavelength was at the isobestic point, where both drugs were detectable with UV detectors, 255 nm. Isocratic mode was employed with a 250 x 4.6 mm i.e. Phenomenex C18, 5 µm column using the mobile phase anorthophosphoric acid-adjusted methanol (20:80) containing 0.02 M potassium dihydrogen phosphate. The samples were quantified at 255nm with a flow rate of 1.0 ml/min. Linearity was determined by external standard calibration method in the concentration range of 20µg/mL to 120µg/mL, with the relative degradation given by the acid hydrolysis of atorvastatin and aspirin being 2.15% and 2.19% respectively after one hour at 60°C. The relative amounts of hydrolysis of atorvastatin and aspirin were 1.98% and 2.69% respectively after one hour at 60°C. The amount of oxide degradation of aspirin and atorvastatin relative to their total against time at normal temperature were 3.86% and 7.56%, respectively after 3 hours. The thermal degradation amounts of aspirin 0.99% and atorvastatin 0.90% after 5 hours at 110°C [67].

Sandhu *et al.* (2022) Drug authentication has been done using a UV spectrophotometric approach. On a UV-Vis Spectrophotometer (UV-1700) that has UV probe software, estimation was done. Atorvastatin and Ezetimibe, each weighing 10 mg, were placed to a 10 ml volumetric flask. Methanol and water, at a ratio of 80:20, were utilised as solvents for drug measurement. To determine the maximum concentration of both medications, the standard solution of atorvastatin and ezetimibe was scanned using a UV spectrophotometer in a 1.0 cm cell against an 80:20 methanol:water mixture. Atorvastatin and Ezetimibe detection was done at 246 nm and 233 nm, respectively. The ICH criteria were followed when performing the validation parameters. The guidelines of linearity, accuracy, precision, LOD, and LOQ were followed. [26].

Vasu* *et al.* (2021) The creation and evaluation of UV-spectrophotometric techniques for the simultaneous estimation of aspirin, atorvastatin, and theophylline in pure drug form was the main objective of the current study.This was accomplished using a simultaneous equation analysis method using methanol as a solvent. The three substances that the simultaneous equation technique principally depends on (Aspirin, Atorvastatin, and Theophylline) are as follows, each absorbing at

a maximum of the others: Maxes of 271 nm, 246 nm, and 270 nm were discovered for aspirin, atorvastatin, and theophylline, respectively. With correlation coefficients of 0.9997, 0.9991, and 0.9938, respectively, their linearity ranges were 4-20 g/ml, 8-24 g/ml, and 4-20 g/ml. System precisions for aspirin, atorvastatin, and theophylline were discovered to be 0.018, 0.042, and 0.029, respectively. Every time, values fell below 2% of the allowed range. The mean percent recovery values for aspirin, atorvastatin, and theophylline were 100.2, 100.5, and 100.4, respectively. The approach was validated for a number of factors in accordance with ICH criteria, and the results were found to be within acceptable ranges [68].

Dehariya *et al.* (2021) It was created and tested to use hydrotropy phenomena to assess the effects of atorvastatin and clopidogrel bisulfate. First, the melting points, solubilities, and FT-IR characteristics of both reference drugs were used to evaluate their quality. ATV and CLP both exhibit their greatest absorbance at wavelengths of 244.0 nm and 228.0 nm, respectively. At their respective maxima, ATV and CLP both exhibited linearity in the concentration ranges of 5–25 g/ml and 10–50 g/ml. Absorbance versus concentration was shown on a calibration curve. The overlaid spectra showed isoabsorptive spots at 233.0 nm as well. The estimations for both medicines were produced using the simultaneous equation technique. The solubility, stability, and spectrum characteristics of the drugs led to the selection of 2M Sodium Citrate as the hydrotropic agent. The spectrophotometric assay is not significantly affected by the presence of a hydrotropic agent, demonstrating the applicability and repeatability of the stated approach. The validity of the simultaneous equation approach was examined using a variety of characteristics, including linearity, accuracy, and precision. One commercial product was also evaluated using a newly created approach, which produced ATV and CLP values of 99.92 and 99.80, respectively [69].

Alrasheed *et al.* (2019) covered the development, validation, and application of spectrophotometric techniques for the atorvastatin calcium pharmaceutical formulation (tablets). In this study, new and validated spectrophotometric techniques that are rapid, easy, accurate, and sensitive have been developed. The calcium atorvastatin's capacity to dissolve in diluted anhydrous methanol is the basis for this approach, which is a direct spectrophotometric analytical procedure. Beer's law was seen to be obeyed in the concentration range of 5 to 35 g/ml, and the maximum absorption wavelength for the detection of ATV drug was found to be 291 nanometer (nm) [70].

Magdy *et al.* (2019) For the simultaneous assessment of atorvastatin (AT) and amlodipine (AML) in bulk powder and pharmaceutical dose form, four novel, simple, and repeatable spectrophotometric approaches were developed and validated. Constant Value (CV) and Concentration Value are the two succeeding techniques, whilst Absorbance Subtraction (AS) and Amplitude Modulation are the two progressing techniques (AM). The linearity range for the two progressive procedures was 5 g/mL-35 g/mL whereas the range for the two succeeding methods was 5 g/mL-55 g/mL. According to ICH standards, the four approaches were evaluated for accuracy, precision, and selectivity. The blend in a pharmaceutical dosage form that is accessible commercially was also identified using these procedures. Findings were contrasted with previously reported methods. Also, a one-way ANOVA statistical test comparing all of the suggested spectrophotometric techniques found no evidence of a significant difference [71].

Bernard *et al.* (2018) used urea as a hydrotropic solubilizing agent in a new spectrophotometric approach to estimate the amounts of aspirin (ASP) and atorvastatin calcium (ATR). The created approach used the simultaneous equation method (method-A), which relies on the measurement of absorptivity at the iso-absorptive point at 239 nm and 243 nm as the absorbance maxima for ATR and ASP, respectively (absorption maximum of atorvastatin). At the concentration range of 10–50 g/ml, it was discovered that the calibration curves for both medicines were linear. For atorvastatin and aspirin using technique A, and for 98.09% and 98.06% using method B, respectively, the mean recovery of the medicines from the combination tablets was found to be 98.83% and 97.77% [72].

Alshabrawy *et al.* (2017) worked on the sensitive ion pair complexation with pararosaniline hydrochloride spectrophotometric detection of atorvastatin in pharmaceutical formulation. In order to create the ideal conditions for the experiment, various parameters impacting the ion pair's creation and stability were researched and improved in this study. The method was validated for concentrations between 1 and 8 g/ml. With a limit for quantitation of 0.93 g/ml and a limit of detection of 0.31 g/ml, the method's sensitivity was established.The red ion pair exhibits maximal absorbance at 547 nm and is readily extractable in organic solvent [73].

Al-Adl *et al.* (2017) used pdimethylaminobenzaldehyde to study the spectrophotometric measurement of atorvastatin calcium and rosuvastatin calcium in bulk and dose form. This procedure relied on the synthesis of coloured chromogen in the presence of pdimethylaminobenzaldehyde (PDMAB) and the calcium salts of atorvastatin, rosuvastatin, and both. For atorvastatin calcium and rosuvastatin calcium, the reaction mixture showed maximum absorbance at max 540 and 570 nm, respectively. For atorvastatin calcium and rosuvastatin calcium, the technique was linear over the concentration range of 20–160 g/ml and 2–16 g/ml, respectively [74].

Virani *et al.* (2015) have reported about estimating irbesartan and atorvastatin simultaneously in their synthetic mixture using a first order derivative spectroscopic approach. The determination of both medicines at their respective zero crossing points served as the foundation for the derivative spectrophotometric approach (ZCP). The determinations were made at 225.20 nm (ZCP of atorvastatin) for irbesartan and 308.15 nm (ZCP of irbesartan) for atorvastatin based on the first order derivative spectra that were obtained in methanol. Irbesartan succinate concentrations of 5–30 g/ml and atorvastatin succinate concentrations of 5–30 g/ml were used to achieve linearity. For irbesartan and atorvastatin succinate, the average recovery was 99.25 and 99.65%, respectively [75].

Naveed *et al.* (2014) a straightforward UV spectrophotometric analysis of the atorvastatin API formulation was performed, and a comparison was made. The assay was based on atorvastatin's maximum ultraviolet UV absorbance at a wavelength of about 244 nm using methanol as the solvent.

To create a solution containing atorvastatin, a medication sample was dissolved in methanol. An identical procedure was used to extract and dilute a sample of powdered tablets from a different brand. At 244 nm, the sample preparation's absorbance was measured against a solvent blank, and the assay's results were calculated by comparing it to the absorbance of a brand that was readily available [76].

Ashour *et al.* (2013) performed a new kinetic spectrophotometric approach for atorvastatin determination in pharmaceutical and pure dose forms. In order to create a colored product with a

maximum absorption at 566 nm, the approach required the oxidative coupling reaction of atorvastatin (AVS) with 3-methyl-2-benzothiazolinone hydrazone hydrochloride monohydrate (MBTH) in the presence of Ce (IV). Using the use of spectrophotometry, the process was monitored by timing the rise in absorbance at 566 nm. The calibration curves were built using the starting rate and fixed time approaches. For initial rate and fixed time techniques, the linearity range was discovered to be 2–20 g/ml. Initial rate and fixed time techniques have detection limits of 0.093 and 0.064 g/ml, respectively.
The method's molar absorptivity was discovered to be 3.36 104 l/molcm [77].

A spectrophotometric estimation of atorvastatin calcium and fenofibrate in tablet dosage form was carried out by **Hirave *et al.* (2013).** UV spectrophotometric method was developed for the estimation of atorvastatin calcium & fenofibrate in tablet dose form using simultaneous equation methodology. The medication shown excellent correlation near to 0.999 and followed Beer's law. The greatest absorption of fenofibrate and atorvastatin calcium was observed at 246 nm and 286 nm, respectively. Beer's rule was seen for the drugs fenofibrate and atorvastatin calcium in the concentration ranges of 1–10 g/ml and 2–20 g/ml, respectively. The linearity, accuracy, and precision of the procedure have all been confirmed. The recovery rate was higher than 99% [78].

In a different study, **Patel *et al.* (2010**) estimated the calcium content of a combination dose form of aspirin and atorvastatin using a spectrophotometric method. The solvent used in this study was methanol. In order to eliminate spectral interference, second order derivative spectroscopy was used during the investigation. Aspirin and atorvastatin calcium have zero crossing points of 266.78 nm and 237.35 nm, respectively [79].

The simultaneous spectrophotometric estimation of atorvastatin calcium and amlodipine besylate in combination tablet dose form was carried out by **Jani *et al.* (2010)** using the area under the curve method. In this investigation, methanol was used as a solvent. The proposed area under curve approach involved measuring area at particular analytical wavelength ranges, using "Cramer's Rule" and "Matrix Method" to interpret the data. ATR (atorvastatin) and AML (amlodipine) were estimated using two analytical wavelength ranges, 256-238.5 nm and 368-352 nm, respectively [80].

Kumbhar *et al.* (2011) created and validated a derivative spectrophotometric method for assessing atorvastatin calcium (AT) and amlodipine besylate (AM) in tablet dosage form. The AT and AM stock solutions were created using a 50:50 V/V methanol to water ratio. By measuring the absorbances of AM and AT at 241 nm and 250 nm, respectively, derivative spectroscopy was utilised as the analysis method to remove spectrum interference. The AT and AM have linear concentration ranges, 0-14 g/ml and 0-7 g/ml, respectively. For AM, the relative limits of quantitation (LOQ) and detection (LOD) were 0.29 and 0.75 g. The detection and quantification limits of AT were 0.21 and 0.60 g, respectively [81].

Other Methods

Table 2-Analytical Methods for estimation of Atorvastatin

Instrument Used	**Conditions**		**Detection**	**Reference**
	Stationary phase	**Mobile phase**		
HPTLC	Precoated silica gel 60 F254	chloroform–benzene–methanol–acetic acid (6+3+1+0.1, v/v/v/v)	250 nm	82
CE	capillary of 50 µm with a length of 33 cm	Sodium acetate buffer 25 mM at pH 6	190-370 nm	83
HPTLC	Aluminum plates precoated with silica gel 60 F254	toluene–methanol 8+2 (v/v)	240 nm	84
UPLC	C18 column 2.1 mm × 100 mm, 1.7 µm	ACN and ammonium acetate buffer (pH 4.7; 0.01 M)	247 nm	85

FT-Raman	Partial least squares, principal component regression, and counter-propagation artificial neural networks methods		Relative standard errors of prediction were calculated	86
X-ray diffraction	Philips 1830/40 apparatus, samples sprayed using Cu Kα radiation (40 kV and 30 mA) and nitrogen filter with scanning speed of 0.005◦ 2θ 1/s		40 Kv	87
IR	Equinox 55 equipment, samples were diluted in potassium bromide		4000 to 400 cm^{-1}	87
FT-Raman	FT-Raman FRA-106/S equipment, incident ray of 370 mW on sample surface		1064 nm	87
MECC	Prolonged light capillary	sodium tetraborate buffer 10 mM pH 9.5, sodium dodecyl sulfate 50 mM and 20% methanol (v/v)	214 nm	88
CE	Fused silica capillary (58 cm × 75 μm internal diameter	), phosphate buffer (2.5 mM, pH 6.7)–methanol (70+30, v/v) as electrolyte solution	210 nm	89
Vis	The samples were prepared in methanol. 2,3-dichloro-5, 6-dicyano-1,4-benzoquinone (DDQ) was used to reaction during 3.5 min at 31 ± 1°C		460 nm	90,91
Voltametry	Cetyltrimethyl ammonium bromide as enhancing agent using cyclic and differential pulse voltammetry		----------	92

Dissolution	The test solution was sampled after 5, 10, 15, 20, and 30 min and filtered through a membrane filter (0.45 μm) using 900 mL of distilled water, 75 rpm; temperature of 37°C		----------	93
UPLC-MS	Acquity UPLC BEH C18 (50 cm × 2.1 mm, 1.7 μm) column	Ammonium formate and acetonitrile	Multiple-reaction monitoring in positive electrospray ionization mode	94
TLC	TLC silica gel 60 plates with fluorescent indicator F254	n-hexane–ethyl acetate–methanol–water–acetic acid (8.4 + 8 + 3 + 0.4 + 0.2, v/v/v/v/v)	265 nm	95
micellar electro kinetic capillary chromatography	silica capillary (48 cm length X 50 μm ID)	25 mM borate buffer electrolyte at pH 9.3	----------	96
LC-MS	C18 column	acetonitrile–water (10 mM CH_3COONH_4, pH 3.0) = 70:30 (v/v)	----------	97
X-Ray diffraction	Measurements were conducted at 30 kV and 15 mA, a scanning angle from 5° to 35°, a scanning speed of 4° 1/min, with a CuKa radiation source			98
HPLC-MS	C18 column 50 mm × 2.1 mm, 3.5 μm, coupled with C18 guard cartridge 2.1	water and methanol, both modified with 2 mM ammonium formate and 0.2 % formic acid	ESI in positive mode using selected reaction monitoring and	99

	mm × 12.5 mm, 5 μm,		m/z 559.20 to 440.21	
HPLC-MS	C18 column	0.005% formic acid in water–acetonitrile–methanol (35+25+40, v/v/v)	ESI in negative mode using MRM and m/z 557.4 to 278.1	100
HPLC-MS	Phenomenex Synergi 4 u polar-RP 80A 150 mm × 4.6 mm, 4 μm	water–methanol (14+86, v/v) adjusted by trichloroacetic acid	Selected reaction monitoring and m/z 559.09 to 440.21	101
HPLC-MS	CAPCELLPAK CR 1+4 column 150 mm × 2.0 mm, 5 μm,	acetonitrile and ammonium acetate buffer (20 mM) containing 0.3 % formic acid (50+50, v/v)	ESI using MRM and m/z 559.42 to 440.25	102
HPLC-MS	C18 column	60+40 (v/v) mixture of acetonitrile and 10 mM ammonium acetate (pH 3.0)	ESI using MRM and m/z 559.5 to 440.4	103
HPLC-MS	C18 column 100 mm × 2.1 mm, 3.5 μm,	water and acetonitrile, both containing 0.1% (v/v) formic acid	ESI using MRM	104
MALDI-MSI[g]	MALDI-LTQ-XL, 10 μJ of nitrogen laser power, 100 μM sample size of 600 × 600 m		Scan in the range m/z 100 to 600 in negative mode (atorvastatin) and positive	105

			mode (lactone of atorvastatin)	
TLC	Silica gel plates	diethyl ether–ethyl acetate (7+3, v/v)	254 nm	106

Conclusion

Atorvastatin was the top-selling medication worldwide in the early 2000s. It lowers the total quantity of cholesterol in the blood, lowers the levels of dangerous fractions, and raises the levels of good cholesterol. The product is sold as calcium atorvastatin tablets. The two main analytical techniques for atorvastatin evaluation are HPLC and HPLC-MS, both of which use acetonitrile as the preferred solvent.

Although research on procedures like UV, Vis miniaturised, and TLC shows them to be intriguing from an economic and environmental standpoint, they can still be made better. It is possible to determine whether the current HPLC and HPLC-MS procedures are enough for taking into account the current sustainable analytical chemistry. Continuous improvement and multidimensionally considering analytical decisions must be the central concepts; only then can the analytical, environmental, and human consciousnesses stay intertwined.

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