World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Research Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 2
Page: 399-422

AN ADVANCED COMPARATIVE EVALUATION OF ATORVASTATIN CALCIUM TABLET BRANDS AVAILABLE IN THE MALAYSIAN MARKET THROUGH COMPREHENSIVE QUANTITATIVE AND QUALITATIVE ANALYSES OF THEIR EFFICACY, SAFETY PROFILES, FORMULATION QUALITY

Nabila Perveen*, Naeem Hasan Khan and Ho Yu Xuan

Faculty of Pharmacy, AIMST University, Malaysia.

Article Received: 27 December 2025 | | ***Article Revised: 17 January 2026*** | | ***Article Accepted: 6 February 2026***

***Corresponding Author: Nabila Perveen**
Faculty of Pharmacy, AIMST University, Malaysia.
DOI: https://doi.org/10.5281/zenodo.18638734

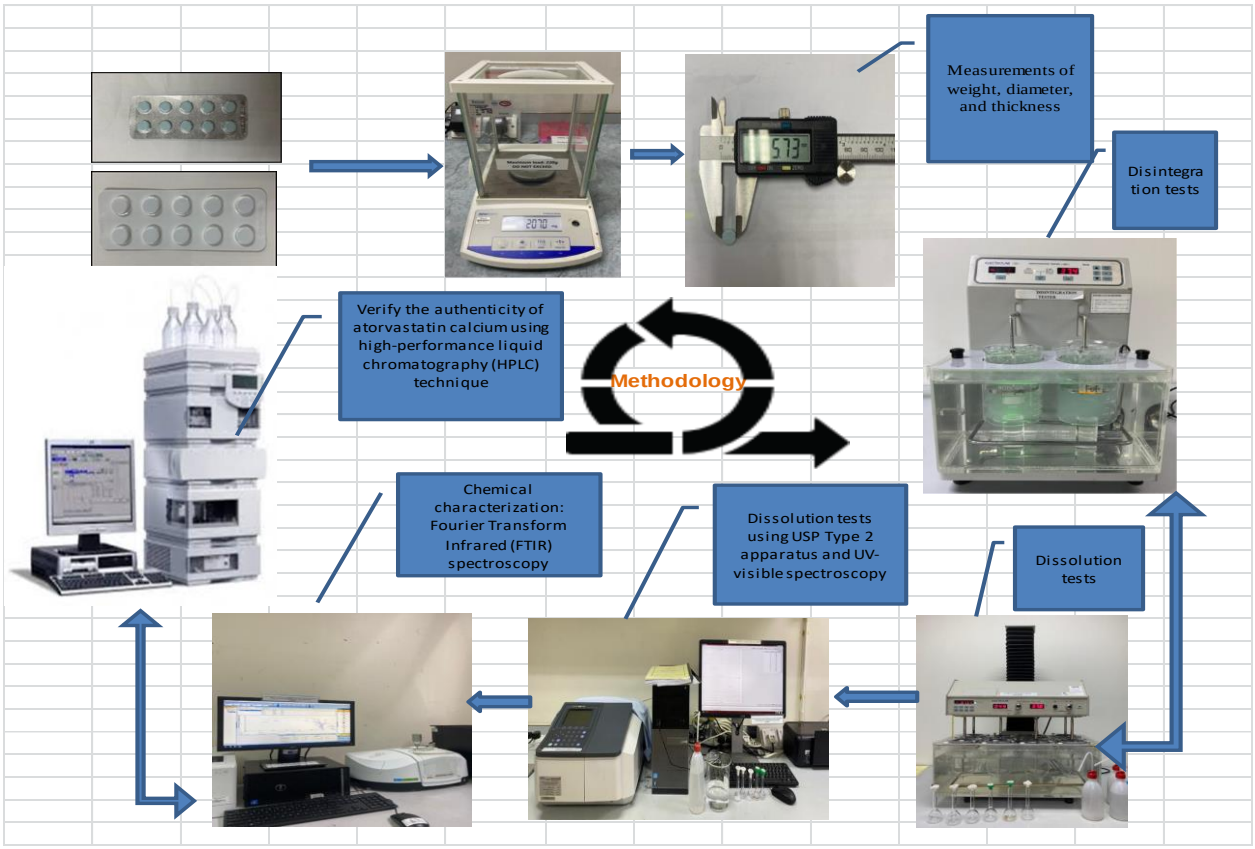
How to cite this Article: Nabila Perveen, Naeem Hasan Khan and Ho Yu Xuan (2026) AN ADVANCED COMPARATIVE EVALUATION OF ATORVASTATIN CALCIUM TABLET BRANDS AVAILABLE IN THE MALAYSIAN MARKET THROUGH COMPREHENSIVE QUANTITATIVE AND QUALITATIVE ANALYSES OF THEIR EFFICACY, SAFETY PROFILES, FORMULATION QUALITY. World Journal of Pharmaceutical Science and Research, 5(2), 399-422. https://doi.org/10.5281/zenodo.18638734

ABSTRACT

Introduction: Atorvastatin calcium is one of the most prescribed members of its class for the treatment of hyperlipidemia. Currently, there are various brands of atorvastatin calcium tablets available in the Malaysian market and the performance of each may vary, leading to patients questioning the interchangeability between innovator and generics. **Objectives:** The main purpose of this study is to assess the quality of different brands of atorvastatin calcium tablets marketed in Malaysia, with emphasis on their dissolution profile, and evaluate their bioequivalence. **Method:** Innovator brand (coded as A) and five generic brands (coded as B to F) of 20 mg atorvastatin calcium tablets were subjected to in vitro tests for organoleptic characterization, identity, content uniformity, weight variation, thickness, diameter, hardness, friability, disintegration, and dissolution according to procedures described in the monograph. **Result**: All brands of atorvastatin calcium tablets complied with the specifications of the tests conducted. With regard to dissolution test, all the investigated brands released more than 80% of their drug content in 30 minutes. Brand A displayed the greatest dissolution profile followed by Brand D where both depicted nearly 100% release of atorvastatin calcium within 60 minutes, while Brand F showed the lowest percentage of drug release at 92.94% in the same time frame. **Conclusion:** The findings support that all the atorvastatin calcium brands under evaluation are of good pharmaceutical quality. Though slight differences exist in the dissolution profile between innovator and generic brands, they are still within the acceptable limits and hence it was determined that these brands could be used interchangeably.

KEYWORDS: Atorvastatin calcium, Malaysia, comparison, dissolution profile, bioequivalence.

GRAPHICAL ABSTRACT



INTRODUCTION

World Heart Federation (2023) reported that cardiovascular diseases (CVDs) have been the leading cause of mortality globally for decades, seeing almost a 70% surge in the number of CVD-related deaths from 12.1 million in 1990 to 20.5 million in 2021. It is considered an important challenge in the healthcare settings of many countries including Malaysia, burdening the societies by impacting people's functional capabilities and quality of life.

Dyslipidemia, which refers to abnormal lipid levels in the bloodstream, is recognized as one of the major attributable risk factors for the occurrence of CVDs such as ischemic heart disease (IHD), acute coronary syndrome (ACS), and stroke (Punithavathi et al., 2009). To illustrate, Fong et al. (2023) mentioned that uncontrolled hypercholesterolemia, a subtype of dyslipidemia where the serum cholesterol level becomes elevated, for a prolonged duration significantly increased the incidence rate of major adverse cardiac event (MACE) by 46%. Another study in Malaysia reported that between 2020 and 2021, 6,054 patients which is 40.6% of those presenting with ACS had dyslipidemia, showing increasing trends compared to previous cohort that demonstrated a 36.7% prevalence between 2018 and 2019 (Azman & Ahmad, 2024).

According to the findings of National Health and Morbidity Survey conducted by Institute for Public Health Ministry of Health Malaysia (2024), at the end of the reporting period for 2023 approximately 33.3% of adults in the country have hypercholesterolemia, which converts to an extremely high figure of 7.6 million adults. The prevalence was higher among females (36.3%) as compared to males (30.5%). In terms of age group, those aged 60 years and above were found to have the highest prevalence at 62.8%. When examining different ethnic groups, it was revealed that hypercholesterolemia is more common among Bumiputera Sarawak (38.7%), followed by Malay (34.6%), Indian

(33.8%), Chinese (33.6%), and Bumiputera Sabah (30.4%). Despite the alarming numbers, 1 out of 2 adults is still unaware that they have elevated serum cholesterol level, possibly due to the reason that hypercholesterolemia is often asymptomatic which gives them a false sense of assurance. This is reflected by the fact that 2 out of 5 adults aged 18 years and above did not took any initiative to undergo health screening in the year 2023, with "no symptoms" being one of the top three reasons for not doing so.

Cholesterol-lowering therapy has long been acknowledged as the cornerstone of cardiovascular (CV) risk reduction ever since the pathogenic role of plasma cholesterol in CVD became quite obvious by the 1960s (Mehta, 2004; Topol et al., 2007). Once it has been decided to commence drug therapy, the next step involves deciding on which drug to be taken. Early clinical trials were associated with using niacin, bile acid sequestrants, and even non-pharmacological interventions like surgery to lower down serum cholesterol levels, but none of them were proven to be very effective. Endo and his colleagues discovering statins in 1976 marks a new era of cholesterol-lowering therapy and subsequent studies proved that they were the most effective approach available (Mehta, 2004).

Statins are currently prescribed for the therapeutic purpose of primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) with various clinical investigations supporting this indication (Davies et al., 2016). In the case of primary prevention, statins allow high-risk patients to maintain a normal level of low-density lipoprotein cholesterol (LDL-C) whereas for patients already diagnosed with ASCVD, statins are employed as a secondary prevention strategy due to their effectiveness in lowering plasma LDL-C levels to a significant extent as well as the risk of a deadly CV event (Davies et al., 2016). For the past few years, there were also ongoing researches aimed at expanding the therapeutic use of statins due to the evidence of them exhibiting cholesterol-independent (pleiotropic) effects which include stabilization of atherosclerotic plaques, improvement in endothelial function, modulation of immune response, and enhancement of anti-inflammatory process (Davies et al., 2016; Liao & Laufs, 2005). These effects could be beneficial in the treatment of various diseases.

In general, statins are safe and well tolerated but there are a few groups of patients who may develop statin-associated myopathy through a mechanism which is not yet fully understood (Topol et al., 2007). This risk is dose-dependent and will be more common when higher dose of statins are administered. Other frequently reported adverse effects are related to the digestive system such as nausea, diarrhea, and constipation (Ye et al., 2015). In this paper, a study will be conducted on one of the members of this class, atorvastatin to appraise its features.

General Understanding of Atorvastatin

3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase (HMGCR) inhibitors or more commonly known as statins largely dominate the global market for lipid-lowering medications. Atorvastatin is the fifth drug developed under this class (Rohmani et al., 2020). First approved by the United States Food and Drug Administration (FDA) in 2001 for the company Pfizer Ireland Pharmaceuticals, it is sold under the brand name Lipitor™ as film-coated atorvastatin calcium (salt form) tablet in four available strengths (10 mg, 20 mg, 40 mg and 80 mg) and has become one of the best-selling drug in the world (AlMuhsin et al., 2022). Patients with hypercholesterolemia, heterozygous familial hypercholesterolemia, and those at high risk of experiencing their first CV event are often prescribed with atorvastatin (AlMuhsin et al., 2022) Atorvastatin's ability to reduce plasma cholesterol levels is attributed to its action of competitively inhibiting the binding of the substrate HMG-CoA to the active site of HMGCR, which is the rate-limiting step in biosynthesis of cholesterol (AlMuhsin et al., 2022). This inhibition blocks cholesterol synthesis which then

triggers a feedback mechanism, leading to increased expression of LDLR on cell surface of hepatocytes and subsequently increased clearance of LDL-C from the bloodstream (Schonewille et al., 2016). Like other statins, it also reduce TG levels in the blood in a dose-dependent fashion and has a modest HDL-C raising effect (Ye et al., 2015).

Atorvastatin is currently marketed as a calcium salt. The chemical formula for atorvastatin calcium (Figure 1) is $C_{66}H_{68}CaF_2N_4O_{10}$ and it has a molecular weight of 1155.363 g/mol (Windriyati et al., 2024). It is a crystalline powder and has a relatively high intestinal permeability at physiologically relevant intestinal pH. It is easily soluble in methanol, partially soluble in ethanol, and very marginally soluble in distilled water, acetonitrile, and phosphate buffer with a pH of 6.8 (Windriyati et al., 2024). Atorvastatin calcium is insoluble in aqueous solution at pH 4 and below. This property is clearly reflected where its solubility in aqueous solution at pH 2.1 and pH 6.0 was found out to be 0.0204 mg/mL and 1.23 mg/mL respectively (Popy et al., 2012). Based on the Biopharmaceutical Classification System (BCS), the low aqueous solubility and high intestinal permeability makes it a Class II compound.

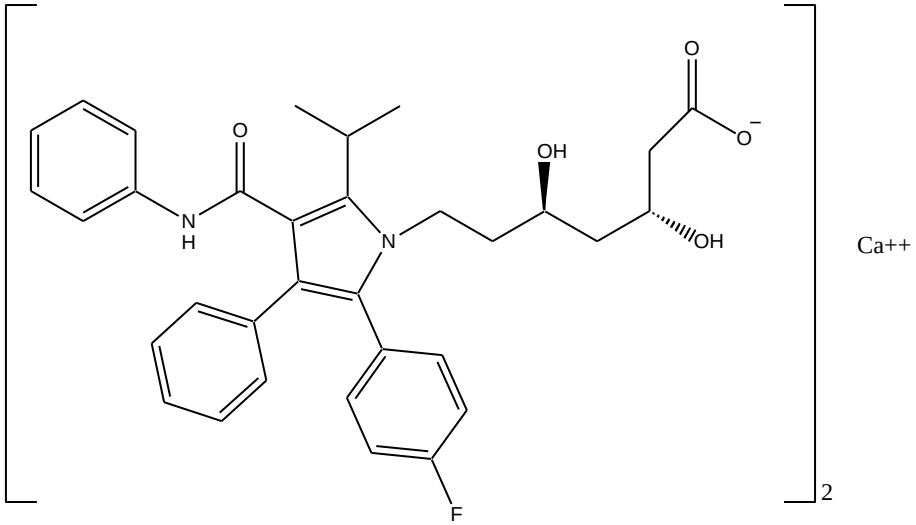


Figure 1: Chemical Structure of Atorvastatin Calcium.

As in all statins, the 3,5-dihydroxycarboxylate moiety in atorvastatin, which is a modified form of hydroxy glutaric acid, mimics the structure of HMG-CoA making it complementary to the hydrophobic pocket of HMGCR (Mehta, 2004). This structural similarity of atorvastatin with HMG-CoA is accountable for its inhibitory activity on HMGCR.

Pharmacokinetics

When given orally, atorvastatin is absorbed rapidly from the intestinal tract and gives rise to a bioavailability of approximately 14% (Alkufi et al., 2023). This poor absolute bioavailability is most probably due to pre-systemic clearance in the gastrointestinal (GI) mucosa and/or first-pass metabolism in the liver where it is broken down by the cytochrome P450 (CYP) isozyme CYP3A4 into two active forms, namely 2-hydroxy-atorvastatin acid and 4-hydroxy-atorvastatin acid (Alkufi et al., 2023). It is extensively bound to plasma proteins up to an extent of 98%. Although the half-life of atorvastatin in blood is only around 14 hours, its inhibitory action on HMGCR can last for 20 to 30 hours owing to the influence of its active metabolites which accounts for 70% of its inhibitory activity (Ye et al., 2015). Atorvastatin is mainly eliminated as metabolites in the bile without entero-hepatic recirculation and less than 2% is recovered in the urine (Ye et al., 2015).

Clinical trials have shown that high-intensity regimen with atorvastatin causes a dramatic decrease in LDL-C. In the Treat to New Targets (TNT) trial, 10,001 patients with coronary heart disease (CHD) and LDL-C below 130 mg/dL were enrolled to double-blind treatment with either atorvastatin 10 mg or 80 mg daily (Waters, 2009). A mean on-treatment LDL-C level of 77 mg/dL was observed in the 80 mg group (compared to 101 mg/dL in the 10 mg group) along with a significant 22% reduction in major CV events. Gibson et al. (2009) mentioned that a comparative study between different statins, called the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, randomized ACS patients to either atorvastatin 80 mg or pravastatin 40 mg daily and proved the intensive atorvastatin 80 mg regimen to be more superior in reducing LDL-C (mean on-treatment level of 62 mg/dL) than the less intensive pravastatin 40 mg regimen (mean on-treatment level of 95 mg/dL). In a more recent trial conducted by Zhang et al. (2020), atorvastatin ranked 2nd among 7 statins being studied in terms of efficacy of lowering LDL-C and was also associated with a remarkable performance in regulating other blood lipid levels.

Current Status in Malaysia

In Malaysia, there are 72 registered products containing atorvastatin which are available either as a single-ingredient product or combination product with other drugs (National Pharmaceutical Regulatory Agency, 2024). According to a report released by Iyzati et al. (2024), the utilization of atorvastatin has shown significant increase from 2018 to 2022 in Malaysia, currently ranked 6th on the national drug use list. According to them, the contributing factors to this observed trend are probably changes in practice after the introduction of 5th edition Malaysian Clinical Practice Guidelines on Dyslipidemia 2017 and European Society of Cardiology 2019 Lipid Guidelines as well as atorvastatin being made available in primary care setting. The same report also revealed that the overall expenditure of atorvastatin increased by 30.4% from 2018 (RM 97.82 million) to 2022 (RM 126.81 million).

METHODOLOGY

Materials and Instruments

Table 1: Materials & Instruments.

USP Atorvastatin Calcium Reference Standard	**Monobasic potassium phosphate**
One innovator brand Atorvastatin Calcium (20 mg tablet) coded as A	6 N sodium hydroxide
Five generic brand Atorvastatin Calcium (20 mg tablet) randomly coded from B- F	UV-visible spectrophotometer
High-performance Liquid Chromatography (HPLC) system	Sonicate
Acetonitrile (HPLC grade)	Tablet Hardness Tester
Stabilizer-free tetrahydrofuran (THF)	Tablet Friability Tester
0.05 M ammonium citrate buffer pH 4.0	Brush
Water (HPLC grade)	Tablet Disintegration Tester
Anhydrous citric acid	Tablet Dissolution Tester
Ammonium hydroxide	pH meter
Distilled water	Pipettes
0.45 μm syringe filter	Simulated gastric fluid
5 mL syringe	Analytical balance
Volumetric flask	FTIR INSTRUMENT

Organoleptic Evaluation

The atorvastatin calcium film-coated tablets from each brand were visually examined for their physical characteristics such as uniformity of colour, shape, size, presence or absence of physical damage, and any sign of contamination.

Identification Test

High-performance Liquid Chromatography (HPLC)

The term “liquid chromatography” typically covers a wide range of chromatographic systems, all of which employ a liquid mobile phase. Classical liquid chromatography methods have been very successful in the separation of closely related components, but they are very time-consuming, require manual assays and large quantities of solvents. The introduction of HPLC successfully addressed these issues as it offers many advantages like high resolving power, speedy separation, automation of analytical procedure and data handling (Vogel et al., 2000).

In the HPLC method, the sample to be analysed is first dissolved in a suitable solvent and injected in a small volume to a stream of mobile phase. A pump will then be responsible for moving the mobile phase through a column that holds the stationary phase. This is where the separation of analytes takes place as they are retarded by specific chemical or physical interactions with the stationary phase. The separation also depends on the nature of the analyte and the composition of both stationary and mobile phase. Finally, a detector will display a series of peaks known as retention times (the time at which an analyte comes out of the end of the column) where each peak corresponds to a specific analyte in the sample (Malviya et al., 2010). By comparing the peak retention time of the analyte of interest to that of the standard, the authenticity of the API, which in this study is atorvastatin calcium, in the tablet can be determined (AlMuhsin et al., 2022).

Preparation of Required Solutions

Buffer

0.05 M ammonium citrate buffer of pH 4.0 was prepared by dissolving 9.62 g of anhydrous citric acid in 950 mL of HPLC grade water, adjusted with ammonium hydroxide to a pH of 4.0, then diluted with HPLC grade water to 1000 mL (United States Pharmacopoeia - National Formulary, 2024).

Mobile phase

Acetonitrile, stabilizer-free THF, buffer (27:20:53) (United States Pharmacopoeia - National Formulary, 2024).

Solution A

9.62 g of anhydrous citric acid was dissolved in 900 mL of HPLC grade water, adjusted with ammonium hydroxide to a pH of 7.4, then diluted with HPLC grade water to 1000 mL (United States Pharmacopoeia - National Formulary, 2024).

Diluent

Acetonitrile and Solution A (1:1) (United States Pharmacopoeia - National Formulary, 2024).

Standard solution

100 mg of USP atorvastatin calcium reference standard was weighed accurately and transferred to a 100 mL volumetric flask. Enough amount of diluent was added to dissolve the powder, and the volume was made up with the same diluent (sonicate if needed). This produces a solution with concentration of 1 mg/mL. 10 mL of this solution was transferred to another 100 mL volumetric flask and the volume was made up with the same diluent to produce the Standard Solution with concentration of 100 μg/mL (United States Pharmacopoeia - National Formulary, 2024).

Sample stock solution

10 tablets from one brand were selected and weighed, noting down their average weight. The tablets were crushed with mortar and pestle, then a quantity of powder equivalent to 100 mg of atorvastatin calcium was accurately weighed and transferred into a 100 mL volumetric flask. Enough amount of diluent was added to dissolve the powder, and the volume was made up with the diluent (sonicate if needed). This produces the Sample Stock Solution with a nominal concentration of 1 mg/mL. The same procedures were repeated with tablets from other brands to produce their respective Sample Stock Solution (United States Pharmacopoeia - National Formulary, 2024).

Sample solution

10 mL of Sample Stock Solution was pipetted out into a 100 mL volumetric flask to produce the Sample Solution with a nominal concentration of 100 μg/mL. A 0.45 μm syringe filter was used to filter it (United States Pharmacopoeia - National Formulary, 2024).

Chromatographic Conditions

The HPLC system consists of Shimadzu CTO-10ASvp Column Oven, Shimadzu SPD-20A Prominence UV/VIS Detector, Shimadzu SIL-20AC HT Prominence Autosampler, Shimadzu CBM-20A Prominence System Controller, Shimadzu LC-20AD Liquid Chromatograph Pump, and Shimadzu DGU-20A5 Degasser. The Shimadzu LC Solution Software will be used to acquire and process the data.

The chromatographic conditions are as follow:

Stationary phase	:	Thermo C_{18} Column (2.1 mm x 50 mm, 5µm)
Mobile phase	:	Acetonitrile, stabilizer-free THF, 0.05 M ammonium citrate buffer pH 4.0 (27:20:53)
Detection	:	244 nm
Flow rate	:	0.2 mL/min
Sample size	:	20 µL
Column temperature	:	30°C

Content Uniformity Tests

UV-Visible Spectrophotometry

UV-visible spectrophotometry is an analytical technique that utilizes light in the UV and visible region. It works on the basis that electrons existing in a chemical compound can absorb light of these wavelengths and move abruptly from the ground state (a state with negligible amount of energy) to an excited state (a state associated with considerably large amount of energy), a process known as excitation (Nikam et al., 2022). The amount of radiation absorbed will always be equal to the energy difference between the ground state and excited state. A detector measures the intensity of the light after it passes through a sample solution in a transparent cuvette, I and compares it to the original intensity of the light, I_o before being attenuated. The ratio of I / I_o, known as transmittance (T), will be automatically calculated and converted to a dimensionless value called absorbance (A) by the UV-visible spectrophotometer using the formula below.

$$A = -\log T$$

According to Beer-Lambert Law, the concentration of the absorbing species in the solution and the path length of the cuvette is directly proportional to the absorbance of a solution. Hence, the concentration of that species can be determined if the path length is kept constant.

$$A = \varepsilon cl$$

where A = Absorbance

ε = Molar absorptivity (M^{-1} cm^{-1})

c = Concentration of solution (M)

l = Path length of cuvette (cm)

Preparation of Blank Solution for Baseline Correction

The purpose of the blank solution is to allow measurement of the intensity of light in the absence of the sample we intend to measure. It typically consists of the buffer only in which the sample will be dissolved in later. 0.05 M phosphate buffer was prepared by dissolving 6.8 g of monobasic potassium phosphate in 900 mL of distilled water, adjusted with 6 N sodium hydroxide to a pH of 6.8 and then diluted with distilled water to 1 L (United States Pharmacopoeia - National Formulary, 2024). 1 mL of 0.05 M phosphate buffer of pH 6.8 was pipetted out into a 10 mL volumetric flask and the volume was made up with distilled water.

Determination of Maximum Wavelength

100 mg of USP atorvastatin calcium reference standard was weighed and transferred to a 100 mL volumetric flask. Enough amount of 0.05 M phosphate buffer of pH 6.8 was added to dissolve the powder and the volume was made up with the same buffer (sonicate if needed). This produces Solution I with concentration of 1 mg/mL. 10 mL of Solution I was transferred to another 100 mL volumetric flask, and the volume was made up with the same buffer to produce Solution II with a concentration of 100 µg/mL. Then, w10 mL of Solution II was transferred into another 100 mL volumetric flask and the volume was made up with the same buffer to produce Solution III with a concentration of 10 µg/mL. The absorbance of Solution III was measured between wavelengths of 200 to 400 nm using UV-visible spectrophotometer (UV-1800, Shimadzu) to determine the maximum wavelength, λ_{max} at which atorvastatin calcium can be read optimally (Rohmani et al., 2020).

Preparation of Standard Atorvastatin Calcium Calibration Curve

0.2, 0.4, 0.6, 0.8, and 1 mL of Solution II was pipetted out into five 10 mL volumetric flask respectively and the volume was made up with the same buffer to produce five different standard solutions with concentrations in the range of 2 – 10 µg/mL. The absorbance of the respective dilutions was measured at the previously determined λ_{max} using UV-visible spectrophotometer. The resultant calibration curve with absorbance on the y-axis and concentration on the x-axis was used in the assay of drug content and dissolution testing (Windriyati et al., 2024).

Assay of Atorvastatin Calcium Tablets

10 tablets from one brand were selected and weighed, noting down their average weight. The tablets were crushed with mortar and pestle, then a quantity of powder equivalent to 10 mg of atorvastatin calcium was accurately weighed and transferred into a 100 mL volumetric flask. Enough amount of 0.05 M phosphate buffer of pH 6.8 was added to dissolve the powder and the volume was made up with the same buffer (sonicate if needed). The mixture was labelled

as Solution A and 10 mL of it was transferred to another 100 mL volumetric flask and the volume was made up with the same buffer to get Solution B.

4 mL of Solution B was pipetted out into a 10 mL volumetric flask, and the volume was made up with the same buffer to produce the sample solution. A syringe filter (0.45 µm) was used to filter and the absorbance was measured at the previously determined λ_{max} using UV-visible spectrophotometer. The concentration of sample solution was calculated using the equation of the standard atorvastatin calcium calibration curve and the percentage label claim of the tablet was determined using the formula given below. The same procedures were repeated with tablets from other brands to determine their respective percentage label claim. According to USP, the acceptance criteria should be not less than 94.5% and not more than 105.0% of the labelled amount of atorvastatin (United States Pharmacopoeia - National Formulary, 2024).

$$Percentage\ label\ claim\ (\%) = \frac{C \times D \times W_A \times 100\ mL}{W \times L} \times 100\%$$

where C = Concentration of sample solution (mg/mL)
D = Dilution factor
W_A = Average weight of tablet (mg)
W = Weight of powder taken (mg)
L = Label claim of tablet (mg)

Weight Variation Test

This test was carried out using an analytical balance (AS 220/C/2, Radwan) in compliance with USP (United States Pharmacopoeia - National Formulary, 2024). 20 tablets were selected from one brand, weighed individually and their average weight was calculated. The individual tablet weight was compared with the average tablet weight, and the weight variation was determined using the formula below. No more than 2 tablets should fall outside the established limit as shown in Table 2. The test was repeated with tablets from other brands.

$$Weight\ variation\ (\%) = \frac{Individual\ tablet\ weight - Average\ tablet\ weight}{Average\ tablet\ weight} \times 100\%$$

Table 2: Weight Variation Limit as per USP.

Average tablet weight (mg)	Weight variation acceptance limit
< 130	± 10%
130 - 324	± 7.5%
> 324	± 5%

Thickness, Diameter and Hardness Test

These tests were carried out using a Tablet Hardness Tester (DHT-250, Campbell Electronics). 10 tablets from one brand were selected and placed one after the other into the loading compartment of the instrument. The machine was started, and it began initializing with the jaw moving forward and back to its original position. The reading for each property was automatically displayed on the main menu. The thickness and diameter are expressed in terms of millimetre (mm), while the force required to crush the tablets is expressed in terms of Newton (N). The test was repeated with tablets from other brands.

Friability Test

Friability refers to a phenomenon in which the tablet tends to crumble or break when subjected to mechanical shock. The main purpose of this test is to evaluate the tablet's resistance to breakage during handling, packaging, and transportation (AlMuhsin et al., 2022).

The Tablet Friability Tester (EF-2L, Electro lab) was used to perform this test in accordance with USP (United States Pharmacopoeia - National Formulary, 2024). 20 tablets from one brand were selected, making sure they are dust-free, and their total weight was measured. The tablets were placed into the friability tester which was set to run at 25 revolutions per minute (rpm) for 4 minutes. After that, the tablets out were taken out and dedusted. The total weight of the tablets was measured again, and the percentage friability was calculated using the formula given below. The test was repeated with tablets from other brands. The difference in total weight should not be more than 1.0%. If the weight loss is greater than 1.0%, the test is repeated two more times and the mean value of three tests is taken, ensuring that it is not more than 1.0% for the tablets to be accepted.

$$Percentage\ friability\ (\%) = \left(1 - \frac{Total\ weight\ after\ testing}{Total\ weight\ before\ testing}\right) \times 100\%$$

Disintegration Test

In order for an API in the tablet to become completely available for absorption into the bloodstream, the tablet must first disintegrate upon contact with water or gastric fluid and release the drug into the body fluids for dissolution (Ansel & Allen, 2014). However, disintegration does not imply that the tablet or API is fully dissolved but rather it increases the surface area of drug particles to facilitate dissolution within the GI tract.

Tablets (whether coated or uncoated) will usually be subjected to a disintegration test even though it has been replaced by the dissolution test in an obligatory sense (drug stability, principles). The disintegration test was performed prior to the dissolution test because any abnormalities in the disintegration time could impact the dissolution parameters (Ameer, 2023). The disintegration apparatus used is the Tablet Disintegration Tester (ED-2L, Electro lab) which complies with USP (United States Pharmacopoeia - National Formulary, 2024). It consists of a basket-rack assembly with two sets of 6 open-ended transparent tubes held in a vertical position by two plates. A woven stainless-steel wire mesh is attached to the under surface of the lower plate. The assembly is immersed in a vessel containing the dissolution medium and driven by a motor to move up and down at a frequency of 29 – 32 cycles per minute through a distance not less than 53 mm and not more than 57 mm. A thermostat maintains the temperature of the medium at 37 ± 2°C.

From each brand, 6 tablets were selected and placed individually inside the tubes. Small metal disks were used to ensure complete immersion of the tablets. The vessel was filled with 800 mL of simulated gastric fluid, and the test ran for 30 minutes. The time required for complete disintegration of the tablet in each tube was recorded. Complete disintegration is a state in which any residue of the dosage unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core (Carstensen & Rhodes, 2000). At the end of the time limit, the assembly was lifted, and the tablets were observed. The brand passes the test if all 6 tablets completely disintegrate. If 1 or 2 tablets fail to disintegrate completely, test on another 12 additional tablets. Not fewer than 16 of the total 18 tablets must completely disintegrate for the brand to be accepted (United States Pharmacopoeia - National Formulary, 2024).

Dissolution Test

For a drug to be bioavailable, it must dissolve in the fluid at the absorption site and the process at which it does so is termed "dissolution". As the drug particle undergoes dissolution, the surface drug molecules will enter into the surrounding fluid and form a saturated layer of drug solution, known as the diffusion layer, that entraps the solid drug particle within it (Ansel & Allen, 2014). The drug molecules will move from this layer throughout the dissolving fluid, contact with biological membranes and absorption ensues. Subsequently, the diffusion layer is replenished with dissolved surface drug molecules, and the absorption process goes on. The in vitro dissolution profile is an important parameter that must be studied, especially when it comes to poorly soluble drugs like atorvastatin, to assess whether or not they will be sufficiently available in the body system to produce the desired therapeutic response (Ulla, 2018).

This test was performed using Tablet Dissolution Tester (TDT-06T, Electro lab) that has six vessels with 900 mL of 0.05 M phosphate buffer of pH 6.8 as the dissolution medium which was maintained at 37 ± 0.5℃ (Ameer, 2023). The stirring element is the paddle type, and the stirring speed was set to 75 rpm. One tablet from each brand was placed into separate vessel and allowed to sink to the bottom before running the test (United States Pharmacopoeia - National Formulary, 2024). 5 mL of samples were drawn from each vessel using a syringe at time intervals of 5, 10, 15, 30, 45, and 60 minutes, with the duration up to a maximum of 24 hours. The sampling point should be halfway between the top of the dissolution medium and the top of the paddle. The vessel was replaced with equal volume of dissolution medium to maintain sink condition. The sample was filtered using 0.45µm membrane filter, dilute as required, and their absorbance was measured at the previously determined λ_{max} using UV-visible spectrophotometer. The absorbance values were correlated with the previously constructed standard atorvastatin calcium calibration curve at the concentration of drug released at each interval was calculated. The area under curve (AUC) between the graphs of different brands was compared.

RESULTS

Organoleptic Evaluation

Atorvastatin calcium tablets from all brands were evaluated based on their organoleptic characteristics and the results for the evaluation are shown in Table 3 below. Additionally, the packaging and labelling information from the different brands of atorvastatin calcium tablets were noted down as well and tabulated in Table 4. All the physical characteristics are laid down in Tables 2-4. Figure 2 indicates different brands of atorvastatin calcium. Identification tests for different brands of atorvastatin calcium are shown in Figures 3-11, including standard.

Figure 2: Atorvastatin Calcium Tablets from Each Brand.

Table 3: Physical Characteristics of Atorvastatin Calcium Tablets.

Brand code	Uniformity of colour	Uniformity of size	Uniformity of shape	Surface spot or contamination	Breaks or cracks
A	✓	✓	✓	×	×
B	✓	✓	✓	×	×
C	✓	✓	✓	×	×
D	✓	✓	✓	×	×
E	✓	✓	✓	×	×
F	✓	✓	✓	×	×

Table 4: Packaging & Labelling Information of Different Atorvastatin Calcium Brands.

Brand code	Medicine strength (mg/tablet)	Dosage form statement	Batch No.	Storage condition	Manufacturing date	Expiry date
A	✓	✓	✓	✓	10/2023	09/2026
B	✓	✓	✓	✓	10/2024	09/2027
C	✓	✓	✓	✓	10/2024	09/2026
D	✓	✓	✓	✓	01/08/2024	31/01/2027
E	✓	✓	✓	✓	06/2024	05/2027
F	✓	✓	✓	✓	07/2024	04/2026

Table 4: Excipients Information of Different Atorvastatin Calcium Brand.

S. No	Composition	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
1.	Anhydrous sodium carbonate	-	-	√	-	-	√
2.	Calcium carbonate	√	√	-	√	√	√
3.	Calcium acetate	-	-	-	-	-	√
4.	Mannitol	-	-	√	-	-	-
5.	Sodium Lauryl sulfate	-	-	√	-	-	-
6.	Microcrystaline cellulose	√	√	√	√	√	-
7.	Lactose mohydrate	√	√	-	√	-	-
8.	Collidal anhydrous silica	-	-	√	-	-	-
9.	Crosscarmellose sodium	√	√	√	√	√	√
10.	Polysorbate 80	√	√	-	√	√	-
11.	Hydroxypropyle cellulose	√	√	-	-	√	√
12.	Butylated hydroxyanisole	-	-	√		-	-
13.	Polyvinylpyrrolidone K-25	-	-	-	√		-
14.	Magnesium stearate	√	√	√	√	√	√
15.	Hydroxypropyl methylcellulose	√	-	-	√		√
16.	Polyethylene glycol 8000	√	-	-	√		√
17.	Polyethylene glycol 6000	-	-	-	-	√	-
18.	Hypromellose 2910	-	-	-	-	√	-
19.	Titanium dioxide	√	-	-	√	√	√
20.	Talc	√	-	-	√	-	-
21.	Simethicone emulsion	√	-	-	-	-	-
22.	Opadry OYS 58910 white	-	√	-	-	-	-
23.	Sepifilm LP010	-	-	√	-	-	-
24.	Colloidal silicon dioxide	-	-	-	-	-	√

Identification Test

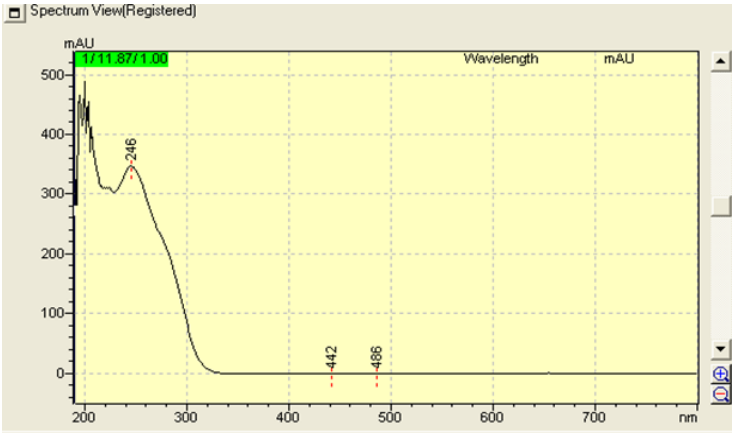


Figure 3: Maximum Wavelength Determination.

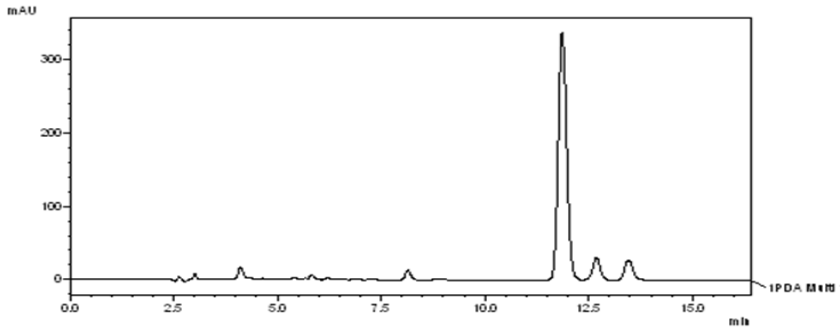


Figure 5: Peak Retention Time of Brand A Atorvastatin Calcium.

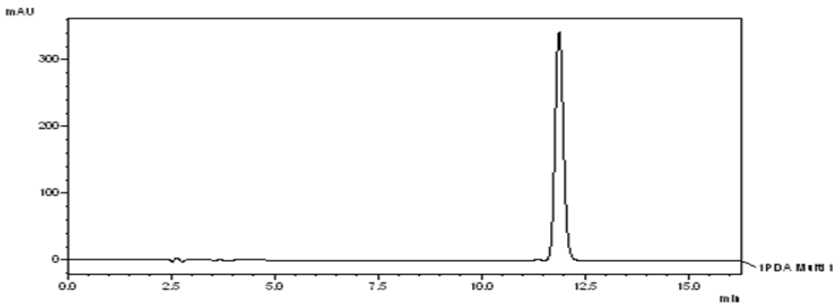


Figure 6: Peak Retention Time of Brand B Atorvastatin Calcium.

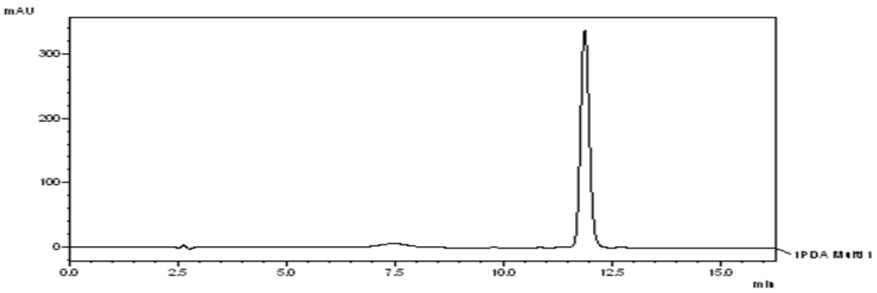


Figure 7: Peak Retention Time of Brand C Atorvastatin Calcium.

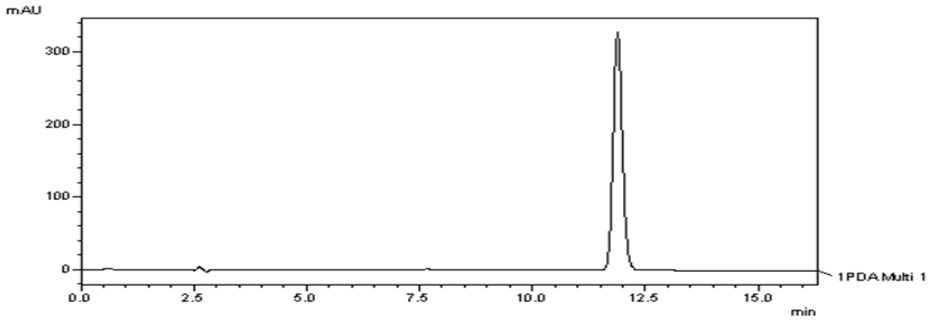


Figure 8: Peak Retention Time of Brand D Atorvastatin Calcium.

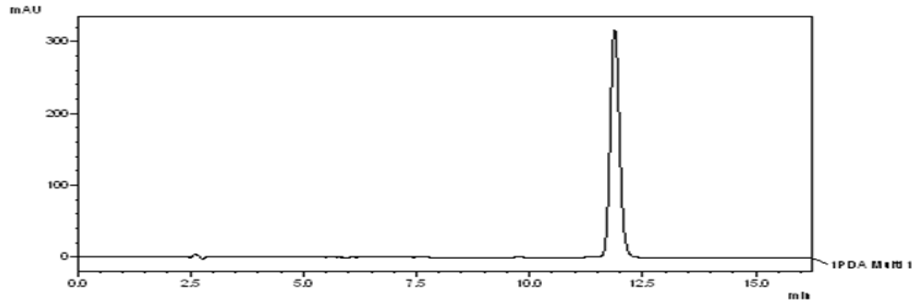


Figure 9: Peak Retention Time of Brand E Atorvastatin Calcium.

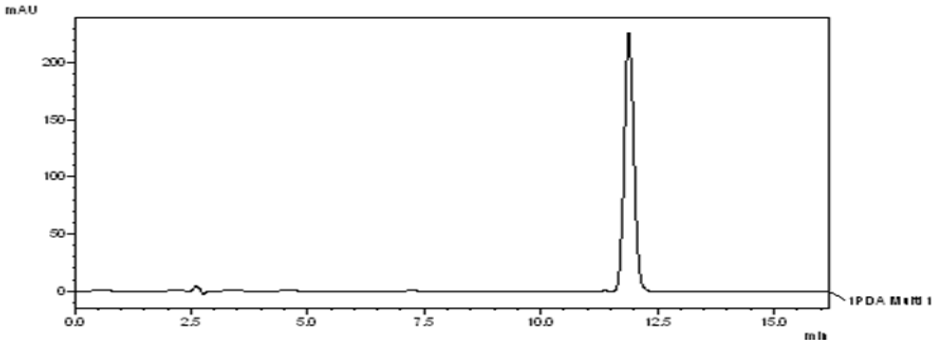


Figure 10: Peak Retention Time of Brand F Atorvastatin Calcium.

Content Uniformity Test

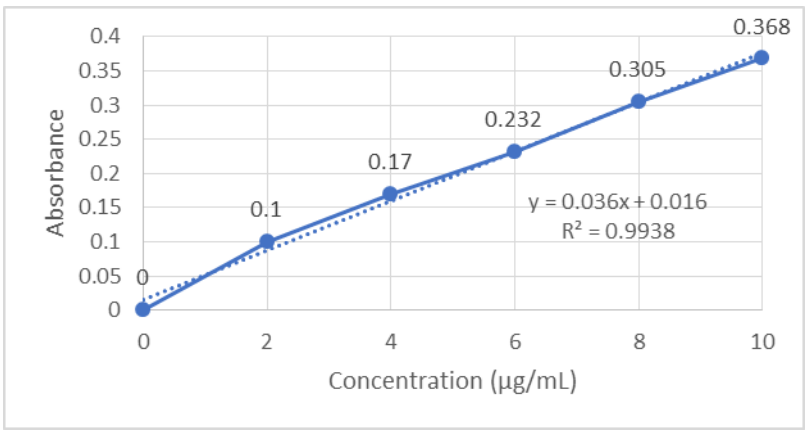


Figure 11: Standard Atorvastatin Calcium Calibration Curve.

Table 5: Assay of Atorvastatin Calcium Tablets for different brands by UV-spectroscopy , N=20

Brand Code	Drug Content (%)
A	98.90
B	95.03
C	96.15
D	97.89
E	100.71
F	96.07

Weight Variation Test

Table 6: Weight Variation in Atorvastatin Calcium Tablets, N=20.

Brand Code	Average Weight (mg) ± Standard Deviation	Average Weight Variation (%)
A	205.93 ± 1.787	0.708
B	305.46 ± 2.704	0.718
C	283.91 ± 3.142	0.968
D	302.08 ± 0.818	0.208
E	256.23 ± 2.700	0.836
F	213.36 ± 2.454	0.923

Thickness, Diameter, and Hardness Test

Table 7: Thickness, Diameter, & Hardness of Atorvastatin Calcium Tablets, N=20.

Brand Code	Average thickness (mm) ± Standard Deviation	Average diameter (mm) ± Standard Deviation	Average hardness (N) ± Standard Deviation
A	4.58 ± 0.019	7.68 ± 0.069	10.92 ± 0.454
B	4.23 ± 0.042	13.32 ± 0.020	13.64 ± 0.951
C	5.18 ± 0.037	13.11 ± 0.019	10.56 ± 1.250
D	5.16 ± 0.011	11.74 ± 0.050	12.43 ± 0.763
E	4.25 ± 0.021	9.66 ± 0.014	10.70 ± 0.672
F	4.34 ± 0.090	12.15 ± 0.021	16.45 ± 1.488

Friability Test

Table 8: Evaluation of Friability in Atorvastatin Calcium Tablets, N=20.

Brand Code	Friability (%)
A	0.24
B	0.16
C	0.00
D	0.00
E	0.19
F	0.00

Disintegration Test

Table 9: Evaluation of Disintegration Time of Atorvastatin Calcium Tablets, N=6.

Brand Code	Disintegration Time (seconds)
A	193
B	210
C	169
D	205
E	175
F	233

Dissolution Test

Table 10: Cumulative Amount of Atorvastatin Calcium Released during Dissolution Test, N=6.

Tim (minutes)	Cumulative Amount of Drug Released (mg)					
	Brand A	Brand B	Brand C	Brand D	Brand E	Brand F
5	16.025±0.004	14.800±0.008	15.575±0.027	15.875±0.002	15.175±0.001	14.425±0.001
10	16.889±0.003	15.557±0.003	15.987±0.001	16.613±0.001	15.984±0.002	14.955±0.001
15	17.757±0.003	16.443±0.001	16.725±0.001	17.105±0.001	16.898±0.003	15.713±0.001
30	18.255±0.013	17.409±0.003	17.617±0.001	17.999±0.002	17.741±0.001	16.724±0.001
45	19.055±0.002	18.479± 0.001	18.338±0.002	18.873±0.001	18.438±0.001	17.791±0.001
60	19.634±0.003	19.205±0.002	18.963±0.001	19.525±0.001	18.863±0.001	18.588±0.001

Table 11: Ranked by Average Release Rate with their rates.

Brand	Drug Released (mg)	Percentage Drug Released	Max rate (mg/min) (0-5 min interval)	Min rate (mg/min)	Average rate (mg/min)
Brand A	19.634	100	3.205	0.033 (15-30 min interval)	**0.613**
Brand D	19.525	99.44	3.175	0.043 (45-60 min interval)	**0.597**
Brand B	19.205	97.82	2.960	0.048 (45-60 min interval)	**0.579**
Brand C	18.963	96.58	*3.115*	0.042 (45-60 min interval)	**0.582**
Brand E	18.863	96.07	3.035	0.028 (45-60 min interval)	**0.585**
Brand F	18.588	94.67	2.885	0.053 (45-60 min interval)	**0.556**

All brands show highest release rates in the first 5 minutes (0-5 min interval). Release rates decrease significantly over time. Later intervals (15-30 min, 30-45 min, 45-60 min) show much slower release rates. Brand A maintains the highest average release rate throughout the process. Brand F has the lowest average release rate. The chart shows this dramatic decrease in release rates over time, with all brands following a similar pattern of rapid initial release followed by much slower sustained release.

Table 12: Relative Error Percentages (at 60 minutes).

Brand	Drug Released (mg)	Error (mg)	Relative Error (%Percent)
Brand A	19.634	0.003	0.02
Brand D	19.525	0.001	0.01
Brand B	19.205	0.002	0.01
Brand C	18.963	0.001	0.01
Brand E	18.863	0.001	0.01
Brand F	18.588	0.001	0.01

All brands have very low relative errors: 0.01-0.02% . Brand A: 0.02% (19.634 ± 0.003 mg) while Brands B-F: 0.01% each so these are extremely small error margins, indicating high measurement precision.

Statistical Significance of Differences

CONFIDENT DIFFERENCES (No overlap in error ranges)

- Brand A vs Brand F: Significant difference (19.634±0.003 vs 18.588±0.001)
- Brand A vs Brand E: Significant difference (19.634±0.003 vs 18.863±0.001)
- Brand D vs Brand F: Significant difference (19.525±0.001 vs 18.588±0.001)

POTENTIAL OVERLAP (Caution needed): Brand A vs Brand D were ranges nearly touch but don't overlap and Brand B vs Brand C were very close but distinguishable while Most adjacent brands show minimal overlap.

High Confidence in Rankings: The extremely small error margins (0.01-0.02%) mean we can be very confident in the performance rankings. Quality Control: All brands show excellent consistency (very low error), suggesting good manufacturing quality. The error analysis confirms that Brand A is definitively the best performer, and the performance differences between brands are statistically significant and not due to measurement uncertainty.

Table 11: Area Under Curve (AUC) of Dissolution Profile.

Brand Code	AUC Value
A	5246.12
B	4992.83
C	5033.02
D	5165.02
E	5044.59
F	4805.79

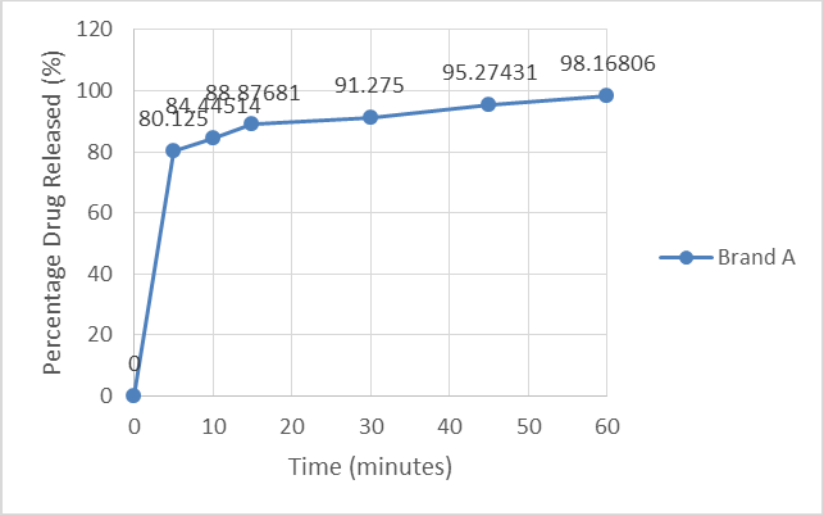


Figure 12: Dissolution Profile of Brand A Atorvastatin Calcium Tablets.

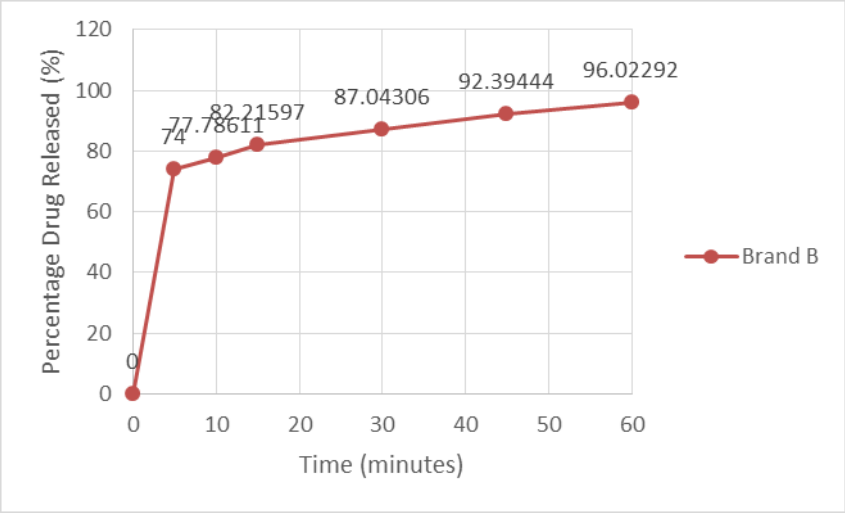


Figure 13: Dissolution Profile of Brand B Atorvastatin Calcium Tablets.

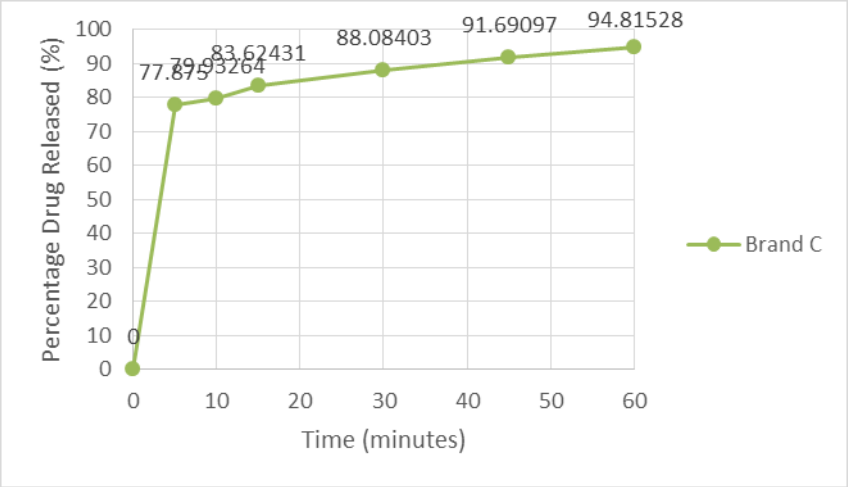


Figure 14: Dissolution Profile of Brand C Atorvastatin Calcium Tablets.

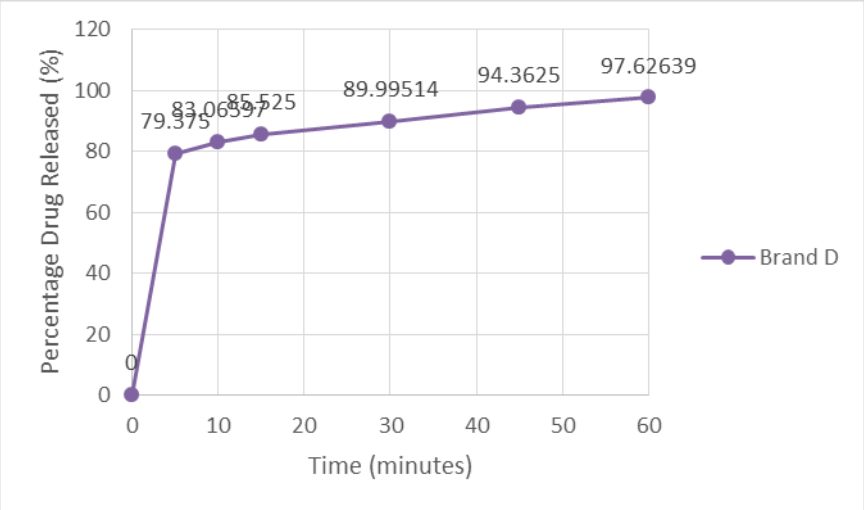


Figure 15: Dissolution Profile of Brand D Atorvastatin Calcium Tablets.

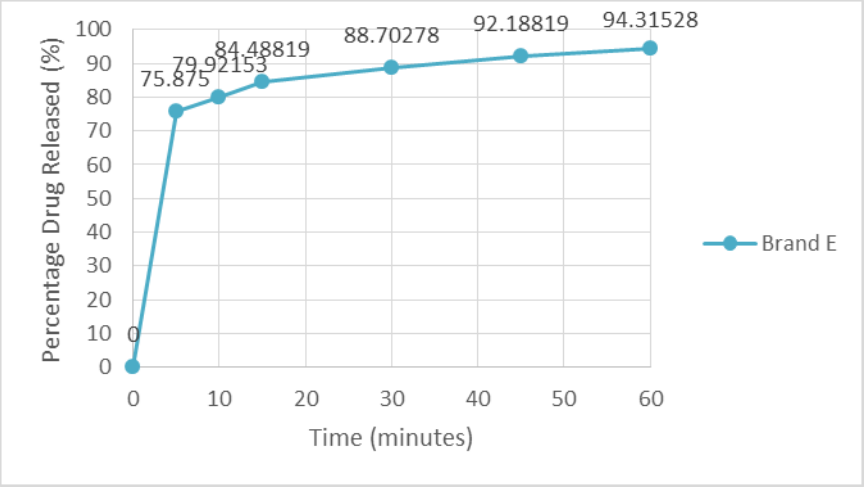


Figure 16: Dissolution Profile of Brand E Atorvastatin Calcium Tablets.

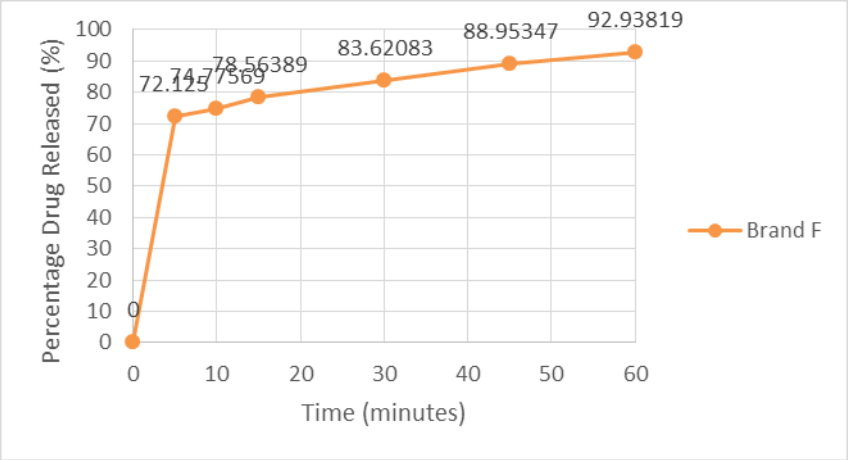


Figure 17: Dissolution Profile of Brand F Atorvastatin Calcium Tablets.

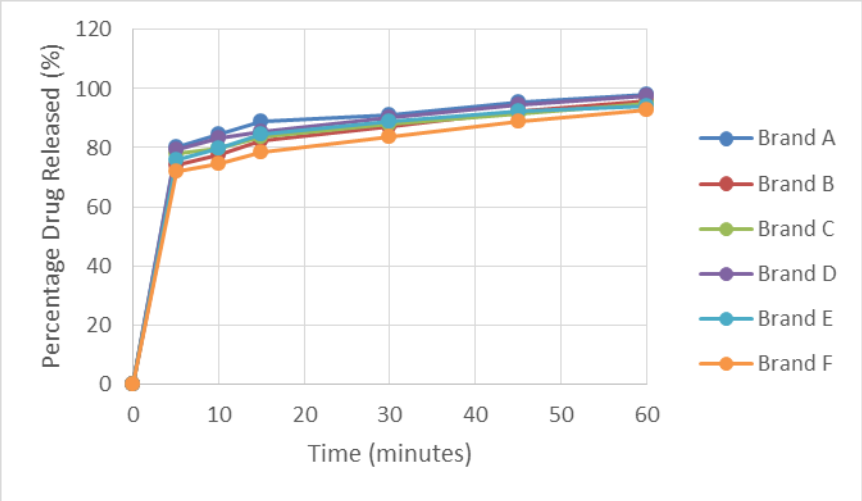


Figure 18: Comparative Dissolution Profile of Different Brands of Atorvastatin Calcium Tablets.

Based on **Figure 18**, Brand A had highest percentage of drug release (98.16%) in 60 minutes while Brand F had lowest percentage of drug release (92.93%) at the same time. Brand B (96.02%), Brand C (94.82%), Brand D (97.63%) and Brand E (94.32%) released the drug at slower rate within the time intervals of 60 minutes.

Fourier Transform Infrared Spectroscopy (FTIR)

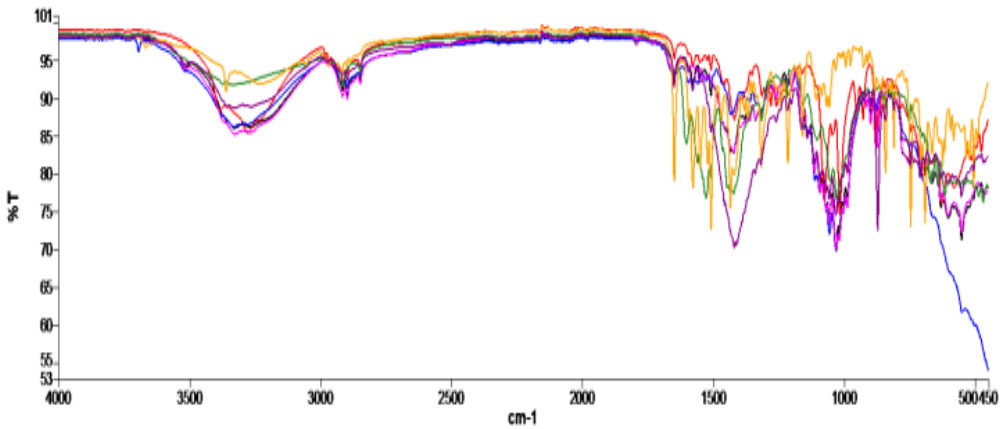


Figure 26: Comparison between FTIR Spectrum of Standard and Sample Atorvastatin Calcium.

DISCUSSION

The marketed atorvastatin calcium tablets were subjected to a series of quality control tests to minimize the chances of obtaining medicines that are unsatisfactory. All the tablets were evaluated based on their physical characteristics and found to be uniform in colour, size, and shape. They were also visually inspected for processing defects like chipping, capping, and mottling, and no physical damage were found. These are all aspects that can affect consumer acceptance and subsequently their adherence to therapy, which makes organoleptic evaluation a complementary part in quality assurance. Atorvastatin calcium was scanned at wavelengths between 200-400 nm and was found to absorb maximally at 246 nm, so HPLC was performed using this detection wavelength. Figure 4 to Figure 10 shows the peak retention time of standard and sample atorvastatin calcium. It can be seen that the peak retention time of the samples were like that of the standard, which is around 12 minutes, supporting the authenticity of atorvastatin calcium contained in the dosage form. The appearance of small peaks is merely due to the presence of excipients in the formulation which happen to absorb at the same wavelength as atorvastatin calcium and is not of concern. According to the findings of the assay of API, Brand E had the highest percentage of API at 100.71% while Brand B had the lowest percentage of API at 95.03%. The variation in percentage content uniformity between different brands can arise from several factors such as non-homogeneity in blending or different composition of tablet powder. All products contain atorvastatin calcium within the USP specification of not less than 94.5% and not more than 105.0% of the labelled claim, indicating that the API is evenly distributed across each individual tablet which is vital for therapeutic consistency. Abnormally low or high amount of API could lead to issues like ineffectiveness or adverse reactions, which is why the products should comply with the compendial requirements.

All the atorvastatin calcium tablets tested successfully passed the weight variation test as they complied with the USP weight variation limit provided in **Table 2** and none fell outside the acceptable range. This suggests that the tablets from all brands are consistent in terms of their amount of ingredients which is crucial for the delivery of accurate dosage. The results for the weight variation test are shown in **Table 6**. Brand A has the smallest average weight of 205.93 mg while Brand B has the largest average weight of 305.46 mg. The relative difference in the mean tablet weights between different brands could be attributed to the manufacturer's formulation such as different granulation methods or amounts of excipients added. The evaluation results for the thickness, diameter, and hardness of the atorvastatin calcium tablets are shown in **Table 7**. All tablets demonstrated consistency in their thickness and diameter. As in the case of weight variation, the variability between brands is most probably due to the differences in their formulation. For the hardness test, it is a measure of the tablets' ability to withstand mechanical shocks during manufacturing, handling, packaging, or transportation. It is observed that the average tablet hardness ranged from 10.56 N to 16.45 N, suggesting that they are strong enough to withstand the stress associated with handling and packaging but not so hard that they're difficult to swallow. Apart from the hardness test, the friability test is another way of predicting the tablet's potential behaviour during handling and packaging as the loss due to abrasion has been proposed to be a more relevant parameter (Hambisa et al., 2019). The percentage friability for each brand is tabulated in Table 8. All the brands investigated gave friability values of less than 1%, which means they passed the USP specification that states that the maximum weight loss should not be more than 1.0%. Based on the USP specifications, the tablets tested should disintegrate completely within the 30 minutes time limit. Of the 6 brands under investigation, all of them met the requirement stated where Brand C has the fastest disintegration time of 169 seconds and Brand F has the longest disintegration time of 233 seconds. It was noted that the disintegration performance of the tablets is inversely proportional to their degree of hardness. In other words, hard tablets take a longer time to disintegrate. Since

disintegration involves fluid penetrating into the tablets, this explains the relationship mentioned above as harder tablets are less porous which makes penetration of fluids more challenging.

The dissolution profile of each brand of atorvastatin calcium tablets is graphically represented from Figure 12 to Figure 17. As per the USP specification, not less than 80% of the labelled amount of atorvastatin should be dissolved within the 30 minutes time frame. In the present study, all 6 brands of atorvastatin calcium tablets analysed passed the specification which means that they released adequate amount of the drug into the systemic circulation for absorption.

Each brand showed different release pattern at different time points. At 5 minutes, it can be observed that Brand F exhibited the slowest dissolution rate, releasing only 72.13% of its drug content and 92.94% at the end of 60 minutes. On the other hand, Brand A demonstrated the fastest and highest drug release performance (80.13%) at the 5^{th} minute and maintained that trend throughout the entire test, with a total of 98.17% of drug being released at the 60^{th} minute. Brand D's performance is consistently second to Brand A across each time point, releasing a final 97.63% of drug at the end of the test. Brands B, C, and E displayed moderate dissolution rate where they released 96.02%, 94.82%, and 94.32% of drug respectively in 60 minutes.

From the AUC values, it can be interpreted that Brand A has the greatest extent of drug dissolution over the 60-minute period while Brand F is the least satisfactory in drug release. Neither generic brand showed AUC values that are like to that of the innovator brand, highlighting that not all brands will demonstrate bioequivalence even though they pass other quality control studies. Moreover the excipients used for the formulation also have a role for the drugs to release in such a smooth way to release the active principal as shown in **Table 4.**

This test was additionally performed to confirm the functional groups present in atorvastatin calcium. FTIR operates on the principle that different functional groups will absorb infrared radiation at different frequencies that correspond to the natural vibrational frequency of their chemical bond, giving rise to a characteristic peak value (Malik et al., 2016).

The broad band absorption near 3400 cm^{-1} confirms the presence of hydroxyl group (– OH) and amine group (– NH). Several absorptions to the right of 3000 cm^{-1} corresponds to aliphatic – CH stretching, indicating the presence of methyl groups in the molecule. Next, a strong absorption around the 1640 cm^{-1} region is due to stretching of the carbonyl group (– C=O) present in amide. Besides that, the presence of aromatic system is verified by absorptions in the 900-690 cm^{-1} region (because of C= CH bending) and in the 1650-1450 cm^{-1} region (because of C=C stretching). Lastly, absorption around the 1200 cm^{-1} region is due to C-F stretching and this confirms the presence of 4-fluorophenyl moiety. When comparing the spectrum of different brands, small differences are observed which is normal and expected due to differences in formulation and excipients used. Other possible reasons include different polymorphic forms of atorvastatin calcium used and moisture content. All formulation can be considered pharmaceutically acceptable as the characteristic peaks remain identifiable. The Malaysian market is flooded with various brands of atorvastatin calcium tablets, be it manufactured locally or imported. This study is aimed at evaluating the bioequivalence of innovator and generic brands of atorvastatin calcium tablets as well as their quality. The investigated brands complied with the quality specifications in terms of authenticity of the API, content uniformity, weight variation, hardness, friability, disintegration, and dissolution. However, there are slight differences in the drug release profile of the generics when compared with the more superior innovator where the generics release drug to a lesser extent. That the being said, the parameters are still within the acceptable range thus making it feasible to switch

to generic atorvastatin calcium as needed. From the results of this study, the post-marketing evaluation of pharmaceutical products is crucial and should be enforced through regulatory mechanisms to improve therapeutic outcomes and public's trust in marketed medications. A multidimensional approach to drug quality evaluation is recommended in future research and other critical areas such as stability or degradation kinetics, pharmacoeconomic, and public health impact shall be explored.

CONCLUSION & FUTURE PERSPECTIVE

The Malaysian market is flooded with various brands of atorvastatin calcium tablets, be it manufactured locally or imported. This study is aimed at evaluating the bioequivalence of innovator and generic brands of atorvastatin calcium tablets as well as their quality. The investigated brands complied with the quality specifications in terms of authenticity of the API, content uniformity, weight variation, hardness, friability, disintegration, and dissolution. However, there are slight differences in the drug release profile of the generics when compared with the more superior innovator where the generics release drug to a lesser extent. That being said, the parameters are still within the acceptable range thus making it feasible to switch to generic atorvastatin calcium as needed. From the results of this study, it is clear that post-marketing evaluation of pharmaceutical products is crucial and should be enforced through regulatory mechanisms to improve therapeutic outcomes and public's trust in marketed medications. A multidimensional approach to drug quality evaluation is recommended in future research and other critical areas such as stability or degradation kinetics, pharmacoeconomic, and public health impact shall be explored.

REFERENCES

1. Akinleye, M. O., Idris, O., Nwachukwu, P. N., & Oyetunde, O. O. (2012). Quality of brands of atorvastatin calcium tablets marketed in Lagos, Nigeria. In *International Journal of Pharmacy and Pharmacology*, 3(10). www.internationalscholarsjournals.org
2. Alkufi, H., Alkanani, A. S., Muhareb, S. H., Alhamidawi, A. K., Shahad, M. A., & Abd, S. H. (2023). Quality Assessment of Brands and Generic in Atorvastatin Tablets Available in Iraq-thi-Qar. *Journal of Medical and Health Studies*, *4*(2). https://doi.org/10.32996/jmhs.2023.4.2.2
3. AlMuhsin, A., Ahad, A., Bin Jardan, Y. A., Raish, M., Ahmad, A., Alkharfy, K. M., & Al-Jenoobi, F. I. (2022). Quality assessment of different brands of atorvastatin tablets available in Riyadh, Saudi Arabia. *BMC Pharmacology and Toxicology*, *23*(1). https://doi.org/10.1186/s40360-022-00598-y
4. Ameer, O. Z. (2023). Release Profile of Branded Atorvastatin Calcium Tablet Relative to Commercially Available Counterpart Generics. *Dissolution Technologies*, *30*(3). https://doi.org/10.14227/DT300323PGC7
5. Ansel, H. C., & Allen, L. V. (2014). *Ansel's Pharmaceutical Dosage Form and Drug Delivery Systems* (10th ed.). Wolters Kluwer Health.
6. Azman, W., & Ahmad, W. (2024). *Annual Report of the Acute Coronary Syndrome (ACS) Registry, 2020-2021*. http://www.acrm.org.my/ncvd
7. Carstensen, J. T., & Rhodes, C. T. (Eds.). (2000). *Drug Stability, Revised, and Expanded: Principles and Practices* (3rd ed.). CRC Press.
8. Davies, J. T., Delfino, S. F., Feinberg, C. E., Johnson, M. F., Nappi, V. L., Olinger, J. T., Schwab, A. P., & Swanson, H. I. (2016). Current and emerging uses of statins in clinical therapeutics: A review. *Lipid Insights*, *9*(1). https://doi.org/10.4137/LPI.S37450
9. Fong, A., Wan Ahmad, W. A., Rosman, A., Mustapha, F., Hussein, Z., Taher, S. W., Shafie, A. A., Khicha, N., Tan, H. H., & Kim, P. (2023). *Heart Matters: The Rising Burden of Cardiovascular Disease in Malaysia and Potential*

Touchpoints for Interventions.

10. Gibson, C. M., Pride, Y. B., Hochberg, C. P., Sloan, S., Sabatine, M. S., & Cannon, C. P. (2009). Effect of Intensive Statin Therapy on Clinical Outcomes Among Patients Undergoing Percutaneous Coronary Intervention for Acute Coronary Syndrome. *Journal of the American College of Cardiology*, *54*(24). https://doi.org/10.1016/j.jacc.2009.09.010
11. Hambisa, S., Belew, S., & Suleman, S. (2019). In vitro comparative quality assessment of different brands of norfloxacin tablets available in Jimma, SouthWest Ethiopia. *Drug Design, Development and Therapy*, *13*. https://doi.org/10.2147/DDDT.S189524
12. Institute for Public Health Ministry of Health Malaysia. (2024). *National Health and Morbidity Survey (NHMS) 2023:Non-communicable Diseases and Healthcare Demand - Key Findings.*
13. Iyzati, A., Shanizza, A., Fakri, A., Aziz, A., Ashari, F., & Su'aidah Nasarudin, S. N. (2024). *Malaysian Statistics on Medicines 2018-2022 A publication of the Pharmaceutical Services Programme Ministry of Health Malaysia*. www.pharmacy.gov.my
14. Jung, E., Kong, S. Y., Ro, Y. S., Ryu, H. H., & Shin, S. Do. (2022). Serum Cholesterol Levels and Risk of Cardiovascular Death: A Systematic Review and a Dose-Response Meta-Analysis of Prospective Cohort Studies. In *International Journal of Environmental Research and Public Health*, 19(14). https://doi.org/10.3390/ijerph19148272
15. Liao, J. K., & Laufs, U. (2005). Pleiotropic effects of statins. In *Annual Review of Pharmacology and Toxicology*, 45. https://doi.org/10.1146/annurev.pharmtox.45.120403.095748
16. Lingwood, D., & Simons, K. (2010). Lipid rafts as a membrane-organizing principle. In *Science*, 327(5961). https://doi.org/10.1126/science.1174621
17. Malik, A. K., Kumar, R., & Heena. (2016). Spectroscopy: Types. *Encyclopedia of Food and Health*, 64–72. https://doi.org/10.1016/B978-0-12-384947-2.00643-7
18. Malviya, R., Bansal, V., Pal, O. P., & Sharma, P. K. (2010). High performance liquid chromatography: A short review. In *Journal of Global Pharma Technology*, 2(5).
19. Mehta, J. L. (2004). *Statins: Understanding Clinical Use* (1st ed.). Saunders.
20. National Pharmaceutical Regulatory Agency. (2024). *QUEST3+ Product Search*.
21. Nikam, S., Suryawanshi, K., Shinde, N., Suryawanshi, V., & professor, A. (2022). *A brief review on principle, instrumentation and analytical parameter of uv spectroscopy*. www.ijnrd.org
22. Popy, F. A., Dewan, I., Parvin, M. N., & Ashraful Islam, S. M. (2012). Evaluation of in vitro equivalence for tablets containing the poorly water-soluble compound atorvastatin. *Dissolution Technologies*, *19*(4). https://doi.org/10.14227/DT190412P30
23. Punithavathi, N., Ong, L. M., L Lena, Y. L., & Leekha on behalf of the Storvas Clinical Trial Study Group, S. (n.d.). *A Multicenter Study in Malaysia to Determine the Efficacy and Safety of a Generic Atorvastatin*.
24. Rohmani, S., Yugatama, A., Suryadi, B. B., Lady, F., Ainurofiq, A., & Prihapsara, F. (2020). *Evaluation of compared dissolution profile of Atorvastatin tablets in markets*. www.japer.in
25. Schonewille, M., De Boer, J. F., Mele, L., Wolters, H., Bloks, V. W., Wolters, J. C., Kuivenhoven, J. A., Tietge, U. J. F., Brufau, G., & Groen, A. K. (2016). Statins increase hepatic cholesterol synthesis and stimulate fecal cholesterol elimination in mice. *Journal of Lipid Research*, *57*(8). https://doi.org/10.1194/jlr.M067488
26. Shi, Q., Chen, J., Zou, X., & Tang, X. (2022). Intracellular Cholesterol Synthesis and Transport. In *Frontiers in Cell and Developmental Biology* (Vol. 10). https://doi.org/10.3389/fcell.2022.819281
27. Tariq, M. H., Khan, I., Ahmad, B., Raheem, A., & Yasmeen, M. (2014). Evaluation of In-vitro Bioequivalence of Commonly Prescribed Generics of Poorly Water Soluble Drug-Atorvastatin Calcium in Pakistan. *Journal of Pharmacy Research*, *8*(3).

28. Topol, E. J., Califf, R. M., Prystowsky, E. N., Thomas, J. D., & Thompson, P. D. (Eds.). (2007). *Textbook Of Cardiovascular Medicine* (3rd ed.). Lippincott Williams & Wikkins.
29. Ulla, M. R. (2018). Comparative assessment of different marketed brands of atorvastatin tablets in Asir region, Saudi Arabia. *MOJ Drug Design Development & Therapy*, *2*(1). https://doi.org/10.15406/mojddt.2018.02.00023
30. United States Pharmacopoeia - National Formulary. (2024a). *⟨1216⟩ Tablet Friability*. https://doi.org/10.31003/USPNF_M99935_02_01
31. United States Pharmacopoeia - National Formulary. (2024b). *⟨701⟩ Disintegration*. https://doi.org/10.31003/USPNF_M99460_03_01
32. United States Pharmacopoeia - National Formulary. (2024c). *⟨711⟩ Dissolution*. https://doi.org/10.31003/USPNF_M99470_03_01
33. United States Pharmacopoeia - National Formulary. (2024d). *⟨905⟩ Uniformity of Dosage Units*. https://doi.org/10.31003/USPNF_M99694_03_01
34. United States Pharmacopoeia - National Formulary. (2024e). *Atorvastatin Calcium Tablets*. https://doi.org/10.31003/USPNF_M6340_10_01
35. Van Meer, G., Voelker, D. R., & Feigenson, G. W. (2008). Membrane lipids: Where they are and how they behave. In *Nature Reviews Molecular Cell Biology* (Vol. 9, Issue 2). https://doi.org/10.1038/nrm2330
36. Vogel, A. I., Mendham, J., Denny, R. C., Barnes, J. D., & Thomas, M. J. K. (2000). *Vogel's Textbook of Quantitative Chemical Analysis* (6th ed.). Prentice Hall.
37. Wan Ahmad, W. A., Rosman, A., Bavanandan, S., Mohamed, M., Abdul Kader, M. A. S., Muthusamy, T. S., Lam, K. H., Kasim, S. S., Hoo, F. K., Fegade, M., Looi, Z. L., & Abdul Rahman, A. R. (2023). Current Insights on Dyslipidaemia Management for Prevention of Atherosclerotic Cardiovascular Disease: A Malaysian Perspective. In *Malaysian Journal of Medical Sciences*, 30(1): 67–81. Penerbit Universiti Sains Malaysia. https://doi.org/10.21315/mjms2023.30.1.6
38. Waters, D. D. (2009). Clinical Insights From the Treating to New Targets Trial. *Progress in Cardiovascular Diseases*, *51*(6). https://doi.org/10.1016/j.pcad.2009.01.001
39. Windriyati, Y. N., Arifin, I., Lailatunnafiah, & Farikhah, A. (2024). Comparative Dissolution Study of Atorvastatin Calcium Tablets in Indonesia. *Dissolution Technologies*, *31*(1): 17–22. https://doi.org/10.14227/DT310124PGC17
40. World Heart Federation. (2023). *World Heart Report 2023: Confronting The World's Number One Killer*.
41. Ye, Y. C., Zhao, X. L., & Zhang, S. Y. (2015). Use of atorvastatin in lipid disorders and cardiovascular disease in chinese patients. In *Chinese Medical Journal*, 128(2). https://doi.org/10.4103/0366-6999.149226
42. Yu Cai Lim, M., & Kiat Ho, H. (2024). Pharmacological modulation of cholesterol 7α-hydroxylase (CYP7A1) as a therapeutic strategy for hypercholesterolemia. In *Biochemical Pharmacology*, 220. https://doi.org/10.1016/j.bcp.2023.115985
43. Zhang, X., Xing, L., Jia, X., Pang, X., Xiang, Q., Zhao, X., Ma, L., Liu, Z., Hu, K., Wang, Z., & Cui, Y. (2020). Comparative Lipid-Lowering/Increasing Efficacy of 7 Statins in Patients with Dyslipidemia, Cardiovascular Diseases, or Diabetes Mellitus: Systematic Review and Network Meta-Analyses of 50 Randomized Controlled Trials. In *Cardiovascular Therapeutics*, 2020. https://doi.org/10.1155/2020/3987065