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Qualitative Evaluation of Marketed Cardiovascular Drug Atorvastatin

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Abstract
Atorvastatin (INN) marketed as a calcium salt under the trade name **Lipitor** is a member of the drug class statins, used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body. Ten different brands of selected company were evaluated for their *in-vivo* properties. For evaluated *in-vivo* properties are included assay, hardness, thickness, friability, weight variation, content uniformity, disintegration and dissolution. This assay was done with ten Pharmaceuticals and their brands are Drug International Ltd., OPSONIN Pharma Limited, SQUARE, General Pharma Ltd., Beximco Pharma Ltd., Pacific pharma Ltd., Aventis Pharmaceutical Ltd., SK+F, Orient, Unimed & Unihealth Ltd., and Divastin, Avas, Anzitor, Lipitin, Atova, Lipigent, Orva, Lipicon, Lipex, Stacor respectively. These ten brands were evaluated separately even no significant statistical variation observed. The assay analysis of ten brands of these company was tested and results within by thickness (4.7 – 3.0) mm, diameter (11.6 – 6.4) mm, hardness (3.17 - 0.90) kg, disintegration time (0.17 – 2.91) min, Dissolution time (25 – 5) min, UV method (99.0 – 83) % and HPLC method (98.7 – 95.2) %. From this comparative study of 10 mg Atorvastatin tablet of these ten pharmaceutical companies meet *in vivo* test parameters. All results are within in the range. So, we conclude that the quality of 10 mg Atorvastatin tablet of these ten pharmaceutical companies were well evaluated.

Keywords: Atorvastatin tablets, Thickness, Diameter

1. Introduction
A drug is any chemical substance which changes a physiological function and modifies a disease process. Medicine is the art and science of healing. It encompasses a range of health care practices evolved to maintain and restore health by the prevention and treatment of illness. A medicinal product must satisfy certain standard to claim it to be a quality drug. The main criteria for quality of any drug in dosage form are its- Safety, Potency, Efficacy, Stability, Acceptability, and Regulatory Compliance. Quality assurance demands a degree of detail in order to be fully implemented at every step. According to WHO, any substance or product that is used or intended to be used to modify or explore physiological system or pathological states for the benefit of the recipient is called drug. We need to analyse that the established drugs are available in market meet their required quality and parameters that already measured.

Atorvastatin (INN) marketed as a calcium salt under the trade name **Lipitor** is a member of the drug class statins, used for lowering blood cholesterol. It was first synthesized in 1985 It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. The primary use of atorvastatin is for the treatment of dyslipidemia and the prevention of cardiovascular disease. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body. It is called is a competitive inhibitor of HMG-CoA reductase. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases *de novo* cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by the hepatocytes, decreasing the amount of LDL-cholesterol in the blood. Like other statins, atorvastatin also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol. The circulatory system is an organ system that passes nutrients (such as amino acids, electrolytes and lymph), gases, hormones, blood cells, etc. to and from cells in the body to help fight diseases, stabilize body temperature and pH, and to maintain homeostasis. This system may be seen strictly as a blood distribution network, but some consider the circulatory system as composed of

the cardiovascular system, which distributes blood, and the **lymphatic system**, which distributes lymph. While humans, as well as other vertebrates, have a closed cardiovascular system (meaning that the blood never leaves the network of arteries, veins and capillaries),

The main components of the human cardiovascular system are the heart, blood, and blood vessels. It includes: the pulmonary circulation, a "loop" through the lungs where blood is oxygenated; and the systemic circulation, a "loop" through the rest of the body to provide oxygenated blood. An average adult contains five to six quarts (roughly 4.7 to 5.7 liters) of blood, which consists of plasma, red blood cells, white blood cells, and platelets. Also, the digestive system works with the circulatory system to provide the nutrients the system needs to keep the heart pumping. Cardiovascular disease or heart diseases are a class of diseases that involve the heart or blood vessels (arteries and veins). While the term technically refers to any disease that affects the cardiovascular system, it is usually used to refer to those related to atherosclerosis (arterial disease). These conditions usually have similar causes, mechanisms, and treatments. There are various types of cardiovascular diseases like atherosclerosis, ischaemic heart disease**,** heart failure, hypertensive heart disease and inflammatory heart disease.

This research study was undertaken to compare the efficacy and tolerability of policosanol with atorvastatin in older patients with type II hypercholesterolaemia. Hypercholesterolaemia is a risk factor for coronary heart disease (CHD). Clinical studies have shown that lowering elevated serum total cholesterol (TC) levels, and particularly low-density lipoprotein-cholesterol (LDL-C) levels, reduces the frequency of coronary morbidity and deaths, whereas high serum levels of high-density lipoprotein-cholesterol (HDL-C) protect against CHD. Policosanol is a cholesterol-lowering drug purified from sugar cane wax with a therapeutic dosage range from 5-20 mg/day. Atorvastatin is an HMG-CoA reductase inhibitor which across its dosage range (10-80 mg/day) has shown significantly greater lipid-lowering effects than all previously marketed statins. ref [1]

A simple, accurate, rapid and precise isocratic reversed-phase high-performance liquid chromatographic method has been developed and validated for simultaneous determination of aspirin, atorvastatin calcium and clopidogrel bisulphate in capsules. The chromatographic separation was carried out on an Inertsil ODS analytical column (150×4.6 mm; 5 µm) with a mixture of acetonitrile: phosphate buffer pH 3.0 adjusted with *o*-phosphoric acid (50:50, v/v) as mobile phase; at a flow rate of 1.2 ml/min. UV detection was performed at 235 nm. The retention times were 1.89, 6.6 and 19.8 min. for aspirin, atorvastatin calcium and clopidogrel bisulphate, respectively. Calibration plots were linear (r^2>0.998) over the concentration range 5-30 µg/ml for atorvastatin calcium and 30-105 µg/ml for aspirin and clopidogrel bisulphate. The method was validated for accuracy, precision, specificity, linearity, and sensitivity. The proposed method was successfully used for quantitative analysis of capsules. No interference from any component of pharmaceutical dosage form was observed. Validation studies revealed that method is specific, rapid, reliable, and reproducible. The high recovery and low relative standard deviation confirm the suitability of the method for routine determination of aspirin, atorvastatin calcium and clopidogrel bisulphate in bulk drug and capsule dosage form.

The previous research was done on the Effects of atorvastatin, an HMG-CoA reductase inhibitor, on hepatic oxidative metabolism of antipyrine and the result was found that Atorvastatin did not significantly alter the fraction of clearance of antipyrine in plasma that occurred by urinary excretion of 4-hydroxyantipyrine and norantipyrine. These results indicate that the recommended highest daily dose of atorvastatin has negligible effects on antipyrine pharmacokinetics and on oxidative pathways responsible for the metabolism of antipyrine [1].

Another research was done that Naturoceutical Agents in the Management of Cardiovascular Disease. In this research a regulatory paradox exists since naturoceuticals are classified as dietary supplements although many possess measurable pharmacologic activity. In reference to cardiovascular disorders, consumers use naturoceuticals for three distinctly recognizable purposes. These are the primary and secondary prevention of cardiovascular diseases and the treatment of diagnosed disorders such as heart failure, angina pectoris or arrhythmia.

Evidence of significant harm (including fatalities) has been observed when certain herbal products are used in excess or in combination with, other herbs or prescription drugs. The safety of use at the extremes of age, or by persons with cardiac, renal or hepatic impairment is also a concern. Healthcare professionals should routinely document patient naturoceutical use, be alert for and report suspected adverse effects [2].

This research done on pharmaceutical issues in the development of a polypill for the treatment of cardiovascular diseases. In that context, a polypill containing combination of a statin, blood pressure lowering agents (among thiazides, beta blockers and angiotensin-converting enzyme inhibitors), aspirin and folic acid has been shown to reduce incidence of CVDs by more than 80% [3].

The study on Targeted versus global approaches to the management of hypercholesterolemia

suggests that universal therapy with phytosterols and/or wider availability of statins has the potential to dramatically decrease rates of CHD [4].

2. Materials and methods

Thickness and Diameter

The thickness of tablets can vary without any change in its weight. This is generally due to the difference of density of granules, pressure applied for compression and the speed of compression. The thickness of a tablet can be determined with the help of slide calipers.

The diameter size and shape of tablets depends on the die and punches selected for making the tablets. The tablets of various sizes and shapes are prepared but generally they are circular with either flat or biconvex faces.

Weight Variation Test

The total weight of a tablet is determined by the depth of the die cavity, bulk density of granules or powder and uniformly of particulate flow. Even with a proper granulation having uniform flow, a volume fill is not as accurate as a fill based on weight. Therefore, tablet weight variation must fall within certain specification established by the USP. All the tablet of a particular batch should be uniform in weight. But it is quite impossible to make tablet of same weight

accurately. So, weight variation is a general thing but variation should follow a certain limit. The test is considered connect if not more than 2 tablets outside the range.

Procedure

At first 10 tablets are taken randomly the individual weight of the tablet was taken and also average weight of the tablet taken. The weight of the individual tablets are then compared with the average weight calculated and see that not more than 2 tablets fall outside the range.

Limit:

The limit depends on average weight of the tablets and in terms BP and USP specification as follows.

USP specification	Mass % deviation	BP specification
Average weight tablet(mg)		Average weight tablet(mg)
130 or less	±10%	80 or less
130-324	±7%	80-250
324 or high	±5%	250 or high

Hardness Test

Hardness test is very important for a good quality of a finish tablet. Because if the finish tablet is too hard, it may not disintegrate in the required period of time and if the finished tablet is too soft, it may not with stand the handling during packing and transporting. The hardness of the tablet depends on the-

- Weight of material.
- Space between the upper and lower punches at the time of compression.
- In appropriate pressure applied on the upper punches.
- Excessive proportion of fatty lubricants such as Magnesium stearate.

Tablet Friability

Tablet requires a certain amount of strength and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. In addition, tablets should be able to withstand reasonable abuse when in the hands of the consumer. Friability test is performed to evaluate the ability of the tablets to withstand abrasion in packaging, handling and transporting. Adequate tablet friability is necessary requisites for consumer acceptance.

A number of tablets are weighed and placed in tumbling chamber which is rotated for minutes or for 100 revolutions. During each revolution the tablet falls from a distance of six inches to undergo shock. After 100 revolution tablets are again weighed and the loose in weight indicates the friability.

Disintegration Test

The disintegration test is performed to find out that within how much time the tablet disintegrates. This test is very important and necessary for all the tablets coated or uncoated to be swallowed because the dissolution rate depends upon the time of disintegration which ultimately affects the rate of absorption of drugs. The apparatus used for this test is known as disintegration test apparatus. This apparatus consists of a glass or plastic tube which is open at one end and the other end is fitted with a rust proof No. 10 mesh sieve.

The tube is suspended in a bath of water or suitable liquid which is thermostatically maintained at a temperature of 37^0C. The tube is allowed to move up and down at a constant rate i.e., 30 times per minute through a distance of 75 mm. The volume of the liquid and distance of movement is adjusted in such a way that at the highest point the mesh screen just breaks the surface of the liquid to give a turbulent movement to the tablets and at the liquid to give a turbulent movement to the tablets and at the lowest point the mesh screen remains about 2.5 cm. above the bottom of the container. About six tablets are placed in the tube along with a plastic disk oven the tablets unless otherwise stated in the monograph. The plastic disk does not allow the tablets to float and imparts a slight pressure on the tablets. The tube is allowed to move up and down and disintegration time noted when all the tablets have passed through the sieve. This time should comply with the time stated in the monograph for the tablet. The test fails if all the tablets do not pass through the sieve within specified time.

Dissolution Test

The rate of dissolution of a solid drug plays an important role in the absorption and physiological availability of the drug in the blood stream. Therefore, determination of dissolution rate of any solid drug is very necessary. For this purpose, there are a number of tests available in the literature but none is official. The test is performed for tablets and capsules when stated in the individual drug monograph. The apparatus for dissolution test consists of a cylindrical stainless-steel basket which is attached to the end of the stirred shaft. A 1000ml vessel made of glass or other inert, transparent material fitted with a cover. A variable speed motor driven stirrer which can rotate at a speed of 25-150 revolutions per minute. A suitable thermostatically controlled water bath to maintain the temperature of the dissolution medium at a temperature of 37°c ± 0.5°c.

Prepared Phosphate buffer (pH- 5.8) by dissolving 1.19 g of Disodium hydrogen orthophosphate anhydrous (Na_2HPO_4) and 8.25 g of Potassium dihydrogen phosphate (KH_2PO_4) in sufficient water to produce 1000 ml.

For performing the test 900ml of dissolution medium (phosphate buffer pH of 5.8) is filled in the glass vessel which is submerged in the water bath maintain at 37°c. The tablet to be tested is introduced in the basket and fitted in position. The motor is started with 75 revolutions per minute. The samples are withdrawn at 5 min. intervals and replaced immediately through a phosphate buffer medium at a pH of 5.8. 10ml sample solution is withdrawn each time which is replaced with 10 ml of medium at 37°c in order to maintain a constant volume in the vessel. The samples are collected and measured the absorbance at 243 nm wavelength.

In assay method for Atorvastatin (Atorvastatin 10 mg as calcium INN Tablet) during Ultraviolet chromatography (UV) standard prepared by taking 25 mg Atorvastatin reference Standard in 100 ml V.F and dilute to the mark with methanol. Pipette out 5 ml of this solution into another 100 ml V.F and dilute to the mark with methanol. See the absorbance at 245 nm (in 1 cm cell)

Sample preparation by weighing out 288 mg powdered granules of Atorvastatin 100ml V.F. and dilute to the mark with Methanol. Pipette out 5 ml of this solution into another 100 ml V.F and dilute to the mark with methanol. Shake the solution and filtered. See the absorbance at 245 nm the blank solution prepared with methanol.

In Analytical method for Atorvastatin (Atorvastatin 10 mg as calcium INN Tablet) during High performance liquid chromatography (HPLC) prepared standard solution & sample solution are injected consequently into a suitable chromatographic column, together with the solvent system, to separate Atorvastatin formulation adjuvant and degradation products. The content of Atorvastatin present in sample is calculated by comparing both the peak area of active Atorvastatin present in standard preparation and sample preparation.

Reagent required: 1) Acetic Acid
2) Acetonitrile
3) Ammonium Acetate

Preparation of buffer: Take 1.54 gm of Ammonium Acetate in 1000 ml purified water, mix well.
Adjust pH to 4.0±0.1 with Acetic Acid. Filter with 0.2µ Membrance filters and sonicate for 5 minutes.

Organic Phase: Acetonitrile Filter with 0.2µ membrance filters and sonicate for 5 minutes.

Mobile Phase: Buffer: Organic phase = 55:45

Diluting solution: Water: Acetonitrile = 60: 40

Standard Prepared by accurately weight about 20 mg of Atorvastatin Calcium into 50ml volumetric flask. Add about 30 ml of diluting solution & sonicate for 5 minutes. Dilute to volume with the same (solution A). Dilute 5 ml of this solution to 50 ml with mobile phase (solution B).
Sample Prepared by weighing and powder 20 tablets. Transfer powdered samples equivalent to 10 mg Atorvastatin calcium (equivalent to 1 tablet weight) into a 50 ml volumetric flask. Add about 30 ml of diluting solution. Shake 250 rpm for 10 minutes by shaker. Sonicate for 5minutes. Make volume with diluting solution. Filter the preparation by Whatman 1 filter paper. Dilute 5 ml of this solution to 25 ml with mobile phase. Filter the resultant solution through 0.22µ - disk filter (solution C).

Chromatographic System:

Apparatus: Shimadzu HPLC-LC solution integrated with SPD10A VP spectrophometic UV Detector.

Column: Neucleosil 100-5 C18, 250 x 4.6 mm, 5µ or equivalent

Temperature: 30ºC

Flow rate: 1.5 ML/ MINUTE (buffer phase 0.825 ml/min, organic phase 0.675 ml/min)

UV detection wavelength: 235 nm

Retention Time: 11.0 minutes (approx.)

Load / inject Volume: 20µl by valve injection.
Place vial containing standard preparation B and sample preparation C into the tray of the auto sample of Shimadzu HPLC. Run the instrument and record the chromatogram. Calculate the quantity of Atorvastain in the sample using the following equation.

3. Result and discussion

In this study the following results are obtained that the average thickness of the tablets - 3.2mm & average diameter of the tablets - 6.4mm. In the term of USP Average weight tablet (mg) 130-324 and in the term of BP Average weight tablet (mg) 80-250 mass % deviation is ±7%. My result is 1.2% and -1.92%. So, it is within the limit. Hardness of 4kg is considered suitable for handling the tablets. Hardness of 6kg or more will produce tablets of highly compact nature. My result is 3.0kg, so it is suitable for handling the tablets. In terms of BP Specification, the uncoated tablets disintegration time as low as (2-5) min. For buccal it is 4 hr. and for coated tablet disintegration time is 1 hour. My result is 1.7min, so it is within limit. Since Atorvastatin is an INN drug, it is not found in BP. My result is 9.84mg which is active in 10mg tablet. In the terms of INN drug, the Atorvastatin limit is (94.53-101.23%). My result is 95.2%. So, it is within limit.

4. Discussion

Atorvastatin (INN) marketed as a calcium salt under the trade name **Lipitor** is a member of the drug class statins, used for lowering blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammatory and other mechanisms. Like all statins, atorvastatin works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue that plays a key role in production of cholesterol in the body. Atorvastatin is highly protein bound (≥98%).
The primary proposed mechanism of atorvastatin metabolism is through cytochrome P450 3A4 hydroxylation to form active ortho- and parahydroxylated metabolites, as well as variousbeta-oxidation metabolites. The ortho- and parahydroxylated metabolites are responsible for 70% of systemic HMG-CoA reductase activity. The ortho-hydroxy metabolite undergoes further metabolism via glucuronidation. As a substrate for the CYP3A4 isozyme, it has shown susceptibility to inhibitors and inducers of CYP3A4 to produce increased or decreased plasma concentrations, respectively. This interaction was tested *in vitro* with concurrent administration of erythromycin, a known CYP3A4 isozyme inhibitor, which resulted in increased plasma concentrations of atorvastatin. Atorvastatin is also an inhibitor of cytochrome 3A4.
The primary uses of atorvastatin is for the treatment of dyslipidemia and the prevention of cardiovascular disease. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels
Secondary prevention in people with coronary heart disease and multiple risk factors for myocardial infarction, stroke, unstable angina, and revascularization
Myocardial infarction and stroke prophylaxis in patients with type II diabetes.
In the term of INN we know Atorvastatin maintain all the rules. We see all test result in Atorvastatin is very good. Its assay result is also very good. So, Atorvastatin manufacturing unit supply the medicine around the country is acceptable.

Table 1: Ten Pharmaceutical Companies name, Brand name, D.A.R no, Batch. No Exp. Date and its Composition

Name of the company	Brand name	D.A.R no	Batch no.	Exp. Date	Composition
Drug International Ltd.	Divastin	210-148-25	0711	2013	Each tablet contains Atorvastatin calcium INN10mg.
OPSONIN Pharma Limited	Avas	025-281-25	TZG001	2013	Each tablet contains Atorvastatin calcium INN10mg.
SQUARE	Anzitor	012-503-25	201001	2013	Each tablet contains Atorvastatin calcium INN10mg.
General Pharma Ltd.	Lipitin	240-56-25	K005	2013	Each tablet contains Atorvastatin calcium INN10mg.
Beximco Pharma Ltd.	Atova	186-238-25	SUL070	2013	Each tablet contains Atorvastatin calcium INN 10mg
Pacific pharma Ltd.	Lipigent	026-128-25	200210	2012	Each tablet contains Atorvastatin calcium INN10mg.
Aventis Pharmaceutical Ltd.	Orva	003-262-25	S-2	2013	Each tablet contains Atorvastatin calcium INN10mg.
SK+F	Lipicon	188-109-25	1015	2013	Each tablet contains Atorvastatin calcium INN10mg.
Orient	Lipex	007-205-25	2045	2012	Each tablet contains Atorvastatin calcium INN 10mg
Unimed & Unihealth Ltd.	Stacor	225-71-25	MK33	2013	Each tablet contains Atorvastatin calcium INN10mg.

Table 2: The Comparative study of ten company's tablets

Company Name	Brand Name	Thickness (mm)	Diameter (mm)	Hardness (Kg)	Weight gain (mg)	Dis-integration time (min)	Dissolution Time (min)	Potency (% stated amount by UV)	HPLC (Purity)
Drug International Ltd.	Divastin	3.47	11.18	2.20	3	1.03	5	96.6%	96%
Opsonin Pharma	Avas	3.03	11.6	0.97	2	0.39	25	95.1%	98.7%
Square	Anzitor	3.14	8.11	1.19	4	2.22	20	90.7%	95.2%
General Pharmaceuticals	Lipitin	3.34	10.4	0.90	2	0.32	05	99.0%	95.3%
Beximco Pharma	Atova	3.66	11.4	1.30	2	1.70	10	83.0%	97.25%
Pacific Pharma	Lipigent	4.12	10.4	2.09	4	1.70	15	98.1%	96.52%
Aventis Pharmaceuticals Ltd	Orva	4.6	7.8	2.25	6	2.90	15	87.0%	96.52%
Eskayef Pharmaceuticals Ltd	Lipicon	3.7	6.6	2.40	3	0.17	10	95.0%	96.0%
Orient Pharma ltd	Lipex	4.7	9.2	3.17	3	1.90	13	98.4%	97.0%
Unimed&Unihealth	Stacor	3.2	6.4	3.0	3	2.91	27	95.0%	97.2%

Table 3: Positive & Negative Deviation of Weight 10 Company's Tablets

Brand Name	Company Name	Positive Deviation	Negative Deviation
Divastin	Drug International	0.74 %	-0.40%
Avas	Opsonin	0.93 %	-0.70%
Anzitor	Square	1.50 %	-2.70%
Lipitin	General	1.60%	-1.30%
Atova	Beximco	1.60%	-2.40%
Lipigent	Pacific	0.5%	-0.5%
Orva	Aventis	1.90%	-4.60%
Lipicon	SK+F	2.70%	-2.70%
Lipex	Orient	1.70%	-1.50%
Stacor	Unimed & Unihealth	1.20%	-1.92%

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