COMPARATIVE EVALUATION OF ATORVASTATIN 20MG TABLETS MARKETED IN BANGLADESH

By

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A thesis submitted to the Department of pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

It's hereby declared that

1. This thesis submitted is my own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted for any other degree or diploma at a university or other institution.

4. I have acknowledge all main sources of help.

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Approval

The thesis titled “Comparative evaluation of Atorvastatin 20 mg tablet marketed in Bangladesh” submitted by Samina Akter Shimu ,ID 18346025 of Summer 2024 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

If review or non-human or animal studies: This project does not involve any kind of animal and human trial.

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For lab-based work, you will need to provide the Ethical Permissions as given by the IRB.

Abstract

Atorvastatin is a member of the HMG-CoA reductase inhibitor pharmacological class, sometimes referred to as statins. These medications function by inhibiting the HMG-CoA reductage enzyme, which is essential for the liver's synthesis of cholesterol. It’s performed to evaluate and compare more about this weight variation, table thickness, hardness, disintegration of tablets of different brand has been performed in the lab carefully. There was the desirable result has been found during the tests. By performing the tests we got to know about how different brand have their different formula to make the tablets. This also shows the desired standard deviation, mean, how the tablet can performs into body metabolism.These helps to know the tablets nature, how they formed, and disintegration rate as well as durability of different brands of atorvastatin. As atorvastatin calcium is a commonly prescribed drug that is useful in controlling cholesterol levels and lowering the risk of cardiovascular events. It can significantly reduce the risk of heart attacks, strokes, and other cardiovascular events, which will eventually enhance patient outcomes and quality of life.

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Chapter 1

Introduction

1.1 Introduction

While ensuring all drug properties requires the creation of competent with the regulatory authorities with the necessary human and resources to control the manufacture ,distribution and sale of medicines. (*Regulatory*, n.d.) With a compound annual growth rate (CAGR) of 9.36% from 2023 to 2030, the global atorvastatin calcium market is expected to reach a valuation of USD 393.44 million, up from USD 229.94 million in 2023. (Hossain et al., 2016) The typical month to month utilization of statin among high-risk patients in 2012 was 269 948.8 tablets, and it expanded essentially to 343 975.3 tablets in 2015. (*Cholesterol-lowering Statin Drugs: Topics by Science.gov*, n.d.) Statins were most generally prescribed in 2012 (71.14) and 2015 (72.91%). In Bangladesh the availability of atorvastatin increases upto (from 8.0% to 30.7%). (Hossain et al., 2016) Bangladesh imports most of its atorvastatin from USA, china and India. (Katella, 2024).Atorvastatin was patented in 1986 an got approved in 1996. (Market.us, 2024).After long-term treatment, statins can reduce LDL cholesterol, or "bad cholesterol," by 1.8 mmol/l (70 mg/dl). (*Atorvastatin Calcium Imports in Bangladesh - Import Data With Price, Buyer, Supplier, HSN Code*, 2023).This translates into a 60% reduction in the incidence of cardiac events, such as heart attacks and sudden cardiac death, and a 17% reduction in the risk of stroke. (World Health Organization: WHO, n.d.). This can also help in increasing the level of HDL cholesterol known as good cholesterol which helps in removing LDL from the bloodstream. (Spritzler, 2023). It's also reduces the triglyceride, a type of fat found in blood that can contributed to heart diseases. (Hoffman, 2024b).Some studies suggest that atorvastatin may have some anti-inflammatory properties which can contribute to its cardiovascular benefits (Gilbert et al., 2017).This drug shows

the benefit for the atherosclerotic plaque which known as fatty deposits in arteries, making them less rupture and can easily cause a heart attack or stroke (*How Statin Drugs Protect the Heart*, 2021). The pharmacological effect includes the cardiovascular effect, anti-inflammatory, endothelial function development, potential effect as well as clinical impact which can be described like- (Hao et al., 2024).

Atherosclerosis prevention can be done by lowering LDL, triglyceride and the drug prevent the formation and progression of atherosclerotic plaque in arteries. (*Atherosclerosis: Symptoms, Causes, and Prevention*, 2023) .The effect particularly beneficial in patience existing cardiovascular condition or those who is in high risk of developing them(Teo & Rafiq, 2021). Atorvastatin improves the function of the endothelium (the inner lining of blood vessel) (Wolfrum et al., 2003).This improvement helps in better vascular relaxation as well as reduces vascular stiffness which contributing to the overall cardiovascular health (Zieman et al., 2005). Atorvastatin may have some anti-thrombotic effect which reduces the tendency for blood clot to form which may be crucial in preventing in heart attack and stroke (Davis et al., 2023). There is evidence to have some antioxidant in this drug which may reduce the oxidative stress. It's also helpful in reducing myocardial infarction (Nuttall, 1999).

Production of atorvastatin as per USP can be described by synthesis of atorvastatin calcium and QC (Rani et al., 2021). There are monograph compliance, GMP and labeling in USP standards (*The USP Monograph and Reference Standard Development Process | USP*, n.d.). For atorvastatin, formulation must comply with the USP monograph that can provide detailed specification for the identification, assay, impurities and dissolution of atorvastatin tablets (Waters, n.d.). As well as

manufacturers must follow the GMP guideline properly to make sure the consistence production and quality control (*What Is GMP | Good Manufacturing Practices | SafetyCulture*, 2024). Labeling is a must have thing in the standard of USP including the information on dosage, administration, storage condition and expiry date (*FDA Error*, n.d.-c).

The purpose of this study was to determine how statins, a class of medication used to decrease blood cholesterol levels, were prescribed in 10 different regions of Bangladesh. (Hasan & Rahaman, 2015).A total of 181 prescriptions out of 1810 contained statins, or 10% of all prescriptions. (*Atorvastatin Calcium Imports in Bangladesh - Import Data With Price, Buyer, Supplier, HSN Code*, 2023). The mean quantity of statins prescribed was 0.1. 10mg of atorvastatin as atorvastatin calcium tri hydrate are present in each film-coated tablet. (Hossain et al., 2016) Excipient having established impact which includes 2.8 mg of salt and 38.3 mg of lactose monohydrate. (*Lactose Monohydrate: What Is It and Where Is It Used?*, n.d.)

Here, the drug atorvastatin is used to evaluate it's thicken, weighting, hardness, friability as well as disintegration . (*Atorvastatin: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD*, n.d.).We have done this lab work for acknowledgment of how these tests should perform and we can easily get the expected information about this statin. (Hansen et al., 2005)

Chapter 2

Material and methods:

2.1 Objectives of the studies:

The best-selling of the statins is Atorvastatin. It has become the best selling .Statins are drugs which is used to lower the cholesterol level. (*Atorvastatin 20 Mg Film-coated Tablets - Summary of Product Characteristics (SmPC) - (Emc)*, n.d.).The best-selling of statin is atorvastatin and it's the best pharmaceutical history. (*Pharmaceutical Mycelia: A Story of Statins | LGC Standards*, n.d.).The present study is observed to evaluate the current identification of the drug's weight, thickness, hardness, friability as well as the disintegration of the tablet. We from the lab work includes (*Pharmaceutical Mycelia: A Story of Statins | LGC Standards*, n.d.)

The determination of weight of 4 different brands of atorvastatin and measure 5 tablets of each brands, weight them and got the mean as well. (*Atorvastatin 20 Mg Film-coated Tablets - Summary of Product Characteristics (SmPC) - (Emc)*, n.d.).Also to identify the hardness value of different brands tables and sometimes they vary from each other (Buehler - Metallography Equipment & Supplies for Sample Preparation, 2021). In lab with the help of friability machine we got to know the tablet's friability from the before and after result of doing friability testing. (Hasan & Rahaman, 2015).Afterwards, the disintegration test has been performed with different brands tablets. (Arshad et al., 2021)

2.2. Study design:

This drug was which was observed under the tests performed with different brands of atorvastatin in Bangladesh. (AlMuhsin et al., n.d.) The medicine samples were all acquired from several local retail pharmacies for example, Mohakhali , Gulsan 1and Banani. (Rahman et al., 2022). Where all the top notch retail pharmacies has been found. (Rahman et al., 2022). Then as needed ,every sample that was purchased was kept out of direct sunlight and in appropriate storage conditions. (Committee, 2015). Before using the samples in any kind of experiment, they were obtained and checked.(*Determining Sample Size Before Starting an Experiment or Run the Experiment Indefinitely?*, n.d.)

Table 1.1 : List of Equipment and Instruments used in the testing analysis

Serial no	Instrument	Model	Country of origin
1	Slide caliper (0-150X0.05mm)	China	China
2	Electronic balance	Shimadzu	Japan
3	Friabilator (USP)	Electro lab, EF-2	India
4	Disintegration tester (USP)	Electro lab , ED-2L	India

Weight variation:

Weight variation test is a common pharmaceutical quality control test performed on pharmaceutical manufacturing tablets as part of the tablets uniformity testing in Quality Control (QC). (Mettler-Toledo International Inc. all rights reserved, 2020). Every tablet among the sample is individually weighed through a balance, and afterwards goes for a chaotic examination. (Joglar et al., 2024).The individual weight is taken, recorded, and subsequently carried on to calculate the average weight of the tablets. (AlMuhsin et al., n.d.).During tests, they also get alternating weight numbers from different brands. (Joglar et al., 2024).

Thickness:

I have universal thickness open every time I do the process (Beaufort et al., 2021). Quantitatively, Tablet thickness with a fixed compressive load depends on the die fill, the compressed particulate mix packing, the particle size distribution, and the tablet weight; at a constant die fill, thickness varies with changes in compressive force. (Natoli et al., 2017). As long as the granulation or powder blend for the tablets is homogenous with regard to particle size and particle size distribution, as long as the punch tooling is constant in length in the repeat batches, and as long as the tablet press is properly maintained and clean, it can be stable both within and between batches. (AlMuhsin et al., n.d.). Slide calipers are a suitable method for measuring individual tablet thicknesses for these types of very flat product that gives high precision and estimates variation, and is more convenient than weighing the tablets on an ultra-microbalance. (*How to Use Slide Callipers? Make the Best Use of the Multi-purpose Design*, n.d.)

Tablet thickness testing importance have shown that ensures the uniformity to maintain the consistency in dosage. (*Hardness Testing: Basic Principles and Methods | Teledyne LABS*, n.d.).

Packaging compatibility ensures the tablets should fit into blisters or bottles. Also ensures tables have the proper strength to withstand in handling and transportation. (AbstraktMarketing, 2024). The properties of the granulation material used for the formulation are one of the factor that influence the tablet thickness. (Abstract Marketing, 2024). The flow ability of the powder mix can impact how well the die cavity is filled influencing thickness. (Jones-Salkey et al., 2023). The force applied during the tablet compression can vary and also affecting the thickness. (Admin, 2021).Troubleshooting is the common issue includes thickness variation which shows due to inconsistence granulation or compression forces. (*15 Common Tablet Problems and How to Address Them - IPharmachine,* n.d.) .If the table got split or lays during the testing then it indicates the poor formulation or compression issue.by investigating the route cause that could range from the material properties t equipment malfunction called the out of specification result. (Jakubowska & Ciepluch, 2021).So if all pharmaceutical company adherence these criteria's while tablet thickness testing, they can ensure the production of high quality, good uniform tablet that meet the regulatory standards and provide consistence therapeutic effect towards the patients. (Jacques & Alexandridis, 2019).

Hardness:

Tablets must have a specific level of strength, hardness, and resistance to friability in order to survive the mechanical shocks involved in production, packaging, and delivery. (Singh, 2024).Tablet hardness, powdering and friability are such required parameters which need to accommodate consumer and perception. ("International Journal of Pharmaceutical Chemistry," 2015).The manufacture of tablets with good tablet hardness is of paramount important specifically for drug products having real or potential bioavailability problems or whose dissolution release

profiles are compression force-dependent (*Hardness Testing: Basic Principles and Methods | Teledyne LABS*, n.d.-b). Things to maintain for tablet hardness testing procedure:

Regulatory standard which indicates the USP as well as Ph.Eur or other relevant authorities. (Jacques & Alexandridis, 2019). The tablet hardness tester is essentials which is known as durometer or tablet hardness tester (*Tablet Hardness Testing Explained - ERWEKA GmbH*, 2023). For the further sample preparation need to ensure that tablets are stored and handles according to the required condition prior to the testing which will be helpful lock the moisture of the tablet (*Sample Preparation for Moisture Analysis*, n.d.).And prevent it from absorption and loss. To maintain the consistency it's good to use the one batch product (Støve, 2024). Testing tablet include calibration of hardness tester according to the manufacturer instruction before using it (*Hardness Testing: Basic Principles and Methods | Teledyne LABS*, n.d.-d). Positioning of the tablet into the tester is much important for the testing need to place the tablet between the anvil and the fore application point called plunger of jaw also need to focus that it's aligned properly to avoid uneven force distribution (*Tablet Crushing Strength: Topics by Science.gov*, n.d.). After that activation of the tester is needed when the force is given until the tablet breaks down need to record the applied breaking point which usually measured the in N or kp. (Sonnergaard et al., 2005). Every tablets measurement needs to be noted down as it can be different at each time of each tablet. (Natoli et al., 2017b). There are also some consideration about tablet testing which enlighten tablet shape and size where adjust the testing procedure to account for the different size and shapes of the tablets cause it can effect on hardness testing readings. (*Hardness Testing: Basic Principles and Methods | Teledyne LABS*, n.d.-e).Environmental factor includes that test must be conducted into the proper controlled environment where temperature and humidity is regulated .cause factors can easily influence tablet hardness (Team, 2024). Need to ensure that tests are repeatable by the

testing operators and across different operators by the standardization the testing procedure (Gordonov, 2016). Comparing hardness result with the other parameter of the quality like friability, thickness, disintegration to ensure the tablet integrity (*Hardness Friability Disintegration: Topics by Science.gov*, n.d.). The detailed result for the testing is necessary. All the procedure can comply with the regulatory requirement and GMP standard. (*What Is GMP?*, n.d.) Periodically review and gathers all the result is necessary for the whole hardness tablet testing for the accuracy. (*Tablet Hardness Testing | Tablet Structural Integrity Testing*, n.d.).

Friability:

The laboratory friability tester is always known as Roche friabilator. (DISINTEGRATION TESTER LB-3D - Drug Testing Instrument - PRODUCTS - DRUG TESTING INSTRUMENT, n.d.). This apparatus uses a plastic chamber that rotates at 25 rpm to subject several tablets to the combined effects of shock and abrasion. The tablets are dropped six inches with each revolution. (Antech, 2024). Normally a reweighed tablet sample is placed in the friabilator which is then operated for 100 revolutions. (Remya et al., 2010). Tablets then require dusting and reweighing after this. (Sharma, 2013b). Generally speaking, conventional compressed tablets that lose less than 0.5% to 1.0% to their weight can be used again. (Chinnala et al., n.d.-b). Using a friabilator which typically consists of a plastic drums which rotate at a specific speed ,causing tablets to fall from a maintained height repeatedly (Team, 2024b).By selecting a representative sample of tablets which is generally equivalent to 6.5 gm or relevant pharmacopeia. (Antech, 2024).Tablets should be free from dust and recommended storage formation before use (Shanmugam, 2017).Tablet weight should be taken initially. (Shanmugam, 2017). Friabilator setting is necessary cause tablet

placement is needs to be done in the drum and then set the drum to be rotate 100 revolution.by starting the friabilator and allow it to complete 100 rotation(Choudhary, 2024).So after the test tablets should be removed and re dust gently avoiding any loss of tablet fragments. (Pharmacydpp1b, 2015).Then the tablets need to reweight for the proper result. For this testing there is some consideration as well.

Disintegration:

The procedure of disintegration, which is the first step to more colloquial dissolution or approach at solution. (Markl & Zeitler, 2017).The time which it takes for a tablet to disintegrate is measured using an apparatus, outlined in the USP. (Health Canada, 2018). USP Apparatus to determine disintegration is equipped with 6 glass tubes (each tube has length of about three inches) which are also open at the top and placed side by side in contact with lower end on a ten mesh screen holder contributed basket rack assembly. (*Disintegration Testing | Laboratory Disintegration Test for Tablets*, n.d.). To test for the time of disintegration, six tablets are separately introduced into cylinders and the basket rack is positioned in a 1 liter beaker containing water at (37±2) ºC , thus, when sweeping downhill, each tablet seems to be no closer than 3 cm from the bottom of the glass and stays 2.5 cm below the surface while moving higher (Academy, 2022b).The basket assembly containing the tablets which is raised and lowered through a distance of 5 to 6 cm, at a frequency ranging from approximately twenty eight cycles per minute *Disintegration Testing | Laboratory Disintegration Test for Tablets*, n.d.). Thus, that takes place just above the tablets and suggests a negative outcome for those resting on top of this. (Academy, 2022b)

Chapter 3

Result:

Every sample that was acquired was kept out of direct sunlight and under ideal conditions for storage.

Before using the samples in any kind of experiment, they were obtained and checked.

1.2 : Table showing different shapes of the different companies tablet

Sample number	Shape
Sample 1	Circle
Sample 2	Oval
Sample 3	Oval
Sample 4	Circle

1.3 : Table showing different weight variation of five different tablets

		Weight (gm)		
Tablet no	Sample 1	Sample 2	Sample 3	Sample 4
1	0.14	0.26	0.31	0.32
2	0.12	0.25	0.32	0.31
3	0.14	0.26	0.33	0.31
4	0.14	0.26	0.31	0.31
5	0.14	0.25	0.31	0.31

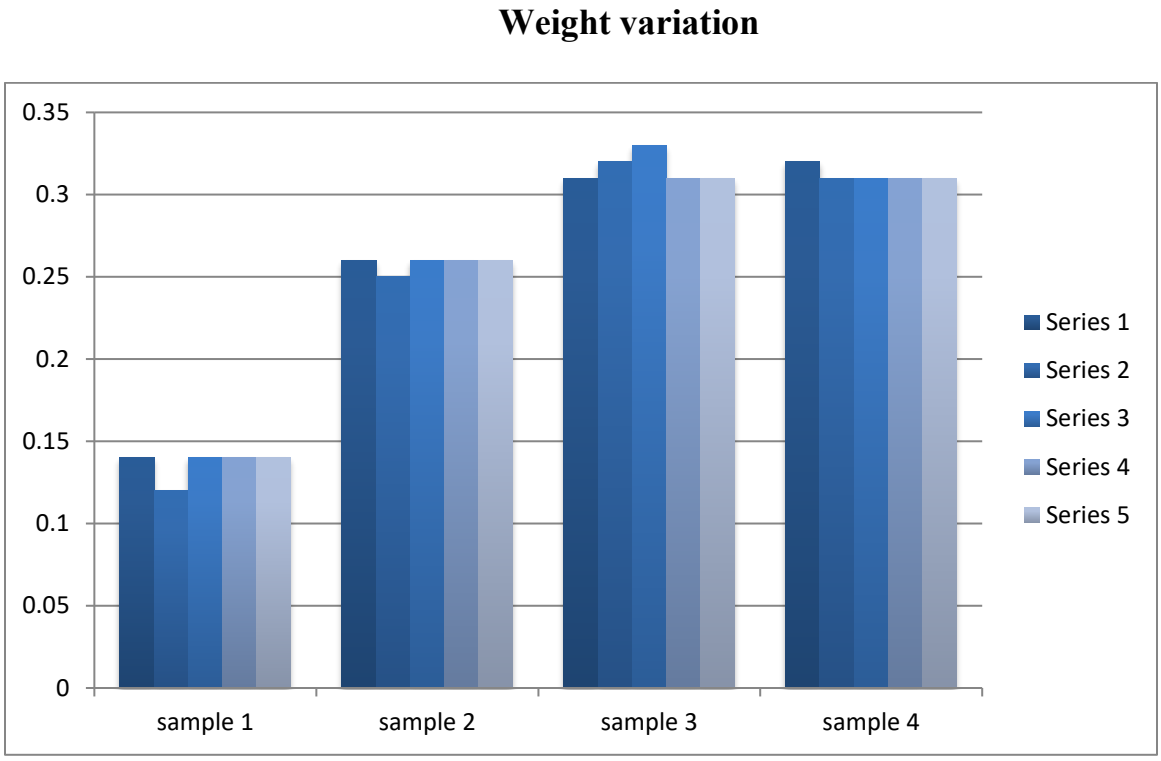

Fig:1 Bar chart showing weight variation of the samples

Table 2.1: Table showing thickness variation of different samples

Thickness (cm)				
Tablet no	Sample 1	Sample 2	Sample 3	Sample 4
1	0.9	0.85	1	1.25
2	1	0.85	1	1.25
3	0.9	0.325	1	0.6
4	0.9	0.85	0.6	1.25
5	0.65	0.325	0.6	0.6

Thickness(cm)

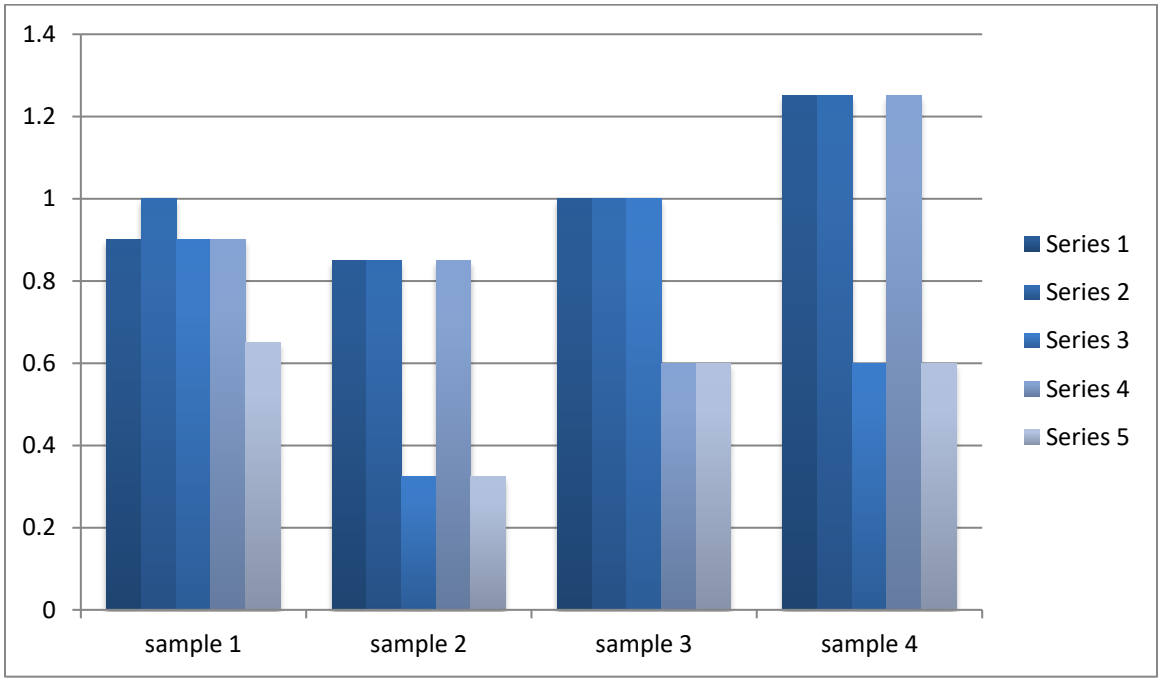

Figure 2: Bar chart showing thickness variation of different samples

Table 2.2: Table showing variation of friability testing of the before and after condition of samples

Total weight of 5 tablets (gm)				
	Sample1	Sample2	Sample 3	Sample4
Before	0.71	1.28	1.56	1.55
after	0.70	1.28	1.57	1.56

Friability test

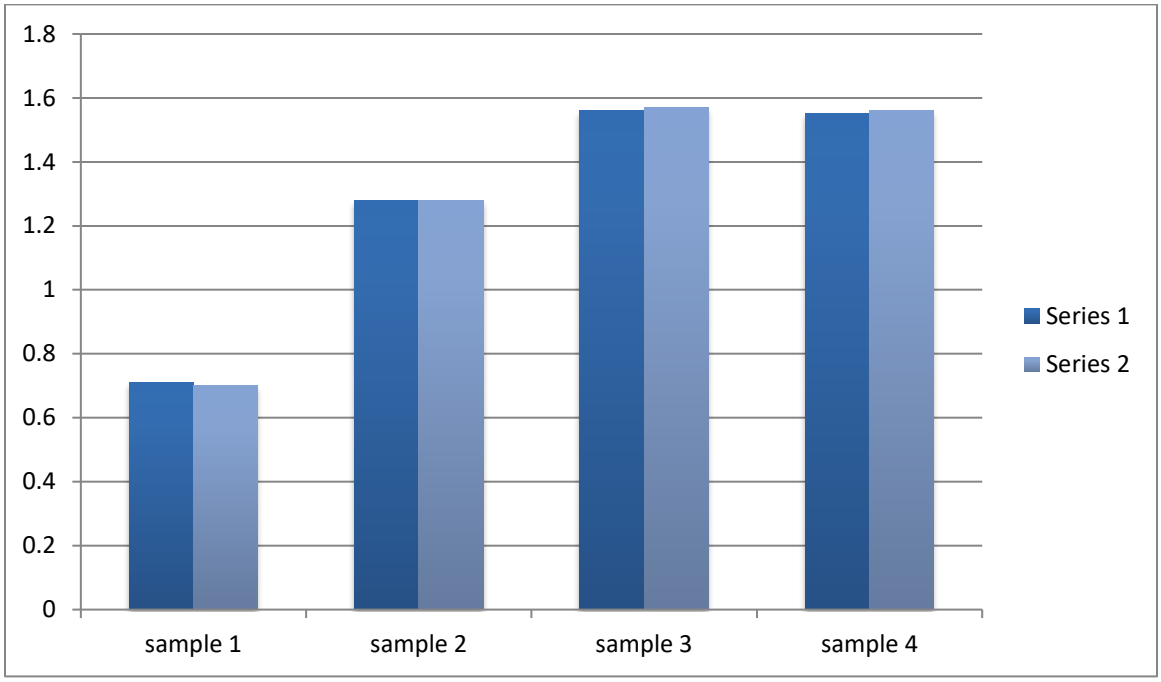

Figure3 : Bar chart showing variation of friability testing of the before and after condition of samples. Five tablets' total weight was found to be sometimes the same and sometimes different before and after the friability test. After the test, the weight of the tablets did not change significantly for any of the samples.

Table 2.3: Table showing the disintegration time of different samples.

Disintegration time				
Table no	Sample 1	Sample 2	Sample 3	Sample 4
1	2.07	3.43	5.14	6.57
2	2.07	3.43	5.14	6.57
3	2.07	3.43	5.14	6.57
4	2.07	3.43	5.14	6.57
5	2.07	3.43	5.14	6.57

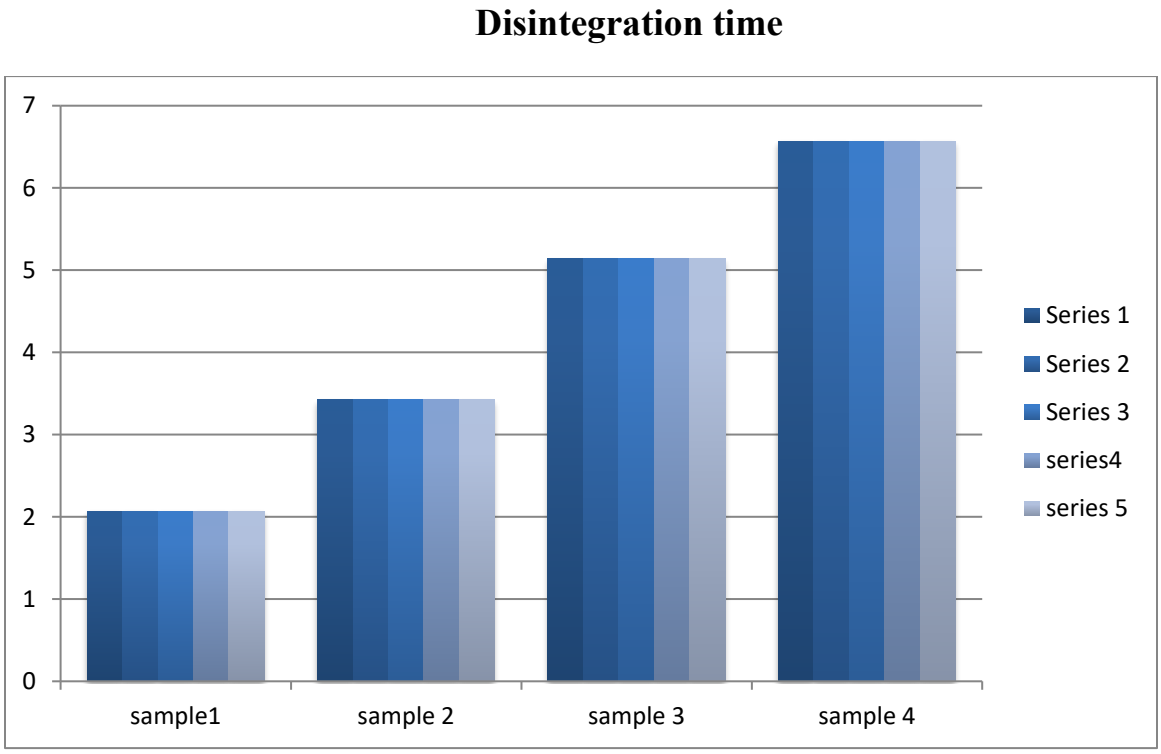

Figure 4: Bar chart showing the different disintegration time of different samples

Table 2.4: Table showing hardness variability of different samples

Hardness (kg)				
Tablet no	Sample 1	Sample 2	Sample 3	Sample 4
1	6.20	3.83	3.24	7.57
2	5.30	5.26	3.07	5.65
3	5.2	3.92	3.25	6.67
4	6.57	4.81	2.92	7.57
5	6.32	4.81	3.46	7.57

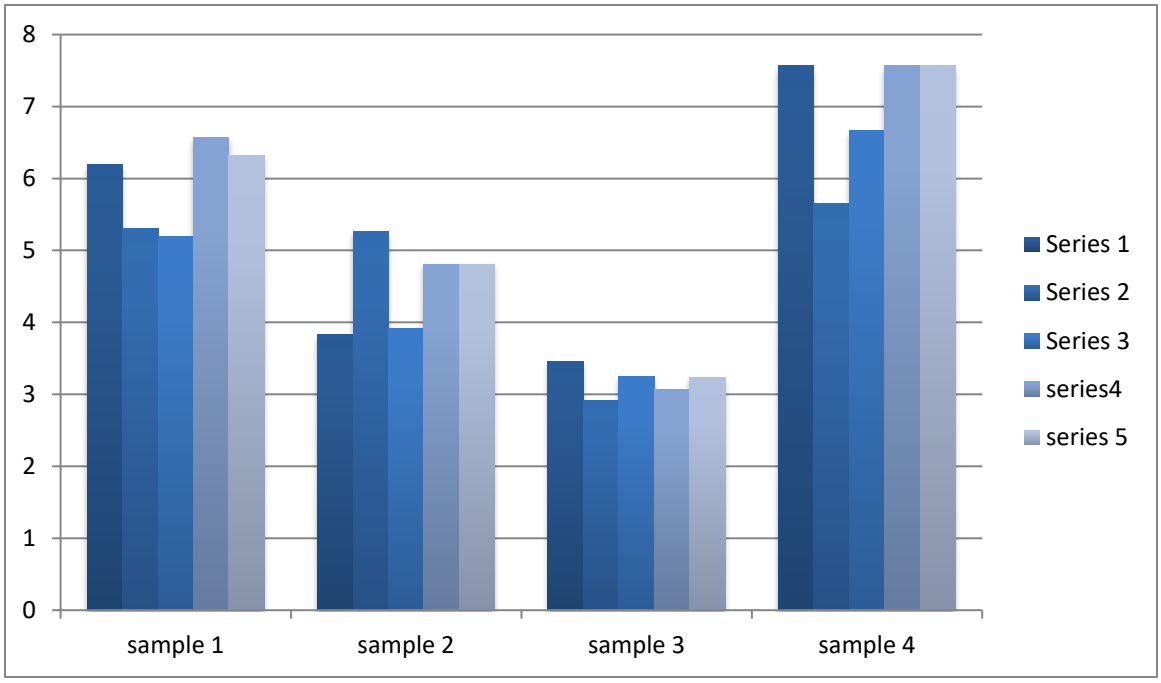

Figure 5: Hardness variability of four tablets of different samples. Hardness of each tablet of each company varies with tablets, but they are in the same range.

Chapter 4

Discussion:

After the critical analysis of different brands of Atorvastatin tablets collecting, doing lab work like friability, weight variation, thicken measurement, hardness, disintegration, we got to know the needed information. The lab work shows the genuine knowledge about the tablet of different brands .how different kind of formulation it's have but still do the same treatment for the heart patients. This researching helps to know the entire process how to do the lab works done potentially by using instrument. No major problem was found in tablet variation, thickness, friability and hardness. (Hao et al., 2024).

Companies typically make claims about atorvastatin based on its intended use and therapeutic effects. Reducing the risk of cardiovascular events, such as heart attacks and strokes, requires lowering LDL cholesterol. Prescribing guidelines contains details on its low frequency of side effects, attractive risk-benefit ratio, and efficacy to prevent cardiovascular events. (Beaufort et al., 2021). Manufacturers frequently highlight the long-term advantages of atorvastatin therapy, such as its capacity to gradually lower the chance of developing cardiovascular problems in the future and to halt the advancement of atherosclerosis, or the hardening of the arteries. The manufacturing and marketing of atorvastatin has also helped pharmaceutical businesses in Bangladesh. Many pharmaceutical companies from Bangladesh have been involved in the production and export of generic atorvastatin, even if precise revenue statistics are not easily accessible. (Rani et al., 2021).

The atorvastatin comparison shows different parameters during the tablet making. When discussing about this drug this referencing to the specification and factors involving in the

manufacturing site. During production tablets weight can be variable. Hardness refers to the physical strength of tablets where friability test shows the tablet will crumble. So balancing the properties is tough to prevent breaking during packaging to ensure the tablet hardness. Tablets are coated for various reason for example to maintain thickness, API, moisture contain. These drugs are film coated to protect the active ingredients from light and moisture and mask the taste. So each of the parameter should be carefully controlled. (*Atherosclerosis: Symptoms, Causes, and Prevention*, 2023) .

The production of atorvastatin in Bangladesh follows the manufacturing standard and local regulation. First of all raw materials is all which is needed like API and excipients. By doing lab scale trials and formulation planning Bangladesh develops the formulation of the tablet. Compression, granulation and coating is has been done while manufacturing the tablet. Testing, validation is necessary for the quality control and assurance. (Spritzler, 2023). Labeling, marketing and distribution is to promote the production. So production of atorvastatin in Bangladesh is likely to reflect the pharmaceutical practice to meet the healthcare meets. (Zieman et al., 2005).

While doing the laboratory tests for the analysis got some limitations as well. Firstly got some time management issue due to lab got engaged for other students' class purposes. (Hossain et al., 2016) Also there is limited time for analyzing data, conduct experiments. There was sample availability issue where it took time to find all brands tablet for testing. Laboratories got equipment constrains like 2 of the equipment got damaged and need to replace with new one which took some days during lab days which is important for effective analysis. Rather than these experiments goes well and got the desired results. . (*Cholesterol-lowering Statin Drugs: Topics by Science.gov*, n.d.)

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