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FORMULATION AND EVALUATION OF ATORVASTATIN TABLETS USING DIFFERENT SUPER-DISINTEGRATING AGENTS AND ITS IVIVC STUDY

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Abstracts:
This article aimed to formulate and evaluate an optimized formulation of atorvastatin using super disintegrants and investigate the in vitro-in vivo correlation (IVIVC) of the developed formulation.A systematic approach was employed to study the compatibility between atorvastatin and various super disintegrants through drug-excipient compatibility studies. Different formulations were developed using various concentrations of the selected super disintegrants, along with other excipients such as diluents, binders, and lubricants. The formulations were evaluated for various parameters including hardness, friability, weight variation, disintegration time, and drug release profile. Furthermore, In vitro in vivo correlation (IVIVC) predicts in vivo performance of products from in vitro (dissolution) data which overcomes the disadvantages of in vivo study for bioequivalence.Thus, a dissolution study was carried and their plasma drug concentration was determined.using this Numerical convolution technique.
In conclusion, the formulation and evaluation of atorvastatin tablets using super disintegrants proved to be effective in improving drug dissolution and enhancing disintegration properties. The IVIVC study established a valuable correlation between the in vitro and in vivo performance, providing a predictive tool for the optimization of atorvastatin formulations. These findings contribute to the development of a more efficient and reliable formulation of atorvastatin, with the potential to improve its therapeutic efficacy and patient compliance.

Keywords:Atorvastatin tablets,superdisinegrating agents,compatibility study,IVIVC,methods,Result and discussion,Conclusion

INTRODUCTION

Atorvastatin is a medication that belongs to a class of drugs known as statins. It is primarily used for the treatment of high cholesterol levels and the prevention of cardiovascular diseases. Atorvastatin works by reducing the production of cholesterol in the liver and helping to lower the levels of LDL (low-density lipoprotein) cholesterol, often referred to as "bad" cholesterol.
The medication was first approved by the United States Food and Drug Administration (FDA) in 1996 and has since become one of the most commonly prescribed medications for managing high cholesterol.
Atorvastatin is typically prescribed as part of a comprehensive treatment plan that includes a healthy diet, regular exercise, and lifestyle modifications to reduce the risk of cardiovascular diseases. It is effective in

reducing LDL cholesterol levels and has also been shown to have some modest effects on increasing HDL (high-density lipoprotein) cholesterol, often referred to as "good" cholesterol.
It is important to note that Atorvastatin is a prescription medication, and its use should be closely monitored by a healthcare professional. Like any medication, it may have potential side effects and interactions with other drugs, so it is crucial to follow the prescribed dosage and consult with a doctor if any concerns arise.
Overall, Atorvastatin is a widely used and effective medication for managing high cholesterol and reducing the risk of cardiovascular diseases, helping individuals maintain a healthy heart and improve their overall well-being.
Atorvastatin works by inhibiting an enzyme in the liver called HMG-CoA reductase, which is responsible for producing cholesterol. By reducing the production of cholesterol, Atorvastatin helps lower the levels of low-density lipoprotein (LDL) cholesterol, often referred to as "bad" cholesterol, in the blood.
High cholesterol is a significant risk factor for heart disease, stroke, and other cardiovascular conditions. Atorvastatin helps to manage cholesterol levels in individuals with hypercholesterolemia, a condition characterized by high levels of cholesterol in the blood. It is also prescribed as a preventive measure for individuals at high risk of cardiovascular events, such as those with diabetes or a history of heart disease.

Superdisinegrating agents and its uses:

Super-disintegrants are the agents added to tablet formulations to promote the breakup of a tablet into smaller fragments in an aqueous environment there by increasing the available surface area and promoting a more rapid release of the drug substance.

Ideal characteristics

- Should produce rapid disintegration
- Compactable enough to produce less friable tablets
- Effective at low concentration
- Have greater disintegrating efficiency

Commonly used super disintegrants are:

- Sodium Starch Glycolate (Explotab, primogel) is used in concentrations of 2-8 % & the optimum is 4%.

  Mechanism of Action: Rapid and extensive swelling with minimal gelling.
  used in the concentration of 2-15% of tablet weight. And Water wicking

- Cross-linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium: Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation.

- Crospovidone

  Mechanism of action: Swelling, Wicking, and deformation
  Due to its high crosslink density, crospovidone swells rapidly in water without gelling. In contrast to sodium starch glycolate and croscarmellose sodium, Crospovidone super disintegrants exhibit virtually no tendency toward gel formation, even at high use levels.

- Low-substituted hydroxy propyl cellulose (L-HPC)

L-HPC is a hydrophilic polymer that undergoes swelling upon contact with water. It exhibits a rapid water uptake and subsequent volume expansion, leading to tablet disintegration. L-HPC also possess a wicking effect, drawing in fluids and distributing them throughout the tablet, further promoting disintegration.

USES:

1. Effective in lower concentrations.
2. Less effect on compressibility and flowability.
3. More effective intragranular.

The primary function of superdisintegrants is to break down the solid dosage form into smaller particles,increasing the surface area and facilitating the dispersion of the drug in the gastrointestinal fluid.This process enables faster disintegration and subsequent dissolution of the drug,leading to its release and absorption.

Superdisintegrants work through various mechanisms, including swelling,wicking,and deformation.Superdisintegrants such as croscarmellose sodium and sodium starch glycolate ,rapidly absorb water causing them to swell and exert mechanical pressure on the tablet matrix,resulting in its disintegration.Wicking superdisintegrants such as crospovidone,enhance disintegration by drawing in water through capillary action.Deformation superdisintegrants ,like low substituted hydroxypropyl cellulose,deform under pressure creating channels within tablet structure that promote its breakup upon exposure to fluid.

The selection of a superdisintegrants depend on several factors, including the characteristics of the API, the desired disintegration time, and the manufacturing process.The excipients were choosed based on compatibility with the drug and other excipients,as well as its ability to provide the desired disintegration and dissolution profiles.

Superdisintegrants are often combined with other excipients such as binders,diluents, and lubricants to formulate tablets with desirable properties.The choice of superdisintegrants depends on various factors such as the nature of the drug,the desired disintegration time, and the manufacturing process.

Drug-Excipient Compatibility study

A drug excipient compatibility study is a crucial step in the formulation development of pharmaceutical products. It involves evaluating the compatibility between a drug substance (active pharmaceutical ingredient, API) and various excipients used in the formulation. The purpose of this study is to identify any potential interactions or incompatibilities between the drug and excipients that could affect the stability, efficacy, or safety of the final dosage form.

Here are the key steps involved in conducting a drug excipient compatibility study:

Selection of excipients: Excipients are selected based on their intended functions in the formulation, such as binders, fillers, disintegrants, lubricants, and preservatives. Excipients are chosen considering their physicochemical properties, regulatory status, and compatibility with the drug substance.

Sample preparation: Pure drug substance and excipients are separately prepared as control samples. Additionally, drug-excipient mixtures are prepared by blending the drug substance with individual excipients or combinations of excipients. Various ratios and concentrations are tested to cover a wide range of potential formulation conditions.

Compatibility testing methods: Various techniques can be employed to evaluate drug-excipient compatibility, including:

- Differential Scanning Calorimetry (DSC): DSC measures the heat flow during heating or cooling of a sample, helping to identify interactions, melting points, and compatibility issues.
- Fourier Transform Infrared Spectroscopy (FTIR): FTIR is used to analyze the functional groups and chemical bonds present in drug and excipient samples, enabling the detection of potential chemical reactions.
- Powder X-ray Diffraction (PXRD): PXRD determines the crystalline nature of drug and excipient samples, assisting in identifying any changes or interactions that may occur.

Stability testing: Accelerated stability studies are performed under controlled temperature and humidity conditions to assess the stability of drug-excipient mixtures over time. Physical changes, such as color, odor, or precipitation, are monitored.

Data analysis and interpretation: The results obtained from compatibility testing are analyzed to determine any changes or interactions that occurred between the drug and excipients. Significant deviations from the control samples or the appearance of new peaks in spectroscopic analysis may indicate incompatibilities.

Formulation optimization: Based on the compatibility study results, excipients that show compatibility issues or potential interactions with the drug substance may be modified or replaced with more suitable alternatives. The formulation is adjusted to ensure compatibility and stability.

The drug excipient compatibility study is an iterative process that may involve multiple rounds of testing and formulation adjustments. It provides valuable insights into the selection and use of excipients in a formulation to ensure product quality, stability, and efficacy. The study findings also support regulatory submissions and provide important information for the development of robust pharmaceutical formulations.

IVIV correlation Analysis:

A predictive mathematical model called an in vitro in vivo correlation (IVIVC) describes the link between a dosage form's in vitro characteristics and a relevant in vivo response. The in vitro property is largely dissolution or drug release, whereas the in vivo response is primarily a drug's plasma concentration or the amount/rate of drug absorbed while doing IVIVC for formulation development.
To put it another way, IVIVC describes the link between drug release in dissolving equipment and the quantity of drug that reaches the bloodstream after delivery. When medicine has a high solubility and dissolving is the rate-limiting element in the absorption process, this sort of connection is likely to exist. IVIVC is critical in a variety of situations, but it is especially critical in the case of extended-release oral formulations.
Regulatory agencies propose using an IVIVC model for most modified-release dosage formulations. The fundamental benefit of IVIVC is that it provides a technique for assessing changes in in-vivo absorption based on changes in in-vitro dissolution when a formulation is changed slightly. After establishing a validated IVIVC model, it may be used to estimate bioavailability and bioequivalence (BA/BE) based on existing in vitro data. In such circumstances, dissolution test findings can be utilized to offer the needed information without the necessity for human participants in clinical BE research.
Another benefit of IVIVC is that it provides a clearer picture of the medicinal product. This can aid in the development of broader therapeutic product acceptability criteria as well as formulation stability. IVIVC is also useful for forecasting the in-vivo impacts of modifications to the formulation components, production site, or process.

This is critical throughout the early stages of product development, but IVIVC's importance does not end there. After the product has been authorized, establishing an IVIVC model can be even more useful in identifying the impact of post-approval manufacturing adjustments, site of manufacture changes, and any difficulties with particular batches of manufactured items. All of this may be determined without the need for costly in-vivo BE studies to be repeated.

METHODS:

All the raw materials were tested before processing for manufacturing.
The active pharmaceutical ingredient (API) in Atorvastatin tablet is Atorvastatin calcium trihydrate which is responsible for the therapeutic effect of the medication. The diluents/fillers used to increase the bulk of the tablet is microcrystalline cellulose PH 102. Sodium lauryl sulfate is used as a surfactant, Starch as a binder, and Croscarmellose, Crospovidone, and sodium starch glycolate as super disintegrants in the formulation.

Similarly, Magnesium stearate is used as a lubricant to reduce friction during tablet compression, and colloidal silicon dioxide as a glidant to improve flow properties during tablet compression

Drug-Excipient compatibility study

First of all drug-excipient compatibility study was done and all the excipients were choosed according to the compatibility study results and the further formulation process was carried out. For the drug-excipient compatibility study the drug is mixed with excipients in a ratio of 1:1. These mixtures were kept in 5ml glass white-colored vials and packed properly. These vials are exposed to 1) room temperature 2) 2 – 8° C and 3) 40˚c / 75%RH. 15gm of the blend is prepared which is filled in 3 vials. Observations for physical appearance are made at zero weeks, 2 weeks, and 4 weeks, the samples were withdrawn for analysis. The drug-excipient interaction study was carried out by physical observation. Furthermore, no physical interaction with the active pharmaceutical ingredient was observed. The initial and final observation is compared in the 2nd and 4th weeks. Fourier Transform Infrared Spectroscopy (FTIR) is commonly used to study drug-excipient compatibility in pharmaceutical formulations. The method involves analyzing the infrared spectra of individual components (drug and excipients) and their physical mixtures to identify any potential interactions or changes in functional groups.

Tablet manufacturing process

- **Granulation**

Carry out Dispensing check before Raw material dispensing.

Check Stores tag on each raw material to Product Name, Material's Name,
Batch number, A. R. No. & Quantity against Raw Material Requisition Sheet, Mfg. date
& Exp. Date of Raw materials Initial the tag and BMR with the date on verification.
Attach all Raw Material tags to BMR, covering them together in a magic seal.

Step 1: Sieving
Sieve Atorvastatin Calcium Trihydrate and Sodium lauryl sulfate through 80 mesh and remaining through 60 mesh.

Step 2:Mixing
Mix the following items for 5mins in the sac

S.no	Items
1	Atorvastatin Calcium Trihydrate IP
2	MCCP 102
3	Sodium Lauryl Sulphate
4	Crospovidone
5	Croscarmellose Sodium

Table 1: Items used for dry Mixing

Step 3:Binder solution preparation
At first soak starch and then cook in hot purified water as required until the slurry is obtained.

Step 4:Wet Granulation
Use the binder solution prepared in step 3 for granulating the powder mix from step 2.
Continue mixing for 5 minutes to get the granules.

Step5:Drying

Dry the granules for 15 minutes with the application of air. And then dry the above-air-dried granules in Tray Drier at 45-50℃ as required

Note: Temperature should not exceed 50℃.

Dry till the moisture of the granules becomes below 2.5%

Step 6:Dry screening
Final sieving is done with 30 mesh sieves.

Step 7:Lubrication
Again mix dry granules with crospovidone, Croscarmellose, and then at last lubricants (colloidal silicon dioxide and magnesium stearate) was added and mixed.

Pre-formulation study
Pre-formulation is the phase of research and development in which pre-formulation studies characterize the physical and chemical properties of a drug molecule to develop a safe, effective, and stable dosage form.

Powder Flow Properties:
The flow property of atorvastatin powder refers to its ability to flow freely and uniformly during manufacturing processes such as blending, filling, and tableting. Good flow properties are desirable to ensure consistent and efficient processing, as well as uniformity of dose in the final product. Poor flow properties can lead to issues such as inconsistent tablet weights, content non-uniformity, and difficulties in filling capsules or tablets.
The flow properties of atorvastatin powder can be influenced by several factors, including the physical properties of the powder itself, such as particle size, shape, density, and surface characteristics. Additionally, the presence of moisture, static charge, and interparticle forces can also affect flowability. Fine particles possess poor flow by filling void spaces between larger particles causing packing and densification of particles.

Various techniques are employed to assess the flow properties of powders, including:

The angle of Repose: This method involves pouring the powder through a funnel onto a flat surface and measuring the cone-like pile's angle. A greater angle of repose indicates poor flow. It should be less than 30 and can be determined by the following equation.

$\tan\theta = h/r$ h=height of pile
r=radius
θ=Angle of repose

The angle of Repose (θ)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 2: Relationship between the angle of repose and flow properties

Carr's Index or Compressibility Index: It is calculated by determining the bulk and tapped densities of the powder.
The compressibility index is defined as [(Tapped density - Bulk density) / Tapped density] × 100. Lower compressibility index values indicate better flow properties.

Compressibility index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to Passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Table 3:Relationship between compressibility index and type of flow

Hausner Ratio: It is calculated by dividing the tapped density by the bulk density.

Hausner's ratio = tapped density/bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.2)

Post-compression parameters

Weight Variation test

Twenty tablets were randomly selected and the average weight was determined. Then, the tablets were individually weighed and the percentage deviation of their weight from the average weight was determined for each tablet. The deviation of individual weight from the average weight should not exceed the limits given below.

Average weight	**% deviation**
80 mg or less	+/- 10%
More than 80 mg but less than 250 mg	+/- 7.5%
250 mg or more	+/- 5%

Table 4:Pharmacopoeial Limit for weight variation of tablets

Thickness and diameter test

Ten tablets of Atorvastatin were picked and the tests for thickness and diameter were measured individually using Vernier calipers. All the results were recorded and the deviations of individual units from the mean diameter were calculated. The deviation of individual units from the mean diameter is calculated and ensured to not exceed ± 5% for tablets with a diameter of less than 12.5 and ± 3% for a diameter of 12.5 mm or more. By calculating the deviation of diameter, the uniformity of the diameter of the tablets can be proven.

Hardness test

The hardness of 20 tablets was tested with the use of a hardness tester. Hardness is measured in kilograms per cm^2. A minimum hardness of 4 kg/cm^2 is required for the tablet to be satisfactory.

Friability Test:

The friability of tablets was determined by using the Roche friabiliator.It is expressed in percentage (%).The friabilator was operated at 25 rpm for 4mins or up to 100 revolutions.The tablets were weighed again.
The % friability was then calculated by

$$\%F=\frac{W(initial)-W(final)}{W(initial)}*100\%$$

Uniformity of content:

Method: HPLC
Column: stainless steel octadecylsilane bonded to porous silica (5µm)

Mobile phase: A mixture of 50 volumes of a buffer solution prepared by dissolving 1.54g of ammonium acetate in 1000ml of water and adjusting the Ph to 4.0 with glacial acetic acid and 50 volumes of a mixture of 92.5 volumes of acetonitrile and 7.5 volumes of tetrahydrofuran.

Flow rate:2ml per minute
Spectrophotometer set at 246 nm
Injection volume:20µl

Reference solution: Weigh about 40mg of Atorvastatin calcium trihydrate in a 50ml Volumetric flask, add the required amount of methanol, and sonicate for 15 mins and make up the volume with the same solvent. Filter and pipette 5ml of the filtrate to 50ml of the volumetric flask, add 20ml methanol and make up the volume with the solvent mixture.

Test solution**:** Insert 1 whole intact tablet in 50 ml of the volumetric flask, disperse with 3 ml to 4 ml of water, and dissolve with methanol. Make up the volume with the same solvent and filter with the help of Whatman filter paper. Dilute 5 ml of the filtrate to 10 ml with the solvent mixture as prescribed in the assay.

Disintegration test:

For tablets, the first important step towards drug dissolution is a breakdown of the tablets into granules or primary powder particles, a process known as disintegration. All tablets must pass a disintegration test, which is conducted in vitro using a disintegration test apparatus.
The apparatus consists of a basket rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen. During testing, a tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in a bath of phosphate buffer pH 6.8, 900 ml at 50 rpm. The temperature was maintained at 37±2°C. The apparatus was operated until no residue remained on the screen or adhered to the inner surface of the disc and the disintegration time was noted.

Tablet type	**Disintegration time**
Uncoated tablet	Not more than 15 minutes
Film-coated tablets	Not more than 30 minutes
Enteric-coated tablets	Not more than 45 minutes

Table 5: Disintegration time limit

Dissolution test:
The in-vitro dissolution study was carried out in the USP dissolution test apparatus, type II (paddle). One tablet was placed in each of the six dissolution flasks containing 900 ml of dissolution medium, previously maintained at 37°C ± 0.5°C. After completion of each specified time interval, a portion of the solution was withdrawn from the zone midway between the surface of the dissolution medium and the top of the rotating blade, not less than 1 cm from the vessel wall, and filtered through a 0.45 µm membrane filter. The samples were collected at specified time intervals and diluted to the required volume with a dissolution medium. The absorbances of the standard and sample preparations were measured at 279 nm in 1 cm cells, with a suitable spectrophotometer using a dissolution medium as blank.

Finally, the percentage of the drug dissolved in Atorvastatin calcium trihydrate tablets was calculated.

Percentage release= (Sample Absorbance/ Standard absorbance) X (standard weight/ sample weight) X (sample dilution/ standard dilution) X percentage purity X 100

IVIVC (In Vitro-In Vivo Correlation):
IVIVC (In Vitro-In Vivo Correlation) is a methodology used to establish a relationship between in vitro dissolution profiles of a drug product and its in vivo pharmacokinetic behavior.

Method for the conversion of in vitro dissolution data into blood concentration

It is based on the following steps:
(a) Percent drug release values obtained from the dissolution test were converted into discrete amounts (mg) within every sampling time.
(b) Since following absorption of drugs, the elimination phase starts with a first-order kinetics, therefore the amount of drug eliminated with time was calculated using the drug's elimination rate (or rate equation), for every amount segment.

Ke= (ln C- ln C2)/ (t2- t1)

Where C1 and C2 are the predicted amount of drug in blood at each time interval (t1 and t2) and Ke is the first-order elimination rate constant.

(c) The total amount of drug present in the blood at different times was calculated by adding all the calculated drug amounts every time.

(d) The last step was to calculate the blood concentration of the drug. This will provide the expected blood level profiles. This was done by dividing the blood amount at every time by volume of distribution and average body weight.

Predicted Concentration (mcg/mL) at Times = Predicted Total Blood Amount (mg) after Absorption * (F/Vd) * body weight

Evaluation of predictability of the model

Percentage prediction error (% PE) for Cmax and AUC can be determined by the following formula:

% Prediction error = (Observed parameter-predicted parameter)/observed parameter*100

A value of +/- 10% or less confirms the predictability of the model. A value between +/- 10% and +/- 20% suggests inconclusive predictability and requires additional data. A percentage prediction error of greater than +/- 20% is indicative of inadequate or lack of predictability

Stability studies

One Formulation was selected for stability studies based on the in-vitro drug release profile. The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The most satisfactory formulation was packed in Alu-Alu foil and stored at 25℃±2℃,60±5% RH and at 40℃±2℃,75±5% RH for 2 months. Tablets were periodically removed and evaluated for physical characteristics, assay, and dissolution study.

RESULTS:

Description: Atorvastatin calcium trihydrate IP is a white-colored, Round, biconvex tablet with a plain surface on both sides.

S.No	Materials	Manufacturers name
1	Atorvastatin calcium trihydrate IP	Reine pharmaceuticals pvt.ltd
2	Microcrystalline cellulose PH 102	NB Enterprises pvt.ltd
3	Sodium lauryl sulfate	Amaga specialties pvt.ltd
4	Starch	Everest starch pvt.ltd
5	Crospovidone	Prachin chemical
6	Croscarmellose Sodium	Amishi Drugs and Chemicals Pvt.ltd
7	Sodium starch Glycolate	Nitika Pharmaceuticals pvt.ltd
8	Colloidal Silicon Dioxide	Cobot sanmar ltd
9	Magnesium stearate	Prachin chemical

Table 1 :List of materials used in formulation

Equipment Name	Capacity	Code no	Company Name
Analytical weighing balance	120 gm	MWM003	Ohaus
Vernier Caliber	12 inch	MTV003	Mitutoyo
Hardness Tester	-	HT-100TP	Campbell
Friability Tester	-	FBT-02	Astha International
Disintegration test apparatus	-	DT-02	Lab india
Rotary compression machine	27 station	CPMD3D	Chamunda
Tray drier	-	TD-02	Chamunda
HPLC	-	QC.INS.001	Agilent technologies
Dissolution Test Appratus	-	DTA-002	Lab india

Table 2 :list of equipments used in formation

S.no	Name of excipient	Ratio of API:exp	Initial observation	Final observation 2nd week	 4th week	compatibility
1	Atorvastatin calcium trihydrate (API)	1	White to yellow white	White to yellow white	White to yellow white	yes
2	API+MCC	1:1	Off-white	Off-white	Off-white	yes
3	API+SLS	1:1	white	white	white	yes
4	API+Starch	1:1	white	white	white	yes
5	API+CP	1:1	white	white	white	yes
6	API+CCS	1:1	white	white	white	yes
7	API+SSG	1:1	white	white	white	yes
8	API+CSD	1:1	white	white	white	yes
9	API+MS	1:1	white	white	white	yes

Table 3:Drug-Excipient compatibility study of Atorvastatin

S.no	Items	F1	F2	F3	F4	F5
1	Atorvastatin calcium trihydrate	10.85mg	10.85mg	10.85mg	10.85mg	10.85mg
2	Microcrystalline cellulose PH 102	52.150mg	57.150mg	57.150mg	52.150mg	52.150mg
3	Sodium lauryl sulphate	5mg	5mg	5mg	5mg	5mg
4	starch	4mg	4mg	4mg	4mg	4mg
5	Crospovidone	5mg	5mg	2.5mg	5mg	3mg

6	croscarmellose	5mg	-	2.5mg	5mg	3mg
7	Sodium starch glycolate	5mg	5mg	-	5mg	5mg
	For lubrication					
1	crospovidone	-	-	2.5mg	-	2mg
2	croscarmellose	-	-	2.5mg	-	2mg
3	Colloidal silicon dioxide	1.5mg	1.5 mg	1.5mg	1.5mg	1.5mg
4	Magnesium stearate	1.5mg	1.5mg	1.5mg	1.5mg	1.5mg
	Weight of a tablet	90 mg	90mg	90 mg	90mg	90mg

Table 4:Hit and Trial formulation of Atorvastatin calcium Trihydrate (10mg)

Formulation	Bulk density	Tapped density	Angle of repose	Carrs index %	Hausner ratio
F1	0.380±0.03	0.420±0.02	24.3°	9.10±0.68	1.10±0.05
F2	0.374±0.04	0.421±0.04	25.6°	10.88±0.37	1.09±0.03
F3	0.388±0.03	0.426±0.04	24.2°	8.93±0.26	1.08±0.04
F4	0.372±0.02	0.432±0.03	24.8°	13.88±0.32	1.09±0.05
F5	0.394±0.04	0.431±0.02	26.8°	8.58±0.18	1.09±0.02

Table 5:Pre-formulation studies of Atorvastatin Calcium Trihydrate

Formulation	Assay percentage
F1	99.6
F2	98.8
F3	100.1
F4	99.7
F5	99.8

Table 6:Assay percentage of Formulation (F1 to F5)

Formulation	Uniformity of content
F1	99%
F2	101%
F3	102%
F4	98%
F5	103%

Table 7: Uniformity of content of Formulation (F1 to F5)

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Weight variation (mg)
F1	2.6±0.15	2.89±0.011	0.38±0.036	91±0.12
F2	2.8±0.21	2.90±0.014	0.48±0.026	92±0.16
F3	3.73±0.14	2.88±0.016	0.28±0.024	90±0.16
F4	2.5±0.19	2.84±0.017	0.36±0.032	91±0.13
F5	3.50±0.17	2.89±0.013	0.31±0.025	90±0.14

Table 8 Post-compression parameters of Atorvastatin (F1 to F5)

Formulation	Disintegration Time
F1	3min 50sec
F2	4min 35sec
F3	3min 5sec
F4	3 min 41sec
F5	4min 55sec

Table 9 Study of disintegration time of Atorvastatin (F1 to F5)

Time (mins)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	60.54	65.25	80.15	58.29	71.18
10	76.42	73.68	95.64	64.26	82.60
15	91.84	89.78	103.94	92.25	93.51
30	95.57	91.27	112.36	95.64	98.68

Table 10 In-vitro dissolution profile of all the formulation

Time (hrs)	% Released (cumulative)	% Released (within sampling interval)	Amt (mg) Released(within sampling interval)
0	0	0	
0.083	82.32	82.32	8.232
0.166	91.78	9.46	0.946
0.25	103.95	94.49	9.449
0.33	106.84	12.35	1.235
0.41	110.52	98.17	9.817
0.5	112.37	14.2	1.42
0.583	110.72	96.52	9.652
0.666	111.49	14.97	1.497
0.75	110.55	95.58	9.558
0.833	110.97	15.39	1.539
0.916	106.97	91.58	9.158
1	110.72	19.14	1.914

Table 11: Percent dissolution at different times with corresponding percent and amount in mg obtained within the sampling interval.Values represent average of 6 tablets

The pharmacokinetic parameters were obtained from the well-authentic published literature and the values reported there are as follows:

Bioavailability, F = 12% =0.12

Volume of distribution, Vd = 381 L/70 kg

=381/70 L/kg

=5.44 L/kg

Body weight = 70 kg

Half-life ($t_{1/2}$) = 14 hours

Elimination rate constant, ke = 0.693/ half- life

= 0.693/ 14

= 0.0495 per hour

Volume of Distribution (Vd) =Dose/Plasma concentration

Plasma concentration =Dose/Vd

=10mg/381

=0.026mg/L

Cmax = 19.82 ng/ml

Tmax= 1hr

AUC=124.027

Dissolution sampling time(hr)	0.083	0.16	0.25	0.33	0.41	0.5	0.583	0.666	0.75	0.833	0.916	1
Amount(mg) equivalent	8.232	0.946	9.449	1.235	9.817	1.42	9.652	1.497	9.558	1.539	9.158	1.914
Time after absorption (h)	Blood amount after absorption											
0	0											
0.083	8.232											
0.16	8.198248	0.946										
0.25	8.164635	0.94212133	9.449									
0.33	8.131159	0.93825857	9.410258423	1.235								
0.41	8.097821	0.93441164	9.371675689	1.229936	9.817							
0.5	8.064619	0.93058049	9.333251147	1.224894	9.77675	1.42						
0.583	8.031554	0.92676504	9.294984149	1.219871	9.736664	1.4142	9.652					
0.666	7.998624	0.92296524	9.256874047	1.21487	9.696743	1.4084	9.6124	1.497				
0.75	7.965829	0.91918101	9.218920201	1.209889	9.656986	1.4026	9.573	1.49086	9.558			
0.833	7.933168	0.91541236	9.181121967	1.204928	9.617392	1.3969	9.5338	1.48475	9.51881	1.539		
0.916	7.900642	0.91165905	9.143478709	1.199988	9.57796	1.3911	9.4947	1.47866	9.47978	1.53269	9.158	
1	7.868249	0.90792118	9.105989791	1.195068	9.538689	1.3854	9.4557	1.4726	9.44092	1.52641	9.120515	1.914

Table 12 :Calculated Drug levels at different times following absorption of drug released in vitro during sampling intervals. Dissolution values represent an average of 6 tablets

Total Blood Amt(mg)	Conc(ng/mL)	AUC
0	0	0
8.232	2.59275591	1.29637795
9.14424821	2.88007818	2.73641704
18.55575614	5.84433264	4.36220541
19.71467621	6.20934684	6.02683974
29.45084462	9.27585657	7.74260171
30.75009405	9.68506899	9.48046278
40.27601646	12.6853595	11.1852143
41.60788191	13.1048447	12.8951021
50.99528661	16.0615076	14.5831761
52.32520228	16.4803787	16.2709431
61.2686652	19.2972174	17.888798
62.93145928	19.8209321	19.5590747

Table 13:Concentrtion of AUC and conc. at different time intervals

Time	Concentration
0	0
0.083	2.59
0.16	2.88
0.25	5.84
0.33	6.2
0.41	9.27
0.5	9.68
0.583	12.68
0.666	13.1
0.75	16.06
0.833	16.48
0.916	19.29
1	19.82

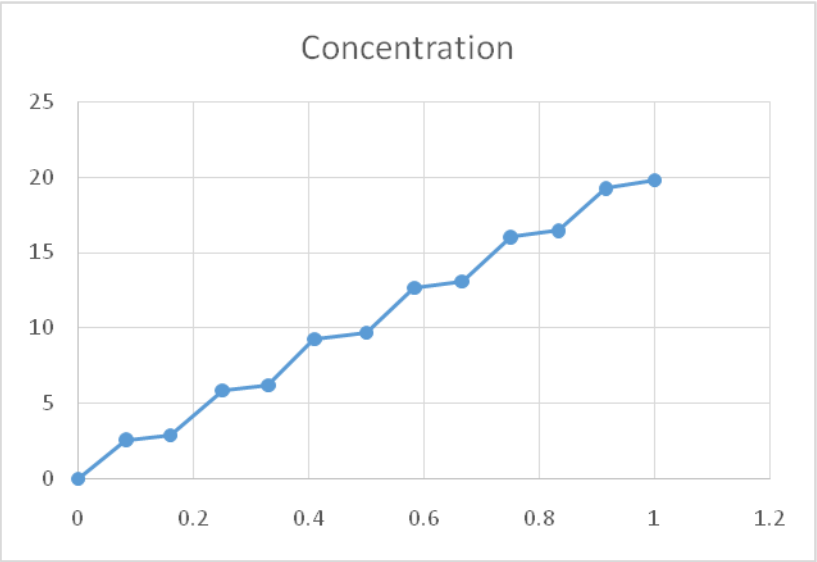

Table 14:Time vs conc.

Interval (month)		Initial	1	2
Test performed	specifications	To Comply	To Comply	To Comply
Description	White-colored, round, biconvex, film-coated tablet	complies	complies	complies
Identification	Positive for Atorvastatin calcium trihydrate	complies	complies	complies
Avg. weight	(90±7.5%)mg/tab	1.820 gm	1.880	1.864
Assay	Between 9.0 mg /tab to 11.0 mg/tab (90.0 % to 110.0 % of the stated amount)	100.1%	99.86%	99.67%
Uniformity of content	85 % - 115 % of the average content of atorvastatin	102%	103.2%	102.4%
Dissolution	D. Not less than 70 % of the stated amount of atorvastatin.	112.36%	110.4%	108.6%
DT	Not more than 30 min	3min 5sec	3min 15sec	3min 58sec

Table 15:Real time stability testing of optimized formulation (F3) of Atorvastatin

Interval (month)		Initial	1	2
Test performed	specifications	To Comply	To Comply	To Comply
Description	White-colored, round, biconvex, film-coated tablet	complies	complies	complies
Identification	Positive for Atorvastatin calcium trihydrate	complies	complies	complies
Avg. weight	(90±7.5%)mg/tab	1.820 gm	1.865	1.886
Assay	Between 9.0 mg /tab to 11.0 mg/tab (90.0 % to 110.0 % of the stated amount)	100.1%	98.89%	97.67%
Uniformity of content	85 % - 115 % of the average content of atorvastatin	102%	103.60%	102.4%
Dissolution	D. Not less than 70 % of the stated amount of atorvastatin.	112.36%	109.4%	107.6%
DT	Not more than 30 min	3min 5sec	3min 30sec	4 min 10 sec

Table 16 Accelerated stability testing of Optimized formulation (F3)of atorvastatin

DISCUSSION

In the present study, various formulations of Atorvastatin calcium trihydrate were prepared by the wet granulation method. Since Atorvastatin falls under BCS class II drug a suitable disintegrating agent was chosen to enhance the solubility. In the hit and trial formulation (F1 to F5) shown in Table 6 super disintegrating agents such as SSG, CP, and CCS were added. The thesis focuses on formulating atorvastatin tablets using different super-disintegrating agents. Superdisintegrants are substances that facilitate the rapid disintegration of tablets, leading to quick drug release and dissolution. The choice of super-disintegrating agents can impact the formulation's disintegration time, dissolution rate, and subsequent drug absorption. The thesis explores various super-disintegrating agents, such as crospovidone, croscarmellose sodium, and sodium starch glycolate, among others. The tablets formulated with different super disintegrants are evaluated for parameters like hardness, friability, disintegration time, and drug content uniformity.

The drug-excipient compatibility study was performed and found no interaction between the drug and excipients.FT-IR spectral analysis was done and it showed that there were no changes in any characteristic peaks of pure drug Atorvastatin calcium trihydrate and excipients which confirmed the absence of chemical interaction between pure drug and excipients.

The results of pre-Formulation parameters such as angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio, of the different formulations(F1 to F5), shown in Table 10 were found within the limits. After the pre-formulation study assay percentage and uniformity of content of formulation (F1 to F5) were also calculated which was shown in Table 11 and Table 12 respectively the result obtained was within the limits.

The results of the post-compression parameters such as thickness, hardness, friability, and weight variation for the prepared formulations shown in Table 13 were found within the limits.
The in-vitro analysis of the formulation F3 shows the best result as shown in Tables 15 and 16. In formulation F3 increasing the concentration of super disintegrants and adding CP and CCS in both intragranular and extra-granular portions increases the cumulative percentage of drug release.
The in-vitro disintegration time for all the formulations is below 4 minutes. All formulations were subjected to dissolution studies. All formulations of Atorvastatin calcium Trihydrate have shown drug release within 30 min.
Finally, formulation F3 was selected as the best formulation by the study of disintegration time and dissolution profile.
The optimized formulation was kept for stability studies. The condition for real-time stability was 25°c ±2°c/60%±5% performed for 2 months and for accelerated stability study 40°c±2°c/75%±5% RH kept for 2 months and parameters like physical appearances. Avg. weight, Uniformity of content, Assay, Dissolution, and DT were evaluated as shown in Table 20 and Table 21.

CONCLUSION

In conclusion, the Optimized formulation of Atorvastatin Calcium Trihydrate showed satisfactory pre and post-compression parameters. Formulation trial 3 is considered to be the best within the desired drug release. The research aimed to enhance the understanding of the impact of different super disintegrants on the formulation characteristics and in vivo drug absorption of atorvastatin.
Through the formulation and evaluation process, it was observed that the choice of a super disintegrating agent significantly influenced the disintegration time, dissolution rate, and subsequent drug release of atorvastatin tablets. The incorporation of different super disintegrants provided an opportunity to optimize the tablet formulation, ensuring rapid disintegration and improved drug release.
Furthermore, the IVIVC study played a crucial role in establishing a correlation between the in vitro dissolution profiles and the in vivo drug absorption behavior of atorvastatin tablets. From IVIVC by convolution method, it is found that the value of Cmax is 19.82 ng/ml, Tmax is 1 hr and AUC is obtained from the graph as 124.027µg.h/ml.

REFERENCES

1. Goodman and Gilman, Drug therapy for hypercholesterolemia and dyslipidemia, the Goodman and Gilmans manual of pharmacology and therapeutics,11th edition pg no.614-620

2. James E. Newby, JR, M.D. Hyperlipidimia, www.NewByFoundation.com

3. Rome R.C, Shesky R.J, and Weller P.J., editors, Handbook of pharmaceutical excipients, Joint publication of A.P.S and R.P.S.G.B, 4th edition,2003

4. Rowe, Paul J.S and Sian C.O. Handbook of Pharmaceutical Excipients fifth edition (2006), published by the pharmaceutical press publications division of the royal pharmaceutical society of Great Britain, UK

5. Textbook of physical pharmaceutics By CVS.Subrahmanyan,vallabhprakashan second edition 2000, page no: 287-289

6. Kriti RODE.N.Thirumoothy, B.parthsarthi, Ajish John, Pankajgawate, Study on formulation development and evaluation of atorvastatin film-coated tablet, JLPWR vol2 issue 2 (mar-jun) -2011

7. Leon Lachman, Joseph L, Kanjg,3rd Ed,1986,-The theory and practice of industrial pharmacy,331-2,364-8, Lea and Fibiger, Philadelphia.

8. Gosai Ar.Patil sb. Sawant kk, Formulation and evaluation of dispersible tablets of ondansetron Hydrochloride by direct compression using super disintegrants, international journal of pharmaceutical sciences and Nanotechnology,2008;1(1):106-111.464

9. Qadir A Et AI "Comparative evaluation of current super disintegrants pharmaceutical technology, Oct (2006)

10. Sekar V, Chellan vr, Immediate release tablets of telmisartan using super disintegrants-formulation, evaluation, and stability studies chem. Pharm Bull (Tokyo),2008 Apr;56(4) 575-7

11. Brown D, orally disintegrating tablets-taste over speed drug delivery technology,2003;3(6)

12. Mohamed, M. F., Trueman, S., Othman, A. A., Han, J. H., Tzuchi R. Ju, and Marroum, P., (2019, November). *Development of In Vitro–In Vivo Correlation for Upadacitinib Extended-Release Tablet Formulation*.Retrieved from: www.ncbi.nlm.nih.gov/pmc/articles/PMC6814631/ Retrieved on: Feb 16, 2022

13. Abhilash, Dr. R. (2001, March 1). *Quality control tests for tablets*. Quality Control Tests for Tablets; Retrieved from: https://www.slideshare.net/mallikarjunvasm/quality-control-tests-for-tablets?fbclid=IwAR3m24BtyjPl3qHMxerB4DeLPJwIEHzGG1JrtotL9My6YIBM0J64Yz4OSLw Retrieved on: March 16, 2022.

14. General Chapters: UNIFORMITY OF DOSAGE UNITS, Retrieved from: http://pharmacopeia.cn/v29240/usp29nf24s0_c905.html Retrieved on: Feb 16, 2022.

15. Siew, A., & Ph.D., A. S. (2016, November 2). *Dissolution Testing*. PharmTech; www.pharmtech.com. Retrieved from: https://www.pharmtech.com/view/dissolution-testing-3 Retrieved on: March 16, 2022.

16. Min-Soo Kim, Shun-Ji Jin, Jeong-Soo Kim, Hee Jun Park, Ha-Seungsong, Reinhard H.H. Neubert, Sung-Joohwang, Preparation, Characterization And In Vivo Evaluation Of Amorphous atorvastatin Calcium Nanoparticles Using Supercritical antisolvent (Sas) Process, European Journal Of Pharmaceutics And Biopharmaceutics 69 (2008) 454–465.

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18. Ankush,C.;Avtar,C.;Geeta,Aggarwal;Kumar,V.andFoziyah,Z.(2012).Development and characterization of an atorvastatin solid dispersion formulation using skimmed milk for improved oral bioavailability.

19. Quadir A Et Al "Comparative Evaluation Of Current Superdisintegrants" Pharmaceutical Technology., Oct (2006).

20. Patel Dipika, Patel Vijay Kumar, Formulation Development And Evaluation Of Immediate Release Tablets Containing Atorvastatin Calcium Drug, International Journal Of Pharmaceutical Erudition, May 2012, 2 (1), 1-8.

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