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FORMULATION DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE SUSTAIN RELEASE TABLETS OF A LIPID LOWERING AGENT WITH FENUGREEK MUCILAGE

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ABSTRACT

The design of oral sustained release DDS depends on various factors such as, physicochemical properties of drug, type of delivery system, disease being treated, and patient condition, and treatment duration, presence of food, gastrointestinal motility, and co-administration of other drugs. Sustained release, sustained action, prolonged action controlled release, extended release, depot release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug. Atorvastatin (Lipitor) is a member of the drug class known as statins. It is used for lowering cholesterol. Atorvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate. Atorvastatin acts primarily in the liver. Decreased hepatic cholesterol levels increases hepatic uptake of cholesterol and reduces plasma cholesterol levels. The aim of the present study to aim to formulate gastro retentive sustained release tablets and evaluate the function of fenugreek seed mucilage as potential matrix forming agent with Atorvastatin for synergistic effect.

KEYWORDS: Atorvastatin, Formulation, Sustain release drug, Analytical parameters.

INTRODUCTION

Atorvastatin is an anti-hyperlipidemic drug which is used in the management of obesity. It inhibits 3-hydroxy-3-methylglutaryl-coenzyme reductase (HMG-CoA reductase) enzyme which is responsible for conversion of HMG-CoA to mevalonate. Mevalonate is an early rate limiting step in sterol biosynthesis.[1] In this mechanism, Atorvastatin is administrated to decrease the cholesterol and triglycerides level in patients with hypercholesterolemia, mixed dyslipidemia and familial hypercholesterolemia.[2] Atorvastatin is very slightly soluble in distilled water, phosphate buffer and acetonitrile whereas freely soluble in methanol and slightly soluble in ethanol.[3] The absolute bioavailability of Atorvastatin is about 14% due to its low solubility and first pass metabolism in liver.[4,5] So the quality parameters assessment of atorvastatin sodium is an important factor for ensuring its effectiveness. Tablet is one of the most suitable dosage form as it is easy to manufacture, convenient to administer, accurate in dosing and more stable compared to other dosage forms. Besides, it is more resistant to temperature as compared to capsules. Various factors like the disintegration and dissolution and physiological properties of drug affect the bioavailability of drugs. The process of quality control is conducted to confirm an expected level of quality in a product. It includes the necessary actions, a business conceives, essential to provide for the control and verification of various parameter of a product.[6] Different quality parameters like weight variation, hardness, friability, disintegration time, dissolution profile etc. which play a significant effect on the drug product formulation.[7] We know that atorvastatin calcium is available in market in different form except sustain release tablet. Therefore, the present study was designed to formulate and evaluate atorvastatin calcium sustain release tablet to enhance its therapeutic action.

MATERIALS

Atorvastatin was collected as a gift sample from Aurobindo Pharma Ltd., Hyderabad. All other chemicals used were of analytical grade and were used as received. Fenugreek seeds were procured from the local market. HPMC K4, Sodium alginate, Gum tragacanth, MCC, Talc, Mg Stearate were used in formulation.

METHODS

Pre-formulation studies

Pre-formulation studies can therefore be defined as; Laboratory studies to determine the characteristics of

active substance and excipients that may influence formulation and process design and performance. It has been described as "Learning before doing".

Identification of drug

Physical Appearance - White solid (powder)**.**

Melting Point- Melting point of the Atorvastatin was found to be in the range of 158 -161°C which was determined with the help of Melting Point apparatus.

Table 1: Solubility study of drug.

S. No.	Solvent	Solubility
1.	Distilled Water	Very Slightly soluble
2.	PBS pH 7.4	Very Slightly soluble
3.	Acetonitrile	Very Slightly soluble
4.	Ethanol	Slightly Soluble
5.	Methanol	Freely Soluble

FT-IR spectroscopy

FTIR spectroscopy was performed and results were compared to the standard it was performed on FTIR (shimadzu Japan). The results of the IR matched to the standard FTIR of the Atorvastatin. Identification of atorvastatin calcium (ATV) by using FTIR has been concern, the region of FTIR started from 400cm-1 to4000cm^{-1}, also it has region started from 4000^{cm-1} to 1500^{cm-1} it called functional group region it interprets any FTIR spectrum. Second region called finger print region it less than1500cm-1, it more complicated region in IR. It compare between standard drug spectrum and sample to attach it. Shimadzu 8400S Fourier Transformation Infra-Red FTIR has been used to analyse of Atorvastatin Calcium for market samples using FTIR. Many repetitions have been repeated more than 20 times to get in Figure. The IR spectrum showing percentage transmission (%T) versus wave number (cm-1) of Atorvastatin calcium (ATV) is shown in Figure 1& 2. Many characteristics of chromatogram of C=O stretching and aromatic N-H stretching at 1649.81cm-1 and, 3364.21cm-1 respectively. However, formulation show similar peaks but with a negligible shift for C=O stretching and aromatic N-H stretching at1647.67cm-1 and 3363.17cm-1. That proves from the figures that are ATV in nanoparticles doesn't undergo any chemical activity and reaction with any of the excipients used in this formulation. A spectrum of ATV showed above by using FTIR instrument showed exhibit many characteristics of different functional groups in different values started from 828 up to 3240 included aromatic functional groups include C-N, O-H, N-H, C=O, C=C,C-O, in ATV drug and aromatic substitution bands, structural of ATV calcium was shown in the Figure 1 & 2.

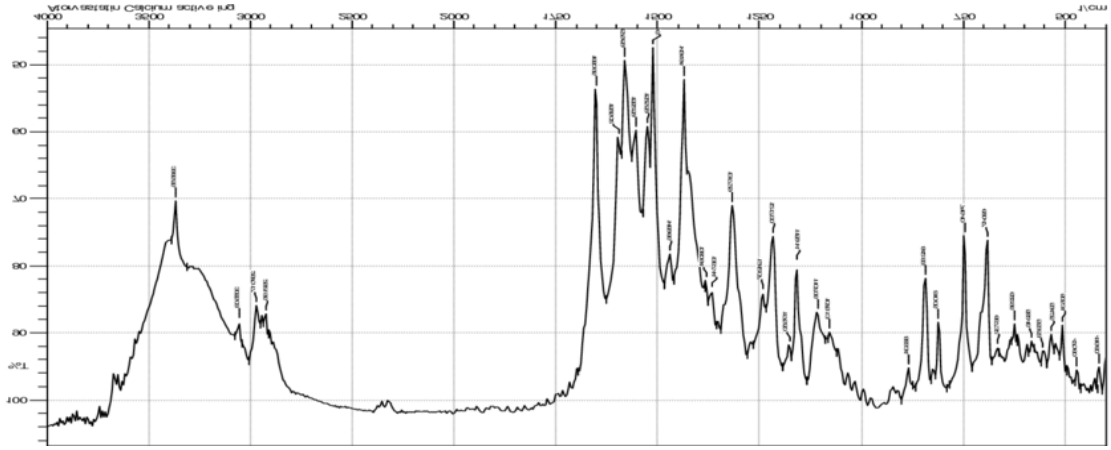


Figure 1: FTIR of the standard.

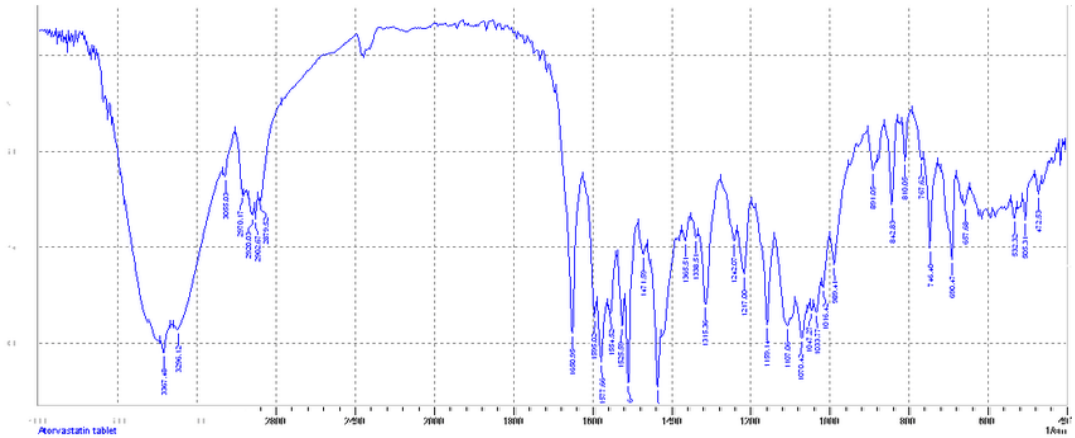


Figure 2: FTIR of the sample.

UV spectrophotometry

Determination of the wavelength of maximum absorption (max) of atorvastatin

0.200 (20mg) of ATV powder was accurately weighed, dissolved and transferred to a volumetric flask, anhydrous methanol was added and dissolved for dissolution and the solution was completed to the mark with deionized water to give 200µg/ml stock solution which was diluted suitably to produce. The above solution was diluted and scanned by UV-Spectrophotometer from the spectrum of the drug obtained λ of ATV was determined 245nm. Atorvastatin solution: 0.020g from Atorvastatin calcium were weighed, dissolved in anhydrous methanol then transferred quantitatively into volumetric flask, completed the max volume to the mark with deionized water and mixed well. From these stock solutions, working standard solutions having different concentrations 5-30µg/ml was prepared by appropriate dilutions with the same solvent.

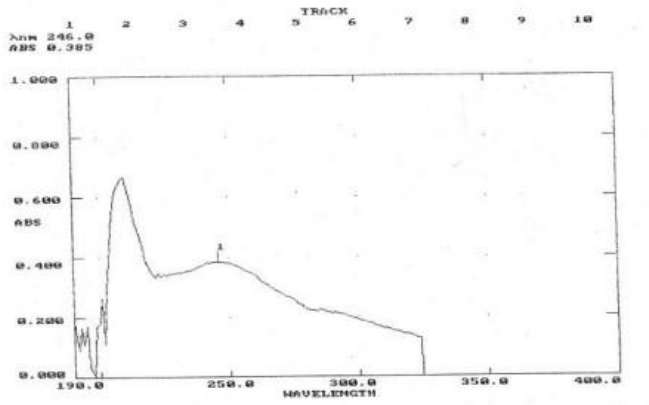


Figure 3: Wavelength of atorvastatin.

Extraction and isolation of fenugreek mucilage

Fenugreek seeds (250g) were soaked in double distilled water at room temperature and then boiled with sufficient amount of double distilled water under stirring condition in a water bath until slurry was prepared. Then the slurry was cooled and kept in refrigerator overnight to settle out undissolved materials. The upper clear solution was decanted off and centrifuged at 1000 rpm for 30 minutes. The supernatant was separated and concentrated at 50-55º C on a water bath to a third of its original volume. Solution was cooled down to room temperature and was poured into thrice volume of acetone by continuous stirring. The precipitate was washed repeatedly with acetone and dried.

Evaluation of mucilage

Determination of percentage yield

Percentage yield of mucilage was determined using this formula.

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} * 100$$

Physico-chemical characterization of mucilage

The separated mucilage was evaluated for swelling index, loss on drying, density, compressibility index and angle of repose.

Determination of swelling index

The swelling index is the volume in ml occupied by 1g of drug; including any adhering mucilage after it has been swollen in an aqueous liquid for 4h. The swelling index of Fenugreek mucilage powder was determined according to the BP, 2000.[8] One gram of mucilage powder was taken in a 25 ml ground glass stopper cylinder graduated over a height of 120 to 130 mm in 0.5 divisions. To this 25 ml of water was added and this was shaken vigorously every 10 m for 1h and then allowed to stand for 24 h. The volume occupied by mucilage was measured. The swelling index was calculated from the mean of three determinations.

Swelling Index % (SI) = (W2 – W1/W1) x 100 ------ (1)

W1= Initial Volume in ml

W2= Final Volume in ml

Loss on drying of isolated mucilage

Loss on drying was directly measured by moisture balance. Firstly, calibrated the instrument by knob then taken 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 15 minutes and constant reading set the knob and check % moisture.

Method for preparation of Atorvastatin sustained release tablet

Atorvastatin, polymers, and excipients were mixed thoroughly and passed though sieve 60. The tablets with different composition (Table 2) were prepared by direct compression technique on a rotary punch tablet compression machine. The powder was weighed and individually filled in the die cavity (8 mm diameter), and constant pressure was applied. The tablets were evaluated for various parameters like thickness, average weight, hardness, drug content, Swelling Index, mucoadhesive strength and in vitro drug release.

Table 2: Optimization of mucoadhesive tablets of atorvastatin.

Excipients (mg)	F1	F2	F3	F4
Atorvastatin	10	10	10	10
HPMC K4	25	50	25	50
Fenugreek mucilage	10	10	10	10
Sodium alginate	10	20	-	-
Gum tragacanth	-	-	10	20
MCC	75	40	75	40
Talc	10	10	10	10
Mg Stearate	10	10	10	10
Total Weight	150	150	150	150

Evaluation of powder blend[9,10]

Bulk density

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup. A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculated the bulk density, in gm per ml gm/ml, by the formula

Bulk density = Bulk Mass/ Bulk Volume

Compressibility index (Carr's index)

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free-flowing material. It was calculated as per given formula:

$$C.I. = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} x100$$

Hausner's ratio

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density / Bulk Density

Evaluation of tablets[11-14]

General appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated.

Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ max of 232.0 nm using 0.1 N HCl blank.

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester.

Friability

The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCl was set into the dissolution flask maintaining the temperature of 37±0.5 °C and rpm of 75. One atorvastatin tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2 hours using 10ml pipette. The new disintegration medium (37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 245nm using spectroscopy. The plot of cumulative percentage drug release V/s time (hrs) for preliminary formulations were plotted.

RESULTS AND DISCUSSIONS

The separated mucilage was evaluated for swelling index, loss on drying, density, compressibility index and angle of repose. In physico-chemical characterization of mucilage appearance was found to be mucilaginous, color was brown and state was solid. The compressibility index and Hauser's ratio of all the formulations was found within limit which show that the powder has good

flow properties. The data obtained of post-compression parameters such as hardness; thickness, friability, weight variation and amount of drug content are shown in table. Tablets obtained were of uniform weight (due to uniformly fill) with acceptable variation as per IP specifications. The percentage drug content of all the tablets were found in the range of 98.78±0.15 to 99.45±0.2 percentage, which was within the acceptable limits. Hardness of the tablets was found to be 5.1±0.2-5to 3±0.3kg/cm^2. The thickness of tablets was found to be 2.11±0.01 to 2.15±0.01mm.The result revealed that the tablets of all the formulations showed uniform thickness. In all the formulations, the friability values were less than 1% and meet the Indian pharmacopoeia (I.P) limits. Drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and Hausner's ratio Table 4. Tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability, and in vitro dissolution Table 5. All formulations showed uniform thickness. In a weight variation test, pharmacopoeias limit for the percentage deviation for tablet so more than 155 mg is ±5%. Average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of tablets and percentage of drug content was more than 95%. Tablet hardness is not an absolute indicator of strength. Another measure of tablets strength is friability. Conventional compressed tablets that less than 1% of their weight is generally considered acceptable. In the present study, percentage friability for all formulations was below1 %, indicating that friability was within the prescribed limits. All tablet formulations showed acceptable Pharmaco-technical properties and complied with the in house specifications for weight variation, drug content, hardness, and friability. The results of *in vitro* disintegration time of all the formulations were found to be within the prescribed limits and satisfied the criteria of sustained release tablets Table 6. The cumulative percentage of the drug released for formulation F4 showed better drug release Table 7.

Table 3: Physico-chemical characterization of mucilage.

S. No.	Physico-chemical characterization	Results of mucilage
1.	Appearance	Mucilaginous
2.	Color	Brown
3.	State	Solid

Table 4: Result of pre-compression properties of atorvastatin powder blend.

F. Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index	Hausnerrato
F1	0.245	0.365	32.877	1.490
F2	0.263	0.374	29.679	1.422
F3	0.252	0.336	25.000	1.333
F4	0.241	0.372	35.215	1.544

Table 5: Results of post compression properties of Atorvastatin sustained release tablets.

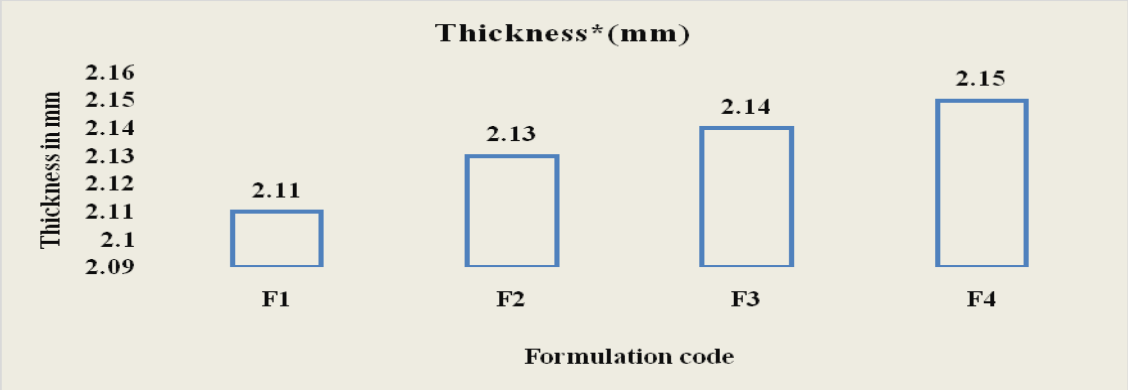
Formulation code	Thickness* (mm)	Hardness (kg/Cm^2)	Weight Variation (mg)	Friability (%)	Drug content (%)
F1	2.11	5.1	203	0.658	98.89
F2	2.13	5.2	205	0.623	98.98
F3	2.14	5.1	198	0.785	98.78
F4	2.15	5.3	203	0.856	99.45

Table 6: *In-vitro* drug release study of tablets.

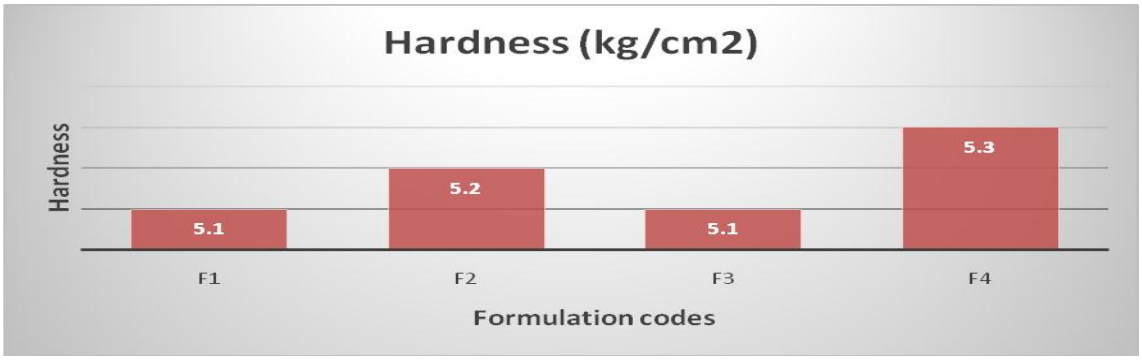
Time(hr)	%Cumulative drug release			
	F1	F2	F3	F4
3	33.45	30.45	28.98	25.65
6	55.48	45.58	40.65	39.98
9	69.98	58.89	50.65	46.65
12	98.85	68.78	61.56	58.78
15	-	99.12	88.98	73.36
18	-	-	98.85	85.65
21	-	-	-	92.56
24	-	-	-	99.45

Table 7: *In-vitro* drug release data for optimized formulation F4.

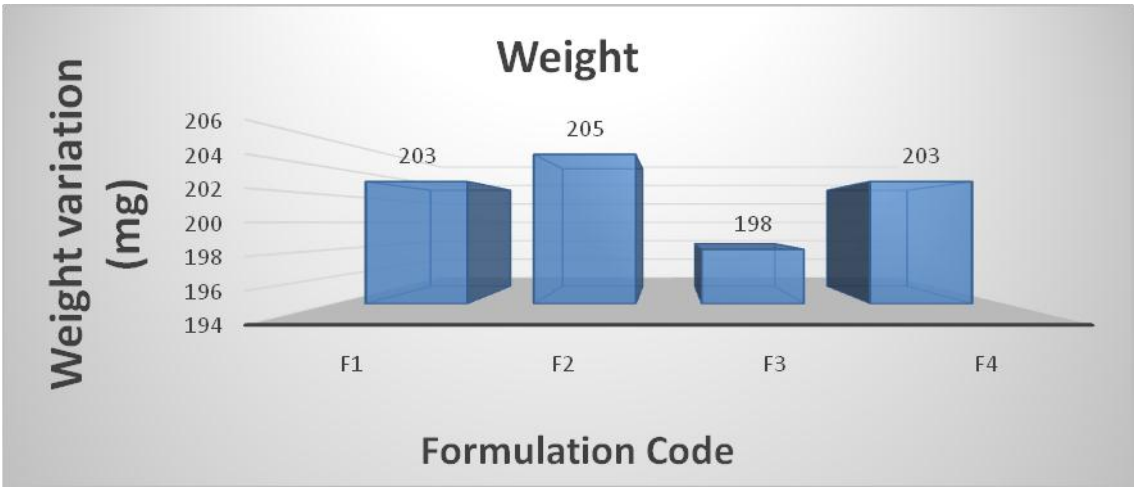
Time(h)	Cumulative*% Drug Release	Cumulative% Drug Remaining
3	18.89	81.11
6	35.56	64.44
9	43.32	56.68
12	55.58	44.42
15	63.32	36.68
18	79.98	20.02
21	85.56	14.44
24	92.14	7.86
28	99.45	0.55



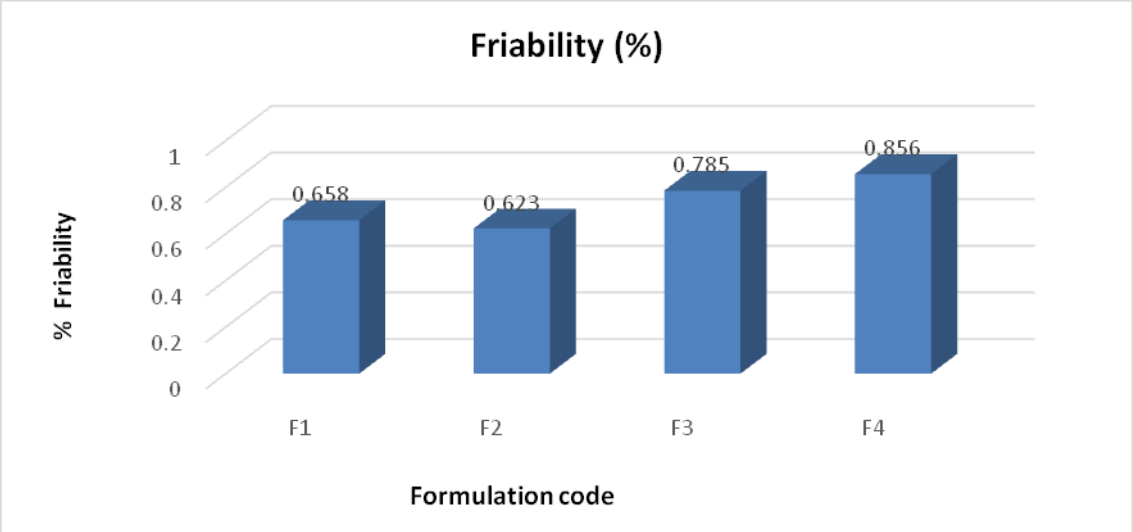
Graph showing thickness of the tablets



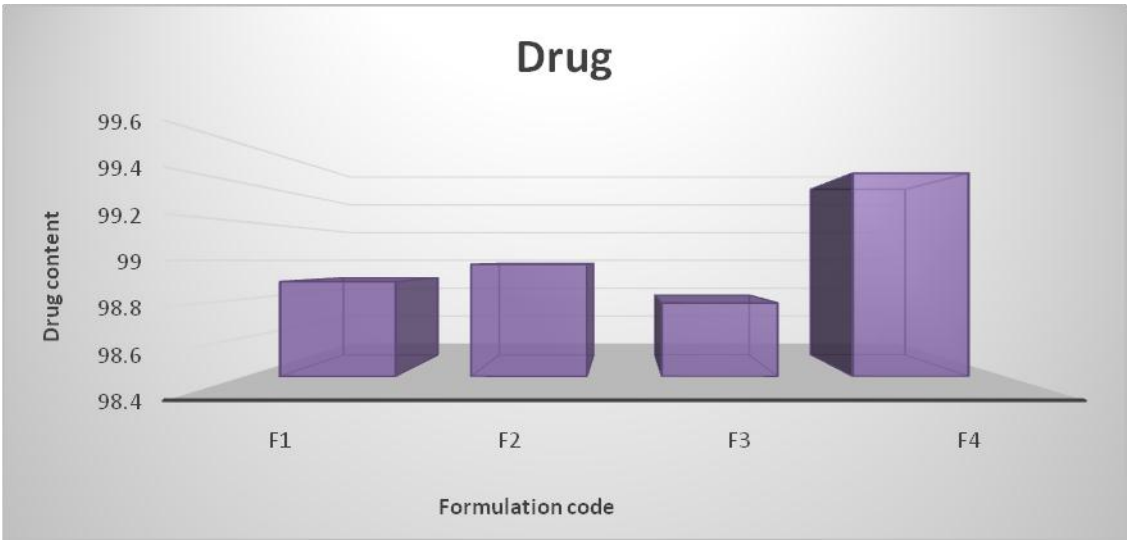
Graph showing hardness of the tablets



Graph showing weight variation



Graph showing % friability



Graph showing % drug content

CONCLUSION

Pre-formulation and drug excipient compatibility study indicate the way and method of drug formulation. Formulation of Atorvastatin calcium tablet fulfill different analytical test like weight variation, hardness, friability, disintegration and dissolution. Besides, method of preparation is simple, cost effective and scalable. So, it can be concluded that formulation of atorvastatin tablet will be beneficial for delivering the drug which will meet the therapeutic action.

REFERENCES

1. Malhotra, H.S. and Goa, K.L., Atorvastatin; Drugs, 2001; 61(12): 1835-1881.
2. Kadu, P.J., Kushare, S.S., Thacker, D.D. and Gattani, S.G., Enhancement of oral bioavailability of atorvastatin calcium by self-emulsifying drug delivery systems (SEDDS); Pharmaceutical Development and Technology, 2011; 16(1): 65-74.
3. McCrindle, B.W., Ose, L. and Marais, A.D., Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebocontrolled trial; The Journal of pediatrics, 2003; 143(1): 74-80.
4. Cilla Jr, D.D., Whitfield, L.R., Gibson, D.M., Sedman, A.J. and Posvar, E.L., Multiple-dose pharmacokinetics, pharmacodynamics, and safety of atorvastatin, an inhibitor of HMG-CoA reductase, in healthy subjects; Clinical Pharmacology & Therapeutics, 1996; 60(6): 687-695.
5. Lennernäs, H., Clinical pharmacokinetics of atorvastatin; Clinical pharmacokinetics, 2003; 42(13): 1141- 1160.
6. Dewan, A., Pacifico, R., Zhan, R., Rinberg, D. and Bozza, T., Non-redundant coding of aversive odours in the main olfactory pathway; Nature, 2013; 497(7450): 486.
7. Sarwar, G., Das, A., Kibria, M.G., Karmakar, P. and Sattar, M.M., In vitro Quality Analysis of Different

Brands of Alprazolam Tablet Available in Bangladesh. Bangladesh Pharmaceutical Journal, 2013; 16(2): 185-188.
8. British Pharmacopoeia Volume-I; British Pharmacopoeia Commission; London, 2000; 79-36-39.
9. Kalakuntla, R., Veerlapati, U., Chepuri, M. and Raparla, R., Effect of various super disintegrants on hardness, disintegration and dissolution of drug from dosage form; J. Adv. Sci. Res, 2010; 1(1): 15-19.
10. Kale, V.V., Kasliwal, R. and Parida, S.K., Formulation and release characteristics of guar gum matrix tablet containing metformin HCl. Int. J. Pharm. Expt, 2004; 75-80.
11. Jain P, Nair S, Jain N, Jain DK, Jain S. Formulation and evaluation of solid dispersion of lomefloxacin hydrochloride. International Journal of Research in Pharmaceutical Sciences, 2012; 3(4): 604-608.
12. Pandey SP, Khan MA, Dhote V, Dhote K, Jain DK. Formulation development of sustained release matrix tablet containing metformin hydrochloride and study of various factors affecting dissolution rate. Scholars Academic Journal of Pharmacy, 2019; 8(3): 57-73.
13. Patel AK, Rai JP, Jain DK, Banweer JI. Formulation, development and evaluation of cefaclor extended release matrix tablet. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(4): 355-7.
14. Gautam SP, Rai JP, Billshaiya U, Jain N, Vikram P, Jain DK. Formulation and evaluation of mouth dissolving tablet of loperamide. International Journal of Pharmaceutical Sciences and Research, 2013; 4(5): 1782.