



CODEN [USA]: IAJ PBB

ISSN : 2349-7750

INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

Available online at: <http://www.iajps.com>

Research Article

FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF POORLY SOLUBLE DRUG ATORVASTATIN USING SUPERDISINTEGRANTS

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Article Received: July 2022

Accepted: July 2022

Published: August 2022

Abstract:

Atorvastatin belongs to the group of medications known as HMG-CoA reductase inhibitors (statins). Sublingual tablets, which disintegrate in the oral cavity beneath the tongue in less than a minute, are solid dosage forms that have the benefit of avoiding first pass metabolism. The need for Sublingual has increased over the past ten years, particularly among the elderly and kids who have swallowing issues. In order to achieve rapid disintegration in gastric pH and quick action to lower cholesterol and triglyceride (fat) levels in the blood, the current study's goal was to create sublingual tablets of atorvastatin using various concentrations of starch (soluble), AC-Di-Sol and polyplasdone-XL as superdisintegrants. There are twelve different Atorvastatin Sublingual tablet formulations that were created using wet granulation technology. There is no interaction between the medications and the numerous excipients employed in the formulation, according to FTIR technology studies on the compatibility of drugs and excipients. When compared to the pharmacopeia, the outcomes of the various precompression and after compression characterizations of tablets were satisfactory. Using a USP II paddle type dissolution equipment, in vitro release experiments for a number of formulations were carried out. Formulation AST₁₁, which contains 2% AC-Di-Sol and 4% Polyplasdone-XL, demonstrated complete drug release in less than 30 minutes (>99%), establishing itself as an optimised formulation. Using both superdisintegrants in tandem also demonstrated an improved drug release profile. However, when compared to the commonly marketed formulation, the formulation AST₈ with 4% Polyplasdone-XL exhibits the highest similarity factor and the lowest difference factor; therefore, it is regarded as the best formulation from the perspective of the dissolving profile. The zero-order kinetic model was the best formulation. Accelerated stability studies for improved formulation were done to confirm the stability of dose forms.

Key words: Atorvastatin, Sublingual tablet, AC-Di-Sol, Polyplasdone- XL, anticholesteremic.

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Please cite this article in press Tabassum Fatima et al, *Formulation And Evaluation Of Sublingual Tablets Of Poorly Soluble Drug Atorvastatin Using Superdisintegrants.*, Indo Am. J. P. Sci, 2022; 09(8).

INTRODUCTION:

The oral route is one of the most frequently utilised drug administration techniques. Tablets continue to be the most popular dosage form due to its constant innovation and adoption of fresh concepts to overcome the fundamental shortcomings of the current formulations. Placing the medication under the tongue is known as sublingual administration. The medicine is absorbed 3–10 times more quickly through the sublingual method than it is through the oral route. [1] Different formulations, including pills, films, and sprays, are helpful for administering medications sublingually. [2,3] The creation of sublingual dosage forms is a very difficult process. Mechanical strength, disintegration speed, flavour masking, tongue feel, susceptibility to environmental conditions, cost, and other factors are problems. Superdisintegrant is a key component in the production of Sublingual tablets, together with other often used excipients including diluents, binder, lubricants, glidants, etc. The sublingual tablets are commonly produced using a range of superdisintegrants, such as sodium starch glycolate (Primojel), crosscarmellose (AC-Di-Sol), and various grades of croscopolvidone, for quick and easy tablet disintegration (Polyplasdone-XL). Wet granulation has gradually increased tablet production over time because of its consistent content and favourable compressibility profile. [4,5]

The statin medicine class, which lowers blood cholesterol, includes atorvastatin calcium. Atherosclerosis is the main condition that atorvastatin is used to treat, and other uses include preventing cardiovascular conditions such coronary heart disease, myocardial infarction, stroke, unstable angina, and revascularization. As with all statins, atorvastatin reduces the activity of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase, which is essential for the body's creation of cholesterol. The rate-limiting step in the synthesis of hepatic cholesterol is the reduction of HMG-CoA to mevalonate, which is catalysed by HMG-CoA reductase. Inhibition of the enzyme raises low-density lipoprotein (LDL) receptors on hepatocytes while reducing de novo cholesterol production. As a result, the amount of LDL cholesterol in the blood decreases due to an increase in LDL uptake by the hepatocytes. Atorvastatin decreases triglyceride levels in the blood and marginally raises levels of high-density lipoprotein (HDL) cholesterol, just as other statins. The absolute bioavailability of atorvastatin (the parent drug) is 14%, whereas the systemic availability of HMG-CoA reductase inhibitory activity is roughly 30%. Poor systemic availability is attributed to presystemic clearance in the

gastrointestinal mucosa and/or hepatic first-pass metabolism. Atorvastatin calcium is only very slightly soluble in distilled water, a pH 7.4 phosphate buffer, and acetonitrile; its half-life is approximately 14 hours, whereas that of its active metabolites is between 20 and 30 hours. It quickly dissolves in methanol and is just slightly soluble in ethanol. It is recommended that adults take 10 or 20 mg once daily. [6,7]

The primary objective of the recent studies was to design and carry out *in vitro* evaluation tests of sublingual atorvastatin tablets using super disintegrants like starch (soluble), AC-Di-Sol and polyplasdone-XL to achieve rapid dispersion when taken through the buccal cavity, bypassing first-pass metabolism and allowing a rapid onset of action. [8]

MATERIALS AND METHODS:**Materials**

Atorvastatin was acquired from NATCO pharmaceuticals Ltd., Hyderabad, where Atorvastatin calcium was purchased as a gift sample. Also provided from Dr. Reddy's Laboratories Pvt. Ltd. was a gift sample of the superdisintegrant sodium starch glycolate and croscopolvidone. The diluent was purchased from Otto Manufacturers. Lactose, PVP K30, talc, and magnesium stearate were purchased from S.D. Fine Chemicals Pvt. Ltd. in Mumbai, India. Each component was of the highest calibre for a lab. The double distillation method was used in the lab to produce the distilled water that was used in the study.

METHODS**Analytical method for the *in vitro* estimation of Atorvastatin in the formulations**

A primary stock solution of atorvastatin with a concentration of 1000 g/ml was made using a phosphate buffer with a pH of 6.8. Following the proper dilution, a secondary stock solution with a concentration of 10 g/ml was made from the initial stock solution using the same phosphate buffer pH 6.8. The created secondary stock solution's greatest absorbance was found to be at 246 nm, which was picked and used for further investigation after being scanned with a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400 nm to 200 nm. Using the same phosphate buffer pH 6.8, the secondary stock solution was first diluted to produce a series of concentrations of 2, 4, 6, 8, and 10 g/ml. Then, the absorbance at the maximum wavelength of 246 nm was determined. Plotting observed absorbencies against matching concentrations resulted in the calibration curve of pure atorvastatin. [9, 10]

Drug and excipients compatibility studies

Drug and excipients used for the formulation of different batch of Atorvastatin Sublingual tablets were analysed for any possible physical and chemical interactions through FTIR.

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transforms infrared (FTIR) spectroscopy tests were performed to identify the peaks in the pure medicine and the excipients used that indicate the existence of a specific functional group. If the functional groups present in the pure drug are replicated in the formulations, the drug and excipients are deemed to be compatible. Both the pure drug and a physical mixture of the drug and all excipients were investigated using FTIR with atorvastatin (optimised formulation). The pellet technique and potassium bromide were employed in the operation (KBr). After the components had been triturated with KBr, a pellet was made by exerting pressure of 100 kg/cm² for two minutes. The obtained pellet was investigated in the FTIR 8400S by Shimadzu, Japan. The analysis of the test samples came first, followed by the acquisition of the KBr backdrop. The same steps were performed for the analysis of the drug, each excipient, and the physical mixing of the excipients and the drug. [11, 12]

Differential scanning calorimeter (DSC) investigation:

A Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) apparatus was used for the DSC study. Both a pure drug, zolmitriptan, and a mixture (zolmitriptan plus excipients), had their DSC thermograms collected. DSC aluminium cells served as the sample container and the reference, respectively. A sample of 2-3 mg was used for analysis. Under nitrogen purge at a rate

of 20 ml/min, thermograms were taken over the temperature range of 20°C-200°C at a constant rate of 20°C/min. Figures 3 and 4 show the results. [13]

Formulation of Atorvastatin Sublingual tablets (AST₁- AST₁₂)

Atorvastatin sublingual tablets were created using the wet granulation process. Before being used in formulations, all materials were weighed precisely and put through filter #80. Atorvastatin, Avicel 101, Lactose, starch (soluble), AC-Di-Sol, Polyplasdone-XL, PVP K30, and Aspartame were just a few of the powders that were combined equally and passed through #20 for each composition. Binder utilised was PVP K30. To lower the moisture content and prevent sticking to the sieve, the aggregates created after the addition of the binder were first dried for five to ten minutes. To obtain granules, the aggregates were sent through filter #20. To lower the moisture content of the granules by up to 2-5%, they are dried at 40° C for 20 minutes. Talc and magnesium stearate were utilised as lubricants, and dried granules were combined with the necessary amounts for 2–3 minutes. Prior to compression, the formulations' angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were assessed after lubrication. On a 10-station rotary punching machine (Saimach Pharmaceutical Pvt. Ltd.), using 8 mm concave punches, the evaluated granules were compressed into tablets. Atorvastatin, 20 mg, is present in each tablet. Table 1 contains the recipes for many formulations, and the same process was used for each formulation. Then, different post-compression parameters were assessed for the generated sublingual tablet formulations, including average thickness, weight variation, hardness, friability, drug content study, disintegration, and in vitro dissolving experiments. [14, 15]

Table 1: Compositions of different formulations of Atorvastatin Sublingual tablets

Formulation s(mg)	AST ₁	AST ₂	AST ₃	AST ₄	AST ₅	AST ₆	AST ₇	AST ₈	AST ₉	AST ₁₀	AST ₁₁	AST ₁₂
Atorvastatin	20	20	20	20	20	20	20	20	20	20	20	20
Starch (Soluble) (mg)	5	10	15	-	-	-	-	-	-	-	-	-
AC-Di-Sol (mg)	-	-	-	5	10	15	-	-	-	5	5	10
Polyplasdon e- XL (mg)	-	-	-	-	-	-	5	10	15	5	10	5
Avicel 101 (mg)	115	110	105	115	110	105	115	110	105	110	105	105
Lactose (mg)	25	25	25	25	25	25	25	25	25	25	25	25
PVP K30 (mg)	25	25	25	25	25	25	25	25	25	25	25	25
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total wt.	250	250	250	250	250	250	250	250	250	250	250	250

Evaluation of precompression parameters of dry granules of Atorvastatin Sublingual tablet formulations

Angle of Repose (θ)

The dry granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\theta = \tan^{-1} \left(\frac{h}{r} \right)$$

Where θ was called as angle of repose, h and r were height and radius of the granule heap respectively. According to the specifications the angle of repose value less than 25° indicates excellent flow whereas angle greater than 40° indicates poor flow. [16]

Bulk density and tapped density

Both the bulk density (BD) and tapped density (TD) of prepared Atorvastatin Sublingual dry granules of all the formulations were determined using the following formulas.^{7,9}

$$BD = \frac{\text{weight of the dry powder}}{\text{volume of the packing}}$$

$$TD = \frac{\text{weight of the dry powder}}{\text{tapped volume of the packing}}$$

Compressibility Index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of granules and the rate at which it packed down. Compressibility index (Carr's index) of prepared Atorvastatin Sublingual dry granules were calculated by following formula

$$\text{Carr's index (\%)} = \frac{TD - BD}{TD} \times$$

100

According to the specification the Carr's index values "between" 5-15 indicates excellent flow whereas between 12-16 indicates good flow. Values "between" 18-21 indicate fair-passable whereas between 23-25 indicates poor. "Between" 33-38 indicates very poor and greater than 40 indicates extremely poor. [16]

Hausner's ratio:

The Hausner's ratios of prepared Atorvastatin Sublingual dry granules were determined by following formula.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), whereas greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, glidant need to be added to improves flow. [17]

Evaluation of post-compression parameters of Atorvastatin Sublingual tablets (AST) formulations

Typical thickness

Ten tablets were randomly chosen from each formulation (AST) and utilised for thickness measurement. Using digital Vernier callipers (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan), the thickness of each tablet was measured. The results were expressed as the mean values of 10 readings with standard deviations. Tablet thickness should be kept within 5% of the standard value, as per the specification. [18]

Tablet Hardness

Using a Monsanto hardness tester, the hardness of all Atorvastatin Sublingual tablet formulations was determined (Cad Mach). Ten Sublingual tablets with known weights from each formulation were tested for crushing strength, which was measured in kg/cm², averaged, and then shown with standard deviation. According to USP requirements, a sublingual tablet's hardness value of 3–4 kg is deemed sufficient for mechanical stability. [18]

Friability

Ten tablets (AST) from each batch that had previously been weighed were placed in the Roche friabilator (Roche friabilator, Secor India). Tablets were found after a hundred friabilator revolutions. The tablets were then cleaned of dust, and the total weight that remained was noted. This formula was used to determine friability.

$$\%F = \frac{(W_i - W_f)}{W_i} \times 100$$

the starting and final weights of the tablets prior to and following the friability test, respectively, were W_i and W_f . Compressible tablets that lose between 0.1% and 0.5% and, at most, 1% of their weight are deemed acceptable. Weight fluctuation test [19]

Weight variation test

The weight variation of each Atorvastatin Sublingual tablet formulation was assessed in accordance with the USP standard. Using an electronic balance, 20 pills from each batch were weighed both collectively and individually. Calculations were made on the average weight and % variance of each tablet. The USP standard states that the weight variation tolerance limit for uncoated tablets with an average weight of 130 mg or less is 10%, 7.5% for tablets with an average weight between 130 and 324 mg, and 5% for tablets with an average weight of more than 324 mg. The weight of the tablet must not differ from the average weight by more than two tablets' weight, and no tablet may deviate by more than 15%. [19]

Content uniformity

Twenty pills were ingested and triturated into powder to test the content homogeneity of all formulations (AST). One tablet's worth of powder was taken, diluted in 100 ml of phosphate buffer with a pH of 6.8, and heated at 37 °C for 15 to 20 minutes while stirring continuously. The atorvastatin concentration was determined using a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 246 nm after the solution had been cooled, filtered, and appropriately diluted. The average medication content of each formulation was computed after each measurement was made in triplicate. [20]

Wetting time and water absorption ratio

The disintegrating process of the tablet formulation is reflected in the wetting time. The disintegration rate increases as wetting time decreases. Twice-folded tissue paper was placed in a petri dish with an internal diameter of 6.5 cm, 10 ml of phosphate buffer pH 6.8, and 0.1% w/v of methylene blue for the purpose of determining the wetting time. Atorvastatin Sublingual tablet samples from each formulation were meticulously arranged on the tissue paper in the petri plate. Wetting time was measured as the length of time it took for the dye to reach the tablet's top surface. The standard deviations were also calculated, and measurements were done in triplicate. [21]

The weight (W_b) of the tablet before it is placed on the Petri dish, followed by the observation of the wetting period, can be used to determine the water absorption ratio (R). The wet tablet was taken out and weighed again (W_a). The following equation was used to calculate the water absorption ratio.

$$R = \frac{(W_a - W_b)}{W_b} \times 100$$

In vitro disintegration time (D_t)

The USP specifies 2 minutes as the acceptable time limit for tablet disintegration meeting official criteria, whereas 2 minutes for Sublingual dosage form when using the disintegration apparatus for oral tablets without the covering plastic discs. The experiment was conducted using a tablet disintegration device (model EI D-16, Electrolab, Mumbai, India). A modified disintegration method was used to conduct an in vitro disintegration test on a disintegration tester that was kept at 37°C ± 0.5°C in phosphate buffer pH 6.8 (n = 6). The time it took for each pill to totally break down into smaller particles was observed while the tablets were stored in the basket. [22]

In vitro drug release (dissolution) study

Utilizing an eight station USP Dissolution Rate Test Apparatus Type-II, the in vitro dissolution

investigation was carried out for all of the formulations (AST) (LABINDIA DS 8000, Mumbai, India.). The dissolution medium, a total volume of 900 ml of phosphate buffer pH 6.8, was kept at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ at 50 rpm. At regular intervals, 5ml of aliquots were removed and replaced with an equivalent volume of new dissolving medium. Samples were taken every 5 minutes and then filtered using Whatmann filter paper. Atorvastatin released from sublingual tablets was determined by spectrophotometric analysis of samples at 246 nm. [23]

Calculation of similarity and difference factors

According to a comparative dissolution research using the Atorvastatin 20mg-containing LIPITOR TAB (Pfizer) as a reference product, the optimum formulation was selected after computing the Moore and Flanner-introduced similarity factor equation (f_2) and difference factor (f_1). The similarity in release profiles between the two pharmacological formulations was assessed using the similarity factor (f_2) established by the U.S. Food and Drug Administration (FDA). The following equation was used to determine the similarity factor, which is a logarithmic transformation of the sum squared error of differences between the test preparation and the reference preparation:

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where R_t and T_t are the accumulated release rates of the reference preparation and test preparation at the predetermined time points, respectively, and n represents the number of the time points. The value of the similarity factor is between 0 and 100. The value 100 indicates that the test and reference profiles are identical; the more it approaches 0, the more dissimilarity of the two preparations occurs. Generally, if $f_2 > 50$, the release profiles are considered to be similar, and the larger the f_2 value, the higher the similarity.

Difference factor (f_1) measures the percent error between two drug release curves over all time points.

$$f_1 = \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \times 100$$

Dissolution profile was considered satisfactory if f_1 values lies below 15 (nearing zero, more it approaches towards zero more similarity between the products is having. [24]

In the present study three time points were taken *i.e* 5th, 15th, and 30th minute for the calculation of

similarity and difference factors of all the formulations.

Characterization of the *in vitro* drug release profile

The rate and mechanism of release of Atorvastatin from prepared Sublingual tablets were analyzed by fitting the dissolution data into following exponential equations.

Zero order release equation is calculated by following equation.

$$Q = K_0 t$$

Where Q is the amount of drug released at time t and K_0 is the zero order release rate constant.

The first order equation is calculated by following equation.

$$\log(100 - Q) = \log 100 - K_1 t$$

Where, K_1 is the first order release rate constant. [25, 26]

Stability studies of best formulation

The short-term stability studies of best formulation of Atorvastatin Sublingual tablet were carried out according to ICH guidelines. The best formulation was subjected to accelerated stress condition at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \pm 5\%$ RH for 90 days. After that period the product was evaluated for friability, hardness, weight variation, thickness, drug content and *in vitro* drug release study. [27, 28]

RESULTS AND DISCUSSION:

Drug-Excipient Compatibility studies by FTIR:

According to the results of the FTIR research, the peaks in the atorvastatin spectrum are caused by N-H stretching at 3244.36 cm^{-1} , C = O stretching at 1650.30 cm^{-1} , C-F stretching at 1422.51 cm^{-1} , C-O stretching at 1317.59 cm^{-1} , C-N stretching at 1216.10 cm^{-1} , and -OH stretching at 3363.93 cm^{-1} . These values complied with the values that had been reported. The N-H stretching at 3284.00 cm^{-1} , C = O stretching at 1651.84 cm^{-1} , C-F stretching at 1417.82 cm^{-1} , C-O stretching at 1280.07 cm^{-1} , C-N stretching at 1245.81 cm^{-1} , and -OH stretching at 3391.69 cm^{-1} exhibit peaks in the FTIR spectra of the optimised formulation AST8 (Atorvastatin with all the Excipients). Therefore, it is clear from the fact that all of the characteristic peaks that were present in the spectra of pure drugs were almost exactly replicated in the same region in the spectra of the best formulations of Atorvastatin Sublingual tablet that there is no meaningful interaction between the drugs and the excipients. **Figures 1 and 2** display the FTIR spectra of the medication Atorvastatin in its purest form and the finest formulations.

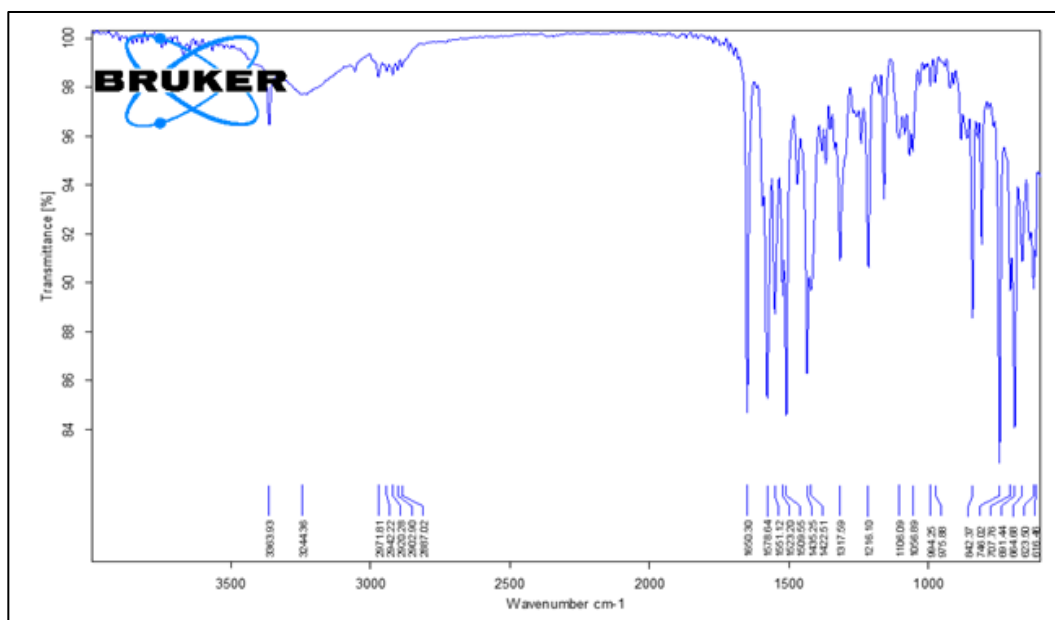


Fig. 1: FT-IR spectra of Atorvastatin pure drug

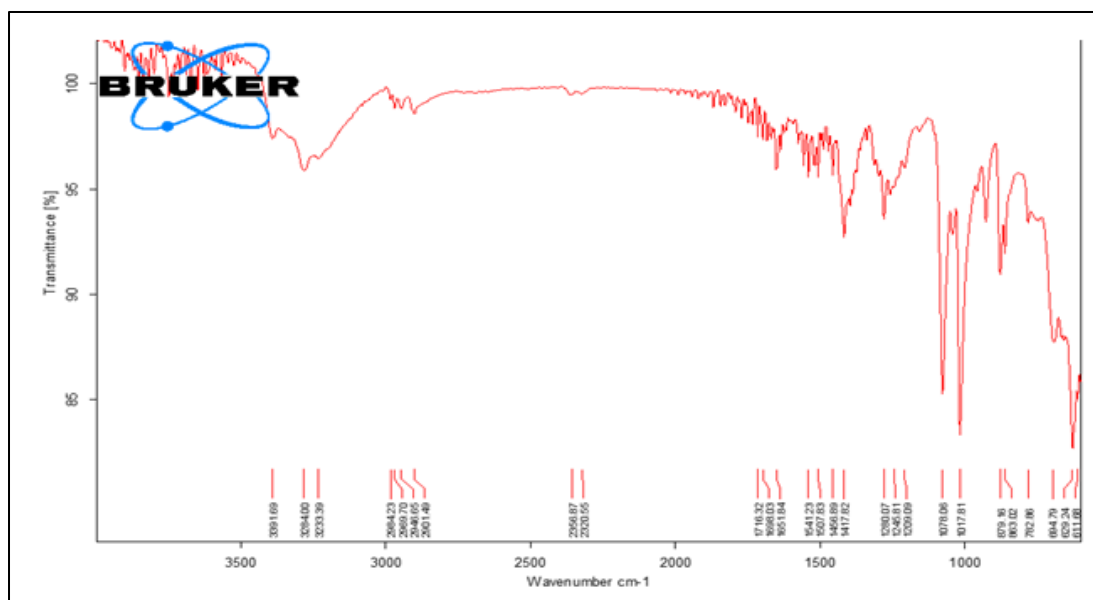


Fig. 2: FT-IR spectra of physical mixture of Atorvastatin with excipients

DSC Studies:

Pure medicine DSC thermogram Atorvastatin and a physical mixture (drug and excipients) were obtained, and it was noticed that the endothermic peaks appeared at 160.7 °C and 160.7 °C, respectively. This finding suggests that the physical mixture (drug and excipients) is thermodynamically stable because the formulation required the same amount of heat for preparation as pure drug even in the presence of a variety of excipients, including MCC, lactose, cross carmellose, cross **Figures 3 and 4** show the DSC thermograms of the pure drug and the physical mixture of the drug and excipients utilised in the formulations.

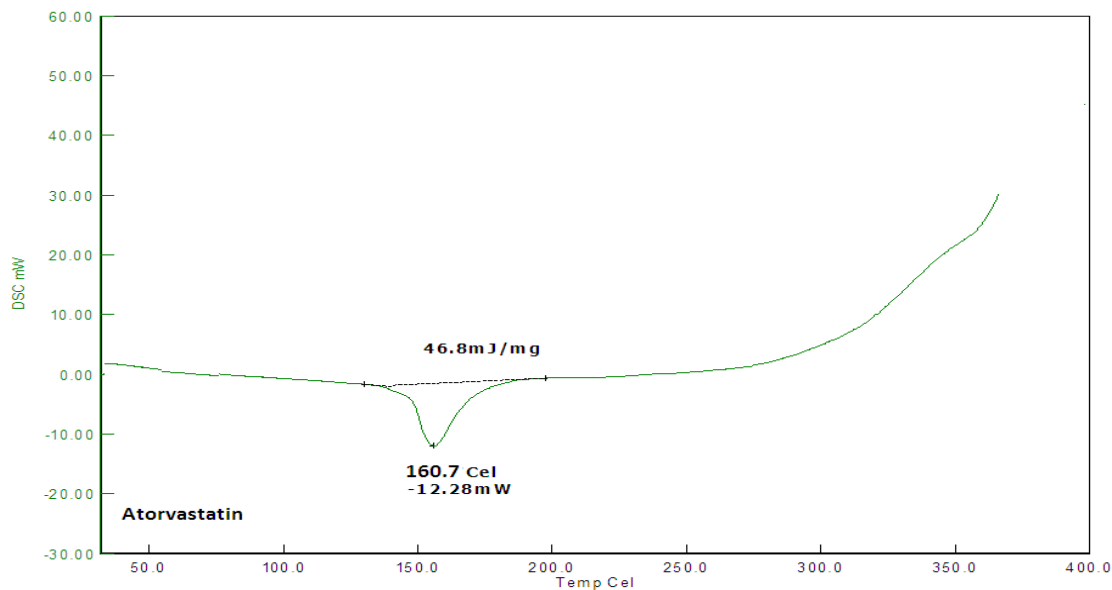


Fig. 3: DSC thermogram of Atorvastatin pure drug

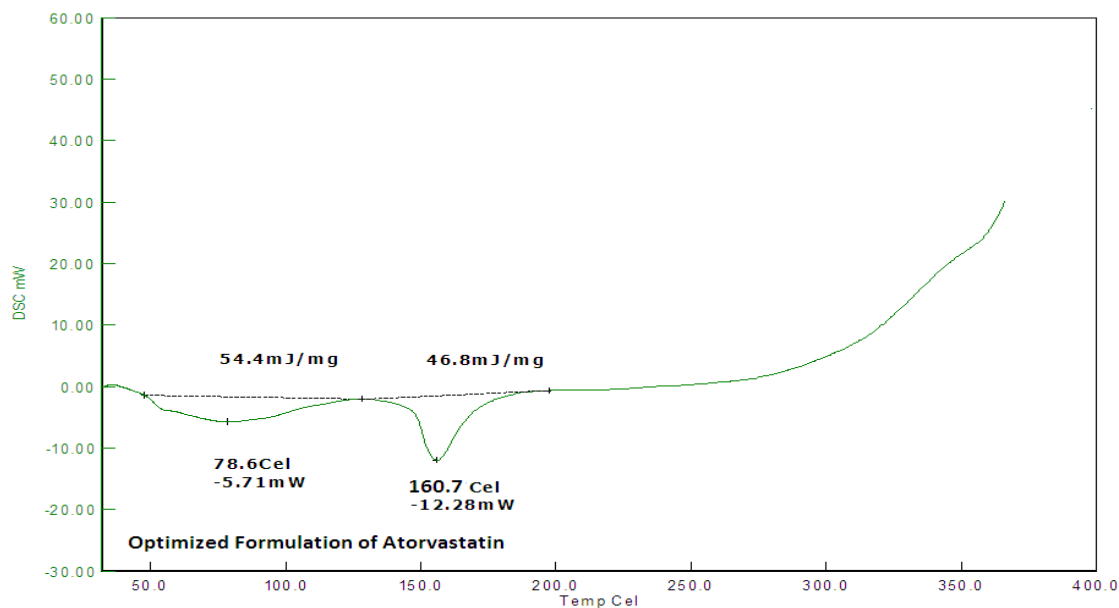


Fig. 4: DSC Thermogram of optimized Atorvastatin Sublingual tablets

Precompression parameters

The bulk densities of all formulations of atorvastatin sublingual dry granules were determined to be between 0.399 and 0.541 g/cm³, and the tapped densities were found to be between 0.475 and 0.589 g/cm³. This suggests that dry granules have considerable packing capacity. According to measurements of bulk density and tapped density, the density of dry granules depends on particle packing and alters when the granule consolidates. Except for

the formulations AST1 and AST2, which may be owing to a lack of consistency in granule sizes and the presence of more tiny particles in those formulations, values of Carr's index for all of the formulations were found to be below 16%, which typically indicates favourable flow characteristics. The Hausner's ratio is an easy way to gauge flow characteristics and assess the stability of the power and granule column. The Hausner's ratio showed a low range, which denotes good flow capacity. The

Hausner's ratios varied from 1.07 to 1.21 in all formulations, indicating good flow properties for dry granules. Angle of repose is appropriate for particles larger than 150 μ m. Angles of repose values between 25 and 40 often imply poorly flowing materials and free-flowing materials, respectively. The flowability of the dry powder or grains is indicated by the angle

of repose. All formulations had angles of repose that ranged from 18.62 to 22.84 degrees, meaning that the dry granules of the atorvastatin sublingual tablet exhibited good flow characteristics and were suitable for compression. Table 2 lists the precompression parameter results for each formulation.

Table 2: Evaluation of precompression parameters of Atorvastatin Sublingual dry granules (AST₁ – AST₁₂)

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose ($^{\circ}$)	Carr's Index (%)	Hausner's ratio
AST ₁	0.432 \pm 0.05	0.521 \pm 0.06	22.41 \pm 0.11	17.08	1.21
AST ₂	0.490 \pm 0.06	0.584 \pm 0.05	21.53 \pm 0.10	16.09	1.19
AST ₃	0.465 \pm 0.08	0.502 \pm 0.06	20.91 \pm 0.14	7.37	1.07
AST ₄	0.501 \pm 0.06	0.573 \pm 0.08	19.62 \pm 0.16	12.57	1.14
AST ₅	0.423 \pm 0.05	0.492 \pm 0.07	22.84 \pm 0.18	14.02	1.16
AST ₆	0.399 \pm 0.08	0.475 \pm 0.05	18.62 \pm 0.12	16.01	1.19
AST ₇	0.482 \pm 0.09	0.521 \pm 0.08	21.52 \pm 0.11	7.48	1.08
AST ₈	0.541 \pm 0.07	0.589 \pm 0.07	20.63 \pm 0.13	8.15	1.09
AST ₉	0.477 \pm 0.05	0.524 \pm 0.06	19.49 \pm 0.14	8.97	1.10
AST ₁₀	0.472 \pm 0.06	0.525 \pm 0.08	22.28 \pm 0.15	10.10	1.11
AST ₁₁	0.482 \pm 0.03	0.521 \pm 0.06	19.46 \pm 0.14	7.48	1.08
AST ₁₂	0.490 \pm 0.08	0.584 \pm 0.09	22.65 \pm 0.12	16.09	1.19

All values are expressed as mean \pm SD; (n=3)

Post-compression parameters

The physical characteristics of all Atorvastatin Sublingual tablet formulations, including hardness, average weight variation, average friability, and average thickness, were found to be good. There were no signs of the typical tablet flaws that are capping, chipping, or picking. The tablets had average thicknesses that varied from 4.12 mm to 4.36 mm. Each batch had a uniform thickness and was within the acceptable limit. Percentage It was discovered that weight differences ranged from 3.97% to 4.04% for various formulations. All formulations passed the test for weight uniformity in accordance with the official criteria since the permissible average percentage variation for tablet formulations with a weight of 250 mg is 5%.

All of the atorvastatin sublingual tablet formulations had an average hardness that ranged from 2.47 to

3.82 kg/cm². The hardness typically reduced with an increase in superdisintegrant content, as was the case with formulations AST₃, AST₆, and AST₉. The percentage friability of all formulations ranged from 0.35% to 0.78%, and the concentration of the superdisintegrant was observed to increase the percentage friability. The percentage of friability in the current study was within the permitted ranges for all formulations. According to the formulations of atorvastatin sublingual tablets, the percentages of drug content for AST₁ to AST₁₂ ranged from 98.45 to 102.59, which was within acceptable bounds. All formulations' disintegration times were measured, and it was discovered that the disintegration time lowers as superdisintegrant concentration rises above 6%, while the hardness value increases.

All of the formulas' wetting times ranged from 28 sec to 168 sec. With regard to wetting time, wetting times

for the formulations of AST₆, AST₉, AST₁₁, and AST₁₂ decreased as superdisintegrant concentration was increased. When AC-Di-Sol™ and Polyplasdone-XL were used in combination, the latter showed a shorter wetting time. The range of formulations AST₁ to AST₁₂'s water absorption ratio

was discovered to be 10.41 to 39.31. The water absorption ratio increased with a rise in superdisintegrant concentration, which may have been caused by an increase in formulation porosity.

Table 3 lists the physicochemical descriptions of several batches of Atorvastatin Sublingual pills.

Table 3: Evaluation of Post-compression parameters of Atorvastatin Sublingual tablets

F. code	Average hardness (kg/cm ²)	Average Weight Variation (%)	Average friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)	D _t (Sec)	Wetting time (Sec)	Water absorption ratio
AST ₁	3.82±0.8	4.01±0.44	0.35±0.05	4.12±0.10	102.29±1.8	360±1.12	168±0.43	10.41±0.24
AST ₂	3.64±0.4	4.04±0.26	0.58±0.02	4.25±0.12	99.48±1.5	342±1.09	132±0.62	12.42±0.35
AST ₃	3.12±0.5	4.02±0.18	0.62±0.06	4.36±0.14	101.26±1.6	306±0.95	114±0.54	14.30±0.28
AST ₄	3.35±0.4	4.01±0.46	0.42±0.02	4.30±0.10	99.36±1.6	214±0.69	98±0.60	19.28±0.27
AST ₅	3.12±0.3	4.03±0.34	0.66±0.05	4.34±0.16	98.66±1.5	128±0.78	60±0.25	25.52±0.34
AST ₆	2.81±0.5	3.98±0.52	0.78±0.03	4.28±0.18	102.59±1.3	74±0.92	32±0.36	32.46±0.30
AST ₇	3.40±0.4	3.97±0.85	0.53±0.07	4.25±0.12	100.42±1.6	242±0.82	89±0.32	18.38±0.42
AST ₈	3.26±0.5	4.02±0.58	0.68±0.02	4.35±0.15	101.81±1.1	126±0.88	76±0.37	22.35±0.35
AST ₉	2.47±0.6	3.97±0.32	0.75±0.06	4.18±0.19	99.72±1.5	66±0.94	44±0.36	36.39±0.27
AST ₁₀	3.18±0.4	3.98±0.46	0.58±0.04	4.25±0.15	98.45±1.6	112±0.86	58±0.45	32.43±0.39
AST ₁₁	2.82±0.7	4.03±0.56	0.78±0.07	4.22±0.19	99.56±1.2	46±0.91	30±0.21	37.56±0.35
AST ₁₂	2.78±0.5	4.04±0.15	0.72±0.05	4.26±0.20	101.82±1.4	56±0.72	28±0.30	39.31±0.29

All values are expressed as average± SD; (n=3)

Using a USP type-II paddle type dissolution device, the in vitro drug release properties of atorvastatin sublingual tablets were investigated for a 45 minute period in phosphate buffer pH 6.8 dissolution medium. By boosting the superdisintegrant concentration to an ideal concentration of 6%, the rate of dissolution increased. The percentage cumulative drug release was 99% after adding 6% more starch (soluble) (AST₃) to the mixture. In comparison to formulation AST₈, which had 4% of Polyplasdone-XL and released almost 99% of the medication in 35 minutes, formulation AST₆ contained 6% of AC-Di-Sol™, and the cumulative percentage of drug release at 6% concentration (AST₉) was nearly 99% at 30 minutes. When both superdisintegrants are used together at a total concentration of 4%, the dissolving profile is improved and the medicine is released virtually completely within 35

minutes. Formulation AST₁₁ releases the drug up to 99% in 30 minutes and has a superdisintegrant concentration of 6% (2% AC-Di-SolTM and 4% Polyplasdone-XL). MCC (Avicel 101) and lactose worked well together as diluents, therefore they were employed in all of the formulations. Figures 5 and 6 depict the dissolving profiles for each formulation (AST₁ to AST₁₂).

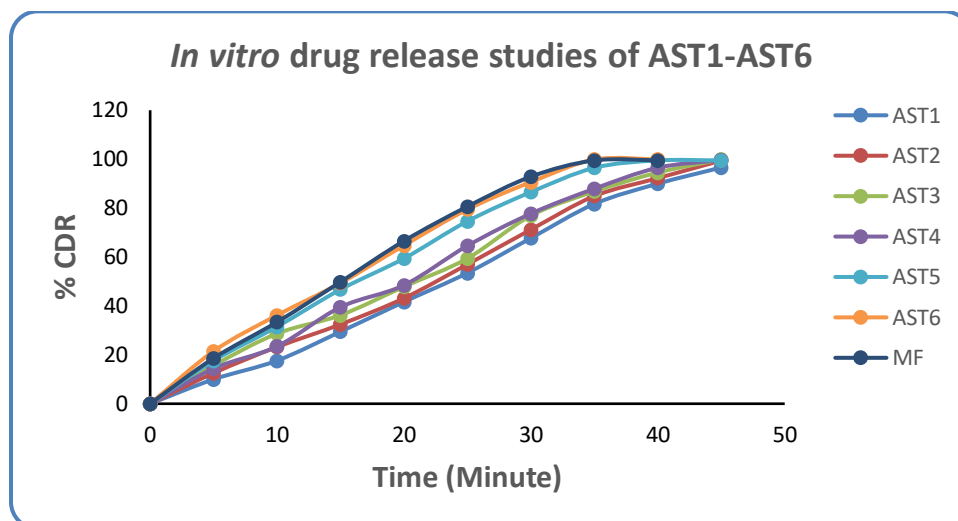


Fig. 5: *In vitro* drug release study of Atorvastatin Sublingual tablet formulations (AST₁ to AST₆)

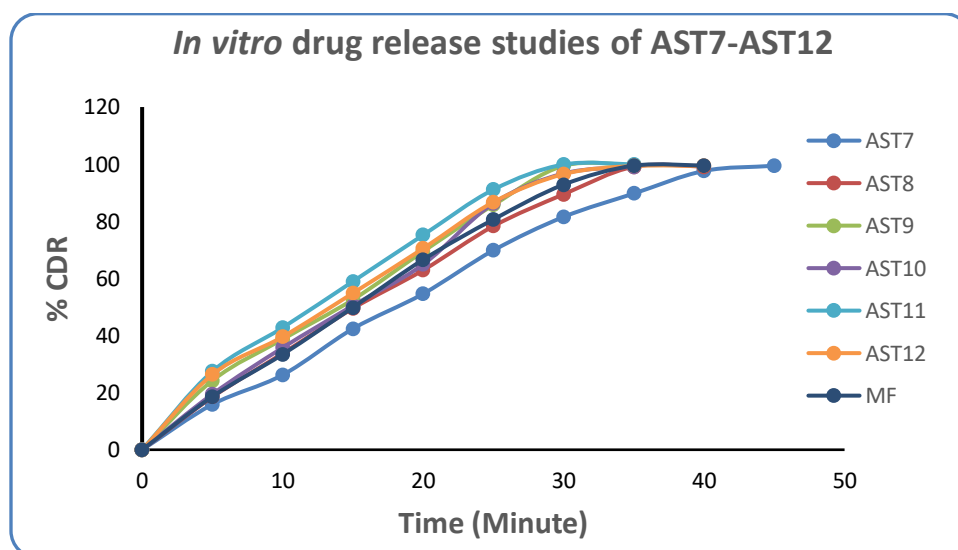


Fig. 6: *In vitro* drug release study of Atorvastatin Sublingual tablet formulations (AST₇ to AST₁₂)

When comparing the release profile of the test formulation with that of a typical commercial formulation, the similarity factor (f_1) and the difference factor (f_2) are both crucial. When the two dissolution profiles are identical, f_2 has a value of 100, and it can be rounded down to zero when one product (the test or reference) has finished dissolving before the other has started. As a result, the value of f_2 is between 0 and 100. If the equation is changed to use the average absolute difference between the test and reference products, which is 10%, f_2 changes to 50. When the f_2 value is between 50 and 100, two dissolution profiles are deemed to be "similar". The two dissolution profiles are closer together when the f_2 value is higher. The equation, however, may only be used to compare curves if the average difference between the reference and test formulation profiles is less than 100 and the percentage of medication released. When the test and drug reference profiles are identical, the percent error is 0; otherwise, it rises proportionately as the two dissolution profiles diverge. The consensus is that f_1 values between 0 and 15 don't signify dissimilarity. In this way, the Atorvastatin Sublingual tablet batches' similarity factor (f_1) and difference factor (f_2) were identified. While the dissolution profiles of formulations AST₁

to AST₄ were different, those of formulations AST₅ to AST₁₂ were similar. The formulation with the lowest f_1 value (2.4) and the highest f_2 value (82.78) overall was deemed to be the best. Based on having the highest f_2 value and lowest f_1 value during drug release kinetic and mechanism of release studies, the formulation AST₈ was chosen. Figures 7 and 8 show the graphs from the fitting of atorvastatin Sublingual Tablets (AST₈) *in vitro* dissolving data using different kinetic models, including zero order and first order. The AST₈ formulation's best regression findings (0.9943) demonstrated that the zero order kinetic graphs were typically linear.

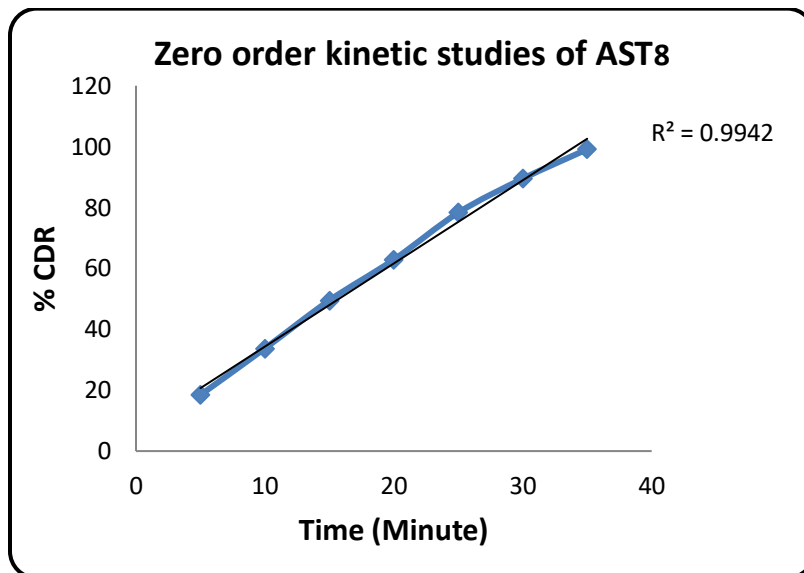


Fig. 7: Zero order release kinetic study of best formulation AST₈

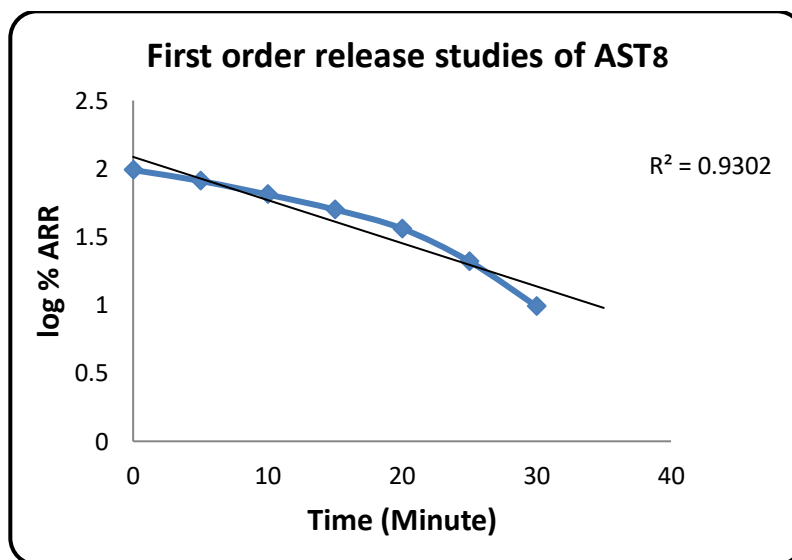


Fig. 8: First order release kinetic study of best formulation AST₈

The best formulation (AST₈) of Atorvastatin Sublingual tablets was selected for accelerated stability studies. The best formulation (AST₈) Atorvastatin Sublingual tablets did not show any significant changes in physicochemical parameters and *in vitro* drug release characteristics. More than 90% of the drug had been retained in the *in vitro* dissolution studies after 90days of exposure to accelerated stress condition. Thus, it was found that the Sublingual

tablets under study were stable under short term accelerated storage conditions for at least 3 months. The comparative physicochemical properties at different interval of time are presented in **table 4** and comparative release profile has been represented in **figure 9**.

Table 4: Comparative physicochemical properties of AST₈ at accelerated conditions (40 °C ± 2 °C/ 75% ± 5% RH)

Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
Physical appearance	Cream white, circular, concave smooth surface without any cracks	No change	No change	No change
Weight variation	4.02±0.58	4.02±0.65	4.02±0.72	4.02±0.62
Hardness	3.26±0.5	3.42±0.6	3.64±0.80	3.84±0.82
Friability	0.68±0.02	0.70±0.03	0.74±0.05	0.77±0.04
Disintegration time {D _t (Sec)}	126±0.88	131 ±0.85	142 ±0.96	155 ±1.04
Wetting time (Sec)	76±0.37	84±0.45	92±0.64	98±0.78
Drug content	101.81±1.1	99.14±1.36	96.46±1.41	93.28±1.32

All values are expressed as mean± SD; (n=3)

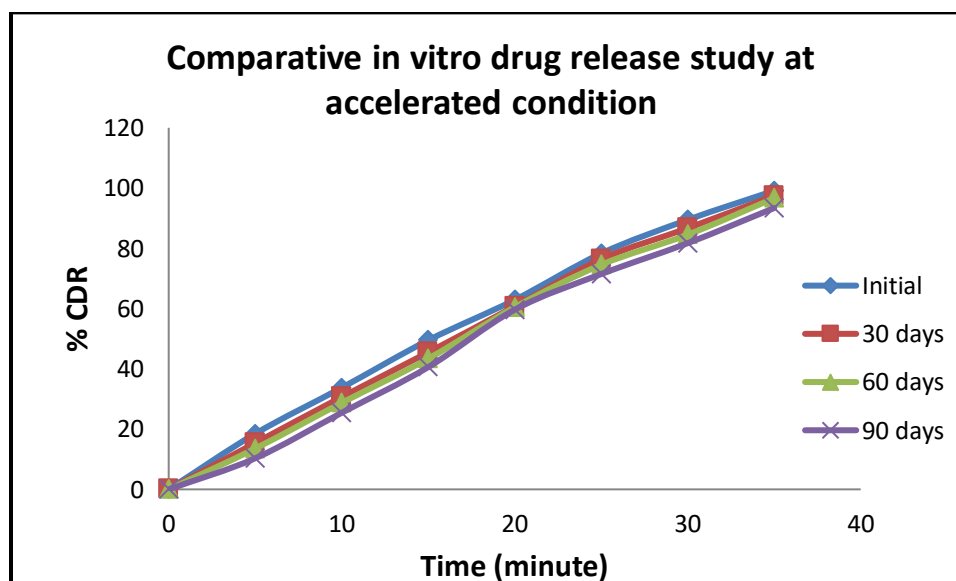


Fig. 9: *In vitro* release study of best formulation (AST₈) at stressed condition

CONCLUSION:

In the present work Atorvastatin Sublingual tablets were successfully developed. The major challenge in this work was to study the effect of Polyplasdone-XL and AC-Di-Sol on *in vitro* release rate of Sublingual tablet of Atorvastatin. The Sublingual drug delivery system was a promising approach to achieve quick release of drug by passing fast pass

metabolism and beneficial for acute diseases like asthma, cardiac disease and migraine. FTIR and DSC studies revealed that the drug and excipients were compatible with each other and formulation is thermally stable. Wet granulation methods were adopted for the preparation of Atorvastatin Sublingual granules and the evaluation results of all the precompression parameters were satisfied the

acceptance criteria that showed excellent flow properties of granules. All the postcompression parameters like average thickness, hardness, friability, weight variation and disintegration also fall within acceptable limit. Lactose along with MCC (Avicel 101) were used both as diluents for all the formulations for better drug release profile. Formulation AST₁₁ containing 2% of AC-Di-Sol and 4% of Polyplasdone- XL showed complete drug release within 30 minute (>99%) emerging as optimised formulation and using both the superdisintegrant in combination showed better drug release profile. But the formulation AST₈ having 4% of Polyplasdone- XL shows highest similarity factor and lowest difference factor when it was compared with the standard marketed formulation and considered as best formulation with dissolution profile point of view. By increase in superdisintegrant concentration the drug release profile became faster but the hardness and friability of the formulation were severely affected. Kinetic of *in vitro* drug release of optimized formulation AST₈ found to follow Zero order kinetic model having highest R² value. The stability studies were carried out according to ICH guideline and selected AST₈ formulation were stable at 40°C/75% RH up to 3 months with a little change in physicochemical as well as drug release characteristics of the formulations. Thus from the results of the current study clearly indicate, a promising potential of the Atorvastatin Sublingual tablets drug delivery system can be used as an alternative to the conventional dosage form because it release the drug quickly with by passing fast pass metabolism and useful for the acute condition of cardiac disease. However, further clinical studies are needed to assess the utility of this system for patients suffering from cardiac disease.

ACKNOWLEDGMENT

The Hyderabad-based NATCO drugs Ltd., is grateful to the authors for giving free samples of medication and superdisintegrant so they could conduct their research. The chairman and principal of the Anwarul Uloom College of Pharmacy in Hyderabad, Telengana, are also acknowledged by the authors for granting permission to conduct the research.

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