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FORMULATION AND IN VITRO EVALUATION OF ATORVASTATIN ORODISPERSIBLE TABLETS USING SODIUM STARCH GLYCOLATE AND CROSS POVIDONE AS SUPERDISINTEGRANT

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ABSTRACTS
The current study's goal was to create an orodispersible Atorvastatin tablet using various concentration of Sodium starch glycolate and Cross Povidone as superdisintegrant in order to achive rapid disintegration in gastric pH and quick action to lower cholesterol and triglyceride (fats) levels in the blood. A class of drugs known as HMG-CoA reductase inhibitors (statins) includes Atorvastatin. Wet granulation technology was used to formulate ten distinct Atorvastatin orodispersible tablet formulations. Studies on the compatibility of drug and excipients using FTIR technology revealed that there is no interaction between the drugs and the various excipients used in the formulation. The results of various precompression and post compression characterizations of tablets were satisfactory when compared to the pharmacopoeia. For several formulations, *in vitro* release tests were performed using a USP II paddle type dissolution apparatus. The formulation containing 4% crosspovidone (AODT4) provided the best release profile, or about 99% within 20 minutes. *In vitro* release kinetic studies like zero order, first order kinetic model were carried out for best formulation. The best formulation followed zero order kinetic model. To verify the stability of dosage forms, accelerated stability experiments were conducted for optimised formulation.

KEYWORDS: Atorvastatin, Orodispersible tablet, Sodium starch glycolate, Cross Povidone, anticholesteremic.

INTRODUCTION
One of the most widely used drug administration methods is the oral route. Due to its ongoing evolution and adoption of novel concepts to get beyond the fundamental flaws of the current formulations, tablets are still the most often utilised dosage form. Orodispersible tablets lack any specific rate-controlling elements, such as special coatings and other approaches, and are made to disintegrate and release their medication in the buccal cavity. When an immediate response is required, immediate release dose forms are most frequently created. Additionally, it improves patient compliance. As a loading dose for bilayer tablets, immediate release dosage forms are occasionally utilised as one of the layers. Superdisintegrant, along with other widely used excipients including diluents, binder, lubricants, glidants, etc., is a crucial ingredient in the creation of orodispersible tablets. For quick and simple tablet disintegration, the orodispersible tablets are typically manufactured utilising a variety of superdisintegrants, such as sodium starch glycolate (Primojel), crosscarmellose (AC-Di-Sol), and various grades of crosspovidone (Polyplasdone-XL).[1] Due to the consistency of its content and favourable compressibility profile, wet granulation has progressively boosted the production of tablets over time.[3,4]

A class of drugs known as HMG-CoA reductase inhibitors includes atorvastatin (statins). It functions by reducing the amount of cholesterol that may accumulate on the artery walls and obstruct blood flow to the heart, brain, and other organs of the body. This is done by delaying the body's creation of cholesterol. Three-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase is competitively inhibited by atorvastatin. Statin drugs reduce the formation of cholesterol in the liver by blocking the conversion of HMG-CoA to mevalonate. The systemic availability of HMG-CoA reductase inhibitory action is around 30%, whereas the absolute bioavailability of atorvastatin (the parent medication) is 14%. Presystemic clearance in the gastrointestinal mucosa and/or hepatic first-pass metabolism are blamed for the poor systemic availability. The half-life of atorvastatin is about 14 hours, while its active metabolites have a half-life of about 20 to 30 hours. In distilled water, a pH 7.4

phosphate buffer, and acetonitrile, atorvastatin calcium is only very marginally soluble. It is mildly soluble in ethanol and readily soluble in methanol. Adults are advised to take 10 or 20 mg once daily.[6]

The main goal of the current studies was to develop and conduct in vitro evaluation studies of orodispersible ator vastatin tablets using super disintegrants like sodium star ch glycolate and crosspovidone in order to achieve rapid dispersion when taken through the buccal cavity, allowin g a rapid onset of action.[7]

MATERIALS AND METHODS

Materials

Atorvastatin was obtained from Dr. Reddy's laboratories Pvt. Ltd. in Hyderabad, India as a gift sample. Additionally, a gift sample of the superdisintegrant sodium starch glycolate and crosspovidone was obtained from Dr. Reddy's laboratories Pvt. Ltd. Mannitol was acquired from Otto Manufacturers as the diluent. The following items were bought from S.D. Fine Chemicals Pvt. Ltd. in Mumbai, India: lactose, PVP K30, talc, and magnesium stearate. Every component was of laboratory-grade quality. The distilled water utilised in the research was created in the lab using a double distillation technique.

Methods

Analytical method for the *in vitro* estimation of atorvastatin in the formulations

Using a phosphate buffer with a pH of 6.8, a primary stock solution of atorvastatin with a concentration of 1000 g/ml was created. Using the same phosphate buffer pH 6.8, a secondary stock solution with a concentration of 10 g/ml was created from the first stock solution following the appropriate dilution. After scanning the generated secondary stock solution with a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400 nm to 200 nm, the solution's maximum absorbance was discovered to be at 246 nm, which was chosen and used for further research. In order to create a series of concentrations of 2, 4, 6, 8, and 10 g/ml, the secondary stock solution was first diluted using the same phosphate buffer pH 6.8. Corresponding absorbance was then measured at the maximum wavelength of 246 nm. In order to achieve the calibration curve of pure Atorvastatin, measured absorbencies were plotted against corresponding concentrations.[5,6]

Drug and Excipients compatibility studies

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

Fourier Transform Infrared (FTIR) spectroscopy

In order to determine the peaks that indicate the existence of a specific functional group in the pure medicine and the excipients employed, Fourier transforms infrared (FTIR) spectroscopy tests were carried out. The drug and excipients are considered to be compatible if the functional groups present in the pure drug reflect in the formulations. Atorvastatin was studied using FTIR for both the pure drug and a physical mixture of the drug and all excipients (optimised formulation). The procedure used the pellet method with potassium bromide (KBr). The materials were triturated with KBr, and a pellet was created by applying 100 kg/cm2 of pressure for two minutes. The obtained pellet was examined in the Shimadzu, Japan, FTIR 8400S. Prior to the analysis of the test samples, the KBr background was first acquired. The same procedures were repeated for the analysis of drug, individual excipients and for physical mixture of drug and excipients.[7,8]

Formulation of Atorvastatin Orodispersible tablets ($AODT_1$- $AODT_6$)

Step 1: Weighing and mixing of formulation ingredients

(Excluding the lubricant). This step involves the weighing, sifting and introduction of specified quantities of drug (Atorvastatin), sodium starch glycolate, cross povidone and mannitol into a powder mixer. These ingredients are mixed using motor pestle until a uniform powder mix is achieved.

Step 2: Preparing the damp mass

Here, the poly vinyl pyrrolidone binder solution is mixed with the powder mixture to form an adhesive mass which can be granulated. The amount of binding agent used as well as the quantity of fluid required to form a damp and coherent mass is part of the operator's skill; however, the resulting binder-powder mixture should compact when squeezed in the hand. The use of insufficient binder tends to poor adhesion, capping and soft tablets. Excessive binder solution yields hard tablets slow disintegrating properties

Step 3: Wet screening/ Screening the dampened powder into pellets or granules

The wet massed powder blend is screened using 6- to 12-mesh screen to prepare wet granules. This may be done by hand or with suitable equipment that prepares the granules by extrusion through perforations in the apparatus. The granules formed are spread evenly on trays and dried in an oven.

Step 4: Drying of moist granules

The screened moist granules are dried in an oven at a controlled temperature not exceeding 55^0C to a consistent weight or constant moisture content.

Step 5: Sizing the granulation by dry screening

The dried granules are passed through a screen of smaller size than that used to prepare the moist granules. The size of the final granules is dependent on the size of the punches (and hence the final tablet size). Screens of 14- to 20- mesh size are generally used for this purpose.

Step 6: Lubrication of granules

After dry screening, the dried and screened granules are separated into coarse and fine granules by shaking them on a 250-mesh sieve. Appropriate quantity of magnesium stearate and talc is passed through a 200 – mesh sieve. This is mixed with the fine granules before the coarse granules are incorporated.

Step 7: Compression of granules into tablets

Here, the mixed granules are compressed (6 mm diameter, circular concave faced punches) on a 10 station rotary tablet punching machine (SHAIMAC Technology Pvt. Ltd, Hyderabad, India). Each tablet contained 20 mg of Atorvastatin. All the tablets were stored in airtight containers for further study.[5,6] Composition of various formulation are given in **table 1**.

Table 1: Compositions of different formulations of Atorvastatin Orodispersible tablets.

Formulations (mg)	$AODT_1$	$AODT_2$	$AODT_3$	$AODT_4$	$AODT_5$	$AODT_6$
Atorvastatin	20	20	20	20	20	20
Sodium Starch Glycolate	6	8	-	-	3	4
Cross Povidone	-	-	6	8	3	4
Mannitol	147	145	147	145	147	145
Poly Vinyl Pyrrolidone	20	20	20	20	20	20
Aspartame	1	1	1	1	1	1
Magnesium stearate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Total wt.	200	200	200	200	200	200

Evaluation of precompression parameters of dry granules of Atorvastatin Orodispersible 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 respectably. According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle greater than 40^0 indicates poor flow.[6,7]

Bulk Density and Tapped density

Both the bulk density (BD) and tapped density (TD) of prepared Atorvastatin Orodispersible dry granules of all the formulations were determined using the following formulas.[7,9]

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

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

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 Orodispersible dry granules were calculated by following formula

$$Carr's\ index\ (\%) = \frac{TD-BD}{TD} \times 100$$

According to the specification the Carr's index values "between" 5-15 indicates excellent flow where as between 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable where as between 23-25 indicates poor. "Between" 33-38 indicates very poor and greater than 40 indicates extremely poor.[7,10]

Hausner's ratio

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

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

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), where as 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.[5,11]

Evaluation of postcompression parameters of atorvastatin orodispersible tablets formulations

Average thickness

From each formulation (AODT); ten tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial Thickness Gauge, Mitutoyo,Japan) and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.[7,11]

Tablet hardness

The hardness was measured for all the formulations of Atorvastatin Orodispersible tablets by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten orodispersible tablets with

known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 3-4 Kg for orodispersible tablet is considered as acceptable limit.[5,12]

Friability

Previously weighed ten tablets from each batch (AODT) were taken in Roche friabilator (Roche friabilator, Secor India, Delhi, India). After hundred revolutions of friabilator, tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

Where W_i and W_f were the initial and final weight of the tablets before and after friability test. For compress tablet that lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.[11,13]

Weight variation test

According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324 mg is 7.5% and for average weight more than 324mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%. All formulations of Atorvastatin orodispersible tablets were evaluated for weight variation as per USP monograph. Twenty tablets from each batch were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated.[14,15]

Content uniformity

For determination of content uniformity of the all formulations (AODT); twenty tablets were taken and triturated to form powder. Powder equivalent to one tablet was taken and dissolved in 100 ml of phosphate buffer pH 6.8 and heated at 37 ^{0}C for 15 to 20 minutes with constant stirring. The solution was cooled, filtered and after suitable dilution the Atorvastatin content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 246 nm. Each measurement was carried out in triplicate and the average drug content in each formulation was calculated.[16]

Wetting Time and Water absorption ratio

Wetting time reflects the disintegration process of the tablet formulation. Lesser the wetting time more is the disintegration rate. For the wetting time determination, twice folded tissue paper was placed in a petri dish having an internal diameter of 6.5 cm containing 10 ml of phosphate buffer pH 6.8 containing methylene blue (0.1% w/v). A tablet from each formulation of Atorvastatin orodispersible tablets was carefully placed on the surface of the tissue paper in the petri dish. The time required for the dye to reach the upper surface of the tablet was recorded as wetting time. Measurements were carried out in triplicate and standard deviations were also determined.[15,17]

Water absorption ratio (R), can be estimated by simple procedure include weighing (W_b) of the tablet prior to the placement on the Petri dish, then after recording the wetting time. The wetted tablet was removed and reweighed (W_a). The water absorption ratio was determined according to the following equation.

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

***In vitro* disintegration time (D_t)**

According to USP the disintegration apparatus for oral tablets is used without the covering plastic disks and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements whereas < 2 min for orodispersible dosage form. The test was carried out using tablet disintegration apparatus (model EI D-16, Electrolab, Mumbai, India). *In vitro* disintegration test was carried out using a modified disintegration method (n = 6) using disintegration tester maintained at 37°C ± 0.5°C in phosphate buffer pH 6.8. The tablets were kept in the basket and the time taken for the tablet to disintegrate completely into smaller particles was noted.[16,17]

***In vitro* drug release (dissolution) study**

The *in vitro* dissolution study was conducted for all the formulations (AODT) using an eight station USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India.). A total volume of 900 ml of phosphate buffer pH 6.8 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 5ml of aliquots were periodically withdrawn and the same volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at each 5 min intervals and filtered by Whatmann filter paper. Samples were analyzed spectrophotometrically at 246 nm for determination of Atorvastatin that were released from orodispersible tablets.[17,18]

Characterization of the *in vitro* drug release profile

The rate and mechanism of release of Atorvastatin from prepared orodispersible 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.

$$\log(100 - Q) = log100 - K_1\, t$$

Where, K_1 is the first order release rate constant.[19,20]

Stability studies of best formulation

The short term stability studies of best formulation of Atorvastatin orodispersible tablet were carried out according to ICH guidelines. The best formulation was subjected to accelerated stress condition at 40 ^{o}C ± 2 ^{o}C/ 75% ± 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.[19,20]

RESULTS AND DISCUSSION

Drug-Excipient Compatibility studies by FTIR

From the FTIR studies it was found that the spectra of Atorvastatin exhibit peak due to 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 were complying with the reported values. The FTIR spectra of optimised formulation $AODT_4$ (Atorvastatin with all the Excipients) exhibit peak due to 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}. Thus it is evident that all the characteristic peaks that were present in the spectra of pure drugs replicated almost in the same region in the spectra of best formulations of Atorvastatin orodispersible tablet indicating that there is no significant interaction between the drugs and the excipients. The FTIR spectra of pure drug Atorvastatin and best formulations were shown in **figures 1 and 2**.

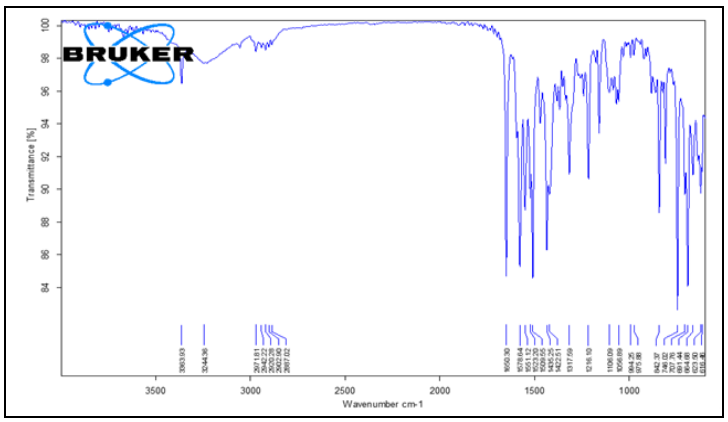

Fig. 1: FT-IR spectra of Atorvastatin pure drug.

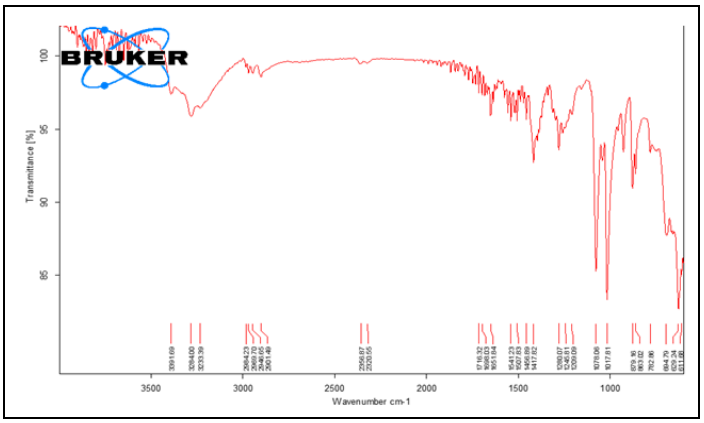

Fig. 2: FT-IR spectra of physical mixture of Atorvastatin with excipients.

The bulk densities of Atorvastatin orodispersible dry granules of all formulations were found in the range of 0.542±0.08 to 0.630±0.07 g/cm^3 and the tapped densities were found in between 0.671±0.08 to 0.721±0.08 g/cm^3. This indicates good packing capacity of dry granules. Bulk density and tapped density measurements found that density of dry granules depends on particle packing and that density changes as the granule consolidates. Values of Carr's index for all the formulations were found below 16% that usually indicates good flow characteristics except the formulations **$AODT_4$** and **$AODT_6$** which may be due to lake of uniformity in granule sizes and presences of more fine particles in those formulations.

Hausner's ratio is simple method to evaluate stability of power and granule column and to estimate flow properties. Low range was observed of Hausner's ratio that indicates good flow ability. In all formulations the Hausner's ratios values were ranged from 1.13 to 1.32 that indicates good flow characteristics of dry granules.

Angle of repose is suited for particle > 150µm.Values of angle of repose ≤ 25 generally indicates the free flowing material and angle of repose ≥ 40 suggest a poor flowing material. The angle of repose is indicative of the flowability of the dry powder or granules. The angle of repose of all formulations fell within the range of 25.65±0.12 to 22.20±0.15 *i.e.* dry granules of Atorvastatin orodispersible tablet showed good flow properties and suitable for compression. The results of precompression parameters for all the formulations were given in **table 2**.

Table 2: Evaluation of precompression parameters of atorvastatin orodispersible dry granules ($AODT_1$ – $AODT_6$).

F. Code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
$AODT_1$	0.581±0.06	0.680±0.05	23.96±0.12	14.7	1.17
$AODT_2$	0.611±0.08	0.701±0.07	25.40±0.13	12.8	1.14
$AODT_3$	0.592±0.07	0.671±0.08	24.41±0.14	11.94	1.13
$AODT_4$	0.561±0.07	0.740±0.05	25.65±0.12	24.23	1.32
$AODT_5$	0.630±0.07	0.721±0.08	22.20±0.15	12.5	1.14
$AODT_6$	0.542±0.08	0.681±0.07	24.94±0.12	20.58	1.25

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

The physical parameters such as hardness, average weight variation, average friability and average thickness of the all the formulations of Atorvastatin orodispersible tablets were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The average thicknesses of the tablets were ranged between 3.12±0.9 to 4.02±0.6 mm. All the batches showed uniform thickness and were within range. Percentage Weight variations for different formulations were found to be 4.32±0.36% to 3.62±0.50%. The acceptable average percentage variation for tablet formulations having weight 100mg is 10% and all the formulations fall within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement.

The average hardness of all the Atorvastatin orodispersible tablet formulations was ranged from 3.1±0.7 to 4.8±0.7 kg/cm^2. By increasing the concentration of superdisintegrant concentration the hardness usually decreased that noticed in case of formulation $AODT_4$ and $AODT_5$. The percentage friability of all the formulations were ranged from 0.229±0.04% to 0.851±0.02% and also the % friability were found more by increased concentration of superdisintegrant concentration. In the present study, the percentage friability for all formulations was within the prescribed limits. The percentages of drug content for $AODT_1$ to $AODT_{10}$ were found to be in between 93.42±1.09% to 100.76±1.25% of Atorvastatin orodispersible tablet formulations which were within the acceptable limits. Disintegration time were determined for all the formulations and it was found that by increasing concentration of superdisintegrant, the disintegration time decreases; but increase in concentration above 6% the hardness value decreases.

The wetting time of all the formulations were found between 51±0.33 to 68±0.46 sec. For the case of wetting time by increasing the concentration of superdisintegrant the wetting time decreases those were noticed in case of formulations of $AODT_2$, $AODT_4$, $AODT_5$ and $AODT_6$. Between sodium starch glycolate and cross crosspovidone, later showed less wetting time than later at equal concentrations. The water absorption ratio of formulations $AODT_1$ to $AODT_6$ was found in the range of 35.25±0.12 to 14.42±0.16. By increasing the concentration of superdisintegrant the water absorption ratio increased that might be due to increase in the porosity of the formulation with increase in superdisintegrant concentration. The physicochemical characterizations of different batches of Atorvastatin orodispersible tablets are given in **table 3**.

Table 3: Evaluation of Post-compression parameters of atorvastatin orodispersible tablets.

F. Code	Average Hardness (kg/cm^2)	Average Weight Variation (%)	Friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)	D_t (Sec)	Wetting time (Sec)	Water absorption ratio
$AODT_1$	3.1±0.5	4.15±0.25	0.851±0.02	3.34±0.7	95.39±1.24	201.27±2.05	53±0.52	35.25±0.12
$AODT_2$	3.2±0.8	4.32±0.36	0.285±0.04	3.79±0.6	93.42±1.09	165.29±2.12	58±0.41	22.31±0.32
$AODT_3$	3.7±0.6	3.64±0.43	0.493±0.03	4.01±0.6	96.95±1.32	187.54±2.34	68±0.46	31.44±0.19
$AODT_4$	4.8±0.7	3.81±0.28	0.229±0.04	3.12±0.9	100.76±1.25	123.06±2.25	51±0.33	19.37±0.25

$AODT_5$	4.7±0.5	3.82±0.31	0.347±0.05	4.02±0.6	95.27±1.41	134.92±2.26	40±0.52	17.15±0.24
$AODT_6$	3.1±0.7	3.62±0.50	0.345±0.06	3.80±0.8	97.54±1.33	152.05±2.37	48±0.39	14.42±0.16

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

The *in vitro* drug release characteristics of Atorvastatin orodispersible tablets were studied in phosphate buffer pH 6.8 dissolution medium for a period of 30 minutes using USP type-II (paddle type) dissolution apparatus. The rate of dissolution increased by increasing the concentration of superdisintegrant upto an optimum concentration of 4%. The formulation **$AODT_4$** having 4% of Crosspovidone released 99.31% of the drug in 20 minutes whereas formulation **$AODT_2$** having 4% of sodium starch glycolate released 90.66% of the drug in 25 minutes. When both the superdisintegrants were used in combination in total concentration of 4% better dissolution profile is not noticed. The dissolution profiles of all the formulations (**$AODT_1$** to **$AODT_6$**) were shown in **figure 3**.

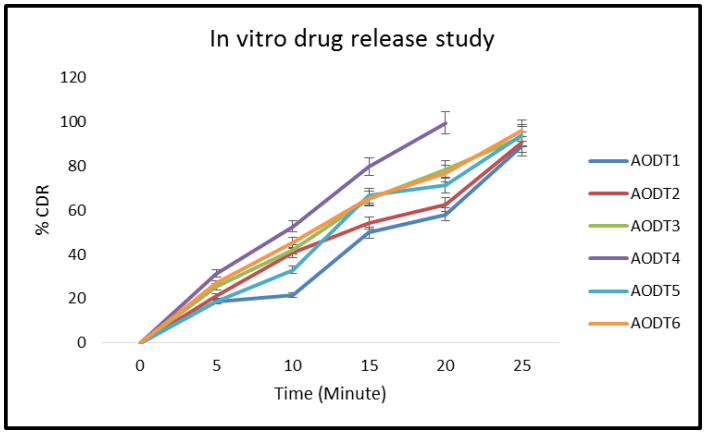

Fig. 3: *In vitro* drug release study of atorvastatin orodispersible tablet formulations ($AODT_1$ to $AODT_6$).

The formulation $AODT_4$ was selected for drug release kinetic and mechanism of release tests based on having the highest dissolving profile. Atorvastatin orodispersible tablets ($AODT_4$) in vitro dissolving data were fitted in various kinetic models, including zero order and first order, and the graphs were displayed in **figure 4 and 5**. The greatest regression results (0.9943) for the $AODT_4$ formulation showed that the zero order kinetic graphs were generally linear. **Table 4** displayed the regression coefficients for the release kinetics.

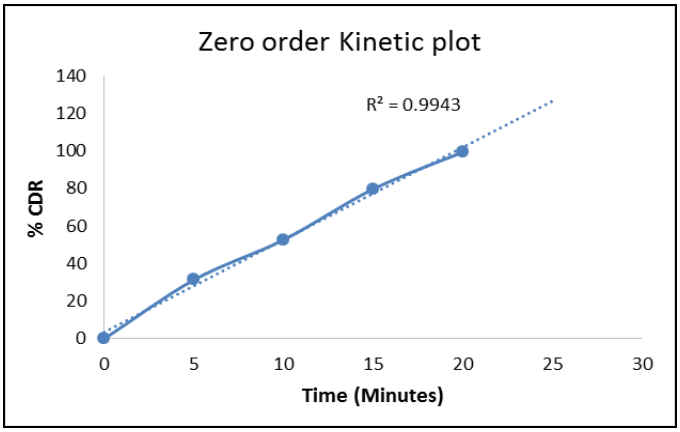

Fig. 4: Zero order release kinetic study of best formulation $AODT_4$.

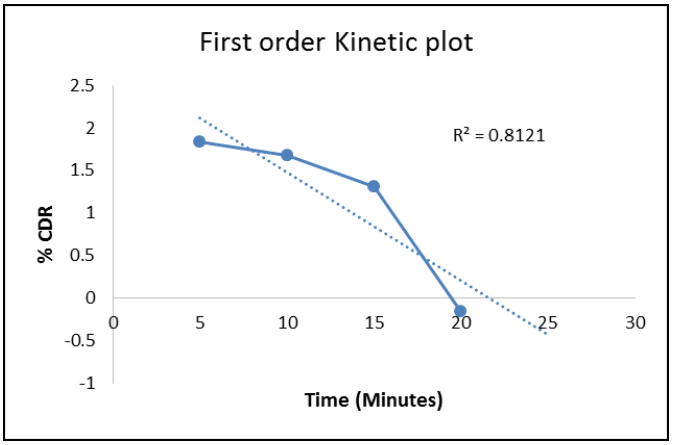

Fig. 5: First order release kinetic study of best formulation AODT$_4$.

Table 4: Regression values of *in-vitro* release kinetic study best formulation (AODT$_4$).

Formulation code	R^2value of Zero order	R^2 value of 1st order	Remarks
AODT$_4$	0.9943	0.8121	Follows Zero order kinetic as it is having highest regression value

The best formulation (**AODT$_4$**) of Atorvastatin orodispersible tablets was selected for accelerated stability studies. The best formulation (**AODT$_4$**) Atorvastatin orodispersible 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 orodispersible 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 5** and comparative release profile has been represented in **figure 6.**

Table 5: Comparative physicochemical properties of AODT$_4$) at accelerated conditions (40 °C ± 2 °C/ 75% ± 5% RH).

Sl. No.	Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
1	Physical appearance	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
2	Weight variation	3.81± 0.28	3.66±0.12	3.52±0.31	3.51± 0.24
3	Hardness	4.8±0.7	4.6±0.3	4.3±0.5	4.2±0.2
4	Friability	0.229± 0.04	0.302±0.03	0.345±0.05	0.423±0.04
5	Wetting time (Sec)	51±0.33	57±0.25	62±0.38	64±0.13
6	Drug content	100.76±1.25	98.26±1.05	96.73±1.24	95.55±1.56
7	D_t (Sec)	123.06±2.25	134.25±2.0	142.31±1.5	151.06±2.1

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

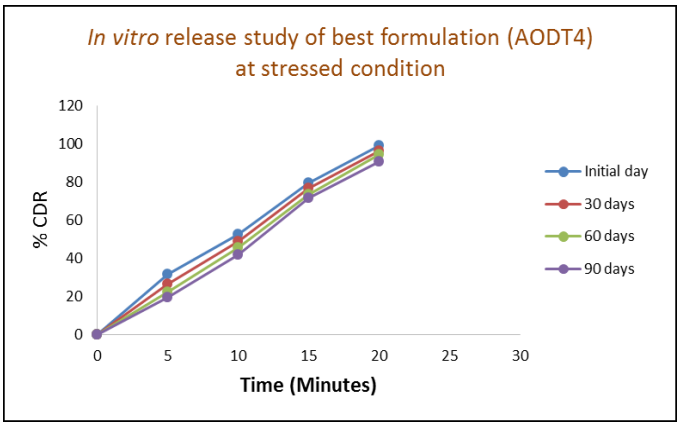

Fig. 6: *In vitro* release study of best formulation (AODT$_4$) at stressed condition.

CONCLUSION

Atorvastatin orodispersible pills were successfully created throughout the current experiment. The main difficulty in this experiment was determining how sodium starch glycolate and crosspovidone affected the orodispersible tablet of atorvastatin's in vitro release rate. A potential method for achieving fast medication release and one that proved helpful for acute diseases was the orodispersible drug delivery system. According to FTIR measurements, the formulation is thermally stable and the drug and excipients are compatible. Atorvastatin orodispersible tablets were made using wet granulation techniques, and evaluation of all precompression parameters for dry granules made with medication and excipients fulfilled acceptance standards and had excellent flow properties. The average thickness, hardness, friability, weight fluctuation, wetting time, water absorption ratio, and disintegration are all within acceptable limits for postcompression characteristics. The best formulation was formulation AODT4, which contained 4% crosspovidone and demonstrated full drug release in less than 20 minutes (>99%). The drug release profile was accelerated by an increase in superdisintegrant concentration, although the formulation's hardness and friability were negatively impacted. The best formulation, AODT4, was shown to follow a zero order kinetic model with the highest R2 value for drug release in vitro. The stability studies were conducted in accordance with ICH guidelines, and the chosen AODT4 formulation was stable in accelerated stressful condition for up to 3 months with a little change in the formulations' physicochemical and drug release properties. As a result, given that the drug releases fast and is effective for treating acute conditions, the Atorvastatin orodispersible tablets drug delivery system has a promising future and can be utilised as an alternative to the traditional dose form. However, more clinical research is required to determine the usefulness of this method for patients with high cholesterol levels.

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