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Formulation and Evaluation of Orodispersible Tablet of Atorvastatin Calcium by Using *Hibiscus rosa sinesis* Mucilage as Natural Superdisintegrant

Gupta Ashish*, Bhadoria Juhi, Darwhekar G.N.

Acropolis Institute of Pharmaceutical Education and Research, Indore, Indore Dewas Bypass Road,Manglia Square, Indore (M.P.) 453771

ABSTRACT

Orodispersible tablets (ODTs), also known as fast melt, quick melts, fast disintegrating have the unique property of disintegrating in the mouth in seconds without chewing and the need of water. Oral bioavailability of Atorvastatin Calcium is low (14%) and shows extensive intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability. In the present work, orodispersible tablets of Atorvastatin calcium were prepared by direct compression method using Hibiscus rosa sinesis mucilage as natural superdisintegrant with a view to enhance patient compliance and to avoid hepatic first pass metabolism and to improve its bioavailability. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water-absorption ratio and in-vitro dispersion time. Short-term stability studies on the promising formulation indicated that there are no significant changes in drug content and in vitro dispersion time.

Keywords: Orodispersible tablet, Atorvastatin Calcium, lipid-lowering agent, Superdisintegrant, Hibiscus Rosa Sinensis, Bioavailability, solubility.

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***Address for Correspondence:**

Gupta Ashish, Acropolis Institute of Pharmaceutical Education and Research, Indore, Indore Dewas Bypass Road,Manglia Square, Indore (M.P.) 453771

INTRODUCTION

Oral delivery is current standard in the pharmaceutical industry wherever it is regarded as the safest, most suitable and most economical method of drug delivery. The oral cavity is an attractive site for the administration of drugs because of ease of administration.

Oro-dispersible drug delivery system are Novel Drug Delivery techniques that make the tablets disintegrate in the mouth without chewing and water, and immediate release and enhanced bioavailability, with better patient compliance.

Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates within a minute or second in the mouth before swallowing.

United States Food and Drug Administration (FDA) defined Oro-dispersible tablet as "a solid dosage form containing medicinal substances or active ingredient which disintegrate or dissolve rapidly within seconds when placed upon the tongue.

Oro-dispersible tablets have a quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pregastric absorption when formulated as ODTs may oral bioavailability of drug is enhanced by avoiding the hepatic first pass metabolism. It provides good stability, accurate dosing, easy of manufacturing. Oro-dispersible tablets are made by a direct compression method using super Disintegrate as an important component.

MATERIAL AND METHODS

Materials

Atorvastatin calcium was obtained as a gift sample from Yarrowchem Products (Mumbai). Beta-cyclodextrin was obtained as a gift sample from Alkem laboratories Ltd (Mumbai). Microcrystalline Cellulose, Mannitol, Magnesium Stearate, Talc, Ethanol, Methanol and Silica gel-G, Lobachem Pvt. Ltd. Aspartame, Potassium Dihydrogen Phosphate, Sodium hydroxide and Hydrochloric acid were purchased from Lobachem and Merck Pvt Ltd.

Methods

Drug Characterization

Melting point determination

Capillary tube was taken and one end was sealed by heating. Capillary tube was filled with drug powder upto 2-3mm high. The capillary tube was putted inside melting point apparatus and temperature was increased slowly. The temperature was noted when the drug gets starts melting and again noted when drugs completely melted.

UV Spectroscopy

50mg of drug was weighed and was dissolved in 50ml of methanol (1mg/ml). 10ml of this solution was withdrawn and volume was made up to 100ml. Appropriate dilutions were made with methanol to give concentration of 10 µg/ml, scanned in UV range from 200- 400nm, which could be utilized for analysis and spectrum was recorded.

Calibration curve

Accurately weighed 50mg of Atorvastatin Calcium was transferred into a 500ml volumetric flask & dissolved in phosphate buffer 6.8. Then sonicated for 15 minute and the volume was made up with phosphate buffer pH 6.8 to obtain a 100µg/ml stock solution of Atorvastatin Calcium.

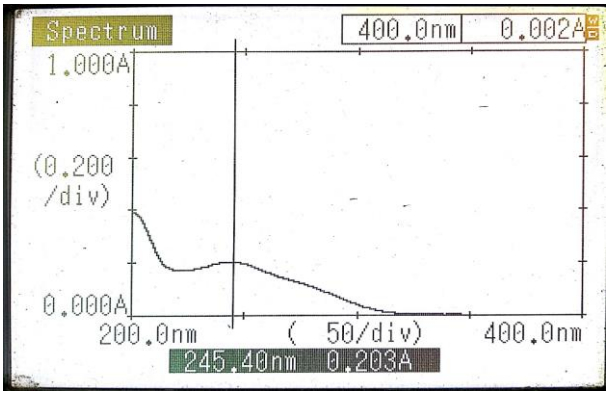

Fig. No. 1 Lambda Max of Atorvastatin Calcium

Solubility studies

An excess amount of prepared Atorvastatin-β-cyclodextrin inclusion complex at different concentration (1:3, 1:4, 1:5) were separately dissolved in 5ml phosphate buffer pH 6.8 in vials and sealed properly and stirred continuously. The process was repeated until saturation solubility of inclusion complex. The solution was kept for 24 hours at room temperature. Then solution was filtered. The adequately diluted with phosphate buffer pH 6.8. Then solution was analyzed by using UV-visible spectrophotometer at 245.40nm.

Table no.1: Solubility data of Atorvastatin Calcium in different mediums:

S.NO.	Solvent	Solubility (mg/ml) Mean±SD (n=3)	Inference
1	Methanol	30.106±2.186	Soluble
2	Phosphate buffer pH 6.8	0.184±0.001	Very Slightly soluble
3	pH 1.2 HCl buffer	0.108±0.007	Very Slightly soluble
4.	Water	0.578±0.010	Slightly soluble

Formulation

- **Solubility enhancement by Inclusion Complex**

An excess amount of prepared Atorvastatin-β-cyclodextrin inclusion complex at different concentration (1:3, 1:4, 1:5) were separately dissolved in 5ml phosphate buffer pH 6.8 in vials and sealed properly and stirred continuously. The process was repeated until saturation solubility of inclusion complex. The solution was kept for 24 hours at room temperature then solution was filtered. The solubility was determined by using UV- Spectroscopy.

Table no. 2

S.No.	Phosphate buffer pH 6.8	Solubility (mg/ml) Mean±SD (n=3)	Inference
1	Pure drug	0.184±0.001	Very Slightly Soluble
2	Drug:β-CD (1:3)	0.471±0.004	Slightly Soluble
3	Drug:β-CD (1:4)	0.694±0.008	Slightly Soluble
4	Drug:β-CD (1:5)	0.840±0.012	Slightly Soluble

- **Experimental design**

A two factor three level factorial design (3^2) was used for the formulation optimization of orodispersible tablet of Atorvastatin and experimental trials are performed at all 9 possible formulation. In which the amount of β-cyclodextrin (X1) and Hibiscus Rosa- Senesis mucilage (X2) were selected as independent variables (factor) varied at three different level: low(-1), medium(0), and high(+1) levels.

Table no. 3

S. No	Name of ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1.	Drug (Atorvastatin)	10	10	10	10	10	10	10	10	10
2.	β-cyclodextrin	30	30	30	40	40	40	50	50	50
3.	Hibiscus Rosa- Senesis Mucilage	4	6	8	10	12	14	16	18	20
4.	Microcrystalline cellulose	120	120	120	120	120	120	120	120	120
5.	Mannitol	40	40	40	40	40	40	40	40	40
6.	Aspartame	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
7.	Magnessium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
8.	Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5

Preparation of Atorvastatin Calcium Fast Disssolving tablet by Direct compression method

Orodispersible tablet of Atorvastatin were prepared by direct compression method. Weighed all the ingredients accurately according to the table no.3. All the ingredients except Talc, Magnessium sterate were mixed step by step and trituration was continued for 15 minute, and passed through sieve no. #60. Subsequently talc, magnesium stearate mixed at last & again mixed. The powder was compressed using multistation tablet punching machine (Aidmach Pvt. Ltd.) with 8mm flat punch, B-tooling and corresponding dies.

Evaluation of Tablet

- **Weight variation**

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5% (USPXX).

- **Thickness**

Thickness of tablet was determined by using vernier calliper (Mitutoya, Model CD-6 CS, Japan).

- **Hardness**

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). Three tablets from each formulation batch were tested randomly and the average reading noted.

- **Friability**

Twenty tablets were weighed and placed in a Roche friabilator (Electrolab, India). Twenty reweighed tablets were rotated at 25 rpm for 4 min. The tablets were then dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets were measured as per the following formula,

$$\text{Percentage friability} = \frac{\text{Initial weight-Final weight x 100}}{\text{Initial weight}}$$

- **Wetting time**

A piece of circular tissue paper (8cm) folded twice was placed in a Petri dish (Internal Diameter = 9cm) containing 10 ml of buffer solution simulating saliva pH 6.8. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted. The results are tabulated in Table 6.

- **Water absorption ratio**

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was the reweighed. Water absorption ratio, R was determined using following equation-

$$R = 100 \times Wa\text{-}Wb/Wa$$

Where, Wa = Weight of tablet after water absorption

Wb = Weight of wetted tablet before water absorption

- **Disintegration Time**

One tablet was introduced into each tube and disc was added to each tube. The assembly was introduced in the beaker containing purified water. The apparatus operated until the tablet completely disintegrate. The time was noted down until the tablets completely disintegrate. The assembly was removed from water.

- **Dissolution Study**

In vitro release of Atorvastatin calcium from tablets was monitored by using 900 ml of simulated intestinal fluid, SIF (USP phosphate buffer solution, pH 6.8) at 37±0.5^{0}C and 50 rpm using programmable dissolution tester [Paddle type, model TDT-08L, Electrolab, (USP), India]. 5 ml Aliquots were withdrawn at one minute time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically (UV- 1700, Shimadzu, Japan) at 245.5 nm.

RESULT AND DISCUSSION

Mouth dissolving drug delivery is rapidly gaining acceptance as an important drug delivery technology. In such drug delivery, different dosage forms disintegrate rapidly in the patient's mouth within a minute and can be gulped easily without need of water. This rapid disintegration can be achieved by use of high levels of disintegrate and/or effervescent agents along with water soluble diluents. Hence, it offers increased patient compliance and convenience. orodispersible tablet of Atorvastatin calcium was formulated. Total nine batches were prepared for orodispersible formulation. All the formulations were subjected to evaluation, Tablet weight varied from 110 to 120 mg, and thickness 3 to 4.1 mm. All the tablets exhibited friability values between 0.5 to 0.8, all tablets disintegrated in less than 1 minute. The drug released at the time interval of 30 minutes upto 97.5% of batch F9.

Table no. 4 Evaluation of Flow properties of powder (Drug excipient mixture)

Formulation	Bulk density (gm/ml) (n=3) Mean±SD	Tapped density (gm/ml) Mean±SD	Carr's index (%) (n=3) Mean±SD	Angle of repose (°) (n=3) Mean±SD	Hausner's ratio (n=3) Mean±SD
MD1	0.314±0.004	0.368±0.004	14.635±1.503	25.406±0.374	1.170±0.026
MD2	0.299±0.002	0.358±0.003	14.634±1.004	29.333±1.106	1.166±0.015
MD3	0.288±0.002	0.345±0.003	16.323±1.047	27.606±0.525	1.186±0.015
MD4	0.332±0.003	0.385±0.006	13.907±0.852	26.966±0.450	1.16±0.01
MD5	0.307±0.003	0.363±0.002	15.260±1.695	25.59±0.213	1.176±0.020
MD6	0.293±0.003	0.355±0.003	17.360±1.663	27.4±0.500	1.206±0.025
MD7	0.344±0.003	0.402±0.004	14.414±0.402	26.74±0.767	1.166±0.005
MD8	0.326±0.003	0.376±0.003	13.354±1.494	30.6±0.888	1.15±0.02
MD9	0.298±0.002	0.330±0.001	9.787±0.459	26.633±0.709	1.103±0.005

Table no. 5 Determination of physicochemical properties of orodispersible tablet

Formulation	Weight variation (mg) (n=3) Mean±SD	Hardness (Kg/cm^2) (n=3) Mean±SD	Friability (%) (n=3) Mean±SD
MD1	210.16±0.378	2.6±0.264	0.460±0.027
MD2	211.75±0.312	2.4±0.173	0.750±0.047
MD3	214±0.938	3.0±0.057	0.460±0.045
MD4	223±0.301	2.9±0.152	0.672±0.045
MD5	232±2.13	3.0±0.1	0.346±0.043
MD6	233±0.28	3.0±0.057	0.343±0.043
MD7	246.58±0.56	3.0±0.057	0.349±0.023
MD8	247.83±1.05	3.1±0.1	0.361±0.040
MD9	251.06±0.17	3.1±0.057	0.358±0.040

Table no. 6 Other Evaluation parameters

Formulation	Disintegration Time (sec) (n=3) Mean±SD	Drug Content (%) (n=3) Mean±SD	Wetting time (sec) (n=3) Mean±SD	Water absorption Ratio (%) (n=3) Mean±SD
MD1	42±1.05	91.833±0.233	32.7±0.590	55.97±3.63
MD2	38±1.86	93.36±0.356	31.37±0.580	49.01±3.59
MD3	37±1.93	95.84±1.362	30.05±0.040	42.18±3.13
MD4	35±1.28	92.19±0.583	32.38±0.540	46.75±1.34
MD5	30±1.25	99.25±0.470	29.71±0.546	30.3±1.56
MD6	33±1.36	96.85±0.584	31.06±0.015	35.90±0.65
MD7	45±1.68	95.76±0.466	33.38±0.580	36.83±0.61
MD8	36±1.26	95.60±1.151	34.69±0.534	40.42±0.61
MD9	39±1.48	93.73±1.113	35.06±0.015	41.96±0.60

Table no. 7 Invitro drug release study

Time (in min	% Cumulative drug Release (Mean±SD) (n=3)								
	MD1	MD2	MD3	MD4	MD5	MD6	MD7	MD8	MD9
0	0	0	0	0	0	0	0	0	0
5	11.4±3.20	16.9± 3.16	21.84± 4.35	28.83± 2.11	27.44± 2.41	30.24± 3.27	21.15±3. 21	23.94± 3.21	21.84± 2.44
10	214± 1.19	25.3± 1.60	37.2± 2.11	34.2± 2.11	35.1± 2.07	39.99± 3.20	28.83± 2.11	34.44± 4.35	28.14± 3.20
15	34.41± 3.16	40.0± 1.20	46.29± 2.44	44.21± 3.18	46.98± 3.21	44.87± 1.280	41.14± 2.07	43.51± 3.62	33.71± 3.16
20	44.2± 4.37	53.9± 5.52	57.45± 6.41	50.51± 4.81	56.07± 2.07	55.34±3.2 2	53.24± 2.45	56.76± 1.95	47± 3.21
25	58.14± 2.07	67.9± 5.25	63.72± 4.34	67.92± 3.20	73.14± 2.14	62.24±1.9 6	75.59± 3.21	72.83± 2.07	68.61± 2.11
30	90.94± 3.17	86.0±1.2 4	89.55± 3.58	88.13± 3.19	95.84± 2.08	84.66±3.2 0	86.76± 1.24	92.34± 4.34	93.72± 2.09

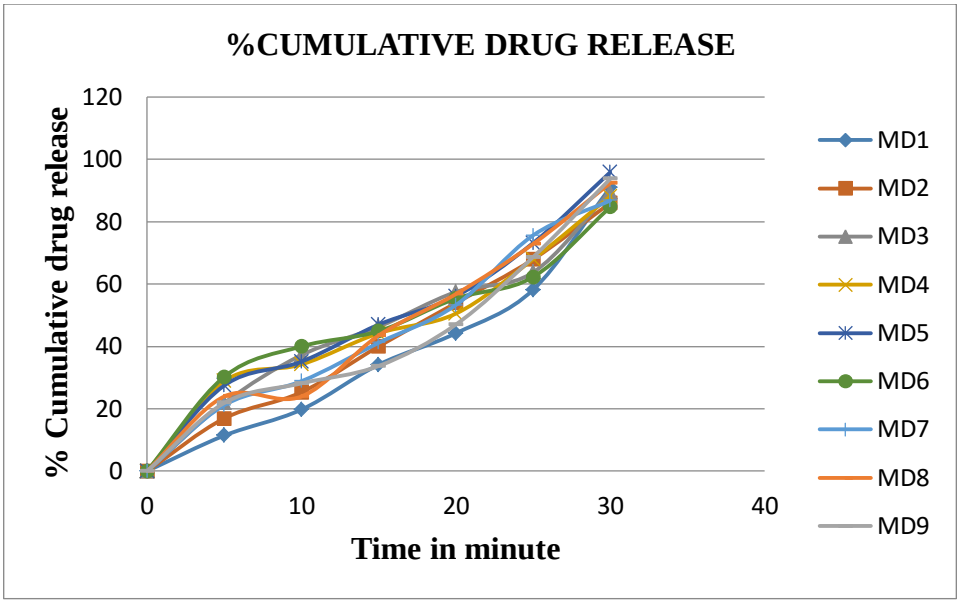

Fig no. 2 Invitro drug release of orodispersable tablet

Table no. 8 Stability studies

S.No.	Parameter	After 30 days	Inference
1.	Weight variation	229.33±0.574	Within Limit
2.	Hardness	3.03±0.055	Within Limit
3.	Drug content	99.36±0.568	Within Limit
4.	Wetting time	27.66±0.364	Within Limit
5.	Water absorption ratio	33.66±0.475	Within Limit
6.	Disintegration	33.48±0.575	Within Limit

CONCLUSION

The present study was carried out to prove that Orodispersible tablet of Atorvastatin calcium can be formulated. The concept explains that formulated tablets avoids hepatic first pass metabolism and improves its bioavailability.

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