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Research Article

**FORMULATION DEVELOPMENT AND EVALUATION OF
FAST DISSOLVING ORAL FILM OF ATORVASTATIN
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Radharaman College of Pharmacy, Bhadbhada Road, Ratibad, Bhopal (MP) -462044**Article Received:** January 2022 **Accepted:** January 2022 **Published:** February 2022**Abstract:**

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. Atorvastatin is a lipid lowering agent and widely used to treat hypercholestermia. However following oral administration, the bioavailability of the drug is only 12% due to extensive first pass metabolism. The aim of present work is to formulate and evaluate fast dissolving oral films of atorvastatin calcium to improve water solubility, dissolution rate, oral bioavailability and reduction of first pass metabolism and increase patient's compliance. Oral fast dissolving films prepared by solvent casting method using water and 95% ethanol as solvents and HPMC as film forming polymer. PEG 400 was the selected plasticizers, Superdisintegrants such as croscarmellose sodium (CCS), crospovidone (CP) and sodium starch glycolate (SSG) alone and also in combinations was incorporated to achieve the aim. The prepared films were evaluated for the drug content, weight variation, film thickness and disintegration time, folding endurance, percentage of moisture content and in vitro dissolution studies and taste mask studies on healthy human volunteers. Among all, the formulation F4 was found to be best formulation which releases 98.95 % of the drug within 15 min and disintegration time is 168sec. which was significantly high when compared to other formulation. The results revealed that, atorvastatin fast dissolving oral films could be considered as promising drug delivery system for hyperlipidemic patients.

Keywords: Atorvastatin, Hypercholestermia, Fast dissolving films, Solvent casting method, Superdisintegrants.**Corresponding author:****Sufiya Tahseen**Radharaman College of Pharmacy, Bhadbhada Road, Ratibad,
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INTRODUCTION:

Fast dissolving films for oral administration was a novel approach, for the patients who experience difficulties in swallowing tablets or capsules. Geriatric, pediatric and dysphasic patients associated with many medical conditions face a problem of difficulty in swallowing the solid dosage forms. One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets [1]. Oral fast-dissolving drug-delivery systems were developed in the late 1970's to overcome the problem of difficulty in swallowing solid dosage forms [2]. These systems consist of oral dispersible tablets (ODT) that disintegrate and dissolve quickly in the oral cavity. Oral strips and oral films which rapidly dissolves under the tongue or buccal cavity, could also improve the dissolution of poorly soluble drug. United States Food and Drug Administration (USFDA) defined the fast dissolving oral thin films as a thin, flexible, non-friable polymeric film strip containing one or more dispersed/dissolved active pharmaceutical ingredients, which is intended to be placed on the tongue for rapid *in vitro* disintegration or dissolution in the saliva prior to swallowing for delivery into the gastrointestinal tract [3]. Atorvastatin calcium ([R-(R*, R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, hemi-calcium salt) [4], a statin analogue is used as hypolipidemic agent. It competitively inhibits the binding sites of 3-hydroxy-3-methyl-glutaryl-coenzyme-A (HMGCoA) reductase [5]. Atorvastatin is white to off-white crystalline powder having molecular weight 1209.42 and melting point range between 176°C and 178°C. It is insoluble in aqueous media but freely soluble in methanol [6]. It is weakly acidic (pKa-11.82), hydrophobic (Log P-5.39) and has an aqueous solubility of 0.00063 mg/ml which leads to high variability in absorption after oral administration [7]. Atorvastatin belongs to the Biopharmaceutical Classification System-II (BCS-II) i.e., drug with low aqueous solubility and high permeability [8]. The absolute bioavailability of atorvastatin (parent drug) is ~12% and the systemic availability of HMG-CoA reductase inhibitory activity is ~30%. Therefore, it is essential to increase the aqueous solubility of atorvastatin by developing different techniques like solid dispersion [9], microsphere [10], emulsion [11, 12], nanosuspension [13], self-microemulsion [14] formation etc., which decrease the particle size of the drug, thereby increase a large surface area for drug absorption [15] in the gastrointestinal tract (GIT)

which ultimately enhance the oral bioavailability of drug. The objective of the present research work was to develop fast dissolving oral films of atorvastatin calcium disintegrating within 170s to enhance the convenience of administration to the patients to improve compliance. The formulation developed was simple, easy to prepare and economical with great applicability and also giving faster *in vitro* drug dissolution rate as compared to the commercially available immediate release tablets.

MATERIAL AND METHODS:

Materials:

Atorvastatin was received from Micro Labs, Goa, India, as a gift sample. HPMC was procured from moly Chemicals, Mumbai. PEG400, sodium starch glycolate, croscarmellose sodium and crospovidone was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid, KH_2PO_4 , NaOH, aspartame was obtained from Merck Ltd, Mumbai, India. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Formulation development of oral film of atorvastatin calcium:

Solvent casting technique:

Drug (Atorvastatin calcium) containing fast dissolving films were fabricated by the solvent casting method [16]. The optimized amount of HPMC was dissolved in 5ml of water and stirred continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm * 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Formulations were prepared using HPMC K15, PEG-400, SSG, CP and CCS at different drug: polymer ratios. The compositions of the formulations were shown in table 1.

Table 1 Selection and optimization of film forming agents

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API	240	240	240	240	240	240
HPMC	300	500	700	300	500	700
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	150	200	-	-	-	-
CCS	-	-	150	200	-	-
CP	-	-	-	-	150	200
Aspartame	50	50	50	50	50	50
Citric acid	100	100	100	100	100	100
DM water qs to (ml)	-	-	-	-	-	-

Dose calculations:

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm² films present whole plate = 12
- Each film contains 20 mg of drug.
- 12 no. of films contains mg of drug? = 20×12 = 240mg
- The amount of drug added in each plate was approximately equal to 240 mg

Evaluation:

The formulations were evaluated by the following tests [17-20].

Thickness:

The thickness of patches was measured at three different places using a vernier caliper.

Weight uniformity:

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding Endurance:

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of Moisture Content:

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Drug Content Analysis:

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 248nm.

Disintegrating time:

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimize the disintegrating time. Three super disintegrating agent were selected for this work.

In vitro dissolution study:

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5° C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm²) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45µm membrane filter and the concentration of the dissolved atorvastatin calcium was determined using UV-Visible spectrophotometer at 248nm. The results were presented as an average of three such concentrations.

RESULTS AND DISCUSSION:

λ_{max} of atorvastatin was found to be 248 nm in 6.8 pH phosphate buffer solution by using U.V. spectrophotometer (Labindia-3000+). The calibration curve of atorvastatin was found to be linear in the concentration range of 5-25µg/ml at 248nm. The general appearance, weight variation and thickness of all the films were within acceptable limits table 2.

The results for tensile strength, folding endurance, disintegrating time % of moisture and drug content were shown in table 3. The formulations containing CCS were showing good results compared to SSG and CP. The assay values of all the formulations were ranging from 95.65 ± 0.45 to $98.99 \pm 0.32\%$. The disintegration time was ranging between 168 ± 4 to 221 ± 6 sec. Tensile strength value of optimized formulation (F4) was 0.753 kg/cm^2 and folding endurance was more than 100. The optimized formulation (F4) shows better drug release

($98.95 \pm 0.89\%$) compared to other formulation within 15 m (Table 4 & Figure 1). The cumulative percentage (%) drug release profile and the assay of the F4 formulation films indicates that the drug remain stable under the ASC without any significant change in its release profile and the drug content. From the stability studies it was clearly observed that the drug showed good stability after subjecting to accelerated stress conditions and the polymers shown significantly compatibility with the drug.

Table 2 Result of general appearance, thickness and weight variation

Formulation code	General Appearance	Thickness in μm	Weight mg
F1	Translucent	95 ± 3	110 ± 4
F2	Translucent	98 ± 2	115 ± 6
F3	Translucent	96 ± 5	125 ± 7
F4	Translucent	98 ± 4	114 ± 5
F5	Translucent	99 ± 6	116 ± 8
F6	Translucent	102 ± 7	114 ± 7

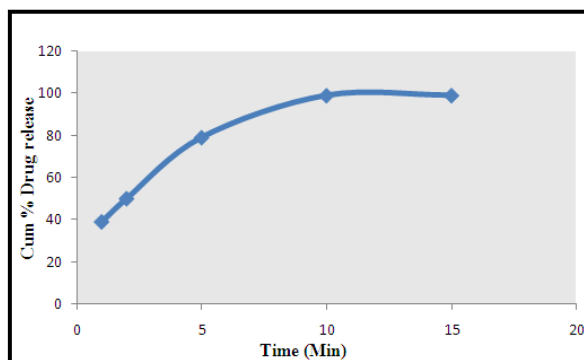
Table 3 Result of folding endurance, disintegrating time tensile strength, % of moisture content & % assay

F. code	Folding endurance (Times)	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	98 ± 5	220 ± 4	0.985	1.25 ± 0.32	98.78 ± 0.32
F2	110 ± 8	195 ± 6	0.658 ± 8	1.65 ± 0.15	95.65 ± 0.45
F3	115 ± 7	189 ± 8	0.789	1.98 ± 0.45	98.78 ± 1.25
F4	96 ± 6	168 ± 4	0.753	0.92 ± 0.65	98.99 ± 0.32
F5	112 ± 9	221 ± 6	0.687	1.65 ± 0.58	98.45 ± 0.78
F6	125 ± 7	200 ± 5	0.712	1.45 ± 0.89	98.74 ± 0.42

Table 4 Results of *In-Vitro* release study of optimized formulation F4

S. No.	Time (Min.)	Cum % Drug release
1.	1	38.98 ± 1.25
2.	2	49.98 ± 0.98
3.	5	78.98 ± 0.56
4.	10	98.89 ± 0.47
5.	15	98.95 ± 0.89

Figure 1 *In-Vitro* release study of optimized formulation



CONCLUSION:

The present study indicates a good orally fast dissolving films containing atorvastatin calcium for systemic delivery with an added advantage of faster drug action. Finally, it is concluded that the drug release from the fast dissolving film was increased by using the increased concentration of superdisintegrant, thus assisting in faster disintegration in the buccal cavity. As the drug having low solubility, fast disintegration may leads to more drug availability for dissolution, resulting in faster absorption in systemic circulation increased systemic availability of drug may leads to quick onset of action.

REFERENCES:

- Arya A, Chandra A, Sharma V, Pathak K (2010) Fast Dissolving Oral Films: An Innovative Drug Delivery System And Dosage Form. *Int J of ChemTech Research* 2: 576-583.
- Naziya Khatoon NG, Raghavendra Rao B, Mahipal Reddy (2013) Overview on fast dissolving oral films. *International Journal of Chemistry and Pharmaceutical Sciences* 1: 63-75.
- Gautam SP, Rai JP, Billshaiya U, Jain N, Vikram P, Jain DK. Formulation and evaluation of mouth dissolving tablet of loperamide. *Int J Pharm Sci Res.* 2013; 4(5): 1782-1788.
- Shah D, Bhatt K, Shankar M, Mehta R, Gandhi T, Baldania S. (2006). RP-HPLC determination of Atorvastatin calcium and Amlodipine besylate combination in tablets. *Ind J Pharm Sci*, 68:796–799.
- Shaik HR, Ramakotaiah M, Vani PS, Arief M, Gajavalli SR. (2010). A stability-indicating LC method for the simultaneous determination of Metoprolol, Atorvastatin and Ramipril in combined pharmaceutical dosage form. *Res J Pharm, Biol and Chem Sci*, 1: 816–29.
- <http://www.rxlist.com/lipitor-drug.htm>, Accessed on 10th October 2009.
- <http://www.drugbank.ca/drugs/DB01076>, Accessed on 10th October 2009.
- Shete G, Puri V, Kumar L, Bansal AK. (2010). Solid state characterization of commercial crystalline and amorphous atorvastatin calcium samples. *AAPS PharmSciTech*, 11:598–609.
- Bobbe K, Subrahmanya C, Suresh S, Gaikwad D, Patil M, Khade T, et al. (2011). Formulation and evaluation of solid dispersion of Atorvatstatin with various carriers. *Int J Compre Phar*, 1:1–6.
- Eroglu H, Nemutlu E, Turkoglu OF, Nacar O, Bodur E, Sargon MF et al. (2010). A quadruped study on chitosan microspheres containing atorvastatin calcium: preparation, characterization, quantification and in-vivo application. *Chem Pharm Bull*, 58:1161–1167.
- Yin YM, Cui FD, Kim JS, Choi MK, Choi BC, Chung SJ et al. (2009). Preparation, characterization and *in vitro* intestinal absorption of a dry emulsion formulation containing atorvastatin calcium. *Drug Deliv*, 16:30–36.
- Talegaonkar S, Mustafa G, Akhter S, Iqbal Z. (2010). Design and development of oral oil-in-water nanoemulsion formulation bearing Atorvastatin: in vitro assessment. *J Disp Sci Tech*, 31:690–701.
- Arunkumar N, Deecaraman M, Rani C, Mohanraj K, Venkateskumar K. (2009). Preparation and solid state characterization of Atorvastatin nanosuspensions for enhanced solubility and dissolution. *Int J Pharm Tech Res*, 1: 1725–1730.
- Chouksey R, Pandey H, Jain AK, Soni H, Saraogi GK. (2011). Preparation and evaluation of the self emulsifying drug delivery system containing Atorvastatin HMG-COA inhibitor. *Int J Phar Pharm Sci*, 3:147–152.
- Aguiar AJ, Krc J Jr, Kinkel AW, Samyn JC. (1967). Effect of polymorphism on the absorption of chloramphenicol from chloramphenicol palmitate. *J Pharm Sci*, 56:847–853.
- K. Senthilkumar and C. Vijaya. Formulation development of mouth dissolving film of etoricoxib for pain management. *Advances in Pharmaceutics*. 2015, Article ID 702963.
- Kumar GV, Krishna RV, William GJ, Konde A. Formulation and evaluation of buccal films of Salbutamol sulphate. *Ind J Pharm Sci* 2005; 67: 160–164.
- Mona Nagar, Mayank Nagar and Vikram Chopra, Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole, *Der Pharm Lett* 2012; 4 (4): 1221-1227.
- Prabhu P, Malli R, Koland M, Vijaynarayana K, D'Souza U, Harish NM, Shastry CS. Formulation and evaluation of fast dissolving films of levocetizine dihydrochloride, *Int J Pharm Inves* 2011;1(2): 99–104. 17.
- Nafee NA, Boraie MA, Ismail FA, Mortada LM. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. *ACTA Pharm* 2003; 53: 199–212.