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Research Article

# Preparation and *in vitro* characterization of gastroretentive atorvastatin calcium mucoadhesive tablets

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**ABSTRACT**

The present investigation concerns the development of mucoadhesive tablets of Atorvastatin calcium which were designed to prolong the gastric residence time after oral administration. Atorvastatin calcium has a maximum rate of absorption in the upper GI tract, but because of poor solubility in this region, it has a low bioavailability of 12%. In the present study mucoadhesion as a strategy to enhance the bioavailability of Atorvastatin calcium by increasing the gastric residence time was studied. Matrix tablets of Atorvastatin calcium were formulated using different viscosity grades of hydroxyl propyl methyl cellulose (HPMC K4M, HPMC K15M and HPMC K100 M) by direct compression method. The tablets were evaluated for physical properties, content uniformity, swelling index, bioadhesion and *in vitro* drug release. Swelling was increased as the concentration and viscosity of HPMC increases. It was evident from the study that the formulation F5 containing HPMC K15M exhibited desirable swelling and *in vitro* drug release of 101.23% at the end of 12 hrs with non fickian diffusion mechanism.

**Keywords:** Atorvastatin calcium; Gastro retention; Mucoadhesive tablets; HPMC different grades; Direct compression.

## INTRODUCTION

Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects (Amit Kumar N et al, 2010). Prolonging the gastric retention of a delivery system is desirable for achieving therapeutic benefit of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in GIT or are degraded by the alkaline pH (Deshpande AA et al, 1996; Singh BN et al, 2000).GRDS are thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose (Chavanpatil MD, 2006). Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach. Many drugs categorised as once-a-day delivery have been demonstrated to have suboptimal absorption due to dependence on the transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within which drug absorption can occur in the small intestine (Mojaverian P et al,1988).Park and Robinson et al., had first introduced the term “Bioadhesion”. Bioadhesive polymers are platforms for oral controlled drug delivery method to study bioadhesion has been studied extensively in the last decade and applied to improve the performance of these drug delivery systems (Park K et al, 1984).

Mucoadhesive tablets, in general, have the potential to be used for controlled release drug delivery, but coupling of mucoadhesive properties to tablet has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive tablets can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs. The application of mucoadhesive tablets to the mucosal tissues of gastric epithelium is used for administration of drugs for localized action. Mucoadhesive tablets are widely used because they release the drug for prolonged period, reduce frequency of drug administration and improve the patient compliance (Rajput G.C. et al, 2010). Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and mucin. The

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**Table 1: Formulae of Atorvastatin calcium Mucoadhesive tablets**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Atorvastatin calcium | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| PEG 4000 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| HPMC K4M | 25 | 37.5 | 50 | - | - | - | - | - | - |
| HPMC K15M | - | - | - | 25 | 37.5 | 50 | - | - | - |
| HPMC K100M | - | - | - | - | - | - | 25 | 37.5 | 50 |
| PVP K30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Lactose monohydrate | 140 | 127.5 | 115 | 140 | 127.5 | 115 | 140 | 127.5 | 115 |
| Magnesium stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

All quantities are in mg

**Table 2: Precompression parameters of Formulations (F1-F9)**

| Batch code | Bulk density (g/cc) | Tapped density (g/cc) | Carr's index (%) | Hausner's ratio | Angle of repose (Ɵ) |
|---|---|---|---|---|---|
| F1 | 0.552 | 0.658 | 16.11 | 1.19 | 18.43 |
| F2 | 0.563 | 0.645 | 12.71 | 1.15 | 17.52 |
| F3 | 0.575 | 0.652 | 11.81 | 1.13 | 15.52 |
| F4 | 0.571 | 0.640 | 10.78 | 1.12 | 21.25 |
| F5 | 0.568 | 0.655 | 13.28 | 1.15 | 14.74 |
| F6 | 0.555 | 0.648 | 14.35 | 1.17 | 13.24 |
| F7 | 0.565 | 0.679 | 16.79 | 1.20 | 27.15 |
| F8 | 0.553 | 0.681 | 18.80 | 1.23 | 21.25 |
| F9 | 0.547 | 0.668 | 18.11 | 1.22 | 15.52 |

adhesion is prolonged due to the formation of vander-vaals forces, hydrogen bonds and electrostatic bonds (Muthukumaran M et al, 2011).

Atorvastatin calcium (Indian Pharmacopoeia, 2010), a HMG-CoA reductase inhibitor is the treatment of choice in moderate to severe familial or non-familial hypercholesterolemia. It has an oral bioavailability of less than 12%. Atorvastatin calcium has a maximum rate of absorption in the upper GI tract, but because of poor solubility in this region, it is less bioavailable. Un-predictable and short gastric emptying time can result in incomplete drug release from the drug delivery system above the absorption region, which may be the stomach or upper component of the small intestine, leading to a reduced systemic availability of the administered dose (Furquan NK et al, 2012). So oral absorption of Atorvastatin caluim can be increased by increasing gastric retention time of the drug (Arunkumar N et al, 2008). Hence an attempt was made to develop mucoadhesive tablets of Atorvastatin calcium using different viscosity grades of HPMC. The prepared tablets were evaluated for Physical properties (thickness, weight variation, friability and hardness, swelling index, bioadhesion test, drug content uniformity and *in vitro* drug release.

## MATERIALS AND METHODS

Atorvastatin calcium was gift sample from Dr.Reddy's Laboratories, Hyderabad. HPMC K4M, HPMC K15M, HPMC K100M and PVP K30 were procured from Yarrow chem products, Mumbai. PEG4000 was procured from M/s Merck Specialities Pvt Limited, Mumbai. Lactose monohydrate, Magnesium stearate and talc were procured from M/s Molychem Industries, Mumbai. All required chemicals were analytical grade.

### Preparation of mucoadhesive tablets

Mucoadhesive tablets of Atorvastatin calcium were prepared by direct compression method using different concentrations of HPMC K4M, HPMC K15M and HPMC K100M. All the ingredients were passed through sieve no 60# and were mixed uniformly in a mortar. The powder was compressed with 9 mm flat punch using 6-station rotary tablet punching machine (Elite Scientific equipments, SELEC MA12). The formulations are shown in table-1 (Kumar SG,2011)

### Evaluation of mucoadhesive tablets

### Pre compression parameters

The uniformly mixed powder was evaluated for its bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

### Physical parameters

Tablets were tested for hardness, thickness, friability and weight variation. Hardness of the tablets was tested using Monsanto hardness tester and friability of the tablets was determined in a Roche friabilator.

### Swelling index

Initial weight ($W_1$) of tablet was carried out and placed it in a beaker containing 200 ml of 0.1N HCl (pH1.2). After each interval of time the tablet was removed

**Table 3: Physical parameters of Formulations (F1-F10)**

| Batch code | Weight variation(mg) | Hardness(kg/cm$^2$) | Thickness(mm) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| F1 | 252.33±3.055 | 2.33±0.289 | 2.92±0.13 | 0.49 | 101.25 |
| F2 | 251.00±2.646 | 2.50±0.500 | 2.94±0.05 | 0.36 | 100.06 |
| F3 | 253.33±1.528 | 2.67±0.289 | 2.85±0.12 | 0.42 | 102.57 |
| F4 | 252.33±2.082 | 2.67±0.577 | 2.94±0.08 | 0.41 | 99.39 |
| F5 | 253.00±2.646 | 3.17±0.289 | 2.84±0.09 | 0.39 | 100.20 |
| F6 | 252.33±2.082 | 3.00±0.500 | 2.78±0.15 | 0.49 | 102.83 |
| F7 | 252.33±1.158 | 2.33±0.289 | 2.87±0.13 | 0.37 | 101.97 |
| F8 | 253.00±1.732 | 2.83±0.289 | 2.80±0.09 | 0.29 | 99.15 |
| F9 | 253.66±1.528 | 3.00±0.500 | 2.75±0.10 | 0.37 | 101.28 |

**Table 4: In vitro mucoadhesive strength for all formulated batches**

| Batch code | Mucoadhesive strength(g) |
|---|---|
| **F1** | 11.233±0.306 |
| **F2** | 14.533±0.252 |
| **F3** | 16.333±0.289 |
| **F4** | 17.900±0.265 |
| **F5** | 19.333±0.451 |
| **F6** | 21.667±0.764 |
| **F7** | 20.900±0.265 |
| **F8** | 22.400±0.458 |
| **F9** | 24.767±0.306 |

from beaker and blotted with filter paper to remove excess of water. Then the tablet was immediately weighed, introduced into the same beaker and note down the weight ($W_2$) and the test was performed upto 8 hrs. The swelling index was calculated using the following formula.

$$\text{Swelling index} = (W_2 - W_1)/W_1$$

**Bioadhesive strength**

Bioadhesion studies were conducted with porcine gastric mucosa as the model membrane. The mucosal membrane was excised by removing the underlying connective and adipose tissue, and equilibrated at 37°C ± 1°C for 30 min in Phosphate buffered saline before the bioadhesion evaluation study. The tablet was lowered on to the mucosa under a constant weight of 5 g for a total contact period of 1 min. Bioadhesive strength(f) was assessed in terms of the weight in grams required to detach the tablet from the membrane. Detachment is typically in the vertical direction and the force is measured via a balance (Dalvadi HP et al, 2011).

***In vitro* drug release studies**

Dissolution studies of all batches were performed employing USP XXIII paddle- type dissolution test apparatus (LABINDIA DS8000) using 900 ml 0.1N HCl (pH1.2) with 0.5% SLS as dissolution medium at 75 rpm and 37°C±0.5°C. A 5 ml aliquot of the sample was withdrawn periodically at suitable time intervals and volume replaced with an equivalent amount of the dissolution medium. The samples were analysed spectrophotometrically at 245 nm using UV Visible Spectrophotometer (ELICO SL 159).

**RESULTS AND DISCUSSION**

Gastro retentive mucoadhesive tablets of Atorvastatin calcium were prepared by direct compression method. Tablets of all the batches had low tablet weight variation (% deviation < 3.05%), whereas percentage weight loss in the friability test was ≤ 0.5% in all the batches. Content uniformity of all the prepared batches is within the limit (Atorvastatin calcium 100 ± 3% of the labelled content). The pre compression parameters are shown in Table-2 and other physical characteristics of tablets like hardness, weight variation and thickness are shown in Table-3. We can conclude that all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

**Swelling study**

Swelling study was performed on all the batches up to 8 hrs. The results of swelling index are shown in figure-1.The batches containing HPMC of higher viscosities had more swelling as compared to batches containing HPMC of lower viscosities (HPMC K4M< HPMC K15M< HPMC K100M). Swelling also had increased with increase in concentration. The rate of swelling increased initially and then slowed down. It was also observed that batches with low concentration and low viscosity HPMC slowly started eroding after certain time.F5, F6, F8 and F9 batches showed higher swelling. Hence, it can be concluded that linear relationship exists between swelling and viscosity, concentration of the polymer.

**Table 5: Correlation Coefficient (r) values in various kinetic models tested to describe drug release from the mucoadhesive tablets formulated**

| Batch code | Zero order | First order | Higuchi | Korsemeyer-Peppas | | Weibull |
|---|---|---|---|---|---|---|
| | | | | n | r | |
| F1 | 0.957 | 0.925 | 0.992 | 0.633 | 0.989 | 0.976 |
| F2 | 0.977 | 0.765 | 0.937 | 0.687 | 0.963 | 0.869 |
| F3 | 0.994 | 0.829 | 0.954 | 0.654 | 0.971 | 0.897 |
| F4 | 0.982 | 0.920 | 0.976 | 0.686 | 0.990 | 0.948 |
| F5 | 0.989 | 0.880 | 0.974 | 0.699 | 0.997 | 0.961 |
| F6 | 0.997 | 0.892 | 0.938 | 0.749 | 0.982 | 0.936 |
| F7 | 0.993 | 0.776 | 0.943 | 0.785 | 0.963 | 0.889 |
| F8 | 0.995 | 0.904 | 0.948 | 0.733 | 0.976 | 0.928 |
| F9 | 0.987 | 0.926 | 0.922 | 0.643 | 0.965 | 0.924 |

**Bioadhesive strength**

Several studies have demonstrated that the bioadhesiveness of tablets depends on the rate of swelling and initial contact time. The highest adhesion force i.e. highest strength of the mucoadhesive bond (24.767±0.306 g) was proposed by F9 containing HPMC K100M at a concentration of 20%. It was concluded that strength of mucoadhesion increased with increase in concentration as well as viscosity of the polymer (HPMC K4M< HPMC K15M< HPMC K100M). As per the diffusion theory of mucoadhesion the bond strength increases with as the degree of interpenetration increase with contact time and diffusion coefficient. The results are shown in Table-4.

***In vitro* dissolution study**

The *in vitro* drug release profiles of Atorvastatin calcium are shown in fig.2. The *in vitro* release study showed satisfactory extended release of Atorvastatin calcium from all formulations. Drug release from different formulations was found to depend on polymer viscosity grade and concentration. FormulationsF1, F2, F3 containing HPMC K4M showed 100.47, 99.78, 102.8% drug release in 6,7,10 hrs respectively. Formulations F4 containing HPMC K15M showed 100.74% drug release in 11 hrs and F5, F6 showed 101.23, 92.94% drug release respectively in 12 hrs. Formulations F7, F8, F9 containing HPMC K100M showed 101.24, 99.00, 81.34% drug release respectively in12 hrs.

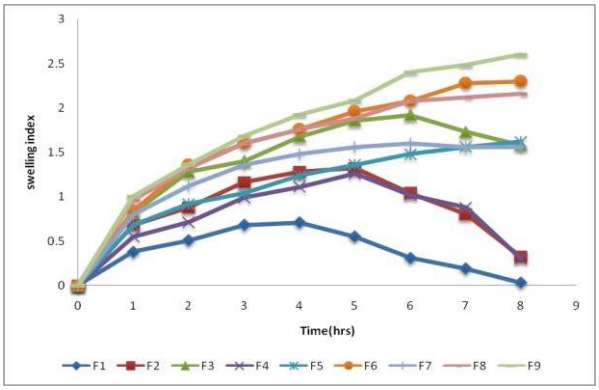


**Figure 1: Water uptake study of mucoadhesive tablets at different time intervals**

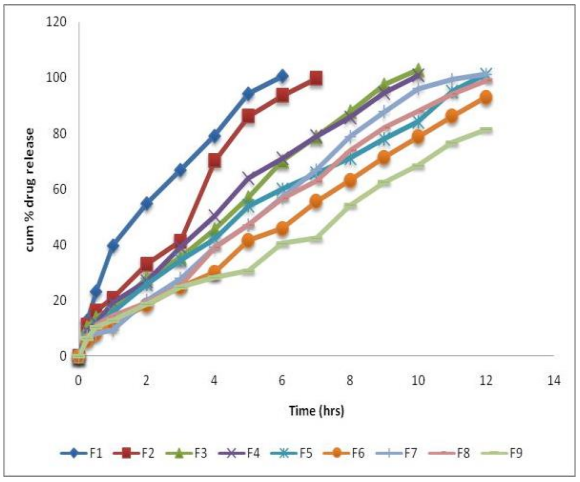


**Figure 2: Drug release profile of Atorvastatin calcium mucoadhesive tablets**

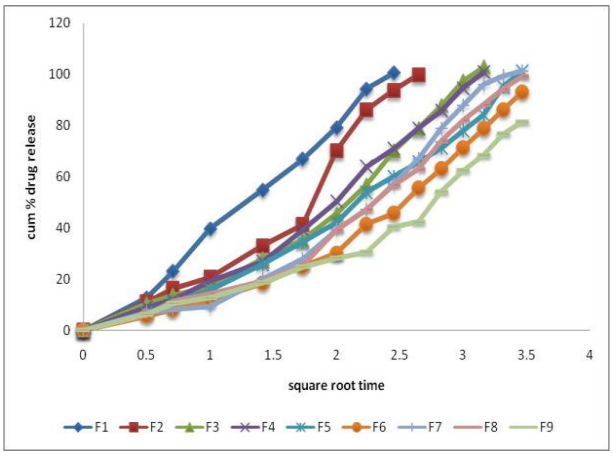


**Figure 3: Higuchi plots of Atorvastatin calcium mucoadhesive tablets**

**Analysis of the drug release data**

The release data obtained were fitted to zero order, first order, Higuchi, Korsemeyer- Peppas and Weibull equations to determine the corresponding release rate and mechanism of drug release from the mucoadhesive tablets. The model that best fits the release data was evaluated by correlation coefficient(r). The correlation coefficient(r) value was used as criteria to choose the best model to describe drug release from the mucoadhesive controlled release tablets. The r-value in various models is given in Table-5. The r-values

(r>0.922) obtained for fitting the drug release data to the Higuchi equation, indicated that the drug release mechanism from these tablets was diffusion controlled (fig.3.). In all the formulated batches the r-values were higher in zero order models than in first order model indicating the drug release from all the formulations was according to zero order kinetics. The values of n=0.5-1 in Peppas model implicate diffusion and non-fickian transport.

## CONCLUSION

The current study indicates that the hydrophilic matrix tablets of Atorvastatin calcium were prepared using HPMC K4M, HPMC K15M and HPMC K100M. The batch F5 is selected as the best formulation as it showed good pre compression parameters, physical properties, drug content uniformity, swelling properties, mucoadhesion and a drug release of 101.23% in 12 hrs.

It may be concluded that mucoadhesive tablets of Atorvastatin calcium prepared using mucoadhesive polymer by direct compression method seems to be the promising formulation, providing controlled delivery of Atorvastatin calcium with improved bioavailability, of drugs such as Atorvastatin calcium that have low bioavailability due to low solubility in the site of absorption.

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## REFERENCES

Amit Kumar, N., Ruma, M., Biswarup, D. 'Gastroretentive drug delivery systems: a review', Asian Journal of Pharmaceutical and Clinical Research, Vol.3 Issue 1, January-March 2010 pp.3-10.

Arunkumar, N., Rani, C., Mohanraj, K.P. 'Formulation and In Vitro evaluation of oral floating tablets of Atorvastatin calcium', Research J. Pharm. and Tech., 1(4): Oct.-Dec. 2008 pp. 492-495.

Chavanpatil, M.D., Jain, P., Chaudhari, S., Shear, R., Vavi, P.R. 'Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for Ofloxacin', Int J Pharm., 316(1), 2006 pp. 86–92.

Dalvadi, H.P., Patel ,J.K., Rajput, G.C., Muruganantham, V., Jayakar, B. 'Development and characterization of controlled release mucoadhesive tablets of captopril', Ars Pharmaceuitca,52(2), 2011 pp. 31-37.

Deshpande, A.A., Rhodes, C.T., Shah, N.H., Malick, A.W. 'Controlled release drug delivery systems for prolonged gastric residence: an overview', Drug Dev Ind Pharm, 22 (6), 1996 pp.531-539.

Furquan, N.M., Dehghan, M.H.G. 'Enhanced bioavailability and dissolution of Atorvastatin calcium from floating microcapsules using minimum additives', Sci Pharm., 80, 2012 pp. 215–228.

Government of India, Ministry of health and family welfare, Indian PharmacopoeiaVol. I & II, The Indian Pharmacopoeia Commission, Ghaziabad. 2010 pp. 849-51.

Kumar, S.G., Mruthunjaya, K., Jain, D.A., Parashar, B., Banerjee, A. **'**Formulation, Characterization & Invitro Evaluation of Aceclofenac Floating Drug Delivery System', Asian Journal of Biochemical and Pharmaceutical Research, Issue 2 (Vol. 1), 2011 pp. 719-726.

Mojaverian, P., Vlasses, P. H., Kellner, P. E., Rocci, M. 'Effects of gender, posture and age on gastric residence time of an indigestible solid: pharmaceutical considerations' Pharm. Res., 10, 1988 pp. 639–644.

Muthukumaran, M., Dhachinamoorthi, D., 1Chandra Sekhar, K .B., Sriram, N. 'A review on polymers used in mucoadhesive drug delivery system', International journal of Pharmacy and industrial research, Vol - 01 Issue - 02 Apr – Jun, 2011 pp. 122-127.

Park, K., Robinson, J.R. 'Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion', Int J Pharm, 19(2), 1984 pp. 107–127.

Rajput, G.C. 'Stomach specific mucoadhesive tablets as Controlled drug delivery system – a Review work ', International Journal on Pharmaceutical and Biological Research Vol. 1(1), 2010 pp. 30-41.

Singh, B.N., Kim, K.H. 'Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention', J Control Rel., 63(3), 2000 pp 235–259.