Original Article

Mucoadhesive Microspheres of Atorvastatin Calcium: Rational Design, Evaluation and Enhancement of Bioavailability

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ABSTRACT

Background: Atorvastatin Calcium (ATC) used for lowering the cholesterol levels in body. It is competitive inhibitor of hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase, followed mevalonate pathway, which have low bioavailability and poor solubility. Present work focus on development of mucoadhesive microspheres of atorvastatin calcium, for improve the delayed transit, continuous longer period release and preclinical pharmacokinetic estimation in rabbit. **Materials and Methods:** Microsphere was prepared by emulsification method in which the independent variables (like polymer amount) were studied on critical quality attributes like entrapment efficiency, percentage yield and *in-vitro* release. Microspheres were characterized in terms of physicochemical parameters, micromeritic properties, FT-IR, DSC and mucoadhesive wash-off test and further, evaluated for their pharmacokinetics study in rabbits. **Results:** The designed microsphere exhibited an average size with smooth surface, negative zeta potential, maximum entrapment efficiency and sustained release. Microspheres fulfil the micromeritic properties and showed no any interaction between drug and polymer, confirmed by FT-IR and DSC. The *in-vivo* study demonstrated that the prepared microspheres are effective for colon targeted drug delivery system at longer duration. In pharmacokinetics study, relatively steady plasma drug concentrations were observed within after oral administration of drug. The $AUC_{0\text{-}24h}$ for formulation were significantly higher than that of pure drug ($p < 0.05$). **Conclusion:** The pre-clinical oral bioavailability study of drug was increased as the relative availability values were high compared with pure drug and it showed delayed transit for longer period of time.

Key words: Atorvastatin calcium, Mucoadhesive, Microspheres, Colon targeting, Bioavailability.

INTRODUCTION

Atorvastatin Calcium [(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrop-1yl]-3,5-dihydroxyheptanoic acid [ATC] is a member of the drug used for lowering the cholesterol levels in body. The primary uses of atorvastatin calcium are for the treatment of disease like dyslipidemia and the prevention of cardiovascular disease.[1-3] It is competitive inhibitor of hydroxyl methylglutaryl-coenzyme A (HMG-CoA) reductase, followed mevalonate pathway. The rate-determining enzyme in cholesterol biosynthesis via the mevalonate pathway.[4,5] In mevalonate pathway HMG-CoA convert to mevalonate in presence of catalyses HMG-CoA reductase. ATC is primarily act on liver cells. In which decrease the hepatic and plasma cholesterol levels.[6,7]

ATC showed low bioavailability and poor solubility. The rate of absorption of ATC was maximum found in the upper GI tract.[8,9] Therefore, mucoadhesive drug system are utilize for the enhancement of

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bioavailability. Mucoadhesive drug system provides the targeted controlled and sustained release of ATC for longer period of time.[10] It is based on delayed transit and continuous release system, so it lives in prolong residence in GIT especially in colon, along with their release.[11] The colon is a site for local and systemic delivery of drugs. Treatment can be made by directly target into colon, so that enhancement of bioavailability and reduction of systemic side effects.[12,13]

The most acceptable oral administration mucoadhesive system of drug offers patient convenience, less pain, less risk of cross infection and injuries caused by needle stick. The rationale is to, a colon delivery system is very specific and quite diverse. The drug substance direct absorbed at the site of colon due to a long transit time, present of neutral pH, proffer of reduced digestive enzymes and responsiveness of absorption enhancers. Thus, the targeting is reliable, effective and completed. Another is to lower surface area and relative 'tightness' of the tight junction in the colon, this can also restricted for transportation of drug across the mucosa layer and into the systemic circulation.[14,15]

Now, present works represent the development and evaluation of mucoadhesive polymeric microspheres. These mucoadhesive polymeric microspheres having an intimate contact with the mucus layer, so improve absorption at the targeting site, enhance bioavailability of the drugs and retention in the gastrointestinal tract. In this paper, different formulations of polymeric microspheres were prepared and evaluated their physicochemical properties (like particle size, entrapment efficiency, percentage yield, morphology), drug release studies, micromeritic properties, FT-IR, thermogram study and mucoadhesive properties. Pharmacokinetics profile of developed microsphere was performed in rabbit.

MATERIALS AND METHODS

Atorvastatin Calcium purchased from Cipla Pharmaceutical Indore. Carbopol and sodium alginate were provided by Oxford chemicals laboratory, Mumbai. Light Liquid Paraffin, Calcium Chloride and Span 80 were obtained from Loba chemical laboratory, Mumbai. All other chemicals as well as Buffer salts used in experiments were analytical grade reagent. Animal used in experiment were treated according to the protocols and the studies were carried out as per the guidelines of CPCSEA (Council for the Purpose of Control and Supervision of Experiments on Animals), Government of India.

Preparation and optimization of microspheres

Fabrication of the drug loaded microspheres (DMPs) is represented in Table 1. In the optimization only one formulation parameter such as ratio of polymer was changed at a time while the remaining variables were kept constant. The amounts of cross-linking agents (5% calcium chloride) and drug amount was kept constant and calculating the percentage drug entrapment and *in-vitro* drug release (%). Microsphere was prepared by emulsification method, followed by cross-linking with calcium chloride. Firstly, Atorvastatin calcium was dispersed in aqueous solution of sodium alginate (5%). Prepared this aqueous solution was again emulsified with light liquid paraffin containing span 80 using a homogenizer at 2000 rpm for 120 min. 5 ml of 2% calcium chloride was added to the emulsion. The solidified microspheres were recovered by centrifugation, washed with petroleum ether and dried in vacuum desiccators. Formulation was observed in microscope under 100 x magnifications.[16,17]

Physicochemical characterization of microspheres

The average particle size, polydispersity index and zeta potential of the microsphere were determined by Zeta sizer nano ZS90, Malvan UK analyser. Samples were prepared by after re-suspension of prepared formulation in distilled water. All measurements were performed in triplicates.[18] The morphology of atorvastatin calcium loaded microspheres was carried out by a scanning electron microscope (Hitachi High Technology, Pleasanton, CA). Diluted samples was dropped into stubs and allow for air drying, then coated with gold (thin layer) and observed under scanning electron microscopy.[19,20]

The amount of ATC loading in the developed microsphere was quantified using direct method. Microspheres were extracted with methanol and dilution with PBS (pH 6.8) in appropriate quantity and analysed by reverse phase high-performance liquid chromatography (Jasco, PU2080 pump HPLC) method containing 5 µm C_{18} column (Hi Qsil, 250 mm x 0.45 ID) and 70:30 ratio of acetonitrile and phosphate buffer as a mobile phase, with a 1ml per minute flow rate at 247 nm wavelength.[21]

$$\text{Drug Loading Efficiency} = \frac{\text{Weight of drug in microsphere}}{\text{Weight of the microsphere}} \times \text{eig}$$

$$\text{Percentage yield} = \frac{\text{Weight of the dried microspheres obtained}}{\text{Total weight of drug and polymer used}} \times 100$$

In-vitro release of atorvastatin calcium from microsphere was carried out by USP paddle type dissolution test apparatus (Model ZRS-8, China). Near about 10 mg of

atorvastatin Calcium loaded microsphere were placed in dissolution vessels and dissolution medium containing 900 ml of phosphate buffered saline (pH 6.8) and maintained 37±0.5°C temperature at 50±5 rpm. At the predetermine time intervals an aliquot amount (5 ml) of the dissolution media was withdrawn and same amount of fresh solvent was replaced immediately. Withdrawn samples were further proceed for reverse phase HPLC analysis at 247 nm.[22] After that the release kinetic was studied by various kinetic models as zero order, first order, Higuchi plot and Korsemeyer-Peppas model. The best fit model was confirmed by the value of correlation coefficient near to one.

Determination of micromeritic properties

Angle of Repose

Microspheres were passed through a fixed funnel, which is stayed in specific height upon graph paper. Due to only gravity force a static heap of powder was found on graph paper. The height (h) and radius(r) of cone were measured. The angle of repose was calculated using formula.[23]

$$\tan\theta = h/r$$

$$\theta = \tan^{-1}h/r$$

Therefore

Where θ = Angle of repose, h = height of cone and r = radius of cone base.

Carr's Index

To check the flow property of prepared microsphere was conducted by comparing the poured and tapped density of a sample. Small amount of microsphere sample was taken in measuring cylinder. Samples height was measured before and after tapping, which represent the poured and tapped density respectively.[24] Further, Carr's Index was calculated as:

$$I = (V_b - V_t/V_b)*100$$

Where V_b= bulk volume and V_t= tapped volume

Determination of Swelling Properties

Swelling index measure the extend of swelling properties of particles in 6.8 pH phosphate buffer. For this purpose weighted amount of 100 mg microspheres were allowed to swell for 24 hr in 6.8 pH phosphate buffer. After 24 hr excess liquid were removed by blotting paper and microspheres were weighed. The degree of swelling was then calculated by the following formula

$$\text{Degree of swelling} = (M_o - M_t/M_t)*100$$

Where M_t= Microspheres initial weight and M_o= Weight of microspheres at equilibrium swelling in the media.[25]

FTIR spectroscopy study

To verify the possible interaction between drug and polymer, flourier transform infrared (JASCO-FTIR, Model-8300) analysis was conducted. Samples of pure atorvastatin calcium, sodium alginate, carbopol 934, physical mixture and prepared formulation were scanned in range from 400–4000 cm^{-1}. All samples were triturated with KBr to get a very fine powder. Powder was transferred to pellet forming die and force applied to get a thin pellet. Pellet was fixed in a die given in IR instrument and scanned.[26,27]

Differential scanning calorimetry study

The possibility of any interaction between drug and polymer was assessed by carrying out the thermal analysis of atorvastatin calcium, sodium alginate, carbopol 934, physical mixture and prepared formulation. The thermal behaviour was determined using differential scanning calorimeter (DSC Q10 V9.4 Build 287) at continue heating rate. The measurements were performed at a heating range of 0°C to 400°C.[28]

In-vitro mucoadhesion wash-off test

Mucoadhesive property of microspheres was estimated by *in-vitro* adhesion test. Eggshell membrane is suitable technique for this purpose. In this 2x1 cm piece of eggshell membrane were taken and fixed on a glass slide (at an angle of 45°C). About 100 mg microspheres were spread on rinsed, tissue specimen and hung onto one of the groves of a USP tablet disintegrating test apparatus containing 6.8 pH phosphate buffer. The disintegrating test apparatus was started, the tissue specimen showed regular up and down movements in a beaker. The time required for detaching of microspheres from mucosal surface membrane was recorded by visual inspection.[29,30]

Pharmacokinetic study of microspheres

Albino rabbit (2-3 Kg Body weight) were used in the pharmacokinetic study. All the rabbits were housed in a cage and maintained on 12 hr light/dark at room temperature 25°C with free access to water and pelleted diet. Animals were deprived of food for 24 hr before experiment. Atorvastatin calcium 25 mg/kg dose was administered to group first and selected formulation equivalent to 25 mg was given to group second. Blood samples (3 ml) were collected in marginal ear vein at 30, 60, 120, 180, 300, 420 and 1440 min. and further centrifuged at 10000 rpm for 20 min to separate serum and stored at -20°C until analysis. Estimation of drug

was performed by reverse phase HPLC (Jasco, PU2080 pump HPLC) method containing 5 µm C_{18} column (Hi Qsil, 250mm x 0.45 ID) and 70:30 ratio of acetonitrile and phosphate buffer, with a 1mL per minute flow rate at 247 nm wavelength.[21] Further pharmacokinetic parameters were calculated like C_{max}, T_{max} and AUC. AUC (Area under the plasma level-time curve) can be calculated by trapezoidal rule. The extent of bioavailability can be determined by following equation

$$Fr = \frac{[AUC]test\ Dstd}{[AUC]std\ Dtest}$$

Where Fr = Relative availability

Statistical Analysis

The two-tailed *t*-test was applied between groups for measurement of statistical significance differences. The method involves dividing the curve by a series of vertical lines into a number of trapezoids, calculating separately each trapezoid and adding them together.

RESULTS AND DISCUSSION

Optimization and physicochemical characterization

The mucoadhesive microspheres were prepared by emulsification method followed by cross-linking with calcium chloride. Optimization of formulation involved selection of external phase, internal phase, dispersing agent, washing solvent and mainly depend upon the ratio of two polymer concentration. The comparatively studies of % drug entrapment, percentage yield and *in-vitro* drug release profile presented in Table 1. The percentage drug loading of microspheres varied from to 37.7 ± 1.34% to 65.9 ± 0.03%. Results demonstrated that an increase in concentration of sodium alginate increased the percentage drug entrapment due to availability of active calcium binding sites in the polymeric chains and quantity of sodium alginate which gives greater degree of cross linking.[31] The optimized AH_4 formulation code selected because when the change in ratio of polymer (500:500), % drug entrapment and *in-vitro* drug release fluctuated.[18] The size and PDI of ATC loaded selected microsphere batch were found to be 3.82 ± 0.07 µm and -30 mv. Microsphere exhibited good polydispersity and micron size range. Prepared microsphere formed a homogeneous population and fairly spherical in shape confirm by scanning electron microscope (Figure 1). The particles were also showed a smoothness. The selected optimized batch was found 60.3 ± 0.31 % drug entrapment and 37 ± 0.32 % yield.

Table 1: Optimization of Polymer Concentration for preparation of microsphere.

S. No.	Formulation Code	Polymer ratio (mg) Sodium alginate: Carbopol 934	Drug (mg)	Drug Entrapment (%)	Percentage yield	*In-vitro* drug release (%)
1.	AH_1	100: 900	100	32.1 ± 1.77	37 ± 0.32	79.22 ± 0.29
2.	AH_2	200: 800	100	34.45 ± 0.33	44 ± 0.45	77.45 ± 0.11
3.	AH_3	300: 700	100	39.2 ± 1.12	49 ± 0.25	75.85 ± 1.23
4.	AH_4	500: 500	100	60.3 ± 0.31	60.2 ± 0.51	72.75 ± 0.26
5.	AH_5	700: 300	100	61.4 ± 0.12	63.1 ± 0.75	71.51 ± 0.21
6.	AH_6	800: 200	100	62.8 ± 1.25	65.2 ± 1.3	69.71 ± 1.01
7.	AH_7	900: 100	100	63.3 ± 1.03	68.2 ± 1.1	67.65 ± 0.70

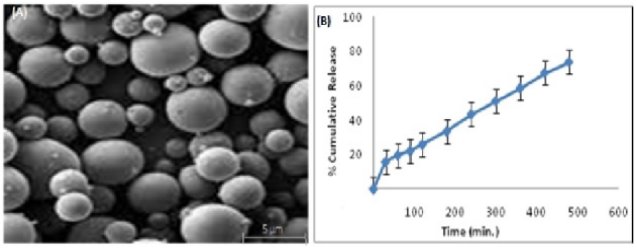

Figure 1: (A) Morphology of prepared microsphere by scanning electron microscope. (B) *In-vitro* drug release of optimized microsphere.

The *in-vitro* drug release profiles of all formulations were studies in phosphate buffer solution at pH 6.8. The commutative release of the drug from the polymeric microsphere shell of different formulation were shown in Figure 2. Release of drug is also depend upon the ratio of polymer. The AH_1 showed maximum% cumulative release (77.39 ± 0.24%), which having the polymer ratio was (100:900) while AH_7 showed minimum 66.08 ± 0.20% cumulative release, which having the polymer ratio was (900:100). It was observed that, when increases the amount of sodium alginate, also the number of COOH groups is increased, which is further cross linked with Ca^{2+} ions and consequential in a formation of more intact matrix, which makes more difficulty of the drug release. The selected optimized

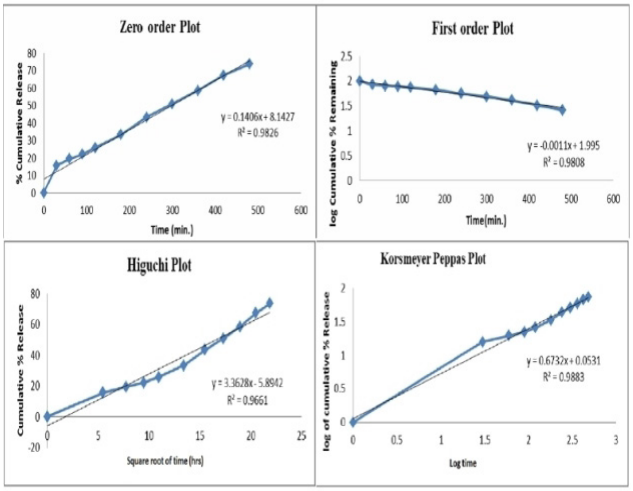

Figure 2: *In vitro* release kinetic of ATC loaded microsphere in phosphate buffer (pH 6.8) using different models such as: Zero order, First order, Higuchi model and Korsmeyer–Peppas model.

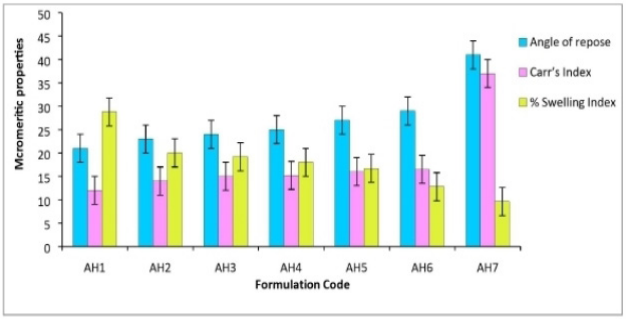

Figure 3: Comparatively studies of micromeritic properties like, Series 1: Angle of repose, Series 2: Carr's Index, Series 3: % Swelling Index.

batch was found to be 72.75 ± 0.26 % drug release. The microsphere exhibited sustained release of drug from polymeric shell because matrix degradation. Several all-other mechanisms like disintegration, desorption, diffusion, surface and bulk erosion were also involved (Figure 2). The microsphere showed an initial burst release; thus, the release of drug was very rapidly.

Determination of micromeritic properties

All formulation showed good flow except formulation AH_7, because it contains more concentration of sodium alginate, having more cross linking between sodium alginate and calcium chloride. The swelling behaviour of both polymers were the major factor for controlling the release of the drug from the microspheres. The degree of swelling increases as increases the concentration of mucoadhesive polymer Carbopol 934. Figure 3 represent the relative swelling Index % of all the formulations.

FTIR spectroscopy of drug and polymers

FTIR spectroscopy checks the possible interaction between drug and polymer. It works on selective absorption of light by vibration modes of specific chemicals bonds. The observation of vibration spectrum of pure atorvastatin calcium, sodium alginate, carbopol 934, physical mixture and prepared formulation was found. There should be no any chemical interaction will be shown in Figure 4.

Differential Scanning Calorimetry

The DSC thermograms of plain drug, sodium alginate, polymer, physical mixture and microspheres are shown

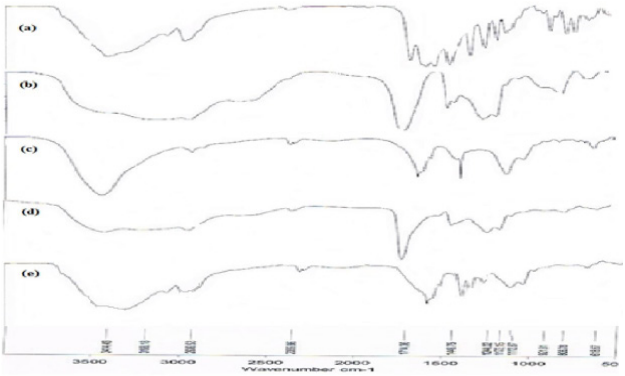

Figure 4: FTIR spectrum of (a) drug (b) Carbopol 934 (c) Sodium Alginate (d) physical mixture (e) microsphere formulation.

in Figure 5. The thermograms represent an endothermic peak of atorvastatin calcium, carbopol 934 and sodium alginate at 158°C to 178°C, 70 to 80°C and 65°C to 70°C respectively. Characteristic peaks of atorvastatin calcium and sodium alginate were well recognized in the drug-polymer physical mixture. Results of DSC thermogram of microspheres indicate that, there are no any physical interaction between the drug and polymer when it was encapsulated in polymeric coat.

In-vitro mucoadhesion wash-off test

In-vitro adhesion testing method was utilized for the evaluation of mucoadhesive property of microspheres. In this study, carbopole have a quality to strong interaction with mucous. Presence of more amount of carbopol, greater retention was noticed. In order to evaluate the mucoadhesion time egg shell membrane was used. It is the substitute of animal stomach mucosa because of similarity (with respect to composition and thickness) between the eggshell membrane and the stomach mucous. Figure 6, shown relative mucoadhesion time of all the formulations.

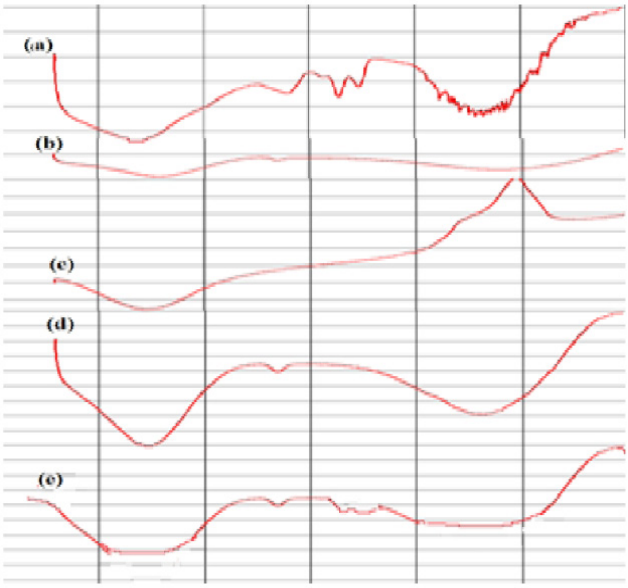

Figure 5: DSC spectrum of (a) drug (b) Carbopol 934 (c) Sodium Alginate (d) physical mixture (e) microsphere formulation.

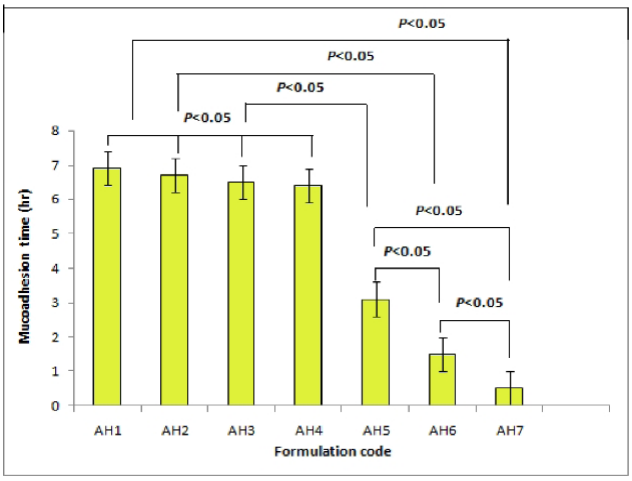

Figure 6: Relative mucoadhesion time of prepared different formulations.

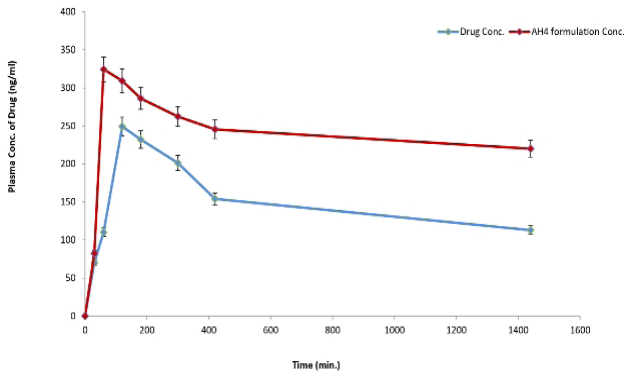

Figure 7: Comparatively graph of plasma concentration versus time profile of optimized formulation batch and drug.

Pharmacokinetic study of microspheres

The plasma concentration versus time profile of optimized formulation AH_4 was shown in Figure 7. After oral administration of the drug, drug concentration reached at peak plasma concentration within 2 hr and then rapidly decreased. The optimized formulation of AH_4 reached rapidly at peak plasma concentration within 1 hr. and given maximum activity. Comparative peak plasma concentration of drug and AH_4 formulation was shown, the C_{max} values for drug and AH_4 formulation were 249.2 ± 0.77 ng/ml and 324.45 ± 1.24 ng/ml respectively in 2 hrs and 1 hr with T_{max} values. The $AUC_{0\text{-}24h}$ for drug and AH_4 formulation was 3541.49±22.01 ng.h/mL and 5095.40 ± 13.77 ng.h/mL. The results shown C_{max} values and $AUC_{0\text{-}24h}$ for AH_4 formulation were significantly higher than that of drug (p<0.05). Therefore, the oral relative bioavailability of drug was increased (43%) compared with pure drug. All results were considered statistically significant when (p<0.05), unless otherwise specified.[29]

DISCUSSION

The atorvastatin calcium loaded microsphere has been successfully developed to improvement of the bioavailability. After the selection of polymer and excipients, applied an emulsification method for development of microsphere. As the optimization, amount of polymer was directly affecting the microsphere entrapment efficiency and size. Prepared microsphere was characterized their physicochemical properties, such as particle size, zeta potential, entrapment efficiency and morphology. The morphology of microsphere showed smoothness and fairly spherical in shape. The physicochemical properties of atorvastatin calcium are having very slightly soluble in aqueous phase environment so the systemic availability is low and attributed to pre-systemic clearance in gastrointestinal mucosa or hepatic first-pass metabolism. The *in vitro* release of atorvastatin calcium showing the maximum amount of drug should be released in polymeric matrix system. In encapsulated or matrix system the drug release is depend upon the amount of encapsulated drug and the polymeric initial burst effect. Generally, when the amount of drug will be higher in encapsulated particle, the release of drug will be also higher. Secondly the particle size affects the dissolution or the release of ATC microsphere. In the gastrointestinal tracts smallest size of particles is easily absorbed though paracellularly followed passive diffusion and reach in systemic circulation.

In a formulation of atorvastatin calcium drug release is also depend upon the ratio of polymer. It was observed that, when increase in the amount of one polymer sodium alginate increases, the number of COOH groups which were cross linked by Ca^{2+} ions resulting in a formation of more intact matrix which makes the drug release more difficult. The maximum release and loading formulation will be achieved. The *in-vitro* drug release studies data were plotted in various kinetic models, (zero order, first order, Higuchi models and Korsemeyer Peppas models), to determine the actual drug release process. The interpretation of data was based on the value of the resulting regression coefficients. Microsphere showed an initial burst release therefore release of drug which adsorbed on to the surface of the microsphere was rapid. It also demonstrated sustained release of ATC from polymeric shell due to matrix degradation and followed other release mechanisms like bulk erosion, disintegration, diffusion and desorption. Prepared microspheres were free from any possible interaction with excipients, which is confirmed by FTIR and DSC studies.

Further, several studies have demonstrated regarding the atorvstatin calcium, in the gastrointestinal tracts ATC absorbed though paracellularly followed passive diffusion. Mucoadhesive microsphere formulation is one of the most capable and continuous drug release approaches which could be retained the drug in the colon. Previous study reported that the gastrointestinal transit time is more if the various mucoadhesive materials incorporated into microspheres. Mucoadhesive materials like carbopol is widely used materials, it having a carboxyl groups which formed the bonds between hydrogen and mucus. The activity of the carbopol is affected by mainly two factors like ionic strength and pH of mucosa. Another is presence of sodium alginate which added in microspheres is an attempt to retard the drug release. For the mucoadhesion evaluation of microsphere, a newly developed eggshell membranes were utilized which is substitute of animal mucosa. Now, the microsphere was prepared and evaluated, to the targeting of colon by delayed transit and continuous sustained release of microspheric particles. After oral administration of the drug pharmacokinetic of the atorvastatin calcium having the plasma peak concentrations are lower (approximately 30% for C_{max} and AUC) follow by evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration while the formulated microsphere particles reached rapidly at highest peak plasma concentration. In comparison to pure drug, C_{max} and $AUC_{0\text{-}24h}$ value were significantly higher. Moreover, the prepared microsphere is suitable and effective for improvement of bioavailability due to prolonged gastric residence.

CONCLUSION

The prepared mucoadhesive microspheres which is composed of carbopol 934 and sodium alginate cross linking, having a good approach to improve the gastric residence time and bioavailability of drug due to mucoadhesive nature of polymer carbopol 934. Sodium alginate was added in microspheres is an attempt to retard the drug release. After administration of atorvastatin calcium loaded microspheres in rabbits, the bioavailability of drug increased as compared with that of pure drug. The pharmacokinetic study like bioavailability was increased in rabbits due to extensive gastric residence time.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ATC: Atorvastatin Calcium; **FTIR:** Flourier Transform Infrared; **DSC:** Differential Scanning Calorimetry; **HPLC:** High Performance Liquid Chromatography.

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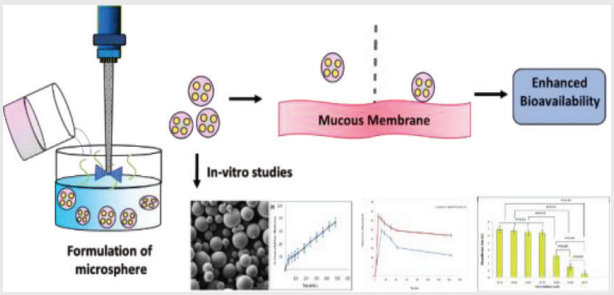
SUMMARY

Atorvastatin Calcium most effective common phytoconstituents used as lowering the cholesterol levels and primarily used for curing of dyslipidemia and cardiovascular disease. It is the competitive inhibitor of hydroxyl methylglutaryl-coenzyme A reductase, followed mevalonate pathway. One of the drawbacks of Atorvastatin Calcium have to low bioavailability and poor solubility. Current work focuses on the development of atorvastatin calcium mucoadhesive microspheres to boost delayed transit, continuous longer-term release and preclinical pharmacokinetic estimation in rabbits. By emulsification process the microsphere was prepared in which the independent variables (like polymer quantity) was studied on critical quality attributes such as entrapment efficiency. The prepare microsphere were characterized as their *in-vitro* release, percentage yield, physicochemical parameters, micromeritic properties, DSC, FT-IR, mucoadhesive wash off test and pharmacokinetic study in rabbit. Developed microsphere have smooth surface, negative zeta potential, maximum trapping efficiency and sustained release. Microspheres satisfy the micromeritic properties and, verified by FT-IR and DSC, showed no interaction between drug and polymer. The *in-vivo* study showed that the prepared microspheres are efficient for longer-lasting colon-targeted drug delivery systems. Relatively steady plasma drug concentrations were observed in the pharmacokinetics analysis after oral drug administration. For the formulation, $AUC0_{-24h}$ was significantly higher than for the pure drug. The preclinical oral bioavailability analysis of the drug was improved as relative availability values were high compared to the pure drug and transit time was delayed for longer periods of time.

PICTORIAL ABSTRACT



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