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Formulation and *In-vitro* evaluation of mucoadhesive buccal tablets of Atorvastatin Calcium

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Abstract

The objective of present study is to prepare buccoadhesive buccal tablets of Atorvastatin calcium (AVC-8mg) using the bioadhesive polymers Carbopol 974P (CP), Guar Gum, and Gum Ghatti as matrix forming agent and Ethyl cellulose (EC-25mg) as impermeable backing layer. The solubility studies were conducted along with PEG 4000 in different medias. Twelve formulations of mucoadhesive buccal tablets of AVC were prepared, which contain the polymers in various combinations. Tablets were prepared by direct compression method and characterized for swelling studies, % matrix erosion, surface pH, bioadhesive properties, *in-vitro* drug dissolution and *in-vitro* diffusion studies. All the formulations shows the satisfactory results in terms of bioadhesive performance. The swelling index was proportional to polymer content. The surface pH of all tablets was found to be satisfactory, close to neutral pH; the AVC released and drug diffusion from these tablets was depended on the ratio and type of the natural polymers used in the formulation. Tablets containing CP (10%) and Guar Gum, HPMCK4M and Gum Ghatti in the ratio of 1:3 (F3, F7 and F8) shows near zero order kinetics release, with non-Fickians diffusion and followed anomalous release. The *ex vivo* permeation concluded that PEG 4000 enhanced the permeability of AVC from the tablets. FT-IR studies revealed that there is no interaction between drug and polymer used in the study.

Keywords: Atorvastatin calcium, Buccal tablets, linear drug release, Zero order kinetics

Introduction

Among the various routes of drug delivery, oral route is the most suitable, convenient and most widely accepted. However, after oral drug administration many drugs are subjected to presystemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability [1,2]. Here the oral cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointestinal tract as well as first pass hepatic metabolism. This is due to direct access of the drug into the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to higher bioavailability [3].

The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract.[4] Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity.[5] A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response. This unidirectional drug release can be achieved using bilayer devices.[6] Atorvastatin calcium is HMGCo-A reductase widely used in the treatment of hyper lipidemias and cardiovascular diseases and it is known to have low oral bioavailability (14%) due to an extensive high first-pass effect and its availability in less dose size i.e. in few milligrams. Hence, it was considered as suitable candidate for administration via buccal route. The aim of the present study was to formulate and evaluate buccoadhesive buccal tablets of Atorvastatin calcium (AVC) that could be applied to the buccal mucosa to release the drug in unidirectional in buccal cavity in order to avoid gastric irritation and avoid first pass effect for improvement in bioavailability, it also reduce dosing frequency and to improve patient compliance.

Materials and Methods

Material

Atorvastatin calcium (AVC) was obtained as a gift sample from Aurobindo Pharma, Hyderabad India. Carbopol 974P and ethyl cellulose were procured from Correl Pharma Ltd , Sd fine chemicals Mumbai, India, respectively. Guar Gum and Gum Ghati (Medium Viscosity grade) (H.B Gum, Kalol, India and Raj enterprises Mumbai, India, respectively. All other reagents and materials were of analytical or Pharmacopoeial grade.

Determination of Solubility of Atorvastatin calcium

An excess of the drug was added to 10mL of the buffer in test tubes and the mixture was agitated in a thermo-stable bath at 37±1ºC for 24 hours. Then aliquot was filtered through a whatman filter, properly diluted with the same buffer and the absorbance was measured at 241nm. The studies were continued to enhance the solubility of the drug by using solid dispersions and physical mixture.

Preparation of Physical Mixture and Solid Dispersion

Physical mixtures of AVC in the mass ratio of 1:3 with PEG 4000 were prepared in a glass mortar by light trituration for 5 minutes. The mixture was passed through a sieve no 60. The prepared mixture was then used to perform the study. [7] For the preparation of the AVC solid dispersions by dropping method, the composition of AVC and PEG 4000 in solid dispersion formulations was in the ratio of 1:3 as in accordance to method reported by Lakshmi NV *et al.* [7] The PEG 4000 was melted in a porcelain dish at 58^0C±1^0C and a measured amount of AVC was added and stirred. The melted AVC-carrier mixture was pipetted and placed into an adjustable heating device to keep the temperature constant.

Preparation of Atorvastatin calcium Buccoadhesive Tablets

Buccoadhesive tablets were fabricated by the direct compression method using the formulations shown in Table 2. All ingredients of the tablets were passed through a sieve no. 40 and were mixed by trituration in a glass mortar with pestle to obtain uniform mixing. The mixture (100mg) was then compressed using an 8mm diameter die on a multi station tablet punching machine. Ethyl cellulose (50mg) was added above the core layer and punched simultaneously making up to a total weight of 150mg.

Drug Content Uniformity

For each formulation, 5 randomly selected tablets were under investigation. Each tablet was weighed accurately, powdered and transferred into a 50ml volumetric flask containing 30ml of methanol and was stirred continuously on a magnetic stirrer. The volume was made up to 50ml with methanol and the absorbance was measured spectrophotometrically at 241nm. The concentration was calculated from calibration curve.

Bioadhesive strength, surface pH, *In vitro* Residence time and swelling Studies.

The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8 The initial weight of the tablet was determined and then tablet was placed in 6ml phosphate buffer pH 6.8 in a petridish. The tablet was removed at different time intervals (1.0, 2.0, 3.0, 4.0, 5.0 and 6.0h) blotted with filter paper and reweighed (W2). The swelling index is calculated by the formula:

Swelling index = 100 (W2-W1) / W1.

Where, W1 = Initial weight of the tablet.

W2 = Final weight of tablet.

Determination of Surface pH for the prepared Tablets

The surface pH of the tablets was determined to evaluate the possible irritative effects of the formulation on the buccal mucosa. The tablets were left to swell for 2 hr in 5ml of phosphate buffer pH 6.8±0.05 after 2hrs, the surface pH was measured by placing the electrode in contact with the surface of the tablets.

In-vitro drug release studies

In vitro drug release was performed by fixing the impermeable layer of the tablet with a glass slide using instant adhesive, and placed in a beaker containing 900 ml phosphate buffer pH 6.8 as dissolution medium. The temperature was maintained at 37±0.5 C and the hydrodynamics was maintained by stirring on a magnetic stirrer at 50 rpm. 5 ml aliquots were withdrawn at predetermined time intervals and replaced with fresh medium. The aliquots were analyzed after appropriate dilution by a UV spectrophotometer (Elico, Model SL-150, Mumbai, India.) at a wavelength of 241nm. The experiments were repeated thrice and the results were taken as average of three test readings with standard deviations. The amount of AVC present in the samples was calculated with the help of appropriate calibration curves constructed from reference standards. During the drug release studies, the formulations were observed for physical integrity at different time intervals.

Characterization of release data

The description of dissolution profiles has been attempted using different release models. The data were evaluated according to the following equations [8-11].

Zero order: $M_t = M_o + K_o t$

First order: $\ln M_t = \ln M_o + K_1 t$

Higuchi model: $M_t = K_H \sqrt{t}$

Korsmeyer –Peppas model: $M_t/M_o = K_k t^n$

Where M_t is the amount of drug dissolved in time t, M_o the initial amount of drug, K_1 is the first order release constant, K_0 the zero order release constant, K_H the Higuchi rate constant, K_k the release constant and *n* is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient (r^2) was used as an indicator of the best fitting, for each of the models considered.

Ex vivo Bioadhesion Strength

A modified balance method was used for determination of the *ex vivo* bioadhesion strength. The balance was modified by replacement of one pan with the metal shaft 5gms heavier in weight on other pan. A piece of buccal mucosa was fixed on a glass vial, which was filled with phosphate buffer pH 6.8, so that it just touched the mucosal surface. The vial was fixed to a bottom of a glass beaker which is filled with buffer. The tablet was stuck to the lower side of a glass slide with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5gms of weight on the right hand pan [12-14]. A weight

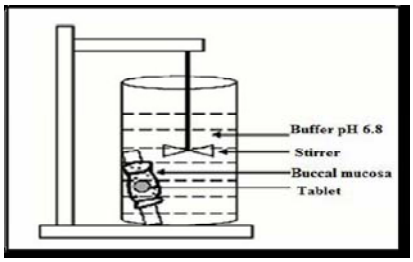
of 5gms was removed from the right hand pan, which lowered the slide along with the tablet over the mucosa. The balance was kept in this position for 3min contact time. The weight was added slowly to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the bioadhesion strength of the buccoadhesive tablet in grams (total weight on right hand pan minus 5gms).

In vitro drug permeation Studies

In vitro drug permeation through sheep buccal mucosa was performed using modified Franz diffusion cell at 37±0.5 C. The mucosa was mounted between the donor and receptor compartments. The prepared Buccoadhesive tablet (F3) was placed with the core facing the membrane and a 5gm weight was placed over the swollen tablet, the receptor compartment was filled with phosphate buffer pH 6.8, and stirred using a magnetic stirrer at 50rpm. A 2ml aliquot was withdrawn at predetermined time intervals and replaced with fresh medium [15, 16]. The absorbance's were measured at 241nm. The results obtained were shown in table 3.

In vitro residence time

The *in vitro* residence time for buccal tablet was determined using a locally modified USP disintegration apparatus as reported by Nakumara *et al.*[17]. The medium was composed of 800ml of phosphate buffer pH 6.8 maintained at 37^0C. A segment of sheep buccal mucosa 3cm length was glued to glass slide. The tablet surface was hydrated using phosphate buffer pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane, as shown in the below figure. The glass slab was vertically fixed to the tablet was completely immersed into the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded [18].



Representation of *ex vivo* residence time

FT-IR studies

The compatibility between the drug and polymer was compared by FT-IR spectra. The position of peak in FT-IR spectra of pure AVC is compared with those in FT-IR spectra of Atorvastatin calcium plus excipients. The spectra are shown in Figures 7.

Stability studies

Stability studies were conducted for the optimized formulations (F3) to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing at 40 C/75% RH for 3 months [22] was seen.

Results and Discussion

Mucoadhesive buccal drug delivery system is a promising tool for the drugs with low oral bioavailability due to extensive first pass effect and also this route provides an easy termination of drug effect. Atorvastatin calcium (AVC) is HMG-CoA reductase inhibitor with low oral bioavailability due to extensive first pass metabolism. In the present work, buccoadhesive tablets of AVC were prepared using Carbopol 974P along with guar gum, HPMC K15M, and gum ghatti by direct compression method. The amount of drug that could be systematically delivered across the buccal mucosa from $2cm^2$ system in one day has been estimated to be 10-20mg [9]. Hence AVC of dose 8mg was incorporated in the present formulations.

The solubility of the AVC was found be more from 57.06±0.67mcg/ml to 81.59±2.35 and 83.62±1.76 in the phosphate buffer pH 6.8 by using PEG 4000 as physical mixture and solid dispersion respectively. Hence an enhancement of solubility with PEG 4000 was determined. The results are similar to the Lakshmi NV *et al.* [7]. Hence, this AVC: PEG4000 in the ratio of 1:3 was taken in the formulation due to enhancement of solubility.

Preparation of AVC Buccoadhesive Tablets

The Buccoadhesive tablets was prepared by direct compression method (table 2) using Carbopol 974P(10mg) in fixed concentration as a primary polymer along with a secondary polymers like guar gum, HPMCK15M and gum ghatti in varying amounts. Ethyl cellulose was applied as backing membrane on the matrix core. All the prepared buccal tablets were evaluated for thickness, hardness, friability, weight variation, drug content uniformity. The results were shown in table 3. The hardness of prepared buccal tablets was found to be in the range of 4-5kg/cm^2. It was found that as the quanitity of polymer in the matrix core was increased, the hardness tend to increased. The formulations, F4, F8 and F12 shows the hardness in the range of 4.54±0.15, 4.48±0.35 and 4.5±0.19Kg/cm^2 respectively. It might be due to absence of the CP 974P and more amount of MCC (33%w/w) in the formulations. The formulation F7 showed the hardness of 5.06±0.23Kg/cm^2, it might be due to the higher amount of HPMC K15M and CP 974P. The thickness of the tablets was in range of 1.19±0.5mm. The drug content was from 97.9% to 103.5% suggested uniform mixing of AVC in the buccoadhesive tablets. The results are shown in table 3.

Table 1. Solubility study and drug content for pure drug, physical mixture and solid dispersion

Drug Mixture	Solubility (µg/mL)		Drug content (%)
	Water	Phosphate buffer 6.8	
Pure drug	27.04 ± 0.56	57.06 ± 0.67	94.46±0.023
Physical Mixture (1:3)	55.45 ± 1.35	81.59 ± 2.35	98.29±0.022
Solid Dispersion (1:3)	57.53 ± 1.46	83.62 ± 1.76	98.48±0.026

Table 2. Composition of Buccal Tablets of AVC with Guar gum, HPMK15M and Gum Ghatti in matrix core.

Ingredients (mg)	Formulation Code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
AVC	8	8	8	8	8	8	8	8	8	8	8	8
PEG 4000	24	24	24	24	24	24	24	24	24	24	24	24
Guar gum	15	30	45	30	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	15	30	45	30	-	-	-	-
Gum ghatti	-	-	-	-	-	-	-	-	15	30	45	30
CP-974P	10	10	10	-	10	10	10	-	10	10	10	-
Mannitol SD	5	5	5	5	5	5	5	5	5	5	5	5
MCC PH-102	38	23	8	33	38	23	8	33	38	23	8	33
Ethyl cellulose (backing layer)	50	50	50	50	50	50	50	50	50	50	50	50
Total Weight	150	150	150	150	150	150	150	150	150	150	150	150

Table 3. Physico-Chemical Characteristics of Prepared Buccoadhesive Tablets of Atorvastatin Calcium

Formulation Code	Thickness (mm) n=10	Weight Uniformity (mg) n=20	Friability (%) n=20	Hardness (Kg/cm^2) n=10	Drug Content (%) n=5
F1	1.09± 0.04	151± 0.03	0.47±0.02	4.65±0.89	100.1± 0.02
F2	1.11± 0.19	149.1± 0.1	0.51±0.05	4.59±1.22	97.9± 0.12
F3	1.15± 0.03	151.6± 0.03	0.52±0.05	4.71±0.84	103.2± 0.19
F4	1.15± 0.21	147.2± 0.14	0.52±0.05	4.54±0.15	102.1± 0.14
F5	1.13± 0.25	148.6± 0.12	0.53±0.07	4.54±0.11	98.3± 0.07
F6	1.20± 0.04	150.1± 0.34	0.54±0.06	4.84±0.35	103.4± 0.19
F7	1.19± 0.05	148.2± 0.25	0.51±0.05	5.06±0.23	102.4± 0.08
F8	1.13± 0.03	147.9± 0.27	0.52±0.05	4.48±0.14	103.5± 0.05
F9	1.18± 0.17	149.6± 0.16	0.56±0.08	4.31±0.19	99.6± 0.12
F10	1.02± 0.21	150.3± 0.34	0.53±0.05	4.51±0.21	100.3± 0.04
F11	1.14± 0.26	147.8± 0.19	0.52±0.05	4.11±0.11	98.5± 0.79
F12	1.12± 0.06	149.5± 0.23	0.56±0.06	4.51±0.19	100.1± 0.29

Swelling Index, Surface pH and *In vitro* Bioadhesion Studies

Bioadhesive polymer swelling is an important aspect in studying bioadhesion property. For this study the swelling behavior of the prepared buccoadhesive tablets were placed in 5mL phosphate buffer solution pH 6.8.The values obtained is shown in Table 4. Formulations (F1 to F4) with natural polymer guar gum in 15%w/w, 30%w/w and 45%w/w in the matrix core, The formulation F3 shows highest rate of swelling 295.00±1.59 with continuous swelling and it also maintained the integrity of the tablets till 6hrs, and showed higher percentage swelling index, it may be due to the presence higher amount of guar gum along with carbopol. The HPMCK15M in 15%w/w, 30%w/w and 45%w/w matrix core formulation (F5 to F8) had shown the lowest swelling rate, when compared to both guar gum and gum ghatti. The formulation F7 shows 220.05±2.22 indicated the lower swelling of the polymer. Among the formulation, F9 to F12 the F11 formulation with Gum Ghatti in 45%w/w in the matrix core shows 275.00±1.89 the swelling index, which is an intermediary between guar gum and HPMC matrix formulations. The percentage swelling index values of the tablets were in the order of F1toF4 > F5toF8 > F9toF12. In general, it was observed that the percentage swelling index values were found to be increased with increasing the concentration of the polymer. The swelling of matrix was found to be dependent on the type and concentration of polymer matrix core. Further the hydration of the polymer results in the relaxation of stretched, entangled or twisted molecules, which are able to liberate their adhesive sites giving them possibility of creating adhesive bonds.

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, *in vivo.* As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was attempted to keep the surface pH as close to as salivary pH. The results were shown in table 4. The surface pH for all the prepared tablets was found to be in range of 6.18 to 7.05 which was nearer to salivary pH 6.5-7.5. Hence the prepared buccal tablets can be used without the risk of mucosal irritation and discomfort. The mucoadhesive properties of the prepared formulations are shown in Table 4. The bioadhesion is either attributable to formation of physical bonds or hydrogen bonding with the mucus components. All the formulations with the Carbopol 974P in the matrix core as a primary polymer upto 10%w/w imparting ample bioadhesive strength, when compared to formulations (F4, F8 & F12) without primary polymer (Carbopol 974P) But, there were effect was observed due to the variance in the concentration of secondary polymers (guar gum, HPMC and gum ghatti). The bioadhesive strength of the tablet was increased gradually with the increase in the amount of secondary polymers, and was ranked as HPMC> guar gum> gum ghatti.

The values obtained suggest that the formulation with gum ghatti showed lesser adhesion characteristics than the formulation with HPMC and Guar gum. The formulation F7 showed the highest bioadhesive strength (51.37±1.55gm) as both the polymers used possessed higher bioadhesion strength. The formulations F4 (guar gum), F8 (HPMC K15M) & F12 (gum ghatti) had lesser values; it might be due to the absence of Carbopol 974P. Thus increased sites for bond formation can be attributed to the increase in bioadhesion with an increase in concentration [21], and also it was found that an increase in bioadhesion, with the increase in quantity of the polymer. All the formulations shown sufficient bioadhesive strength and were within the limits.

Table 4. Bioadhesive strength, surface pH, *In vitro* Residence time and swelling index of Different Buccoadhesive Tablets

Formulation code	*In vitro* Bioadhesive Strength (g)	Surface pH	*In vitro* Residence time	Swelling Index mean±SD
F1	23.41±0.75	6.32±0.03	6 hr 59min	275.00±0.18
F2	32.19±0.99	6.91±0.09	7 hr 59min	289.00±0.00
F3	41.12±1.59	6.82±0.03	7 hr 59min	295.00±1.59
F4	22.49±0.57	6.57±0.06	6 hr 59min	280.00±1.66
F5	26.99±0.67	6.03±0.12	7 hr 59min	177.00±0.00
F6	37.35±3.76	6.18±0.02	>8hrs	213.16±2.01
F7	51.37±1.55	6.85±0.05	> 8hrs	220.05±2.22
F8	28.73±0.56	6.22±0.05	6 hr 49min	180.07±1.11
F9	21.87±0.94	6.13±0.05	6 hr 10min	240.01±1.11
F10	28.89±0.54	6.18±0.08	6 hr 22min	250.20±1.99
F11	39.52±0.61	6.36±0.05	6 hr 35min	275.00±1.89
F12	19.04±0.58	7.05±0.10	6 hr 42min	248.01±1.11

In vitro Drug Release Studies

The release of AVC from buccoadhesive tablets varied according to the type and ratio of the matrix-forming polymers.

Effect of Guar Gum along with CP 974P in the Matrix Core

In vitro drug release from (guar gum along with Carbopol934P) in the matrix core of buccal tablets, formulation (F3), showed gradual decrease in the release rate of AVC, due to the extensive swelling of the guar gum with an increase in polymer concentration, which forms a thick gel barrier for drug diffusion is shown in figure 1. However at higher concentrations, the formulation (F3) with 45%w/w of guar gum shows a linear release of the AVC, when compared to formulations F1 and F2. Presence of CP 974P in formulations F1, F2 and F3 retarded the drug release, but however prevented from erosion, and controlled the release of the drug, when compared to F4 formulation this might be due to the absence of CP 974P. The drug release from formulation F1 to F4 were compared and showed in figure 1.

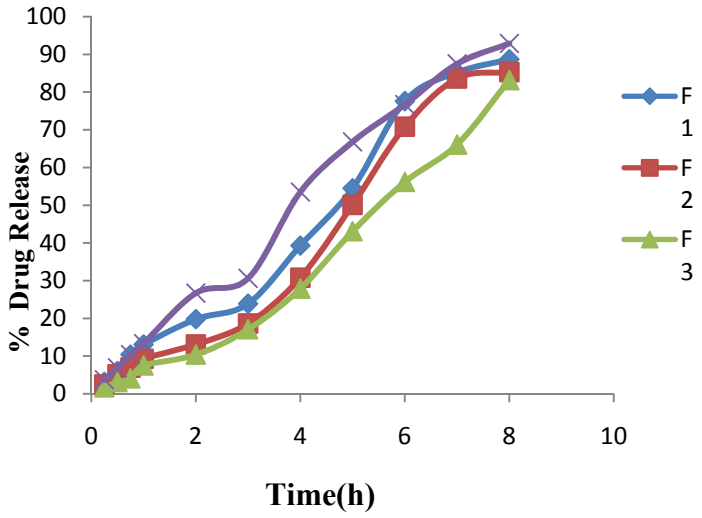


Figure 1. *In-vitro* Dissolution profile of AVC released from Guar gum based Buccoadhesive tablet (F1-F4)

The correlation coefficient (r^2) of the Guar gum matrix tablet (F3) for Zero order release kinetics was found to be higher (0.986), when compared to that of first order kinetics (0.937) indicating that the drug release from the matrix tablets followed Zero order kinetics is shown Table 5. From this data, it can be observed that formulation F3 (45%w/w guar gum) provides better control over the release of AVC than formulations with 15%w/w and 30%w/w of the guar gum along with CP 974P in the matrix core. This might be attributed to the cationic interactions between guar gum and CP 974P in the matrix core. Hence it can be stated that AVC with 45%w/w of guar gum 10%w/w of CP 974P shows zero order release. The Release mechanism, correlation coefficient values (r^2) for the Higuchi plots (Table 5) ranged from 0.753 to 0.877 for the prepared buccoadhesive tablets, indicating that the drug release from the tablets occurred by matrix diffusion. The diffusion coefficient values for (F3) obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet followed case-II transport and a zero order release, as the diffusion coefficient *'n'* value was found to be greater than 0.89. Hence, the results of the study indicated that the release of drug from the prepared buccoadhesive tablet followed zero order kinetics via diffusion controlled mechanism.

Effect of HPMC K15M along with CP 974P in the Matrix Core

In vitro drug release studies, HPMC K15M along with Carbopol934P in the matrix core of buccal tablets, formulation (F7), showed gradual decrease in the release rate of AVC, when compared to F5 and F6. It might be due to the formation of intricate between HPMC K15M and CP974P. (Figure 2) Formulations F5 with 15%w/w of HPMC K15M showed rapid release of the AVC, when compared to formulations F6 and F7, it is due to lesser amount of HPMC K15M. Formulation F8 also shows drug sustained release, with a linear fashion. The drug release from formulation F5 to F8 were compared and showed in Figure 2. The correlation coefficient (r^2) of the HPMC K15M buccoadhesive tablet (F5) for Zero order release kinetics was found to be higher (0.981), when compared to that of first order kinetics (0.934) indicating that the drug release from the buccoadhesive tablets followed Zero order kinetics. The data is shown in table 5, it may be observed that, the 'r^2' values for prepared buccoadhesive tablets with 15%w HPMC in the matrix core are 0.981, 0.934 & 0.872, for tablets with 30%w/w HPMC in matrix core the 'r^2' values are 0.969, 0.914 & 0.842 and 0.979, 0.930 & 0.815 in case of 45% of HPMC in the matrix core. From this data, it can be observed that formulation F7

(45%w/w HPMC) provides better control over the release, over other formulations, (30%w/w and 45%w/w of HPMC). This might be attributed to the higher concentration of HPMC in the matrix core. The diffusion coefficient values obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet followed case-II transport and a zero order release, as the diffusion coefficient '*n*' value was found to be greater than 0.89 (table 5). The correlation coefficient values r^2 for the Higuchi plots, is ranged from 0.815 to 0.872 for the buccoadhesive tablets, indicating that the drug release from the tablets occurred by matrix diffusion. Hence, the results of the study indicated that the release of drug from the prepared matrix tablet followed zero order kinetics via diffusion controlled mechanism.

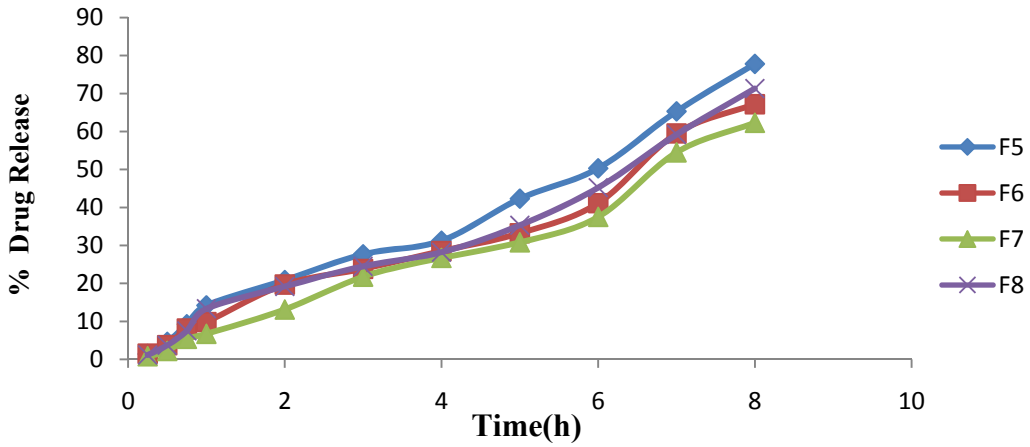


Figure 2. *In-vitro* Dissolution profile of AVC released from HPMC K15M based Buccoadhesive tablet (F5-F8)

In vitro drug release studies of Gum ghatti matrix core tablets

Gum ghatti along with Carbopol934P in the matrix core of buccal tablets, formulation (F11), showed gradual decrease in the release rate of AVC, formulations showed a gradual decrease in the release of drug similar to the release pattern of guar gum. Figure 3, however at higher concentrations, the formulation (F11) with 45%w/w of Gum ghatti shows a linear release of the AVC, when compared to formulations F9 and F10. Presence of CP 974P in formulations F9, F10 and F11 retarded the drug release, when compared to formulation F12, this might be due to the absence of CP 974P. The drug release from formulation F9 to F11 were compared and showed in Figure 3.The correlation coefficient (r^2) of the Gum ghatti matrix tablet (F11) for Zero order release kinetics was found to be higher (0.942), when compared to that of first order kinetics (0.863) indicating that the drug release from the matrix tablets followed Zero order kinetics. From the Table 5 it may be observed that, the 'r^2' values for tablets with 15%w/w gum ghatti in the matrix core are 0.970, 0.800&0.823, for tablets with 30%w/w gum ghatti in matrix core the 'r^2' values are 0.960, 0.870&0.772 and 0.942, 0.863&0.708 in case of 45%w/w of gum ghatti in the matrix core for zero order, first order and Higuchi respectively. From this data, it can be concluded that formulation F11 (45%w/w gum Ghatti along with CP974P) provides better control release of AVC when compared to other formulation F9, F10 and F12. The diffusion coefficient values obtained according to the model developed by Korsemeyer *et al* showed that matrix tablet followed case-II transport and a zero order release, as the diffusion coefficient *'n'* value was found to be greater than 0.89 (table 5). The correlation coefficient values 'r^2' for the Higuchi plots (table 5) ranged from 0.708 to 0.978 for the buccoadhesive tablets, indicating that the drug release from the tablets occurred by matrix diffusion. Hence, the results of the study indicated that the release of drug from the prepared buccoadhesive tablets (F11) followed zero order kinetics via diffusion controlled mechanism.

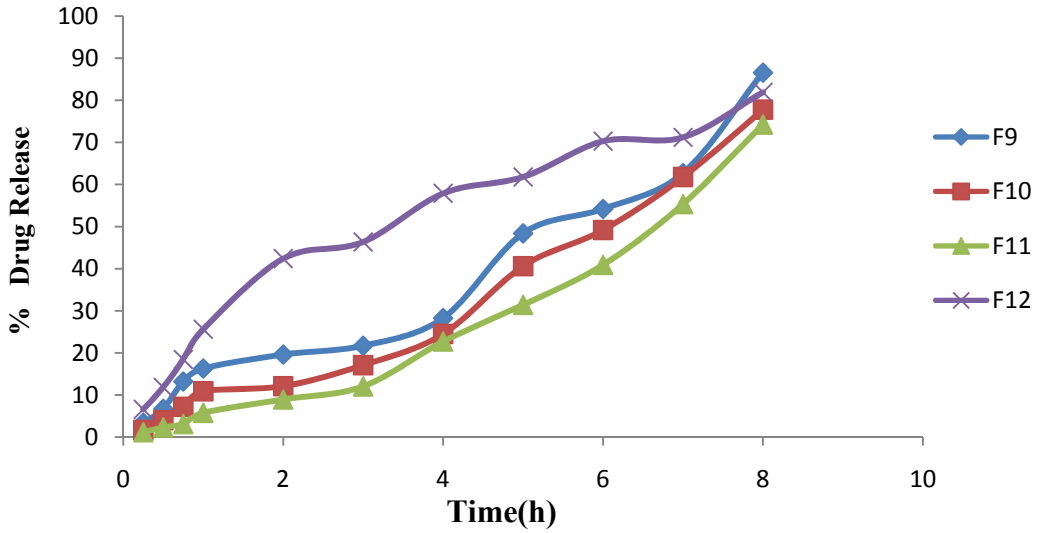
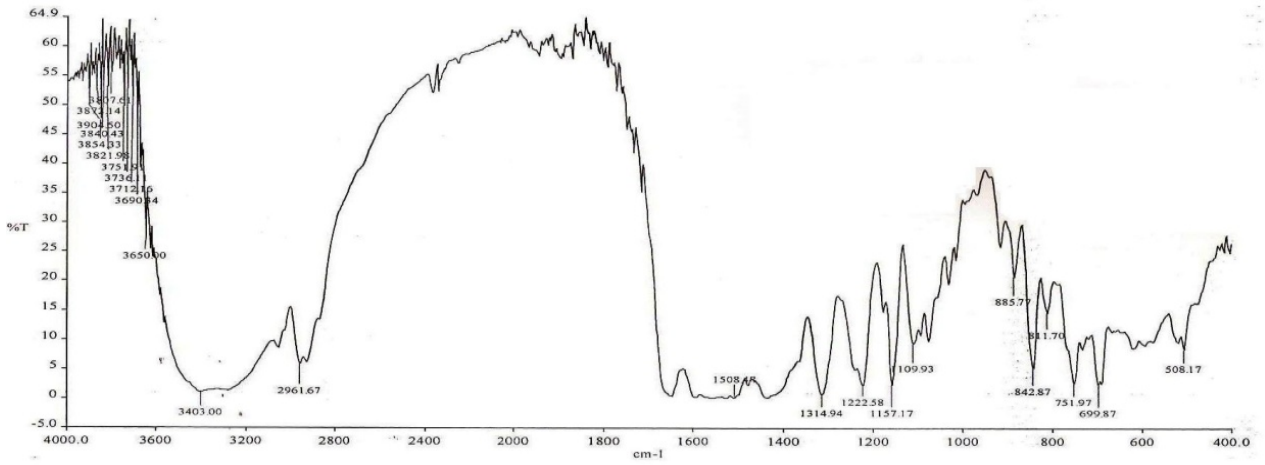


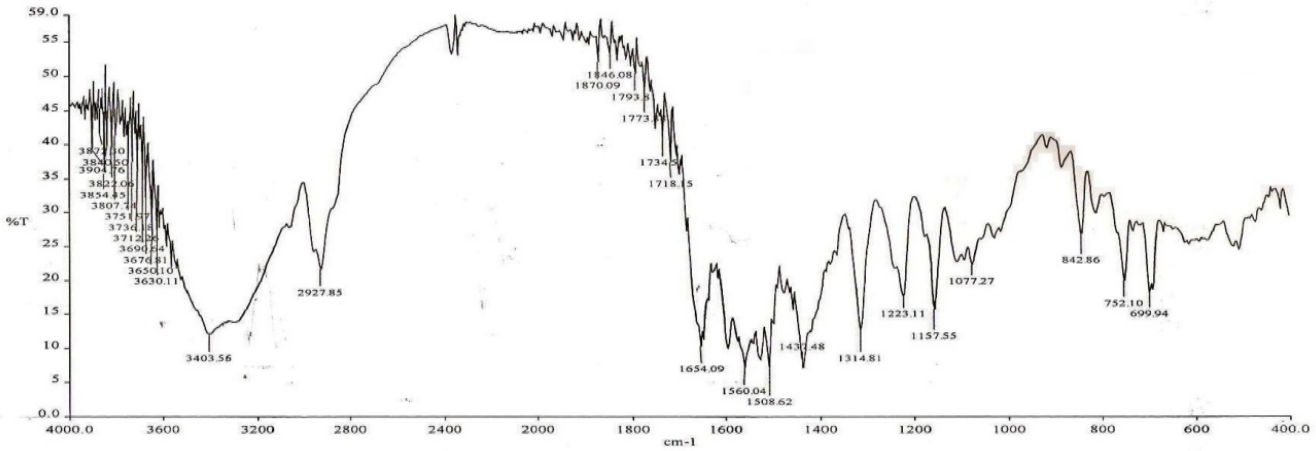
Figure 3. *In-vitro* Dissolution profile of AVC released from Gum ghatti based Buccoadhesive tablet (F9-F12)

FT-IR studies

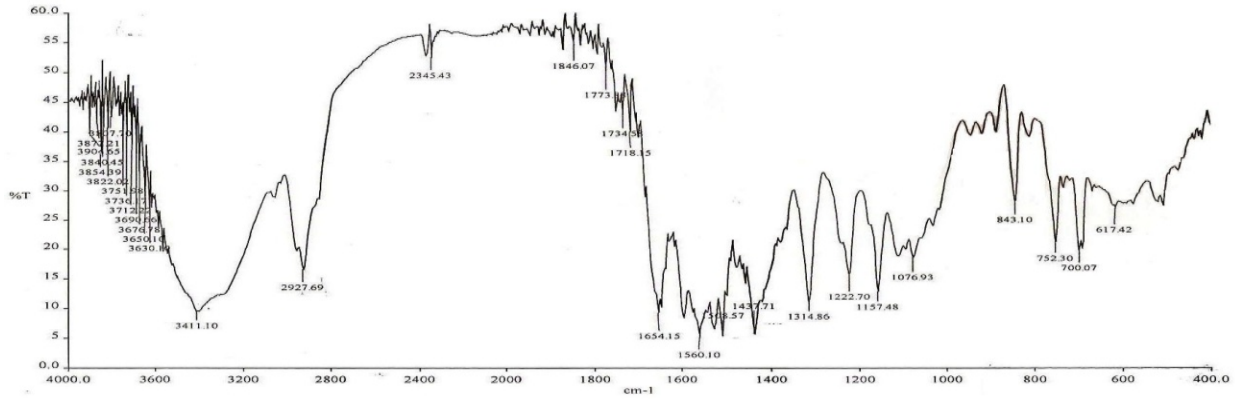
The drug-polymer interaction was studied using FT-IR spectroscopy for selected combination of drug with different polymers used. The IR spectrum of AVC gave absorption peak at 3043cm^{-1}due to hydroxy group (O-H) and in the form of amine with absorption peak at 3180cm^{-1}. The IR spectrum of carbopol gives absorption peak at 3408cm^{-1} for its O-H group. The IR spectrum of the HPMC K15M exhibited a broad hump around 3411cm^{-1} to 3122cm^{-1}. The IR spectrum of guar gum gives absorption at 3403.56cm^{-1} for O-H group of polysaccharide along with carboxylic C=O absorption peak at 1654cm^{-1}. The IR spectra of gum ghatti gives broad hump at 3411cm^{-1} for O-H group and absorption peak at 1654.05cm^{-1} for carboxylic C=O. The IR spectrum of pure drug and formulation indicates that there is no interaction between the pure drug and the formulations.



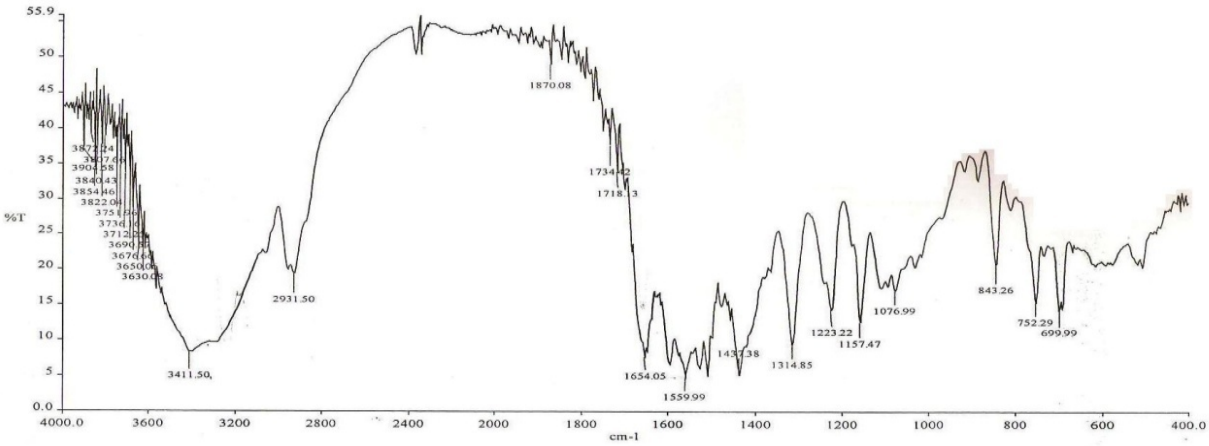
(a)



(b)



(c)



(d)

Figure 4. FT-IR Spectra of (a) Pure AVC (b) F3 (c) F7 (d) F11

In-vitro Drug permeation study of formulation

Based on the results, the F3 formulation was selected for *in vitro* drug permeation studies. The oral mucosa of sheep resembles that of humans more closely in terms of structure and composition and therefore sheep buccal mucosa was selected for drug permeation studies. The result of drug permeation from buccal tablets through the sheep buccal mucosa is shown in table 4 and figure 5, It reveal that AVC was released from the formulation and permeated through the sheep buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady and 79.87±1.82% of AVC could permeate through the buccal membrane within 8hrs.

Stability Studies

Stability study was performed on the promising formulation (F3) by storing the samples at 40^0C±2 C/75%RH for 3 months. The samples were tested for any changes in physical appearance , drug content and *in-vitro* drug release studies, The graph was shown in figure 6 These results indicate that there were no significant changes in Physical appearance, drug content and dissolution profile after storage.

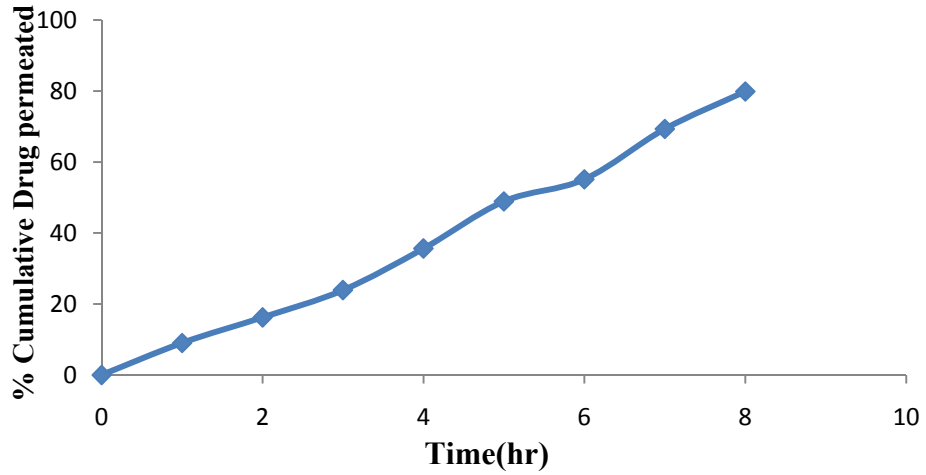


Figure 5. *In vitro* Percent AVC Permeated across the sheep buccal mucosa (F3)

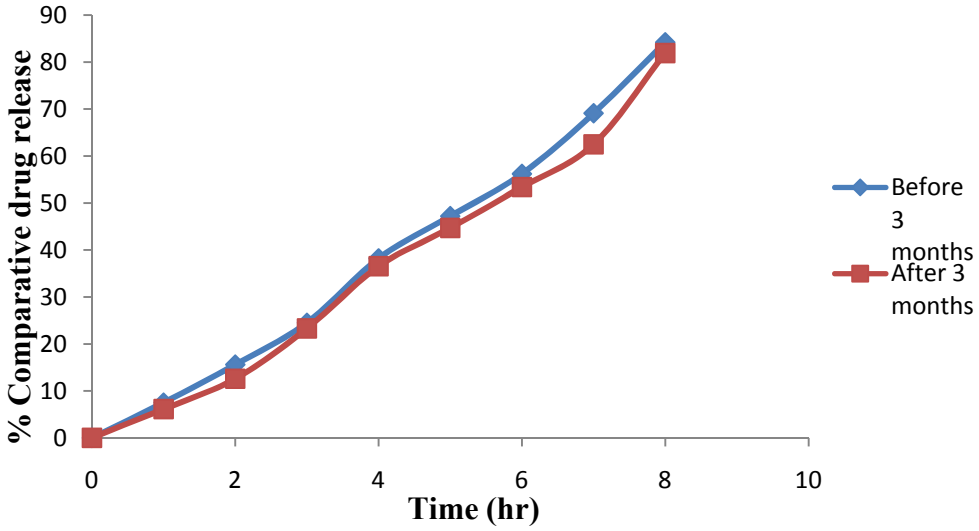


Figure 6. *In vitro* dissolution profiles of formulation (F3) before and after storage at 40±2 C /75±5% RH for 3 months

Conclusion

The mucoadhesive buccal tablets of Atorvastatin calcium (AVC) could be prepared using carbopol 974P as primary polymer along with the combination of secondary polymers like HPMC K15M, guar gum and gum ghatti by direct compression method. Mucoadhesive, Ethyl Cellulose being hydrophobic as backing material prolonged the release up to 8h. It also indicated good

adhesive capacity of polymers used. The *ex vivo* permeation concluded that PEG 4000 enhanced the permeability of AVC from the tablets. FT-IR studies revealed that there is no interaction between drug and polymer.

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Author's contribution

All authors had equally contributed inthe manuscript for literature search, study design, in analysis, data collection and interpretation analysis, data interpretation, writing etc. If all authors contributed equally, please state this

Conflict of interest

no conflicts of interest,

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References

[1]. Santanu RC, Rajesh G, Sourav Saha. A Review on Buccal Mucoadhesive Drug Delivery Systems. Indo-Global Journal of Pharmaceutical Sciences 2011; 1(3): 223-233.

[2]. Surapaneni MS, Das SK, Das NG. Effect of excipient and processing variables on adhesive properties and release profile of pentoxifylline from mucoadhesive tablets. Drug DevInd Pharm 2006; 32(3): 377-87.

[3]. Gandhi RE, and Robinson JR., Bioadhesion in drug delivery, Int. J. Pharm. Sci., 1988; 50:145-152.

[4]. Pranshu T, Satheesh NV. Oral mucoadhesive drug delivery systems: A review. Int. J. of Bio pharmaceutics 2011; 2(1): 36-46.

[5]. Nakhat P, Kondawar A, Babla I, Rathi L, Yeole P. Studies on Buccoadhesive Tablets of Terbutaline Sulphate. Indian J Pharm Sci 2007; 69(4): 505-10.

[6]. Yamsani VV, Gannu R, Kolli C, Rao ME, Yamsani MR. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm 2007; 57(2): 185-97.

[7]. Lakshmi NV, Kalyan RB, Raj Kumar M, Kiran KA, Raju Ch, Sanjeeva KA and Venkateshwara Reddy. Improved dissolution rate of Atorvastatin calcium using solid dispersions with PEG-4000, J Chem Pharm. Res., 2010; 2(3): 304-311.

[8]. Higuchi T. Mechanism of sustained-action medication: theoretical analysis of rate of release of solid drug dispersed in solid matrices. J Pharm Sci 1963; 52:1145–1149.

[9]. Korsmeyer RW, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm 1983; 24: 25–35.

[10]. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers, Pharm. Acta Helv 1985; 60: 110–111.

[11]. Gohel MC, Panchal MK, Jogani VV. Novel mathematical method for quantitative expression of deviation from the Higuchi model. AAPS Pharm Sci Tech 200; 1: 45-50.

[12]. Ahagon A, Gent AN. Effect of interfacial bonding on the strength of adhesion. J. Polym. Sci. Polym. Phys 1975; 13: 1285-1300.

[13]. Lee VHL, Lee VHK, Robinson JR. Controlled drug delivery. 2nd Ed., vol 29, New York; Marcel Dekker Inc: 1987, 4.

[14]. Bomberag LE, Buxton DK, Friden PM. Novel periodontal drug delivery system for treatment of periodontis. J. Control. Rel 2001; 71 (3): 251-259.

[15]. Jimenez-Castellanous MR, Zia H, Rhodes CT. Mucosal drug delivery system. Drug Dev. Ind.Pharm 1993; 19,143-194.

[16]. Tiwari D, Goldman D, Sause R, Madan PL. Evaluation of polyoxy ethylene homopolymers for buccal bioadhesive drug delivery formulations. AAPS Pharm SciTech 1999; 1:E13.

[17]. Nakamura F, Otha R, Machida Y, Nagai T. *In vitro* and *in vivo* nasal mucoadhesion of some water soluble polymers, Int J Pharm. 1996; 134: 173-181.

[18]. Mathias NR, Hussain AM. Non-invasive systemic drug delivery: develop ability considerations for alternate routes of administration. J. Pharm. Sci 2010; 99: 1-20.

[19]. Shojaei Amir H. Buccal Mucosa as a route for systemic drug delivery. Journal of Pharmacy and Pharmaceutical Sci. 1998; 1(1): 15-30.

[20]. Hoogstraate JAJ, Wertz PW. Drug delivery via the buccal mucosa. Pharm Sci Techn Today 1998; 1(7): 309-316.

[21]. Khairnar GA, Sayyad FJ. Development of buccal drug delivery system based on mucoadhesive polymer. International Journal of Pharm Tech Research 2010; 2(1): 719-735.

[22]. Mathews BR, Regulatory aspects of stability testing in Europe. Drug Dev Ind Pharm. 1999; 25: 831–856.