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ROSUVASTATIN CALCIUM BIOADHESIVE BUCCAL TABLETS FORMULATION AND EVALUATION

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ABSTRACT

Rosuvastatin calcium is a lipid lowering agent which has been selected as a model drug for investigation, because of its very low bioavailability (20%) due to extensive first pass metabolism. The present investigation is aimed at design and evaluate bi-layered buccal-adhesive tablet of rosuvastatin calcium by direct compression method using bio-adhesive polymers in combination of Carbopol and sodium carboxy methyl cellulose (CMC), Carbopol and sodium alginate. All the formulation were subjected to quality control(QC) test and evaluation test like thickness, weight variation, hardness, drug content, swelling index, surface pH, *ex-vivo* Mucoadhesive strength, *in-vitro* drug release and *ex-vivo* permeation studies. The modified *in- vitro* assembly was used to measure and compare the bio-adhesive strength of tablet with fresh porcine buccal mucosa as a model tissue. The tablets were evaluated for in vivo release in pH6.6 citrate buffer for 6hr in standard dissolution apparatus. The order of drug release from the dosage form has been determined. The optimized formula followed non-fickian release mechanism with zero order kinetics. The physiochemical interaction between the drug and polymer were investigated using FTIR. The results of post compressional characteristic were found to be within the pharmacopoeial limits. Optimized formulation containing Carbopol, sodium alginate showed good bio-adhesion strength and 96.0% of *in-vitro* release of drug in 6hrs, and 86.11% permeation of drug through porcine buccal mucosa. The excipients used in study did not alter physic-chemical properties of the drug, FTIR is confirmed. The present study concludes that buccal delivery of rosuvastatin calcium tablets can be a good way to bypass the first pass metabolism and it will render great bio availability.

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INTRODUCTION:

Oral controlled release (CR) systems continue as the most popular one among all the drug delivery systems. Bio-adhesive delivery systems offer several advantages over other oral CR systems by virtue of prolongation of residence time of drug in the gastrointestinal tract, targeting and localization of the dosage form at a specific site. Also, these bio-adhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in a high drug flux through the absorbing tissue. In addition, bioadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce the overall dosage required and to minimize the side effects that may be caused by the systemic administration of the drugs. Bio-adhesive formulations the polymer used as adhesive component (Wade A and Weller PJ, 1994). These polymers are often water soluble, they attract water from the mucosal surface and this water transfer leads to strong interaction. These polymers also form viscous layers when hydrated with water, which increases the retention time over the mucosal surfaces and leads to adhesive interactions. Several studies reported bio-adhesive oral drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes; however, very few reports on bio-adhesive tablets using natural hydrophilic polymers are available. Prolonged contact time of a drug with a body tissue through the use of a bio-adhesive polymer can significantly improve the performance of many drugs (Vyas SP and Khar RP, 2002). In our study, Rosuvastatin Calcium is used as a model drug. The objective of this study is to develop, characterize, and evaluate bio-adhesive tablets of Rosuvastatin Calcium employing various natural bio-adhesive polymers such as Carbopol 934P with Sodium alginate and sodium CMC, for prolonged absorption. The prepared tablets were evaluated for different parameters such as hardness, friability weight variation swelling index, *In-vitro* drug release rates, and *ex-vitro* bio-adhesive strength.

MATERIALS AND METHOD:

Materials:

Rosuvastatin calcium was obtained as a gift sample from Aurobindo Pharma Ltd Chennai, Carbopol, Sodium CMC, Sodium Alginate are purchased from Yarrow Chem Products, Mumbai, and all the remaining excipients are purchased from Scientific Labs, Chennai.

Fourier transforms infrared spectroscopic (FTIR) studies:

IR spectroscopy has been studied using an FTIR spectrophotometer (spectrum BX-FT-IR, PERKINELMER). The spectrum was recorded in the range of 4000-400cm^{-1}. The procedure consisted of dispersing a sample in KBr followed by gentle mixing. The spectrum was scanned at a resolution of 4.00cm^{-1}.

Pre-formulation studies on the Rosuvastatin calcium:

Ex-vivo permeation of drug solution through porcine buccal mucosa

The aim of the study was to investigate the permeability of buccal mucosa to Rosuvastain calcium. It is based on the generally accepted hypothesis that the epithelium is the rate limiting barrier in buccal absorption. The buccal epithelium was carefully mounted in between the two compartment of a Franz diffusion cell with internal diameter of 2.4 cm and with a receptor compartment volume of 14ml of citrate buffer pH (6.6) was placed in the receptor compartment. The donor compartment contained a 5ml of drug solution in methanol. The entire setup was placed over magnetic stirrer and temperature was maintained at about 37^{o}C. The sample of 1ml were collected at predetermined time intervals and stored under refrigerated condition till the analysis was carried out. All the experiment were performed in triplicate (n=3) and mean values were used to calculate flux (J) and permeability coefficient (P).

$$J = \left(\frac{dQ}{dt}\right)/A$$

$$P = (dQ/dt)/\Delta CA$$

Where J, flux (mg.hrs^{-1}cm^{-2}); P- Permeability co efficient (cm/h); dQ/dt- slope obtained from the steady state portion of the curve; ΔC, the concentration difference across the mucosa and A, area of diffusion (cm^2).

Formulation of Rosuvastatin bilayer buccal tablets

The drug can be incorporate in the adhesive layer of the tablet which comes in contact with mucosal surface. The drug containing Mucoadhesive layer is then protected from the oral cavity environment by a second upper inert layer, which faces in to the oral cavity. Buco-adhesive tablets were formulated by direct compression method. All the ingredients of the formulation were passed through a mesh #60 and blended with a mixer to obtain a uniform mixing. The blend and the powder of the core was compressed on a 6mm punch in a single stroke 8 station tablet punching mission. After punching the core layer the second compression was done on it by adding ethyl cellulose. Tablet weighing 125mg with hardness of 4.5kg/cm^{2+} were prepared. The following excipients like MCC as filler, manitol as permeation enhancer, magnesium stearate as lubricant, saccharine as sweetener used with total bio adhesive polymer in different mixing ratios of Carbopol 934P, sodium CMC and Carbopol 934P, sodium alginate with respect to 100mg core of tablet. The formulation are coded as shown in table 1.

Evaluation of buccal tablets:

The following post compression evaluation parameter has been performed such as thickness, hardness, weight variation, friability, assay, swelling studies.

Measurement of bio adhesion strength

Muco-adhesion strength of the tablet was measured on a modified physical balance employing the method as described by Gupta el al, 1992 using porcine buccal mucosa as model mucosal membrane. The mucoadhesive performance of the buccal tablet was evaluated using porcine buccal tissue. The time for film to detach from the porcine buccal **tissue in a well-stirred beaker** were used to assess the mucoadhesive performance. The fresh cut porcine buccal tissue was fixed on the side of the beaker with glue. Before addition of the buffer, the films were attached to porcine buccal tissue by applying light force (approximately 0.5N) with fingertip for 20 s. The beaker was then filled with 800 ml phosphate buffer and kept at 37°. A stirring rate of 150 rpm were used to simulate buccal and saliva movement. The attachment of films was monitored until drug release time. The time for the film to detach from the porcine buccal tissue was recorded as the mucoadhesion time

Determination of *ex-vivo* resident time:

The *ex-vivo* resident time was determined using a modified USP disintegration apparatus, based on the apparatus applied by Nakamura. The disintegration medium was composed 800ml of citrate buffer, pH 6.6 maintain at 37$\pm$ 2^{o}C. The porcine buccal tissue was fixed to the surface of the glass layer, vertically attached to the apparatus. The buccal tablet was hydrated from the surface using 0.5ml of citrate buffer, pH6.6 and then hydrated surface was brought in to contact with the mucosal membrane. The time necessary for complete erosion are de-attachment of the tablet from the mucosal surface was recorded. All the experiments were performed in triplicate and mean of triplicate was determined.

Surface pH study:

Surface pH study of the buccal tablet was determined in order to investigate the possibility of any side effect in-vivo. As an acidic or alkaline pH may cause irritation to the mucosa, it was determined to keep the surface pH as close to neutral as possible. The Bottenberg method was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1ml of distilled water (pH 6.5+ 0.05) for 2hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1minute.

***In-vitro* drug release of buccal tablet:**

The United States pharmacopoeia (USP) XXII rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 500 ml of citrate buffer, pH 6.6. The release was performed at 37± 0.5^{0}C, with a rotation speed of 50rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed into the bottom

of the dissolution vessel. Samples (5ml) were withdrawn at predetermined time intervals and aliquot of same quantity replaced with citrate buffer. The samples were Whatman filtered through filter paper and analyzed by UV spectrophotometer at 244 nm.

***Ex-vivo* permeation of buccal tablets**:

Ex-vivo permeation study of buccal tablets through the porcine buccal mucosa was performed using Franz-diffusion cell at $37^0 \pm 0.2^0$C and 50 rpm. This temperature and rpm was maintained by using magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2hrs of slaughter. The tissue was stored in Krebs buffer at 4^0c upon collection the epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Franz-diffusion cell.

After the buccal membrane was equilibrated for 30min with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh pH 6.6 buffer solution. The buccal tablet was placed in donor chamber and 1ml of buffer solution (pH 6.6) was added. Aliquots (1ml) were collected at predetermined time intervals the same quantity of fresh buffer solution replaced to maintain sink condition. The test samples are filtered through a filter paper, and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 244 nm using a UV spectrophotometer.. The experiments were performed in triplicate (n=3).

Stability of buccal tablets in human saliva:

Stability studies of the buccal tablet were performed for optimized formulation in normal human saliva. The human saliva was collected from humans volunteers and filtered. The buccal tablets were placed in 5ml of human saliva in a temperature controlled oven for 6hrs at 37 ± 0.2^0C, the buccal tablet was examined at regular intervals (0,2,4and 6 h)for change in color, surface area, and integrity.

RESULTS AND DISCUSSION:

Fourier transforms infrared (FTIR) spectroscopic studies:

FTIR spectrums were used to identify the chemical interaction between the drug and carrier. FTIR spectra of drug, drug-polymer and final optimized formulation were shown in figure 1. The FTIR spectra of pure drug showed characteristic peaks at 3812.92, 3854.23, 3751.88, 3736.01, 3649.94 and 3391.93cm^{-1} for hydroxyl O-H stretching; 2968.80cm^{-1} for C-H stretching; 1546.85and1509.22$cm^{-1}$for aromatic C=C stretching,1381.75 and 1335.82 for methyl C-H bending; 1155.30 for C-F stretching; 1068.33cm^{-1} for sulfoxide group of S=O stretching respectively. The drug and Carbopol FTIR spectra showed characteristic peaks of drug at 1544.64 and 1509.19$cm^{-1}$for aromatic C=C stretching, 1381.50 for methyl C-H bending1156.26cm^{-1} for C-F stretching, 1074.12cm^{-1} for sulfoxide group of S=O stretching and peaks of polymer were appeared at 3403.33cm^{-1} for hydroxyl group of O-H stretching, 1716.28cm^{-1} for C=O stretching respectively. The drug and polymer sodium alginate FTIR spectra showed characteristic peaks of drug at 1549.61cm^{-1} for aromatic C=C stretching, 1380.32for methyl group of C-H bending, 1161.77cm^{-1} for C-F stretching and polymer peaks were appeared at3407.42 for O-H stretching and 1637.00cm^{-1} for C=O stretching of carboxyl group respectively. The final optimized formulation of drug with polymers Carbopol and sodium alginate FTIR spectra showed characteristic peaks of drug at 1560.03, 1542.63, 1508.44 and 1430.68 cm^{-1} for aromatic C=C stretching, 1380.43cm^{-1} for methyl group of C-H stretching,1159.88cm^{-1} for C-F stretching, 1079.85cm^{-1} for sulfoxide group of S=O stretching; and Carbopol peaks appeared at 1718.15cm^{-1} for C=O stretching; and sodium alginate peaks were appeared at 1637.03 and 1654.15cm^{-1} for C=O stretching; and the peaks at 3412.05cm^{-1} is responsible for hydroxyl group O-H stretch of both polymers Carbopol and sodium alginate. These results were indicates there was no drug polymer interaction after processing of the drug into formulation. The results were shown in figure 1(a) to 1(d).

Solubility & Physical evaluation study:

The solubility study was conducted in citrate buffer pH 6.6, because the pH value of oral cavity is the same. Solubility of rosuvastatin calcium in the citrate buffer, pH 6.6 was found to be 4.5 mg/ml respectively. The values of weight variation and friability were found to be within the limits of conventional oral tablets as stated in the Indian pharmacopoeia (I.P, 1996). No tablet was disintegrated with in 4 hr except R1 and RA1 formulations containing drug: Carbopol and sodium CMC (R2-R6), drug: Carbopol and sodium alginate (RA2-RA6), disintegrated within 4 hrs because of low concentration of polymers. Thickness of the tablets varied from 2.12 mm to 2.52 mm and complied with the theoretical value (2.3mm). Hardness of the tablets was increased as the concentration of the Carbopol increased and the tablets containing Carbopol and sodium CMC shown hardness in the range of 4.1 to 4.3 kg/cm^2 and the hardness tablets containing Na alginate and Carbopol was, ranging from 3.9 to 4.9 kg/cm^2. The assay values are also within the limits 93.5% and 103.5% as shown in table 2.

Swelling studies of buccal tablets:

Appropriate swelling property of a buccal tablet is essential for proper muco-adhesion, uniform and prolonged release of drug(Peppas and Bury, 1985). The formulations containing the polymers Carbopol-934P and sodium CMC (R3) in 2:1 ratio showed swelling index of 198.49; Carbopol-934P and sodium CMC in 2:3 ratio (R6) showed high swelling index of 279.40-and the formulation containing the combination of Carbopol-934P and sodium alginate (RA2) in 1:2 ratio showed the swelling index i.e. 161.23. Optimized formulation containing Carbopol-934P and Sodium alginate (RA6) in 2:3 ratios has swelling index of 284.26. The formulation containing Carbopol and sodium alginate showed higher swelling index values than the combination of Carbopol and Na.CMC. (The swelling index is directly proportional to Carbopol and Na alginate content and inversely proportional to cellulose polymers such as Na.CMC). Due to high amount of water intake by Carbopol and Na alginate at faster rate which might have resulted in higher rate and extent of swelling. Formulations R1 and RA1 showed maximum swelling index due to lower concentration of polymer and lost integrity within 4 hrs. Swelling index values of all the formulations were given in table 13. Swelling behavior of buccal tablets of all formulations as a function of time was shown in table 3.

Measurement of Bio-adhesion Strength:

Bio adhesion is defined as the attachment of a synthetic or natural macro molecule to mucous and/or an epithelial surface (Longer and Robinson ,1986). Bio adhesion strength depends on the molecular weight, swelling behavior of the polymers and contact time with mucus (park et al., 1987). The bi-layered tablet containing high proportion of Carbopol and Sodium alginate showed good bio-adhesive strength for a period of 1min contact time. The maximum bio-adhesion strength (15.5+/- 0.27) was found for formulation RA6 (formulation containing Carbopol and Na alginate) and the formulation containing R1 (Carbopol and Na CMC) shown lower bio adhesion strength (3.2 +/- 0.04).

Bio adhesion characteristics were found to be affected by the nature as proportion of bio adhesive polymers used. As the concentration of Carbopol increased the bioadhesive strength was also increased, the reason for such findings might be ionization of Carbopol at salivary pH, which leads to the formation of secondary bio adhesion bonds with mucin and interpenetration of the polymer changes in the interfacial region, while other polymers undergo superficial bio adhesion. The increase in polymer concentration increased the bio adhesive strength of all the formulations. The order of bio adhesion was Carbopol and Na CMC > Carbopol and Na alginate. Buccal tablets formulated with Carbopol and Na alginate showed stronger mucoadhesion than Carbopol and Na CMC in combination of polymers. Very strong bio adhesion could damage the epithelial lining of the buccal mucosa. Optimized formulation (RA6) showed 15.5 $\pm$ 0.27g of bio adhesion strength. Bio adhesion strength values of all the formulations represented in table 4.

Residence time:

The residence time for selected formulations varied from 3 to 6 hrs. The optimized formulation (RA6) showed 6.5±0.35hrs. The difference in the resident time could be due to the combination of different ratios of polymers, which may affect the muco-adhesion. In fact with bi-layered tablets containing higher proportion of Carbopol, the muco-adhesive time was found to be increased. This is because of high muco-adhesive nature of

the Carbopol and interpenetration of polymeric chains into the mucous membrane. Residence time values were given in table 4. The maximum residence time (6.5±0.35hrs) was found for formulations RA6 (Carbopol and Na alginate containing formulations) and low residence time (3.20 ± 0.25) was found for formulations R1 (Carbopol and NA CMC). As the polymer concentration in formulation increased, residence time increased. The results are shown in table 4.

Surface pH of buccal tablets:

The surface of buccal tablets is determined in order to investigate the possibility of any side effects *in-vivo*. In an acidic or alkaline pH which may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. Surface pH of the optimized formulation RA6was found to be 6.33 ± 0.037. The pH is near to the neutral, so the formulation does not cause any irritation on the mucosa. Surface pH values for all the formulations shown in table 4.

***In-vitro* drug release of buccal tablets:**

An ideal controlled release system should be able to release the drug immediately to attain the therapeutic level at faster rate and maintain this drug level for a prolonged period of time (lopez et al., 1998). *In-vitro* drug release studies revealed that the release of rosuvastatin calcium from different formulations varied according to the type and ratios of the matrix forming polymers as shown in the graphs. The *in-vitro* dissolution was carried out in citrate buffer pH 6.6 *in-vitro* dissolution studies clearly indicating that the formulation containing Carbopol (grade: CP934P) : Na alginate showed higher drug release as compared to other formulations containing Carbopol (grade:CP934P) :Na CMC. The drug release profile of formulations R1-R3, R4-R6, and RA1- RA3, RA4-RA6 has been well depicted in figure 2 respectively. The cumulative percentage drug release from formulations for R1-R6 and for RA1-RA6 was found to be 80 $\pm$10 %. The maximum drug release was found in formulation R1 as 101.3$\pm$0.315 and RA6 as 96.1±0.355%.

Burst release was shown in formulation containing lowest polymer concentration. (R1, RA1) the *in-vitro* drug release studies revealed that the release of rosuvastatin calcium from different formulations varies with characteristics and composition of matrix forming polymer. Carbopol is more hydrophilic it swells rapidly. Compared to Na alginate and Na CMC, Na alginate greater swelling properties then Na CMC, hence drug release from CP : Na alginate is greater as compared to CP : Na CMC formulations. Drug release rate was increased with increasing amount of hydrophilic polymer. Another explanation includes, high water up take which leads to considerable swelling of polymer and causes drug to diffuse out from polymer matrix. More over the hydrophilic polymers would leach out and hence create more pores and channels for drug diffuse out from the device.

RA6 was found to be best formulation on basis of *in-vitro* drug release mechanism, optimum swelling index and good bio-adhesive strength. The drug release from optimized formulation RA6 was found to be 96.1±0.35% at 6h. Hence RA6 is selected for further studies like *in-vitro* drug permeation studies.

Formulation RA6 selected for ex vivo permeation studies depending on its maximum drug release pattern of all the formulations were also subjected to different kinetic models, such as zero order, first order, higuchi matrix, Peppa's models to predict the mechanism of drug release. The obtained results have been shown in table 5 .the values of n were estimated from Peppa's model and these values in between 0.5 to 1.0, indicated that release of rosuvastatin calcium from prepared buccal tablets is by non-fickian diffusion and erosion mechanism. A water soluble drug incorporated in a matrix is mainly released by diffusion, while for low water soluble drug the self erosion of the matrix will be the principal mechanism. Rosuvastatin calcium is low water soluble drug, hence the drug release of drug is mainly depends on the self erosion of matrix. Observation of all the r^2 values indicated that the highest r^2 (0.995) value was found for zero order release. The result has been tabulated in table 5, 6 and figure 2,3.

Release kinetics and mechanism:

To know the release mechanism and kinetics of rosuvastatin calcium optimized formulations (RA6) were attempted to fit into mathematical models and n, r^2 values for zero order, first order, Higuchi and peppas models were represented in table 6. The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation (peppas et al., 1985) shown as

$$Mt/M\infty = kt^n$$

Where, $Mt/M\infty$ is fraction of drug release at time't', k represents a constant, and n is the diffusion exponent, which characterizes the type of release mechanism during the dissolution process. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n=0.5; for zero order release (case II transport), n=1; and for super case II transport, n>1 (agarval et al., 1999) Observation of all the r^2 values indicated that the highest r^2 (0.995) value was found for zero order release.

Ex vivo permeation of buccal tablets:

Based on the *in-vitro* drug release studies, RA6 was selected for the ex vivo permeation study. The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition, therefore porcine. Buccal mucosa was selected for drug permeation studies. The ex vivo buccal permeation study was carried out by using porcine buccal mucosa, the formulation RA6 (CP: Na alginate) showed drug diffusion up to 6h. The studies which were carried out by using porcine buccal mucosa showed drug diffusion of 86.1% and these were mentioned in table 7.

***In-vitro* and *ex vivo* correlation:**

The *ex-vivo* study was carried out by using porcine buccal mucosa revealed that the consistence *in-vitro* release pattern of the formulation RA6 was reproducible even biological environment (B.De Spiegeleer et al., 2001). At the end of the 6th hour the *in-vitro* and *ex-vivo* drug release showed 96.1%and 86.1% respectively and values are mentioned in table 8. The release pattern has followed the predicted zero-order kinetics in biological systems. The results were shown in table 8 and figure 4.

Stability of buccal tablets in human saliva:

The stability study was conducted only for optimized formulation (RA6). There was no change in the color and integrity of the tablets. The data obtained from the study are presented in table 9. From the stability results it was known that formulation RA6 has stability in human saliva. Physical properties of the rosuvastatin calcium tablets such as diameter slightly changed owing to swelling of the system in human saliva. Buccal tablets maintained their integrity in the human saliva throughout the study, conforming the sufficient strength of the system.

Conclusion:

It was concluded that the *in-vitro* drug release, bio adhesion strength, ex vivo residence time of the optimized formulation is suitable for buccal delivery. The release pattern followed non fickian diffusion with zero order release. FTIR studies concluded that there is no interaction between drug and excipients. Carbopol. The buccal bilayered tablets showed a mucoadhesion time more than 6hr. similarly *in-vitro* permeation studies showed 96.1% drug release. It can be concluded that formulation RA6 could be used to release the drug unidirectional in buccal mucosa without the risk of mucosal irritation.

Table 1: Formulation table of Rosuvastatin calcium buccal tablets

Formulation code	Thickness	Weight Variation	Friability	Hardness	% Drug Content
R1	2.30±0.16	125.3± 1.17	0.39	4.1± 0.29	101.5
R2	2.40±0.24	126.6± 1.24	0.17	4.1± 0.14	94.3
R3	2.35±0.17	125.1± 0.81	0.28	4.2± 0.48	95.2
R4	2.30±0.17	126.1± 2.16	0.23	3.9± 0.22	93.5
R5	2.39±0.21	126.1± 2.16	0.25	4.1± 0.20	102.5
R6	2.35±0.18	126.3± 1.24	0.33	4.1± 0.17	101.5
RA1	2.10±0.16	124.5± 1.17	0.41	4.1± 0.11	99.5
RA2	2.50±0.24	123.6± 1.24	0.47	4.1± 0.01	96.3
RA3	2.35±0.17	125.3± 0.81	0.38	4.1± 0.13	95.2
RA4	2.40±0.17	124.1± 2.16	0.37	4.1± 0.14	100.5
RA5	2.41±0.21	125.3± 1.24	0.35	4.1± 0.02	103.5
RA6	2.25±0.18	125.3± 1.17	0.39	4.1± 0.01	99.5

Table 2: Physical/Chemical properties of the buccal tablet

S. No	List of Ingredients	Formulation Code											
		R1	R2	R3	R4	R5	R6	RA1	RA2	RA3	RA4	RA5	RA6
1.	Rosuvastatin calcium	10	10	10	10	10	10	10	10	10	10	10	10
2.	Carbopol	10	10	10	20	20	20	10	10	10	20	20	20
3.	Na.CMC	10	20	30	10	20	30	-	-	-	-	-	-
4.	Na Alginate	-	-	-	-	-	-	10	20	30	10	20	30
5.	Manitol	35	20	15	25	15	5	35	20	15	25	15	5
6.	Microcrystalline cellulose	30	30	30	30	30	30	30	30	30	30	30	30
7.	Talc	1	1	1	1	1	1	1	1	1	1	1	1
8.	Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3
9.	Saccharin	1	1	1	1	1	1	1	1	1	1	1	1
10.	Ethyl cellulose	25	25	25	25	25	25	25	25	25	25	25	25

Table 3: Swelling index profile of the Rosuvastatin calcium tablet

Formulation Code	% Swelling index * Time (hours						
	0.5	**1**	**2**	**3**	**4**	**5**	**6**
R1	Structure deformed						
R2	49.28±O.O9	82.48±1.47	179 .48±1.21	190.37±2.41	209.37±2.41	218.48±1.47	227.64±2.01
R3	45.49±0.09	92.64±1.23	189.49±1.48	20 1.27± 1.41	231.64± 1.34	239.64±1.23	261.48± 1.66
R4	38.42±0.95	74.84±0.52	147.43±1.66	153.64±1.34	168.27±1.41	183.84±0.52	198.49±1.21
R5	41.42±0.99	84.14±1.48	167.49±1.66	175.43±1.41	182.43±1.41	204.14±1.48	218.68±1.98
R6	52.63±0.88	88.96±2.11	182.46±3.32	216.34±3.04	236.11±3.45	248.96±2.11	279.40±3.14
RA1	Structure deformed						
RA2	32.14±0.58	61.76±.87	131.64±0.88	142.37±1.02	152.37± 1.02	156.76±.87	161.23±1.18
RA3	50.24±1.16	83.48±1.21	185.67±0.78	20 1.29± 1.06	218.37±1.23	223 .48±	1248.47±1.l4
RA4	32.67±1.24	81.24±1.46	161.75±3.14	192.67±2.25	186.34±3.04	191.24± 1.46	214.37±1.33
RA5	l44.38± 1.41	84.56±1.72	171.24±3.14	206.11±3.45	214.67±2.25	224.56± 1.72	242.67±2.55
RA6	61.04±O.08	1 04.46± 1.25	221.48±O.098	245.72±0.95	254.49±.68	271.46±1.25	284.26± 1.48

* Indicates mean ± S.D Values

Table 4: Measurement of bio-adhesion strength (gm) and resident time (Hr) of the Rosuvastatin calcium tablet

S. No	Formulation code	Bio Adhesion strength (gm)	Resident time (hr)	Surface pH
1.	R1	3.2	3.2	6.10±0.30
2.	R2	6.1	3.34	6.30±0.45
3.	R3	9.6	4.6	6.10±0.30
4.	R4	8.1	4.8	6.30±0.30
5.	R5	11.1	5.3	6.01±0.73
6.	R6	14.3	5.9	6.01±0.37
7.	RA1	5.02	3.5	6.10±0.30
8.	RA2	8.4	3.9	6.30±0.45
9.	RA3	12.3	4.3	6.30±0.30
10.	RA4	8.1	4.9	6.10±0.30
11.	RA5	11.9	5.9	6.35±0.73
12.	RA6	15.5	6.5	6.33±0.37

Table 5: In-Vitro Dissolution of Rosuvastatin calcium bucco-adhesive tablet using Carbopol and Sodium CMC in different ratios

Time (hr)	Percentage of *In-vitro* Drug release (n=3±SD)					
	R1	**R2**	**R3**	**R4**	**R5**	**R6**
0	0	0	0	0	0	0
0.5	15.5±0.157	8.5±0.337	10.75 ± 0.235	10.25 ±0.076	10.75±0.031	12.75± 0.362
1	35.82 ± 0.215	15.33 ±0.257	14.10 ±0.303	14.10 ±0.061	14.60 ±0.021	17.37± 0.338
1.5	49.56± 0.322	20.98 ±0.148	20.74 ±0.127	18.49 ±0.318	21.25 ±0.031	24.05± 0.065
2	63.50±0.346	27.44± 0.353	26.45 ±0.096	23.42 ±0.072	29.96± 0.056	31.53± 0.095
3	81.2±0.380	33.21 ±0.221	38.71± 0.150	31.90± 0.081	34.75± 0.075	41.09± 0.072
4	89.5±0.357	43.04 ±0.145	54.84± 0.158	44.46 ±0.015	42.09± 0.026	56.75± 0.355
5	96.10±0.45	65.46± 0.250	76.88 ±0.211	60.15 ±0.020	61.25± 0.035	75.30± 0.071
6	101.3±0.315	82.1 ±0.150	89.85± 0.135	81.49 ±0.253	84.10 ±0.269	94.54± 0.353

Table 6: *In-Vitro* Dissolution of Rosuvastatin calcium bucco-adhesive tablet using Carbopol and Sodium alginate in different ratios

Time (hr)	Percentage of *In-vitro* Drug release (n=3±SD)					
	RA1	**RA2**	**RA3**	**RA4**	**RA5**	**RA6**
0	0	0	0	0	0	0
0.5	14.5±0.157	7.0±0.337	8.25 ± 0.235	5.25 ±0.051	7.25±0.078	7.75± 0.386
1	31.69 ± 0.215	15.82 ±0.257	14.83 ±0.303	15.30 ±0.045	12.50 ±0.045	13.07± 0.336
1.5	45.10± 0.322	25.97 ±0.148	27.48 ±0.127	27.45 ±0.369	22.65 ±0.012	24.20± 0.078
2	56.71±0.346	34.98± 0.353	35.5 ±0.096	34.72 ±0.078	32.67± 0.011	35.44 ± 0.056
3	73.10±0.380	43.83 ±0.221	49.10± 0.150	43.07± 0.085	42.24± 0.045	45.04± 0.073
4	85.30±0.357	57.76 ±0.145	59.08± 0.158	53.99 ±0.026	54.66± 0.014	61.24± 0.345
5	91.20±0.45	70.82± 0.250	80.91 ±0.211	69.02 ±0.078	72.19± 0.015	77.84± 0.096
6	99.5±0.31	86.15 ±0.150	91.23± 0.135	82.44 ±0.245	85.4 ±0.262	96.1± 0.362

Table 7: *In-vitro* release kinetics and mechanism of drug release for the optimized batch

Formulation code	Mathematical model (Kinetics)				
	Zero Order	First order	Higuchi	Peppas model	
	r^2	r^2	r^2	n	r^2
RA6	0.995	0.984	0.971	0.82	0.991

Table 8: *In-vitro* and *Ex-vivo* cumulative percentage drug release of the optimized formulation

Time (hr)	*In-vitro* cumulative percentage drug release (n=3±SD)	*Ex-vivo* cumulative percentage drug release (n=3±SD)
0	0	0
0.5	7.75± 0.386	5.1 ± 0.219
1	13.07± 0.336	11.6 ± 0.056
1.5	24.20± 0.078	21.02± 0.265
2	35.44 ± 0.056	31.62± 0.148
3	45.04± 0.073	42.72± 0.066
4	61.24± 0.345	57.77± 0.021
5	77.84± 0.096	70.71± 0.124
6	96.1± 0.362	86.11± 0.021

Table 9: Stability of buccal tablets in human saliva

Sampling interval(h)	Change in color	Change in diameter	Change in integrity
0	NC*	NC	NC
2	NC	1.35	NC
4	NC	2	NC
6	NC	NC	NC

NC*- No change

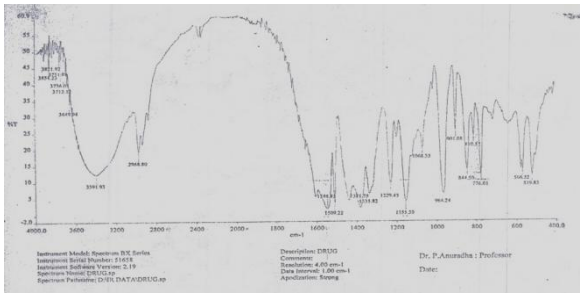

Figure 1(a): FTIR Spectra of Pure drug Rosuvastatin Calcium

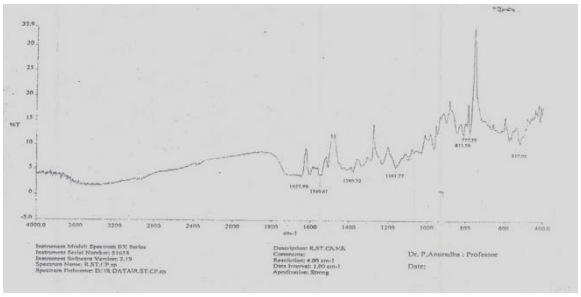

Figure 1(b): FTIR spectra of Drug Rosuvastatin Calcium + sodium Alginate

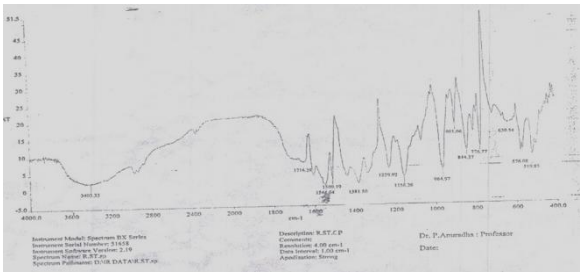

Figure 1(c): FTIR spectra of Drug Rosuvastatin calcium + Carbopol

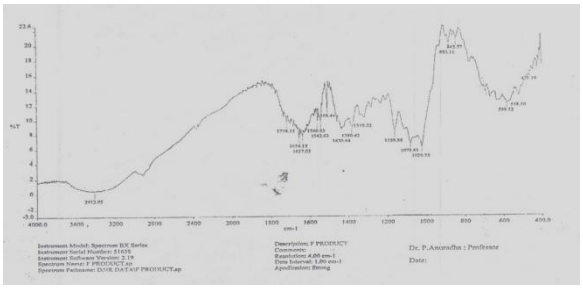

Figure 1 (d): FTIR spectra of drug Rosuvastatin calcium + Carbopol + Sodium Alginate

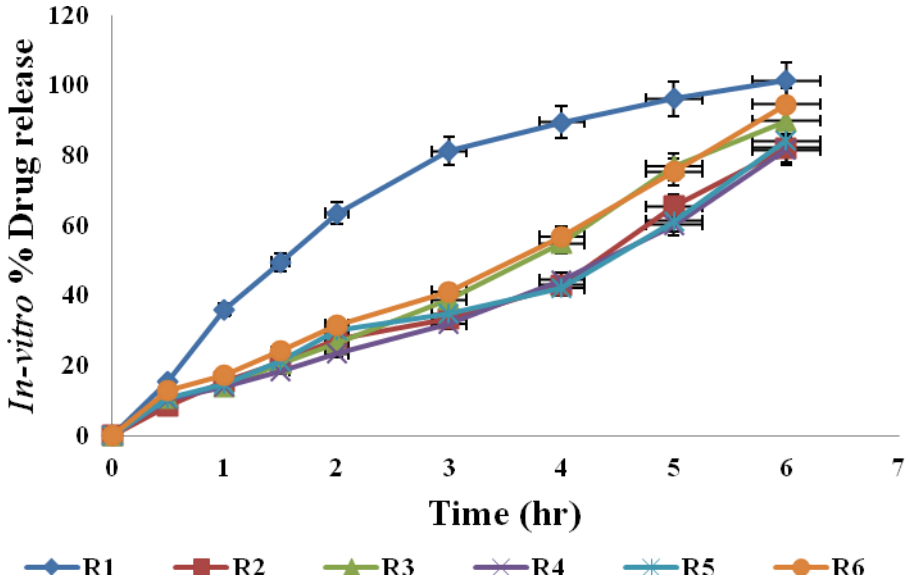

Figure 2: *In-Vitro* Dissolution of Rosuvastatin calcium bucco-adhesive tablet using Carbopol and Sodium CMC in different ratios

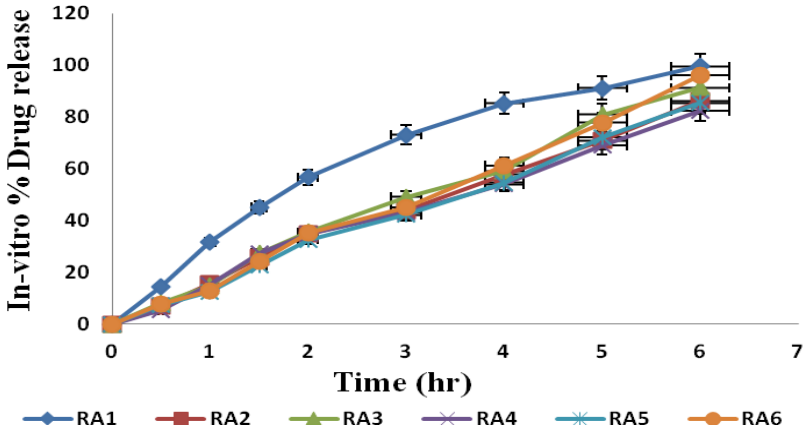

Figure 3: *In-Vitro* Dissolution of Rosuvastatin calcium bucco-adhesive tablet using Carbopol and Sodium Alginate in different ratios

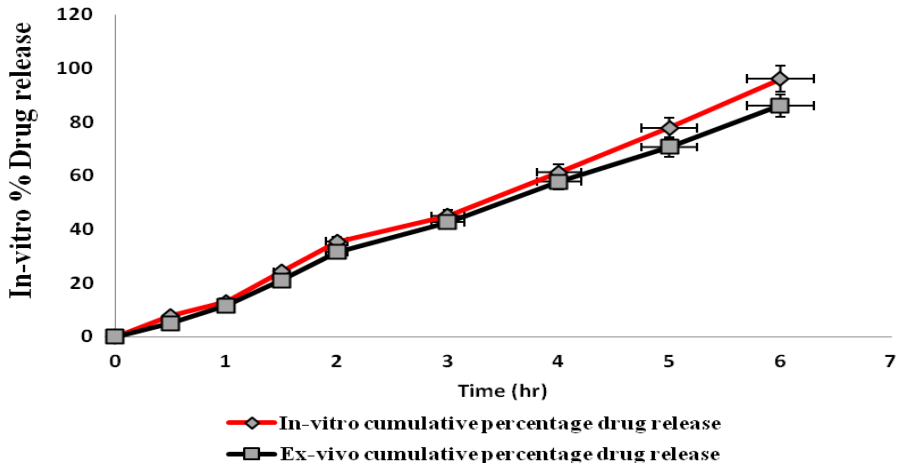

Figure 4: *In-vitro* and *Ex-vivo* cumulative percentage drug release of the optimized formulation

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