IJPSR (2012), Vol. 3, Issue 08 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 20 April, 2012; received in revised form 09 May, 2012; accepted 27 July, 2012

FORMULATION AND *IN-VITRO* EVALUATION OF MUCOADHESIVE BILAYERED BUCCAL TABLETS OF ROSUVASTATIN CALCIUM

Amish V. Panchal*, Markand Mehta, Viral H. Shah, Umesh Upadhyay

Department of Pharmaceutics, Sigma institute of Pharmacy, Baroda, Gujarat, India

Keywords:
Mucoadhesion,
Bilayered buccal tablet,
Unidirectional buccal drug delivery, natural gums,
Rosuvastatin calcium

Correspondence to Author:

Amish V. Panchal

Department of Pharmaceutics, Sigma institute of Pharmacy, Baroda, Gujarat, India

E-mail: panchal.amish1989@gmail.com

ABSTRACT

The purpose of this research work was to establish mucoadhesive buccal device of Rosuvastatin Calcium(RC) in the form of bilayered tablet. The tablets were prepared using natural gums like Xanthan gum, Tamarid gum, Gellan gum and Chitosan as bioadhesive polymers to impart mucoadhesion as well as permeation enhancement property to the formulation. Ethyl cellulose & magnesium stearate were added to act as an impermeable backing layer which gives unidirectional buccal drug delivery. Buccal devices were evaluated for different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, ex vivo mucoadhesive time, in vitro drug release, and in vitro drug permeation. The results of study revealed that the formulation containing a combination of polymers like chitosan and natural gums shows suitatble drug permeation rate as well as mucoadhesive strength. So, it can be concluded that buccal mucoadhesive tablet is potential way of delivering Rosuvastatin in order to prevent its extensive first pass metabolism and to improve its bioavailibility.

INTRODUCTION: The interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs impaired by the narrow absorption window in the gastrointestinal tract. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. This route has been used successfully for the systemic delivery of number of drug candidates [1-5].

Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route [6-7]. Moreover, buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity.

It as an alternative route to administer drugs to patients who are unable to be receive dose orally. As well as bilayered buccal mucoadhesive approach cop up other drawback like loss of drug resulting from wash out with saliva to the GIT by applying the impermeable bilayer. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets [8-9], adhesive gels [10-11] and adhesive patches.

Here, permeation problem was overcome by using natural gum as penetration enhancers. There is a possibility for mucosal (local effect) and transmucosal (systemic effect) drug administration via buccal route. As well as in buccal mucosa maxillary artery blood flow is faster and (2.4 ml/min/cm^2) than that in the sublingual, gingival and palatal regions, thus facilities passive diffusion of the drug molecules across the

mucosa. The thickness of the buccal mucosa is 500-800 µm and rough texture, hence suitable for retentive delivery systems [12].

Rosuvastatin calcium (RC), a HMG CO-A Reductase enzyme inhibitor, is widely used in the treatment of Hyper-lipoproteinemia. Hyperlipidaemia is the condition indicating increase in lipid level. Both these conditions may cause narrowing and hardening of the arteries, i.e. atherosclerosis (coronary artery disease-CAD). Thus, hyperlipoproteinemias is one of the leading causes of ischemic heart disease, myocardial infarction and cerebral vascular accidents. Thus there is emergent need of the treatment of hyper-lipidaemia [13].

The first line of the treatment in CAD is antihyperlipidemic drugs. There are several lipid lowering drugs, i.e. HMG Co-A reductase inhibitors, Fibric acids, Bile acid binding resins. In these categories, HMG Co-A reductase inhibitors (statins) are mostly suggested in hyper-lipidaemia. Rosuvastatin is one of the candidates of statin class.

Although, it is well absorbed in the gastrointestinal tract, its bioavailability is low (20%), as a result of extensive first-pass metabolism. In the present study, the objective was to prepare mucoadhesive buccal device of RC, which ensure satisfactory drug release in a unidirectional fashion to the mucosa, to avoid loss of drug resulting from wash out with saliva [14-18].

MATERIALS AND METHODS:

Materials: Rosuvastatin calcium was obtained as a gratis sample from Alembic Research Center. (Baroda, India). Polyvinylpyrrolidone K-30 (PVP-K30), and D-mannitol was purchased from S. D. Fine Chemicals Ltd., Mumbai, India. HPMC K4M, Xanthan gum, Tamarid gum,Gellan gum and Chitason were purchased from loba chem. Ltd., Baroda, India. All other reagents and chemicals used were of analytical reagent grade.

Compatibility studies: The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra-red spectra of pure drug and physical mixture of drug and excipients were recorded.

Preparation of Mucoadhesive Bilayered Buccal Tablet: The tablets were prepared by wet granulation method. Medicated tablets containing 5 mg drug (RC) were compressed using flat face punch, 9 mm in diameter as per formula given in formulation **Table 1**. Before compression, the powder were screened through a 60 µm sieve and then thoroughly blended then granulation was done by using IPA as granulating fluid and granules were dried. Aluminum hydroxide was incorporated to avoid the stability problem of drug. To prepare bilayer tablets, the non-medicated layer was first compressed, then the medicated layer was filled into the die cavity and both were compressed together with compression force of 0.5 ton [19-22].

TABLE 1: FORMULATION TABLE

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Rosuvastatin	5	5	5	5	5	5	5	5	5	5	5	5	5
PVP K30	30	30	30	30	30	30	30	30	30	30	30	30	30
Mannitol	45	30	15	45	30	15	45	30	15	45	30	15	15
Tamarind Gum	20	35	50	---	---	---	---	---	---	---	---	---	---
Xanthan Gum	---	---	---	20	35	50	---	---	---	---	---	---	---
Gellan Gum	---	---	---	---	---	---	20	35	50	---	---	---	---
Chitosan	---	---	---	---	---	---	---	---	---	20	35	50	30
HPMC K4M	---	---	---	---	---	---	---	---	---	---	---	---	20
Aluminum Hydroxide (stabilizer)	5	5	5	5	5	5	5	5	5	5	5	5	5
BACKING LAYER													
Ethyl Cellulose	40	40	40	40	40	40	40	40	40	40	40	40	40
Mag. stearate	10	10	10	10	10	10	10	10	10	10	10	10	10

All quantities are in mg.

***In-vitro* Mucoadhesive strength determination of polymers:** Mucoadhesive strength of polymer is one of the most important physical parameter for the buccoadhesive tablet. Mucoadhesive strength was determined by following two methods,

1. **Time-based**: In this method time require detaching the tablet from mucosa was measured. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hours after collection. The collected membrane was treated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8.

   In this method the porcine buccal mucosa was adhered to the paddle of the dissolution apparatus with cyanoacrylate adhesive. Then at one side of each tablet of plain polymer was wetted with 50µl simulated saliva and pressed over porcine buccal mucosa for 30 secs. Then paddle was immersed in a basket of the dissolution apparatus containing 500 ml of 6.8 pH phosphate buffer, at 37^{o}C. The paddle was rotated at 50 rpm. Time required to detach the tablet from the mucosa was measured [22-25].

2. **Force-based**: In this method the mucoadhesive strength of the polymer study was determined by measuring the force required to detach the tablet from the mucosal tissue. Here also primary treatment of porcine buccal mucosa was carried out as above mention procedure. Modified physical balance was used for this procedure. At one side of balance, a piece of buccal mucosa was tied to the Teflon tap coated anvil by cyanoacrylate adhesive. The tablet was adhered on another anvil. Then, both the anvils were made in contact with 30 secs of contact time. In another pan of the balance consequently addition of the weight was done until the tablet dose not detach from the mucosa. Force require to detach was measured [25-26].

Standardization of Natural Gums: Standardization of natural gums was done by following parameters.

Loss on drying: 1 gm natural gum powder was weighed and placed in weighing bottle. Then bottle was placed in drying chamber for 1 h. Then powder was reweighed (As per USP). Loss on drying was calculated by following formula.

%LOD = (W1-W2)/W1 * 100

W1 = weight of powder before drying.

W2 = weight of powder after drying.

Viscosity: 1% solution of gum was prepared and viscosity was measured by Brookfield viscometer.

Particle size: Particle size was measured by sieving technique.

pH: 1% solution of gum was prepared, pH was measured by pH meter.

Bacterial load determination: 1% solution of gum was prepared in distilled water, than incubated in agar medium for 24hrs at 37±0.5^{o}C. Colony was counted in colony counter.

Evaluation test for Buccoadhesive Tablet: Buccoadhesive tablets were evaluated for for various tests as Weight variation, Hardness, Friability, Thickness and content uniformity.

Surface pH: It is determined in order to investigate the possibility of any side effects *in vivo*due to pH difference between formulation and mucosal tissue. A combined glass electrode was used for his purpose. The tablet was allowed to swell by keeping it in contact with 5 ml of pH 6.8 phosphate buffer for 1 h [27-29]. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min.

***Ex-Vivo* Mucoadhesive Strength of Formulation:** Mucoadhesive strength of the formulation was determined by two methods.

1. Time-based
2. Force-based

Both methods were performed as explained above in mucoadhesive strength determination of polymer.

Swelling Study: Six buccal tablets were individually weighed (W_1) and placed separately in Petri dishes with 5 ml of phosphate buffer of pH 6.8. At the time interval of 1, 2, 3, 4, and 6 h, tablets were removed from the petri dish and excess water was removed carefully using the filter paper. Then the swollen tablet were reweighed (W_2) and the percentage hydration was calculated using the following formula [29-32].

% Hydration= $[(W_2-W_1)/W_1] \times 100$

***In-vitro* Release Study:** The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the bilayered and multilayered tablets. The dissolution medium consists of 500 ml of phosphate buffer pH 6.8. The release study was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Aliquots (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The aliquots were filtered through 0.2-µm What-man filter paper and analyzed after appropriate dilution by UV spectrophotometer at 244nm wavelength [32-35].

***In vitro* Drug Permeation:** The *in vitro* buccal drug permeation study of tablet through the porcine buccal mucosa was performed using Keshary-Chien type glass diffusion cell at 37°C±0.2°C. Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments were clamped together. The receptor compartment (20-ml capacity) was filled with phosphate buffer pH 6.8., and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. A 1-ml aliquot was withdrawn at predetermined time intervals and analyzed for drug content using a UV-spectrophotometer at 244nm wavelength [17, 36, 37].

Calculation of J_{flux} for Rosuvastatin Calcium: The targeted J_{flux} (permeability constant) of drug was calculated by following formula.

$$J_{flux} = \frac{C_{SS}\ CL_T\ Bw}{A}$$

Css = Steady state concentration.

CL_T = Clearance from systemic circulation.

BW = Body weight.

A = Area.

RESULTS AND DISCUSSION:

Compatibility studies: The incompatibility between the drug and excipients were studied by FTIR spectroscopy. The IR spectra of Rosuvastatin calcium is characterized by the absorption frequency of two stretching band at 3394.72 cm^{-1} and that of carbonyl group at 1604.77 cm^{-1}. The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation.

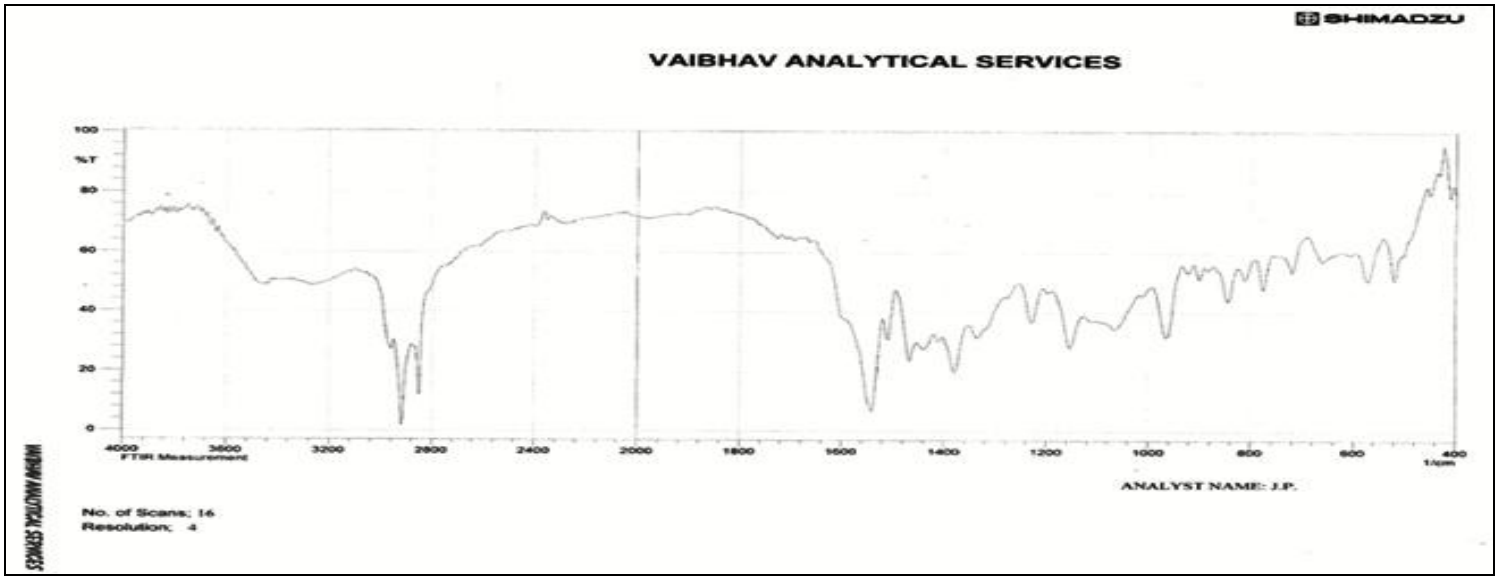

FIGURE 1: FTIR OF PHYSICAL MIXTURE OF OPTIMIZED BATCH

***In-vitro* mucoadhesive strength of polymers:** Mucoadhesive strength of the individual natural polymers was measured by time based and force based study. Results are mentioned in TABLE-2. Results revealed that chitosan has low mucoadhesive strength of 6.8 ± 0.8 gm.

Standardization of natural gums: Results of standardization of natural gums are shown in TABLE-2. Standardization of gums was done to avoid variance due to different Biological source. All gums show the pH ranging from 7 to 7.2 and having sufficient mucoadhesive strength.

Evaluation of buccoadhesive tablet: Results of various tests as weight variation, hardness, friability, thickness, and content uniformity are mentioned in **Table 3**.

Surface pH: Surface pH of the formulations was ranging between 6.2 to 7.6, which is well within the limit of acceptable salivary pH range. Hence, it can be interpreted that none of formulation would any local irritation to buccal mucosal surface.

***Ex-vivo* mucoadhesive strength:** The *ex vivo* mucoadhesive strength study was performed and the results are shown in Table 3. Study was performed on the modified physical balance and force required to detach the tablet from the buccal mucosa was measured in gm. Results revealed that the mucoadhesive characteristic of formulation was depends on mucoadhesive polymer and its concentration. Gellan gum shows highest mucoadhesive strength of 8.9 ± 0.6 g. Where xanthan gum and tamarind gum shows comparable mucoadhesive strength. Formulation F1 to F9 shows mucoadhesive strength ranging from 7.9 to 8.9 g. Formulation F10 toF12 shows mucoadhesive strength ranging from 4.0 to 4.5 g, which contain chitosan as mucoadhesive polymer having low bioadhesive characteristic, where formulation F13 shows 8.6 ± 0.5 g which containing chitosan and HPMC K4M as mucoadhesive polymer. HPMC was incorporated to impart bioadhesion strength. A result shows that HPMC serve the purpose comparatively to the formulation F10 to F12 having low mucoadhesive strength. Results revealed that formulation F13 having sufficient mucoadhesive strength.

TABLE 2: STANDARDIZATION OF NATURAL GUMS

Parameters	Xanthan gum	Tamarind gum	Gellan gum
LOD	12%	9.5%	8%
Total ash	9.7%	3%	11.5%
Viscosity	900 cps	850 cps	1000 cps
Particle size	200#	200-300#	80-100#
pH	7	7	7.2
Bacteriological data	5 CFU/10mg	45 CFU/10mg	3 CFU/10mg
Mucoadhesive strength	15.25 ± 0.42 hrs	15.15 ± 0.25	16.50 ± 0.25

TABLE-3 EVALUATION OF BILAYERED TABLET

Formulation	Mean hardness (kg/cm^2)	Mean Thickness (mm)	Weight variation (mg)	Friability (%)	Surface pH	Swelling index (after 5 hrs)	Mucoadhesive strength (gm)	% Drug Content uniformity
F1	4.3 ± 0.3	1.6 ± 0.1	150 ± 2	0.22 ± 0.05	6.7 ± 0.5	21.61	8.7 ± 0.6	99.24
F2	3.3 ± 0.2	1.7 ± 0.1	152 ± 1	0.32 ± 0.05	6.3 ± 0.6	29.72	7.9 ± 0.3	98.68
F3	4.6 ± 0.7	1.6 ± 0.1	149 ± 1	0.35 ± 0.05	7.1 ± 0.5	32.63	8.2 ± 0.5	97.24
F4	4.0 ± 0.5	1.5 ± 0.1	148 ± 1	0.67 ± 0.1	7.0 ± 0.4	22.37	7.9 ± 0.3	99.41
F5	4.6 ± 0.5	1.4 ± 0.1	148 ± 1	0.72 ± 0.1	6.9 ± 0.4	27.48	7.9 ± 0.3	96.28
F6	3.6 ± 0.2	1.5 ± 0.1	150 ± 2	0.81 ± 0.1	6.4 ± 0.4	33.61	8.4 ± 0.3	97.24
F7	3.6 ± 0.3	1.5 ± 0.1	152 ± 1	0.72 ± 0.1	6.6 ± 0.4	15.17	8.4 ±0.3	98.29
F8	4.0 ± 0.5	1.7 ± 0.1	152 ± 1	0.52 ± 0.1	6.7 ± 0.4	18.19	8.6 ± 0.3	96.88
F9	4.0 ± 0.4	1.6 ± 0.1	150 ± 2	0.50 ± 0.1	7.0 ± 0.4	24.29	8.9 ± 0.6	95.98
F10	3.3 ± 0.2	1.7 ± 0.1	151 ± 2	0.62 ± 0.1	7.2 ± 0.4	19.21	4.1 ± 0.3	98.61
F11	3.6 ± 0.5	1.7 ± 0.1	152 ± 1	0.71 ± 0.1	7.3 ± 0.4	21.47	4.2 ± 0.3	97.22
F12	3.6 ± 0.6	1.6 ± 0.1	149 ± 1	0.72 ± 0.1	7.1 ± 0.4	26.22	4.2 ± 0.3	99.15
F13	4.3 ± 0.5	1.6 ± 0.1	150 ± 1	0.42 ± 0.2	6.2 ± 0.5	35.22	8.6 ± 0.5	99.02

Swelling Study: The swelling studies were conducted for all formulations i.e. F1 to F13 and the results were shown in TABLE-3.The highest hydration (swelling) i.e. 35.22% was observed with the formulation F13. This may be due to quick hydration of polymers (chitosan and HPMC K4M).

In-vitro Release Study: Formulation F1 to F3 shows total drug release within 3 h containing tamarind gum. Formulation F4 to F6 were containing Xanthan gum requires 4 to 5 h for approx 99% drug release, where formulation F7 to F9 shows drug release within 3 to 4 h containing gellan gum. Results indicate that as concentration of gum was increase, drug release was retarded for longer period of time. Formulation F10 to F12 containing chitosan shows drug release just within 30 to 40 min. It may be due to disintegration property of chitosan, where formulation F13 shows 99.8% drug release within 1 h. In Formulation F13 release was little bit sustained due to incorporation of HPMC in comparison of formulation F9 to F12. Results revealed that released was well programmed by incorporation of HPMC for 1 h.

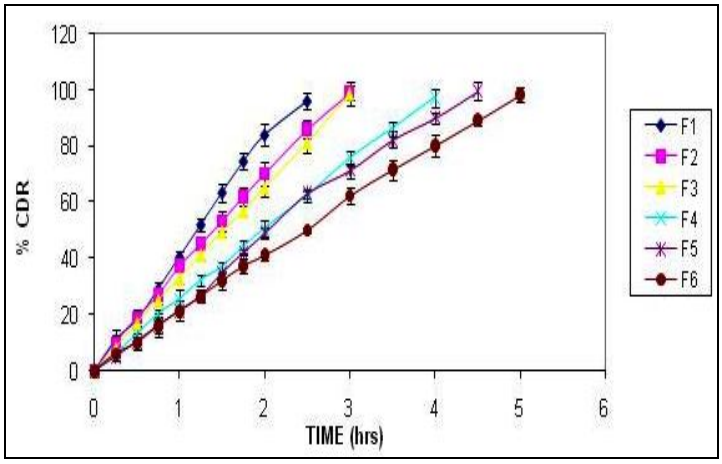

FIGURE 1(A): % DRUG RELEASE OF BATCH F1 TO F6

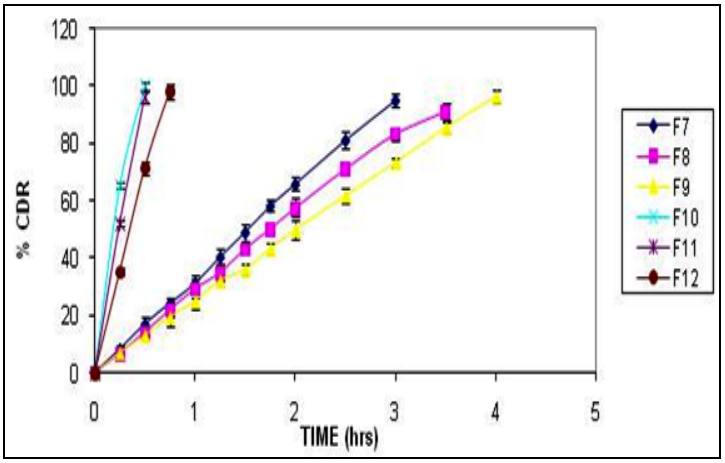

FIGURE 1(B): % DRUG RELEASE OF BATCH F7 to F12

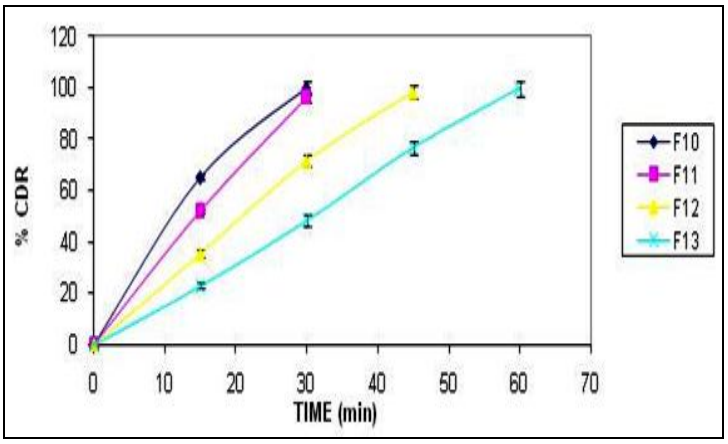

FIGURE 1(C): % DRUG RELEASE OF BATCH F10 TO F13

***In-vitro* Drug Permeation:** Formulation F1 to F9 shows permeation ranging from 15% to 34%, where formulation F10 to F12 shows permeation 70 ± 1.5% to 82 ± 2.1%. The optimization of the bilayered tablets (F13) was performed on the basis of *in vitro* drug release, *ex vivo* mucoadhesive strength and *in vitro* drug permeation. The optimized bilayered tablets (F13) subjected to in vitro permeation study, showed highest drug permeation 94.8% in 1 h.

Here, F13 batch shows 8.6±0.5 g mucoadhesive strength. As well as shows 99.8% drug release and having 94.8% drug permeation in 1 h. Here, chitosan serve both the purpose of mucoadhesive polymer as well as permeation enhancer. Results revealed that the optimized batch F13 shows good in vitro drug permeability achieved by natural permeation enhancer-chitosan.

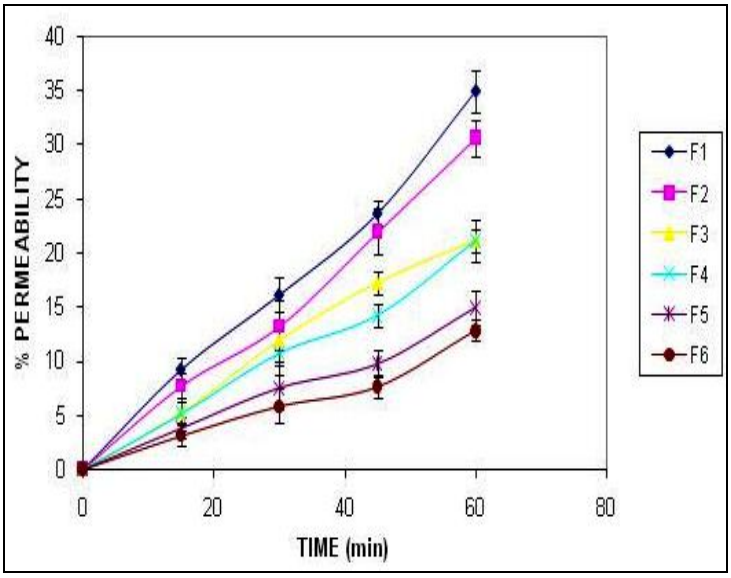

FIGURE 2(A): % PERMEABILITY OF BATCH F1 TO F6

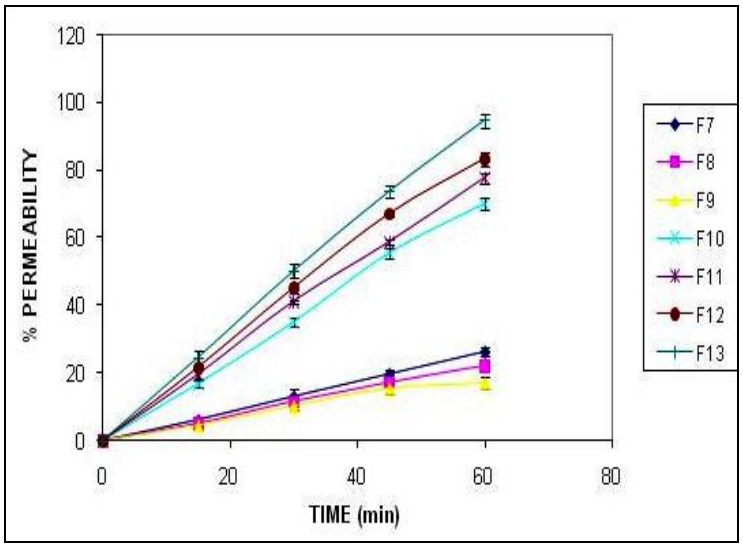

FIGURE 2(B): % PERMEABILITY OF BATCH F7 TO F13

F13 shows all the characteristics for the immediate release buccal tablet was optimized.

J_{flux} of Rosuvastatin Calcium: The calculated *J flux* of rosuvastatin Calcium was found to be 44.09µg/min/cm^2. Where calculated *J flux* of optimized formulation F13 was found to be 133.69µg/min/cm^2. From results it can be interpreted that optimized formulation having better permeability then the pure drug. So, it can be concluded that chitosan enhance the permeability of drug, which ultimately leads to enhancement of bioavailability of Rosuvastatin Calcium.

CONCLUSION: Results of the study reveal that the mucoadhesive buccal tablet of Rosuvastatin Calcium was prepared using chitosan and HPMC K4M providing well regulated release for 1 h. The formulation of Rosuvastatin Calcium containing chitosan and HPMC as a mucoadhesive polymers shows desired drug release, permeation and mucoadhesive strength. Study reveals that chitosan serve the purpose of the natural permeation enhancer. So, it may be concluded that buccal mucoadhesive tablet would prove to be a potential tool to bypass the extensive first pass metabolism and improve the bioavailability of Rosuvastatin Calcium.

ACKNOWLEDGEMENT: Authors wish to show their deep gratitude to Alembic Research Center, Baroda, India for providing the gratis sample of Rosuvastatin Calcium. Authors also wish to thank Vaibhav laboratory, Ahmadabad, for carryout the FTIR study of formulation.

REFERENCES:

1. Anders R, Merkle HP: Evaluation of laminated mucoadhesive patches for buccal drug delivery. International Journal of Pharmaceutics 1989; 49:231-40.
2. Chen WG, Hwang G: Adhesive and *in vitro* release characteristics of propranolol bioadhesive disc system. International Journal of Pharmaceutics 1992; 82:61-6.
3. Alur HH, Pather SI, Mitra AK: Transmucosal sustained-delivery of chlorpheniramine maleate in rabbits using a novel natural mucoadhesive gum as an excipient in buccal tablets. International Journal of Pharmaceutics 1999; 188:1-10.
4. Guo JH: Bioadhesive polymer buccal patches for buprenorphine-controlled delivery: formulation in vitro adhesion and release properties. Drug Dev Ind Pharm 1994; 20:2809-21.
5. Ahuja A, Dorga M, Agarwal SP: Development of buccal tablets of diltiazem hydrochloride. Indian Journal of Pharmaceutical Sciences 1995; 57:26-30.
6. Nagai T, Konishi R: Buccal/gingival drug delivery systems. Journal of Control Release 1987; 6:353-60.
7. Harris D, Robinson JR: Drug delivery via the mucous membranes of the oral cavity. Journal of Pharmaceutical Sciences 1992; 81:1-10.
8. Dortunc B, Ozer L, Uyanik N: Development and in vitro evaluation of a buccoadhesive pindolol tablet formulation. Drug Dev Ind Pharm 1998; 24:281-88.
9. Ishida M, Nambu N, Nagai T: Highly viscous gel ointment containing Carbopol for application to the oral mucosa. Chem Pharm Bull (Tokyo) 1983; 31:4561-64.
10. Bremecker KD, Strempel H, Klein G: Novel concept for a mucosal adhesive ointment. Journal of Pharmaceutical Sciences 1984; 73:548-52.
11. Bandyopadhyay AK, Yajaman S, Kuotsu K: Buccal bio-adhesive drug delivery- A promising option for orally less efficient drugs. Journal of Control Release 2006; 114:15-40.
12. Gupta A, Garg S, Khar RK: Measerement of bioadhesive strength of mucoadhesive buccal tablets: design of an in-vitro assembly. Indian Drugs1992; 30:152-55.
13. Velmurugan S, Vinushitha S, Deepika B: Formulation and *in vitro* evaluation of buccal tablet of Metoprolol Tartrate. International Journal of pharmacy and pharmaceutical sciences2011; 3(2):239-246.
14. Pandey S, Gupta A, Yadav JS: Formulation and *in vitro* evaluation of bilayered buccal tablet of Carvedilol. Indian Journal of Pharmaceutical Education and Research2010; 44(3)
15. Satyabrata B, Ellaiah P, Tiwari SP, Ds D: Formulation and *in vitro* evaluation of mucoadhesive buccal tablets of Timolol mleate.Internaitonal Journal of Pharmaceutical and Biomedical Research2010; 1(4):129-34.
16. Patel VM, Prajapati BG, Patel MM: Formulation, evaluation and comparison of bilayered & multilayered muco-adhesive buccal device of propranolol hydrochloride. AAPS pharmscitech2007;*8*(1)
17. Artursson P, Mohmand MI, Magnus KH: Chitosan and the mucosal delivery of biotechnology drugs. Drug Discovery Today: Technologies2005; 2(1):1-6.
18. Borgaonkar PA, Virsen TG, Najmuddin M: Formulation and *in vitro* evaluation of buccal tablet of Loratidine for effective treatment of allergy. International Journal of Research in Pharmacy and Chemistry2011; 1(3):551-59.
19. Hanes J, Wirtz D, Lai SK: Micro- and macrorheology of mucus. Advance drug delivery reviews2009; 61:86-100.

20. Hirlekar RS, Kadam VJ: Design of buccal drug delivery system for poorly soluble drug. Asian Journal of Pharmaceutical and Clinical Research2009; 2(3):49-53.
21. John AS, Sathesh BPR, Purohit KK: Development and evaluation of bucco-adhesive drug delivery system for Atorvastatin Calcium. Journal of Current Pharma Research2010; 1:31-38.
22. Johnston TP, Chittchang M, Sallamat-miller N: The use of muco-adhesive polymers in buccal drug delivery. Advance Drug Delivery Reviews2005; 57:1666-91.
23. Khanna R, Agrawal SP, Ahuja A: Preparation and evaluation of bio-erodible buccal tablet containing Clotrinazole. International Journal of Pharmaceutics 1996; 138:67-73.
24. Lansley AB, Pritchard k, Martin GP: Evaluation of bio-adhesive properties of Hyaluranan: Detachment weight and mucociliary transport rate studies. International Journal of Pharmaceutics1996; 129:137-45.
25. Narentra C, Srinath MS, Rao BP: Development of three layered buccal compact containing Metoprolol tartrate by stastical optimization technique. International Journal of Pharmaceutics2005; 304:102-14.
26. Narkhede H, Nazarkar S, Oswal A: Formulation of buccal bio-adhesive tablet of Diltiazem Hydrochloride and its evaluation. International Journal of Pharmtech Research2010; 2(4):2407-14.
27. Needleman IG, Smales FC: *In vitro* assessment of bio-adhesion for periodontal and buccal drug delivery. Elsevier science limited-biomaterials1995; 16:617-24.
28. Pande S, Parikh JR, Solanki AB: Bucco-adhesive tablets of Losartan Potassium: design & characterization. International Journalof Pharmaceutical & Biological Archives2010; 1:150-54.
29. Patel B, Patel P, Mutha S: Evaluation of Tambrind seed polysaccharide as a muco-adhesive & sustained release component of nifedipine bucco-adhesive tablet and comparison with HPMC & Na-CMC. International Journal of Pharmtech Research2009; 1:404-10.
30. Peppas NA, Leobandung W, and Huang Y: Molecular aspects of muco- and bioadhesion: tethered structure and site specific surface. Journal of Control Release2000; 65:63-71.
31. Satyabrata B, Ellaiah p, Singh P: Design and *in vitro* evaluation of muco-adhesive buccal tablet of Repaglinide. International Journal of Pharmscitech2010; 4(1):42-53.
32. Satyabrata B, Murthy KVR, Padhy S: Design and *in vitro* evaluation of muco-adhesive buccal tablet of Perindopril prepared by Sintering technique. Asian Journal of Pharmaceutical and Clinical Research2010;3(4):4-10.
33. Senel S, Wilson CG, Sumnu M: Development of buccal bioi-adhesive Nicotine tablet formulation for smoking cessation. International Journal of Pharmaceutics 2004; 277:173-78.
34. Shivanand K, Raju SA, Nizamuddin S: In vivo bio-availability studies of Sumatriptan Sccinate buccal tablet. DARU2011;19(3):224-30
35. Sigurdsson HH, Loftsson T: Assessment of muco-adhesion by a resonant mirror biosensor. International Journal of Pharmaceutics2006; 325:75-81.
36. Smart JD: The basic and underlying mechanism of muco-adhesion. Advance Drug Delivery Reviews2005; 57:1556-68.
37. Swamy PV, Kinagi MB, Gada SN: Formulation design and evaluation of bilayer buccal tablet of Granisetron hydrochloride. Indian Journal of Pharmaceutical Education and Research. 2011; 45(3):242-47.

How to cite this article:
Panchal AV, Mehta M, Shah VH and Upadhyay U. Formulation and *In-Vitro* Evaluation of Mucoadhesive Bilayered Buccal Tablets of Rosuvastatin Calcium. *Int J Pharm Sci Res* 2012; Vol. 3(8): 2733-2740.