Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Preparation and Physicochemical Characterization of Simvastatin Loaded Mucoadhesive Bilayered Tablet

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ARTICLE DETAILS

Article history:
Received on 26 August 2009
Accepted on 9 September 2009

Keywords:
Bilayer tablets
Buccal delivery
Simvastatin
In vitro release

ABSTRACT

The purpose of this research work was to prepare the buccoadhesive bilayered tablet of simvastatin for the treatment of hypercholesterolemia, by using the mucoadhesive polymers such as carbopol (CP), hydroxy propyl methyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) in different concentration. Ethyl cellulose is used in backing layer because of its water impermeable nature. Tablets were prepared by direct compression method. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water impermeable agent was compressed on the first layer. Tablets were subjected for physicochemical characterization tests such as FTIR, DSC, hardness, weight variation, friability, mucoadhesive strength, *in vitro* drug release study, *in vitro* drug permeation, and stability in human saliva. The FTIR and DSC analysis of drug, polymers, physical mixture and formulation indicated that the compatibility of drug with excipients. Tablets were found to be satisfactory when evaluated for weight variation, thickness, hardness and friability. The surface pH of all the tablets was close to neutral pH. The bilayered tablets containing a higher proportion of CP showed good mucoadhesive strength. The buccal tablets were found to be stable when tested for 8 h in natural human saliva. The present study concludes that mucoadhesive buccal devices of simvastatin can be a good way to bypass the extensive hepatic first pass metabolism and to improve the bioavailability of simvastatin.

INTRODUCTION

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal drug delivery involves administration of desired drug through buccal mucosal membrane lining the oral cavity. For many drugs, especially peptides and proteins, the buccal route offers many advantages over conventional routes of delivery with an improved bioavailability due to the avoidance of degradation in the gastrointestinal tract and hepatic first pass metabolism [1].The mucosal lining of oral cavity offers some distinct advantages. The buccal mucosa is highly vascularized and more accessible for the administration and removal of dosage form. However, advantages of buccal route include rapid cellular recovery and achievement of a localized site on the smooth surface of buccal mucosa [2]. Moreover a significant reduction in dose can be achieved, thereby reducing dose dependent side effects. Simvastatin, a hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor (statin) is an antilipedemic agent. Simvastatin lowers the lipid level in blood and thereby prevent cardiovascular disease.

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It is used in treatment of hypercholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides, and raises high-density lipoprotein levels. Simvastatin undergoes extensive first pass metabolism in liver due to which the oral bioavailability of simvastatin is very low and variable [3]. The physiological properties of drug like short half life (2 to 3 h), dose size (5 to 80 mg) and low molecular weight (418.57) makes it suitable candidate for administration by buccal route [4]. The aim of present study was to prepare and examine buccoadhesive bilayer buccal tablets of simvastatin using carbopol 934P (CP), HPMC K4M, PVP K25 and PVP K32 as mucoadhesive polymers and ethyl cellulose (EC) as an impermeable backing layer. The buccal tablets were characterized by FTIR, DSC, hardness, weight variation, friability, surface pH, swelling characteristics, disintegration test, *ex vivo* mucoadhesive strength, *in vitro* drug release, *in vitro* drug permeation, and stability in human saliva.

MATERIALS AND METHODS

Simvastatin (G. Amphray Ltd. Mumbai), hydroxyl propyl methyl cellulose (HPMC K4M) (Colorcon Asia ltd. Goa) and Polyvinylpyrrolidone (PVP K 32 and PVP K 25) (Sanofi-aventis ltd Goa) were obtained as a gift sample. Carbopol 934 (CP) and ethyl cellulose (EC) (Loba Chemie Pvt. Ltd.), magnesium stearate (Himedia laboratories Pvt

ltd. Mumbai) and sodium saccharin (S.D. fine chem. Boisar) were obtained from commercial sources. All other reagents and chemicals used were of analytical grade.

Preparation of buccal tablets

Mucoadhesive bilayer tablets were prepared by a direct compression method [5, 6]. Various batches of buccal tablets were prepared by varying the concentration of CP, HPMC K4M, PVP K25 and PVP K32. The composition for core layer and backing layer is shown in Table 1. The drug and mucoadhesive polymer mixture (core layer) was prepared by homogeneously mixing the drug with CP, HPMC K4M, PVP K25, PVP K32 and magnesium stearate in a glass mortar for 15 m. The mixture (150 mg) was then compressed using indigenously developed and standardized stainless steel punches and die (Fig. 1) in pellet press. The upper punch was raised and the backing layer of EC granules (50 mg) was placed on the first layer; the 2 layers were then compressed to form mucoadhesive bilayer tablet. Each tablet weighed around 200 mg with a thickness of 2.0 to 2.1 mm.

FTIR analysis

Infrared spectroscopy (Model-V-5300, JASCO, Japan) was performed for pure drug, pure polymers, physical mixture of drug and polymers and drug loaded buccal tablets. All the samples were mixed with KBr and vacuum packed to obtain pellets of the material, which were analyzed. All the spectra acquired scans between 400 to 4000 cm^{-1} at a resolution of 4 cm^{-1} [4].

DSC analysis

DSC studies were carried out using differential scanning calorimeter equipped with an intracooler (Mettler-Toledo, Switzerland). Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples (Pure simvastatin, polymers, physical mixture and formulation) were sealed in aluminum pans and heated at a constant rate of 20^0C/m over a temperature range of 20-150^0C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/m [4].

Surface pH determination

The surface pH of the buccal tablets was determined to investigate the chances of any side effects. As an acidic or alkaline pH may irritate the buccal mucosa, the surface pH should be close to neutral. The method used to determine surface pH of the formulation was according the reported method [6]. In briefly, a combined glass electrode was used to measure the surface pH. The tablet was allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.6 ± 0.05) for 2 h and pH was noted by bringing the electrode in contact with the surface of the formulation and allowing it to equilibrate for 1 m [6] .

Swelling studies

The swelling property of buccal tablets was evaluated by determining percentage hydration. Each tablet was weighted (W1) and placed in phosphate buffer pH 6.6 for predetermined time intervals. After immersion for a specified time, tablets were wiped out to remove excess of surface water by using filter paper and again weighted (W2). Percent hydration was calculated by using following formula [7].

$$\% \text{ hydration} = \frac{W2-W1}{W1} \times 100$$

Table 1: Composition of simvastatin buccal tablets

A. Composition for core layer

Formulation code	Drug (mg)	Carbopol 934 (mg)	HPMC K4M (mg)	PVP K 25 (mg)	PVP K 32 (mg)	Mg. Stearate (mg)	Total weight (mg)
F1	5	71.50	71.50	-	-	2.00	150
F2	5	47.66	95.34	-	-	2.00	150
F3	5	95.34	47.66	-	-	2.00	150
F4	5	57.20	85.80	-	-	2.00	150
F5	5	71.50	-	71.50	-	2.00	150
F6	5	47.66	-	95.34	-	2.00	150
F7	5	95.34	-	47.66	-	2.00	150
F8	5	57.20	-	85.80	-	2.00	150
F9	5	71.50	-	-	71.50	2.00	150
F10	5	47.66	-	-	95.34	2.00	150
F11	5	95.34	-	-	47.66	2.00	150
F12	5	57.20	-	-	85.80	2.00	150

B. Composition for backing layer

Ethyl cellulose (mg)	Carbopol 934 (mg)	PVP K 32 (mg)	Sodium saccharin (mg)	Tartrazine (mg)	Total weight (mg)
22.50	6.25	18.75	2.5	0.05	50

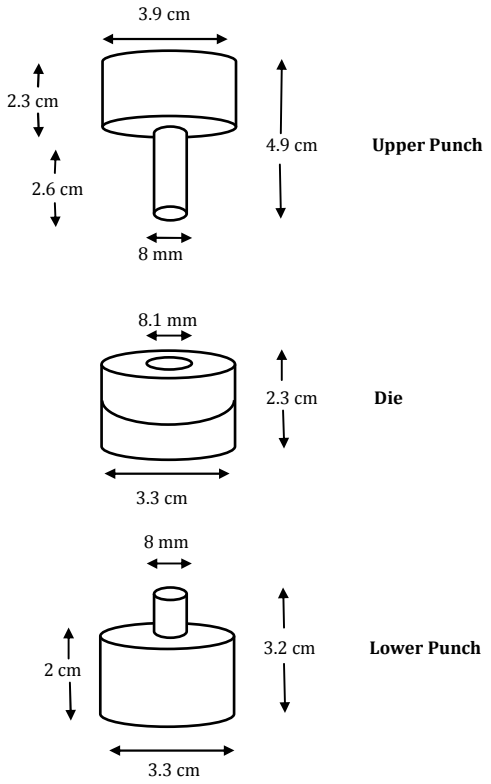

Figure 1: Indigenously developed and standardized punches and die for development of buccal tablets

***Ex vivo* mucoadhesive strength**

Bioadhesive strength of the buccal tablets was measured on modified physical balance followed by a reported method [8]. A modified physical balance was used for determining the *ex vivo* mucoadhesive strength of prepared buccal tablets. Fresh sheep buccal mucosa was obtained from a local slaughterhouse (Approved by institutional ethical committee, Dept. of Pharmacology, NET College of Pharmacy, Raichur, Karnataka, India). The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.6 at 37 ± 1^{0}C. Sheep buccal mucosa was tied to the glass petri dish, which was filled with phosphate buffer so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a thread with cyanoacrylate adhesive. The two sides of the balance were made equal by keeping a 5 g weight on the right hand pan. Next, weight of 5 g was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 m contact time. Then weight was added slowly to the right hand pan until the tablet detached from the mucosal surface [6, 8].

Disintegration test

The disintegration pattern of each mucoadhesive buccal tablet was determined by immersing the tablet in a glass petri dish containing 20 to 25 ml of water at room temperature (37 ± 1^{0}C). The morphological changes of each buccal tablet are observed [9].

***In vitro* drug release studies**

To study the drug release from the bilayered tablets, the United States Pharmacopeia (USP) XXIII rotating paddle method was used. The dissolution medium used consisted of 500 ml of phosphate buffer (pH 6.6) containing 0.5 % dodecyl sodium sulphate. The release was performed at 37 ± 0.5^{0}C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The glass slide was placed to the bottom of the dissolution vessel. At a predetermined time intervals, samples (5 ml) were withdrawn and replaced with fresh medium. The samples were filtered through whatman filter paper and after appropriate dilution analyzed by UV spectrophotometer (Pharmaspec-17, Shimadzu, Japan) at 238 nm [6, 10].

***In vitro* drug permeation study**

The *in vitro* buccal drug permeation study of simvastatin through the sheep buccal mucosa was performed using keshary chien type glass diffusion cell at 37 ± 0.2^{0}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 clamped together. The donor compartment was filled with 5 ml of phosphate buffer pH 6.6. The receptor compartment (50 ml capacity) was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. Aliquots of 1 ml sample was withdrawn from the receptor compartment at predetermined time intervals and analyzed at 238 nm using UV spectrophotometer [6].

Stability study in saliva

The stability study of prepared and optimized buccal tablets was performed in fresh human saliva. The ethics committee of the NET College of pharmacy, India, approved the study and subjects were determined to be in good health before commencement of the study. The written consent was obtained from human volunteers for collecting the fresh saliva. Buccal tablets were placed in separate a petri dishes containing 5 ml of natural human saliva and placed in a temperature controlled oven at 37 ± 0.2^{0}C for 8 h. At predetermined time intervals (up to 8 h); the tablets were examined for changes in color, shape, and drug content [11].

RESULTS AND DISCUSSION

In the present work, an antihyperlipidemic drug simvastatin and the mucoadhesive polymers were selected on the basis of bioadhesive property, non-toxicity, non-irritancy, stability and compatibility with the drug for the development of buccoadhesive tablets. Core layer was composed of drug and polymers, i.e. combinations of CP 934P: HPMC K4M, CP 934P: PVP K25, CP 934P: PVP K32 in varying ratios (1:1, 1:2, 2:1, and 2:3). Ethyl cellulose was selected as backing layer compound due to its water impermeable nature [12]. CP 934P and PVP K32 (1:3) was added in to backing layer to avoid premature cracking. Sodium saccharin was added as sweetening agent to allow good mouth feel and coloring agent (tartrazine) was also incorporated to distinguish the backing layer from core layer. All buccal tablets observed were round in shape, small in size (8

mm diameter) with flat surface and having a good physical appearance. Due to the color difference between two layers (yellow and white), tablet became easily distinguishable and attractive in nature. FTIR spectroscopic analysis was carried out to ascertain whether there is any interaction between drug and excipients used (Fig. 2).

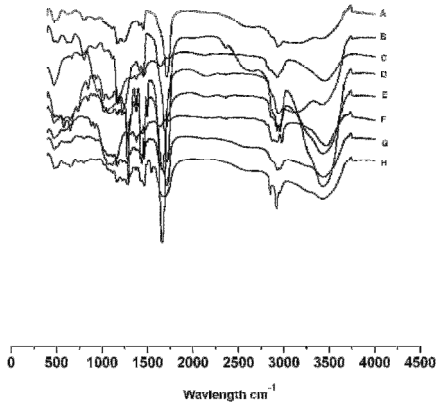

Figure 2: FTIR spectrum of pure drug, polymers, physical mixture and formulation. (A) Pure simvastatin, (B) carbopol 934, (C) HPMC K4M, (D) PVP K32, (E) PVP K25, (F) ethyl cellulose, (G) physical mixture, (H) optimized formulation

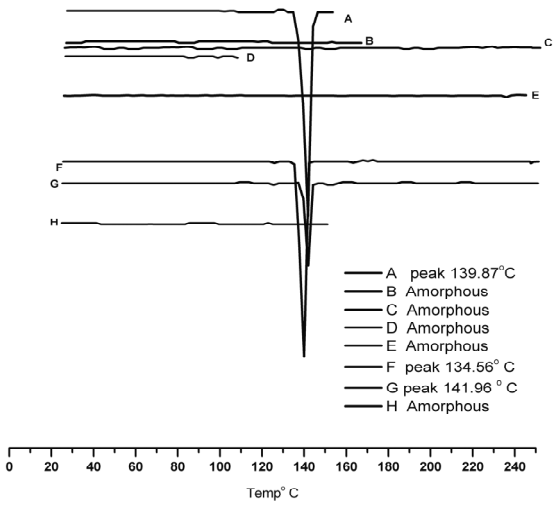

Figure 3: DSC thermograms of, (A) simvastatin, (B) carbopol 934, (C) PVP K32, (D) HPMC K4M, (E) ethyl cellulose, (F) physical mixture, (G) optimized formulation, (H) PVP K25

The IR spectra of pure drug shows characteristic functional peaks at 2929.1, 1709.8, 1369.1, 1269.0, and 1055.6 cm^{-1}, while physical mixture shows characteristic peaks at 2928.5, 1712.7, 1366.0, 1268.4, 1062.7 cm^{-1} with negligible shift in wave numbers. The negligible shift in wave numbers might be due to presence of amorphous nature of polymers and excipients used. The IR spectra of optimized formulation show characteristic functional peaks at 2928.5, 1692.8, 1372.0, 1268.4 and 1057.1 cm^{-1}. The similarity in the peaks indicated that the compatibility of drug with excipients. The obtained results from FTIR studies were also proved by DSC analysis. DSC thermogram of simvastatin, polymers, physical mixture and formulation was carried out to study change in thermal properties of drug (Fig. 3). Pure simvastatin thermogram was a single, sharp melting endotherm at 139.5^{0}C. There is no endothermic peak appearance in case of all the polymers and excipients due to the amorphous nature of polymers and excipients. In the physical mixture, the sharp peak was observed at 134.56^{0}C with negligible change in endotherm. This clearly indicates that, the excipients used to formulate buccal tablet had no effect on thermal properties of drug. DSC thermogram of formulation was compared with pure drug and physical mixture. A sharp melting endothermic peak appeared at 141.96^{0}C. The slight change in melting temperature of drug may be attributed due to addition of amorphous excipients. Thus the obtained results clearly indicated that the excipients and method of preparation of buccal tablet had no effect on thermal properties of the drug. Table 2 shows the evaluation of different parameters for prepared buccal tablet. Mucoadhesive bilayered tablets of simvastatin were found to be satisfactory when evaluated for average thickness (2.01 ± 0.01 mm), hardness (6.20 ± 0.47 kg/cm^2), weight variation (200 ± 0.98 mg), friability (0.321 ± 0.11%) and drug content (94.97 ± 1.68%).

Surface pH determination

Surface pH of bilayered tablets was found to be in between 6.23 ± 0.05 to 6.66 ± 0.25. The investigated results indicated that the developed buccal tablets will not cause any irritation to mucosal surface.

Swelling studies

Appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion [11]. Swelling index is increased as the weight gain by tablet is increased proportionally with the rate of hydration [13]. Swelling indices of the prepared buccal tablets containing CP: HPMC and CP: PVP increases with increasing amount of CP. The swelling index for buccal tablets containing CP:HPMC was found to be in between 63.05 ± 1.92 to 82.65 ± 1.45% respectively, in which the ratio 2:1 of CP: HPMC exhibit highest value (82.65%). For tablets containing CP: PVP K25 (F5-F8) swelling index was found to be in between 54.27 ± 2.33 to 77.77 ± 0.47% respectively, while for CP: PVP K32 (F9-F12) in between 55.61 ± 1.00 to 81.81 ± 1.75% respectively.

***Ex vivo* mucoadhesive strength**

Mucoadhesion may be defined as the adhesion between a polymer and mucus. The strength of mucoadhesion is affected by various factors such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer, and biological membrane used in the study [14]. In this study, sheep buccal mucosa was used as biological membrane for mucoadhesion. The bioadhesive strength of buccal tablets was found to be in between 20.33 ± 1.52 to 27.66 ± 0.57 g. Bilayered tablets containing CP and HPMC in ratio of 2:1 (F3) exhibited the highest bioadhesive strength (27.67 ± 0.57 g). The bilayered tablets containing a higher proportion of CP showed good mucoadhesive strength. The high bioadhesive strength of CP may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, while the other polymers only undergo superficial bioadhesion [15].

Table 2: Evaluation parameters of simvastatin buccal tablet formulations F1-F12

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Average weight (mg)	Surface pH	Mucoadhesive strength (gm)	Drug content (%)	Disintegration time (h)
F1	2.02 ± 0.01	6.40 ± 0.69	0.370 ± 0.14	200.00 ± 1.73	6.36 ± 0.05	23.67 ± 1.52	91.59 ± 1.46	15.00 ± 1.00
F2	2.01 ± 0.01	6.56 ± 0.40	0.374 ± 0.15	199.34 ± 0.57	6.56 ± 0.05	20.33 ± 0.57	97.35 ± 1.30	11.00 ± 0.50
F3	2.01 ± 0.01	5.83 ± 0.35	0.222 ± 0.10	200.34 ± 0.57	6.43 ± 0.23	27.67 ± 1.52	98.17 ± 0.88	16.00 ± 0.20
F4	2.02 ± 0.01	5.60 ± 0.60	0.344 ± 0.17	198.67 ± 0.57	6.46 ± 0.05	21.33 ± 0.57	98.70 ± 0.84	14.00 ± 1.00
F5	2.01 ± 0.01	6.13 ± 0.61	0.329 ± 0.10	199.34 ± 1.52	6.56 ± 0.28	20.67 ± 1.15	96.17 ± 1.86	13.00 ± 1.00
F6	2.01 ± 0.00	6.40 ± 0.52	0.359 ± 0.09	200.67 ± 0.57	6.46 ± 0.11	18.00 ± 1.00	92.65 ± 2.00	10.00 ± 0.50
F7	2.01 ± 0.01	6.26 ± 0.11	0.207 ± 0.06	200.00 ± 1.73	6.66 ± 0.25	22.33 ± 0.57	93.55 ± 2.49	14.00 ± 1.00
F8	2.02 ± 0.02	6.33 ± 0.50	0.316 ± 0.14	199.67 ± 0.57	6.60 ± 0.34	20.33 ± 0.57	94.02 ± 0.72	12.00 ± 0.50
F9	2.02 ± 0.02	5.80 ± 0.20	0.325 ± 0.15	199.00 ± 1.00	6.36 ± 0.23	24.33 ± 1.52	93.10 ± 1.97	13.50 ± 0.50
F10	2.02 ± 0.02	6.53 ± 0.61	0.364 ± 0.14	200.34 ± 1.15	6.43 ± 0.05	22.67 ± 2.08	94.64 ± 2.50	11.00 ± 1.00
F11	2.01 ± 0.01	6.20 ± 0.60	0.265 ± 0.08	200.34 ± 1.15	6.23 ± 0.05	26.67 ± 1.52	95.06 ± 2.16	14.00 ± 1.00
F12	2.01 ± 0.01	6.40 ± 0.52	0.285 ± 0.10	198.67 ± 0.57	6.53 ± 0.15	23.67 ± 1.52	95.73 ± 3.08	12.00 ± 1.00

Disintegration test

The disintegration test for buccal tablet is required to check the integrity of formulation. When tablets immersed in water initially it hydrates and swells for longer time and then disintegrates slowly. Disintegration time for prepared buccal tablets was found to be in between 10.00 ± 0.50 to 16.00 ± 0.20 h. The obtained results indicated that disintegration time increases as amount of carbopol increases due to its high molecular weight and viscosity

***In vitro* drug release studies**

The *in vitro* dissolution was carried out in phosphate buffer pH 6.6 containing 0.5 % dodecyl sodium sulphate. *In vitro* dissolution studies clearly indicated that the formulation containing CP 934P: HPMC K4M showed higher drug release as compared to other formulations containing CP 934P: PVP K25 and CP 934P: PVP K32. The drug release profile of formulations F1-F4, F5-F8, and F9-F12 have been well depicted in Fig.4, 5 and 6 respectively. The cumulative percentage drug released from formulations F1-F4 was found to be 64.07 ± 0.24, 56.60 ± 0.30, 66.76 ± 0.07, and 60.57 ± 0.23%, respectively, while for F5-F8 the drug release was 53.54 ± 0.07, 47.73 ± 0.24, 57.19 ± 0.08 and 50.66 ± 0.07%, respectively. The formulations F9-F12 showed that the drug release 61.35 ± 0.26, 53.56 ± 0.09, 63.11 ± 0.24 and 57.06 ± 0.23%, respectively. The maximum drug release was found in formulation F3 (66.76 ± 0.07%). The *in vitro* drug release studies revealed that the release of simvastatin from different formulations varies with characteristics and composition of matrix forming polymer. The release rate of simvastatin decreased with increasing amount of HPMC K4M and PVP K25 and PVP K32. The decrease in the amount of drug released in formulations F2 (56.60 ± 0.30%), F6 (47.73 ± 0.24%) and F10 (53.56 ± 0.09%) may be attributed due to increase in proportion of HPMC and PVP, which form complex matrix network and leads to delay in drug release. Carbopol is more hydrophilic than HPMC and PVP; it swells rapidly, therefore decrease in carbopol content may delay in the drug release [5]. HPMC have greater swelling properties than PVP, hence the drug release from CP: HPMC is greater as compared to CP: PVP formulations. Drug release rate was increased with increasing amount of hydrophilic polymer. Another explanation includes, high water uptake which leads to considerable swelling of polymer and causes drug to diffuse out from polymer matrix. Moreover the hydrophilic polymers would leach out and hence creates more pores and channels for drug to diffuse out from the device [16]. F9 was found to be best formulation on the basis of *in vitro* drug release mechanism, optimum swelling index and good bioadhesive strength. The drug release from optimized formulation F9 was found to be 61.35 ± 0.26% at 8 h. Hence F9 is selected for further studies like *in vitro* drug permeation and stability studies. Formulation F3 selected for *in vitro* permeation studies depending on its maximum drug release. The obtained *in vitro* drug release pattern of all the formulations were also subjected to different kinetic models, such as zero order, first order, higuchi matrix, peppas and hixson crowell models to predict the mechanism of drug release. The obtained results have been shown in Table 3. The values of n were estimated from peppas model and these values were in between 0.5 and 1.0, indicated that the release of simvastatin from the 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 a low water soluble drug the self-erosion of the matrix will be the principal mechanism [17]. Simvastatin is low water soluble drug, hence the release of drug is mainly depends on the self erosion of matrix.

Table 3: Model fitting for simvastatin buccal tablet formulation F1-F12

Formulation code	Zero order $Q_t = Q_o + K_o t$	First order $\ln Q_t = \ln Q_o + K_o t$	Higuchi $Q_t = K_H$ sq.t	Krosmeyer-Peppas $Q_t/Q_{inf} = K_k t^n$	Hixon crowell	n (Value)
	R^2	R^2	R^2	R^2	R^2	
F1	0.9895	0.9862	0.9587	0.9971	0.9935	0.7608
F2	0.9613	0.9957	0.9978	0.9985	0.9922	0.5578
F3	0.9307	0.9831	0.9804	0.9691	0.9696	0.7243
F4	0.9330	0.9971	0.9977	0.9980	0.9955	0.5379
F5	0.9774	0.9914	0.9728	0.9943	0.9929	0.6198
F6	0.9820	0.9990	0.9717	0.9986	0.9984	0.7288
F7	0.9783	0.9977	0.9752	0.9992	0.9979	0.7089
F8	0.9372	0.9854	0.9925	0.9938	0.9791	0.6198
F9	0.9094	0.9859	0.9958	0.9866	0.9773	0.5513
F10	0.9497	0.9924	0.9896	0.9929	0.9873	0.6495
F11	0.9367	0.9975	0.9977	0.9993	0.9974	0.5412
F12	0.9193	0.9903	0.9976	0.9939	0.9860	0.5386

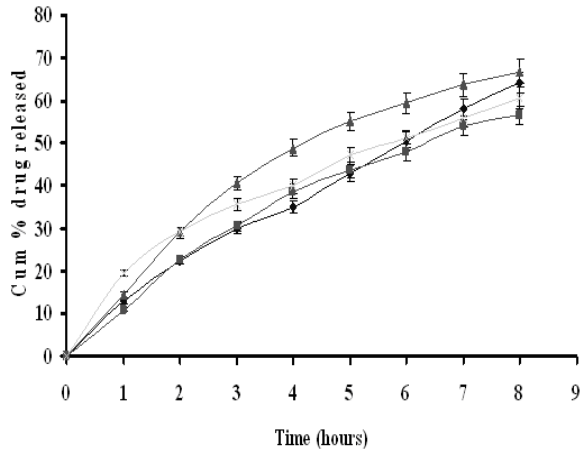

Figure 4: *In vitro* drug release profile of simvastatin buccaltablet formulation F1 (♦), F2 (■), F3 (▲), F4 (×)

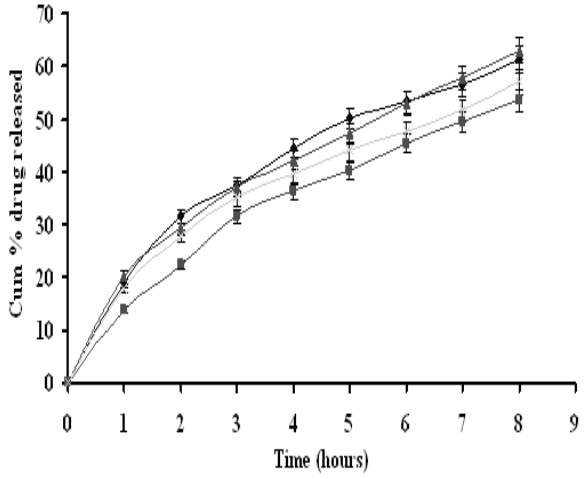

Figure 6: *In vitro* drug release profile of simvastatin buccal tablet formulation F9 (♦), F10 (■), F11 (▲), F12 (×)

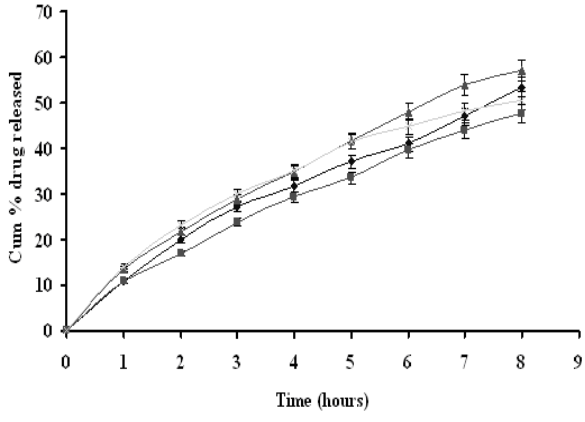

Figure 5: *In vitro* drug release profile of simvastatin buccal tablet formulation F5 (♦), F6 (■), F7 (▲), F8 (×)

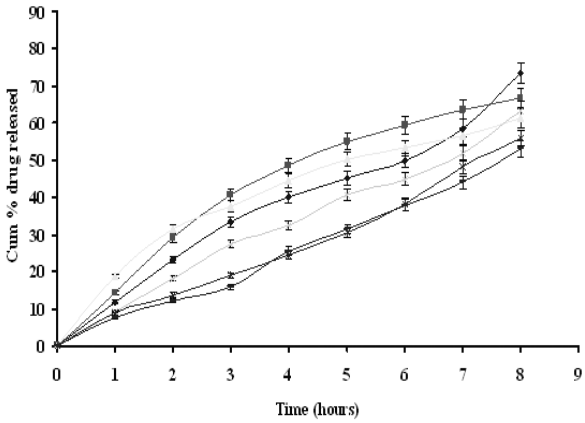

Figure 7: Comparison of in vitro dissolution profile of simvastatin (♦), F3 (■), F9 (×) and *in vitro* permeation of SIM (▲), F3 (ж), F9 (-)

***In vitro* drug permeation study**

The prepared and optimized buccal tablet formulations F3 and F9 as well as pure drug were subjected for *in vitro* drug permeation through sheep buccal mucosa. Fig. 7 shows the comparison of *in vitro* dissolution profile and *in vitro* permeation of pure drug, formulations F3 and F9. The *in vitro* permeation of simvastatin was found to be 63.38±0.32% in 8 h. The average flux of simvastatin was found to be 0.126 $mg/cm^{-1}/hr^{-1}$. Formulation F3 showed 56.03 ± 0.25% and Formulation F9 showed 53.14 ± 0.14% of drug permeated in 8 hours through sheep buccal mucosa. The *in vitro* permeation of simvastatin, formulations F3 and F9 was found to be less as compared to *in vitro* dissolution due to presence of mucosal membrane. The presence of barriers such as membrane coating granules, lipids in the buccal mucosa may reduce the permeation of drug through mucosa. The correlation between *in vitro* drug release and *in vitro* drug permeation across the sheep buccal mucosa for simvastatin, formulation F3 and F9 was found to be satisfactory with correlation coefficient of 0.9781, 0.9307 and 0.9098, respectively.

Stability study in human saliva

The stability studies are generally performed in phosphate buffer solutions whose pH pertains to buccal cavity. But, the stability studies performed in natural human saliva may be more accurate to determine the stability of drug and buccal device in the oral cavity. Therefore, the stability study of optimized buccal tablets (F9) was examined in natural human saliva. The buccal tablets were evaluated by their appearance characteristics, such as color and shape, and their drug content in natural human saliva. Bilayered tablets did not exhibit change in color or shape, suggesting the satisfactory stability of the drug and buccal device in the human saliva. Physical properties of the buccal tablets such as thickness and diameter increased slightly due to swelling of the system in saliva.

CONCLUSION

The present work demonstrated that the possibility of making a buccoadhesive drug delivery system for simvastatin which will be more efficacious and acceptable than the conventional drug delivery of simvastatin and it could be a drug delivery of choice in the treatment of hypercholesterolemia.

AKNOWLEDGEMENTS

The authors thank to Prof S. R. Reddy, Secretary and Founder, NET Pharmacy College for his continuous support of this research work. We are thankful to G Amphree Ltd. Mumbai, India, for generously providing the gift sample of simvastatin.

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