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Research Article **Novel drug delivery system**

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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF SIMVASTATIN

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ABSTRACT

In present study mucoadhesive buccal tablet of simvastatin was prepared. Solubility of Simvastatin was enhanced by complexing Simvastatin with β-CD in 1:2 molar concentrations. Six different formulations of tablets of Simvastatin containing the polymers in various combinations were prepared by direct compression method and characterized for swelling studies, % matrix erosion, surface pH, mucoadhesive properties, *in-vitro* release studies. All the formulations showed the satisfactory results bioadhesive performance, surface pH ,physical& mechanical properties . The swelling index was proportional to carbopol content & other bio-adhesive polymer. The surface pH of all tablets was found to be satisfactory, close to neutral pH; hence, buccal cavity irritation should not occur with these tablets. Drug release and drug diffusion from the tablets were depended on the ratio and type of the polymer used in the formulation. Tablets containing Carbopol and HPMC K100 in the ratio of 4:1 had the maximum percentage of *in-vitro* drug release for 7h. The formulation F 4 was optimized based on good bioadhesive strength (45 ± 0.55 g) and sustained in vitro drug release (65.96 % for 7h). The chosen tablet containing 10 mg of simvastatin performed 7h sustained drug release with desired therapeutic concentration.

KEYWORDS: Mucoadhesion, Buccal tablets, Simvastatin and Sustained drug delivery

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INTRODUCTION

Mucoadhesive drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers. Bioadhesionis defined as an ability of a material to adhere a particular region of the body for extended period of time not only for local targeting of drugs but also for better control of systemic delivery. Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, rapid termination of therapy anadministration to unconscious patients. Drug which are destroyed by the enzymatic / alkaline environment of the intestines are unstable in the acidic environment of the stomach can be administered by this route[1]. From technical point of view, an ideal buccal dosage form must have three properties. It must maintain its position in the mouth for a few hours, release the drug in a controlled fashion and provide the drugrelease in a unidirectional way towards the mucosa. In regar to the first requirement, strong adhesive contact to the mucosa in established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can be fulfilled by preparing a system have uniform adhesiveness and impermeable backing layer. Various mucoadhesive devices such as include tablets, film, patches, discs, strips, ointments and gel have been recently developed[2] During the past decade, Several researchers has formulated & evaluated mucoadhesive buccal tablets for delivery of therapeutic agents such as glipizide[3], propranolol hydrochloride[4] ,carvedilol[5], timolol maleate[6] ,lisinopril[7] Simvastatin[8] (SV) is lipid lowering agent derived structurally from fermentation of Apergillus terreus . SV is HMG Co-A reductase widely used in the treatment of hyperlipidemias & cardiovascular diseases. It is known to have low oral bioavailability (5%) due to an extensive high first-pass effect and its availability in less dose size i.e.in few mg.& simvastatin is practically insoluble in water. Due to its short half-life (3-4 hrs), low molecular weight & small dose size, it can considered as a suitable candidate for a administration via buccal route. The objective of the present study is to enhance the solubility of SV by forming the inclusion complex with β-CD & to design and evaluate the sustained release of mucoadhesive buccal tablet of SV (SV- β-CD) with a goal to increase the bioavalability, reduce dosing frequency and improve patient compliance, employing the mucoadhesive polymers like Carbopol-934, Hydroxy propyl methyl cellulose (HPMC) K15M and HPMC K100M.

MATERIALS AND METHODS

Simvastatin, β-Cyclodextrin (M.W.=1135), Microcrystalline Cellulose (MCC), Carbolpol 934P, HPMC K15M, HPMC K100M were obtained as a gift sample from Glenmark, Mumbai. All other reagents and materials were of analytical or pharmacopoeial grade. Double distilled water was used throughout the study.

(i) Preparation and characterization of Simvastatin +β-CD complex[9,10]

For preparation of complex, Simvastatin and β-CD were used in 1:1 & 1:2 molar ratios in different glass mortar. First, β-CD was placed in a mortar; a small quantity of 50% methanol was added to it while triturating to get slurry like consistency. Then the drug was slowly incorporated into the slurry and trituration was further continued for one hour. Slurry was then air dried at 25°C for 24 hours, pulverized, passed through sieve # 100 and stored in desiccator over fused calcium chloride.

(ii) FT-IR Spectroscopy[10]

Infrared (IR) spectra of the materials were recorded with FT-IR Spectrophotometer (FT-IR-8101 A, Shimadzu Japan). The samples were prepared by processing compressed potassium bromide (KBr) pellets.

(iii) Preparation of mucoadhesive buccal tablet[3-7, 11]

For preparation of mucoadhesive buccal tablets,

equivalent weight of drug was taken & all other ingredients were passed through sieve#100 and were blended in mortar with pestle to obtain uniform mixing. The prepared blend of each formulation was subjected to flow properties of granules. The blended powder of the core was compressed on a 8mm punch in a single stroke multi station tablet punching machine (Rimek, Karnavati, Ahemadabad) by direct compression method. Tablet weighing ≈245 mg and hardness 7.5kg/ cm² were obtained. Formulation chart is given in Table 1. All tablets contained 28% API, 11% MCC as a filler, 11-40% mucoadhesive polymer with different ratios of carbopol 934P, 3% magnesium sterate as lubricant, 8% mannitol. For comparison purpose 3 different types of tablets were also prepared. First containing only Simvastatin, second containing physical mixture of simvastatin+ β-CD (1:2) and third containing kneaded mixture of simvastatin + β-CD (1:2)

Table 1
Formulation of mucoadhesive buccal tablets of Simvastatin

Ingredient (mg)	Formulation Code					
	F1	F2	F3	F4	F5	F6
Simvastatin	68	68	68	68	68	68
MCC	25	25	25	25	25	25
Carbopol 934P	75	50	25	100	75	50
HPMC K15M	50	75	100	-	-	-
HPMC K100M	-	-	-	25	50	75
Magnesium sterate	7	7	7	7	7	7
Mannitol	20	20	20	20	20	20
Total Weight	245	245	245	245	245	245

(iv) Evaluation of Tablets[7-10]

The tablets from different formulation (F1 to F6) were subjected to following tests

(a) Hardness

Tablets were evaluated for their hardness using Monsanto hardness tester(Harrisons, Pharma Machinary Ltd., India. . The results are shown in table 2.

(b) Weight variation

Ten tablets from each formulation were weighed using an electronic digital balance (Shimadzu, Japan) and the average weight was calculated. The results are shown in table 2.

(c) Thickness

Tablets were evaluated for their thickness using slide caliper. The results are shown in table 2.

(d) % Friability

Ten tablets from each formulation were weighed using an electronic digital balance & % friability was determined using Roche Friabilator (Electrolab, India).

(e) Drug Content

Five Tablets were accurately weighed and powdered. A quantity of the powder equivalent to 10 mg of Simvastatin was weighed accurately and extracted in 100 ml methanol by shaking for 20 min. After filtration through whatman filter paper no.1 and sufficient dilution with methanol, samples were analyzed spectrophotometrically at 238 nm.This procedure was repeated thrice. Amount of drug present was determined from the standard curve of simvastatin in methanol.

(f) Surface pH Study

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects *in-vivo*. As the acidic or alkaline pH may cause irritation to the buccal mucosa, the pH was maintained to neutral as closely as possible. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 h 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 1 min

(g) Swelling study[12]

Three buccal tablets were weighed individually (W_1) and placed separately in 2% agar gel plates with core facing the gel surface and incubated at 37 ± 1°C. After every 1 h time interval until 6 h, the tablet was removed from the petri dish and excess surface water was removed carefully with blotting paper. The swollen tablet then reweighed (W_2) and the swelling index (SI) separately was calculated using the formula given in equation

Swelling Index = [(W2-W1) ÷ W1] × 100

Where, W_1 = initial weight of the tablet

W_2 = final weight of the tablet

(h) Matrix erosion

After swelling study, the swollen tablets were dried at 60°C for 24 h in an oven and kept in descicator for 48 h and reweighed (W_3).Matrix erosion was calculated using following formula

% Matrix erosion = [(W1-W3) ÷ W3] × 100

(i) Mucoadhesion Time[13]

The ex-vivo mucoadhesion time was examined after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with two drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and kept at 37± 1°C. After 2 minutes, stirring was applied slowly to stimulate the buccal cavity environment, and tablet adhesion was monitored for 7 h. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time

(j) Mucoadhesive strength[13]

Modified Physical Balance method was used to determine mucoadhesive strength of the buccal tablet. In this method sheep buccal membrane was used as model mucosal membrane. The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8 and tied to glass slide which was moistened with phosphate buffer pH 6.8.The tablet was stuck to the lower side of another glass slide with glue. The both pans were balanced by adding an appropriate weight on the left side pan. The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa, the balance was kept in the position for 1min. contact time. Mucoadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane. The experiment was performed in triplicate and average value was calculated (k) In-vitro dissolution studies The USP dissolution test apparatus (apparatus II paddle type) was used to study the drug release from the tablet. The dissolution medium was 500 ml of phosphate buffer pH 6.8.The release was performed at 37±0.5°C, with a rotation speed of 50 rpm. The tablet was placed on watch glass and the watch glass was allocated to the bottom of the dissolution vessel.5 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analysed after appropriate dilution by UV spectrophotometer at 238 nm (l) Kinetic modelling of drug dissolution studies. The dissolution profile of best formulation was fitted to Zero order & Hixson Crowell's cube root to ascertain the kinetic modelling of the drug release. The method was adopted for deciding the most appropriate model (m) Stability studies. The purpose of stability study is to provide evidence on the quality of the drug substance or drug product varies with time under the influence of variety of environmental factors such as temperature, humidity, light. One formulation was selected for stability studies on the basis of the *in-vitro* drug release profile. The formulation was subjected to accelerated stability studies as per ICH (The International Conference on Harmonization) guidelines. The most satisfactory formulation was sealed in an aluminum foil and stored at 30±2ºC, 65±5% RH and at 40±2ºC, 75±5 % RH for 2 months. Tablet were periodically removed and evaluated for physical characteristics, mucoadhesive properties, *in-vitro* drug release.

RESULTS AND DISSCUSSION

The main aim of this work was to develop mucoadhesive buccal tablets to release the drug at mucosal site in unidirectional pattern without wash out of drug by saliva. MCC, carbopol 934P, HPMC K15M, HPMC K100 were selected as mucoadhesive polymers due to their matrix forming and mucoadhesive properties. At preformulation study for drug polymer compatibility by FTIR gave conformation about their purity and showed no interaction between drug and selected polymers. [Figure 1]

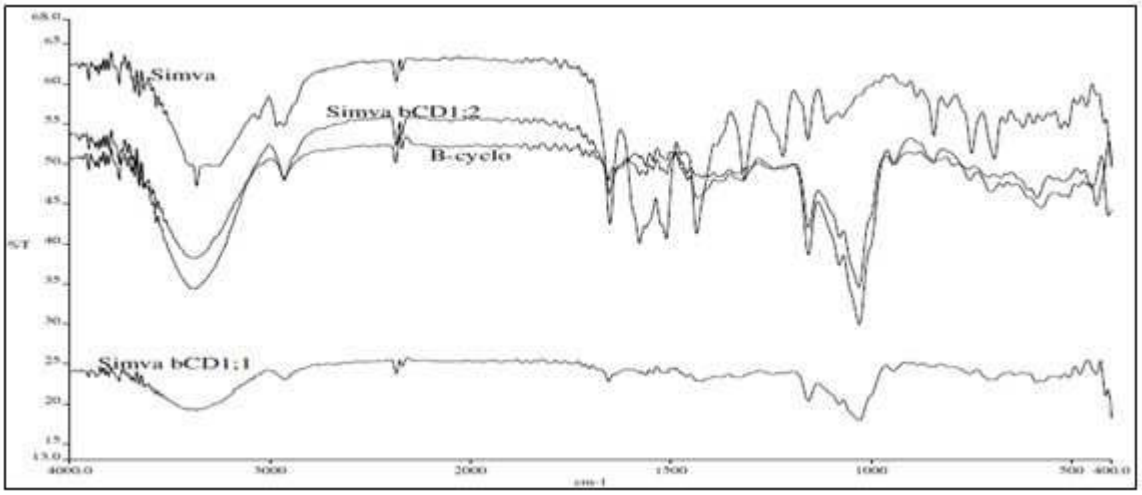


Figure 1
FT IR spectra of a) SV b) BCD C) SV+β-CD 1:1 d) SV+β-CD 1:2

Table 2
Physico-chemical parameters of developed mucoadhesive buccal tablets of Simvastatin (mean, ± SD in parenthesis; n = 3)

Code	Diameter mm	Hardness (kg/cm2)	Thickness Mm	Weight Uniformity (mg)	Friability % loss	% Drug content	Surface pH
F1	8±0.02	7.5±0.55	2.8±0.03	245±2.20	0.43	103±1.81	6.24±0.29
F2	8.1±0.03	7.6±0.54	2.9±0.02	245±1.95	0.42	96.75±0.83	6.87±0.25
F3	8.1±0.02	7.6±0.56	2.7±0.04	245±2.15	0 .47	99.23±0.85	6.52±0.23
F4	8±0.01	7.5±0.44	2.7±0.03	245±1.54	0.43	104.68±0.87	6.93±0.27
F5	8±0.02	7.5±0.54	2.8±0.02	245 ±2.1	0.44	103.2±1.87	6.11±0.31
F6	8.1±0.03	7.6±0.55	2.7±0.04	245±2.32	0.43	101.71±0.87	6.33±0.25

All the formulations were found to be satisfactory when evaluated for weight uniformity (245mg), content uniformity (101.42%), thickness (2.7mm), hardness (7.5 kg/cm2) and friability (0.44%).Thus all tablets comply with the IP standards. The surface pH of all formulations was within a range of 6.1 to 6.9, close to neutral pH. These results reveal that all the formulations provide an acceptable pH in the range of salivary pH (5.5 to 7.0). They did not produce any local irritation to the mucosal route. The results of all the above mentioned tests are shown in [Table-2]. The mucoadhesion and drug release profile are dependent upon swelling behaviour of the tablets. Due to hydration tablet gain the weight & thus Swelling index was increased In swelling study, it was found that the amount of carbopol 934P plays an important role in swelling of the matrix and leads to the drug diffusion. It was observed that swelling rate increased with an increase in CP content of the prepared tablets. Maximum swelling was seen in the formulations F1, F2 and F6. The mucoadhesive polymers used were hygroscopic and retain large amounts of water therefore tablets

containing more amount of mucoadhesive polymer shows less matrix erosion. The plots of matrix erosion (Figure 2), percentage swelling index [Figure 3] and matrix erosion are shown in [Figure 2].

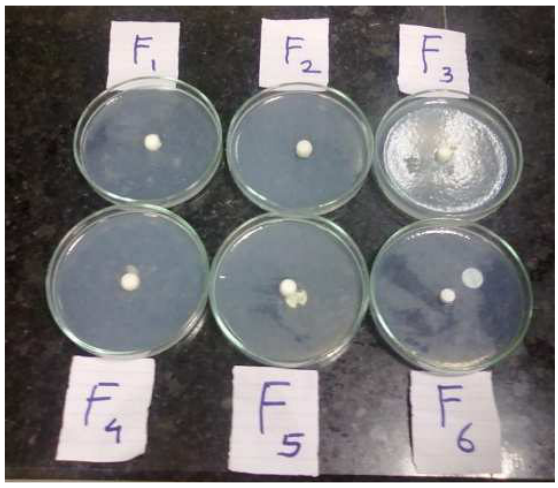
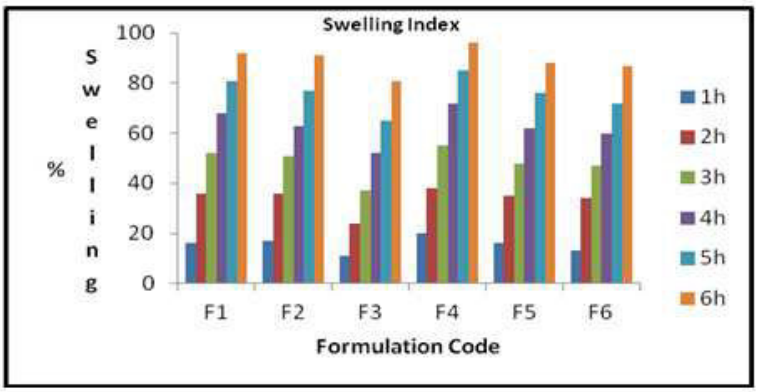


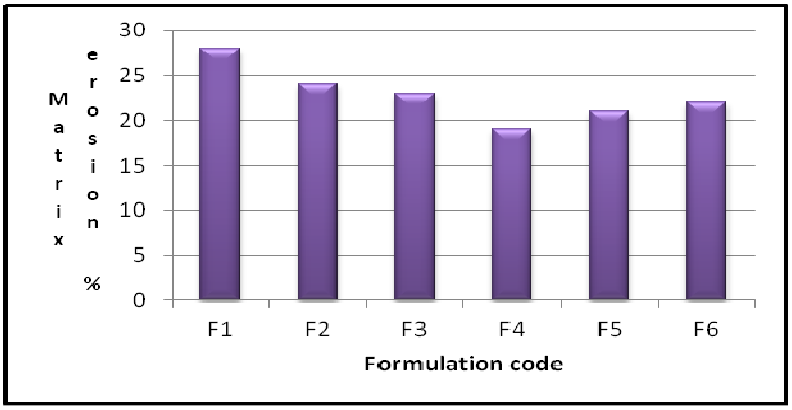
Figure 2
Swelling of tablet in agar plates

Graph 1
Percentage swelling of developed buccal tablets



The *ex-vivo* mucoadhesive properties of the tablets were determined using sheep buccal mucosa. Tablets containing a higher proportion of CP showed higher mucoadhesion. The reason might be ionization of CP at salivary pH and formation of secondary bonds with mucin because of rapid swelling and interpenetration of the polymer chains in the interfacial region, which leads to improved attachment of the device to mucosal surface, while other polymer undergo superficial mucoadhesion only. As the amount of CP increases adhesion force also increases. Tablet containing CP and HPMC K100M in ratio of 4:1 & 3:2 (F4, F5 respectively) exhibited highest mucoadhesion. The mucoadhesion characters of the prepared tablet against time are shown in [Table-3].

Graph 2
Percentage matrix erosion of buccal tablets



Release of drug from the buccal mucoadhesive tablets varied according to the type and ratio of matrix-forming polymer. Carbopol 934P has excellent mucoadhesive, gelling properties and also helps in sustaining effect. Carbopol is more hydrophilic. It can swell rapidly, therefore decrease of carbopol content delays the drug release from tablet core. The maximum cumulative percent of drug release from formulation F4 could be attributed to the presence of higher amount of carbopol which will ionizes at pH environment of the dissolution medium. Ionization of CP leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counter ion diffusion inside & creates an additional osmotic pressure leading to the considerable swelling of the polymer. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate. In theory, the higher the uptake of water by polymer, the more the amount of drug diffused out from the polymer matrix. Thus, this high amount of water uptake by polymers may lead to considerable swelling of polymer matrix, allowing drug to diffuse out at faster rate [2]. Tablets from the formulation F4 (highest CP content) showed a higher percentage of drug release compared to other groups. The plots of percentage cumulative drug release against time are shown in Figure 7.

Figure 3
In-vitro mucoadhesive strength measurement apparatus.

A- Wooden Frame, B-Left pan, C- Porcine buccal mucosal membrane tied on glass Slide, D-Petri Dish containing Phosphate buffer pH6.8, E- Modified Physical Balance, F-Pointer & scale, G-Weight, H-Right pan

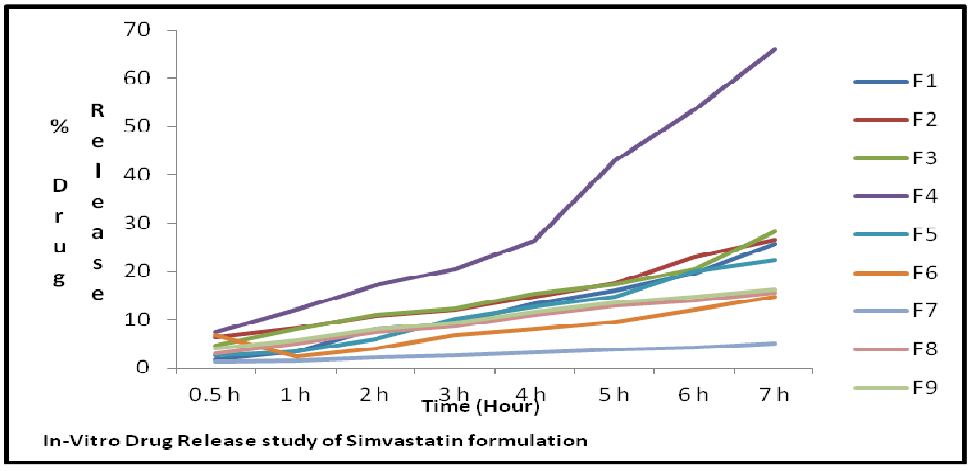
Figure 4
Detachment of SV tablet.

A-Modified Physical Balance, B-Left pan, C- Slide with buccal mucosal membrane, D-Petri Dish containing Phosphate buffer pH6.8, E-Wooden Frame, F-Scale, G-Weight, H-Right pan

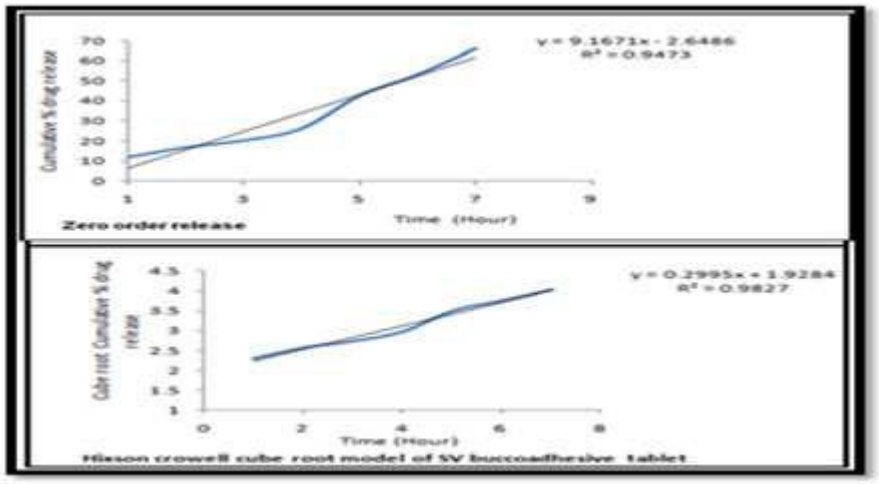
Table 3
Mucoadhesive properties of prepared mucoadhesive buccal tablet (mean, ± SD in parenthesis; n = 3)

Formulation Code	Mucoadhesive time (h)	Mucoadhesive Strength (g)
F1	7.7±0.21	41±0.65
F2	7.2±0.25	36±0.57
F3	7.0±0.19	33±0.40
F4	7.7±0.22	45±0.55
F5	7.8±0.26	41±0.78
F6	7.3±0.15	37±0.58

Graph 3
In vitro Drug release of Simvastatin Formulation (F1 to F9), F7-Simvastatin, F8-Physical mixture of SV+β-CD, F9-Kneaded mixture of SV+β-CD



Graph 4
Mechanism of Drug release



Formulation F4 was selected for further studies based on *in-vitro* drug release (65.96%), swelling index (93.67%), matrix erosion (16.90%), bioadhesive time (6.37h) and mucoadhesive strength (19.0g).Kinetic treatment (Peppas et.al) of obtained result from *in-vitro* drug release data represents the anomalous release mechanism. The values of n and k are inversely related. A higher value may suggest burst drug release from the matrix. To investigate the kinetics of SV release from mucoadhesive buccal tablets the release data was applied to zero order, first order, Higuchi, Hixson Crowell and Korsmeyer-Peppas models and best fit was determined [Table-4].It is known that a value of release exponent(n) = 0.45, 0.45< n < 0.89, and 0.89< n<1.0 indicates Fickian (case-I), non-fickian (anomalous) and zero order (case-II) transport, respectively[Table 5]. The result indicated the drug release followed zero order and Hixson Crowell's cube root model.

Table 4
Correlation coefficients of drug release curves from the most satisfactory Formulations of mucoadhesive tablets on kinetic models

Kinetic Models	R^2
Zero order	0.94
Hixson Crowell's cube	0.98

Table 5
Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion Exponen	overall solute diffusion mechanis
0.45	Fickian diffusion
0.45< n< 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

From the results it was found that formulation F4 can be considered as the most satisfactory formulation because of its good adhesive properties, least matrix erosion and good release behaviour and have chosen for the stability studies. After the 2 months storage of formulation F2, values of all parameters like diameter, thickness, % drug content, friability, surface pH, mucoadhesive properties, swelling index and % matrix erosion were checked

periodically and found to be almost similar to the initial values. The drug dissolution and diffusion profile were similar to the initial profile (Fig. 6). There was not any significant change in any value. So it can be said that formulation is stable.

CONCLUSION

The prepared mucoadhesive buccal tablets of Simvastatin can help bypass extensive hepatic first-pass metabolism and improve bioavailability. The mucoadhesive tablets showed a mucoadhesion time of more than 6 h. Similarly, in-vitro permeation studies showed 65.96% drug release of the sustained dosage form. It can be concluded that formulation F4 could be used to release the drug in controlled way in buccal cavity without the risk of mucosal irritation.

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