

TRANSBUCCAL DELIVERY OF SPRAY DRIED LOVASTATIN FROM MUCOADHESIVE BUCCAL PATCHES AND *IN VITRO* CHARACTERIZATION

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ABSTRACT

Objective: The aim of the present work was to develop and characterize mucoadhesive film of spray dried Lovastatin (LVS) for buccal delivery to enhance bioavailability.

Methods: Mucoadhesive films were prepared by solvent casting technique by using different polymers HPMCK4M, HPMC E5LV and chitosan. The successful patches were evaluated for film thickness, weight, content uniformity, surface pH, swelling index, folding endurance, *ex-vivo* residence time, *ex-vivo* bioadhesion test, *in vitro* drug release, *ex-vivo* drug permeation and stability study.

Results: The thickness of all prepared patches ranged from 0.21±0.07 to 1.5±0.39 mm, the weight of the film 89.10±0.6 to 128.57±0.3 mg, drug content 85.47±0.87 to 97.33±0.31%, surface pH 5.6±0.67 to 7.6±0.98, swelling index 23.0±4.1 to 76.5±3.6%, folding endurance 165±1.9 to 350±2.5 respectively. *Ex-vivo* residence time ranged from 2.2±0.08 to 8.2±0.17 h and *ex-vivo* bioadhesive strength 30±0.64 to 66±0.43 g. The formulations with HPMC E5 shown short period of residence time and shows weak force of adhesion, which might be because of low viscosity of the polymer which resulted into weak adhesion. The percentage drug release and *ex-vivo* drug permeation was in the following descending order HPMC K4M>HPMC E5LV>chitosan. These results confirm the extension of drug release in case of ionic polymer chitosan. The kinetics data shows that drug release and permeation follows nonfiction diffusion. Accelerated stability data revealed that there is no significant change in drug content, *in vitro* drug release and *ex-vivo* permeation.

Conclusion: It can be concluded that mucoadhesive buccal patch is a promising dosage form to enhance the drug bioavailability by preventing first-pass metabolism thus providing better therapeutic efficacy.

Keywords: Lovastatin, HPMCK4M, HPMC E5LV, Chitosan, *Ex-vivo* bioadhesion, Swelling index, *Ex-vivo* permeation

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INTRODUCTION

The oral drug delivery is considered to be the most preferred route by majority of the patients amongst the various available routes of drug delivery. However, oral administration of drugs has certain disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the GI tract that prohibits oral administration of various classes of drugs [1]. Since last three decades researchers have been focusing on buccal drug delivery, as it has shown ability to enhance the therapeutic efficacy of poorly effective oral drugs [2]. The direct entry of the drug into the systemic circulation avoids the first-pass hepatic metabolism leading to increase in bioavailability. Other advantages are low enzymatic activity, painless administration, easy drug withdrawal, facility to include permeation enhancers/enzyme inhibitors or pH modifiers in the formulation and versatility in designing as multidirectional or unidirectional release systems for local or systemic actions. Various mucoadhesive formulations were suggested for buccal delivery that includes buccal patches, adhesive tablets, and adhesive gels. However, buccal films are preferred over adhesive tablets in terms of flexibility and comfort [3]. Mucoadhesive formulations use polymers as adhesive components. These polymers form viscous liquids when hydrated, increasing their retention time over mucosal surfaces which may lead to interaction between polymers chain and the oral mucosa. Thus, the adequate selection of the polymer is crucial for the correct delivery of drugs in mucoadhesive formulations [4].

Lovastatin (LVS) is an antihyperlipidaemic drug. Its principal metabolite that is hydroxy acid is potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, which catalyses the conversion of hydroxy methyl glutarate to mevalonate which is an early and rate limiting step in biosynthesis of cholesterol [5]. It has been proven that LVS is effective as therapeutic and prophylactic

agent in the management of major morbidities such as atherosclerosis, peripheral arterial disease and cardiovascular disease [6]. The drug lovastatin possesses some major limitations such as low solubility, less bioavailability (5%), short half-life (1.1-1.7 h), excretion in the bile (85%), gastrointestinal side effects [7]. It is a white crystalline powder which has low aqueous solubility, which is 0.4 µg/ml at room temperature [8].

To overcome the low aqueous solubility of model drug LVS an attempt has been made to enhance the aqueous system solubility of LVS by preparing solid dispersion by spray drying technique by using PVPK30 polymer. The result findings are published in our previous paper "Physicochemical characterization and dissolution study of spray-dried amorphous Lovastatin with PVPK30"; The Pharma Innovation journal; 7(3)2018:498-502.

In the current study, the solid dispersions (prepared by spray drying technique SD4) showing best *in-vitro* drug release profile is selected and further developed into transbuccal patches, which helps to facilitate drug absorption through transbuccal route and overcome the other problems such as first-pass metabolism, excretion in the bile and other side effects. Hence by formulating spray-dried lovastatin into transbuccal films, an attempt has been made to improve the bioavailability of the drug LVS.

MATERIALS AND METHODS

Materials

LVS is obtained as gift sample by Biocon Limited, Bangalore Karnataka India. HPMCK4M by Yarrow chemical products Mumbai Maharashtra India and chitosan from Central Institute of fisheries technology Cochin, Kerala India. All other chemicals and solvents used in this study were of analytical grade reagents.

Methods

Compatibility studies

Compatibility studies were carried out for SD4 and polymers used to prepare the transbuccal film. SD4, HPMC K4M, HPMC E5LV, chitosan polymers and transbuccal films were subjected for Infrared spectroscopic analysis.

Fourier transform infrared spectra of moisture-free powdered samples were obtained by using spectrophotometer (FT-IR Shimadzu Co., Japan) by potassium bromide (KBr) pellet method (2 mg of sample in 200 mg of KBr). The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1} .

Formulation of transbuccal films

The solvent casting technique was used for the preparation of spray-dried LVS mucoadhesive buccal patches. The buccal patches were formulated by using different polymers i.e., HPMCK4M, HPMC E5LV and chitosan. These polymers were

chosen from a series of trials on the base of the chemical compatibility, organoleptic properties and adhesiveness property. The placebo films were prepared. The processing variables used while formulating the placebo patches were the concentration of polymers and plasticizers. After results of placebo films were found to be satisfactory, the formulations containing different concentrations of polymers were prepared by using above-said polymers.

Transbuccal film by using HPMC K4M

The polymer HPMCK4M is dissolved in 10 ml of mixture of ethanol and distilled water (3:2) and soaked for overnight. The polymeric solution was stirred on magnetic stirrer for 2 h. The solid dispersion equivalent to 120 mg LVS was added followed by addition of plasticizer 4 % glycerol and 20 mg of menthol as permeation enhancer. The mixture was stirred for 30 min and then poured into Petri dish, which is stored at 4 °C to remove air bubbles entrapped and finally dried at 37 °C for 4 h. The dried films were cut into 1 cm^2 and packed in aluminum foil and stored [1, 4, 9].

Table 1: Composition of the transbuccal film by using HPMC K4M

Formulation code	Solid dispersion equivalent to LVS (mg)	HPMC K4M (mg)	Plasticizer Glycerol (%)	Permeation enhancer menthol (mg)
F1	120	100	5	20
F2	120	200	5	20
F3	120	300	5	20
F4	120	400	5	20
F5	120	500	5	20
F6	120	600	5	20

Transbuccal film by using HPMC E5

The polymer HPMC E5 is dissolved in 10 ml of a mixture of dichloromethane and ethanol (1:1) and soaked for overnight. The polymeric solution was stirred on magnetic stirrer for 2 h. The solid dispersion equivalent to 120 mg LVS was added followed by

addition of plasticizer 0.7 % glycerol and 20 mg of menthol as permeation enhancer. The mixture was stirred for 30 min and then poured into Petri dish, which is stored at 4 °C to remove air bubbles entrapped and finally dried at 37 °C for 4 h. The dried films were cut into 1 cm^2 and packed in aluminum foil and stored [4, 10].

Table 2: Composition of transbuccal film by using HPMC E5

Formulation code	Solid dispersion equivalent to LVS (mg)	HPMC E5 (mg)	Plasticizer Glycerol (%)	Permeation enhancer menthol (mg)
F7	120	100	0.7	20
F8	120	200	0.7	20
F9	120	300	0.7	20
F10	120	400	0.7	20
F11	120	500	0.7	20
F12	120	600	0.7	20

Transbuccal film by using chitosan

Citric acid 20 mg was dissolved in water. To this solution, chitosan polymer was added and soaked for overnight. The polymeric solution was stirred on magnetic stirrer for 2 h. The solid dispersion

equivalent to 120 mg LVS was added. The mixture was stirred for 30 min and then poured into petridish, which is stored at 4 °C to remove air bubbles entrapped. The patches were finally dried at 25 °C for 24 h. The dried films were cut into 1 cm^2 and packed in aluminium foil and stored [4].

Table 3: Composition of the transbuccal film by using chitosan

Formulation code	Solid dispersion equivalent to LVS (mg)	Chitosan (mg)	Plasticizer Glycerol (%)	Permeation enhancer citric acid (mg)
F13	120	100	3	20
F14	120	200	3	20
F15	120	300	3	20
F16	120	400	3	20
F17	120	500	3	20
F18	120	600	3	20

Physicochemical characteristics of transbuccal patches

Film thickness and weight

The thickness of all the formulations was measured by screw gauge (Mitutoyo Corporation, Kawasaki, Japan) and the weight of these films were determined by using electronic balance [1].

Content uniformity

The film was dissolved in 100 ml isotonic phosphate buffer pH 6.8±0.2, filtered (0.22 µm), and resultant solutions were analyzed by UV Spectrophotometer at 238 nm. The experiment was performed in triplicate [1].

Surface pH

The microenvironmental pH of all the formulations was measured so as to predict its effect on buccal mucosa. The formulations were first wetted by adding distilled water to its surface. The surface pH was then recorded by bringing a glass electrode near the surface of the formulation and allowing it to equilibrate for 1 min. The average pH±SD was determined for all formulations [1].

Swelling index

The buccal patches were weighed individually (designated as W_1) and placed separately in 2% agar gel plates, incubated at 37±1 °C and examined for any physical changes. At regular 1 h time intervals until 3 h, films were removed from the gel plates and excess surface water was removed carefully using the filter-paper. The swollen films were then reweighed (W_2) and the swelling index (SI) was calculated using the following formula:

$$SI = \frac{W_2 - W_1}{W_1} \times 100$$

The experiment was performed in triplicate and average±SD values were recorded [1].

Folding endurance

Folding endurance of the films was determined by repeatedly folding and unfolding the films at the same place till it broke or for 300 times, which is considered to be a satisfactory value to reveal good folding-endurance properties. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance [1].

Ex-vivo residence time/adherence time

The *ex-vivo* residence time is studied (n=3) to know the time required for complete erosion and/or detachment of the film from the mucosa surface. The fresh goat mucosa is fixed to the inner side of the beaker about 2.5 cm from the bottom. One side of the film was wetted with 1 drop of phosphate buffer pH 6.8 and it is adhered to the surface of the buccal mucosa by applying slight force with fingertips for 30 s. The beaker was filled with 500 ml of phosphate buffer pH 6.8 and was kept at 37±0.5 °C. After 2 min, a 50 rpm stirring rate is applied to simulate the buccal cavity environment and film adherence is monitored for 8 h [1].

Ex-vivo bioadhesion test

Modified physical balance method is used to measure the *ex-vivo* mucoadhesive strength of prepared films. Fresh goat's buccal mucosa is taken and cut into piece and washed with phosphate buffer pH 6.8 and tied to the open mouth of glass vial which is tightly fitted into a glass beaker which is filled with phosphate buffer pH 6.8 in such way that, it just touched the buccal surface. The temperature of this beaker is maintained at 37 °C±1 °C. The film is adhered to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance are balanced with 5g weight on the right side of the pan, which is lowered the pan along with the film over the mucosa. The balance is kept in this position for 5 min of contact

time. The water drops are added slowly to the right-hand side pan, until the film detached from the mucosal surface. The weight required to detach the film from the mucosal membrane surface is a measure of mucoadhesive strength. All the experiments are performed in triplicates and mean±SD are reported. The following formula is used to calculate the detachment force [1].

$$\text{Force of adhesion (N)} = (g \times 9.81) / 1000$$

$$\text{Detachment force (N/m}^2\text{)} = \text{Force of adhesion (N)} / \text{Surface area (m}^2\text{)}$$

In vitro drug release study

In vitro drug release is carried out by paddle over disc dissolution apparatus. The transbuccal patch is placed beneath the disc in the dissolution jar containing 900 ml phosphate buffer (pH 6.8) solution. The bath temperature is maintained at 37±1 °C with 50 rpm speed. Aliquots of 5 ml are withdrawn at prespecified time intervals for 6 h. same volume of fresh buffer solution is replaced. The withdrawn sample solution is filtered through 0.4 µm membrane filter and the amount of drug is determined by measuring the absorbance of the aliquots at 238 nm using UV spectrophotometer and percentage drug release were plotted [1].

Ex-vivo drug permeation study

Franz diffusion cell is used to carry out *ex-vivo* drug permeation study. Fresh goat buccal mucosa is fixed on a diffusion cell between the donor and receptor compartment. The transbuccal patch is fixed on the mucosal membrane. Five ml of phosphate buffer pH 6.8 in the donor compartment and 45 ml of the phosphate buffer pH 6.8 in the receptor compartment is filled as dissolution fluid. The fluids maintained at 37±1 °C and stirred continuously at speed of 50±5 rpm. Aliquots of 1 ml of the sample are withdrawn at prespecified time interval. Same volume of fresh buffer solution is replaced. The withdrawn sample solution is filtered through 0.4 µm membrane filter and the amount of drug is determined by measuring the absorbance of the aliquots at 238 nm using UV spectrophotometer and percentage drug permeated were plotted [1].

Stability study

The accelerated stability of optimized formulation F3 is conducted as per ICH guidelines at 40 °C/75% RH up to 6 mo. Periodically samples are removed (initial, 1 mo, 2 mo, 3 mo) and analyzed for drug content, *in vitro* release and *ex-vivo* permeation [9].

RESULTS AND DISCUSSION

Compatibility studies

The IR Spectra of SD4 (SDSP) and transbuccal formulations (SD-HPMCK4M, SD-HPMCE5LV and SD-chitosan) are shown in the fig. 1. Upon comparison of IR Spectra of SD4(SDSP) and transbuccal formulations(SD-HPMCK4M, SD-HPMCE5LV and SD-chitosan), it was found that the characteristic peaks of LVS in SD4 were 3535 cm⁻¹(alcohol OH stretch), 3016 cm⁻¹ (olefinic CH stretching vibrations) 1725 cm⁻¹and 1695 cm⁻¹ (lactone and ester carbonyl stretch) also found in transbuccal formulations along with characteristic peaks of respective polymers. It can be concluded by these observations that there are no possible interactions between the SD4 and polymers.

Formulation of transbuccal films

The formulations containing different concentrations of polymers were prepared and their effects on physicochemical characteristics were studied. However, the selections of plasticizer were finalized during placebo film preparation.

Physicochemical characteristics of transbuccal patches

The physicochemical characteristics data of transbuccal patches are shown in the tables (4-6) below.

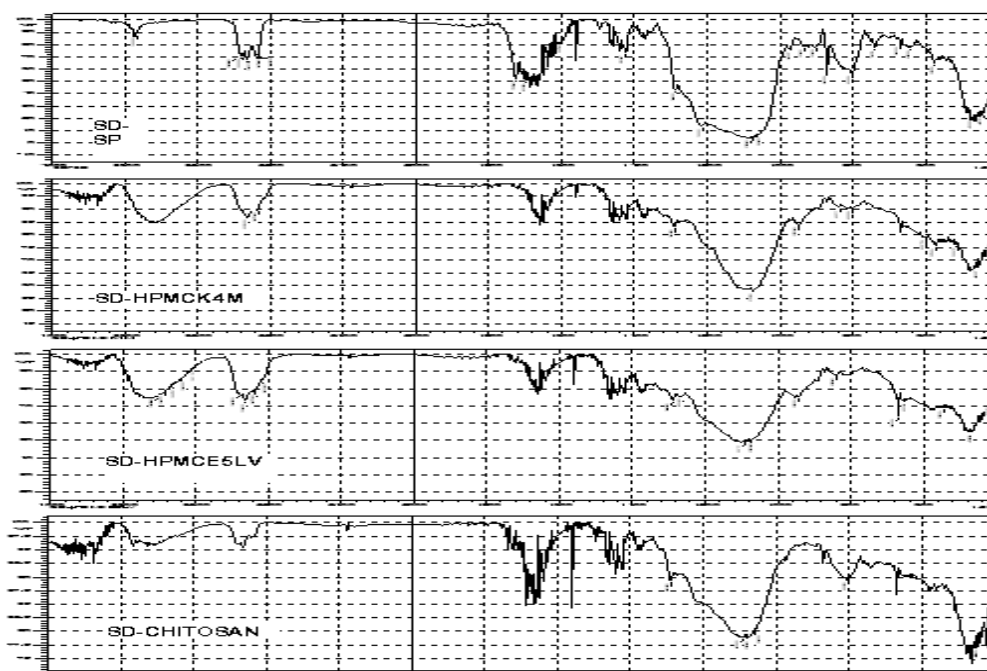


Fig. 1: FTIR spectra of SD4 (SDSP) and transbuccal formulations (SD-HPMCK4M, SD-HPMCE5LV and SD-Chitosan)

Table 4: Physicochemical characteristics of transbuccal film by using HPMC K4M (F1-F6)

Formulation code	Thickness (mm)*	Weight of film (mg)*	Drug content (%)*	Surface pH*	Swelling index (%)*	Folding endurance*
F1	0.27±0.05	91.91±0.2	91.71±0.33	6.2±0.07	31.7±3.5	315±7.5
F2	0.34±0.02	101.25±0.3	93.23±0.41	6.4±0.05	42.9±5.1	312±5.0
F3	0.51±0.04	108.32±0.4	95.75±0.56	6.7±0.04	56.0±2.1	350±2.5
F4	0.62±0.01	115.56±0.2	94.80±0.61	6.4±0.12	57.9±2.8	340±6.0
F5	0.68±0.03	125.46±0.6	91.68±0.23	6.3±1.23	49.4±1.8	324±4.5
F6	0.81±0.1	132.03±0.8	89.34±0.17	5.8±0.98	61.3±1.6	307±9.0

*Data are expressed as mean±standard deviation of the mean [SD], n=3.

Table 5: Physicochemical characteristics of transbuccal film by using HPMC E5 (F7-F12)

Formulation code	Thickness (mm)*	Weight of film (mg)*	Drug Content (%)*	Surface pH*	Swelling Index (%)*	Folding endurance*
F7	0.21±0.07	89.10±0.6	90.23±0.51	7.6±0.98	23.0±4.1	326±4.7
F8	0.27±0.04	98.91±0.5	95.27±0.47	6.7±0.07	27.0±3.6	319±5.1
F9	0.55±0.03	103.25±0.3	97.33±0.31	6.9±0.12	48.2±1.1	345±1.8
F10	0.82±0.02	112.16±0.2	93.82±0.11	6.3±0.83	52.0±2.6	337±3.1
F11	0.88±0.06	121.36±0.5	88.67±0.61	7.2±1.23	61.3±2.3	312±2.5
F12	0.91±0.1	128.57±0.3	85.47±0.87	6.4±0.03	56.4±5.2	336±4.5

*Data are expressed as mean±standard deviation of the mean [SD], n=3.

Table 6: Physicochemical characteristics of transbuccal film by using chitosan (F13-F18)

Formulation code	Thickness (mm)*	Weight of film (mg)*	Drug content (%)*	Surface pH*	Swelling index (%)*	Folding endurance*
F13	0.92±0.03	91.91±0.4	93.51±0.43	5.6±0.67	54.4±5.2	193±1.1
F14	0.98±0.06	104.25±0.5	94.23±0.71	6.2±0.12	58.2±1.7	194±2.5
F15	1.15±0.07	103.32±0.2	93.75±0.76	6.5±0.27	63.3±1.6	199±3.7
F16	1.12±0.53	108.56±0.1	95.80±0.41	6.7±1.63	68.3±1.6	208±0.8
F17	1.5±0.39	122.46±0.7	92.68±0.73	7.2±0.28	76.5±3.6	176±3.8
F18	1.4±0.81	128.03±0.4	91.62±0.82	6.5±0.83	73.3±6.1	165±1.9

*Data are expressed as mean±standard deviation of the mean [SD], n=3.

As the concentration of polymers increases, both film thickness and weight of the patches also increases. Weight of the film ranged from 89.10±0.6 to 132.03±0.8 mg. Weight and thickness are directly

related to the accuracy of the dose distribution in the film. The thickness of the film ranged from 0.21±0.07 to 132.03±0.8 mm. The films of chitosan shown highest thickness. Drug content ranges from

85.47±0.87 to 97.33±0.31. Uniformity in drug content is important parameter in formulation which confirm reproducibility of the product. The assay of drug content at three different places in each film showed that the drug was uniformly distributed throughout the films. The surface pH ranged from 5.6 to 7.6 which ensure there is no mucosal irritation due to the formulation.

The swelling index study was carried out to find out the degree of swelling of buccal films in simulated saliva solutions. HPMCK4M and HPMC E5 films started swelling after 5 min and chitosan after 30 min when hydrated on agar medium due to the swellable hydrophilic polymers. The results shown that as the polymer concentration increases the swelling index was also increased. As per the study carried out by the authors Pankaj kumar *et al.*, [1] swelling of the polymers makes strong secondary hydrogen bonding with buccal mucosa and thus results in good mucoadhesion which provides unidirectional release of the drug. Chitosan buccal films (F13 to F 18) shown high values of swelling index as compared to HPMC films (F1 to F12). H. Castan *et al.*, [2] stated that this may be due to chitosan when wetted can gain weight and size by 150%. This high value of swelling index causes discomforts to the patient.

All the developed formulations were flexible and shown good folding endurance. However, HPMC K4M and HPMC E5 formulations (F1 to

F12) shown good folding endurance but in case of chitosan containing formulations (F13 to F18), the films became brittle, lost elasticity as the polymer concentration increased. Hence the folding endurance values decreased as the polymer concentration increased.

Ex-vivo residence time

Residence of film is directly related to the mucoadhesive strength, which is consequence of interaction between mucin and polymers. Further adequate hydration is required for the polymers to get charged and impart sufficient mucoresidence. *Ex-vivo* residence time ranged from 2.2±0.08 to 8.2±0.17 h. In the formulations with HPMC K4M polymers (table 7) containing films, the presence of hydroxyl groups which facilitate uptake of water into polymer matrix and enhance mucoadhesiveness. These polymers also form viscous liquids when hydrated with increasing their retention time over mucosal surfaces, which may lead to adhesive interactions. The formulations with HPMC E5 (table 8) shown short period of residence time, which might be because of low viscosity of the polymer which resulted into weak adhesion. In case of formulations with chitosan (table 9), there is interaction between positively charged amino group and negatively charged mucin of membrane and helps in bioadhesion for longer duration of time.

Table 7: Physicochemical characterization, cumulative percentage release and percentage drug permeated of F1-F6

Formulation code	Ex-vivo residence time*	Ex-vivo bioadhesive strength(g)*	Detachment force (N/m ²)	% Drug released after 6 h*	% Drug permeated after 6 h*
F1	6.1±0.12	40±1.41	3920	97.78±1.08	96.78±1.1
F2	6.2±0.08	42±0.86	4116	95.32±3.5	94.24±1.0
F3	6.5±0.10	43±1.07	4214	94.17±0.62	93.27±2.6
F4	7.2±0.15	44±1.43	4312	92.34±1.4	87.34±4.4
F5	7.3±0.11	45±1.86	4410	89.24±2.0	77.43±3.0
F6	7.4±0.13	47±0.88	4606	86.17±1.2	68.42±1.3

*Data are expressed as mean±standard deviation of the mean [SD], n=3.

Table 8: Physicochemical characterization, cumulative percentage release and percentage drug permeated of F7-F12

Formulation code	Ex-vivo residence time*	Ex-vivo bioadhesive strength (g)*	Detachment force (N/m ²)	% Drug released after 6 h*	% Drug permeated after 6 h*
F7	2.2±0.08	30±0.64	2940	94.5±1.4	90.45±3.2
F8	2.3±0.13	31±0.76	3038	92.7±1.1	89.57±3.9
F9	2.6±0.18	32±0.63	3136	91.32±1.2	86.45±3.0
F10	2.7±0.16	34±0.35	3332	90.88±1.7	81.37±0.8
F11	2.7±0.16	36±0.41	3528	89.88±1.7	78.73±1.3
F12	2.8±0.17	37±0.36	3626	86.47±3.1	71.56±0.5

*Data are expressed as mean±standard deviation of the mean [SD], n=3.

Table 9: Physicochemical characterization, cumulative percentage release and percentage drug permeated of F13-F18

Formulation code	Ex-vivo residence time*	Ex-vivo bioadhesive strength(g)*	Detachment force (N/m ²)	% Drug released after 6 h*	% Drug permeated after 6 h*
F13	7.2±0.17	54±0.52	5292	76.44±3.1	73.25±1.7
F14	7.5±0.08	57±0.84	5586	74.15±1.0	69.83±4.8
F15	7.9±0.12	60±0.57	5880	72.35±2.2	65.23±2.8
F16	8.1±0.61	62±0.33	6076	71.83±3.6	63.12±3.6
F17	8.1±0.91	65±0.57	6370	70.79±2.5	60.56±2.6
F18	8.2±0.17	66±0.43	6468	68.73±1.1	57.34±2.1

* Data are expressed as mean±standard deviation of the mean [SD], n=3.

Ex-vivo bioadhesion test

Mucoadhesive strength plays an important role in proper adherence of the film to the mucosal surface. Excessive adhesion may cause discomfort to the patient leading to the patient in compliance. Hence optimum mucoadhesion is required for film for effective therapy.

The *Ex-vivo* bioadhesive strength and Detachment force value are shown in the above table (7-9). Transbuccal films with HPMC K4M (F1-F6); shows good mucoadhesion, which may be attributed to the

hydration and liquid entrapment in the polymer network, after formation of viscous polymeric network, however HPMC E5 (F7-F12) polymer films shows the weak force of adhesion. According to Magdy *et al.*, [12] this might be because of its low viscosity of the polymer. Apart from this, hydrophilicity PVP K30 (from Solid dispersions which is incorporated in the transbuccal film) might further have weakened the force of adhesion. The transbuccal films of chitosan (F13-F18) also show good mucoadhesion. According to Cui *et al.* [13] the strong viscoelastic property and structure of

chitosan might be attributed to its high mucoadhesive force which occurs because of interaction between amino group of chitosan and mucin of biomembrane.

In vitro drug release

The drug release study was carried out over a period of no longer than 6 h given that formulations cannot remain for longer periods on the surface of the buccal membrane.

The drug release profile of formulations is shown in the fig. 2. At the end of the 6th h F₁ showed highest drug release of 97.78% and F₆ is 86.17%. In case of HPMC E5 formulations, at the end of the 6th h F7 showed highest drug release of 94.5% and F12 is 86.47%. The significant decrease in drug release is found as the polymer concentration increases in formulations from F1 to F6. Meher *et al.* [2] states that this could be related to the increase in thickness of the

film with an increase in HPMC concentration. Thus the time requires for dissolution medium to penetrate into the polymer chain located through the depth of the film increases.

Similar observation is made with HPMC E5 formulations also. However initial drug release (30 min) is more as compared to other formulations. This might be because of low viscosity of HPMC E5 polymer as observed by Magdy *et al.*, [12]

At the end of the 6th h F13 showed highest drug release of 76.44% and F18 is 68.73%. In the case of chitosan containing formulations drug release values after completion of 6th h is lower as compared to other formulations. Similar observation is found by author Patel R P *et al.*, [1] chitosan is a cationic polymer which might have formed complex with PVP K30 (polymer used to prepare solid dispersions which is incorporated in the transbuccal films), which is non-ionic polymer leading to extension of the drug release.

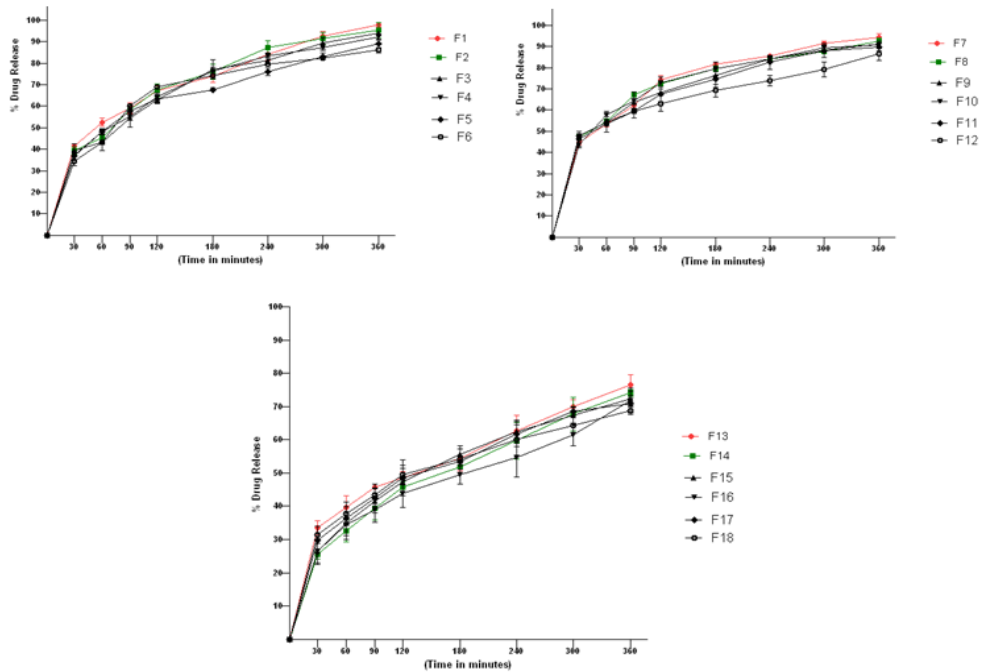


Fig. 2: Percentage drug release profile of transbuccal films (F1-F18) (Values are expressed as mean±SD, n=3)

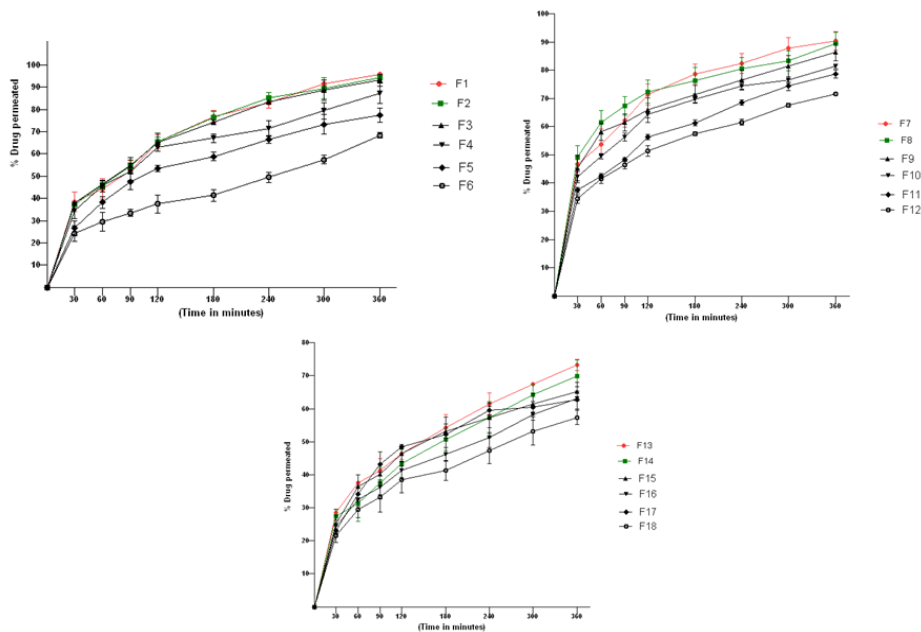


Fig. 3: Percentage drug permeation profile of transbuccal films (F1-F18) (Values are expressed as mean±SD, n=3)

Ex-vivo drug permeation study

The fig. 3 shows the drug permeation profile of formulations. Drug permeated at the 6th h of F₁ is 96.78% and F₆ is 68.42%. Similarly, F₇ is 90.45 % and F₁₂ is 71.56 %. In case of HPMC polymers, formation of hydrogel occurs at the surface of biomembrane, which leads to hydration and swelling of mucoadhesive films which promotes diffusion of drug. Drug permeated at the end of the 6th h of F₁₃ is 73.25 % and F₁₈ is 57.34 %. As discussed in the study of swelling index, chitosan films when wetted can gain weight and size by 150% due to swelling of mucoadhesive films, formation of very thick hydrogen layer leads to the longer diffusion path length leading into delayed diffusion. Castan *et al.* [4] states that drug diffusion is delayed in the case of ionic polymers such as chitosan as compared to nonionic polymers (HPMC).

To investigate the release kinetics of drug release from buccal films, the *in vitro* drug release and *ex-vivo* permeation data were subjected

to fit various kinetic models using PCP Disso ver 2 software Pune India. The r^2 and n values are determined. All the buccal films showed n values in the range of 0.73 to 0.87, indicating that the drug release followed by nonfickian diffusion and the best fit model observed to be Higuchi model.

Based on results of Drug content, swelling index, folding endurance *in vitro* bioadhesion, *in vitro* drug release and *ex-vivo* permeation, we can conclude that HPMCK4M formulations (F₁-F₆) are best formulations. The formulation F₃ is selected for the further stability study.

Stability study

Accelerated stability data is given in table 10. The results of the stability study revealed that there is no significant change in drug content, *in vitro* drug release and *ex-vivo* permeation.

Table 10: Accelerated stability data of the best formulation F3

Time	Drug content*	% drug released*	% drug permeated*
Initial	93.80±0.71	93.13±2.15	92.34±1.14
1 mo	93.21±0.37	92.17±3.17	92.23±1.67
2 mo	92.34±0.54	92.45±1.13	91.45±2.44
3 mo	91.46±0.56	91.17±2.23	91.87±1.24

* Data are expressed as mean±standard deviation of the mean [SD], n=3.

CONCLUSION

Mucoadhesive films of spraydried LVS were successfully developed by using 3 different polymers HPMCK4M, HPMCE5LV and chitosan. An *in vitro* characterisation result shows that HPMCK4M formulations are best formulations. Drug release and permeation were found to be nonfickian diffusion and best fit model observed to be Higuchi model. Stability study data revealed that there is no significant change in the drug content, *in vitro* drug release and *ex-vivo* permeation. By using transbuccal mucoadhesive films, it can enhance the drug bioavailability by preventing the first-pass metabolism thus providing better therapeutic efficacy.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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