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Original Article

MUCOADHESIVE BILAYER BUCCAL PATCHES OF VERAPAMIL HYDROCHLORIDE: FORMULATION DEVELOPMENT AND CHARACTERIZATION

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ABSTRACT

Objective: To develop mucadhesive bilayer buccal patches of Verapamil Hydrochloride (VPH) to enhance its bioavailability and reduce its dosing frequency

Methods: Mucoadhesive bilayered buccal patches of VPH were formulated using solvent casting method. Ethyl cellulose and cellulose acetate butyrate were used for backing layer where as hydroxypropylmethyl cellulose (K15M and K100M), polyvinyl alcohol and polyethylene oxide-303 were used for mucoadhesive matrix layer. Combination of hydroxypropylmethyl cellulose K15M with polyvinyl alcohol and polyethylene oxide-303 were used to obtain desired characteristics. Menthol and sodium glycocholate were used as a permeation enhancer and goat buccal mucosa used as model membrane. The patches were evaluated for their characteristics like thickness, tensile strength, percentage elongation, drug content, surface pH, swelling index, *ex-vivo* residence time, *ex-vivo* mucoadhesion using texture analyzer, *ex-vivo* permeation using Franz diffusion cell and *in-vitro* drug release using USP-23 dissolution apparatus-V with slight modification (paddle-over-disc).

Results: Optimized patches batch showed more satisfactory results in terms of residence time (6.50±0.10h), mucoadhesive strength (223.00±20.00g) and drug release 83.20% in 10h. The permeation of drug increased from 44.43% to 71.70% by using 12%w/w of menthol.

Conclusion: Mucoadhesive bilayered buccal patches of VPH may have enhanced bioavailability. For sustained delivery HPMC K100M and combined polymers HPMC K15M-PEO 303 in 2:1 ratio authenticate the best characterization.

Keywords: Verapamil Hydrochloride, Bilayered-patches, backing layer, mucoadhesive, QTS-texture analyzer, permeation enhancers.

INTRODUCTION

In recent trend, buccal delivery system provides an attractive alternate to the oral route of drug administration. Problems such as high first - pass metabolism and drug degradation in gastrointestinal environment can be circumvented by administering the drug via the buccal route [1, 2]. The buccal route offers many advantages including good accessibility, nonkeratinized mucosa, dense capillary vessel network, large absorption area, low enzymatic activity, patient acceptance, lack of the hepatic first-pass metabolism, better control of plasma levels, lower variation in bioavailability and minimum fluctuations [3-6]. It's worthwhile to note that, buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by easy removal of the patches. In addition, it's quite easier to administer drugs to patients who cannot be dosed orally. Therefore, adhesive mucosal dosage forms were suggested for oral delivery that includes adhesive tablets, [7, 8] adhesive gels [9, 10] and adhesive patches [11, 12]. However, buccal patches are preferable over adhesive tablets in terms of flexibility and comfort [13]. Delivery of various therapeutic agents via buccal route using conventional matrix tablets, patches and hydrogel has been studied and reported by several research groups [14-19]. Technically, an ideal buccal adhesive system must maintain its position in the mouth for a few hours, which releases the drug in a controlled fashion in a unidirectional way toward the mucosa [20, 21].

Verapamil Hydrochloride (VPH) is phenykalkylamine derivative belong to a group of heterogeneous compounds known as calcium channel blocker and a class IV antiarrhythmic agent. It is widely used in the treatment of supraventricular tachyarrhythmia, angina pectoris hypertension and myocardial infarction [22, 23]. The oral absorption of the drug from oral dosage forms is about 90% but it is subjected to a very extensive first-pass metabolism in the liver [24] and its bioavailability is only about 20% [23, 25, 26].

Since this drug has a short elimination half-life of 2-4 hours and is eliminates rapidly, therefore repeated daily administration are required to maintain effective plasma levels [27]. It has been suggested that drugs with biological half lives in the range of 2-8 hours are good candidates for sustained release formulations [28]. The short half-life and extensive first pass metabolism of VPH makes it a suitable candidate for administration via a buccal delivery system that provides sustained delivery without pre-systemic metabolism. Developing mucoadhesive buccal patches of VPH, may counter act the problems associated with conventional system. Thereby, Mucoadhesive bilayered buccal patches of VPH were prepared using various polymers such as Ethyl cellulose (EC), Cellulose acetate butyrate (CAB) for backing layer and Hydroxypropylmethyl cellulose (HPMC K15M and HPMC K100M), polyvinyl alcohol (PVA), polyethylene oxide (PEO 303) for mucoadhesive matrix layer. Polyethylene glycol (PEG 400), glycerol, propylene glycol (PG) and di-n-butyl phthalate (DBP) were used as a plasticizer. Combination of polymers HPMC K15M with PVA and PEO 303 were tried to obtain desired film forming properties. Menthol and sodium glycocholate (SG) were used for permeation enhancer. Acetone, water and dichloromethane were used as solvents. Goat buccal mucosa was used as model membrane. It has been suggested that an ideal buccal drug delivery system should possess flexible, elastic, soft yet strong enough to withstand breakage due to stress from activities in the mouth, good mucoadhesive properties so that it can be retained in the oral cavity for the desired duration and release the drug in a unidirectional way toward the mucosa in a sustained and predictable manner [29, 30]. In addition, to prevent discomfort, swelling of the patch should not be too extensive and buccal patches should be generally based on mucadhesive polymers which, once hydrated, adhere to the buccal mucosa and withstand salivation, tongue movements and swallowing for a significant period of time [31, 32]. The present study has been designed on the basis of all these desirable properties for buccal patches.

MATERIALS AND METHODS

Materials

The following materials were used: VPH was obtained as gift from (Nicholas Piramal India Limited, Chennai, India), HPMC K15M and HPMC K100M were gifts from Colorcon Asia Pvt. Ltd, Goa, India. PEG 400, PG, glycerol, DBP, acetone and dichloromethane purchased from CDH Pvt. Ltd. India. PEO 303, Cellulose acetate butyrate, EC and SG was purchased from HIMEDIA Laboratory Pvt. Ltd, India. PVA, Methanol and Menthol were purchased from S.D.Fine Chemicals Ltd, Mumbai, India and goat buccal mucosa was purchased from local slaughter house (Ahmedabad, Gujarat). All ingredients used were of analytical reagent grade.

Methods

Preformulation study was carried out to check the compatibility between drug and various polymers. Melting point was determined by Thiele's tube method. FTIR spectra of physical mixtures of polymer and drug were studied. FTIR Spectra of VPH was measured and it was compared with the standard FTIR spectra and UV spectrophotometer (UV 2450 Shimadzu Scientific) was used for the estimation of VPH. The absorbance was measured at 278 nm.

Preparation of backing layers

The backing layer was prepared by a solvent casting technique [33]. EC and CAB were dissolved in different proportion of plasticized acetone and dichloromethane solution respectively and stirred on magnetic stirrer and then, cast onto a petridish and allowed to dry at room temperature until completely dry. (Table 1)

Preparation of mucoadhesive buccal patches

Patches containing drug and different proportions of polymers were formulated by solvent casting method. Plasticized polymer solutions were prepared by dissolving different proportions of polymer in a solvent containing drug and adding a suitable plasticizer. An amount of drug was added in such a way that it would give final dose of drug 40 mg, in a patch of 2×2 cm^2 area. The viscous solution was left overnight at room temperature to ensure a clear, bubble free solution.

The plasticized drug and polymer solution was poured into a glass Petridish (7.2 cm diameter) and allowed to oven drying at 40ºC until a constant weight flexible film was formed. Dried films were carefully removed, checked for any imperfections or air bubbles and cut into patches of 2×2 cm^2 area containing 40 mg of drug per patch.

The patches were packed in aluminium foil and stored in desiccators to maintain the integrity and elasticity of the patches until further use. (Table 2). In addition to the mucoadhesive component, also incorporated additives as a permeation enhancers. Menthol and SG were taken in different concentrations to incorporated in plasticized polymer solution and cast on petridish as mentioned above. (Table 3)

Thickness

Thickness of the patches was measured using micrometer at different places. The average film thickness and standard deviation were computed.

Folding endurance

Folding endurance [34] of the film was determined by repeatedly folding one patch at the same place till it broke or folded manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three films.

Tensile Strength and percentage elongation

Tensile Strength and percentage elongation [35, 36] were evaluated using a Digital Tensiometer, (EIE Instruments, Ahmedabad) to determine mechanical properties of films. Film strip in dimension (3cm × 5.5cm) and free from air bubbles or physical imperfections, was held between two clamps positioned at a distance of 5.5cm. During measurement, the film was pulled by top clamp at a rate of 20 mm/min. The force and elongation were measured when the films broke. Measurements were run three times for each film. The tensile strength and elongation at break were calculated as below-

$$\text{Tensile strength (N/cm2)} = \frac{\text{Force at break (kg)}}{\text{Cross sectional area of sample (cm2)}} \times 9.8$$

$$\text{\% Elongation at break} = \frac{\text{Increased in length at breaking point (cm)}}{\text{Original length (cm)}} \times 100\%$$

Table 1: Composition of backing layer

Component	B1	B2	B3	B4	B5	B6
Ethyl cellulose (%w/v)	3	3	3	-	-	-
CAB (%w/v) [a]	-	-	-	3	3	3
DBP (%w/w) [b]	10	30	50	-	-	-
PG (%w/w) [c]	-	-	-	10	30	50
Acetone (mL)	20	20	20	-	-	-
Dichloromethane (mL)	-	-	-	20	20	20

[a] CAB Cellulose acetate butyrate, [b] DBP Di-n-butyl phthalate, [c] PG Propylene glycol

Table 2: Composition of mucoadhesive buccal patches

Component	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
VPH (mg)	400	400	400	400	400	400	400	400	400	400
HPMC K15M (%w/v)	3	-	-	-	2	1.5	1	2	1.5	1
HPMC K100M (%w/v)	-	3	-	-	-	-	-	-	-	-
PVA (%w/v)	-	-	6	-	1	1.5	2	-	-	-
PEO 303 (%w/v)	-	-	-	3	-	-	-	1	1.5	2
Glycerol (%w/v)	-	-	40	-	40	40	40	-	-	-
PEG 400 (%w/w)	30	30	-	30	-	-	-	30	30	30
Acetone + Water (mL) [e]	40	40	-	40	-	-	-	40	40	40
Water (mL)	-	-	20	-	40	40	40	-	-	-

[e] Acetone : Water [4:1], VPH Verapamil hydrochloride, HPMC Hydroxypropylmethyl cellulose, PVA polyvinyl alcohol, PEO Polyethylene oxide, PEG Polyethylene glycol

Table 3: Composition of mucoadhesive buccal patches containing permeation enhancer (Menthol and sodium glycocholate)

Component	P1	P2	P3	P4
Verapamil hydrochloride (mg)	400	400	400	400
HPMC K15M (%w/v)	-	2	-	2
HPMC K100M (%w/v)	3	-	3	-
PEO 303 (%w/v)	-	1	-	1
Menthol (%w/w)	12	12	-	-
Sodium glycocholate (%w/w)	-	-	4	4
PEG 400 (%w/w)	30	30	30	30
Acetone + Water (mL) [e]	40	40	40	40

[e] Acetone : Water [4:1], VPH Verapamil hydrochloride, HPMC Hydroxypropylmethyl cellulose, PVA polyvinyl alcohol, PEO Polyethylene oxide, PEG Polyethylene glycol

Swelling Study

Swelling study of prepared buccal patches was performed by calculating the function of weight increase due to swelling, which was measured for each formulation as according to [37]. Buccal patches were weighed individually (designated as W1) on a pre-weighed cover slip and were placed separately in petridish and 10 mL of isotonic phosphate buffer (IPB), pH 6.8. At a regular time intervals, the cover slip was removed and weighed (W2), until 4 hours. The difference in weights increased due to absorption of water and swelling index (SI) were calculate. The experiments were performed in triplicate, and average values were reported.

$$SI = \frac{W2 - W1}{W1} \times 100$$

Where, W1=Initial weight of patches, W2= Weight of swell patches after regular time intervals.

Surface pH Study

The method adopted by [38, 39] was used to determine the surface pH of patches. A combined glass electrode was used for this purpose. Each patch was allowed to swell by keeping it in contact with 5 mL of distilled water for 2 hours at room temperature, and the pH was noted by bringing the electrode into contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate, and average values were reported.

Percentage moisture absorption (PMA)

The PMA [28, 40] test was carried out to check the physical stability of the buccal patches at high humid conditions. In the present study the moisture absorption capacity of the patches were determined as follows. Three 2×2 cm^2 areas of films were cut out and weighed accurately then the films were placed in desiccators containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators at 60 ± 5 % RH (Relative Humidity). After 3 days the patches were removed, weighed and average percentage moisture absorption of three patches was calculated.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture loss (PML)

The PML [28, 40] was also carried to check the integrity of films at dry condition. Three 2×2 cm^2 area films was cut out and weighed accurately and kept in desiccators' containing fused anhydrous calcium chloride. After 3 days the films were removed, weighed and average percentage moisture loss of three films was calculated.

$$\text{Percentage moisture loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Drug Content Uniformity

Drug content uniformity [28] was determined by dissolving the patch by homogenization in 100 mLof IPB, pH 6.8 for 10 h under occasional shaking and the resulting solution was filtered through a 0.45 µm Whatman filter paper. The drug content was then determined after proper dilution at 278 nm using a UV spectrophotometer (UV 2450 Shimadzu scientific). The experiments were performed in triplicate, and average values were reported.

$$\text{Content Uniformity} = \frac{\text{Actual amount of drug in film}}{\text{Theoretical amount of drug present in film}} \times 100$$

***In-vitro* Drug Release**

The USP 23 Dissolution test apparatus 5 (Electrolab TDT-06, Mumbai) with slight modification (paddle over disc) method was used to study the *In-vitro* drug release from buccal patches [41]. The dissolution medium consisted of 500 mL of IPB, pH 6.8. The release was performed at 37ºC, at a paddle rotation speed of 50 rpm. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate). The disk was put in the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples 5 mL were withdrawn at predetermined time intervals and fresh medium was used to replace sample volume. The samples were filtered through 0.45 µm Whatman filter paper with appropriate dilutions with phosphate buffer pH 6.8 and analyzed using a UV spectrophotometer (UV 2450 Shimadzu Scientific) at 278 nm.

***Ex-vivo* mucoadhesive strength**

Mucoadhesive strength [41] of the patches was measured by the QTS Texture Analyzer. The design used for measuring the mucoadhesive strength was shown in Figure 1. Goat buccal mucosa was used as a model membrane and IPB, pH 6.8 was used as moistening fluid. The goat buccal mucosa was obtained from local slaughter house and kept in a Krebs buffer during transportation. The mucous membrane was separated by removing the underlying fat and loose tissues using surgical blade and wash thoroughly with IPB, pH 6.8. The goat buccal mucosa was mounted onto a base of texture analyzer. A foam tape was placed on the perspex support (underneath the goat buccal mucosa) at the cross sectional end to provide a cushioning effect. The goat buccal mucosa was further secured and fastened to the foam tape by placing an aluminium cap over the base. This was to ensure that the tissue adhered firmly to the foam tape and base so that no movement of the tissue from the foam tape occurred during measurements. All measurements were conducted at room temperature of 25°C and 60 ± 5 % RH. During measurement, 2 mL of simulated saliva solution was evenly spread on the surface of the tissues. The work of adhesion and peak detachment force was used to evaluate the mucoadhesion strength of the patches. Put the following parameter in texture analyzer software test type (compression), probe speed (30 mm/min), trigger point (5 g), target value (1.5 cm), hold time (100 s), recovery time (0 s) and number of cycle one. Texture analyzer software recorded the data when the probe started withdrawing from the patch. The peak adhesive force and load vs time curve obtained from the texture profile were used to assess the mucoadhesive strength of the extruded patch. Each measurement was repeated three times. (Figure 1)

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength (gm)}}{1000} \times 9.8$$

$$\text{Bond strength (N/m2)} = \frac{\text{Force of adhesion (N)}}{\text{Surface area}}$$

Fig. 1: *Ex-vivo* mucoadhesive strength testing using the QTS texture analyzer.

***Ex-vivo* Residence Time**

The *ex-vivo* residence time [32] was determined using modified USP disintegration apparatus (Disintegration tester, type ZT4, Erweka, Germany). A segment of goat buccal mucosa, 3 × 2 cm^2 area, was glued to the surface of a glass slide and vertically attached to the apparatus. The mucoadhesive patch was hydrated with 0.5 mL of IPB and the hydrated surface was brought into contact with goat buccal mucosal membrane by applying a light force with a fingertip for 30 seconds. The disintegration medium was composed filled with 900 ml IPB, pH 6.8 maintained at 37ºC ± 1ºC. The glass slide was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the IPB solution at the lowest point and was out at the highest point and patch detachment or erosion was monitored. The time required for the patch to detach from the goat buccal mucosa was recorded as the residence time.

***Ex-vivo* Buccal Permeation Study**

The *ex-vivo* buccal permeation [42] study of drug through the goat buccal mucosa was performed using a Franz diffusion cell. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the mucosa, and the compartments were clamped together. The donor compartment was filled with 2 mL of IPB, pH 6.8. The receptor compartment (30 mL capacity) was filled with IPB, pH 7.4 and the receptor compartment keep in shaker water bath The permeation was performed at 37ºC ± 0.2ºC, and shaker water bath speed of 50 rpm. At predetermined time intervals, 3 mL sample was withdrawn and analyzed using a UV spectrophotometer (UV 2450 Shimadzu Scientific) at 278 nm.

RESULTS AND DISCUSSION

Baking layer

DBP and PG were used as plasticizer for EC and CAB respectively. DBP 30 % w/w found to be suitable plasticizer for EC (batch B2) where as PG 50 %w/w was suitable for CAB (batch B6) because of their good appearance (i.e. colour, elegance, stickiness and texture). The thickness of film was uniform. The tensile strength of EC and CAB noted to inversely proportional to concentration of plasticizer whereas percentage elongation directly proportional to concentration of plasticizer. Folding endurance of patches containing plasticizer 10 % w/w were less as compared to 30 % w/w and 50 % w/w due to more elastic on increasing concentration of plasticizer. (Table 4)

Table 4: Characterization of backing layer

Bach code	Thickness (mm) [d]	Tensile strength (N/cm^2) [d]	Elongation (%)[d]	Folding endurance [d]
B1	0.15 ± 0.01	0.84 ± 0.10	5.25 ± 0.5	25 ± 3
B2	0.15 ± 0.01	0.70 ± 0.08	16.67 ± 1.0	>100
B3	0.15 ± 0.02	0.50 ± 0.01	25.50 ± 2.0	>100
B4	0.15 ± 0.01	2.11 ± 0.02	5.75 ± 0.5	29 ± 5
B5	0.15 ± 0.02	1.75 ± 0.03	15.18 ± 1.0	>100
B6	0.15 ± 0.02	1.56 ± 0.03	25.25 ± 2.5	>100

[d] Values represented as mean S.D., n=3

Muco adhesive matrix layer

Table 5: Characteristic of muco adhesive buccal patches containing VPH

Bach code	Thickness (mm) [d]	Tensile strength (N/cm^2) [d]	Elongation (%) [d]	Folding endurance [d]	% Drug content [d]	Surface pH [d]
F1	0.20 ± 0.02	4.42 ± 0.40	74.48 ± 6.55	>200	98.40 ± 1.3	6.74 ± 0.11
F2	0.32 ± 0.04	3.27 ± 0.31	86.50 ± 4.25	>200	100.25 ± 1.3	6.89 ± 0.05
F3	0.18 ± 0.05	2.82 ± 0.28	358.14 ± 3.25	>200	101.15 ± 0.8	6.65 ± 0.12
F4	0.26 ± 0.02	<0.852	>627.27	>200	98.28 ± 2.0	6.90 ± 0.03
F5	0.32 ± 0.02	2.61 ± 0.28	55.32 ± 8.50	>200	97.65 ± 1.5	6.72 ± 0.07
F6	0.31 ± 0.05	2.02 ± 0.28	125.50 ± 4.60	>200	98.85 ± 0.5	6.57 ± 0.15
F7	0.32 ± 0.05	1.07 ± 0.28	156.20 ± 5.66	>200	101.95 ± 0.7	6.92 ± 0.10
F8	0.30 ± 0.02	2.19 ± 0.28	50.55 ± 3.45	>200	104.48 ± 0.6	6.79 ± 0.02
F9	0.30 ± 0.05	1.09 ± 0.28	450.50 ± 9.80	>200	100.15 ± 2.2	6.76 ± 0.09
F10	0.32 ± 0.03	<0.6844	>627.27	>200	99.03 ± 0.7	6.86 ± 0.12

[d] Values represented as mean ± S.D., n=3

Thickness, Drug content uniformity, Folding endurance and Surface pH Study

The prepared buccal patches were good in appearance, thickness, drug content, folding endurance and surface pH were uniform due to same diameter of petridish. However, characteristics of patches vary with polymers, the range of thickness 0.18 ± 0.05 to 0.32 ± 0.05, drug content 98.28 ± 2.0 % to 104.48 ± 0.6 % and Surface pH surface pH 6.57 ± 0.15 to 6.92 ± 0.10. The all prepared formulation of VPH buccal film showing the pH range within the range of salivary pH i.e.

6.5 to 7.0. The results are found that there is no significant difference of surface pH in all the formulation. (Table 5)

Tensile Strength and percentage elongation

Tensile strength and percentage elongation were varied with polymers. The observed tensile strength was in order of. HPMC K15M > HPMCK100M > PVA > PEO303. Whereas, percentage elongation at break was in order of F4 ≈. PEO 303 > PVA > HPMC K100M > HPMC K15M. (Table 5)

Swelling Study

Figures 2 and 3 depict the degree of swelling in order of F4 > F2 > F1 > F3 i.e. the formulation containing PEO 303 and HPMC K100M possess more swelling percentage as compare to HPMC K15M and PVA. The swelling percentage in combination of two polymers (HPMC K15M : PVA and HPMC K15M : PEO 303 with ratio 2:1, 1:1 and 1:2) are in the order of F10 > F9 > F8 > F5 > F6 > F7. Swelling increases as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of polymer.

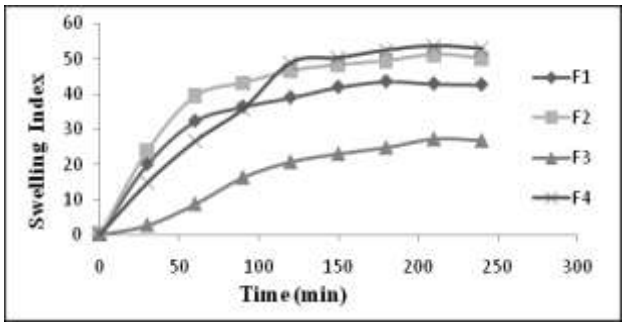

Fig. 2: Swelling index vs time profile of patches containing HPMC K15M (F1), HPMC K100M (F2), PVA (F3) and PEO 303 (F4) polymers.

Percentage moisture absorption (PMA) and Percentage moisture loss (PML):

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML. The observed results of PMA and PML were shown in Table 6. The observed PMA was in order of F4 > F10 > F2 > F9 > F8 > F1 > F5 > F6 > F3 > F7 and the PML was in the order F4 > F2 ≈ F8 > F9 > F10 > F1 > F5 > F6 > F7 > F3. Amongst all the formulation the high value of PMA and PML was observed in mucoadhesive polymers PEO 303 and HPMC K100M than other due to their increase swelling behavior and high degree of hydration respectively.

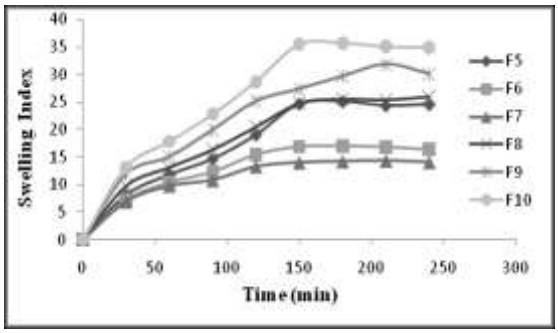

Fig. 3: Swelling index vs time profile of patches in different combination of polymers HPMC K15M : PVA (F5, F6 and F7 in proportion 2:1, 1:1 & 1:2 respectively) and HPMC K15M : PEO 303 (F8, F9, and F10 in proportion 2:1, 1:1 & 1:2 respectively).

***Ex-vivo* mucoadhesive strength**

Figure 4 shows the mucoadhesion characteristics were varied with mucoadhesive polymers. The force of adhesion was observed in formulation, F1, F2, F3 and F4 were found to be 1.35 ± 0.06N, 1.88 ± 0.10N, 0.78 ± 0.03N and 2.81+0.12N respectively. However, mucoadhesive property of PEO 303 and HPMC K100M were found to be more as compared with HPMC K15M and PVA due to more swelling index as well as hydrophilicity with time proceeds.

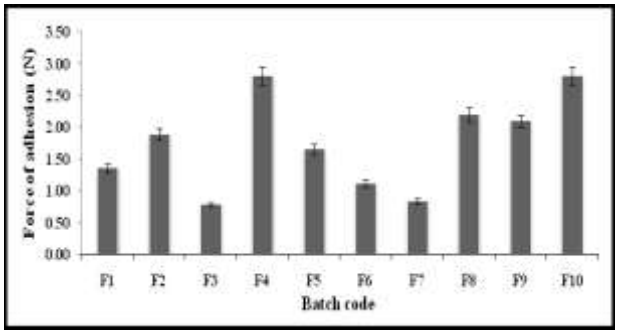

Fig. 4: *Ex-vivo* mucoadhesive strength patches HPMC K15M (F1), HPMC K100M (F2), PVA (F3), PEO 303 (F4) HPMC K15M : PVA(F5, F6 and F7 in proportion 2:1, 1:1 & 1:2 respectively) and HPMC K15M : PEO 303 (F8, F9, and F10 in proportion 2:1, 1:1 & 1:2 respectively) (SD bars, n = 3).

Table 6: Characteristic of mucoadhesive buccal patches containing VPH

Bach code	Mucoadhesive strength (g) [d]	Force of adhesion (N) [d]	Bond strength (Nm^{-2}) [d]	Residence time (min) [d]	Percentage moisture absorbed [d]	Percentage moisture lost [d]
F1	138 ± 6	1.35 ± 0.06	3383.29 ± 147.10	290 ± 4.12	9.25 ± 0.21	19.40 ± 0.50
F2	192 ± 10	1.88 ± 0.10	4707.19 ± 245.17	430 ± 5.63	10.30 ± 0.50	24.35 ± 1.28
F3	79 ± 3	0.78 ± 0.03	1936.81 ± 73.55	180 ± 2.05	7.72 ± 0.45	10.63 ± 0.33
F4	286 ± 12	2.81 ± 0.12	7011.76 ± 294.20	460 ± 4.74	13.38 ± 1.25	26.07 ± 0.47
F5	168 ±15	1.65 ± 0.15	4118.79 ± 367.75	270 ± 1.96	8.45 ± 0.18	15.25 ± 0.45
F6	113 ± 9	1.11 ± 0.09	2770.38 ± 220.65	240 ± 4.24	8.01 ± 0.15	12.38 ± 0.25
F7	85 ± 6	0.83 ± 0.08	2083.91 ± 196.13	210 ± 1.81	7.56 ± 0.02	10.87 ± 0.66
F8	223 ± 20	2.19 ± 0.20	5467.21 ± 490.33	390 ± 3.67	9.75 ± 0.10	24.35 ± 0.38
F9	213 ± 23	2.09 ± 0.23	5222.04 ± 563.88	410 ± 4.59	9.92 ± 0.24	21.45 ± 0.32
F10	286 ± 25	2.81 ± 0.25	7011.76 ± 612.92	430 ± 5.02	11.14 ± 0.54	19.85 ± 0.22

[d] Values represented as mean ± S.D., n=3

***Ex-vivo* Residence Time:** Values of the *ex-vivo* residence time observed from one polymer to other. The batch F3 (180 min) was very less in comparison to batches F1 (290 min), F2 (430 min) and F4 (460 min), because PVA polymer are more soluble in water with comparison to HPMC K15M, HPMC K100M and PEO 303. So, batch F1 was not suitable for sustained delivery buccal patches, while, batches F1, F2 and F4 were suitable for sustained delivery buccal patches.

***In-vitro* Drug Release**

The *in vitro* drug release profiles of VPH from buccal patches are shown in the Figure 5. No lag time was observed as the patch was directly exposed to the dissolution medium. There are no significance differences in the final percentage of drug release, which might be due to the fact that in all the formulations the drug dissolved in the dissolution medium.

Distinguishable difference was observed in such formulation containing polymers (HPMC K15M, HPMC K100M, PVA and PEO 303) and their combination (HPMC K15M with PVA and PEO 303). The drug release rate appeared to increase with increasing amount of hydrophilic polymers i.e. the batch F3 (PVA) faster release rate than batches F1 (HPMC K15), F2 (HPMC K100M) and F4 (PEO 303) where as batch F4 have slow release rate because polymer PEO 303 gradually absorb water due to considerable swelling and gel formation than PVA, HPMC K15M and HPMC K100M. The cumulative percentage release was observed in the formulations F1, F2, F3 and F4 after 5 h were found to be 93.10 %, 75.45 %, 96.89 % and 70.47 % respectively. From above observation it was concluded that high viscosity grade polymers increases duration of release.

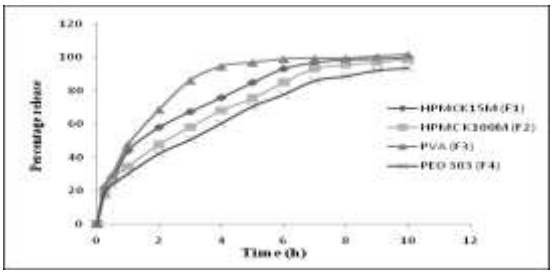

Fig. 5: Release profile of VPH from patches containing HPMC K15M (F1), HPMC K100M (F2), PVA (F3) and PEO 303(F4) polymers.

The drug release profiles of patches containing polymers HPMC K15M and PVA in different ratios. It is noticeable from the plots the drug release could be sustained and was governed by the PVA content. The cumulative drug release rate was observed in order- F5 < F6 < F7. An increase the polymer PVA content was associated with corresponding increase in the drug release rate. The drug release rate appeared to increase with increasing amount of the hydrophilic polymers. (Figure 6)

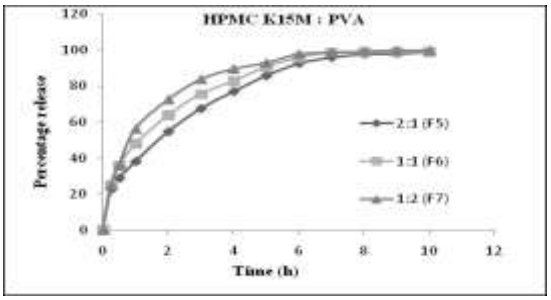

Fig. 6: Release profile of VPH from patches comprising HPMC K15M and PVA (F5, F6 and F7 in proportion 2:1, 1:1 & 1:2 respectively)

Figure 7 shows the drug release profile of patches containing polymers HPMC K15M and PEO 303 in different ratios. The cumulative drug release rate was observed in order- F8 > F9 > F10. The rate of drug release was decreases corresponding to the increase the content of PEO 303. Examination of the patches during the dissolution studies revealed that the patches containing polymer PEO 303 showed considerable swelling and gel formation at higher concentrations. This may help to explain the decrease the drug release rate with increasing the content of PEO 303.

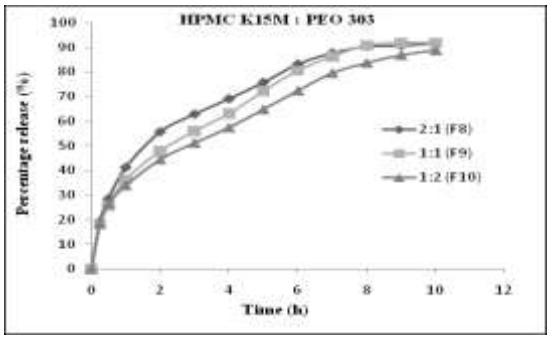

Fig. 7: Release profile of VPH from patches comprising HPMC K15M and PEO 303 (F8, F9 and F10 in combination 2:1, 1:1 and 2:1).

***Ex-vivo* Buccal Permeation Study**

The comparative permeation studies from buccal mucosa membrane (up to 10 h) are shown in Figure 8**.** Batch F1 (49.33 %) possess more permeation than F2 (37.40 %), but batch F1 (HPMC K15M) is less effective for sustained delivery than F2 (HPMC K100M), because, HPMC K15M has less mucoadhesive strength and residence time than HPMC K100M. Batch F5 (HPMC K15M : PVA, 2:1) and batch F8 (HPMC K15M : PEO 303, 2:1) showed permeation 58.80 % and 42.43 % respectively. But batch F5 was found not to be suitable for sustained delivery because it was having less mucoadhesive strength, residence time and film properties than batch F8. For sustained delivery buccal patches formulation, batches F2 (HPMC K100M) and F8 (HPMC K15M : PEO 303, 2:1) were selected to enhance the permeation by using permeation enhancer menthol and SG.

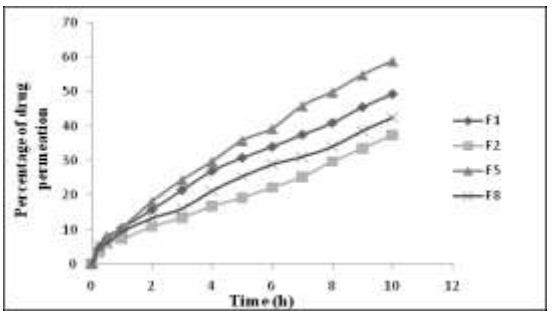

Fig. 8: The *ex-vivo* permeation profile of VPH buccal patches comprising polymer HPMC K15M (F1), HPMC K100M (F2) and HPMC K15M : PVA, in proportion 2:1(F5) and HPMC K15M : PEO 303, in proportion 2:1 (F8)

Comparative permeation studies of VPH using permeation enhancer through the porcine buccal mucosa (up to 10 h) are shown in figure 9. The percentage drug permeation in batches P1 (HPMC K100M) 64.59 % and batches P3 (HPMC K100M) 56.76 % using menthol (12 % w/w) and SG (4 % w/w) respectively were observed. Whereas, percentage of permeation in batch P2 (HPMC K15M: PEO 303, 2:1) 71.67 % and batch P4 (HPMC K15M : PEO 303, 2:1) 60.28 % were observed using menthol (12 % w/w) and SG (4 % w/w) respectively. The results of drug permeation from buccal patches of VPH through the porcine buccal mucosa reveal that VPH was released from the formulations and permeated through the porcine buccal membrane. Thereby, it may permeate through the human buccal membrane. This contention is further supported by fact that *ex-vivo* permeation of drug depends upon the hydrophilicity, swelling index and residence time of polymers.

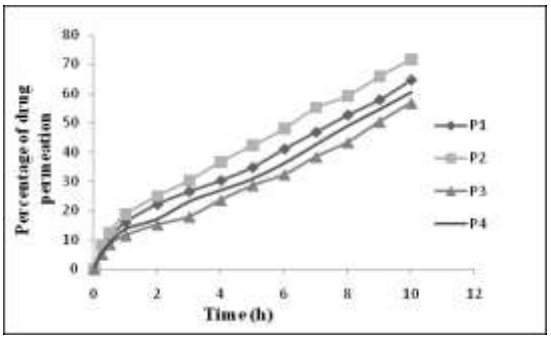

Fig. 9: The *ex-vivo* permeation profile of VPH buccal patches comprising polymer HPMC K100M (P1) and HPMC K15M (P2) with permeation enhancer menthol and HPMC K100M (P3) and HPMC K15M (P4) with permeation enhancer SG.

The results indicated that permeation of VPH was increases by adding permeation enhancer form 37.40 % (batch F2) to 64.59 % (batch P1, using 12 % w/w menthol) and 56.76 % (batch P3, using 4 %w/w SG) and 42.43 % (batch F8) to 71.67 % (batch P2, using 12 % w/w menthol) and 60.28 % (batch P4, using SG). On adding permeation enhancer, it has been observed that permeation of VPH was comprehensively increased. This increase permeation of VPH may be due to increase in solubilizing ability of the aqueous site in the stratum corneum, which is considered to be a main mechanism for to improve the skin permeation of drugs.

CONCLUSION

New mucoadhesive system for the sustained release of VPH has been developed using HPMC K15M, HPMC K100M, PVA, PEO 303 and their combination. All the formulated polymeric mucoadhesive buccal patches had good appearance and physical characteristics, folding endurance, residence time, surface pH and release rate. For sustained delivery HPMC K100M and combined HPMC K15M: PEO 303, 2:1 ratio showed the best characterization. The use of permeation enhancers SG showed the more permeation of VPH as compare to menthol. Thus, it may also be suggested that these bilaminated buccal patches are the better dosage form for VPH in comparison to present/conventional dosage form.

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