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Research Article

# CHITOSAN BASED SUSTAINED RELEASE MUCOADHESIVE BUCCAL PATCHES CONTAINING VERAPAMIL HCL

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## ABSTRACT:

The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Sustained release formulations have been developed and are gaining in popularity and medical acceptance. To increase bioavailability and prevent first pass metabolism of drug, verapamil hydrochloride was embedded in sustained released buccal patch over period of 6 hour. The objective of present work was to characterize the effect of chitosan with PVP K-30 on water soluble drug by preparing mucoadhesive buccal patch. Each formulated batch was subjected to various evaluation parameters. The swelling percentage was found to be function of solubility of drug and PVP K-30. The mucoadhesive strength, vapour transmission and in-vitro released of water soluble drug through water insoluble chitosan base matrix were found satisfactorily. The physical appearance of buccal patch was examined by scanning electron microscopy. The released kinetic model best to fit for the optimized batch was Hixson Crowell, indicating that the drug release from systems in which there is a change in the surface area and the diameter of particles present in dosage form.

**Keyword:** Buccal Patch, Sustained Drug Delivery, Bioadhesion, Mucoadhesive Buccal Delivery.

## INTRODUCTION

Conventional routes of drug administration such as oral, intramuscular and intravenous have, in many cases, been supplanted by the advent of new, novel drug delivery systems. The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance[1]. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectables and enterable methods[2]. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. Primary bond arises due to chemisorptions and secondary bond due to and Vanderwaals forces, hydrophobic interaction and hydrogen bonding between dosage form and mucosal membrane[3]. The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane[4]. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Unlike oral drug delivery, this presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic “first-pass” effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption. Chitosan has been used in a wide variety of biomedical applications like sustained release of drugs[5-7]. Buccoadhesive buccal film of isosorbide

dinitrate using different combination of Carbopol 934 P, Eudragit RL100 and PVP K-30 had been made[8]. The buccoadhesive patch of carvedilol using HPMC, Carbopol, and Eudrahgit-RS100 has been made[9]. Buccoadhesive film and its evaluation for ex vivo buccal permeation, mechanical strength and in vivo buccal permeation of atenolol have also done[10]. Mucoadhesive buccal patches containing cetylpyridinium chloride, characterized by Fatma et al., 2003[11]. The work on buccoadhesive patch containing verapamil HCl, yet not found, hence this is an area of our interest. Being a non-toxic, biocompatible and biodegradable polymer, chitosan has been widely used for pharmaceutical and medical applications. A wide variety of pharmaceutical applications for chitosan have been reported over the last two decades due to its preservative and haemostatic properties[12-14]. It has also been used as a pharmaceutical excipient in conventional dosage forms as well as in novel applications involving bioadhesion and transmucosal drug transport.

Verapamil hydrochloride (VPH) is a calcium channel blocker and a class IV antiarrhythmic agent. 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 and its bioavailability is only about 20%. Since this drug has a short elimination half-life of 2 - 4 hours and is eliminated rapidly. Repeated daily administration is required to maintain effective plasma levels[15]. 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 drug delivery without pre-systemic metabolism. For the sustained action of VPH through oral mucosal route, 50 mg drug had incorporated. The mucoadhesive, natural and unique polymer, chitosan was the base of dosage form.

## MATERIAL AND METHODS

Verapamil Hydrochloride obtained as gift sample from Cipla, Pharma R & D, Vikhroli, Mumbai, India; Chitosan (pH = 4.0–6.0, 1% w/v aqueous solution)was provided by Central Institute of Fisheries Technology, Cochin as gift sample; Polyvinyl Pyrrolidone K-30 was obtained from Alkem labs, Navi Mumbai, India. The other chemicals were used are of analytical grade. The compatibility study of drug and polymers were carried out with FT-IR spectroscopic study, there was no chemical interaction found.

### Preparation of mucoadhesive buccal patch

The buccal mucoadhesive patches from chitosan polymer were prepared by solvent casting technique [7] in different concentration. Table 1 contains the composition of prepared buccal patch. The polymeric solution of chitosan was prepared using 1.5% (V/V) acetic acid in distilled water under occasional stirring for 48 h. The resulting viscous chitosan solution was filtered through nylon gauze to remove debris and suspended particles. The drug release characteristic was increased on use of a water-soluble hydrophilic additive polyvinylpyrrolidone (PVP K-30) into the chitosan solution under constant stirring. Propylene glycol (5%, V/V) was added as plasticizer under constant stirring. The resultant solution was left overnight at room temperature to ensure a clear, bubble-free solution. The solution was poured into a glass petri dish having 6 cm

diameter. The amount of drug required to dissolve in petri dish, so patch of 10 mm diameter size containing 50 mg of Verapamil HCl was calculated by the ratio of surface area of petri dish and buccal patch (10 mm). The dummy patch without drug was also prepared. The Petri dishes were kept on leveled surface and covered by inverted funnel to allow controlled evaporation of solvent at room temperature till a flexible film was formed. Dried films were carefully removed, checked for any imperfections or air bubbles and cut into patches of 10 mm in diameter by using fabricated punch. The patch containing 50 mg of VPH drug was packed in aluminum foil and stored in an airtight glass container to maintain the integrity and elasticity of the patches.

**Table 1: Composition of Verapamil HCl buccal mucoadhesive patches**

| Formulation Code | Chitosan [a] (20 ml) | PVP K-30 (mg) | Propylene Glycol | Drug [b] (mg/28.26cm$^2$ area) |
|---|---|---|---|---|
| Placebo | 1 % | 50 | 5 % | ------ |
| C01 | 1 % | 50 | 5 % | 1800 |
| C02 | 1 % | 100 | 5 % | 1800 |
| C03 | 1 % | 150 | 5 % | 1800 |
| C04 | 1.5 % | 50 | 5 % | 1800 |
| C05 | 1.5 % | 100 | 5 % | 1800 |
| C06 | 1.5 % | 150 | 5 % | 1800 |
| C07 | 2 % | 50 | 5 % | 1800 |
| C08 | 2 % | 100 | 5 % | 1800 |
| C09 | 2 % | 150 | 5 % | 1800 |
| C10 | 2 % | 200 | 5 % | 1800 |

[a] Chitosan solution has been made in 1.5 % acetic acid.
[b] 50 mg drug per 1x1 cm$^2$ patch.

**Evaluation of buccal patches**

Thickness and weight uniformity

The thickness of three randomly selected buccal patches from every batch was determined using a standard screw gauge. Weight uniformity of patch determined by taking weight of ten patches of sizes 10 mm diameter from every batch and weigh individually on electronic balance.

**Surface ph study**

The surface pH of the buccal patches was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible [16]. A combined glass electrode was used for this purpose. The buccal patch was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 hour at room temperature. The pH was measured by bringing the electrode in 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.

**Content uniformity**

Drug content uniformity was determined by dissolving the buccal patch (10 mm in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.6) for 6 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.6 up to 20 ml, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined after proper dilution at 278 nm using a UV-spectrophotometer.

**Folding endurance**

Folding endurance of the patch was determined [17] by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on randomly selected three patches from each.

**Swelling percentage study**

Swelling study of prepared buccal patch was calculated by function of weight and area increase due to swelling, which was measured for each formulation as follows [9].

Weight increase due to swelling: A patch of 10 mm size (1 x 1 $cm^2$) diameter from every batch was weighed on a preweighed cover slip. It was kept in a petridish and 10 ml of phosphate buffer, pH 6.6 was added. After one hour, the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Area increase due to swelling: similarly patch of 10 mm diameter from each batch was place on cover slip and this cover slip was placed in a petridish. Ten ml of phosphate buffer, pH 6.6, was poured into the petridish. A calibrated measuring scale was used to measure the increase in the area of each patch. An increase in the area in diameter of the patch was noted at one hour intervals for 6 hour and the area was calculated. The percentage weight and area swelling ratios was calculated from the average of three measurements using the following equation:

$$\% S = (Xt - Xo / Xo) \times 100$$

Where, Xt - weight or area of the swollen patch after time t and Xo - is the original patch weight or area at zero time.

**Tensile strength**

A tensile strength study of patch is total weight, which is necessary to break or rupture the dosage form and this was done by a device has rectangular frame with two plates made up of Plexiglas's [18, 19]. The one plate is in front and is movable part of device and can be pulled by loading weights on the string, which is connected to movable part. The 1x1 $cm^2$ buccal patch equivalent to 50 mg drug from each formulation was fixed between the stationary and movable plate. The force needed to fracture the film was determined by measuring the total weight loaded in the string. The weight corresponds to break the patches were taken as tensile strength and the values were shown in table 3. The following equation was used to calculate the tensile strength (TS).

TS ($g/cm^2$) = Force at break (g) / Initial cross-sectional area of patch.

**Determination of In vitro residence time**

The in vitro residence time was determined using a locally modified USP disintegration apparatus, based on the apparatus applied by Nakamura et al [20]. The disintegration medium was composed of 800 ml pH 6.6 isotonic phosphate buffer (IPB) maintained at 37 ± 0.5 °C. A porcine buccal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15µl pH 6.6 IPB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch of each batch from the mucosal surface was recorded in table 3.

**Vapour transmission test (VTR)**

Vapour transmission method [21] was employed for the determination of vapor transmission from the patch. Glass-bottle (length= 5 cm, narrow mouth with internal diameter =0.8 cm) filled with 2 g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2 °C. The difference in weight after 24 h, 3rd day and 1 week was calculated [18]. The experiments were carried out in triplicate and vapor transmission rate was obtained as follow:

VTR = (Amount of moisture transmitted) / (Area x Time)

**Measurement of mucoadhesive strength**

The strength of bond formed between the formulation and mucosa membrane excised from porcine buccal mucosa was determined using two-arm balance method [22]. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with isotonic phosphate buffer pH 6.6 (IPB) as moistening fluid. Briefly, buccal mucosa section (2.4 mm thick, 3×5 cm) was fixed on the plane surface of glass slide (3×5 cm) attached (with adhesive tape) to bottom of smaller beaker, kept inverted in 500 ml beaker attached to the bigger beaker. Isotonic phosphate buffer pH 6.6 was added to the beaker up to the upper surface inverted beaker with buccal mucosa. The buccal patch of size 10 mm in diameter (1x1 $cm^2$) was stuck to the lower side of the upper clamp with cyanoacrylate adhesive. The exposed patch surface was moistened with 15 µl of IPB and left for 30 s for initial hydration and swelling. Then the platform was slowly raised until the patch surface came in contact with mucosa. Two sides of the balance were made equal before study. After a preload (50 g) time of 2 minutes, water was added to the polypropylene bottle present in another arm, until the patch was detached from the buccal mucosa. The water collected in the bottle was measured and expressed as weight (g) required for the detachment (table 5). The force measurement was repeated 3 times for each formulation. The following parameters

were calculated from the bioadhesive strength:

Force of adhesion (N) = (Bioadhesive strength (g) × 9.81)/1000

Bond strength (N $m^{-2}$) = Force of adhesion / Disk surface area

**In vitro release study**

The USP 23 (1995) [23] rotating paddle method was used to study the drug release from buccal patches. The dissolution medium consisted of 400 ml of isotonic phosphate buffer pH 6.6. The release was performed at 37 ± 0.5 °C, at a rotation speed of 50 rpm. One side of the buccal patch was attached to a 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 (1 ml) were withdrawn by using calibrated pipette at pre-determined time (1 hour) intervals and replaced with fresh medium. The samples were filtered through 0.45 μm Whatman filter paper with appropriate dilutions with phosphate buffer pH 6.6 and were assayed spectrophotometrically at 278 nm.

**Ex vivo buccal permeation study**

The buccal permeation test planned for optimized batch only. The test was carried out using porcine buccal mucosa because of non-keratinized buccal mucosa similar to that of human and their inexpensive handling and maintenance cost. The buccal epithelium was used within two hour upon removal [24]. The modified Franz diffusion cell was used to permeation studies, it consists of two compartments, one is donor compartment and another is receptor compartment of 25 ml capacity [25]. The receptor compartment was cover with water jacket to maintain temperature 37°C. The separated buccal epithelium was mounted between the chamber, and in receptor chamber phosphate buffer solution having pH 7.4 was filled and buccal epithelium was allow to stabilized for the period of 1 h. after stabilization, patch was kept on epithelium and periodically (for 6 h) samples were withdraw and maintain sink condition. The aliquot were analyzed spectrophotometrically at 278 nm. The drug permeation was correlated with cumulative drug released.

**Drug release kinetic study**

To describe the kinetics of the drug release from the matrix base buccal patch of optimized batch C06 mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas models are were use. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

**Scanning electron microscopy**

Film morphology was characterized by scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive tape and then sputter coated for 8 min at 1.1 LV under argon atmosphere with gold palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilford PANF 50 black and white 35mm film.

**RESULTS**

The thickness (Table 2) of formulated patches was ranges from 0.81 ± 0.04 to 1.25 ± 0.02 mm, while the average weight of patch from each batch ranges from 63.63 ± 0.53 to 93.98 ± 0.20. The surface pH of patches was ranges from 5.53 ± 0.30 to 6.04 ± 0.098 were found around neutral pH. The content uniformity

recovery was possible to the tune of 91.35 to 101.19 %. Films did not show any cracks even after folding for more than 200 for all batches.

**Table 2: Physicochemical characteristics of prepared buccal patches of VPH**

| Formulation Code | Thickness [a] (mm) | Weight [b] Uniformity (mg) | Surface pHa | Content Uniformity (%) | Folding Endurance |
|---|---|---|---|---|---|
| Placebo | 0.63 ± 0.015 | 28.47 ± 0.59 | 6.23 ± 0.075 | ------- | > 200 |
| C01 | 0.81 ± 0.04 | 63.63 ± 0.536 | 5.53 ± 0.30 | 94.97 | > 200 |
| C02 | 0.82 ± 0.03 | 65.86 ± 0.536 | 5.50 ± 0.12 | 93.38 | > 200 |
| C03 | 0.86 ± 0.036 | 68.37 ± 0.642 | 5.73 ± 0.068 | 95.22 | > 200 |
| C04 | 0.88 ± 0.026 | 67.37 ± 0.615 | 5.91 ± 0.057 | 97.43 | > 200 |
| C05 | 1.02 ± 0.07 | 68.22 ± 0.313 | 6.03 ± 0.091 | 101.19 | > 200 |
| C06 | 1.01 ± 0.81 | 74.25 ± 0.387 | 5.98 ± 0.077 | 97.51 | > 200 |
| C07 | 1.11 ± 0.01 | 68.28 ± 0.382 | 5.83 ± 0.11 | 91.35 | > 200 |
| C08 | 1.14 ± 0.02 | 86.33 ± 0.338 | 6.02 ± 0.023 | 96.13 | > 200 |
| C09 | 1.20 ± 0.01 | 89.16 ± 0.253 | 6.04 ± 0.098 | 99.92 | > 200 |
| C10 | 1.25 ± 0.02 | 93.98 ± 0.2 | 5.95 ± 0.071 | 95.68 | > 200 |

[a] n=3; standard deviation for three determinations.
[b] n=10; standard deviation for ten determinations.

The placebo chitosan base matrix shows less swelling index. The increasing order of swelling percentage of batches are C10 > C06 > C09 > C07 > C03 > C08 > C05 > C01 > C02 > C04. The increased in area after 6 hour was reported in Table 3. The area after 6 hour increased in ordered of C03 > C06 > C10 > C05 > C02 > C09 > C04 > C08 > C01 > C07 > Placebo (fig. 1).

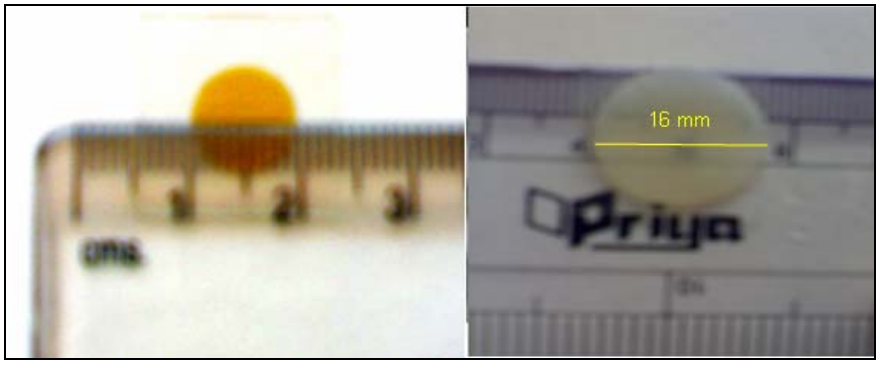



**Fig. 1: Increased in area due to swelling of buccal patch**

Time requires for the complete erosion or detachment of buccal patches from the mucosa was found satisfactory. Table 3 had shown in order of decreasing the residence time for C10 < C09 < C06 < C03. The mechanical strength require to break the patch are shown in table 3. The tensile strength 212.99 to 277.90 g.cm$^{-2}$

for chitosan based patches was found. Overall study of tensile strength on chitosan base buccal patches had good tensile strength.

**Table 3: Physical and mucoadhesive characteristics of prepared buccal patches**

| Formulation Code | Swelling index [a] | | Tensile Strength ($g/cm^2$) | In-vitro [a] Residence Time (hour) |
|---|---|---|---|---|
| | % Weight Increase After 1 Hour | % Area Increase After 6 Hour | | |
| Placebo | 13.37 ± 0.37 | 33 ± 6.08 | 277.90 | 3.13 ± 0.49 |
| C01 | 15.96 ± 3.96 | 46.33 ± 4.04 | 252.48 | 3.08 ± 0.46 |
| C02 | 15.43 ± 2.30 | 56.66 ± 5.50 | 261.14 | 3.10 ± 0.1 |
| C03 | 22.06 ± 1.34 | 67.33 ± 4.61 | 256.19 | 2.73 ± 0.66 |
| C04 | 15.24 ± 2.20 | 48.33 ± 3.05 | 275.92 | 3.95 ± 0.39 |
| C05 | 16.99 ± 1.16 | 58 ± 5.0 | 228.02 | 3.42 ± 0.11 |
| C06 | 34.96 ± 2.81 | 61 ± 2.0 | 246.75 | 3.39 ± 0.11 |
| C07 | 24.18 ± 4.26 | 41.66 ± 4.04 | 231.21 | 4.95 ± 0.39 |
| C08 | 18.58 ± 5.09 | 47 ± 4.35 | 270.70 | 3.67 ± 0.37 |
| C09 | 26.49 ± 6.57 | 52.66 ± 1.52 | 215.28 | 3.17 ± 0.11 |
| C10 | 36.15 ± 2.66 | 59.33 ± 2.88 | 212.99 | 2.25 ± 0.21 |

[a] n=3; standard deviation for three determinations

In vapour transmission, the formulation batches C02, C04 and C07 of chitosan formulation were indicate less vapour transmission as compared to other chitosan based buccal patches on day seven. The highest vapour permeation 1.81 $\times10^{-3}$ ± 0.30 $\times10^{-3}$ g $cm^{-2}$ $h^{-1}$ was found with patch C03 on day seven. While less permeation 0.65 $\times10^{-3}$ ± 0.26 $\times10^{-3}$ g $cm^{-2}$ $h^{-1}$ was found on day seven with patch C07, containing higher concentration of water insoluble chitosan and less PVP K-30.

**Table 4: Vapour transmission rate through the patches at different time intervals**

| Formulation Code | Moisture vapour transmission, g $cm^{-2}$ $h^{-1}$ (mean±SD[a]) | | |
|---|---|---|---|
| | Day 1 | Day 3 | Day 7 |
| Placebo | 8.68 $\times10^{-3}$ ± 1.41 $\times10^{-3}$ | 3.65 $\times10^{-3}$ ± 0.97 $\times10^{-3}$ | 1.61 $\times10^{-3}$ ± 0.44$\times10^{-3}$ |
| C01 | 7.60 $\times10^{-3}$ ± 0.80 $\times10^{-3}$ | 3.18 $\times10^{-3}$ ± 0.46 $\times10^{-3}$ | 1.64 $\times10^{-3}$ ± 0.45 $\times10^{-3}$ |
| C02 | 7.07 $\times10^{-3}$ ± 0.93 $\times10^{-3}$ | 1.91 $\times10^{-3}$ ± 0.98 $\times10^{-3}$ | 0.90 $\times10^{-3}$ ± 0.50 $\times10^{-3}$ |
| C03 | 10.67 $\times10^{-3}$ ± 1.64$\times10^{-3}$ | 4.0 $\times10^{-3}$ ± 0.97 $\times10^{-3}$ | 1.81 $\times10^{-3}$ ± 0.30 $\times10^{-3}$ |
| C04 | 4.41 $\times10^{-3}$± 1.33 $\times10^{-3}$ | 1.82 $\times10^{-3}$ ± 0.41 $\times10^{-3}$ | 0.80 $\times10^{-3}$ ± 0.15 $\times10^{-3}$ |
| C05 | 7.43 $\times10^{-3}$ ± 0.53 $\times10^{-3}$ | 3.0 $\times10^{-3}$ ± 0.53 $\times10^{-3}$ | 1.51 $\times10^{-3}$ ± 0.07 $\times10^{-3}$ |
| C06 | 6.07 $\times10^{-3}$ ± 1.37 $\times10^{-3}$ | 2.83 $\times10^{-3}$ ± 0.10 $\times10^{-3}$ | 1.33 $\times10^{-3}$ ± 0.15$\times10^{-3}$ |
| C07 | 3.35 $\times10^{-3}$ ± 2.33 $\times10^{-3}$ | 1.41 $\times10^{-3}$ ± 0.63 $\times10^{-3}$ | 0.65 $\times10^{-3}$ ± 0.26 $\times10^{-3}$ |
| C08 | 3.71 $\times10^{-3}$ ± 0.53 $\times10^{-3}$ | 1.58 $\times10^{-3}$ ± 0.17$\times10^{-3}$ | 0.73 $\times10^{-3}$ ± 0.08 $\times10^{-3}$ |
| C09 | 7.42 $\times10^{-3}$ ± 3.22 $\times10^{-3}$ | 2.65 $\times10^{-3}$ ± 0.81 $\times10^{-3}$ | 1.31 $\times10^{-3}$ ± 0.41$\times10^{-3}$ |
| C10 | 7.60 $\times10^{-3}$± 1.33 $\times10^{-3}$ | 2.82 $\times10^{-3}$± 0.47 $\times10^{-3}$ | 1.28 $\times10^{-3}$ ± 0.22 $\times10^{-3}$ |

[a] n=3; standard deviation for three determinations

In general, mucoadhesion is considered to occur in three major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular mass of polymers, contact time with mucus, swelling rate of the polymer and the biological membrane used in the study Thus, mucoadhesion strength of batch C02 from 1% chitosan, C06 from 1.5% chitosan and C07 from 2% chitosan was found to be 3.51 ± 0.67 g, 4.32 ± 2.97 g and 6.92 ± 1.11 g respectively, had shown good bioadhesion properties (fig.2).

**Table 5: Bioadhesive parameters of verapamil hydrochloride buccal patches**

| Formulation Code | Bioadhesive Strength (g) [a] | Force of Adhesion (N) | Bond Strength (N $m^{-2}$) |
|---|---|---|---|
| Placebo | 5.31 ± 1.27 | 0.052 | 662.4 |
| C01 | 3.10 ± 0.93 | 0.030 | 382.1 |
| C02 | 3.51 ± 0.67 | 0.034 | 433.1 |
| C03 | 1.78 ± 1.31 | 0.017 | 216.5 |
| C04 | 2.14 ± 2.37 | 0.020 | 254.7 |
| C05 | 3.56 ± 0.74 | 0.034 | 433.1 |
| C06 | 4.32 ± 2.97 | 0.042 | 535 |
| C07 | 6.92 ± 1.11 | 0.067 | 853.5 |
| C08 | 6.34 ± 0.55 | 0.062 | 789.8 |
| C09 | 5.73 ± 0.31 | 0.056 | 713.3 |
| C10 | 4.46 ± 2.21 | 0.043 | 547.7 |

[a] n=3; standard deviation for three determinations

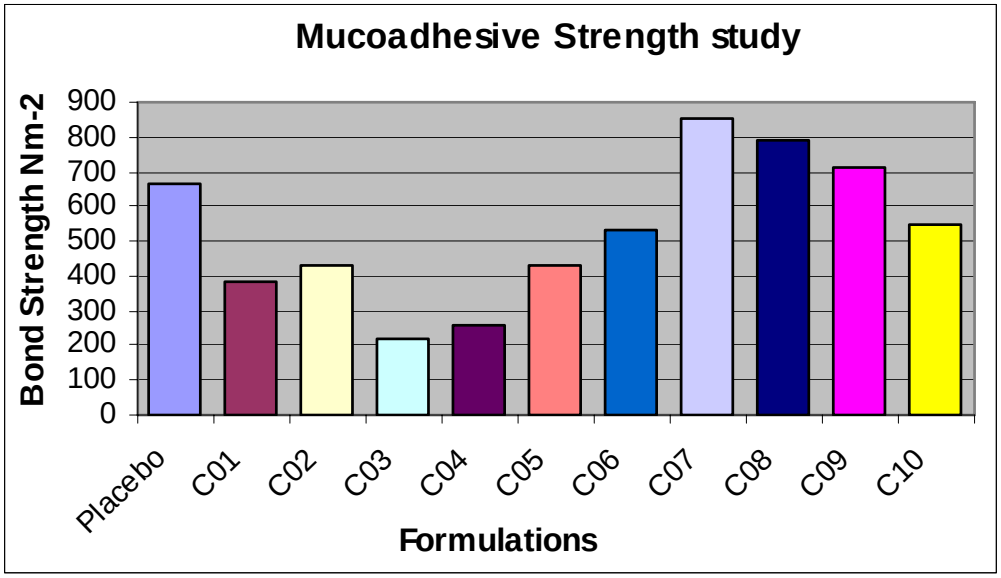



**Fig. 2: Bond strength of patches C01 to C10 containing VPH**

The cumulative percentage of drug dissolved in buffer pH 6.6 for the period of 6 h at temperature 37 $^{o}$ C are analyzed by using UV-Spectrophotometer at 278 nm wavelength. The drug release increased linearly with the increasing concentration of PVP K-30 from batches C01 to C03, C04 to C06, and C07 to C10 containing 1%, 1.5 %, and 2 % Chitosan base respectively. The maximum in vitro release was found to be 95.68 % over a period of 6 h in batch C06, containing 20 ml of 1.5 % chitosan base and high concentration of PVP K-30 (Fig. 3). The ex-vivo buccal permeation study of optimized C06 batch diffused maximum 82.42 % drug in 6 h through porcine buccal mucosa. Correlation Coefficient between In Vitro Drug Release and in Ex-vivo Drug Permeation Study is indicated in fig. 4 with r value 0.9927. The optimized batch C06 gave Hixson-Crowell cube root law as best fit model with R value 0.9946 (fig.5).

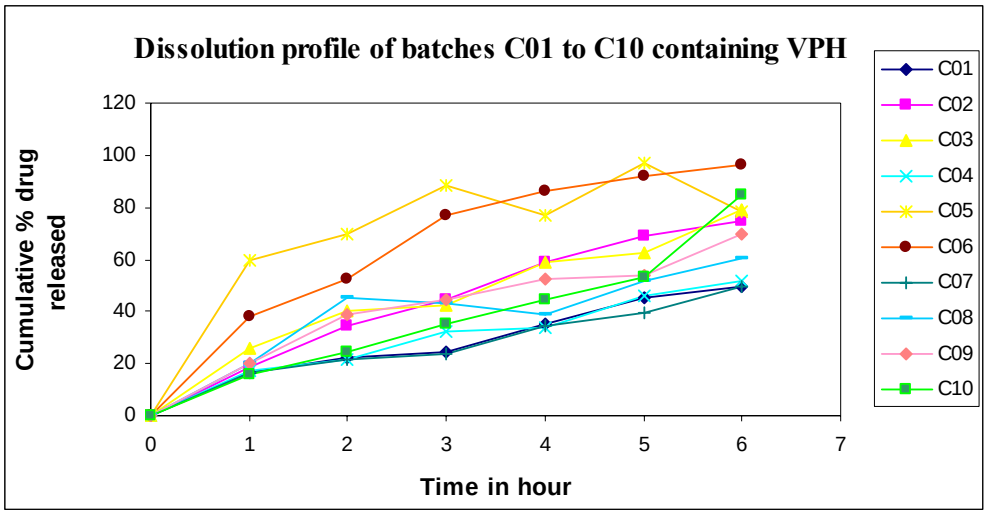



**Fig. 3: Comparative dissolution profile of batches C01 to C10**

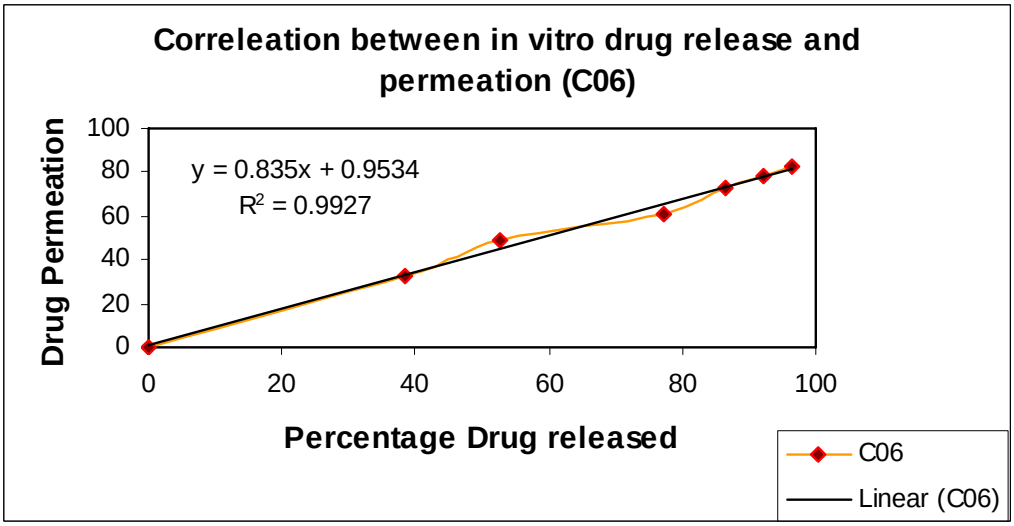



**Fig. 4: Correlation coefficient for batch C06 containing VPH**

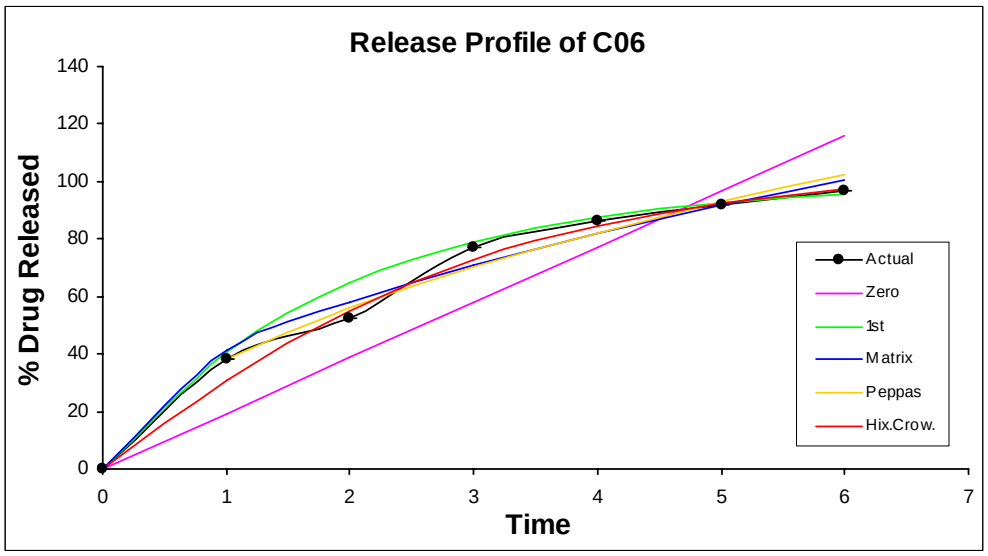



**Fig. 5: Drug released profile for batch C06 with models fitting**

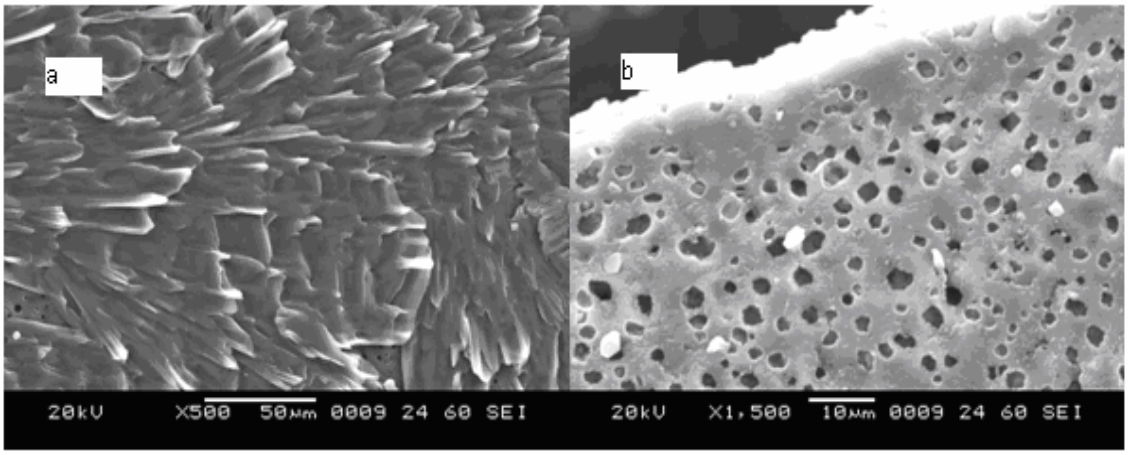
The Scanning Electron Microscopy (SEM) study of optimized batch was found at different set. The SEM photograph of optimized batch C06 were shown in figure 6.

**DISCUSSION**

The thickness and weight variation might be due to increasing concentration of chitosan and PVP K-30. The surface pH study indicates no mucosal irritation was expected between the pH reported in table 2 for each batch. Folding endurance did not vary when the comparison was made between plain films and drug loaded patches (Table 2). Due to poor aqueous solubility of chitosan the placebo chitosan base matrix shown less swelling index. The results mentioned cleared that; the increasing concentration of PVP K-30 increases the swelling percentage. Also the swelling percentage of placebo batch was found less, might be due to absence of water soluble drug. PVP K-30 increased the surface wettability and consequently water penetration within the matrix, hence increased weight and area. In residence time, the increasing concentrations of PVP-K30 allow swelling the buccal patch and made hydrogen bonding weaker. The buccal patch from group-I C07 has highest 4.95 ± 0.39 hour and batch C01 has less 3.08 ± 0.46 hour residence time. . The tensile strength of buccal patch was stronger in absence of drug, while increasing the concentration of chitosan base with increasing PVP K-30 concentration has less but acceptable tensile strength. Vapour transmission from day first to third the vapour transmission through patches given the idea of good permeability, but after that patch became saturated and no more moisture absorbed or transmitted. This kind of result gave the idea of presence of less concentration of PVP K-30. During mucoadhesive study, we conclude that the Chitosan base has good bioadhesion properties in appropriate concentration, and good bond strength forming capacity with mucin (Fig.3). But as the concentration of PVP K-30 increases, the bioadhesive strength was found very less, may be due to hydrophilic natures which loosen the bond strength with mucosal area. So patch might be detached as it absorbed water molecule. Mean while some formulation batches had shown

less mucoadhesion. The reason might be due to increasing concentration of both Chitosan and PVP K-30, while placebo shows highest mucoadhesion may be due to absence of drug. The drug release finding was also supported by the reported swelling studies where the highest swelling index was also exhibited by batch C06, indicating that the increase in water-soluble polymer PVP K-30 content result in faster swelling and release from patches. In ex vivo permeation study, the cationic chitosan with negative charge of epithelium, creates the strong bonding with mucus layer and on hydration of the patch with buffer 6.6, the drug get diffused 82.42 % into the accepter compartment. The drug kinetic study describes the drug release from systems in which there is a change in the surface area and the diameter of particle present in dosage form with R value 0.9946. The SEM photograph (fig. 6a) indicates the uniform dispersion of polymeric solution with drug molecule and the chitosan based patch shown porous surface, which may be suitable for the matrix system (fig. 6b).

**Fig. 6: Scanning Electron Microscopy of C06 buccal patch**




## CONCLUSION

A new buccoadhesive patches for sustained released of Verapamil hydrochloride was developed by chitosan in appropriate ratio. Chitosan has not only film forming but also good bioadhesion properties with drug VPH. The drug release rate increases on inclusion of PVP K-30 into the chitosan base matrix system and can be modifying for kinetic study. So lastly we conclude that, chitosan with PVP K-30 can meet the ideal requirement for buccal devices, which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability.

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