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*Original Article*

# Use of Okra Mucilage and Chitosan Acetate in Verapamil Hydrochloride buccal patches development; *In vitro* and *Ex vivo* Characterization

**Raja Navamanisubramanian[1], Raghunandan Nerella[1], Chamundeeswari D[3], Shanmuganathan Seetharaman[2]***
[1]Balaji Institute of Pharmaceutical Sciences, Warangal, Telangana, INDIA.
[2]Department of Pharmaceutics, College of Pharmacy, Sri Ramachandra University, Chennai, Tamilnadu, INDIA.
[3]Department of Pharmacognosy, College of Pharmacy, Sri Ramachandra University, Chennai, Tamilnadu, INDIA.

## ABSTRACT

**Objective:** Transmucosal buccal drug delivery could be an alternative for oral administration for systemic delivery of Verapamil Hydrochloride (VH), as it has low bioavailability 20 - 35 % due to its extensive first pass metabolism and variable absorption at GIT. **Method:** Buccal patches of VH were prepared by solvent casting method using bioadhesive polymers HPMC K4M, Carbopol 934P, Chitosan acetate and Okra mucilage isolated from *Hibiscus esculantus* fruits, in various combinations as per $2^4$ half factorial model. The prepared medicated patches were subjected for *in vitro* and *ex vivo* characterization. **Results:** The mass uniformity, thickness, drug content, surface pH and folding endurance for the medicated patches were found satisfactory. The formulation contains Chitosan acetate and Okra mucilage has moderate swelling 38.86 % w/w in 2h, *ex vivo* mucoadhesion strength 27.78 ± 0.12 g on porcine buccal membrane and sustained *in vitro* release rate as 73.14 % (F7) compared to 93.06 % (F1) in 120 min with non-Fickian mechanism. The flux value of F1 (0.635 mg/cm²/h) was modified to the range of 0.538 mg/cm²/h to 0.294 mg/cm²/h by addition of Chitosan acetate and Okra mucilage in combination with HPMC K4M and Carbopol 934P. No significant changes were observed in the Physical and chemical characteristics during short term stability study. Chemical compatibility of VH with polymers was confirmed by FTIR spectroscopy. **Conclusion:** Overall, Chitosan acetate and Okra mucilage imparts good physical properties to the buccal patch, significantly controls release and diffusion of VH from the matrix film with satisfactory bucco-adhesion.

**Keywords:** Buccal Patches, Mucoadhesive, Transmucosal, Verapamil HCl, Okra Mucilage, Chitosan Acetate.

**Correspondence:**

**Dr. Shanmuganathan Seetharaman,**

Professor & Head, Department of Pharmaceutics, College of Pharmacy, Sri Ramachandra University, Porur, Chennai, INDIA.

Mob: +91 9444039291

**E-mail:** pharmaresearch2016@gmail.com

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## INTRODUCTION

Drug delivery via buccal route is an alternative to the oral route of drug administration, especially to overcome deficiencies associated with the oral route like high first-pass metabolism, drug degradation in the harsh gastrointestinal environment[1] and administrative difficulties associated in patients with dysphagia.[2] The buccal route includes other advantages like low enzymatic activity,[3] painless administration,[4] reasonable patient acceptance,[5] easy drug withdrawal at any time,[6] possibility to include permeation enhancers[7] and versatility in designing multidirectional or unidirectional release systems for local or systemic actions.[8]

Verapamil Hydrochloride (VH) is a calcium channel blocker and a class IV antiarrhythmic agent used in the supraventricular arrhythmias, in the management of angina pectoris, hypertension and myocardial infarction.[9] Bioavailability of VH after oral administration is 20-35% due to its extensive first pass metabolism and variable absorption at GIT. As VH has a short elimination half-life of 2-8 hrs and is eliminated rapidly, repeated daily administration are required to maintain effective plasma levels.[10]

The aim of the present investigation is to develop bioadhesive patches for buccal sustained release of VH using cellulose derivatives (HPMC E10, HPMC K4M), Poly acrylic acid derivatives (Carbopol 934P), Water soluble Chitosan derivative (Chitosan Acetate), Natural mucilage isolated from *Hibiscus esculentus* fruits (Okra Mucilage), Poly Vinyl Alcohol and poly Ethylene Glycol 400 as plasticizer.

## MATERIALS AND METHODS

Verapamil Hydrochloride (VH) was gift sample from Glochem Industries Ltd., Hyderabad, India. HPMC K4M and Carbopol 934P (CP) were purchased from Yarrow chem products, Mumbai, India. Chitosan received as gift sample from Central Institute of Fisheries Technology, Cochin, India. Okra (*Hibiscus esculentus*) fruits were purchased from local market, Poly Vinyl Alcohol (PVA), Polyethylene glycol-400 (PEG 400), Barium Hydroxide ($Ba(OH)_2$) and Zinc Sulphate ($ZnSO_4$) were purchased from SD Fine-Chem Limited, Mumbai, India. Biaxially-oriented polypropylene (BOPP) film was supplied by pidilite, India. All other reagents used were analytical grade.

### Preparation of Chitosan Acetate

Chitosan Acetate (CA) was prepared by the modified method of originally reported by Nunthanid *et al.*[11] Chitosan powder, 10 g, was dissolved in small amount of distilled water containing acetic acid, 6.41 g, in molar ratio of glucosamine unit/acetic acid, 1:2 mols. The solution was adjusted to 500 g with distilled water to make a 2% w/w solution and stirred for 12 h. Acetone was added to the solution to precipitate the CA, filtered, dried at 60°C. The obtained powders was collected and stored in a desiccator containing dry silica gel prior to use in each experiment.

## Preparation of Okra Mucilage

Okra mucilage (OM) is a natural polysaccharide isolated from *Hibiscus esculentus* fruits, composed of D-galactose, L-rhamnose and L-galacturonic acid.[12] Okra fruits were purchased from a local market; hence the seeds do not contain mucilage, were removed prior to extraction, sliced and macerated with five folds its weight of distilled water for 12 h. This was followed by filtration through muslin cloth, treated with 0.3 N $Ba(OH)_2$–5% aqueous $ZnSO_4$ for deproteinization and centrifuged at 5000 g for 30 min. The mucilage was precipitated from the clear viscous supernatant with equal volume of ethanol, filtered, washed with excess ethanol followed by acetone and dried at 60°C.[13]

### Preparation of buccal patches

Mucoadhesive buccal patches of VH were prepared using the polymers HPMC K4M, CP, CA and OM in various combinations (Table 1) as per $2^4$ half factorial model design, using design expert software (version 9, stat-Ease Inc., USA), by the solvent casting technique.[14] CP was allowed to swell in 10 mL of Ethanol for 6 h and to this 510 mg of VH was added. Separately, in 10 mL of distilled water HPMC, CA and OM were added, mixed on a magnetic stirrer to dissolve the polymers completely. The drug solution was transferred to the aqueous polymer mixture slowly with constant mixing. To this 0.5 mL aqueous PVA (1% m/v) and 1.5 mL PEG were added. The volume of the mixture was made up to 25 mL (1:1 Alcoholic water), stirred for 30 min on magnetic stirrer to get the homogeneity. The resulting mixture was kept aside for 2 h to remove entrapped air, poured in a petri dish pre-lubricated with liquid paraffin and allowed to dry in humidity controlled oven at 40°C. After careful examination, the dried patches were removed, checked for any imperfections or air bubbles and cut as circular patches with internal diameter 1.2 cm (1.13$cm^2$ area) using a circular stainless steel cutter. The patches were laminated on one side with a water impermeable backing layer (BOPP film, Pidilite), another side with easily removable aluminum foil. The covered patches were kept in air tight pouch and stored in desiccator at room temperature.

### Evaluation of patches

### Physical and Mechanical properties

Mass uniformity and thickness for the VH patches were estimated without backing membrane using precision electronic balance (0.1 mg, Denver), standard screw gauge respectively. Folding endurance of the unwrapped film was ascertained by repeatedly folding one patch at the same place up to 300 times continuously until the patch broke or visual crack observed.[15]

### Drug content

The medicated patch (without backing membrane) was added to 100 mL of phosphate buffer pH 6.8, stirred at 300 rpm on temperature controlled (37 ± 0.5°C) magnetic stirrer for 3 h. To filter undissolved matter, the resultant solution was passed through membrane filter (0.45 µm). After suitable dilution, the amount of VH was determined spectrophotometrically at 278 nm (PG instrument, UK).

### Measurement of surface pH

The surface pH of the medicated patch (without backing membrane) in triplicate was determined using combined glass electrode to predict the possibility of any side effects, *in vivo*. The patches were induced to swell by kept in contact with 1 ml of distilled water (pH 6.6 ± 0.2) for 30 min at room temperature, and the pH was determined by surface contact of the electrode with the patch and allowing it to equilibrate for 1 min.[16]

### Swelling studies

Randomly selected (n=3) different drug loaded patches were weighed, placed on the surface of a solid agar plate (2% m/v agar in hot distilled water pH 6.6 ± 0.2) and incubated at 37±1°C.[13] At predetermined time interval the individual patches were reweighed for change of weights. The % Swelling index was calculated using the equation as follows:

$$SI\ (\%) = [(W_t - W_0) / W_0] \times 100$$

Where SI (%) is the percent swelling index, $W_t$ is the weight of the swollen patch after time t and $W_0$ is the original patch weight at time zero.

### *Ex vivo* Mucoadhesive strength

Mucoadhesion strength of buccal patch was measured in triplicate, on a modified physical balance, originally described by Gupta *et al.*[17] The individual patch was fixed at bottom of a vial (replaced for left arm) with the help of a cyanoacrylate adhesive. The balance arm was brought down so as the formulation to make contact with buccal membrane, Load weight of 5 gm was applied on the formulation for 5 min to enhance the contact of the patch with buccal membrane. Load weight was removed, balance arm was raised up, and water was added drop wise into the disposable plastic cup placed on right arm of balance until the patch completely detached from the mucosa.

### *In vitro* drug dissolution

The rotating paddle (USP Type-2) dissolution test apparatus was used to study the dissolution profile of VH buccal patches.[18] The dissolution medium used was 900 mL simulated saliva solution (pH 6.2) at 37 ± 0.5°C, stirred at 50 rpm. The individual patch was fixed on the 2x2 cm glass slide using a cyanoacrylate adhesive and placed at the bottom of the dissolution vessel as the patch remained on the upper side. Samples (5 mL) were withdrawn at prefixed time intervals, filtered through 0.45 µm filter paper, appropriate dilution was made with simulated saliva solution (pH 6.2) and estimated for VH, spectrophotometrically at 278 nm.

### *Ex vivo* drug permeation

The *ex vivo* buccal permeation of VH through the porcine buccal mucosa was studied using Franz-diffusion cell.[17] The patch was placed on the freshly collected porcine buccal mucosa which was mounted between the donor and receptor compartments, clamped together and the donor compartment was slightly wetted with 1 mL of simulated saliva. The receptor compartment was loaded with isotonic phosphate buffer pH 7.4. The diffusion cell was thermostated at 37 ± 0.2°C and stirred at 100 rpm.[17] At pre-determined time intervals 1 mL of sample was withdrawn using a butterfly canula and syringe, filtered through 0.45 µm membrane filter, diluted appropriately and the samples were analyzed for the drug content spectrophotometrically at 278 nm.

### Drug-Polymer Interaction Study

The presence of possible interactions between the VH and polymers used in the formulation were determined by Fourier Transform Infrared study (Bruker FTIR, alpha). The drug sample and drug-polymer physical mixture (1:1 ratio) was prepared as pellets, utilizing KBr pellet method. The IR spectrum, in % Transmittance mode, was obtained in the spectra region of 400 $cm^{-1}$ to 4000 $cm^{-1}$.

### Stability studies

The short term stability studies were conducted according to the International Conference on Harmonization (ICH) guidelines.[19] The selected formulations (with covering layers) were placed in the stability chamber at a temperature of 40 ± 0.5°C and 75 ± 5% RH for 3 months. At monthly

**Table 1: Composition of VH buccal patches**

| Materials | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| Verapamil HCl* | 510 | 510 | 510 | 510 | 510 | 510 | 510 | 510 |
| HPMC E10* | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| HPMC K4M* | 0 | 250 | 250 | 0 | 250 | 0 | 0 | 250 |
| Carbopol 934P* | 0 | 50 | 0 | 50 | 0 | 50 | 0 | 50 |
| Chitosan Acetate* | 0 | 0 | 100 | 100 | 0 | 0 | 100 | 100 |
| Okra Mucillage* | 0 | 0 | 0 | 0 | 100 | 100 | 100 | 100 |
| PVA (1% Solution)** | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| PEG 600** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |

*All the ingredients were added in weight (mg)

**All the ingredients were added in Volume (mL)

Total volume of the polymer solution including drug and plasticizer was 25 mL.

**Table 2: Physicochemical parameters of VH buccal Patches**

| Code | Mass uniformity# (mg) | Thickness* (mm) | Folding Endurance* | Drug content* (% w/w) | muco adhesive strength* (g) | Amount of Drug Diffused* in 6 h | Flux* (mg/cm²/h) |
|---|---|---|---|---|---|---|---|
| F1 | 52.3 ± 0.25 | 0.25 ± 0.006 | 245.0 ± 5.5 | 95.1 ± 0.6 | 4.3 ± 0.1 | 12.8 ± 0.1 | 0.63 ± 0.12 |
| F2 | 62.8 ± 0.36 | 0.43 ± 0.015 | 264.6 ± 3.0 | 96.3 ± 0.7 | 22.8 ± 0.6 | 10.9 ± 0.3 | 0.50 ± 0.09 |
| F3 | 64.5 ± 0.35 | 0.42 ± 0.015 | 274.6 ± 2.5 | 93.9 ± 0.4 | 28.5 ± 0.1 | 10.7 ± 0.2 | 0.44 ± 0.05 |
| F4 | 57.6 ± 0.50 | 0.34 ± 0.006 | 264.3 ± 4.7 | 97.1 ± 0.8 | 22.9 ± 0.1 | 10.6 ± 0.1 | 0.44 ± 0.03 |
| F5 | 64.5 ± 0.40 | 0.43 ± 0.006 | 269.0 ± 5.5 | 94.6 ± 0.7 | 27.4 ± 0.3 | 10.7 ± 0.2 | 0.53 ± 0.11 |
| F6 | 57.4 ± 0.30 | 0.34 ± 0.012 | 288.3 ± 8.5 | 95.7 ± 1.4 | 39.0 ± 0.4 | 11.3 ± 0.2 | 0.51 ± 0.08 |
| F7 | 59.3 ± 0.57 | 0.42 ± 0.012 | 275.0 ± 3.6 | 95.5 ± 1.0 | 26.7 ± 0.1 | 9.8 ± 0.2 | 0.41 ± 0.06 |
| F8 | 69.5 ± 0.59 | 0.65 ± 0.015 | 280.0 ± 4.5 | 96.0 ± 0.9 | 59.5 ± 0.8 | 7.2 ± 0.1 | 0.29 ± 0.03 |

*Mean ± SD, n=3. # Mean ± SD, n=10.

**Table 3: Estimated values of correlation coefficient ($R^2$), release exponents (n) of drug release for all formulations**

| Formulation Code | Zero order | First order | Higuchi's | Korsmeyer-Peppa's | |
|---|---|---|---|---|---|
| | (R2) | (R2) | (R2) | k | n |
| F1 | 0.811 | 0.68 | 0.972 | 0.239 | 0.892 |
| F2 | 0.848 | 0.698 | 0.983 | 0.305 | 0.815 |
| F3 | 0.936 | 0.805 | 0.979 | 0.265 | 0.794 |
| F4 | 0.922 | 0.794 | 0.981 | 0.213 | 0.848 |
| F5 | 0.784 | 0.614 | 0.962 | 0.436 | 0.73 |
| F6 | 0.827 | 0.96 | 0.967 | 0.282 | 0.834 |
| F7 | 0.942 | 0.836 | 0.959 | 0.204 | 0.83 |
| F8 | 0.955 | 0.893 | 0.986 | 0.344 | 0.696 |

**Table 4: Short term stability study results of VH patch (F8)**

| Time | Drug recovered* (% w/w) | % Drug Released* in 3 h | Similarity Factor (f2) | Physical property | |
|---|---|---|---|---|---|
| | | | | Appearance | Flexibility |
| Initial | 95.38 ± 1.02 | 77.91 ± 1.46 | 100.00 | good | Good |
| 1 Month | 94.32 ± 1.34 | 75.82 ± 1.98 | 83.08 | No change | Good |
| 2 Month | 93.98 ± 1.22 | 73.92 ± 2.13 | 75.84 | No change | Good |
| 3 Month | 93.57 ± 1.54 | 74.24 ± 1.71 | 75.22 | No change | Good |

*Mean ± SD, n=3.

frequency the samples were withdrawn and analyzed for physical appearance, flexibility, and drug content.

## RESULTS AND DISCUSSION

### Physico-Chemical and Mechanical Properties

Physico-chemical characteristics of the VH buccal patches are shown in Table 2. The prepared patches were smooth, uniform in thickness, mass, drug content and no visible cracks or folds. The mass of the prepared patches without backing membrane were ranged from 52.3 ± 0.25 to 69.5 ± 0.59 g and the thickness ranged from 0.24 ± 0.004 to 0.65 ± 0.015 mm. All the medicated patches had satisfactory folding endurance of >245 and the highest folding endurance were found as 288.3 ± 8.5 for F6. The drug content in the patches ranged between 93.9 ± 0.44 to 97.1 ± 0.87 % w/w, indicating favorable drug loading in the medicated patches.

### Surface pH

The surface pH of the patches was determined to investigate the possibility of any irritation or side effects, *in vivo*.[15] Since pH of the saliva range from 5.5 to 7,[22] the attempt was made to keep the surface pH of the medicated patches within the pH range of saliva. The surface pH of all the prepared patches was varied between 6.42 ± 0.08 to 6.55 ± 0.04, overall the results were near or above 6.5 and hence, these patches may not cause any irritation in the buccal cavity.

### Swelling Studies

The swelling behavior of the prepared VH patches as a function of time was depicted in Figure 1. The extent of water uptake by the polymer matrix and their erosion was revealed by the corresponding graphs of the formulations and gravimetric data of the curve. The swelling index of the prepared patches was found to be moderate and varied between the formulations, could be explained by the contrast in resistance of the matrix network structure (hydrogen bond) to entry of water molecules within the patch.[23] Among all the formulae F8 shows highest swelling value as 57.36 ± 1.98 % w/w in 120 min, due to presence of larger hydrophilic group of polymers. While the film prepared with lowest concentration of polymer was eroded soon, this could be ascribed to over hydration of films leading to disentanglement of polymer chains.

### *Ex vivo* mucoadhesion study

The bioadhesive strength of the VH buccal patches, forces in weight (g) required for complete detaching of patches from porcine buccal membrane were reported in Table 2. The mucoadhesive strength of the VH patches was increased with respect to the polymer concentration, as the swollen polymer forms a gel like structure resulting in larger surface/contact area and forms strong entanglement between polymers and mucus membrane.[24] However, addition of CA increased the bioadhesion of patches by electrostatic interactions with negatively charged mucus.[25]

### *In vitro* Release Study

*In vitro* release profile of VH from the prepared buccal patches was illustrated in Figure 1. All the formulation from F1 to F7 showed >90% w/w drug release in 180 min whereas, the F8 showed 77.91% w/w. The plots clearly indicated that, dug release was governed by the polymer content and without lag time, as the patches were directly exposed to the dissolution medium. Addition of CA and OM along with HPMC K4M and CP in the patch was associated with a reduction in drug release rate as the polymers forms thick swollen layer, may retards the entry of aqueous medium further and diffusion of drug from the patches.[26]

The drug release from controlled drug delivery system ruled by variety of complex mechanisms, and is not yet completely defined. Many of these mechanisms are either purely diffusion controlled or purely erosion

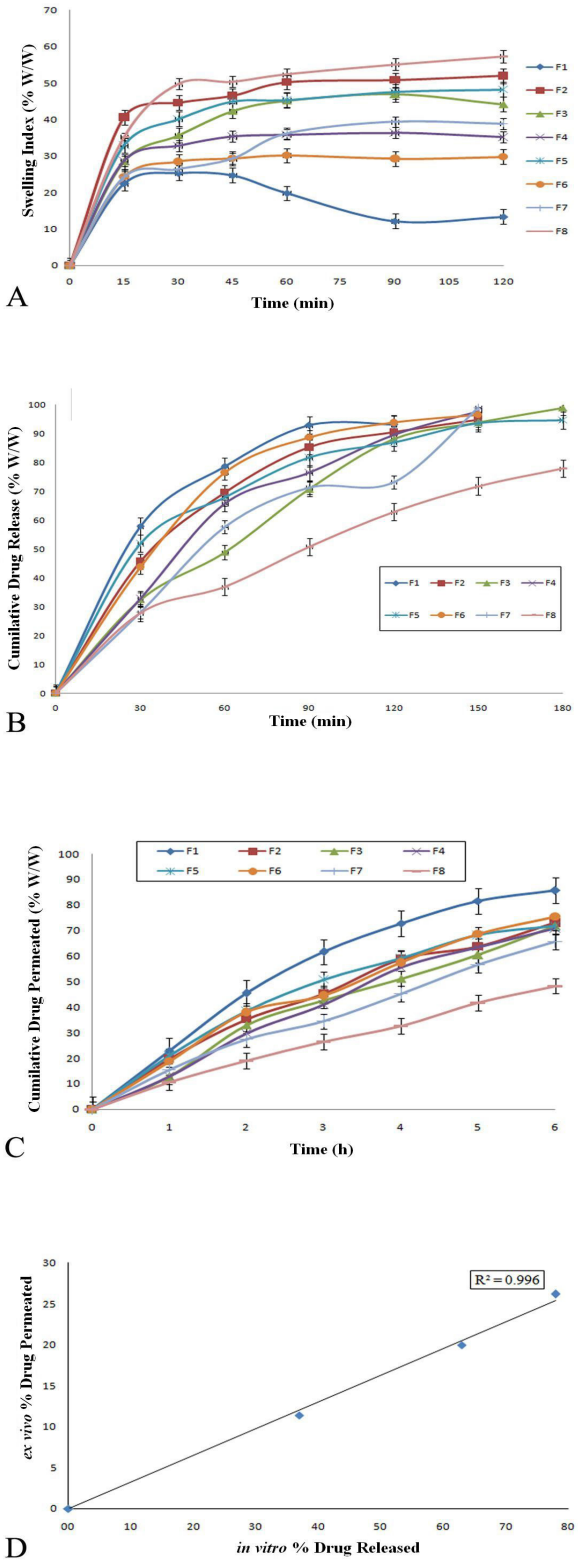


**Figure 1:** (A) Plot of water uptake (Swelling) of VH patches, expressed as %w/w; (B) Plot of *in vitro* drug release profile of all the formulation; (C) Results of ex vivo permeation of VH buccal patches, All Values represented in A, B, C as mean ± SD, n=3. (D) Correlation between *in vitro* Drug Release and *ex vivo* Drug Permeation of VH from F8.

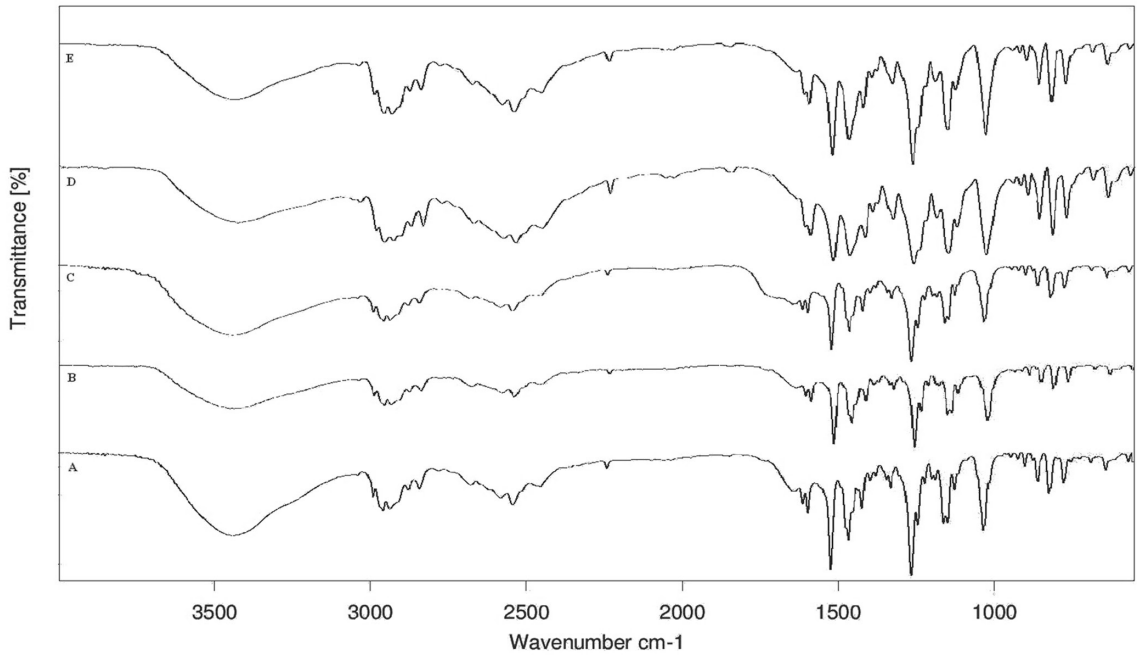


**Figure 2:** FITR spectrum of (A) VH, (B) VH+HPMC K4M, (C) VH+CP, (D) VH+CA and (E) VH+OM Physical mixture (1:1 Ratio).

controlled; many others being governed by both. To describe the drug release profile attempt was made to best fit of drug release by a model function using zero order, first order; release pattern using Higuchi's and Korsmeyer's model.[27] The results were revealed that the release of VH from the buccal patches obeyed zero order rather than first order except F6 obeyed first order (Table 3). All the formulations were result a good fit to Higuchi's model indicates the drug release from the patches predominantly controlled by diffusion, non-Fickian ($0.696 \geq n \leq 0.892$) and might be erosion at the terminal.

## *Ex vivo* diffusion study

The *ex vivo* permeation profile of VH from all the buccal patches were illustrated in Figure 1 and the results of flux were shown in Table 2. The *ex vivo* permeation rate of VH was slower than the *in vitro* release profile, could be explained by limited rate of hydration and surface area for drug permeation. Formulation F1 showed higher drug permeation (85.59 % w/w), whereas F8 consist four polymers combination showed least drug permeation (48.29 % w/w) at the end of 6 h and the difference was statistically significant ($t=4.65$, $P < 0.05$). The formulations containing two polymers combination showed 65.54 % (F7) to 75.42 % w/w (F6) and almost similar diffusion profile indicates; presence of CA and OM decelerates the drug permeation by retarding drug availability on porcine buccal membrane ready to absorb. This was further supported by the reduction of average flux value up to 15 to 50% compared to F1 (0.635±0.11 mg/cm$^2$/h), could be attributed by the combinations of polymers employed. Good correlation between *in vitro* drug release and *ex vivo* permeation were observed (Figure 1; $R^2 = 0.987$). Overall, the study revealed that VH was released from the formulations, permeated through the porcine buccal membrane and perhaps the drug permeates across human buccal membrane, *in vivo*.

## FTIR Study

The FTIR spectrum of VH and physical mixture of VH-polymer were shown in Figure 2. The IR absorbance peak for characteristic functional group of VH at 3442.20 cm$^{-1}$(N-H Stretch), 2956.53 cm$^{-1}$(C-H Stretch), 1154.97 cm$^{-1}$(Aliphatic C-N Stretch), 1027.27 cm$^{-1}$(C-O Stretch) and 1518.86 cm$^{-1}$(C=C Stretch) were exhibited in VH-Polymer mixture indicates no chemical interaction between VH and polymers used.

## Stability Study

The stability of the selected formulation (F8) of VH was studied for 3 months as per the ICH guidelines and the results were shown in Table 4. Even though, the drug degradation was found as 1.81 % w/w at the end of 3 months, the difference in mean drug content was statistically not significant ($P = 0.157$). The physical appearance of the tested patches was good, flexible and translucent till the end of 3 months. The similarity factor ($f_2$) value of the dissolution profiles between initial and after 3 months was found as 75.22 indicates the drug release character of formulation was remaining unchanged during the stability period.

# CONCLUSIONS

From the present investigation, the conclusion was made that the Bucco-adhesive patches of VH were prepared using HPMC, CP, CA and OM by solvent casting method can meet the ideal requirements for trans-mucosal drug delivery. The addition of CA and OM in the formulation could improve the mucoadhesive strength, retards the drug release of the buccal patch and modifies the permeation of VH across porcine buccal membrane and with appropriate stability. Hence, the OM and CA could be used as effective excipients in buccal adhesive formulation as alone or combined with other polymers. Further, *in vivo* studies are warranted to confirm its efficacy claims.

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## CONFLICT OF INTEREST

No conflict of interest are declared.

## ABBREVIATION USED

**HPMC:** Hydroxy Propyl Methyl Cellulose; **GIT:** Gastro Intestinal Tract; **HCl:** Hydrochloride; **g:** Gram, **mg:** milligram; **h:** Hour; **°C:** degree Celsius; **%:** Percentage; **m:** mass, **w:** weight; **v:** volume; **rpm:** Revolution per minute; **cm:** Centimeter; **mL:** Milliliter; **µm:** Micrometer; **nm:** Nanometer; **RH:** Relative Humidity.

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