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Design and Characterization of Mucoadhesive Buccal Patches of Diclofenac Sodium

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Mucoadhesive patches for delivery of diclofenac sodium were prepared using polyvinyl alcohol, hydroxyethyl cellulose and chitosan. Swelling and bioadhesive characteristics were determined for both plain and medicated patches. The results showed an increase in radial swelling after addition of diclofenac sodium to the plain formulation. A decrease in residual time observed for polyvinyl alcohol and chitosan containing formulae. High drug release was obtained from polyvinyl alcohol compared to the hydroxyethyl cellulose. Physical characteristics of the studied patches showed promising with good bioadhesion.

Development of new drug delivery systems has been one of the major thrust areas of pharmaceutical research these days. Film type dosage forms have been used for transdermal and also buccal or sublingual use[1]. Buccal cavity has a wide variety of functions and it acts as an excellent site for the absorption of drugs. It provides direct entry of drug molecules into the systemic circulation, thus avoiding hepatic first pass effect[2]. The ease of administration and ability to terminate drug delivery when required makes it either a potential route or an attractive route for drug delivery[3]. Rojanasakul *et al.*[4] investigated the permeability of rabbit mucosal membranes and found the order of permeability to be intestinal=nasal>vaginal>rectal>skin. The study also indicated that the permeability of all epithelial was similar, with most being more selective for positively charged molecules. Diclofenac sodium (DS) is a potent nonsteroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis and other rheumatic disorders[5]. It possesses a narrow therapeutic index due to short biological half-life[6]. The physicochemical properties of DS and its short half life make it a suitable candidate for administration by buccal route. The effectiveness of mucoadhesive formulation is greatly determined by the nature of the polymer composition used[7]. In the present study, we attempted to formulate mucoadhesive patches of DS, which undergoes first pass effect using non-ionic polymers, polyvinyl alcohol (PVA) and hydroxyethyl cellulose (HEC) and as well as chitosan as a cationic polymer to improve mucoadhesion and to examine the usefulness of the device for delivery of DS.

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MATERIAL AND METHODS

Diclofenac sodium was a gift from Cipla Ltd., Mumbai, Chitosan (CarboMer, USA), Polyvinyl pyrrolidone (BASF AG, Germany), Hydroxyethyl cellulose-10 cps (S. D. Fine Chemicals, Mumbai), Gelatin (Gelita, USA), polyvinyl alcohol (Loba Chemi Pvt. Ltd., Mumbai) was procured and other chemical and plasticizer used of AR grade.

Preparation of mucoadhesive patches:

The polymer studied, PVA, HEC and chitosan, were applied in concentrations of 10, 2 and 1.5 % (w/v), respectively. In all cases, 5% (v/v) glycerol was added as plasticizer. PVA powder 10% (w/v) was dissolved in hot water at 60 to 100°, and then glycerol was added under stirring. For HEC, calculated amount of polymer was dispersed in a 75%

water volume under stirring using a mechanical stirrer. The plasticizer was gradually added and the final volume was adjusted with distilled water. The prepared gels were left overnight at room temperature till clear, bubble-free gels were obtained. The gels were cast into glass Petri dish (15 mm in diameter) and allowed to dry in an oven maintained at 40° till a flexible film was formed[9].

One gram chitosan was dissolved in 50 ml of 1.5% (v/v) acetic acid under constant stirring using a magnetic stirrer for 48 h. The resultant viscous solution was filtered through 100 mesh nylon filter. The filter was left to stand until all air bubbles disappeared. The solution was poured into a clear, dry, glass Petri dish (15 mm in diameter) and left to dry at room temperature. To improve elastic and film forming property of the patches, polyvinyl pyrrolidone (PVP 1% w/v) were added. Hydrophilic additives were first dissolved in a small volume of distilled water, and then added to the chitosan solution prepared as described above[9].

The dried films (placebo patches) were carefully removed from the petri dish, checked for any imperfections or air bubbles and cut into patches, 10 mm in diameter. The samples were packed in aluminum foil and stored in glass container maintained at room temperature and 58% relative humidity[10]; this condition maintained the integrity and elasticity of the patches. Patches containing DS were prepared by dissolving the calculated amount of the drug in 20 ml distilled water. The drug solution was added to the polymer gel under stirring. The films were cast and then cut into patches, 10 mm in diameter, so that each patch contains 20 mg of the drug.

Mass uniformity and patch thickness:

Assessment of mass uniformity was done in 10 different randomly selected patches from each batch and thickness of the film was measured at 10 different randomly selected spots using a screw gauge from each batch. The mean and standard deviations were calculated.

Content uniformity:

Drug content uniformity of medicated patch was determined by weighing 5 patches (5 cm^2) and allowed to dissolve in 100 ml isotonic phosphate buffer, pH 6.8 (IPB) for 6 h. After suitable dilution the resultant solution was filtered and analyzed for DS content spectrophotometrically at 277 nm[11].

Moisture absorption:

A modification of the ASTM test No-D570-59T was used for testing of moisture absorption/loss of patches (1.8×1.8 cm) and the MVT of the patches (2.5 cm^2) were determined using a modified ASTM Test No E-96-53T as described by Kanig and Goodman[12].

Surface pH:

Buccal patches (5 cm^2) were allowed to swell in for 2 h on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into the Petri dish[13] till gelling at room temperature. The surface pH was measured by means of pH indicator paper to determine the surface pH. After 90 s the colour developed was compared with the standard colour scale. The mean of the six reading was recorded.

Viscosity:

Aqueous solutions containing both polymer and plasticizer were prepared in the same concentration as that of the patches. A model LVDV-II Brookfield viscometer attached to a helipath spindle number 4 was used. The viscosity was measured at 20 rpm at room temperature. The record values were the mean of three determinations.

Folding endurance:

As described by Khanna *et al.*[14], the folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times at the same place without breaking gave the value of the folding endurance.

Swelling:

Three patches were tested for each formulation. Samples of 5 cm^2 patch diameter were allowed to swell on the surface of an agar plate kept in an incubator maintained at 37±1°. Measurement of the diameter of the swollen patch was done at one-hour intervals for 5 h. Radial swelling was calculated using equation[15] $S_D(\%)=[(D_t-D_o)/D_o]\times100$, where $S_D(\%)$ is the percent swelling obtained by the diameter method, D_t is the diameter of the swollen patch after time t, D_o is the original patch diameter at time zero.

Residence time:

The *in vitro* residence time was determined using a modified USP disintegration apparatus, as reported by Nakamura *et al.*[16]. The disintegration medium was composed of 800 ml IPB maintained at 37±1°. A segment of rabbit intestinal mucosa, 3 cm long was glued to the surface of the glass slab, vertically attached to the apparatus. The

mucoadhesive patch was hydrated from one surface using 50 µl 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 at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded.

Bioadhesion force:

The tensile strength required to detach the bioadhesive patch from the mucosal surface was applied as a measure of the bioadhesive performance. The apparatus was locally assembled and was a modification of the apparatus previously applied by Parodi *et al.*[17] using rabbit small intestine mucosa. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by a small platinum lamina vertically suspended through a wire. At the same side, a movable platform was maintained in the bottom in order to fix the model mucosal membrane. For determination of the bioadhesion force, the mucoadhesive patch was fixed to the platinum lamina using cyanoacrylate adhesive. A piece of rabbit intestinal mucosa, 3 cm long, was also glued to the platform. The exposed patch surface was moistened with 50 µl of IPB, and left for 30 s for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into contact with the mucosal surface. A preload of 20 g was placed over the platinum lamina for 3 min as initial pressure. On the right pan, a constant weight of 5 g was added at 2 min intervals. The total weight required for complete detachment of the patch was recorded and the bioadhesion force was calculated per unit area of the patch as per equation. $F=(W_w \times g)/A$, where F is the bioadhesion force (kg/m.s^2), W_w is the mass applied (g), g is the acceleration due to gravity (cm/s^2), A is the surface area of the patch (cm^2). The adhesion force data reported represent the mean of six determinations.

Preparation of mucosal tissue:

Overnight fasted rabbits were sacrificed and the small intestine was carefully removed and rinsed with normal saline to remove any loose materials. The small intestine was cut into segments of 3 cm length and cut open longitudinally along the mesentery to expose the inner mucosal surface[18]. The small intestine was stored in cold (5-8°) normal saline and used within three days[19]. Before experiment the intestine was taken out and thawed until it reached room temperature, and was kept soaked in IPB for 1 h. It was gently blotted dry with a filter paper. The integrity of the intestine was tested microscopically, before use to detect any histological change[20]. No significant histological changes were observed.

***In vivo* mucoadhesion studies:**

The compatibility of the placebo patches, medicated patches and the maximum time of bioadhesion were determined in healthy human volunteers, by a blind crossover study design. Five healthy human volunteers (28±5.25, 6 males and 4 females) participated in the study. The site of application/ adhesion on the buccal mucosa was wiped with a cotton swab and a patch (2 cm^2 area) was pressed voluntarily on the buccal mucosa for 30 s. The volunteers were allowed to drink water from 30 min after fixing of the patch and were advised to perform their normal oral activities and not to disturb the patch by any means. The volunteers were asked to note the retention time of the patch and opinion about the acceptability of the patch. An index for irritation of mucosa, taste alteration and hindrance due to swelling were used to describe side effect of the patches. A score [21,22] was used to describe the biocompatibility of the patch. After Completion of the study, a questionnaire was given to volunteers to score the parameters such as irritancy, comfort, taste, dry mouth, salivation of the patch at the place of attachment.

***In vitro* release study:**

The patches were evaluated for drug release using Keshary-Chien type glass cells. Cellophane sheets treated with 5% v/v of glycerol[23,24] were mounted between the donor and receptor compartments. The patch was placed on the cellophane sheet and the compartment clamped together. The cell was placed in a water bath maintained at 37±1°. The receptor compartment (25 ml capacity) was filled with phosphate buffer, pH 6.8 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. At pre-determined time intervals samples were withdrawn and an equal volume of pre-warmed buffer was replaced. The samples were analyzed, after appropriate dilution, for DS content at 277 nm.

RESULTS AND DISCUSSION

Physical characteristics of the plain patches containing individual polymer are shown in Table 1. The thickness of the patches was varied from 0.51±0.15 to 0.75±0.31. The mass ranged from 80 to 231 mg. The surface pH of all formulation was within ± 1.0 units of the natural pH and hence

no mucosal irritations were expected. The recorded folding endurance of the patches was less than 300 times. Assessment of the swelling behavior was done by measuring radial swelling. HEC patches showed high radial swelling, followed by PVP and then chitosan ones, the recorded swelling values after 5 h were 40.1, 20.1 and 3.01%, respectively. The lowest swelling recorded for chitosan may be attributed to its poor solubility in water[25]. Differences in swelling of the tested hydrophilic polymers could be explained by the difference in resistance of the matrix network structure (hydrogen bond) to the movement of water molecule[26]. Values of the *in vitro* residence time are reported in Table 1. All patches, except chitosan, remained attached to the mucosal surface until complete erosion. PVP patches showed convenient duration for complete erosion in 3.9 h, where as HEC patches were erosion in 8.2 h. Chitosan patches completed erosion in 11 h without detachment; this is in agreement with Needleman *et al.*[27], who recorded a prolonged *in vitro* adhesion time of 4 days for chitosan. *In vivo* results showed chitosan patches superior adhesion on the buccal mucosa of the volunteers. *In vitro* residence time of patches were higher compared to the *in vivo*, this may be due to the movement of the mouth when speaking, laughing and swelling, representing a shearing force promoting faster erosion of the patch despite the comparatively larger dissolution medium applied *in vitro*[28].

TABLE 1: CHARACTERISTICS OF PLAIN MUCOADHESIVE PATCHES

Composition/ characteristics	Batch code				
	F1	F2	F3	F4	F5
PVA (%,w/v)	10	-	-	-	-
HEC (%,w/v)	-	1.5	-	-	-
Chitosan (%, w/v)	-	-	2	2	2
PVP (%, w/v)	-	-	-	1	-
Gelatin (%, w/v)	-	-	-	-	5
Patch thickness (mm)[a]	0.75±0.15	0.59±0.22	0.51±0.31	0.54±0.28	0.62±0.25
Patch mass (mg)[a]	231±0.7	156±0.09	80±0.18	84±0.11	95±0.12
Surface pH[a]	5.5±0.1	5.5±0.2	5±0.15	5±0.15	5±0.1
Folding endurance	287	292	298	292	295
Radial swelling 5 h (%)[a]	20.1±2.2	40.1±1.99	3.01±1.14	6.05±1.48	7.52±0.99
Residence time (h)					
in vitro[a]	3.9±0.28	8.2±0.52	11±0.16[b]	1.2±0.17[b]	2±0.24[b]
in vivo[a]	2.6±1.15	2.92±0.72	5±1.011[b]	1.8±1.12[b]	2.4±1.25[b]
Bioadhesive force (10^2, kg/m.s^2)[a]	502±3.25	60.1±2.48	84.2±1.99	89±1.69	89±1.87
MVT (75% RH) (g.cm^{2}h.10^{-4})					
(1d)	5.91	4.93	3.24	3.58	3.97
(7d)	8.12	7.22	6.43	7.21	7.89
Moisture absorbed (%)					
(1d)	7.52	6.42	4.21	4.58	5.21
(7d)	12.5	11.4	8.45	9.2	10.3

[a]Mean±SD (n=6, for patch thickness, and for patch mass n=10), [b]The patches showed no erosion, disintegration, or detachment during the study.

Maximum bioadhesion was recorded for PVA patches (502×10^2 kg/m.s^2), followed by the cationic polymer, chitosan (884×10^2 kg/m.s^2), then HEC (60.1×10^2 kg/m.s^2). Although non-ionic, the polymeric nature of PVA provides the polymer with unique gelling characteristics, which in turn are responsible for its adhesive properties, in addition to its high mechanical strength, tack and high elasticity. Linear chains of PVA exhibit strong bioadhesive behavior either because of hydrogen bonding due to hydroxyl group or because of significant chain penetration or both[29].

According to Henriksen *et al.*[30], chitosan is a bioadhesive material with promise at neutral or slightly alkaline pH, which is found to be advantageous for adsorption on the mucosal surface. It was suggested that, at this pH, chitosan has numerous amine and hydroxyl groups as well as a number of amino groups that may increase the interaction with the negative mucine[31]. A study of the rheological interaction between chitosan and mucin suggested a positive rheological synergism in the presence of excess mucin, which causes a strengthening of the mucoadhesive interface[32].

No correlation was found between the bioadhesion force and residence time of the polymers. It seems that higher bioadhesive polymers do not necessarily reside longer on the mucosal surface. Surface charge density and chain flexibility are considered to be prerequisites for bioadhesion, whereas the residence time is primarily dependent on the dissolution rate of the polymer. However, as regards in Table 1 the *in vivo* residence time data , none of the polymers was detached from the oral mucosa over the study period, which indicated that the bioadhesion values of all polymers were satisfactory to retain the patch on the buccal mucosa.

Properties of the medicated patches are summarized on Table 2. The patch thickness varied from 0.92±0.06 to 1.15±0.18 mm and their mass ranged from 81 to 240 mg. The patches were characterized by convenient surface pH, good film properties and exhibited remarkable radial swelling. Maximum radial swelling was shown by HEC the diameter progressed with time till a 68% increase after 5 h. PVA patches enlarged radially by 29% within the first three hours and then a plateau was formed. Chitosan containing patches exhibited relatively a lower increase in diameter within 5 h (10.1%, 18% and 22% for F3, F4 and F5, respectively). The

TABLE 2: COMPOSITION AND CHARACTERISTICS OF MUCOADHESIVE BUCCAL PATCHES CONTAINING 5% (W/V) DICLOFENAC SODIUM

Composition/characteristics	Batch code				
	F1	F2	F3	F4	F5
PVA (%,w/v)	10	-	-	-	-
HEC(%,w/v)	-	1.5	-	-	-
Chitosan(%,w/v)	-	-	2.0	2.0	2.0
PVP(%,w/v)	-	-	-	1	-
Gelatin(%,w/v)	-	-	-	-	5.0
Patch thickness (mm)[a]	1.02±0.08	1.12±0.045	0.92±0.057	1.05±0.038	1.15±0.178
Patch mass (mg)[a]	240±0.03	160±0.78	81±0.07	89±0.87	100±0.45
Surface pH	5.5	5.5	5	5	5
Radial swelling 5 h (%)[a]	29.0±1.78	68.0±1.98	10.11±1.88	18.0±1.22	22.0±2.88
In vitro residence time(h)[a]	3.8±0.86	9.2±1.43	11.0±0.88[b]	1.52±0.72[c]	2.9±0.99[c]
t_{50} (h)	2.6	6.9	2.4	6.1	-
Release kinetics (n)	0.956	0.725	0.615	0.722	0.638
(k)	12.57	7.02	12.66	7.96	4.65
(R)	0.983	0.994	0.980	0.997	0.995

[a]Mean±SD (n=6, for patch thickness, and for patch mass n=10), [b]The patches showed no erosion, disintegration, or detachment during the study of 12 h. [c]The patches were detached from the membrane before complete erosion.

presence of the hydrophilic additives, PVP and Gelatin in chitosan patches seemed to increase the surface wettability and swelling of the patches. The plateau seen in the swelling profile may be due to either the solvent front on each surface meeting in the center of the patch, thus there was no further unhydrated polymer to hydrate and expand or to the protective gel coat only allowing a small quantity of water to diffuse into the inner core[33].

Comparing the radial swelling of plain patches and those containing DS an increase in patch swelling by the addition of the drug was noted. Undoubtedly the presence of the drug would modify the way water is bound to or taken by the polymer. Alteration in water distribution within such systems would thus modify the matrix structure. In addition, the presence of a water soluble drug might improve the surface wetting of the matrix[34].

Values of the *in vitro* residence time differ from one polymer to the other. PVA and HEC patches reside on the membrane until complete erosion after 3.8 and 9.2 h, respectively. Chitosan patches remained attached to the membrane during the time of the study without erosion. However, the addition of PVP and gelatin to chitosan caused patch dislodgement within 1.5 and 2.9 h, respectively, without erosion. The presence of DS slightly affected the residence time of the patch. Comfortability of the buccal patch in the oral cavity is an important concern in buccal drug delivery. Hence this study documented the response of human volunteers to some of the parameters associated with the comfort of the patch in the oral cavity. The response of the healthy human volunteers to each subjective parameter was calculated and obtained results are presented in table 3. Based on these results, it can be concluded that the patch would be comfortably placed in the human oral cavity.

The release profile of DS is illustrated in fig. 1. The extent of DS release within 1 h from PVA and HEC formulae was 15.2 and 8.2%, respectively. In time, a marked rise in the release rate from PVA patches was observed compared to HEC patches, 50% DS was released within 2.8 h in the case of PVA patches compared to 6.9 h in case of HEC patches. The higher release of DS from PVA patches can be explained by the viscosity of the polymer solution. A preliminary study showed that a 10% w/v solution of PVA had lower viscosity than 1.5 w/v solution of HEC. As the viscosity is related to the strength and durability of the gel layer, the diffusion of the drug will be easier in case of PVA patches. In addition, the relatively high swelling of the HEC

TABLE 3: RESPONSE OF HEALTHY HUMAN VOLUNTEERS TO VARIOUS PARAMETERS.

Criteria	Volunteers Response
Irritation	100
None	
Slight	
Moderate	
Severe	
Taste	
Normal	80
Slightly unpleasant	20
Very unpleasant	
Pleasant	
Very pleasant	
Comfort	
Very Comfortable	30
Comfortable	70
Slightly uncomfortable	
Moderately uncomfortable	
Severely uncomfortable	
Dryness of Mouth	
None	80
Slightly	20
Moderate	
Severe	
Salivary secretion	
None	10
Slight	70
Moderate	20
Severe	
Heaviness of patch at the place of attachment	
None	80
Slight	20
Moderate	
Severe	

increased gel layer thickness and consequently the diffusion pathways, which in turn may be the cause of the slower drug release from HEC patches compared to PVA patches.

Formulation F3 containing chitosan alone provided the higher release profile with sustain but almost complete release within 7 h. At pH 6.8, chitosan (pKa=6.3) was partly positively charged[10]. As well as DS molecules, thus inducing an electrostatic repulsion, which enhances the drug release rate. However a lower release profile was observed when 1% w/v PVP was added to the formula, a complex may be formed between PVP and the cationic drug and/or

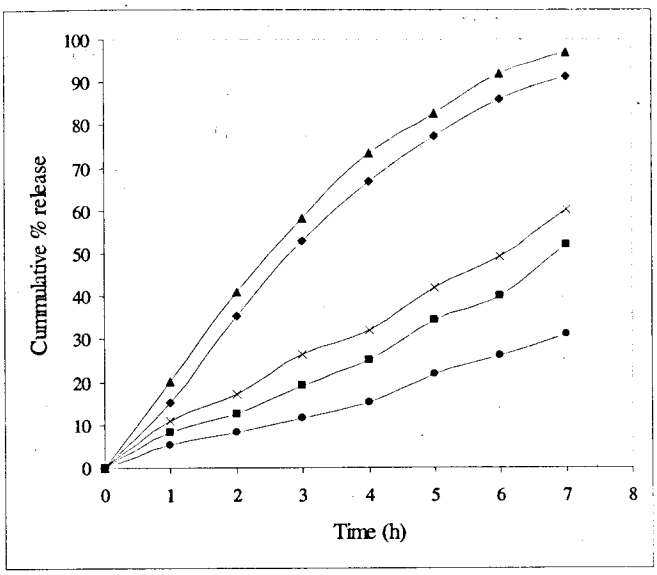

Fig.1: Release profile of diclofenac sodium from various formulations.

Release profile of DS from various formulation containing different polymer concentration viz. F1 (-♦-); F2 (-◘-); F3 (-▲-); F4 (-x-); and F5 (-●-).

polymer, which may lead to a decrease in the release rate of the drug. PVP was reported to form a complex with various drug or polymers[34]. It was also observed that the addition of 5% (w/v) gelatin to chitosan significantly delayed the release rate of the drug. The amount of DS release progressed slowly from 5 to 30% during 7 h. It was reported that gelatin contains cationic and anionic amino acid residues[35], the majority of these residues being amino and carboxylic groups. At pH 6.8, the net charge of gelatin was negative whereas a positive charge was observed on the DS molecule suggested the possibility of an electrostatic attraction between the oppositely charged molecules. This attraction may reduce the diffusional mobility of the cationic drug from the swollen gel, leading to a decrease in the release rate. In addition a possible interaction between the anionic gelatin and the cationic polymer, chitosan may also produce a complex, allowing a more extended release of the drug. The phenomena of inter polymer complex formation between chitosan and anionic polymers have been extensively reported[36,37].

The release kinetic parameters were calculated according to the Peppas equation[38] $M_t/M_\infty = Kt^n$, where M_t/M_∞ is the fractional release of the drug t denotes the release time; K is a constant incorporating structural and geometric characteristic of the controlled release device and n is the release exponent, indicative of the drug release mechanism. The value of the diffusional exponent n is 0.95 for PVA patches, indicating the zero order release behavior. The release was, thus controlled by the viscoelastic relaxation of the matrix during the solvent penetration as well as the diffusivity of the drug in the gel layer formed as the patch swelled. In this case, the relative rates at which the swelling and eroding fronts moved relative to each other were synchronized and a constant diffusional path length was obtained. For HEC patches n is 0.73 indicating a non fickian release behavior. When swelling is predominant, drug diffusion probably occurs through the solvent filled pathways of the swollen patch. Erosion of the matrix can also influence the drug release from this polymer matrix. A relative contribution of erosion and diffusion to the overall release mechanism is suggested. Chitosan containing patches have n values ranging from 0.62 to 0.72.

In conclusion, investigation has shown that mucoadhesive patches are a promising drug delivery system for DS. The data presented in this work clearly demonstrates that the non ionic polymer PVA showed good mucoadhesive and swelling characteristics. Medicated PVA patches maintained a satisfactory residence time in the buccal cavity and ensure zero order release of the drug over relatively longer period, which made them good candidate for drug delivery system through buccal mucosal route.

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