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Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride

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Mucoadhesive patches for delivery of cetylpyridinium chloride (CPC) were prepared using polyvinyl alcohol (PVA), hydroxyethyl cellulose (HEC) and chitosan. Swelling and bioadhesive characteristics were determined for both plain and medicated patches. The results showed a remarkable increase in radial swelling (S_D) after addition of the water-soluble drug (CPC) to the plain formulae. A decrease in the residence time was observed for PVA and chitosan-containing formulae. Higher drug release was obtained from PVA patches compared to HEC ones, while both are non-ionic polymers. A considerable drop in release was observed for chitosan formulae after the addition of water-soluble additives, polyvinyl pyrrolidone (PVP) and gelatin. Ageing was done on PVA formulae; the results showed there was no influence on the chemical stability of CPC, as reflected from the drug content data. Physical characteristics of the studied patches showed an increase in the residence time with storage accompanied with a decrease in drug release. This may be due to changes in the crystal habit of the drug as well as to slight agglomeration of the polymer particles.

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Cetylpyridinium chloride (CPC), a quaternary antiseptic, has been found effective in controlling the accumulation of bacterial plaque and the consequent gingivitis (1). The drug has bactericidal activity against Gram-positive and, at higher concentrations, against Gram-negative organisms. It has a good activity against *Candida albicans* (2). Lozenges and mouthwashes are available but none of these dosage forms can release the antiseptic drug into the oral cavity for a prolonged period because of their short residence time (3). Multilayered bioadhesive lozenges containing CPC were evaluated (4); they were not erodible and required removal after 3 h. A buccoadhesive erodible disk was designed (1), which showed a controlled and delayed release pattern at the targeted

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site at concentrations above the minimum inhibitory concentration (MIC) for prolonged periods of time.

In this study, we attempted to formulate mucoadhesive patches, which would release the drug in a sustained manner using non-ionic polymers, polyvinyl alcohol (PVA) and hydroxyethyl cellulose (HEC), as well as chitosan as a cationic polymer. In addition, the effect of ageing on the mucoadhesive characteristics and the *in vitro* release pattern of a selected patch was investigated.

EXPERIMENTAL

Materials

Cetylpyridinium chloride monohydrate (Merck KgaA, Germany) was kindly supplied by Amriya Pharmaceutical Industries (Egypt). Chitosan (maximum granule size 0.2 mm, degree of acetylation > 80%, CarboMer, USA), polyvinyl alcohol (PVA, Mowiol® 40-88, E.I. du-Pont de Nemours, USA), hydroxyethyl cellulose (15000MPAS, HEC, Natrosol®, Alexandria Pharmaceutical Co., Egypt), polyvinyl pyrrolidone (PVP, Povidone®, Kollidon®25, BASF Aktiengesellschaft, Germany) and gelatin powder (ADWIC, El-Nasr Pharmaceutical Chemicals Co., Egypt) were used. Other chemicals were of analytical grade.

Preparation of mucoadhesive patches

The polymers studied, PVA, HEC and chitosan, were applied in concentrations of 10, 1.5, and 2% (*m/V*), respectively. In all cases, 5% (*V/V*) glycerol was added as plasticizer. According to Tsutsumi *et al.* (5), PVA powder 10% (*m/V*) was dissolved in hot water at 80 to 100 °C, and then glycerol was added under stirring. For HEC, the calculated amount of the polymer was dispersed in a 75% water volume under continuous 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 a glass Petri dish and allowed to dry in an oven maintained at 40 °C till a flexible film was formed.

According to Sawayanagi *et al.* (6), 1 g 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 gauze. The filtrate was left to stand until all air bubbles disappeared. The solution was poured into a clean, dry, glass Petri dish (10 mm in diameter) and left to dry at room temperature. To improve elastic and film forming properties of the patches, PVP (1%, *m/V*) and gelatin (5%, *m/V*) were added. Hydrophilic additives were first dissolved in a small volume of distilled water, then added to the chitosan solution prepared as described above.

The dried films (plain 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 a glass container maintained at room temperature and 58% relative humidity (7); this condition maintained the integrity and elasticity of the patches.

Patches containing cetylpyridinium chloride 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 contained 10 mg of the drug.

Evaluation of patches

Mass uniformity and patch thickness. – Assessment of mass and thickness was done on ten patches. The mean and standard deviation were calculated.

Surface pH. – Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (*m/V*) agar in warmed isotonic phosphate buffer of pH 6.75 under stirring and then pouring the solution into a Petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of two readings 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 recorded values were the mean of three determinations.

Folding endurance test. – As described by Khanna *et al.* (8), 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, which is considered satisfactory to reveal good film properties. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

Swelling. – Three patches were tested for each formulation. After determination of the original patch diameter, the sample was allowed to swell on the surface of an agar plate kept in an incubator (hot air incubator, VEB MLW, type 8468, MLW, Germany) maintained at 37 °C. Measurement of the diameter of the swollen patch was done at one-hour intervals for 5 h. Radial swelling was calculated from the following equation:

$$S_D\ (\%) = [(D_t - D_o)/D_o] \times 100 \qquad (1)$$

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 locally modified USP disintegration apparatus (Disintegration tester, type ZT4, Erweka, Germany), based on the apparatus applied by Nakamura *et al.* (9). The disintegration medium was composed of 800 mL isotonic phosphate buffer of pH 6.75 (IPB) maintained at 37 °C. A segment of rabbit intestinal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15 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 out at the highest point. The time necessary for complete ero-

sion or detachment of the patch from the mucosal surface was recorded (mean of triplicate determinations).

Four healthy subjects (25–50 years old) agreed to participate in the *in vivo* study. The experiment was carried out with plain patches only. The bioadhesive patch was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30 s. The patch and the inner upper lip were carefully moistened with saliva to prevent patch from sticking to the lip. The subjects were not allowed to eat or drink during the study (5 h). They were asked to monitor the ease with which the system was retained on the mucosa and note any tendency to detachment. The adhesion time was indicated by either complete erosion of the patch or failure of the adhesive bond. Any complaints and bad feelings were also recorded. Repeated application of the bioadhesive patches by the same volunteer was allowed after a two-day period.

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.* (10). 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 15 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 follows:

$$F = (W_w \times g)/A \tag{2}$$

where F is the bioadhesion force (kg m^{-1} 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 three determinations.

Content uniformity. – The medicated patch was allowed to dissolve in 100 mL isotonic phosphate buffer, pH 6.75. The amount of cetylpyridinium chloride in the patch was measured spectrophotometrically at λ_{max} of 258 nm (n = 5).

In vitro *release study.* – The release study was carried out in a USP 24 dissolution apparatus type 1 (six-station dissolution apparatus, Hanson Research Corp., USA), slightly modified in order to overcome the small volume of the dissolution medium. The dissolution medium was 50 mL IPB, pH 6.75, maintained at 37 ± 0.5 °C and kept in a glass beaker fixed inside the USP dissolution flask. The patch was fixed to the central axis, which rotated at 50 rpm. Filtered samples (2 mL) were manually collected at intervals of 1, 2, 3, 4, 5, 6 and 7 h. The samples were compensated with an equal volume of IPB kept

at the same temperature. The concentration of drug released in the medium was assayed spectrophotometrically at 258 nm after suitable dilution with the dissolution medium when necessary. The experiment was carried out in triplicate.

Ageing. – Optimized medicated patches were subjected to accelerated stability testing. Patches were packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37 ± 0.5 °C and 75 ± 5% RH for 6 months. Changes in the appearance, residence time, release behavior and drug content of the stored bioadhesive patches were investigated after 1, 2, 3, 4, 5, and 6 months. The data presented were the mean of three determinations. Fresh and aged medicated patches, after 6 months storage, were investigated using a Jeol, JSM-5300 scanning electron microscope (Jeol, Japan). The patches were coated with gold using the direct current sputter technique. Samples containing powder drug were also analyzed.

RESULTS AND DISCUSSION

Physical characteristics of the plain patches containing individual polymers are shown in Table I. The patches were 10 mm in diameter, 0.6 ± 0.2 mm in thickness. The mass ranged from 84 to 234 mg. The surface pH of all formulations was within ± 1.5 units of the neutral pH and hence no mucosal irritation was expected. The recorded folding endurance of the patches was > 300 times. Assessment of the swelling behavior was done by measuring radial swelling. In the case of patches intended for local therapy, the contact area should be as large as possible, a requirement that must be balanced with patient compliance; excessive increase in patch diameter might cause discomfort and/or dislodgment of the swollen patch. HEC patches showed high radial swelling, followed by PVA and then chitosan ones; the recorded swelling values after 5 h were 41.9, 22.6 and 3.1%, respectively (Fig. 1, insert, and Table I). The lowest swelling recorded for chitosan (3.1%) may be attributed to its poor solubility in water (11). Differences in swelling

Table I. Characteristics of plain mucoadhesive patches

Characteristics	PVA	HEC	Chitosan
Polymer concentration (%, *m/V*)	10	1.5	2
Patch thickness (mm)[a]	0.801 ± 0.114	0.61 ± 0.208	0.516 ± 0.35
Patch mass (mg)[a]	234 ± 0.2	162 ± 0.07	84 ± 0.09
Surface pH	5.5	5.5	5
Folding endurance	> 300	> 300	> 300
Radial swelling 5 h (%)[a]	22.56 ± 2.493	41.93 ± 2.088	3.05 ± 0.629
Residence time (h): *in vitro*[a]	4 ± 0.215	8.5 ± 0.487	10 ± 0.166[b]
in vivo[a]	2.6 ± 1.25	2.915 ± 0.86	5 ± 1.097[b]
Bioadhesion force (x 10^2, kg m^{-1} s^{-2})[a]	511.85 ± 4.7	58.43 ± 1.6	88.99 ± 1.51

[a] Mean ± SD (n = 3, for patch thickness, and for patch mass n = 10).
[b] The patches showed no erosion, disintegration, or detachment during the study.

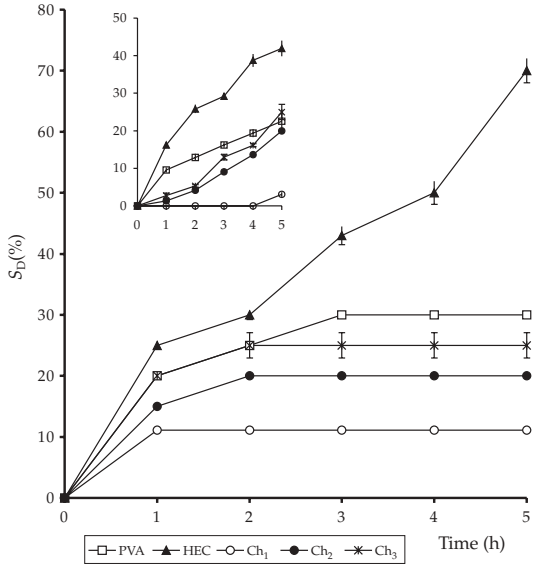

Fig. 1. The radial swelling profiles of mucoadhesive patches containing CPC. The insert represents the radial swelling of plain patches (SD bars, n = 3).

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 molecules (12). Values of the *in vitro* residence time are reported in Table I. All patches, except chitosan, remained attached to the mucosal surface until complete erosion. PVA patches showed convenient duration for complete erosion (4 h), longer duration was recorded for HEC (8.5 h). Chitosan patches retained their integrity during the study time (10 h) without detachment; this is in agreement with Needleman *et al.* (13), who recorded a prolonged *in vitro* adhesion time for chitosan (4 days). *In vivo* results (Table I) demonstrated the superiority of chitosan to reside on the buccal mucosa of the volunteers. Comparing the *in vivo* and *in vitro* residence time of the tested patches, higher values were obtained *in vitro* (Table I). This may be due to the movements of the mouth when speaking, laughing, and swallowing, representing a shearing force promoting faster erosion of the patch despite the comparatively larger dissolution medium applied *in vitro* (14).

Maximum bioadhesion was recorded for PVA patches (511.85×10^2 kg m^{-1} s^{-2}), followed by the cationic polymer, chitosan (88.99×10^2 kg m^{-1} s^{-2}), then HEC (58.43×10^2 kg m^{-1} 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 groups or because of significant chain penetration or both (15).

According to Henriksen *et al.* (16), chitosan is a promising bioadhesive material 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 mucin (16). A study of the rheological interaction between chitosan

and mucin suggested a positive rheological synergism in the presence of excess mucin, which caused a strengthening of the mucoadhesive interface (17).

No correlation was found between the bioadhesion force and the residence time of the polymers. It seems that highly 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 the *in vivo* residence time data (Table I), 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 in Table II. The patches had a mean thickness of 1.1 ± 0.1 mm and their mass ranged from 98 to 140 mg. The patches were characterized by convenient surface pH, good film properties and exhibited remarkable radial swelling (Table II and Fig. 1). Maximum radial swelling was shown by HEC; the diameter progressed with time till a 70% increase after 5 h. PVA patch enlarged radially by 30% within the first three hours and then a plateau was formed. Chitosan-containing patches exhibited relatively a lower increase in diameter within 5 h (11.1%, 20%, and 25% for Ch_1, Ch_2, and Ch_3, respectively). The presence of the hydrophilic additives,

Table II. Composition and characteristics of mucoadhesive buccal patches containing 2% (m/V) cetylpyridinium chloride

Composition/ characteristic	Code				
	PVA	HEC	Ch_1	Ch_2	Ch_3
PVA (%, *m/V*)	10	-	-	-	-
HEC (%, *m/V*)	-	1.5	-	-	-
Chitosan (%, *m/V*)	-	-	2	2	2
PVP (%, *m/V*)	-	-	-	1	-
Gelatin (%, *m/V*)	-	-	-	-	5
Patch thickness (mm)[a]	1.02 ± 0.06	1.14 ± 0.059	0.96 ± 0.051	1.08 ± 0.042	1.17 ± 0.133
Patch mass (mg)[a]	98 ± 0.029	136 ± 0.54	100 ± 0.097	123 ± 0.201	140 ± 0.043
Surface pH	5.5	5.5	5	5	5
Radial swelling 5 h, (%)[a]	30 ± 0.5	70 ± 2.001	11.11 ± 0.07	20 ± 0.225	25 ± 2.06
In-vitro residence time (h)[a]	3.5 ± 0.872	10 ± 1.542	10 ± 0.909[b]	1 ± 0.631[c]	2.5 ± 0.786[c]
CPC released (%) (after 1 h)[a]	14.6 ± 1.33	12.71 ± 2.088	24.56 ± 1.359	13.41 ± 0.677	5.1 ± 0.118
(after 7 h)[a]	95.82 ± 2.3	50.34 ± 3.745	99.68 ± 3.802	58.95 ± 2.32	21.14 ± 1.491
t_{50} (h)	2.7	6.9	1.7	4.8	-
Release kinetics *n*	0.975	0.779	0.637	0.767	0.655
k	16.95	10.23	32.07	14.5	4.62
R	0.985	0.995	0.992	0.998	0.995

[a] Mean ± SD (n = 3 for patch thickness, and for patch mass n = 10).
[b] The patches showed no erosion, disintegration, or detachment during the study (10 h).
[c] The patches were detached from the membrane before complete erosion.

PVP and gelatin in chitosan patches seemed to increase the surface wettability and swelling of the patches. The plateau seen in the swelling profiles 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 (18).

Comparing the radial swelling of plain patches and those containing CPC (Fig. 1), 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 up 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 (19).

Values of the *in vitro* residence time, as shown in Table II, differed from one polymer to the other. PVA and HEC patches resided on the membrane until complete erosion after 3.5 and 10 h, respectively. Ch_1 patches remained attached to the membrane during the time of the study (10 h) without erosion. However, the addition of PVP and gelatin to chitosan caused patch dislodgment within 1 and 2.5 h, respectively, without erosion. The presence of CPC, a water-soluble drug, slightly affected the residence time of the patch (Fig. 2).

The release profile of CPC patches is illustrated in Fig. 3. The extent of CPC release within 1 h from PVA and HEC formulae was 14.6 and 12.7%, respectively (Table II). In time, a marked rise in the release rate from PVA patches was observed compared to HEC

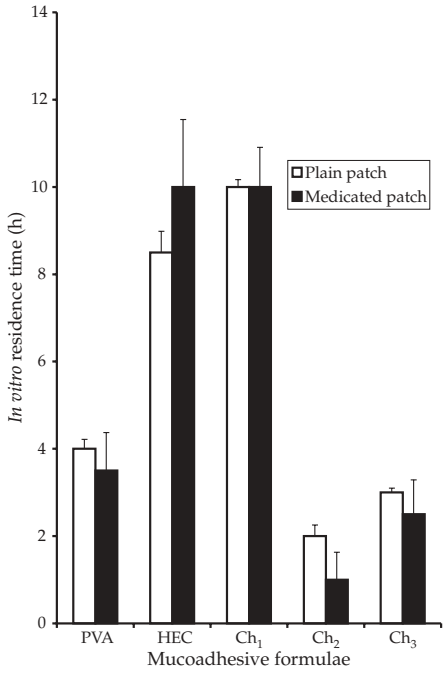

Fig. 2. The *in vitro* residence time of plain and medicated mucoadhesive patches (SD bars, $n = 3$).

patches; 50% CPC was released within 2.7 h in the case of PVA patches compared to 7 h in the case of HEC patches (Fig. 3a). The higher release of CPC from PVA patches can be explained by the viscosity of the polymer solution; a preliminary study showed that a 10% *m/V* solution of PVA had lower viscosity than a 1.5% *m/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 the case of PVA patches. In addition, the relatively high swelling of HEC increased the gel layer thickness and consequently the diffusion pathlength, which in turn may be the cause of the slower drug release from HEC patches compared to PVA patches.

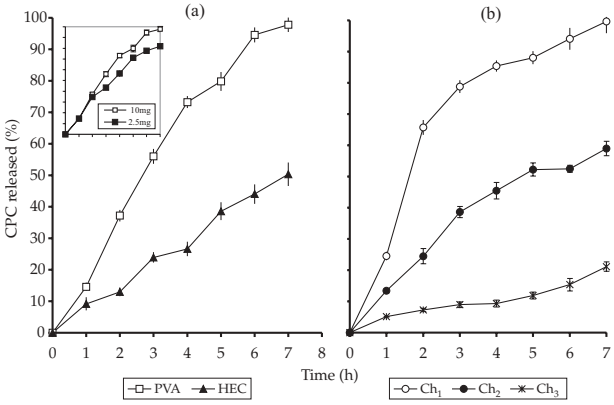

Fig. 3. The release profiles of CPC from: (a) PVA, HEC and (b) chitosan mucoadhesive patches. The insert shows the effect of drug loading on the release behavior of CPC from PVA patches (formulae containing 2.5 and 10 mg CPC) (SD bars, n = 3).

Fig. 3b depicts the release profile of CPC from chitosan-containing formulae. Formula Ch_1, containing chitosan alone, provided the highest release profile, with sustained but almost complete release within 7 h. At pH 6.8, chitosan (pK_a = 6.3) was partly positively charged (6) as well as CPC molecules, thus inducing an electrostatic repulsion, which enhanced the drug release rate. However, a lower release profile was observed when 1% (*m/V*) PVP was added to the formula; a complex may be formed between PVP and the cationic drug and/or the cationic polymer, which may lead to a decrease in the release rate of the drug. PVP was reported to form a complex with various drugs or polymers (20). It was also observed that the addition of 5% (*m/V*) gelatin to chitosan significantly delayed the release rate of the drug. The amount of CPC released progressed slowly from 5 to 20% during 7 h (Fig. 3b). It was reported that gelatin contained cationic and anionic amino acid residues (21), the majority of these residues being amino and carboxyl groups. At pH 6.8, the net charge of gelatin was negative whereas a positive charge was observed on the CPC molecule suggesting 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 interpolymer complex formation between chitosan and anionic polymers have been extensively reported (22, 23).

The release kinetic parameters were calculated according to the Peppas equation (24);

$$M_t/M_\infty = K\,t^n \tag{3}$$

where M_t/M_∞ is the fractional release of the drug, t denotes the release time, K is a constant incorporating structural and geometric characteristics 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 0.975 for PVA patches, indicating a zero-order release behavior. The release was, thus, controlled by the viscoelastic relaxation of the matrix during 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 pathlength (concentration gradient) was obtained. For HEC patches, n is 0.779 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 0.637 to 0.767.

In order to study the effect of drug loading on the release characteristics of CPC, the dose of the drug was reduced from 10 to 2.5 mg in PVA patches (Fig. 3a, insert). A lower release profile was observed when the drug dose was reduced from 10 to 2.5 mg; t_{50} was delayed by one hour and 81.9% CPC was released after 7 h from the formula containing a low dose compared to 95.82% CPC released from the highly loaded formula. A 4-fold increase in polymer-to-drug ratio was observed when the dose was reduced. This increase was reflected in the delayed release rate of CPC. The reduction of the CPC dose in PVA patches did not markedly affect the release mechanism; n varies from 0.975 to 0.881, revealing that a slight deviation in the release mechanism from zero-order to non-Fickian release behavior occurred. Further investigations revealed an increase in the relative contribution of erosion, as compared to diffusion, to the overall release mechanism as the dose of the drug was increased (25).

Results in Table I reveal acceptable swelling and residence time for PVA patches, as well as optimum release with zero-order kinetics (Table II). These characteristics make them good candidates for stability studies. PVA patches containing 10 mg CPC were subjected to 6-month storage at 37 ± 0.5 °C and 75 ± 5% RH. Patches exhibited an excellent drug content over the storage period. The folding endurance test revealed good flexibility and elastic properties. However, a delay in the residence time of the stored patches was noticed (Table III). The percent CPC released *versus* time demonstrates a decrease in the amount of drug released with time. Non-stored patches released 79.4% CPC after 5 h, whereas patches stored for six months released 54.4% drug in the same period (Table III). The decrease in release during storage may be a direct consequence of the reduced erosion rate of the patches. Values of n are all close to unity, indicating that the zero-order release behavior is the main release mechanism. It is concluded that a six-month storage under these conditions does not change the release behavior despite an obvious prolongation in the release rate. The electron micrographs (Figs. 4a, b) illustrate the surface of the fresh and stored patches. Fresh patches appeared as a smooth

Table III. Short-term stability data of PVA patches containing 10 mg CPC, stored at 37 °C and 75% RH

Characteristic	Duration of storage (months)						
	0	1	2	3	4	5	6
In vitro residence time (h)[a]	2 ± 0.54	2 ± 0.713	2.5 ± 0.4	3 ± 1.8	3.2 ± 0.9	4.5 ± 1.3	4.5 ± 0.8
In vitro released (1h) (%)[a]	15.84 ± 3.418	12.71 ± 1.27	12.113 ± 0.084	11.58 ± 0.738	10.39 ± 0.635	9.49 ± 0.964	5.13 ± 0.462
(5h) (%)	79.36 ± 3.377	75.61 ± 1.368	63.61 ± 0.912	59.5 ± 0.999	57.88 ± 1.208	56.74 ± 2.724	54.44 ± 1.491
t_{50} (h)	2.8	3	3.9	4.1	4.35	4.5	4.65
Release kinetics *n*	0.965	0.944	1.085	1.007	0.963	1.094	1.05
k	16.16	13.79	10.37	11.72	13.14	10.91	5.13
R	0.994	0.998	0.998	0.999	0.994	0.995	0.999

[a] Mean ± SD (n =3).

surface of a supersaturated solution of the drug in polymer solution and some cracks were identified on the patch surface as well (Fig. 4a). Upon ageing, agglomeration of some polymer particles was observed (Fig. 4b). It is suggested that phase separation occurred during storage, giving rise to the agglomeration of the mucoadhesive polymer with or without inclusion of some drug crystals. Therefore, the pure drug crystals were

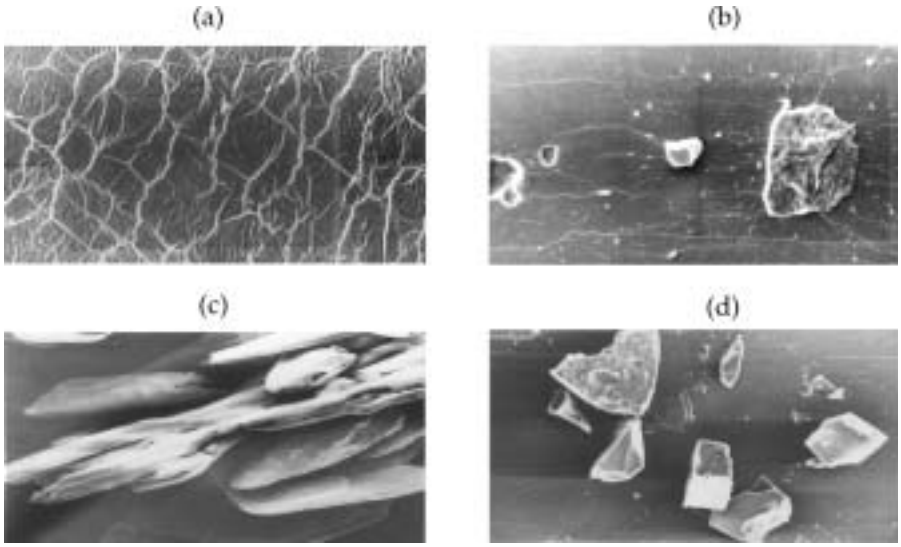

Fig. 4. Scanning electron micrographs of: (a) fresh and (b) stored PVA patches containing CPC (magnification 500×). Micrographs (c) and (d) represent pure crystals of CPC and stored patches containing the drug, respectively (magnification 1000×).

compared with the crystals formed during storage (Figs. 4c, d). A different crystal habit is noted where the crystals of the pure drug appear as large flakes (> 50 μm). Crystals of the drug in the stored patch are cubic or prismatic and smaller (< 30 μm). Crystallization of CPC from the polymeric solution may result in the formation of drug crystals of different shape and size compared to pure CPC. It is concluded that the crystallization of CPC during storage, as evidenced by the electron micrographs, may be responsible for the decrease in its release rate after storage.

CONCLUSIONS

It may be concluded that mucoadhesive patches are a promising drug delivery system for CPC in maintaining buccal cavity hygiene. The non-ionic polymer, PVA, showed good mucoadhesive and swelling characteristics. Medicated PVA patches maintained a satisfactory residence time in the buccal cavity and ensured zero-order release of the drug over relatively long periods (7 h), which made them good candidates for stability studies. Ageing did not affect the elastic properties of the PVA patches but affected the extent of drug release; this may be attributed to changes in the crystal habit of the drug as well as to slight agglomeration of the polymer particles.

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SAŽETAK

Priprava i karakterizacija mukoadhezivnih flastera za bukalnu primjenu s cetilpiridinij-kloridom

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Pomoću polivinil alkohola (PVA), hidroksimetil celuloze (HEC) i kitozana priređeni su mukoadhezivni flasteri s cetilpiridinij-kloridom (CPC). Ispitivana su bioadhezivna svojstva i sposobnost bubrenja flastera s ljekovitom tvari (CPC) i bez nje. Dodatak vodotopljive ljekovite tvari u polimernu podlogu za flastere značajno povećava radijalno bubrenje (S_D). U pripravcima s polivinil alkoholom i kitozanom smanjilo se vrijeme zadržavanja. Oslobađanje ljekovite tvari bilo je veće iz PVA nego iz HEC pripravaka, iako su oba polimera neionizirana. Iz kitozanskih pripravaka s dodatkom vodotopljivih aditiva,

polivinilpirolidona (PVP) i želatine, oslobađanje je usporeno. Praćena je stabilnost PVA pripravaka. Rezultati ukazuju da je CPC kemijski stabilan te da se njegov sadržaj u pripravku ne mijenja, dok se povećava vrijeme zadržavanja ljekovite tvari. To može biti uzrokovano primjenom u kristalnoj strukturi ljekovite tvari ili aglomeracijom čestica polimera.

Ključne riječi: flasteri za bukalnu primjenu, cetilpiridinij-klorid, mukoadhezija, polimeri, oslobađanje, stabilnost

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