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Evaluation of bioadhesive buccal tablets containing triamcinolone acetonide in healthy volunteers

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Abstract

The behaviour of bioadhesive buccal tablets prepared from different ratios of poly(acrylic acid-2,5-dimethyl-1,5-hexadiene) (PADH) and hydroxypropylmethylcellulose (HPMC) with and without triamcinolone acetonide (TAA) has been investigated in the buccal cavities of healthy human volunteers. The results indicate that tablets with a higher ratio of PADH swell faster, causing the disintegration of the tablets and consequently give rise to more rapid release of drug. The inclusion of higher percentages of HPMC provides more prolonged release of drug through its properties of gelling and slow dissolution. However, adhesion of the tablet is reduced in the excessive flow of saliva and there is also a tendency for the tablet to be dislodged from the mucosa. The tablet with a PADH/HPMC ratio of 50:50 seems to provide a suitable compromise for good bioadhesion and prolonged release of drug.

Keywords: Bioadhesive buccal tablet; Mucosal adhesion; Drug release; Poly(acrylic acid-2,5-dimethyl-1,5-hexadiene); Hydroxypropylmethylcellulose; Human

During the last decade, bioadhesive polymers have received considerable attention as platforms for buccal controlled delivery due to their ability to localize the dosage form in specific regions to enhance drug bioavailability (Gu et al., 1988). The mucoadhesive buccal formulations that have been developed include ointments, creams, solutions, microparticles, bandages and tablets (Ishida et al., 1982, 1983; Gurny et al., 1984; Ponchel et al., 1987a,b; Satoh et al., 1989a,b; Bottenberg et al., 1991, 1992; Bouckaert and Remon, 1993). However, the disadvantage of most of these delivery systems is that they are easily washed away by the saliva. Bioadhesive tablets appear to be attractive because the preparations can be readily attached to the buccal cavity, retained for a longer period of time and can be removed at any time.

In our previous in situ study (Mumtaz and Ch'ng, 1995), the results showed that the combination of PADH and HPMC in a certain ratio in the polymer mixture can provide good bioadhesion and prolonged release of drug from the buccal tablets produced. It was the aim of the present study to investigate further the suitability of these buccal tablets in healthy human volunteers.

The tablets were prepared from different compositions with 100 (formulation I), 75 (III), 50

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(V), 25 (VI) and 0% (VIII) of PADH in the polymer mixtures according to the method of Mumtaz and Ch'ng (1995) and were evaluated for their mucoadhesion and acceptability in healthy human volunteers. The study was conducted in six healthy male and female volunteers. Food and water were prohibited from 0.5 h before and until the end of the experiment. Each tablet was attached to the mucosa of the lower lip of the subject and was removed when discomfort was experienced or dislodgment of the tablet occurred.

Table 1 shows the times when the tablets were removed from the buccal cavities of the volunteers. The time of removal or the end point is defined as the time when the extent of disintegration of the tablet causes discomfort to the volunteer. Formulation I had the shortest time of removal. This is because the rapid swelling of the PADH content causes the tablet to disintegrate at a very rapid rate. The disintegration of the tablet will, consequently, cause the swollen PADH particles to be dislodged from the tablet and to scatter throughout the buccal cavity, leading to the feeling of discomfort by the volunteer. The remains of the tablet are then removed by the volunteer.

Tablets from formulations III and V remained adhered to the oral mucosa for 1.791 and 4.137 h mean times, respectively. Most of the subjects find it difficult to remove the tablets, especially for the tablet from formulation V which sticks on the mucosa tenaciously after absorbing the saliva.

It was also observed that at the beginning of administration, tablets from formulations VI and VIII attached very strongly to the surface of the mucosa but upon further hydration in the presence of excessive saliva, the tablets became slippery due to extensive gelling of HPMC and started to be dislodged. Therefore, the removal of tablets from formulations VI and VIII is based on either discomfort or dislodgment of the tablet. The wide variation of removal times observed for formulations VI and VIII is attributed to the variation in saliva flow among the volunteers which is critical for tablets containing a high ratio of HPMC. Tablets in volunteers with a high saliva excretion rate tend to be dislodged quickly but stick very well in subjects with a low excretion rate. One volunteer left the tablet (formulation VI) in the cavity overnight which accounted for the long duration of 9 h. Two subjects found that tablets (formulation VIII) did not disintegrate after 4 h and decided to keep the tablet on the buccal mucosa overnight. Observation shows that tablets from formulations VI and VIII containing a high ratio of HPMC do not disintegrate but slowly dissolve in the saliva and become smaller in size. Wermerskirchen and Merkle (1988) also reported the same phenomenon. They observed that in the initial stage of adhesion, the binding force between hydrated hydrocolloid and glycoprotein chains of the oral mucosa was very high. However, due to the gradual dissolution of the polymer, the adhesive force then slowly faded. In the present study, no subject complained of any irritation and all the formulations tested were well accepted by the volunteers except for some minor complaints of a dry mouth, heaviness at the place of attachment and movement of PADH particles

Table 1
Adhesion study of drug-free tablets in the buccal cavities of healthy volunteers

Subjects	Time (h) of removal of tablet				
	I	III	V	VI	VIII
A	0.483	1.633	3.283	1.650	10.000
B	0.183	1.167	3.500	0.920	2.750
C	0.483	2.567	3.867	9.000	9.000
D	0.167	1.300	3.000	1.585	1.167
E	0.500	3.000	8.500	4.000	4.000
F	0.350	1.080	2.670	1.333	1.750
Mean ± SD	0.361 ± 0.141	1.791 ± 0.733	4.137 ± 1.987	3.081 ± 3.095	4.778 ± 3.795

PADH/HPMC ratios: I, 100:0; III, 75:25; V, 50:50; VI, 25:75; VIII, 0:100.

to the tongue and cavity after disintegration of the tablets. These results are in contrast to the study of Bottenberg et al. (1991) who reported that PAA (carbopol 934) or PAA/HPMC formulations could cause irritation and lesions in some of the volunteers.

From the above results it can be concluded that variability between subjects is substantial, possibly depending on the subject's habits like saliva flow, talking, jaw and tongue movement and perception of discomfort. However, the results also indicate that by choosing the right mixture of the polymers, the required duration of adhesion without excessive disintegration of the tablet can be achieved. Formulations III, V and VI had good adhesion to the buccal mucosa and the tablets could maintain their integrity for a sufficient period of time. Therefore, they were chosen for further behaviour and drug release study.

In this further study, the same six healthy volunteers were chosen. Food and water were prohibited from 0.5 h before and during the experiment. Three bioadhesive buccal formulations, III, V and VI, each containing 8 mg of TAA were chosen for this study. Each tablet was placed on the mucosa of the lower lip of the subject and was removed after the pre-determined interval. The time intervals used were 15, 30 min, 1, 1.5, 2, and 3 h. The sampling was conducted in random order. The tablets after removal were weighed (wet weight), dried at 40° C for 24 h and reweighed (dry weight).

Each dried, recovered tablet from the above was soaked in 1 l of distilled water in a volumetric flask for 24 h with intermittent shaking followed by a further 3 h of magnetic stirring. The extract was filtered through 0.22 μm membrane and the triamcinolone acetonide concentration was determined by a UV spectrophotometer (Hitachi, Model 2000U, Japan) at 240.8 nm. The blank tablet was also treated in the same way to be used as a reference.

Fig. 1 shows that tablet III hydrates and swells immediately and disintegration occurs within 30 min which reaches the maximum at 1.0 h. The relatively large fall in wet weight after 1.5 h is probably due to difficulty in removing all the swelled PADH particles from the mucosa. The large error bars demonstrate considerable varia-

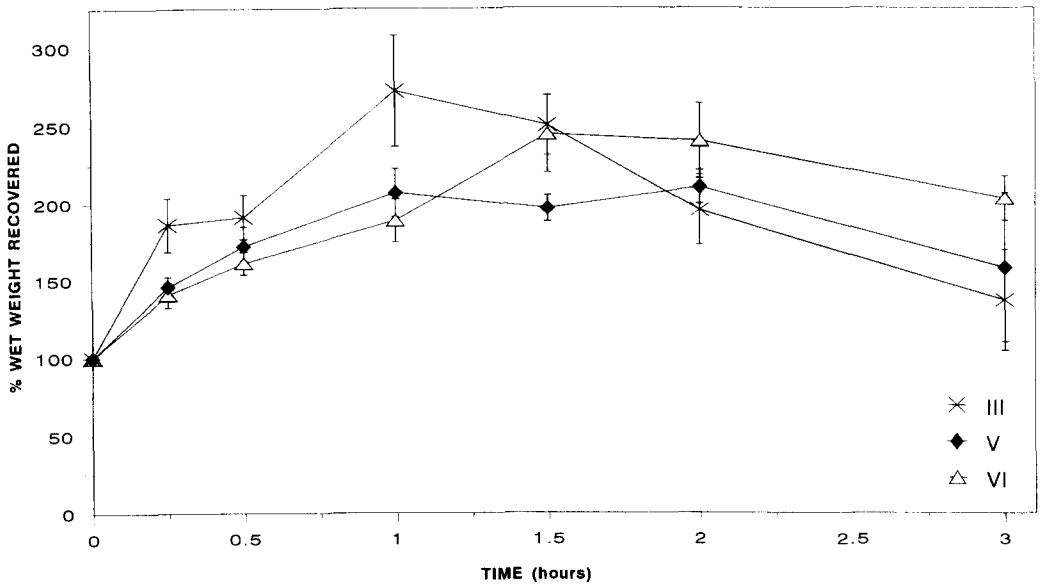

Fig. 1. Percentage wet weight recovered at various time intervals. Error bar ± S.E. (n = 6). PADH/HPMC ratio: III, 75:25; V, 50:50; VI, 25:75.

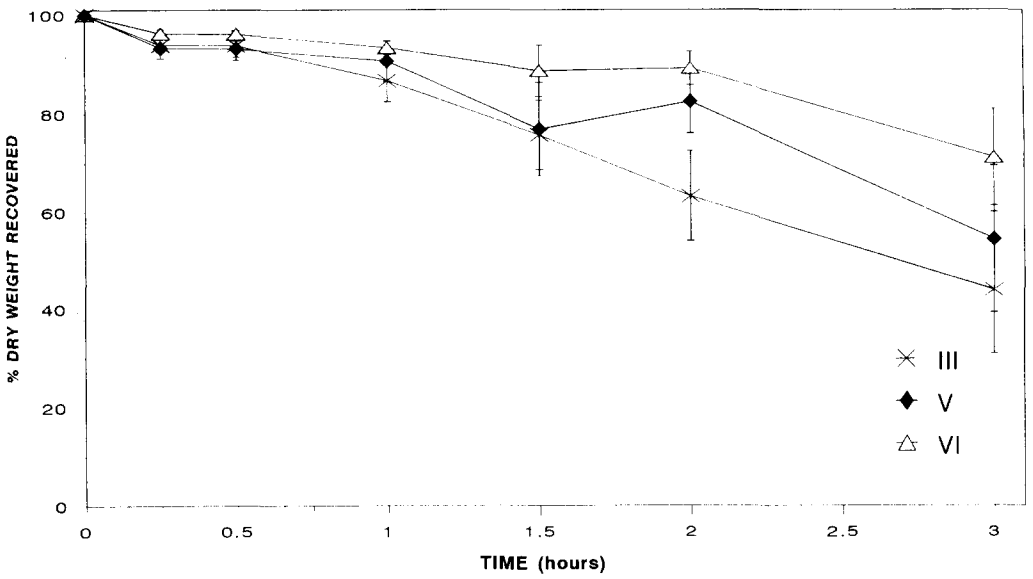

Fig. 2. Percentage dry weight recovered at various time intervals. Error bar ± S.E. ($n = 6$). PADH/HPMC ratio: III, 75:25; V, 50:50; VI, 25:75.

tion among subjects. Tablets V and VI show a slower increase in wet weight which reaches the maximum at 2.0 and 1.5 h, respectively. Thereafter, they fall gradually from 2.0 to 3.0 h. Fig. 2 shows that the curves plotted from the percentage of dry weight recovered vs time are relatively parallel between 0 and 1.5 h for all three formulations. However, after this time interval, distinct

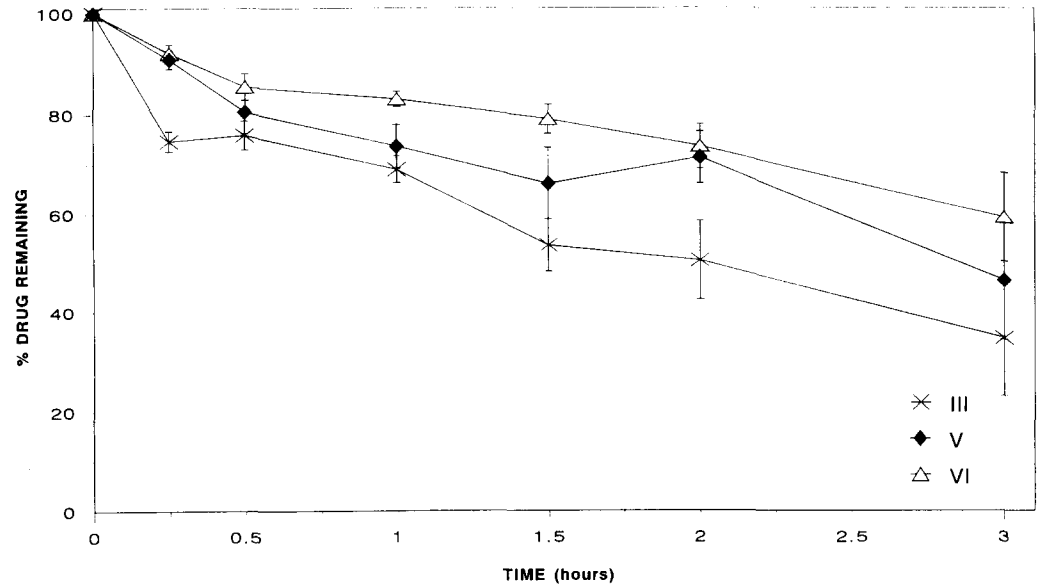

Fig. 3. Percentage of drug remaining at various time intervals. Error bar ± S.E. ($n = 6$). PADH/HPMC ratio: III, 75:25; V, 50:50; VI, 25:75.

differences between the three formulations are observed with formulation III losing the most dry weight followed by formulation V then formulation VI.

Water was used as a solvent for the extraction of TAA from the recovered, dried tablets. The recovery of the drug with the above extraction procedure produced a good 96% yield. Other solvents such as acetone, alcohol and chloroform gave much lower recoveries.

Fig. 3 demonstrates the fraction of drug remaining in the tablets at different time intervals. Each of the data points is an average of six subjects. The results coincide with the loss of dried weight in each formulation. Formulation III with the highest loss of dried weight releases the drug faster than other formulations. After 3 h of retention in the buccal cavities of volunteers, the percentages of drug remaining in formulations III, V and VI were 34.7, 46.5 and 59.3%, respectively. The above results were also analyzed by split plot design as described by Kirk (1968). Statistical analysis shows significant difference ($P < 0.05$) for the main effect of both factors A and B. These factors were further analysed at various other levels and vice versa, whilst the tests of the individual main effects (factors A and B) were of lesser interest. A significant interaction between factors A and B was present. The results also indicate there is no significant difference ($P > 0.05$) at time intervals 15 min and 1.0 h, whilst there is a significant difference ($P < 0.05$) between factor A at time intervals 1.5 to 3.0 h. The ANOVA of mean of drug remaining in formulations III, V and VI at different time intervals revealed a significant variation ($P < 0.05$) at time intervals 15 min, 1.0, 1.5 and 2.0 h. In contrast, at time periods 30 min and 3.0 h, no significant difference was observed ($P > 0.05$). This is because of the sharp fall of drug in formulation III, which is inconsistent with recovery of the dried tablet. It was observed that the removal of intact tablets after 3.0 h was difficult for all the formulations. The results indicate that the overall rate of release of TAA from formulation III is quite consistent and is about parallel to the graph of dry weight recovery of the tablet. Formulations V and VI also show the same pattern as above but with more gradual reduction of dry weight recovery and drug remaining in the tablets. The difference in release rate of TAA of the above tablets can be attributed to the presence of different ratios of PADH/HPMC which can affect a number of processes for the release of TAA such as permeation of water into the matrix, gelation rate, dissolution of the drug in the penetrating water, diffusion rate of the drug through the gel and erosion of the gel. The tablet with a higher ratio of PADH (formulation III) in the polymer mixture shows more complete hydration of the whole tablet and a very small, if any, unhydrated core was present after 3 h. In contrast, in the tablets containing a lower percentage of PADH or higher percentage of HPMC in the polymer mixture (formulations V and VI) two distinct regions of hydration are demonstrated. The outer region consists of swollen PADH particles and gel of HPMC and the core region shows a progressive uneven hydration with the central area either poorly or totally unhydrated. The outer erosion due to the dissolving HPMC can also be observed.

In conclusion, the above study has shown that a tablet with suitable properties for use in the buccal cavity can be formulated with a mixture of PADH and HPMC. The PADH polymer would provide the initial rapid hydration and hence the fast initial release of drug and good bioadhesion of the tablet. In contrast, the HPMC would provide more prolonged release of drug and additional bioadhesion to compromise PADH. A mixture of PADH and HPMC in the ratio of 50:50 seems to provide the best compromise. The tablets prepared from this ratio possess good bioadhesion, less chance of dislodgment from the mucosa, more prolonged release of drug and good flexibility which is important for ease of application of the tablet to the affected part in the buccal cavity.

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