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Design of a dissolution apparatus suitable for in situ release study of triamcinolone acetonide from bioadhesive buccal tablets

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Abstract

A new and simple dissolution apparatus which is capable of evaluating the release of drug and bioadhesive properties of buccal tablets has been developed. The apparatus consists of a dissolution cell and an outer assembly. The cell has been designed to hold the chicken pouch membrane and bioadhesive tablet together and also to allow the dissolution medium to flow over them. The outer assembly is to provide adjustment of the angle of flow of the medium over the cell. The release study of triamcinolone acetonide from various bioadhesive buccal tablets containing different proportions of poly(acrylic acid-2.5-dimethyl-1,5-hexadiene) (PADH) and hydroxypropylmethylcellulose (HPMC) with the apparatus reveals that the bioadhesion of the tablet and the release of drug are influenced by the different proportions of polymers. With higher concentrations of PADH, the tablets disintegrate much more rapidly, leading to a faster release of the drug and they give better adhesion to the membrane. Tablets with higher concentrations of HPMC provide more prolonged release of the drug. However, they can be dislodged from the membrane more easily. The results produced by the apparatus concur with the predicted patterns.

Keywords: Dissolution apparatus; Bioadhesive buccal tablet; Poly(acrylic acid-2,5-dimethyl-1,5-hexadiene); Hydroxypropylmethylcellulose; Triamcinolone acetonide

1. Introduction

In recent years, there has been increasing interest in the development of bioadhesive controlled release dosage forms for treatment of both topical and systemic diseases (Nagai and Machida, 1985; Gursoy and Bayhan, 1992). These dosage forms can bind to mucin or epithelial surfaces and be detained in that position for a certain length of time, thus increasing overall drug absorption and providing local effects (Garren and Repta, 1988; Gu et al., 1988). Oral mucosal delivery of drug has numerous advantages such as excellent accessibility and can be applied, localized and removed easily. A number of these new dosage forms were introduced by several researchers (Ishida et al., 1982; Gurny et al., 1984; Anders and Merkle, 1989; Bottenberg et al., 1992; Bouckaert and Remon, 1993). The methods used for studying the release of drugs from these bioadhesive polymeric matrices were mainly based on standard dissolution tests (Ishida

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et al., 1982, 1983; Bottenberg et al., 1991; Chen and Hwang, 1992; Gursoy and Bayhan, 1992; Smart, 1992; Hosny, 1993) in which the tablets were immersed in the dissolution media to determine their dissolution rates. Hence, all these methods cannot be used to simulate the buccal condition for testing the bioadhesive buccal tablet. Various methods for measuring bioadhesion have also been reported and most of them are based on the measurement of either the shear or tensile stress between the dosage form and the membrane or tissue of various animals (Ishida et al., 1981; Ch'ng et al., 1985; Robert et al., 1988; Helliwell et al., 1991; Lehr et al., 1992; Sam et al., 1992; Woolfson et al., 1992). No report is available on the determination of bioadhesion by measuring the time taken for the tablet to dislodge from the tissue under the simulated conditions.

The mechanisms of interaction between bioadhesive/mucoadhesive polymers have been proposed by several researchers (Park and Robinson, 1984, 1987; Park et al., 1987) which included the mechanical, electrostatic, diffusion and adsorption theories.

The aim of the present study was to design a dissolution apparatus which would give a more realistic in situ assessment of the release of drug from a bioadhesive buccal tablet. The investigation also includes the development of buccal tablets which consist of triamcinolone acetonide with different proportions of poly(acrylic acid-2,5-dimethyl-1,5-hexadiene) (PADH) and hydroxypropylmethylcellulose (HPMC) and their effects on the release of drug and bioadhesion of the tablets.

2. Materials and methods

2.1. Materials

Triamcinolone acetonide (Sigma Chemical Co., USA), hydroxypropylmethylcellulose 50 cps (Sigma Chemical Co., USA), acrylic acid (E. Merck, Darmstadt), 2,5-dimethyl-1,5-hexadiene (Kasai Chemical Co., Japan) and magnesium stearate (BDH, UK) were used as received.

2.2. Synthesis of bioadhesive polymer

The bioadhesive polymer, PADH was prepared according to the method of Ch'ng et al. (1985). The washed polymer was dried in a hot air oven at 90°C for 12 h then ground with a mortar and pestle to give a size range of 400–620 μm with the help of sieves.

2.3. Preparation of bioadhesive buccal tablets

The tablets were prepared from different compositions as shown in Table 1. The various components in each formula were mixed for 5 min and compressed with a hydraulic press (Model P16, Beckman RIIc Ltd, UK) at a pressure of 8

Table 1
Compositions of bioadhesive buccal tablets

Formulation code	Composition in mg				Percentage (%) of PADH in polymer mixture
	PADH	HPMC	TAA	Magnesium stearate	
I	190	–	8	2	100
II	171	19.0	8	2	90
III	142.5	47.5	8	2	75
IV	114.0	76.0	8	2	60
V	95.0	95.0	8	2	50
VI	47.5	142.5	8	2	25
VII	19.0	171.0	8	2	10
VIII	–	190.0	8	2	0

PADH, poly(acrylic acid-2,5-dimethyl-1,5-hexadiene); HPMC, hydroxypropylmethylcellulose; TAA, triamcinolone acetonide.

tons for 30 s into a tablet. All the final tablets possessed a weight of 200 mg, diameter of 13 mm and thickness varying from 1.67 to 1.72 mm depending on the formulation. Drug-free tablets were also prepared as above with a total weight of 192 mg.

2.4. Water uptake determination

Water uptake measurement was performed by using an apparatus consisted of a no. 3 Buchner sintered glass filter of 3.8 cm diameter with one end connected to a graduated 1 ml pipette via a silicone rubber tube. The lower part of the filter and the pipette were filled with distilled water at room temperature (28°C) just before the experiment. The evaporation of water was minimized with aluminum foil wrapped around the filter. The bioadhesive buccal tablet without drug was placed at the center of the filter and the uptake of water for 48 h was determined by the change in volume of the water in the horizontally positioned graduated pipette. The mean of six determinations was taken to represent the uptake volume.

2.5. Tablet disintegration test

The disintegration pattern of each bioadhesive buccal tablet was observed by immersing the tablet in a glass petri dish of 10 cm containing 25 ml of water at room temperature (28°C). The morphological changes of each tablet were observed for 20 h.

2.6. Design of the dissolution apparatus

The apparatus consisted of two parts, the dissolution cell and the outer assembly. The dissolution cell was fabricated from a semi-circular tube of 9 cm length and 3 cm diameter. A small inlet tube of 0.5 cm diameter was attached to one end of the cell and another outlet tube of the same diameter was attached to the opposite end. The outer assembly was constructed from perspex of 10 cm length, 4.8 cm width and 7.5 cm height and

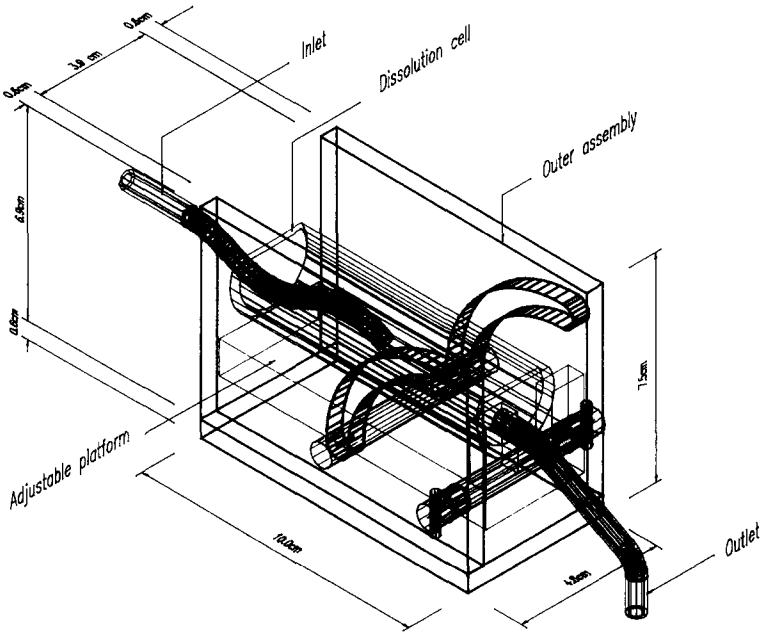

Fig. 1. Schematic drawing of the dissolution apparatus.

a perspex adjustable platform was attached to the inside of the assembly to allow the adjustment of the resting angle of the cell during the experiment (Fig. 1).

2.7. In situ dissolution test

Fresh chicken pouches from recently slaughtered chicken were collected and immediately cut open to remove the content The pouch was further washed with distilled water before being placed in a well aerated normal saline solution.

The pouch was further prepared by removing all the fatty and loose tissues before it was cut into strips of 4 cm long and 2 cm wide. A strip of the membrane was then fastened to a glass slide with thread before a bioadhesive buccal tablet was placed at the center of this slightly wetted surface. A 20 g weight was then placed on top of the tablet for 5 min to allow the polymer(s) from the tablet to interact with the membrane. After this time interval the glass slide together with the membrane and the tablet was placed in the cell which was previously attached to the outer assembly at an angle of 40°. Water, previously prewarmed to 37 ± 0.5°C from a USP dissolution apparatus, was circulated to the cell over the tablet and membrane at a rate of 4 ml/min with the help of a peristaltic pump (Fig. 2). 5 ml of the sample was removed at different time intervals (0.5 h for the first 2 h then every 1 h for 10 h) for UV absorption measurement at 240.8 nm (Hitachi, Model 2000U, Japan). The samples were immediately replaced in the USP dissolution apparatus after each measurement.

3. Results and discussion

Various formulations of tablets containing triamcinolone acetonide were developed with the use of different proportions of the sparingly soluble polymer HPMC and water swellable PADH as the matrices. The reasons for using HPMC are that it swells and dissolves slowly in the presence of aqueous medium (Gursoy and Bayhan, 1992) giving rise to a more prolonged release of drug when the ratio of HPMC is high. Its binding property and low solubility can maintain the integrity of the tablets for a longer period of time. This is important in the case of buccal tablets because the disintegrated tablet will be scattered throughout the buccal cavity and can be easily swallowed. The softness of the HPMC polymer can also impart good flexibility to the tablet so that it can be applied readily to the membrane or ulcer without breaking up. In contrast, PADH polymer has a stronger bioadhesive nature and tends to swell faster and to a greater extent, giving rise to the opposite effect compared to HPMC. However, this effect can be utilized to provide fast initial release of drug. Therefore, by varying the proportions of two different polymers, a bioadhesive buccal tablet with suitable properties can be produced.

3.1. Water uptake determination

The water uptake profiles of the eight tablet formulations with water swellable polymer (PADH) and water soluble polymer (HPMC) are shown in Fig. 3 and 4. It was observed that when a tablet came into contact with aqueous medium,

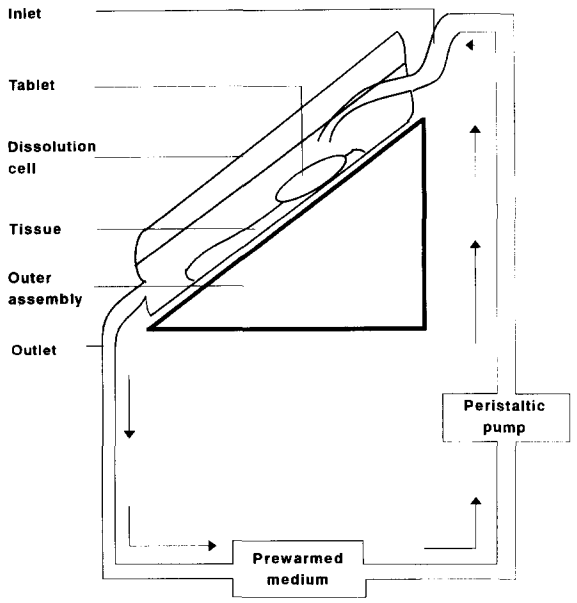

Fig. 2. Schematic drawing of the dissolution apparatus with all accessories.

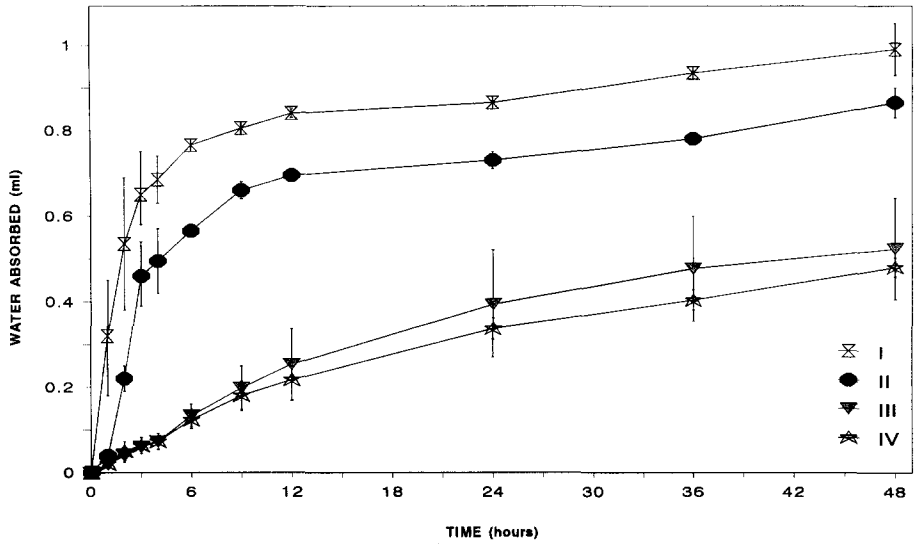

Fig. 3. Water uptake profiles of bioadhesive buccal tablets prepared from various polymer mixtures (PADH/HPMC); error bar = ±SD ($n = 4$). PADH/HPMC ratio: I = 100:0, II = 90:10, III = 75:25, IV = 60:40.

wetting occurred, first at the lower surface of the tablet and then progressed to the whole tablet. The rate of spreading of water was dependent on the ratio of the two polymers used. Tablets with high concentrations of PADH (formulations I and II) swell more extensively when compared with other tablets containing more HPMC, the reason being that each segment of PADH polymer contains four -COOH groups giving rise to a high capacity for hydration and hence large hydrodynamic volume (Ch'ng et al., 1985). The polymer can absorb a large quantity of water rapidly and

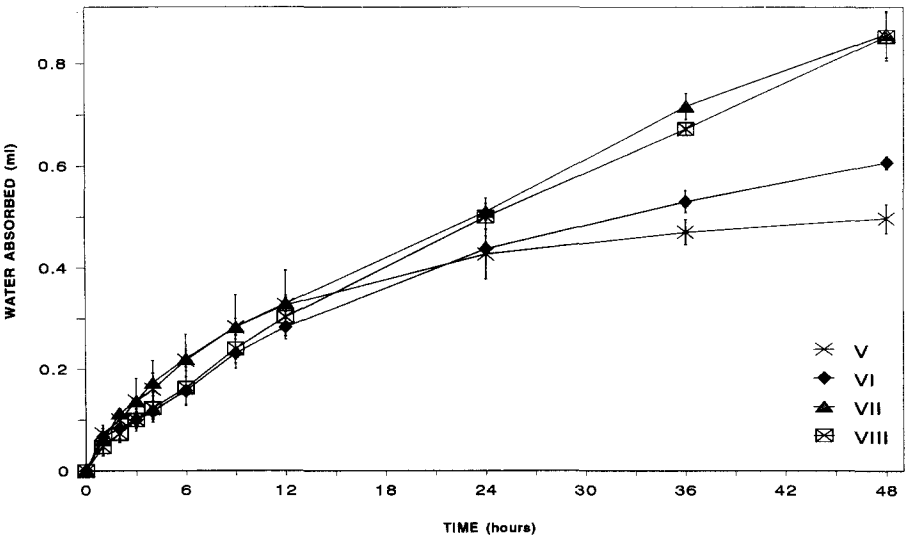

Fig. 4. Water uptake profiles of bioadhesive buccal tablets prepared from various polymer mixtures (PADH/HPMC); error bar = ±SD ($n = 4$). PADH/HPMC ratio: V = 50:50, VI = 25:75, VII = 10:90, VIII = 0:100.

swell to its maximum hydrated size without dissolving in the aqueous medium. As the liquid molecules penetrate into the interstices, the polymer starts to swell and increases in size and the polymer chains rapidly begin to unfold and become solvated. Voids created as the polymer unfolds are further occupied by the water molecules. The net effect is the bursting of the tablet containing a high proportion of PADH into small particles. The presence of a small amount of HPMC was not sufficient to hold the particles together. Tablets with concentrations of PADH lower than 75% in the polymer mixture (formulations III–VI) have less effect on the uptake of water as shown by the curves. However, the disintegration of the tablets still follows the predicted patterns with the higher concentration of PADH disintegrating first (Fig. 5a,b). The uptake of water by HPMC is a slower process compared with PADH and the absorption of water was only accelerated after 18 h for formulations containing high proportions of this polymer (formulations VII and VIII). HPMC is a hydrophilic polymer which swells slowly to form a gel which then

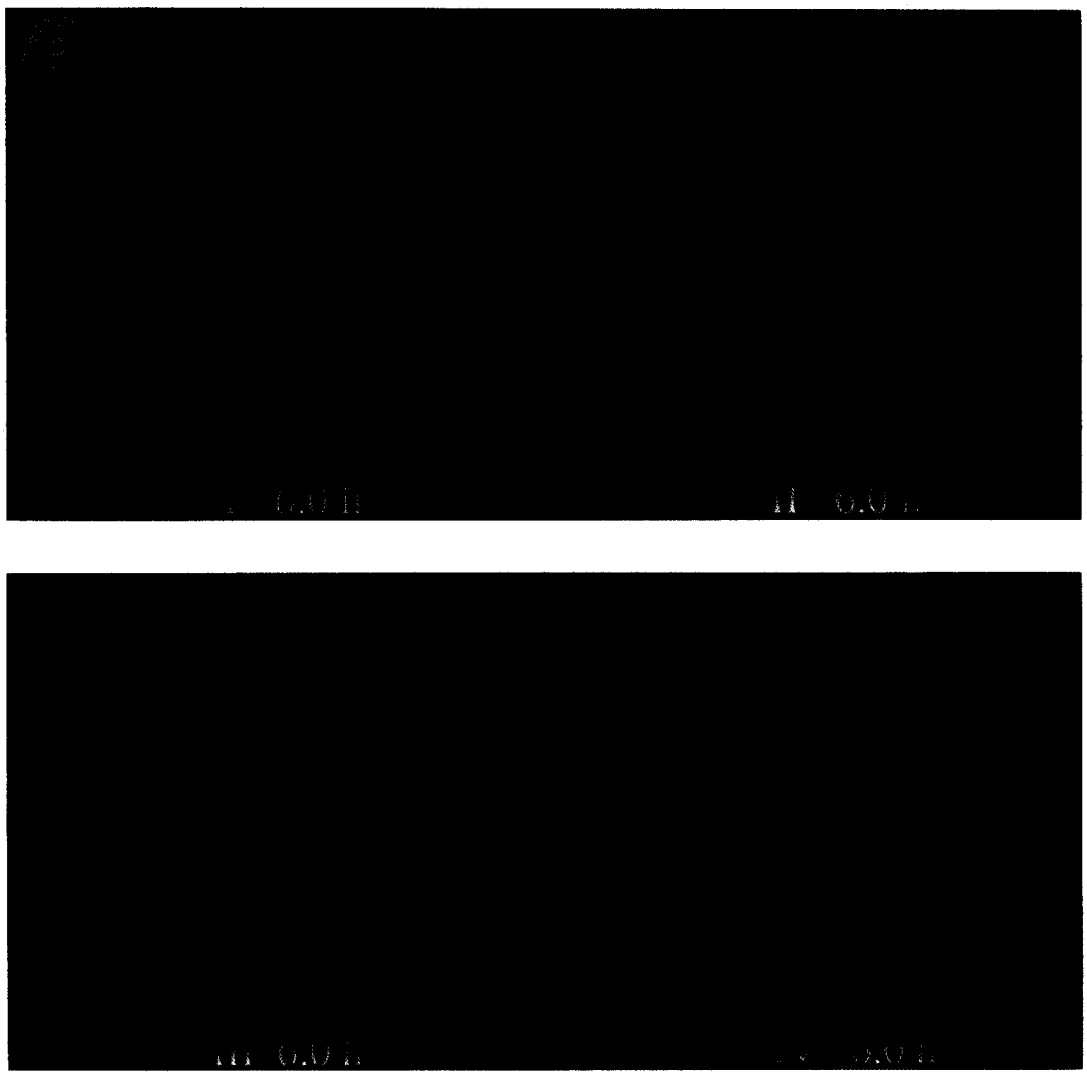

Fig. 5. Disintegration of bioadhesive buccal tablets in water at 6.0 h. PADH/HPMC ratio: (a) I = 100:0, II = 90:10, III = 75:25, IV = 60:40; (b) V = 50:50, VI = 40:60, VII = 25:75, VIII = 10:90, VIII = 0: 100.

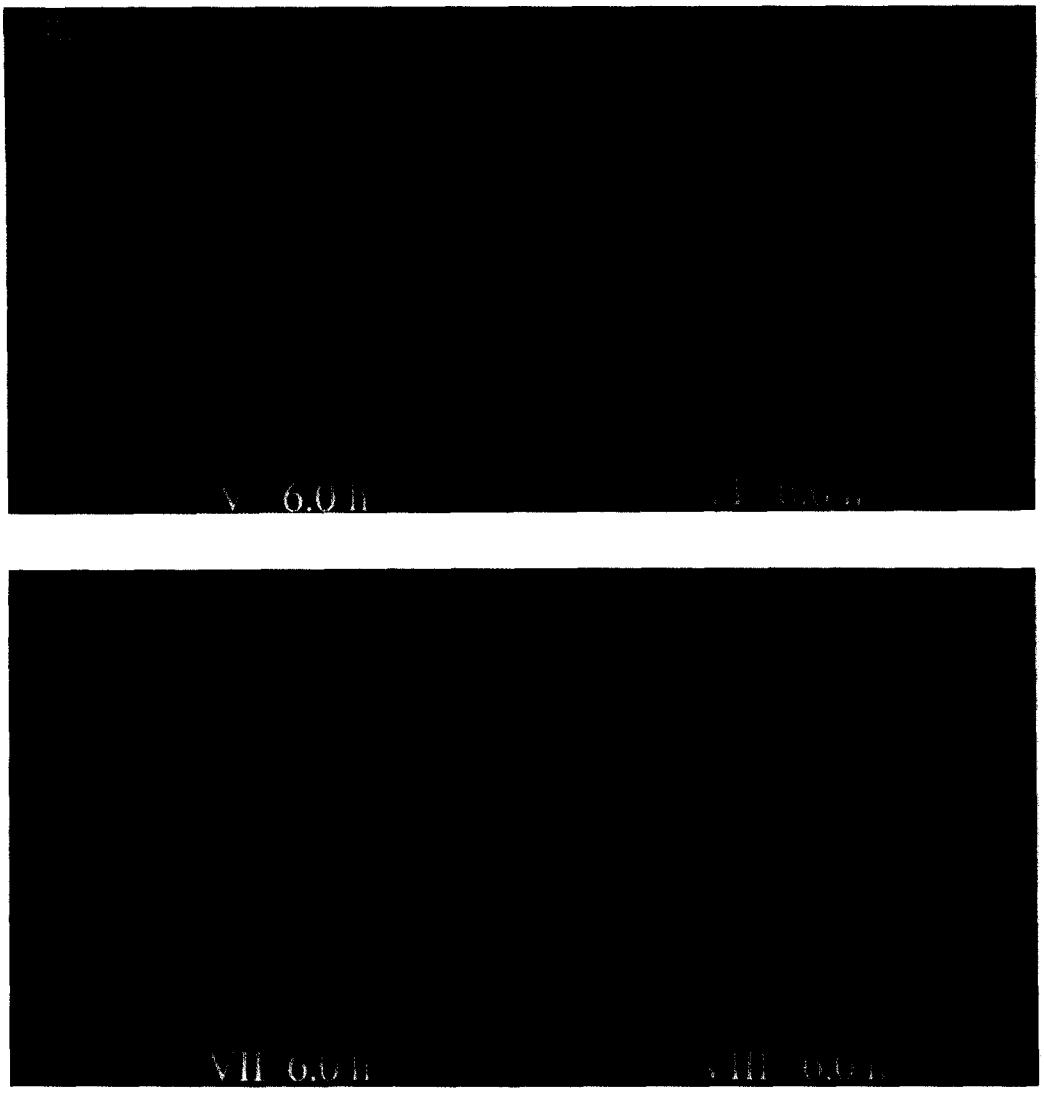

Fig. 5 (continued).

dissolves in the presence of water. The gelling of this polymer will provide the binding strength to oppose the bursting effect of PADH. Hence, the integrity of the tablet was maintained for a further period of time until most of HPMC was dissolved.

3.2. *In situ drug release of bioadhesive buccal tablet*

There are a number of methods can be used to determine the dissolution of bioadhesive tablets. However, most of these methods are not suitable to simulate the buccal condition. It is therefore desirable to develop a method which can simulate as closely as possible the condition of the buccal cavity for the determination of the release of drugs. The apparatus was fabricated as shown in Fig. 1 with the capability of adjusting the flow of water over the tablet which is adhered to a tissue. In our experiment, the USP dissolution apparatus was used to maintain the temperature of the medium and to supply medium via a peristaltic

pump to the testing cell. A constant flow rate of 4 ml/min of medium was allowed to flow over the tablet in the assembly in order to simulate the flow of saliva. Wilson and Washington (1989) have reported that in humans the resting flow of saliva is 0.5 ml/min which can be increased to more than 7 ml/min upon maximal stimulation of the parasympathetic system. Therefore, it is reasonable to use 4 ml/min in the experiment to simulate the normal flow rate of saliva in humans.

In all the above experiments, a weight of 20 g was used to increase the contact between the surfaces of the tablet and the chicken pouch membrane so as to simulate the force used to apply the tablet to the buccal cavity. The applied pressure can increase the molecular contact area, mechanical entanglement, interpenetration and provide good mucoadhesion in order as to hold the tablet on the surface of the membrane during the whole experiment. It was also necessary to spread a small amount of water (15 μl) on the tablet surface in order to provide good adhesion to the membrane for tablets containing high proportions of PADH (formulations I–IV). In contrast, extra water was not used for tablets with high proportions of HPMC (formulations V–VIII). The excess water can produce a layer of gel between the boundary layer of the tablet and the membrane resulting in the reduction of adhesion of these tablets. This observation is in agreement with the observation of Chen and Cyr (1970) that excessive water absorption in the soluble polymer could lead to the formation of a low viscosity interface at the mucosal side of the tablet or within the tablet and cause detachment. The mucoadhesive property of tablets containing high proportions of PADH is determined by the swelling property of the cross-linked polyacrylic acid polymer. Excessive hydration such as in simulated intestinal fluid causes extensive uncoiling and ionization of the polymer chains, leading to loose mechanical entanglement and penetration. In contrast, when the polymer is insufficiently hydrated (e.g., in gastric fluid), only a limited amount of uncoiling of the polymer chain occurs which leads to insufficient mechanical entanglement and penetration to the mucin chain. Our experiments indicated that hydration with a small amount of water is sufficient to provide suitable amount of uncoiling of the chain to give good bioadhesion with the chicken pouch membrane. The combination of the two different polymers in a 50:50 ratio seems to provide the best solution

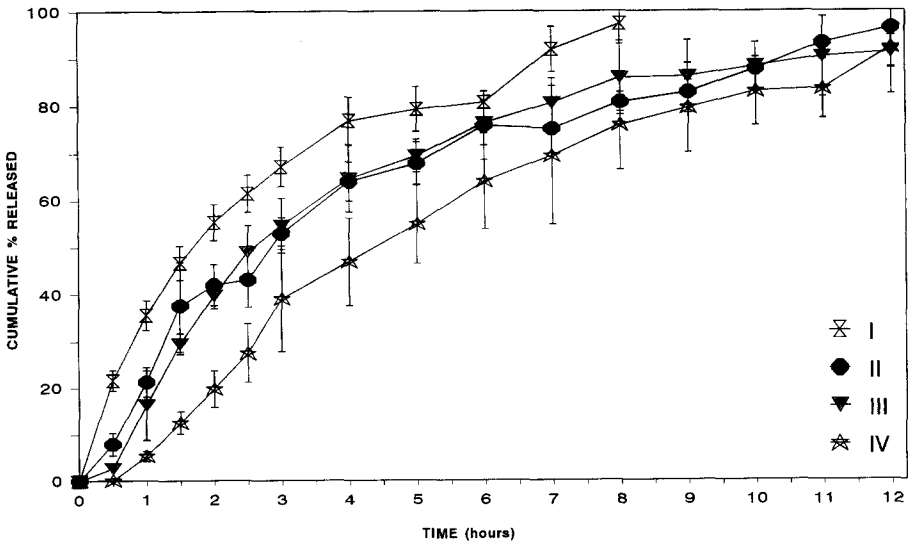

Fig. 6. In situ triamcinolone acetonide release profiles from bioadhesive buccal tablets in water; error bar ± SD ($n = 6$). PADH/HPMC ratio: I = 100:0, II = 90:10, III = 75:25, IV = 60:40.

for the formulation of the buccal tablet. The PADH provides the mucoadhesion and the HPMC maintains the integrity of the tablet.

Triamcinolone acetonide is frequently used to reduce inflammation in preparations for treatment of mouth ulcer. For the same reason it was chosen as a model drug for the above in situ drug release study. Chicken pouch membrane was used in this experiment because of its ease of accessibility and consistency of tissue conditions. Chickens from the same batch of the same age were used. The pouch was removed immediately after slaughtering into a beaker containing well-aerated normal saline solution. Tissues cut from the same location were used throughout the experiment to minimize biological variation. The plate holding the tissue and tablet in the dissolution cell must be maintained at a constant angle of 40°. Variation may introduce inaccuracy into the result. The tablet must be attached to the tissue in a position just below the flow of dissolution fluid.

Fig. 6 and 7 show the release profiles of TAA from various formulations containing different proportions of PADH and HPMC. Tablets with a higher content of PADH (formulations I–III) swelled very quickly and disintegrated within 15–30 min. The bursting effect of the swelling particles of PADH exposes the drug particles to the flow of dissolution medium and hastens the dissolution of the drug. Table 2 demonstrates the rapid release of TAA from the above formulations with 2.30, 2.70 and 2.65 h, respectively, for their $t_{50\%}$ values. Tablets containing 40% and above of HPMC in the polymer mixture (formulations IV–VIII) show slow swelling and correspondingly slow dissolution of the drug with $t_{50\%}$ ranging from 4.45 to 6.15 h. The differences in $t_{50\%}$ between these formulations are small. The results also indicate there is no significant difference in $t_{90\%}$ for all formulations except for formulation I which contains 100% of PADH in the

Table 2
Time required for the release of TAA at different $t_{\%}$

Formulation code	Time (h) of drug release		
	$t_{30\%}$	$t_{50\%}$	$t_{90\%}$
I	0.80	2.30	6.75
II	1.30	2.70	10.75
III	1.50	2.65	11.20
IV	2.65	4.45	11.60
V	3.25	5.40	> 12
VI	3.60	5.75	12.00
VII	3.80	5.40	11.25
VIII	4.05	6.15	10.35

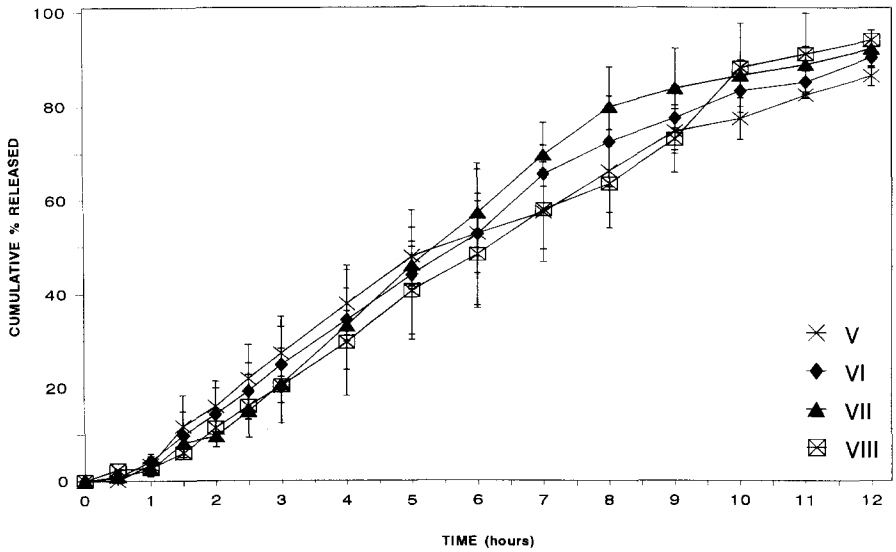

Fig. 7. In situ triamcinolone acetonide release profiles from bioadhesive buccal tablets in water; error bar ± SD ($n = 6$). PADH/HPMC ratio: V = 50:50, VI = 25:75, VII = 10:90, VIII = 0:100.

polymer mixture. Therefore, it can be concluded that with lower concentration of HPMC in the polymer mixture, the rapid and extensive swelling of PADH polymer determines the initial rapid dissolution of the drug but with a higher concentration of HPMC the effect of PADH is superseded by the influence of HPMC polymer. The comparatively slow swelling and formation of the gel of HPMC polymer serve as a barrier to the diffusion of TAA. The above results are consistent with the findings of Wan et al. (1992) for a HPMC-drug matrix.

In conclusion, a new dissolution apparatus which can be used to evaluate the dissolution of mucoadhesive tablets was developed. The results obtained by using this apparatus for the release of drug from bioadhesive tablets concurred with the predicted patterns. The above study demonstrates the importance of the use of mixed polymers to provide a good mucoadhesive property and a suitable release pattern of drug.

The proportion of PADH in the tablet imparts good adhesion whereas the HPMC controls the release of the drug. The results obtained from this study would be helpful for the further development of controlled release buccal tablets.

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