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Buccoadhesive Films of Triamcinolone Acetonide: Development and Evaluation of a Buccoadhesive-Erodible Carrier for Treatment of Oral Lesions

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Buccoadhesive films of triamcinolone acetonide (TA) for local delivery of the drug to the oral cavity for the treatment of oral lesions were prepared by the solvent casting technique. Different bioadhesive polymers were evaluated for film formation. Propylene glycol was used as the plasticizer while the choice of solvents was based on the type of polymer chosen. The films were characterized on the basis of their physical characteristics, bioadhesive performance, release characteristics, surface ph, folding endurance and stretchability. The optimized film exhibited an *in vitro* adhesion time of 3.24 hours and an *in vitro* release of 89.98% in 3.5 hours. The buccoadhesive films were accepted well by healthy human volunteers and no irritation of buccal mucosa was reported.

TOPICAL oral therapy with triamcinolone acetonide as kenalog in orabase is the most widely used preparation by dentists and physicians[1]. Oral bioadhesive mucosal sustained release devices have proved to be viable alternative to the conventional local oral medications[2] since they have the disadvantages of an initial burst of activity followed by rapid decrease in concentrations to below therapeutic levels and are difficult to retain in the mouth for longer periods of time[3]. The objective of the present study was to develop a sustained release device in the form of erodible-buccoadhesive polymeric film containing TA for treatment of oral lesions.

TA was obtained as gift sample from M/S Cyanamid India Ltd. Polymers were obtained as gift samples from M/S Ranbaxy Labs.Ltd. All other materials used were of analytical reagent grade. The films were prepared by the solvent casting technique[4]. A number of substrates were tried for the film formation but mercury surface gave best results. Initially, placebo films using various polymers, plasticizer and solvents in different combinations were prepared. Films which were complete, homogenous, flexible, non-sticky and smooth were then loaded with the drug and evaluated (Table1). The requirement of the drug was about 158.41 mg for the formation of a film of 6.23 cm diameter from which small patches of 14 mm diameter

Table 1: Composition of selected buccoadhesive films

Ingredients	Composition P-1	P-2	P-3	P-4
Triamcinolone acetonide (mg.)	158.4	158.4	158.4	158.4
CP-934P (mg.)	100	120	75	50
HPC-M (mg.)	-	-	200	-
HPMC-E4M (mg.)	-	80	-	-
HPMC-E15 (mg.)	100	-	-	-
HPC-L (mg.)	-	-	-	250
Propylene glycol (ml)	0.125	0.10	0.075	0.10
Ethanol (95%) (ml.)	-	-	10	10
Isopropanol : Dichloromethane (1:2) (ml.)	10	10	-	-

CP-934P = Carbopol-934P, HPC-M = Hydroxy Propyl Cellulose-M, HPMC-E4M = Hydroxy Propylmethyl Cellulose-E4M, HPMC-E15 = Hydroxy Propylmethyl Cellulose-E15, HPC-L = Hydroxy Propyl Cellulose-L

Table 2 : Determination of important parameters of buccoadhesive films *(in vitro)*

Formula Code	Bioadhesive Strength (g) (±S.D.) n=3	Adhesion Time (min.) (±S.D.) n=3	Surface pH (±S.D.) n=3	Folding Endurance (±S.D.) n=3	% Elongation at break (±S.D.) n=3
P-1	8.73 (±0.68)	149.33 (±5.13)	7.03 (±0.076)	252.66 (±4.04)	22.58 (±4.2)
P-2	9.33 (±0.28)	194 (±10.14)	6.7 (±0.05)	232.33 (±10.01)	29.04 (±4.70)
P-3	14.33 (±0.76)	215 (±4.07)	5.90 (±0.1)	355 (±8.18)	46.73 (±6.15)
P-4	12 (±0.58)	228.33 (±7.63)	6.01 (±0.076)	305.66 (±7.76)	30.56 (±4.98)

containing 8 mg drug were punched out. Bioadhesive strength of the film was measured on a modified physical balance using the method described by Gupta *et al.*[5] using bovine cheek pouch as model mucosal membrane[6]. For *in vitro* drug releases studies and determination of duration of bioadhesion/erosion self designed flow-thru apparatus was designed based on the modification of flow device cell[7]. The drug release occured from only one side of the film (flat and perimetric edges)[8]. Isotonic phosphate buffer pH 6.6 (simulating the salivary pH) was pumped at a flow

Table 3 : Adhesion time of buccoadhesive films (placebo films) determined *in vivo*

Formula Code	Adhesion time (min.) Mean (±S.D.)	Condition of film at the end of adhesion (erosion dislodgement)
P-1	225.00 (±5.0)	Erosion
P-2	165.00 (±5.56)	Erosion
P-3	228.33 (±4.04)	Erosion
P-4	232.66 (±2.08)	Erosion

rate of 0.65 ml/min which corresponds to, the mean resting salivary flow rate[9]. Five ml of the sample was removed at different time intervals from the reservoir till the film eroded completely or dislodged whichever was earlier. The cumulative % drug release was determined by measuring the absorbance spectrophotometrically at 242 nm. The surface pH of the films was determined to investigate the possibility of any side effects, *in vivo*. The method used was similar to that described by Bottenberg *et al.*[10]. The mechanical property of the films was studied using a self designed apparatus. A film strip (2 x 1 cm) was pulled at a rate of about 5 mm/min till break. The initial and final length of the strip was noted and the % elongation of the film was calculated. A film (2 x 2 cm) was cut and repeatedly folded at the same place till break which gave the value of folding endurance. *In vivo* evaluation of the placebo buccoadhesive films was carried out to determine the time of erosion/ adhesion, investigate the acceptability of different polymers and to determine any irritation or side effects produced by placebo films. The study was conducted in healthy human volunteers (age group 21-28 yrs) Written consent was obtained from the volunteers. For *in vivo* studies the films were cast on sterilized glass plates in order to eliminate any contamination from elemental mercury. The films were kept in the vacuum desiccator for 24 hours to remove any residual solvent which might cause irritation *in vivo*. Volunteers were asked to record the time of film insertion and the time and circumstances at the end of adhesion[11]. They were also asked to complete a questionnaire after trial period.

Table 2 shows important parameters of selected films. Film patch P-3 exhibited maximum bioadhesive strength quite comparable to film Patch P-2. There was no significant difference in the adhesion time *in vitro*. The maximum adhesion time was exhibited by P-3 followed by P-4. The surface pH of all the films was with in ±1.5 units of neutral pH and hence should not cause irritation. The folding endurance and % elongation at break of the films were optimum and therefore the films exhibited good physical and mechanical properties[12].

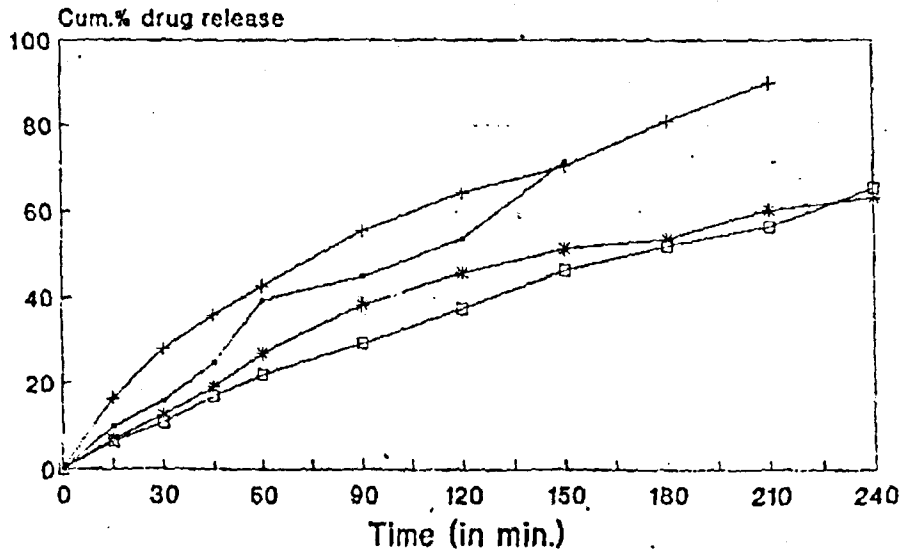

Fig. 1 : *In vitro* release rate curves for different buccoadhesive films

Fig. showing maximum drug release in the case of P-2 and comparable drug release in the case of P-3 and P-4

Fig. 1 shows drug release which was satisfactory. The film patch containing CP-934P and HPMS-E4M in the ratio of 3:2 gave maximum drug release whereas film containing HPC-M and HPC-L in combination with CP-934P exhibited comparable drug release. Table 3 shows adhesion time *in vivo*. A lot of inter-individual variation was observed for the time of erosion due to variation in the individuals with respect to the salivary flow rate, the oral anatomy and the tongue movement. All the films eroded completely and none had to be removed due to irritation. The films did not cause any discomfort to the volunteers and their taste was acceptable. No side effects like taste alteration, heaviness, dry mouth or severe salivation were reported.

The present study was a successful attempt to develop erodible-buccoadhesive films of TA, for the treatment of oral lesions. Successful topical treatment of lesions is difficult due to constant flow of saliva and mobility of involved tissues. Therefore buccoadhesive films overcame this problem[13] and were able to prolong the release of the drug in the oral cavity. The erodible buccoadhesive films resulted in the complete erosion and guaranteed the delivery of drug, thereby obviating the need to remove any undisintegrated residual fragment after predetermined time. The system claims the potential clinical usefulness in the discrete oral lesions.

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