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"MEASUREMENT OF BIOADHESIVE STRENGTH OF MUCOADHESIVE BUCCAL" PATCHES: DESIGN OF AN *IN VITRO* ASSEMBLY"

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ABSTRACT

An *in-vitro* assembly has been developed to measure and compare bioadhesive strengths of mucoadhesive buccal patches of Propranolol hydrochloride, prepared by the method of solvent casting technique. The strength of the bond formed between the formulation and the mucous membrane excised from goat cheek pouch was determined using tensile experiments on an especially fabricated assembly. It was seen that the assembly gave reproducible results of mucoadhesion and also maximum strength was observed with carbopol 974P as compared to other mucoadhesive polymers. The assembly simulated the buccal conditions in respect of the amount of sheer, pH, mucosal surface and the wetness of the contact surface.

KEY WORDS: Mucoadhesion, Solvent casting technique, Modified balance, tensile experiments.

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INTRODUCTION

Bioadhesion is defined as a state in which two bodies, one or both of which are of a biological nature, are held together for extended period of time by interfacial forces. When the biological membrane involved is a mucous membrane, the term bioadhesion is replaced by mucoadhesion[1]. For bioadhesion to occur, certain stages with their role depending on the nature of the bioadhesive are required. The first stage involves an intimate contact between a bioadhesive and a membrane, either after wetting of the bioadhesive surface or from the swelling of the bioadhesive. In the second stage, after contact is established penetration of the bioadhesive into the crevices of the tissue surface or interpenetration of the chains of the bioadhesives with those of the mucous take place. Low chemical bonds can then settle[2].

Determination of mucoadhesive bond strength is important in the development of adhesive dosage forms, and several methods have been developed to investigate this. Techniques

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that measure the tensile force required to break the adhesive bond between a model membrane and the test polymer have been reported[3].

In the present study, an apparatus for testing mucoadhesive bond strength was fabricated and used to make a comparison between bond strength of the buccal patches of Propranolol hydrochloride prepared using different polymers. Goat cheek pouch was used as a model mucous membrane.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride was received as a gift sample from micro labs. Carbopol 974 P (CP), hydroxy propyl cellulose (HPC), hydroxy propyl Methyl cellulose K100M (HPMC) was purchased from S.D fine chemicals Ltd, Mumbai. Sodium carboxy methyl cellulose (SCMC), Sodium Alginate (S.A.), Ethyl Cellulose (EC) was procured as a gift sample from Ranbaxy labs, Delhi.

Selection of the Model Mucosal Surface

In the evaluation of adhesion, it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds.

In the present study, goat cheek pouch was used as a model mucosal surface for bio adhesion testing. After the cheek pouch was excised and trimmed evenly, it was then washed in isotonic phosphate buffer (PH7.4) and then used immediately.

Fabrication of Buccal Patches[4]

Buccal patches were prepared by the method of solvent casting technique. Among the various substrates for film formation including mercury, Teflon, glass and aluminum, mercury surface was found to give best results. All further work was done using this substrate.

Fabrication of Drug Reservoir Film

Accurately weighed quantity of Hydroxy Propyl Methyl Cellulose – K 100M (HPMC K100M) was mixed with 156.8mg of Propranolol Hydrochloride. Then add 9ml of distilled water and Glycerin as plasticizer. Stirring was continued until a clear solution was obtained. Then the medicated gels were left 2 hour at refrigeration temperature to ensure clear, bubble – free gels[5]. The solution was then transferred quantitatively to glass rings (diameter 5.6cm) kept on the surface of mercury in Petri plates. The Petri plates were covered with inverted funnels to allow controlled evaporation of the solvent. These were left undisturbed in room temperature for two to three days. After complete drying, the films could be retrieved intact by slowly lifting the rings from the mercury substrate. Circular patches of 2cm diameter, each containing 20mg of drug were cut and sealed by using rate controlling membrane on either side to control the drug release from periphery. Similarly, rate controlling membrane was prepared using polymers such as sodium carboxy methyl cellulose, hydroxyl propyl cellulose, sodium alginate, carbopol 974P and ethyl cellulose while water and ethanol was used as casting solvent and dibutyl phthalate as plasticizer.

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Fabrication of the Test Assembly (Figure 1)

The working of a double beam physical balance formed the basis of bio adhesion test apparatus fabricated.

The two pans of a physical balance were removed. The right pan was replaced with a lighter base and on the left side; a Teflon ring was hanged with a copper wire. A Teflon cylinder of 1.5cm diameter and 3cm height was hanged with a copper wire on the opposite side of this ring. The height of the total set up was adjusted to accommodate a glass container of 4.2cm diameter and 4.2cm height below it, leaving a head space of about 0.5cm in between.

A Teflon block of 3.8cm diameter and 2 cm height was fabricated with an upward protrusion of 2cm height and 1.5 cm diameter on one of its face. This was kept inside the glass container, which was then placed below the left hand setup of the balance. The two sides were then balanced so that right hand side was exactly 5gms heavier than the left.

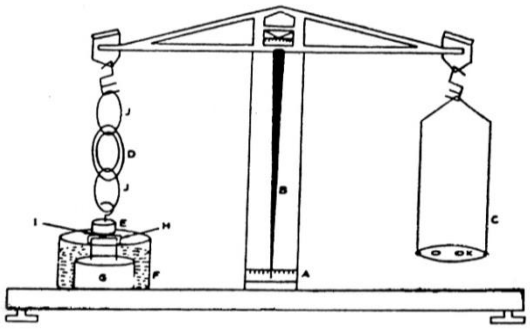

Figure No. 1 Bioadhesion Test Assembly (Modified balance)

A- Scale, B – Pointer C- pen, D- Teflon ring for balancing, E- Teflon cylinder for sticking the buccal patches, F- Glass Container, H-Goat cheek pouch mucosal surface, I-Patches to be tested, J-Copper wire, K- Weight

Measurement of adhesion force

The two sides of the balance were balanced with a 5gms weight on the right hand side. The goat cheek pouch, excised and washed was tied tightly with the mucosal side upwards using thread over the protrusion in the Teflon block. The block was then lowered into the glass container, which was then filled with isotonic phosphate buffer (pH7.4). Such that the buffer just reaches the surface of mucosal membrane and keeps it moist. This was then kept below the left hand set up of the balance. The patches was then stuck with a little moisture, on to the cylinder hanging on the left hand side and the balance beam raised with the 5gm weight on the right pan removed. This lowered the Teflon cylinder along with patches over the mucosa, with a weight of 5gms.

The balance was kept in this position for 3 minutes and then slowly weight were added on the right pan, till the patch separated from the mucosal surface. The excess weight on the right pan i.e. total weight minus 5 gm is the force required to separate the patches from the mucosa. This gave the bioadhesive strength after patch in Gms.

After each measurement the tissue was gently and thoroughly washed with

isotonic phosphate buffer pH 7.4 and left for 5 minutes before the next measurement. Care was taken not to use a broken mucosa. Fresh tissue was used for each batch of patches.

RESULTS

The present study revealed that the test system was reproducible for the bio adhesive measurement. From the result it was found that carbopol 974p had higher mucoadhesive strength than the other three polymers. Increasing the concentration of carbopol 974p also increased the bio adhesive strength. The bioadhesive strength of the polymers were found to be carbopol 974p > sodium Alginate> Sodium carboxy Methyl Cellulose> Ethyl cellulose. Though sodium carboxy methyl cellulose showed good hydrophilicity but low mucoadhesiveness was attributed due to the easily erodable gel formed due to excessive swelling. While Ethyl cellulose showed very least mucoadhesiveness because of its less hydrophilicity.

DISCUSSION

Keeping in view the necessity and importance of bioadhesion testing in the development of bioadhesive dosage forms and the complexity of the instruments available, a simple physical balance used in the lab was modified for this purpose. It was observed that this assembly gave reproducible results and performed efficiently. Using goat cheek pouch membrane as the model membrane, isotopic phosphate buffer (pH 7.4) as the test medium and maintained a constant temperature and pressure of adhesion, the conditions were simulated as the human buccal cavity. Care was taken not to use a broken mucosa and a single membrane was used not more than three times, till it retained its original cellular form without being damaged.

Using different polymer combinations, it was observed that carbopol 974P exhibited maximum strength. But since it cannot be used alone due to its water insolubility, it was combined with hygroscopic polymers to aid in drug release from the dosage forms.

CONCLUSION

From the results and discussion of the present study it was concluded that carbopol 974P had higher mucoadhesive strength than the other three polymers. Increasing the concentration of carbopol 974P also increased the bioadhesive strength.

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Composition of formulations

Formulation code	Drug Reservoir In % HPMC K100M	Rate Controlling Membrane					Plasticizer	
		HPC	SCMC	EC	SODIUM ALGINATE	CARBOPOL 974P	Drug Reservoir	Rate Controlling Membrane
A_1	4%	5%	0.5%	-	-	-	Glycerin	Dibutyl Phthalte
A_1	4%	5%	0.75%	-	-	-	Glycerin	Dibutyl Phthalte
A_1	4%	5%	1%	-	-	-	Glycerin	Dibutyl Phthalte
B_1	4%	5%	-	1%	-	-	Glycerin	Dibutyl Phthalte
B_1	4%	5%	-	11.5%	-	-	Glycerin	Dibutyl Phthalte
B_1	4%	5%	-	2%	-	-	Glycerin	Dibutyl Phthalte
C_1	4%	5%	-	-	1%	-	Glycerin	Dibutyl Phthalte
C_1	4%	5%	-	-	1.5%	-	Glycerin	Dibutyl Phthalte
C_1	4%	5%	-	-	2%	-	Glycerin	Dibutyl Phthalte
D_1	4%	5%	-	-	-	0.5%	Glycerin	Dibutyl Phthalte
D_1	4%	5%	-	-	-	0.75%	Glycerin	Dibutyl Phthalte
D_1	4%	5%	-	-	-	1%	Glycerin	Dibutyl Phthalte

Table No. I: (A_1 to D_3 represent various formulations prepared using HPC,SCMC,EC,Sodium alginate and Carbopol 974P in rate controlling membrane and 4% HPMC as drug reservoir 33.33% w/w glycerin and dibutyl phthalate were used as plasticizers for drug reservoir and rate controlling membrane respectively)

Table No. II: *Invitro* Bioadhesive Strength of Different Buccal Patches

Formulation Code	Bioadhesive Strength (gms)(mean ± S.D)
A1	20.80 1.9
A2	23.10 2.0
A3	27.50 2.14
B1	19.30 1.79
B2	20.10 1.83
B3	21.80 1.90
C1	21.50 1.89
C2	29.70 2.22
C3	29.70 2.22
D1	22.10 1.9
D2	26.50 2.10
D3	31.41 2.28

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