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DESIGN AND EVALUATION OF BUCCAL FILM OF DICLOFENAC SODIUM

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ABSTRACT

Diclofenac Sodium causes gastro-intestinal irritation and ulceration on prolonged use. The buccal delivery of Diclofenac Sodium avoids direct contact to mucosa so it should reduce the possibility of ulceration. The buccal films of Diclofenac Sodium were formulated using mucoadhesive polymers like PVA and HPMC. The films were evaluated for their mechanical strength, folding endurance, drug content uniformity, swelling, *in vitro* residence time, *in vitro* release, *in vitro* bioadhesion and *in vivo* mucoadhesion. Films were found to have good tensile strength and elasticity. The drug content was found to be uniform**.** The films prepared with HPMC had satisfactory residence time, good bioadhesive strength and the release of drug was matrix diffusion type. The films prepared with PVA have comparatively less bioadhesion and *in vitro* residence time. The buccal films prepared with PVA can be used for the fast release of drug and so fast action, whereas HPMC films can be used for the sustained release of the drug.

KEYWORDS: Buccal film, Diclofenac Sodium, Mucoadhesive polymers, PVA, HPMC, Gastro intestinal ulceration.

INTRODUCTION:

Transmucosal route of drug delivery offers distinct advantages over per oral administration for systemic drug delivery. These advantages include possible bypass of the first pass effect, avoidance of pre-systemic elimination within the GI tract.Within the oral mucosal cavity the buccal region offers an attractive route of administration for systemic drug delivery.

Buccal mucosa has rich blood supply and it is relatively permeable[1]. Buccal drug delivery has become an important route of administration;

so when it is combined with mucoadhesive drug delivery, it can be called as transbuccal mucoadhesive drug delivery system.

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Various mucoadhesive dosage forms have been developed including adhesive tablets, gels, ointments, patches and films [2-5]. Buccal film is preferred over adhesive tablets. They can circumvent the relatively short residence time of oral gels. The buccal film also protects the wound surface thus reduces pain and also can treat oral diseases more effectively.

Diclofenac sodium is a potent non-steroidal anti-inflammatory drug (NSAID) used for the treatment of rheumatoid arthritis and other rheumatic disorders. The long-term use causes gastro-intestinal irritation and ulceration. The physico-chemical properties of Diclofenac sodium and its short half-life make it a suitable candidate for administration by buccal route[6].

The buccal delivery of Diclofenac Sodium avoids direct contact to mucosa hence the formulation reduces the possibility of gastro-intestinal ulceration. The objective of this research project is to formulate the buccal film of Diclofenac sodium using mucoadhesive polymers like PVA and HPMC.

MATERIALS AND METHOD

Materials

Diclofenac Sodium was a gift sample from Ar-Ex Laboratories Pvt.Ltd., Mumbai, India; Polyvinyl alcohol (PVA), hot water soluble (M.W.1, 25,000) (S.D. Fine Chemicals Ltd., Mumbai, India); Hydroxypropyl methyl cellulose (HPMC) – 15 cps (S.D.Fine Chemicals Ltd., Mumbai, India); Polyvinyl pyrollidone K-30 (PVP)(Central Drug House, New Delhi, India); Isopropyl Alcohol (IPA)(S.D. Fine Chemicals Ltd. Mumbai, India) and Dichloromethane (S.D. Fine Chemicals Ltd. Mumbai, India)

PREPARATION OF BUCCAL FILM:

(A) Preparation of PVA Buccal film

The film was prepared in three layers. For the first layer 5% w/v solution of PVA was prepared by dissolving it in the distilled water at 70 – 100^0. 1% v/v propylene glycol was added under stirring. Bubble free solution was cast at room temperature into glass petri dish (12 mm in diameter) and allowed to dry under

IR lamp till a dry film was formed. For the second layer, calculated amount of Diclofenac sodium was triturated with 5% w/v PVA solution and poured on to dried first layer. Third layer was the same as first layer and the solution was poured onto the dried second layer and dried under IR lamp.

The three-layered buccal film was formed in which drug layer was sandwiched between the PVA layers. It was then cut into 15 mm diameter film, so that each buccal film contains 20 mg of the drug. These films were packed in aluminium foil and stored in vacuum desiccator.

(B) Preparation of PVA Buccal film containing 1% w/v PVP:

The method of preparation for this buccal film was the same as PVA buccal film except 1% w/v PVP was added by trituration into the 5%w/v PVA Solution.

(C) Preparation of HPMC buccal film:

It was also prepared in three layers. For the first layer 1.5% w/w HPMC was dissolved in 1:1 Isopropyl alcohol: Dichloromethane mixture and poured into the glass petri dish. It was air-dried. For the second layer, the required quantity of the drug was dissolved in 1:4 propylene glycol: ethyl alcohol solvent mix and poured onto the dried first layer. It was then air-dried. Third layer was the same as first layer. Drug was sandwiched between two HPMC layers.

EVALUATION OF BUCCAL FILM:

Measurement of mechanical properties:

Mechanical properties of the film were evaluated using Universal testing machine (Instron, India). The film strip in dimension of 50x15 mm, free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 5 cm. The strip was pulled by the top clamp at a rate of 300 mm/min till it broke. The force and elongation were measured when the film broke [6].

The following equations were used to calculate mechanical properties of the film:

$$\text{Tensile strength (Kg/cm}^2\text{)} = \frac{\text{Force at break (Kg)}}{\text{Initial cross sectional area of the sample (mm}^2\text{)}}$$

$$\text{Elongation at break (\%)} = \frac{\text{Increase in length (mm)} \times 100}{\text{Original length (mm)}}$$

Folding endurance

Three films of each formulation of size 2x2 cm were cut. Folding endurance was determined by repeatedly folding one film at the same place till it broke or folded upto 300 times at the same place. The number of times the film could be folded at the same place without breaking gave the value of folding endurance.

Measurement of film thickness

The thickness of the film was measured using a Screw gauge micrometer at 10 different spots from each batch. The mean and standard deviation were calculated.

Mass uniformity

The assessment of mass uniformity was done by weighing 10 randomly selected films from each batch. The test was performed on three films from each formulation then mean and standard deviation were determined.

Drug content uniformity

5 films were weighed and dissolved in 100 ml isotonic phosphate buffer pH 6.8 using magnetic stirrer. The solution was filtered and after suitable dilution analyzed for drug Diclofenac sodium spectrophotometrically at 277 nm.

Surface pH

The agar plate was prepared by dissolving 2% w/v agar in isotonic phosphate buffer pH 6.8 and pouring the solution into the petridish till gelling at room temperature. Buccal films were allowed to swell on the surface of agar plate for 2 h. The surface pH was measured using pH indicator paper, the change in colour determined after 90 s and compared with the standard colour scale.

Viscosity

The viscosity of the solution used for buccal films were determined using Brookfield viscometer. Viscosity of 5% w/v aqueous PVA

solution with 1% v/v propylene glycol and viscosity of 5% w/v aqueous PVA solution with 1% w/v PVP was determined using spindle number RV2 at 50 rpm. For HPMC 1.5% w/v solution of HPMC in 1:1 isopropyl alcohol and dichloromethane was prepared. Because the solution of HPMC was in organic solvent, proper care was taken to avoid vaporization of solvent. Viscosity was determined using spindle number RV4 at 50 rpm.

Film swelling:

The film swelling studies were conducted using two media, namely, distilled water and simulated saliva fluid.[7] The Buccal film was weighed and placed in a pre-weighed wire mesh with sieve opening 800 mμ. The mesh containing a film sample was submerged into 15 ml medium. Increase in weight of the film was determined at preset time intervals until a constant weight was observed.

The degree of swelling was calculated using the formula = $\frac{W_t - W_0}{W_0}$

Where W_t is the weight of the film at time t

W_0 is the weight of film at time 0

The degree of swelling was determined for three films of one type of formulation.

***In vitro* residence time**

The *in vitro* residence time was determined using a modified USP disintegration apparatus. 800 ml of isotonic phosphate buffer (IPB) maintained at 37^0 was used as a medium. The segment of rabbit intestinal mucosa of 3 cm length was glued vertically to the glass slab. Then this glass slab was attached to the apparatus vertically. The film was hydrated on one surface using 50 µl IPB and then this hydrated surface was applied to the rabbit mucosa with little pressure. The glass slab was then allowed to move up and down so that patch was completely immersed

in the buffer solution at the lowest and highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded.

***In vitro* release study**

The release of drug from the buccal film was determined using Keshary-Chein diffusion cell. The diffusion medium was phosphate buffer pH 6.8, maintained at 37^0. The parchment paper was soaked in phosphate buffer pH 6.8 for 1h and then air-dried. It was mounted between the donor and receptor compartment and film was placed on it. Both the compartments were clamped together. The phosphate buffer pH 6.8 was filled in the receptor compartment (11ml capacity) and stirred using magnetic stirrer. At different time intervals samples were withdrawn and replaced with an equal volume of buffer. The samples were analyzed spectrphotometrically after appropriate dilution at 277 nm [8-10].

***In vitro* bioadhesion strength**

To evaluate the bioadhesion strength the tensile strength required to detach the bioadhesive film from mucosa was measured. For this evaluation the apparatus described by Gupta et al was used [8,9].

Measurement of adhesion force

The two sides of the balance were balanced with 5 g weight on the right hand side. The rabbit intestine excised and washed was tied tightly with the protrusion in the block. The block was then lowered into the glass container, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37 ± 1^0, such that the buffer just reaches the surface of the mucosal membrane and keeps it moist. This was then kept below the left hand setup of the balance. The film was then stuck with a little moisture on to the cylinder hanging on the left hand side and the balance beam raised, with 5 g weight on the right pan removed. This lowered the teflon cylinder along with the film over the mucosa with a weight of 5 g. The balance was kept in this position for 3 min and then slowly weights

were increased on the right pan till the film separated from the mucosal surface, the total weight on the pan minus 5 g is the force required to separate the film from the mucosa. This gives the bioadhesive strength of the film in grams.

***In vivo* mucoadhesion studies**

The *in vivo* mucoadhesion of the buccal films were determined in healthy human volunteers. The volunteers were asked to apply the film by gently pressing it in the buccal mucosa for 30 s. The volunteers were advised to perform their normal activity except eating food. They were asked to note down the retention time of the film as well as various criteria related to acceptability of the film for example irritation of mucosa, taste, dryness of mouth, comfort, salivary secretion etc.

RESULTS

MECHANICAL PROPERTIES

Physical properties of the films were determined. The tensile strength test gives an indication of the strength and elasticity of the film reflected by the tensile strength and elongation at break as given in Table I .

Table I : Characteristics of buccal film

Characteristics	F1 PVA film	F2 PVA with PVP	F3 HPMC film
Tensile strength: Direction 1 (Kg/cm^2) Direction 2	34.75 39.14	30.65 34.40	9.05 13.14
Elongation at break (%): Direction 1 Direction2	550 605	470 593	96 143
Folding endurance	>300	>300	>300
Thickness (mm)	0.6±0.013	0.66±0.015	0.308±0.049
Mass (mg)	107.26±1.53	125.6 ±1.58	48.1±1.45
Drug content DS in mg	19.90±0.68	19.2±1.30	18.03±1.57
Surface Ph	pH 6.5- 7	pH 6.5- 7	pH 6.5- 7
Viscosity (cps)	67	70	5.16
Degree of swelling: In distilled water In simulated saliva fluid	3.092±0.11 3.407±0.54	4.254±0.97 6.388±1.22	16.18±0.49 14.08 ±0.25
In vitro residence time (min)	25	50	74
In vitro bioadhesive strength (g)	13.163± 1.79	12.904±1.548	13.352±1.767
In vitro release (%) (in 6 h)	98.6	86.64	66.86

The folding endurance was found to be more than 300 for all the three films.

Thickness

The thickness of the film was found to be 0.60±0.013 mm for F1, 0.66±0.015 mm for F2 and 0.308±0.049 mm for F3.

Mass and content

The mass of the film was 107.26±1.53 mg for F1, 125.6±1.58 mg for F2 and 48.1±1.45 mg for F3. The drug content in buccal film was found to be uniform with a range of 19.90±0.68 mg for F1, 19.2±1.3 mg for F2 and 18.03±1.57 mg for F3.

Surface pH

The surface pH of all the films was between pH 6.5 to 7.0.

Viscosity

Viscosity of the polymer solution was determined in their respective solvent system. The viscosity of 5% w/v aqueous solution of PVA was found to be 67 cps, aqueous solution of 5% w/v PVA with 1% w/v PVP was found to be 70 cps, and 1.5% w/w solution of HPMC in dichloromethane and isopropyl alcohol (1:1) was found to be 5.16 cps (Table I).

Degree of swelling

The degree of swelling was determined in both distilled water and simulated saliva fluid for F1, F2 films prepared with PVA, maximum swelling was seen in 6 min in both distilled water and simulated saliva fluid (**Fig.1, 2**).

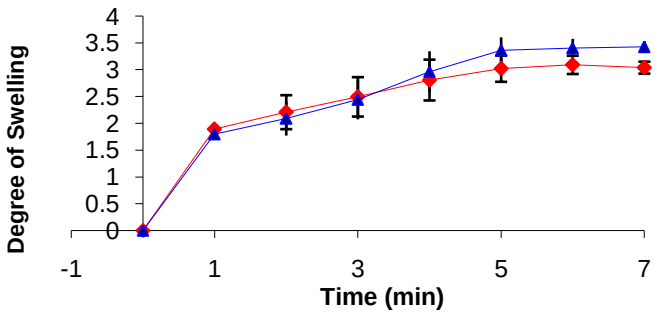

Fig. 1: **Graph showing degree of swelling of film F1**

Swelling in distilled water ---◆---- simulated saliva fluid --- ▲ ---

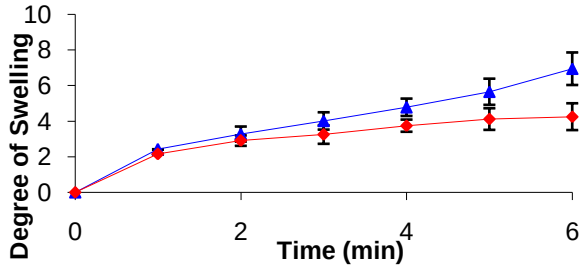

Fig. 2 : **Graph showing degree of swelling of the film F2**

Swelling in distilled water ---◆---- , simulated saliva fluid ---▲---

The swelling was not affected much because of difference in medium i.e. distilled water and simulated saliva fluid for F1 and F2. In case of F3 prepared with HPMC, it took 20 min for maximum swelling in distilled water and 40 min in simulated saliva fluid (**Fig.3**).

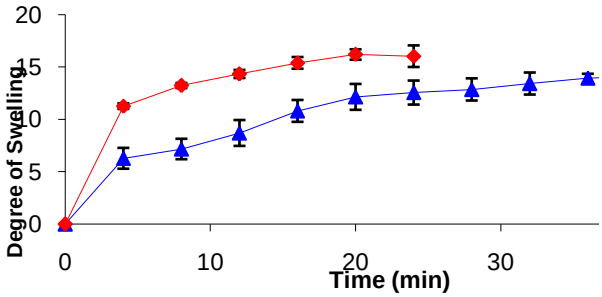

Fig. 3: Graph showing degree of swelling of the film F3
Swelling in distilled water ---◆---- , simulated saliva fluid --- ▲ ---

In vitro residence time

The *in vitro* residence time was determined using rabbit intestinal mucosa. PVA film F1 remain adhered to the mucosa for 25 min. The addition of PVP in PVA film F2 had increased the residence time to 50 min. The HPMC film F3 had the maximum residence time of 74 min. The *in vivo* residence time was always found to be more, as during *in vitro* testing the film is exposed to higher agitation.

In vitro bioadhesive strength

The *in vitro* bioadhesive strength test was performed using modified double beam balance for mucoadhesion studies. The HPMC film F3 showed the maximum strength 13.352 g followed by F1 was 13.613 g and F2 was 12.904 g.

IN VIVO MUCO ADHESION STUDIES

Studies were performed on healthy volunteers to check the acceptability/ biocompatibility of the film. The films did not cause any irritation and dryness of mouth and were found to be very comfortable. The taste

of the films was found to be slightly unpleasant due to the inherent bitter taste of the drug (**Table II**).

Table II : Response of human volunteers to various parameters

Criteria	Volunteer response		
	F1	F2	F3
Irritation	No	No	No
Taste	Slightly unpleasant	Slightly unpleasant	Slightly unpleasant
Comfort	Comfortable	Comfortable	Comfortable
Dryness of mouth	No	No	No
Salivary secretion	Very slight	Very slight	Very slight

In vitro release study

The release of Diclofenac Sodium (DS) from the buccal film was studied using Keshary-Chein diffusion cell .The release of DS after 1h from PVA film F1 was 10.57%, PVA-PVP film F2 was 8.62% and HPMC film F3 was 7.82%. After six hours 98.6% drug was released from F1, 86.64% from F2 and 66.86% from F3 (**Fig.4, 5**).

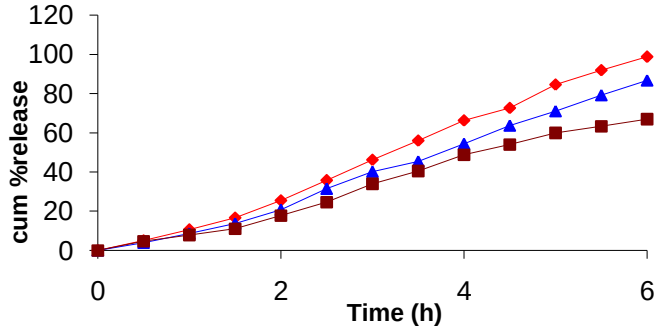

Fig. 4: *In vitro* release profiles of various formulations

Formulations F1 ---◆--- , F2 ---▲--- , F3 ---■

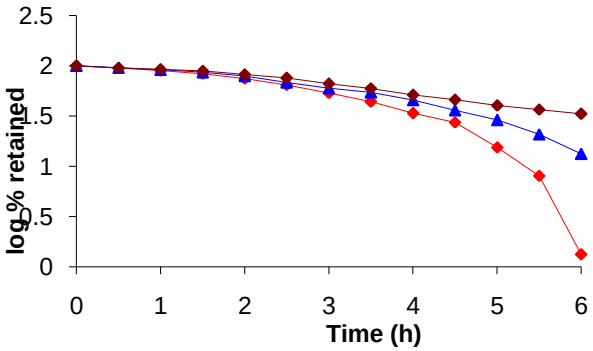

Fig. 5: Log percent-retained at different time intervals of various formulations

Formulations F1 --◆--- , F2 --▲--- , F3 ---■--

DISCUSSION

The film F1 prepared with PVA showed high value of tensile strength and elongation at break compared to film F3 prepared with

HPMC. The high value of tensile strength and elongation at break for PVA film showed that PVA buccal film was strong and elastic. The inclusion of PVP in the PVA film reduced the strength and elasticity of the film but not to a very significant extent. The film F3 prepared with HPMC had less tensile strength and elasticity compared to F1 and F2.

The surface pH of all the films was between pH 6.5 to 7.0 and hence these films are expected to cause no irritation.

The drug content was found to be uniform as the drug was dispersed uniformly throughout the film.

Rate of swelling in distilled water was comparatively faster than in simulated saliva fluid. If we compare PVA and HPMC films, the PVA film exhibited faster rate of water uptake and hydration than HPMC films. The swelling of the polymer was crucial for its bioadhesion behaviour. Adhesion occurs short after beginning of swelling but the bond formed is not very strong. The adhesion will increase with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer tissue interface.

The swelling properties of the polymer matrix are primarily dependant on substituted group of polymer. The hydroxyl group in the molecule plays an important role in the matrix integrity of the swollen hydrophilic film. The PVA film swells very fast, the water influx weakens the network integrity of the polymer, the structural response to the swollen matrices is greatly influenced and so erosion of the film takes place. The addition of PVP increases the swelling characteristics of the film.

The F2 film had more residence time compared to F1. The addition of PVP in PVA film F2 had increased the residence time. The HPMC film F3 had the maximum residence time. The *in vivo* residence time was always found to be more, as during in vitro testing the film is exposed to higher agitation.

The HPMC film F3 showed the maximum *in vivo* bioadhesion strength followed by F1 and F2. There was a direct correlation found between the in vitro residence time and bioadhesive strength. HPMC had maximum residence time with maximum bioadhesive strength. So it proves that HPMC had maximum mucoadhesion power.

The residence time of HPMC film F3 was found to be maximum compared to the PVA. The short residence time of PVA film was because of high aqueous solubility of PVA.

The higher release of DS from PVA film can be explained by the viscosity of the polymer solution and the solubility of PVA in water. 5% w/v solution of PVA was having less viscosity compared to the 5% w/v PVA containing 1% w/v PVP. The diffusion of the drug from the less viscous PVA was easier than the PVA-PVP combination. The HPMC buccal film F3 had lesser release compared to F1 and F2 as there was no formation of gel after swelling of buccal film as was seen in case of F1 and F2. But with HPMC very high degree of swelling was observed which must be responsible for the formation of pores in the buccal film through which the diffusion of the drug took place. The release of HPMC suggested that the release mechanism was matrix diffusion type.

CONCLUSION

The research study shows that transmucosal buccal delivery using mucoadhesive polymer is a promising approach for delivering Diclofenac Sodium. The evaluation data demonstrate that the film prepared with HPMC has satisfactory residence time, good bioadhesive strength and the release of the drug is matrix diffusion type. The films prepared with PVA have comparatively less bioadhesion and the *in vivo* residence time was also less, which is due to the aqueous solubility of polymer PVA. It shows that PVA films can be used for their fast release and so fast action whereas HPMC films can be used for the sustained release of the drug.

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