

Formulation and Evaluation of Mucoadhesive Buccal Film of Flurbiprofen

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Abstract: A new formulation Mucoadhesive buccal film designed particularly for anti-inflammatory and analgesic therapy in the oral cavity and for good retention property on the site. Mucoadhesive Buccal films formulated to obtain treatment effectiveness, reduction of drug dose, increase and residence time at the site and to avoid the first pass hepatic metabolism and gastrointestinal degradation. Mucoadhesive buccal films were prepared using film casting method, Initially only film forming polymer were used then they were combined with the mucoadhesive polymer with plasticizer. Then films were characterized under following parameters swelling index, percentage hydration, matrix erosion, *ex vivo* mucoadhesive time, *in vitro* release, tensile Strength and elongation at break. Excellent adhesion and retention on the site observed by the prepared mucoadhesive buccal films with better release in controlled manner. On the basis of the results obtained in terms of mucoadhesion time which was 4 to 9 hr and percent matrix erosion, hydration, *in vitro* release was 63%, percent elongation at break was 16 and tensile strength was 95.3kg/cm². The film containing PVP and NaCMC was selected best promising film for the delivery of the anti-inflammatory drug.

Key words: Mucoadhesive Buccal Film of Flurbiprofen, Formulation and Evaluation.

INTRODUCTION

In recent years, delivery of therapeutic agents through various mucosal routes has gained significant attention owing to their pre-systemic metabolism or instability in the acidic environment associated with oral administration. Absorption of therapeutic agents from the oral cavity provides a direct entry of such agents in to the systemic circulation, thereby avoiding the first pass hepatic metabolism and gastrointestinal degradation. However, the sublingual routes of drug delivery have received much more attention because of its unique advantages over other oral transmucosal routes.¹

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of

drugs. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the GI tract and liver (Edith *et al.*, 1999).²

The advantages reside on the reduction of drug dose because of its localization in the inflammatory process site. One particular problem to drug delivery system, aim to the treatment of the oral cavity disease, is the short residence time at the site of application. This problem may be resolved by using bioadhesive polymer i.e. - polymer that exhibits characteristic adhesive interaction with biological membrane.³

A few drugs, such as buprenorphine (Guo, 1994)⁴, propranolol (Coutel, 1992)⁵, salbutamol sulphate (Pavankumar *et al.*, 2005)⁶, diclofenac sodium (Patil and Rao, 2003)⁷, and fexofenadine (Thimmasetty *et al.*, 2007)⁸ have been successfully administered via the buccal route. Buccal films are also suitable for protecting wound surfaces, thus reducing pain and increasing treatment effectiveness.⁹

Present study is undertaken to prepare Mucoadhesive Buccal film with aim to increasing the contact time achieving controlled release, reducing the frequency of administration and obtain greater therapeutic efficacy.

MATERIALS AND METHODS

Materials

Flurbiprofen was collected from FDC Limited (Mumbai, India). Polyethylene glycol, Carbopol, Sodium Carboxyl methyl cellulose Sodium, Hydroxyl propyl methyl cellulose, polyvinyl pyrrolidone, disodium hydrogen phosphate, Sodium dihydrogen orthophosphate, sodium chloride were obtained from CDH chemicals India. Distilled water was used throughout the experiments. All chemicals were pharmaceutical grade and used without further modification.

Buccal film preparation¹⁰

Initially films were prepared using only film forming polymer.

Polyethylene glycol in case of Batch Code BF1, BF2, BF5 and BF6, and polyvinyl pyrrolidone in case of BF3, BF4, BF7 and BF8. First film forming polymer dissolved in water (40 %) then in various ratio, ethanol was added such that water solution/ dispersion: Ethanol (1:5; 2:4, 4:2, 5:1) and glycerin were used as a plasticizer.

The mixture were prepared with magnetic stirrer and cast on petridish. The volume of cast was determined so that 10mm thickness was obtained after casting the mixture. The petridish was stored at 4°C for 24 h to remove air bubbles entrapped and dried at 60 °C for 16 h. The film were accurately observed and checked for possible imperfection upon the removal from petridish then a water solution of mucoadhesive polymer was added to the film forming polymer mixture in the ratio specified in the table below, the preparation procedure was repeated as previously described and same method were used to make drug loaded films (Table 1).

CHARACTERIZATION

Film weight and thickness:¹¹

The weight of each film (1x1 cm²) was measured using digital balance from different positions of the

film and the average was calculated. Similarly the thickness of each film was measured using thickness tester at different positions of the film and the average was calculated.

Folding endurance:¹¹

The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. The mean value of three observations and standard deviation was calculated.

Drug content uniformity:¹¹

Three film units (each of 20 mm diameter) of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.6 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed at 274 nm in a UV spectrophotometer. The average of drug contents of three films was taken as final reading.

Surface pH of the films:¹²

The buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (m/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and then pouring the solution into a petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of two observations was calculated.

Swelling Index:¹³

After determination of the original film weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37±0.2°. Increase in the weight of the films ($n = 3$) was determined at preset time intervals (1-5 h). The percent swelling, %S, was calculated using the following equation: Percent Swelling (%S) = $(X_t - X_o) / X_o \times 100$, where X_t is the weight of the swollen film after time t , X_o is the initial film weight at zero time.

Residence time:¹⁴

The *in-vitro* residence time was determined employing a modified USP disintegration procedure. The disintegration medium was composed of 800 ml isotonic phosphate buffer of pH 7.4 maintained at 37°C. A piece of porcine buccal tissue was used for this study. The tissue was attached to a rectangular glass piece using cyanoacrylate adhesive from non mucosal surface. The patch was tuck to the mucosal surface by applying small pressure. The glass piece

with tissue and patch placed in the basket of disintegration apparatus and set in motion. The time necessary for complete erosion or detachment of the patch from the mucosal surface was observed and recorded.

***In vitro* release**

A standard USP basket apparatus was employed to evaluate drug release. For release portion of 4 cm² (2 cm x 2 cm) of film was used. The film was placed in basket after 2 min; the vessel was filled with PBS 6.6 and maintained at 37 °C ± 0.5 while stirring at 50 rpm. 5ml samples were collected at predetermined time intervals and replaced with an equal volume of PBS 6.6. Flurbiprofen concentration was determined by UV spectrophotometer. (Table 6).

Measurement Of Mechanical Property

Tensile Strength Tensile strength (T.S.) gives indication of strength and elasticity of the film.

Tensile Strength (kg/cm²) = Force at Break (kg) / (Initial cross - Sectional area of sample) (cm²).

Percent elongation at Break

percent elongation at Break =

Increase in length (cm) x 100 / [Original length (cm) x {Cross - Sectional area} (cm²)].

Method of analysis as per IS: 2508-1984.

RESULT AND DISCUSSION

Drug estimation

Calibration curves of flurbiprofen in phosphate buffer (pH 6.6) solutions were obtained at λ_{max} 268.5 nm with a UV-VIS spectrometer (UV-1700, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 10-50 µg/ml. Analyses were done in triplicate.

Weight uniformity:

Drug loaded patches (1 x 1 cm²) were tested for uniformity of weight. The patches were found uniform.

The average weight of the patch found was about 18.23 mg.

Folding endurance: Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain films and drug loaded films.

Surface pH: The surface pH of all formulations was within + 0.5 units of the neutral pH and hence no mucosal irritation were expected and ultimately achieve patient compliance.

Content uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 88 to 94 %.

Swelling Index : All the films hydrated very quickly, & reached 80% hydration after just few minutes. Maximum hydration (92-98%) was obtained with formulations containing NaCMC film code BF1 to BF4.

Films containing HPMC K15M showed a slightly lower hydration of 83-86%. These results inferred that NaCMC films exhibited higher capacity of water uptake than HPMC films as expected.

Fragmentation was already evident at 100 minute when HPMC instead of NaCMC was employed. The highest losses were observed for films containing HPMC as mucoadhesive polymer; for some of these films fragmentation was so high that it was not possible to recover and handle the film from the PBS 6.6, even immediately after the beginning of the experiment (BF8). This higher fragility of the HPMC films might be due to the larger swelling in water of this polymer with respect to NaCMC. The consequence could be the formation of empty spaces within the film matrix that could make this structure less resistant to mechanical stresses. (Table-4)

Table 1. Different concentration of polymer used in Buccal film formulation.

Formulation number	PEG (mg)	PVP (mg)	Sodium CMC (mg)
BF1	1000	-	700
BF 2	1000	-	300
BF 3	-	1000	300
BF 4	-	1000	700

Table 2. Different concentration of polymer used in buccal film formulation.

Formulation number	PEG (mg)	PVP (mg)	HPMC K-15(mg)
BF 5	1000	-	700
BF 6	1000	-	300
BF 7	-	1000	300
BF 8	-	1000	700

Table 3. Muco-adhesive time of different films.

S.no	Muco-adhesive Film Code	Muco-adhesive time(Hour)
1	BF1	3.5
2	BF2	4:40
3	BF3	5
4	BF4	4
5	BF5	6
6	BF6	5.15
7	BF7	5:30
8	BF8	6

Table 4 percent hydration ,matrix erosion tensile strength and drug release of selected buccal films.

S. no	Percent Hydration	Percent matrix erosion	Tensile strength	Percent elongation at break	Percent drug release
BF1	95.68	84.36	14.3	7.2	61
BF4	97.91	85.50	95.3	16.0	61
BF5	93.48	89.68%	16.1	4.0	63
BF8	85.90	94.31	3.0	2.0	65

Table 5 Data treatment of different films

Release	BF1	BF4	BF5	BF8
Zero Order	0.9112	0.9112	0.9142	0.9137
First Order	0.9572	0.2498	0.2364	0.2237
Higuchi	0.9607	0.9678	0.97	0.9683
Korsmeyer	0.5181	0.5278	0.5561	0.5755

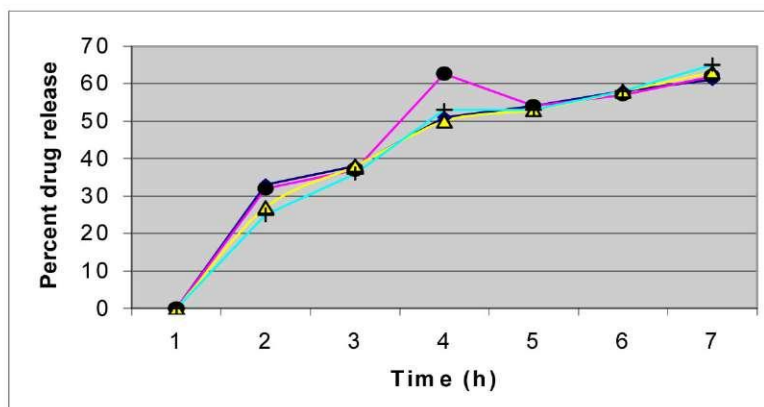
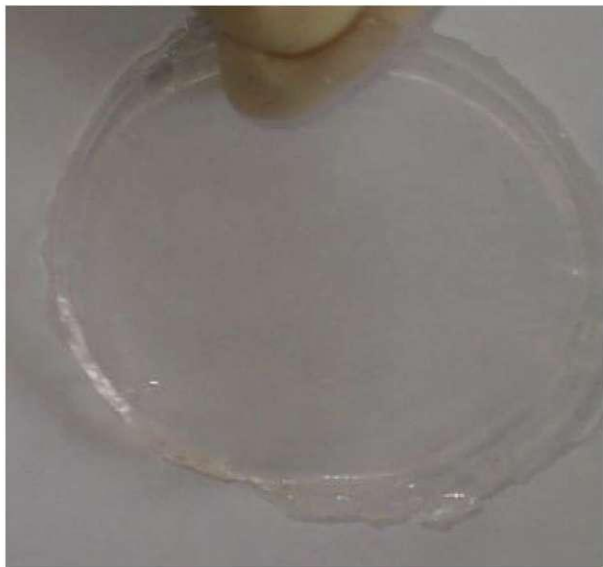
Figure 1 Percent drug released of the optimized buccal films

Figure 2 Prepared Buccal film.**Ex vivo mucoadhesive time**

Film mucoadhesion times varied from 3 to 6.5h BF8 showed the highest adhesion time whereas the films from BF1 showed the lowest mucoadhesion time.

This difference depends upon several factors that affect the effectiveness of such a formulation. First of all, the use of NaCMC favors hydration and the outward diffusion of the drug from the film matrix. Moreover, NaCMC, due to its solubility in water, results less effective as mucoadhesive polymer and it was demonstrated by the already cited lower mucoadhesion times of BF1. In fact, when using HPMC, mucoadhesion time always resulted high, because the polymer although manifesting decisively higher swelling is less water affined and hence tends to retain its structure better than NaCMC that, in turn, is better dissolved. Another important factor to be considered is the kind of film forming polymer used for the film preparation and the goodness and homogeneity of the polymer solution mixtures.(Table-3)

Tensile strength and Elongation at break

Measurement of mechanical property for different films resulted tensile strength between 3-95.3 kg/cm² and percent elongation at break between 6-16% that indicated strength of different prepared films for delivery of Drug .Tensile strength and Elongation at break showed by Batch code BF4 was 95.3kg/cm² and 16%.which was good among all the batches prepared by film casting method.(Table-4)

***In vitro* drug release**

In vitro drug release of prepared film showed that Flurbiprofen was rapidly released during the first 1h (30%), and the release was completed after 6 h and 30 min. % drug release after 6 h. was found out to be 62% for film code BF1 and for film code BF4, and BF5 found to be 63% (Table 4).we also evaluated all the data of drug released of batches and it showed that prepared buccal films follows Higuchi pattern of drug release. (Table-5)

CONCLUSION

On the basis of the results obtained in terms of hydration, mucoadhesion time and % matrix erosion, the film containing PVP and NaCMC (BF4) was selected for its characteristics that resulted suit formulations. Hence, this film was loaded with a anti-inflammatory drug, such as Flurbiprofen to test its behavior as carrier for Flurbiprofen sustained release in the oral cavity. For this purpose, Flurbiprofen containing film was prepared and tested for *In vitro* drug release. *In vitro* release profile showed a burst effect of the drug during the first 1 h (30%), followed by a more sustained pattern. The Flurbiprofen concentration in the film was resulted 50 mg/cm² drug release after 6 hr. was found out to be 62% for film code BF1 and for film code BF4, and BF5 found to be 63%.

Optimized batch BF4 was selected as best batch and loaded with model anti inflammatory drug Flurbiprofen, it showed Percent hydration between, 95% and 97.93% and matrix erosion between 85.24% and 85.52% this indicated that NaCMC films exhibited higher capacity of water uptake then HPMC films

Mucoadhesive time for film BF4 of 4 h. indicate moderate mucoadhesive time and *in vitro* release of 63% is suitable parameter for development of mucoadhesive buccal film of Flurbiprofen.

The main advantage of this formulation is that it contain a lower drug dose i.e. 50mg/cm² sufficient for therapeutic effect as it is located directly on the site of inflammation, if compared to traditional systemic therapies. Moreover this buccal film is very tolerable and comfortable because it is non-irritant and may be preferred over adhesive tablet in terms of elasticity, flexibility and capability to protect the wounded or inflamed surface.

REFERENCES

1. Silvia R., Giuseppina S, Caramella C. Buccal Delivery Systems for Peptides: Recent Advances. *American Journal of Drug Delivery* 2005; 3: 215-225.
2. Edith M, Donald EC and Claus ML . Bioadhesive Drug Delivery Systems. Marcel Dekker Inc., New York,1999, 541-562.
3. Jones DS, Woolfson AD, Brown AF. Textural analysis and flow rheometry of bioadhesive, antimicrobial oral gels. *Pharm*1997; 14 : 450–457.
4. Guo JH . Bioadhesive polymer buccal patches for buprenorphine controlled delivery: Formulation *in vitro* adhesion and release properties. *Drug Dev. Ind. Pharm*1994; 20:2809-2821.
5. Coute Ergos A, Maitani Y, Veillard M, Machida Y and Nagai T. Combined effects of pH, cosolvent and penetration enhancers on the *in vitro* buccalabsorption of propranolol through excised Hamster cheek pouch. *Int. J. Pharm*1992; 84: 117-128.
6. Pavankumar GV, Ramakrishna V, William J and Konde A. Formulation and evaluation of buccal films of salbutamol sulphate. *Ind. J. Pharm. Sci.*, 2005;2: 160-164.
7. Patil JS , Rao KP. Design and evaluation of mucoadhesive buccal patches of diclofenac sodium. *Ind. J. Pharm. Sci*2003; 4: 420-422.
8. Thimmasetty J, subrahmanyam CVS, Manish kumar DS, Manjunath K and Shivanand K. Design and evaluation of fexofenadine HCl buccal mucoadhesive patches. *Biomed*2007; 2: 73-83.
9. Peh KK, Wong CF. Polymeric films as a vehicle for buccal delivery: swelling, mechanical and bioadhesive properties. *J. Pharm. Sci* 1999; 2: 53–61.
10. Periolia L, Ambrogia V, Fausta A. et al, Development of mucoadhesive patches for buccal administration of ibuprofen. *Journal of Controlled Release*2004; 99: 73– 82.
11. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. *Ind J. Pharm Sci* 2008;70:43-48
12. Nafee NA, Ismail FA, Boraie NA, Mortada LM, Mucoadhesive buccal patches of miconazole nitrate: *in vitro/in vivo* performance and effect of ageing. *Int J Pharm* 2003;264:1-14.
13. Semalty A, Bhojwani M, Bhatt GK, Gupta GD, Shrivastav AK. Design and evaluation of mucoadhesive buccal films of diltiazem hydrochloride. *Indian J Pharm Sci* 2005;67:548-52.
14. Patel R S, Poddar S S. Development and Characterization of Mucoadhesive Buccal patches of Salbutamol Sulphate. *Current Drug Delivery* 2009; 6: 140-144.
15. Han R., Fang J, Sung KC, Hu OYP. Mucoadhesive buccal disks for novel nalbuphine prodrug controlled delivery: effect of formulation variables on drug release and mucoadhesive performance. *Int. J. Pharm* 1999; 177 : 201–209 .
