Formulation and Evaluation of Buccal Patches of Diclofenac Sodium

Shubhra Pandey

Abstract: Bilayerd films were prepared by solvent casting technique using different concentration of two polymers namely, sodium alginate and pectin. The backing membrane was prepared by using sodium alginate. The drug containing layer was prepared by using pectin. Different concentrations of plasticizers and permeation enhancers were added. Prepared films were evaluated for surface properties, weight variation, thickness, folding endurance, surface pH, drug content, swelling index and in vitro release. The release kinetics indicated first order release of drug from all formulation.

Keywords: Buccal mucosa, buccal patch, diclofenac sodium, buccal delivery, sodium alginate, pectin

1. INTRODUCTION

Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which included adhesive tablets, gels, ointments and more recently films. Buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva. Moreover, the buccal film is able to protect the wound surface, thus reduce pain and also could treat oral diseases more effectively. Diclofenac is 100% absorbed after oral administration compared to IV administration as measured by urine recovery. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available.

• *Shubhra Pandey*
Meerut Institute of Engineering &Technology, Meerut

When Diclofenac Sodium extended-release is taken with food, there is a delay of 1 to 2 hours in the Tmax and a two-fold increase in Cmax values. The extent of absorption of diclofenac, however, is not significantly affected by food intake.

1.1 Physical Description of Oral Cavity

The oral cavity can be divided into two regions; the outer oral vestibule which is bounded by lips and cheeks and the oral cavity itself. The borders being formed by the hard and soft palates, the floor of the mouth and the pillars of the fauces and tonsils. Virtually all of the membranes that line the oral cavity could potentially be used for systemic drug delivery. However each region possesses different properties and characteristics and therefore requires different approaches in the design and formulation of suitable delivery systems.

1.2 Buccal Mucosa: Physiology

The various regions (sublingual, buccal, gingival) of the oral mucosa vary anatomically and physiologically. Due to these differences

in structure as well as function, considerable variation exists in permeability among these regions. This difference could make one region more or less suitable for delivery of a particular drug. In addition, just as the microstructure and function of the integumentary system differs between and within species, the buccal mucosa also exhibits some dissimilarity. The oral mucosa is comprised of an outer layer of stratified squamous non-keratinized epithelium. Below the epithelium lies a basement membrane, a lamina propria, and submucosa, respectively oral epithelium is very similar to epithelium found elsewhere in the body. It consists of a basal cell layer, several intermediate layers, and a superficial layer from which cells shed. There are approximately 40-50 cell layers that make up the buccal epithelium, with a cellular turnover time of 5-6 days. In humans, dogs, and rabbits, the buccal mucosa measures 500-800 μm in thickness. Other areas of the oral epithelium (gingiva, hard and softpalates, floor of mouth) vary in size.

Likewise, the composition of the epithelium varies in accordance with location. Areas that endure mechanical stress such as the gingiva and hard palate, like the epidermis, are keratinized. In contrast, the buccal mucosa, sublingual region, and the soft palate are not keratinized. Large quantities of protein are present in the cells of both keratinized and non-keratinized epithelium. Keratinized regions of the mucosa contain large amounts of acylcermides and ceramide, while the more permeable non-keratinized mucosal regions (buccal, floor of mouth) contain smaller quantities of lipid. The basement membrane forms the boundary between the lamina propria and the basal layer of the epithelium. Composed of collagen, the basement membrane is thought to provide support and adherence between the epithelium and the lamina propria, and to form a mechanical barrier to cells and some large molecules across the mucosa. The lamina propria lies underneath the basement membrane and consists of a continuous sheet of collagenous connective tissue and elastic fibers. The capillaries and nerve fibers that supply the mucosa are present in this region.

2. MATERIALS

Diclofenac sodium was obtained as a gift sample from Leroi Pharma, Roorki. Pectin, Sodium alginate, Polyethylene glycol 400, Polyethylene glycol 600, Calcium chloride, Sodium glycodeoxycholate, Sodium taurocholate, Glycerin, Menthol were obtained from Central drug house (C.D.H) Delhi, India. All other reagent and chemicals were of analytical grade.

3. FORMULATION DEVELOPMENT

3.1 Preparation of Bilayered Films

Bilayerd films were prepared by solvent casting technique using different concentration of two polymers namely, sodium alginate and pectin. The backing membrane was prepared by dissolving sodium alginate in distilled water as solvent and glycerin as plasticizer.

The plasticized sodium alginate solution was poured into a petridish and solvent was allowed to evaporate at room temperature by covering the petridish with inverted glass funnel, to avoid blistering effect on dried films. The drug containing layer was prepared by dissolving pectin in distilled water. Different concentrations of plasticizers and permeation enhancers were added. This solution was poured onto the dried sodium alginate layer (i.e. backing layer) and allowed to dry at room temperature overnight. The sodium alginate layer of the dried film was exposed to calcium chloride solution to cross-link the film surface and to provide unidirectional release.

4. EVALUATION

4.1 Buccal Absorption Test

Diclofenac sodium solution 2 mg was prepared in 20 mL phosphate buffer (pH 7.4). This solution was placed in the volunteer's mouth and with the movement of cheeks and tongue, the solution was circulated for about 300-400 times round the mouth for 5 min. Then the solution was expelled. The volunteers were instructed to quickly rinse the mouth with buffer solution (10 mL) for 10 sec and expelled the rinsing solution. The expelled solutions were combined and used for analysis after necessary dilutions. Appropriate blank solutions were simultaneously prepared. The drug content was analyzed at λmax 277 nm.

4.2 Thickness Uniformity

The thickness of each film was measured using thickness tester (screw gauge) at different positions of the film and the average was calculated.

4.3 Swelling Studies

A drug-loaded film of 1 cm2 was weighed on a preweighed cover slip. It was kept into a petridish and 50 mL of phosphate buffer (pH 7.4) was added. After every two min, the cover-slip was removed and weighed again. The difference in the final and initial weight gave the weight increase due to absorption of water and swelling of film.

4.4 Surface pH

For the surface pH determination, the patches were left to swell for 2 h on the surface of the agar plate, prepared by dissolving 2% (w/v) agar in warmed phosphate buffer of pH 7.4 under stirring and then pouring the solution in to the petridish till gelling at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch. The mean of three readings was recorded.

4.5 Folding Endurance

The folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance.

4.6 Drug Content Uniformity

The films were tested for the content uniformity. A film of size 1 cm2 was cut and placed in a beaker and 20 mL of phosphate buffer pH 7.4 solutions was placed. The contents were warmed to dissolve the film. The contents were transferred to a volumetric flask. The absorbance of the solution was measured against the corresponding blank solution at 277 nm.

4.7 In Vitro Release Study

A film of 1cm2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 7.4). This slide was kept at an angle of 450C in a 250 mL beaker containing 100 mL of phosphate buffer (pH 7.4) solution. The beaker was kept on magnetic stirrer and temperature was maintained at 370C. Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 1 mL of sample was withdrawn using a graduated pipette. The slide was quickly reintroduced into the beaker and 1 mL of the buffer was replaced immediately and the beaker was kept covered with a petridish to prevent evaporation of the fluid. The samples were taken at predetermined intervals and analysed for drug content at 277 nm. The release studies were conducted for three times and average was determined.

.

5. RESULTS AND CONCLUSION

The table 1.1 shows cumulative % of drug released of different batches and figure 1.1 shows its release graph. To find out the mechanism of drug release, and also to verify the fact that whether diffusion is Fickian or non-Fickian, the in vitro dissolution data of the ideal batches was plotted according to Peppas' equation, in which log cumulative percentage of drug released was plotted against log time (fig 1.2). The in vitro release of diclofenac sodium from films F1, F2, F3, F4 and F5 were about 86.44, 93.11, 95.32, 93.43 and 87.71 respectively, with in 3 h, in phosphate buffer, pH 7.4. The release kinetics indicated first order release of drug from all formulations. All the log-log plots, except those of F1 and F4 batches had slope values less than 0.5, indicating that the release of drug occurred following Fickian diffusion without swelling. In case of F1 and F4, the mechanism of release was found to be diffusion with swelling. Based on the results of all above studies it can be concluded that the developed mucoadhesive buccal patches of diclofenac sodium can sustain the drug release, improve the bioavailability of the drug and overcome the first pass metabolism of the drug.

TABLE 1.1
IN VITRO RELEASE OF DICLOFENAC SODIUM FROM FILMS

Time (min)	Cumulative % of drug released (Mean±SD)*				
	F1	F2	F3	F4	F5
0	-	-	-	-	-
5	11.89 ±2.35	16.35±5.27	18.05±1.20	15.56±1.52	18.53±1.77
10	19.11±3.25	25.15±9.55	26.71±0.22	22.48±2.06	26.48±4.17
15	27.44±2.65	35.89±9.04	33.73±1.71	28.10±2.43	37.01±2.48
30	45.51±5.08	46.08±6.00	41.10±1.68	40.81±3.11	49.11±5.60
45	57.82±3.91	57.84±6.06	52.27±1.27	63.83±3.00	62.78±7.65
60	71.96±2.86	70.88±6.64	62.84±1.47	70.01±0.71	74.51±3.13
90	81.09±3.69	78.51±4.47	77.77±1.28	82.18±2.48	79.81±1.07
120	85.58±2.35	89.41±3.30	90.42±1.69	90.13±0.49	84.63±3.00
150	86.23±3.33	92.17±0.66	95.24±1.47	92.12±0.61	86.58±1.53
180	86.44±3.68	93.11±0.92	95.32±1.46	93.43±1.38	87.71±1.74

*n=3

FIGURE 1.1
IN VITRO RELEASE OF DICLOFENAC SODIUM FROM FILMS

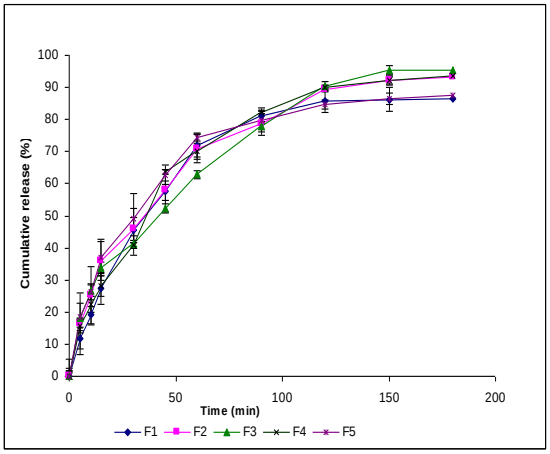
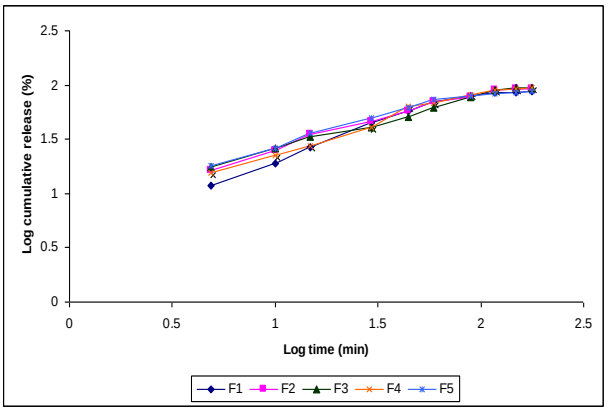


FIGURE 1.2
PEPPAS PLOTS FOR DRUG RELEASE DATA FROM VARIOUS BATCHES OF BUCCAL films



6. REFERENCES

1. Shojaei AH. Buccal mucosa as a route for systemic drug delivery. J Pharm Pharmaceut Sci. 1998; 1: 15-30.
2. Deirdre FV. Pharmacokinetics of albuterol and butorphanol administered intravenously and via a buccal patch. M Pharm Thesis. 2003.
3. Beckett AH, Moffat AC. Influence of alkyl substitution in acids on their performance in the buccal absorption test. J Pharm Pharmacol. 1968; 20: 239-247.
4. Wani MS, Parakh SR, Dehghan MH, Polshettiwar, Chopade VV, Pande VV. Current status in buccal drug delivery. www.pharmainfo.net. 2007.
5. Park K, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery methods to study bioadhesion. Int J Pharm. 1984; 19: 107-127.
6. Thirawong N, Nunthanid J, Puttipipatkhachorn S, Sriamornsak P. Mucoadhesive Properties of Various Pectins on Gastrointestinal Mucosa: An in vitro evaluation using texture analyzer. Eur J Pharm Biopharm. 2007; 67: 132–140.
7. Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capuccella M, Rossi C. Development of mucoadhesive patches for buccal administration of ibuprofen. J Control Release. 2004; 99: 73-82.
8. Consuelo ID, Falson F, Guy RH, Jacques Y. Ex vivo evaluation of bioadhesive films for buccal delivery of fentanyl. J Control Release. 2007; 122: 135–140.
9. Miller NS, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery.

Advanced Drug Delivery Reviews. 2005; 57: 1666–1691.

10. Senel S, Hincal A. Drug permeation enhancement via buccal route: possibilities and limitations. J Control Release. 2001; 71: 133–144.
11. Nozaki Y, Ohta M, Chien YW. Transmucosal controlled systemic delivery of isosorbide dinitrate: in vivo/in vitro correlation. J Control Release. 1997; 43: 105-114.
12. Semalty M, Semalty A, Kumar G. Formulaion and characterization of mucoadhesive buccal films of glipizide. Int J Pharm. 2008; 70: 43-48.