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Formulation and Evaluation of Diclofenac Sodium Polymeric Buccoadhesive Film

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A B S T R A C T

In this study the attempt was made for preparation of buccoadhesive films of Diclofenac sodium by using bioadhesive polymers like sodium alginate and PVP K-30 which will improve oral bioavailability by sparing the drug from first pass metabolism and reduce the dosing frequency. Drug: HPβ-CD complex was incorporated in the buccoadhesive film to improve the dissolution of poorly water soluble drug from the polymeric film. The Preformulation study was carried out using raw materials. Buccoadhesive films were formulated by using solvent casting method. Films were prepared by varying the percentage of sodium alginate and PVP K-30. All prepared films were evaluated for physical characterization, in vitro swelling, in vitro bioadhesion, in vitro drug release, in vitro drug permeation. From the prepared film F3 was selected as it showed appropriate swelling, duration of bioadhesion, drug release and permeation. Results indicated that the release rate from film F3 best fitted Korsemeyer and Peppas (R^2=0.9996), followed by zero order (R^2=0.9963) and then square root t kinetics (0.9075). The value on n =1.1655 indicated that release from film followed Super Case II transport. The optimized film was subjected to stability study and histopathological examination on porcine buccal mucosa. Also the film was stable in human saliva, no color change was observed. Histo-pathological studies revealed no effect on the mucosal histology after application of film for 10 hrs. The optimized formulation showed better stability under accelerated stability conditions for three months.

Keywords: Buccoadhesive films, Bioadhesion, Bioavailability, Diclofenac, HPβ-CD complex.

A R T I C L E I N F O

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1. Introduction

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Oral mucosa is relatively permeable with a rich blood supply. Furthermore, oral transmucosal drug delivery avoids first pass effect and provides facile removal of dosage form in case of need. Within the oral mucosal cavity, delivery of drugs is classified into three categories: (A) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; (B) buccal delivery, which is drug administration through mucosal membranes lining the cheeks (Buccal mucosa); and (C) local delivery, which is drug delivery into the oral cavity. Two of the major limitations associated with buccal route of administration are the lack of dosage form retention at the site of absorption and the low flux, which results in low drug bioavailability [1]. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems in the form of adhesive patches, adhesive films [2], adhesive tablets [3] and buccal gels [5]. For those drugs that penetrate the oral mucosal membranes slowly or in- completely, one strategy can be used, that is the co administration with a penetration enhancer [5].

Bucco-adhesives have long been employed to improve the bioavailability of drugs undergoing significant hepatic first pass metabolism [6] and control their release of drugs from hydrophilic matrices [7]. Drug buccal administration, on the other hand, is highly acceptable by patients and the Diclofenac sodium is an example of drugs, which are subject to first pass metabolism, since only 50–60% of the drug reaches the systemic circulation in the un-changed form. Moreover, peroral administration of Diclofenac sodium results in gastro intestinal disturbances ranging from abdominal discomfort, nausea, vomiting to serious gastrointestinal bleeding or peptic ulcers. Since the buccal route bypasses the hepatic first pass effect, the dose of Diclofenac sodium could be reduced [8]. The main objective in this work is to formulate diclofenac sodium bucco-adhesive films that could be applied to the buccal mucosa giving systemic effects to decrease gastric irritation and avoid the first pass effect. The products prepared were evaluated through *in vitro* release and *in vivo* testing of their adhesive properties.

2. Materials and Methods

Materials: Diclofenac sodium was obtained as a gift sample from the Halmak pharmaceuticals Pvt. Ltd, Secunderabad. Sodium alginate, PVP K-30, Hydroxypropyl β cyclodextrin obtained commercially from S.S.R Enterprises, Tirupati, Andhra Pradesh, India.

Preparation and development of buccoadhesive film

Films containing different polymers were prepared by the solvent casting method. First the rate controlling layer of ethyl cellulose was cast and then drug containing polymeric layer was cast over it.

Rate controlling layer

A rate controlling membrane was cast on glass plate using 3% ethyl cellulose (20cps) by incorporating dibutyl phthalate (30 %w/w of ethyl cellulose) as plasticizer.

Drug containing polymeric layer

Films were prepared by varying the percentage of sodium alginate and PVP K-30. Polymer solution 10 %w/w was prepared and kept overnight to allow complete swelling of polymer. Propylene glycol (15 %w/w of polymer) was added as plasticizer to the polymeric solution and to it drug - HP β-CD complex (equivalent to the drug needed for the area of glass mould such that 3.14 cm^2 film contains 12.5 mg of drug) was added. These films were dried at room temperature for 12 hrs.The films were observed and checked for possible imperfections upon their removal from the glass plate. They were stored in a desiccator till the evaluation tests were performed. These new films were examined in order to select the film having the best characteristics. Formulated patches were subjected to weight variation, thickness, and content uniformity tests. The composition of all films is given in table 1.

Table 1: Composition of the prepared buccoadhesive film.

Sr. No.	Formulation	% of Sodium alginate	% of PVP K-30
1	F1	100	0
2	F2	80	20
3	F3	70	30
4	F4	50	50
5	F5	30	70
6	F6	20	80
7	F7	0	100

Evaluation of buccoadhesive film [9]

All the prepared buccoadhesive films were evaluated for various parameters.

Film thickness: The thickness of patches was measured at three different places using Tablet tester and mean values were calculated. Results were depicted in table 2.

Film weight Films of specified area (3.14 cm^2) were cut and were weighed individually using Electronic weighing balance and the average weight was calculated. Results were depicted in table 2

Folding endurance: Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance. Results were depicted in table 2.

Tensile strength

Tensile strength of the prepared bucco adhesive films were determined in order know the strength of the film. Results were depicted in table 2

Swelling study

Buccal film was weighed (W1), placed in a 2% agar gel plate and incubated at 37 ± 1°C. At regular one-hour time intervals (to 2 h), the film was removed from the Petridish and excess surface water was removed carefully using the filter paper. The swollen film was then reweighed (W2) and the swelling index (SI) were calculated.

Characterization of complex

The drug content was determined by taking the complexes equivalent to 25 mg of drug and dissolving in phosphate buffer 6.8 containing 2% sodium lauryl sulphate. The absorbance of this solution was taken against phosphate buffer containing 2% sodium lauryl sulphate as blank at 242.4 nm using UV visible spectrophotometer (Model No. UV 2401 PC, Shimadzu Corporation, Singapore). Drug content per 100 mg of complex was determined.

***In-vitro* drug release [10]**

The drug release was determined using USP dissolution test apparatus Type II thermostated at 37±1°C and stirred at rate of 50 rpm. Sink condition was maintained throughout the study. Each film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be released only from upper face. Slide was immersed in vessel containing 500 ml simulated salivary solution (pH 6.8). Aliquots of 5 ml were withdrawn at different intervals and replaced with equal volume of dissolution medium. The samples were diluted suitably and were analyzed spectrophotometrically at 242.4 nm and cumulative amount of drug release at various time intervals was calculated. (Table 3).

***In-vitro* permeation studies [10]**

The permeation study was carried out by using Keshary-Chein diffusion cell. The method used porcine buccal mucosa as the model mucosal membrane. The membrane was placed between the donor compartment (salivary pH 6.8) and the reservoir compartment (isotonic phosphate buffer pH 7.4, blood pH) to mimic the physiological conditions. The diffusion cell was thermostated at 37±1°C. One ml of sample was withdrawn from receptor compartment at interval of 1, 2, up to 12 hr and replaced with same amount of buffer, filtered through Whatmann filter paper no.42. The sample was diluted suitably and analyzed spectrophotometrically for determining the amount of Diclofenac sodium permeated. *In vitro* permeation was carried out in triplicate.

Kinetic Treatment to dissolution data

Analysis of drug release from buccoadhesive film was performed with a flexible model that can identify the contribution to overall kinetics, mechanism of drug release and the dissolution data obtained for optimized formulation was treated with the different release kinetic equations.

Stability study in human saliva [11]

The stability of buccoadhesive film was performed in natural human saliva using the optimized film (F3) selected on the basis of swelling, bioadhesion, drug release and drug permeation.

Histological examination on porcine buccal mucosa [12]

Histomorphological analyses were performed to evaluate the pathological changes occurring in cell morphology and tissue organization. For analysis the epithelial tissues were fixed in 10% neutral-buffered formalin for 2 h, washed in water for 1 h, dehydrated in graded ethanol (60%, 80%, 90%, 95%, and 100%) and, after permeation in xylene, embedded in paraffin using the standard procedures.

Stability study

The film F3 was selected as an optimized film and the stability study was carried out at accelerated condition of 40 ± 2^0C, 75 ± 5% RH conditions for period of three months. Film was wrapped using aluminium foil and packed in ambered color screw cap bottle and put at above specified condition in incubator for 3 months. After each month, film was analyzed for physical characteristics, bioadhesion properties, duration of bioadhesion and the in vitro drug release study.

3. Results and Discussion

The Pre-formulation study was carried out using raw materials. Buccoadhesive films were formulated by using solvent casting method. Films were prepared by varying the percentage of sodium alginate and PVP K-30. All prepared films were evaluated for physical characterization, in vitro swelling, in vitro bioadhesion, in vitro drug release; in vitro drug permeation. The drug content in the prepared complex was found to be 97.08% (Table 2).FTIR of drug, HP β-CD and drug: HPβ-CD complex showed that there was no interaction between drug and HPβ-CD. The results of XRD revealed that the drug was present in amorphous state in the complex.

The prepared films were smooth in appearance, uniform in thickness, mass and drug content. The film exhibited good folding endurance (more than 150 except film containing PVP alone). Film thickness ranged from 0.52 -1.17 mm and film weight ranged from 37.76 -42.56 mg. From the prepared film, F3 was selected, as it showed appropriate swelling, duration of bioadhesion, drug release and permeation. Results indicated that the release rate from film F3 best fitted Korsemeyer and Peppas (R^2=0.9996), followed by zero order (R^2=0.9963) and then square root t kinetics (0.9075).

The value on n =1.1655 (Table 4) indicated that release from film followed Super Case II transport. The optimized film was subjected to stability study and histopathological examination on porcine buccal mucosa. Also the film was stable in human saliva, no color change was observed. Histopathological studies revealed no effect on the mucosal histology after application of film for 10 hrs. The optimized formulation showed better stability under accelerated stability conditions for three months.

Table 4: Kinetic treatment to dissolution data of F3

Equation	Variable	
	R^2	n
Zero order	0.9963	--
Korsemeyer and Peppas	0.9996	1.1655
First order	0.9025	--
Higuchis (Square root of time)	0.9075	--

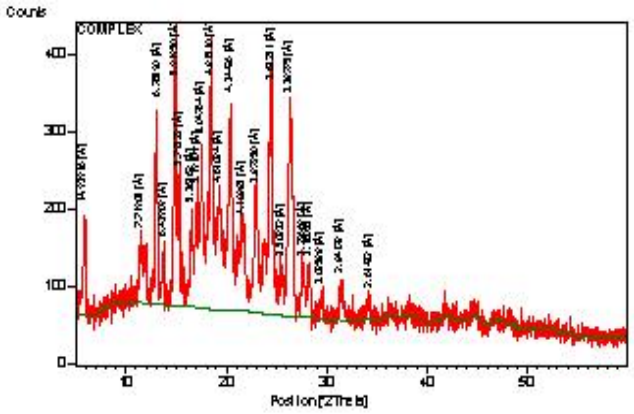


Figure 1: XRD of drug-HPβ-Drug complex

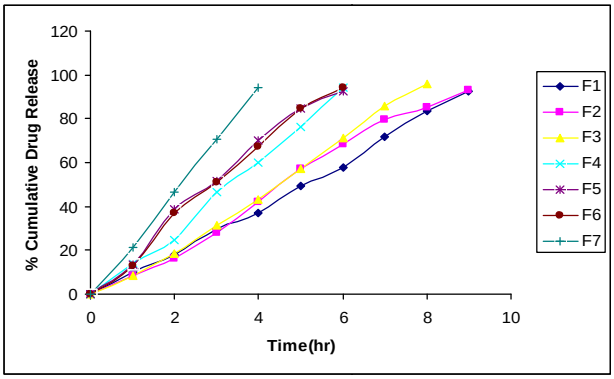


Figure 4: *In-vitro* drug release from prepared buccoadhesive film

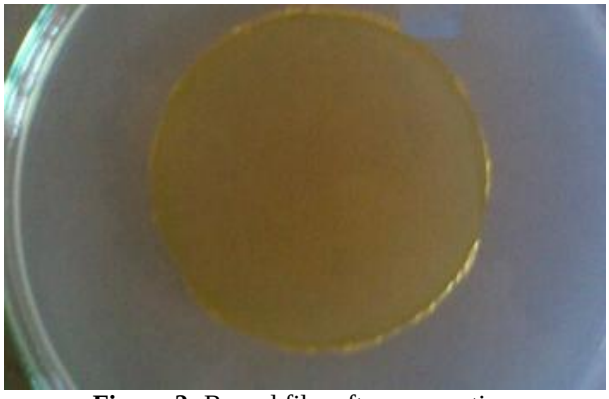
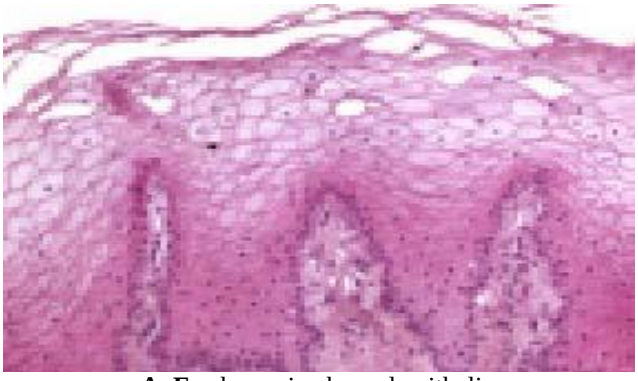
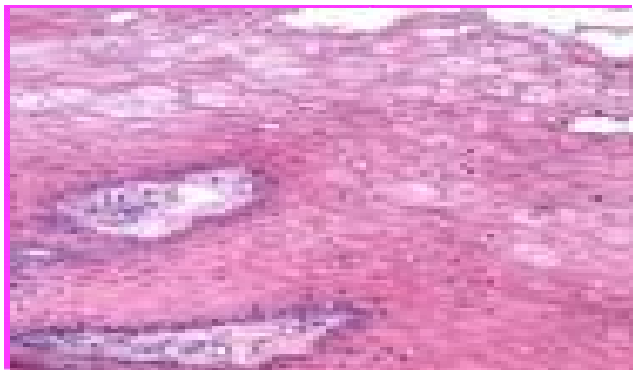


Figure 2: Buccal film after preparation

Figure 3: At the stage of swelling - buccal films



A. Fresh porcine buccal epithelium



B. Porcine buccal epithelium after application of F3 for 10hrs

Figure 5: Histopathological examination on porcine buccal mucosa

Table 2: Evaluation results of Folding endurance, surface pH and swelling index, tensile strength and drug content of the prepared buccoadhesive film

Sr. No.	Formulation	Folding Endurance	Surface pH	Swelling index	Tensile strength (M Pa)	Drug Content (%)
1	F1	188±16	7.1	48.47 ±0.947	6.556	95.02 ± 0.155
2	F2	176±12	6.8	49.13 ±1.244	6.231	95.26±0.395
3	F3	172±08	6.7	50.27 ±1.880	6.192	98.78±0.721
4	F4	161±12	7.0	54.15 ±0.410	5.623	94.06±0.282
5	F5	159±18	6.8	53.88 ±0.975	3.333	95.14±0.395
6	F6	155±04	6.9	53.78 ±0.473	3.225	96.46±0.480
7	F7	142±07	7.1	54.53 ±1.527	2.997	96.52±0.551

Table 3: *In Vitro* drug release from prepared buccoadhesive film

S. No.	Time (hr)	F1	F2	F3	F4	F5	F6	F7
1	0	0	0	0	0	0	0	0
2	1	10.13 ±0.510	8.28 ±0.680	8.55 ±0.64	14.07 ±0.275	13.3 ±0.185	12.63 0.182	21.15 ±1.324
3	2	17.78 ±1.123	16.17 ±0.321	18.46 ±0.324	24.49 ±1.077	38.55 ±0.598	36.77 ±0.860	46.28 ±0.311
4	3	29.47 ±0.923	27.92 ±0.629	31.54 ±0.762	6.79 ±1.153	51.71 ±1.210	50.85 ±1.181	70.81 ±0.681
5	4	36.97 ±0.836	41.98 ±1.136	43.21 ±0.46	60.17 ±0.731	70.21 ±1.053	67.44 ±0.530	94.38 ±0.251
6	5	49.18 ±0.355	57.07 ±0.196	56.92 ±0.810	76.39 ±0.556	84.56 ±1.045	84.41 ±1.428	00
7	6	57.95 ±1.040	68.17 ±0.134	71.44 ±1.156	94.44 ±0.658	92.36 ±0.407	94.17 ±0.642	00
8	7	71.66 ±1.07	79.52 ±0.776	85.74 ±1.033	00	00	00	00
9	8	83.28 ±1.235	85.42 ±0.680	95.84 ±0.112	00	00	00	00
10	9	92.3 ±0.61	93.03 ±0.242	00	00	00	00	00

4. Conclusion

From the present investigation, it can be concluded that optimized muccoadhesive film of Diclofenac sodium with the combination of 70% sodium alginate and 30% PVP K-30 can meet the ideal requirements for buccal devices, which can be a good way to bypass the extensive hepatic first pass metabolism.

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6. References

[1] Samaligy MS, Yahia SA, Basalious EB. Formulation and evaluation of diclofenac sodium buccoadhesive discs. Int. J. Pharm. (**2004**) 286: 27-39.

[2] Khoda Y, Kobayashi H, Baba Y, Yuasa H, Ozeki T, Kanaya Y, Sagara E. Controlled release of lidocaine hydrochloride from buccal mucosa adhesive films with solid dispersion. Int. J. Pharm. (**1997**) 158: 147–155.

[3] Nozaki Y, Ohta M, Chien YW. Transmucosal controlled systemic delivery of isosorbide dinitrate, in vivo/in vitro correlation. J. of Con. Rel. (**1997**) 43: 105-114.

[4] Shin SC, Bum JP, Choi JS. Enhanced bioavailability by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits. Int. J. Pharm. (**2000**) 209: 37-43.

[5] Aungst BJ, Rogers NJ. Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. Int. J. Pharm. (**1989**) 53: 227-235.

[6] Choi HG, Kim CK. Development of Omeprazole buccal adhesive tablets with stability enhancement in human saliva. J. Con. Rel. (**2000**) 68: 397-404.

[7] Singh B, Ahuja N. Development of controlled-release buccoadhesive hydrophilic matrices of diltiazem hydrochloride, optimization of bioadhesion, dissolution, and diffusion parameters. Drug. Dev. Ind. Pharm. (**2002**) 28: 431-442.

[8] Sweetman SC, Martindale. The Complete Drug Reference. 33rd Ed., the Pharmaceutical Press (**2002**).

[9] Gupta A, Sanjay G, Roop KK. Measurement of Bioadhesive strength of mucoadhesive Buccal Tablets. Design of an *in vitro* Assembly. Ind. Drugs. (**1992**) 4: 152-155.

[10] Vamsi VY, Ramesh G, Chandra SK, In vitro dissolution profile, In vitro permeation studies. Acta. Pharm. (**2007**) 57: 185-196.

[11] Bhatt PP, Johnston TP. Evaluation of a mucoadhesive buccal patch for delivery of peptides, in vitro screening of bioadhesion. Drug Dev. Ind. Pharm. (**1998**) 24: 919-926.

[12] Choi H, Jung J, Yong CS, Rhee C, Lee M, Han J, Park K, Kim C. Formulation and in vivo evaluation of Omeprazole buccal adhesive tablet, J. Con. Rel. (**2000**) 68: 405-412.