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# Formulation and evaluation of mucoadhesive buccal films of Diclofenac Sodium

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## Abstract

Buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. A buccal film for systemic administration of diclofenac sodium has been developed using hydroxyl propyl methylcellulose, poly vinyl pyrolidone, glycerin, eudragit and ethanol by solvent casting method. The prepared films characterized by means of film thickness, swelling capacity, *in- vitro* adhesion, drug release, weight variation, folding endurance, etc. The *in vitro* release studies were conducted for diclofenac sodium patches in phosphate buffer-pH-6.6 solution. The mechanism of release is diffusion process followed by first order kinetics. The formulated patches exhibit drug release in the range of 76.92 to 92.12% in four hours.

***Keywords**:* Mucoadhesive film; Diclofenac sodium; First order kinetics; *In- vitro* release.

## Introduction

The quest for alternative modes of drug delivery to the ever-popular oral route of administration (Remington, 2005) has led to exploration of the various mucosa as possible delivery routes. The interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs impaired by the narrow absorption window in the gastrointestinal tract. Drug delivery (Agarwal *et al*., 1998) via the buccal route using bio-adhesive dosage forms (Ilango *et al*., 1997) offers such as novel route of drug administration. It is well known that the absorption (Goodman and Gillman, 2001) of therapeutic compounds from the oral mucosa provides a direct entry of the drug into the systemic circulation, therefore, avoiding the first-pass hepatic metabolism and gastrointestinal drug degradation (Tripathi, 2011), which is associated with oral administration. It has an excellent accessibility an expansion of smooth muscles and relatively immobile mucosa, suitable for administration of retentive dosage forms. It is well accepted by patients and is safe since the device can be easily administrated and even removed from the site of application stopping the input of drog whenever desired.

Diclofenac sodium is a potent non-steroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis and other rheumatic disorders (Tripathi, 2011). It poses a narrow therapeutic index due to short biological half-life. There is a substantial first pass metabolism, such that only about 50% of diclofenac is available systemically (Pai *et al*., 1998; Khanna *et al*., 1998). The physicochemical properties of diclofenac sodium and its short half-life make it a suitable candidate for administration by buccal route. In the current study, the films were prepared by solvent casting technique (Alka Ahuja *et al*., 1998; Saisivam et al., 2000), using good bio adhesive (Alka Ahuja *et al*., 1997; Ilango *et al*., 1997) polymers like HPMC (Hydroxy propyl methylcellulose) as major polymer and the effect of addition of co-polymers like PVP K-30 and Eudragit L-100-55 were studied. The *in-vitro* release studies were carried out by using dialysis-sac and further physical characteristics of the films were evaluated.

## Materials and Methods

Diclofenac sodium (Merck Index and Encyclopedia, 2001) was purchased from Nicholas

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*Table1*. Formulation of mucoadhesive buccal films of Diclofenac Sodium

| S.No. | Ingredients mg/ml | F1 | F2 | F3 | F4 | F5 |
|---|---|---|---|---|---|---|
| 1 | Diclofenac Sodium | 50 | 50 | 50 | 50 | 50 |
| 2 | HPMC | 300 | 300 | 300 | 300 | 300 |
| 3 | Polyvinyl pyrolidone | - | 50 | 100 | - | - |
| 4 | EudragitL-100-55 | - | - | - | 50 | 100 |
| 5 | Ethanol | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 |
| 6 | Glycerine | 0.12 | 0.14 | 0.14 | 0.14 | 0.16 |

Piramal. HPMC from S.D. Fine chem. Ltd., Mumbai. Poly venyl pyrolidine purchased from S.D fine Chem. Ltd., Mumbai. Eudragit L-100-55-Aurobindo pharma., Hydrabed. Glycerine from S.D Fine Chm. Ltd., Mumbai.

*Preparation of buccal mucoadhesive films*

Solvent casting method (Alka Ahuja *et al*., 1998; Saisivam *et al*., 2000) was followed in this study for preparation of buccal films. The films were observed for dispersion of drugs, flexibility and glossy structure. Based on the observations five formulations were developed and used for further analysis. The compositions of five were given in the table 1. Buccal films were prepared using polymer or polymer blends along with the drug and suitable solvents. 50mg of Diclofenac sodium, HPMC, ethanol were added for all the five formulations. Glycerin was used as a plasticizer-50 of w/w of polymer, and PVP was added in formulations F2 and F3. Eudragit was added in F4 and F5 respectively.

The prepared polymeric drug solution was poured on fabricated glass rings placed mercury substrate. 4.5ml of this solution was added in each of the glass rings. Drying was carried out under low temperatures. After complete drying, the films were having a diameter of 5.0 cm and were used throughout the work. The films were found to be smooth, flexible and could be cut to any desired size and shape.

*Reagents used*
*0.2M Sodium Hydroxide*

8g of sodium hydroxide dissolved and make upto1000ml with distilled water and dilute with distilled water to 1000ml.

*0.2M Potassium Dihydrogen Orthophosphate*

Dissolve 27.22g of Potassium dihydrogen ortho phosphate in distilled water again dilute it with distilled water to 1000ml.

*Preparation of phosphate bufferof ph 6.6*

To 250ml of 0.2M potassium dihydrogen ortho phosphate solution, 82ml of 0.2M sodium hydroxide solution was added and the volume was made up to 1000ml with distilled water.

*Preparation of standard stock solution*

Accurately weighed 100mg of Diclofenac sodium was dissolved in 100ml of phosphate buffer and with pH 6.6 to give 1000µg/ml.

*Determination of λ max*

The stock solution of Diclofenac sodium was scanned in shimadzu spectrophotometer in U.V range of 200-300 nm. Wavelength of 276 nm was selected and utilized for further studies in this work.

*Standard plot of Diclofenac sodium*

The stock solution, 1ml was pippeted out and diluted to 100ml. From the solution, 2,4,6,8, and 10ml were pipetted out in different 10ml Volumetric flasks and the volume was made up to the mark (10ml). The absorbance of the solutions

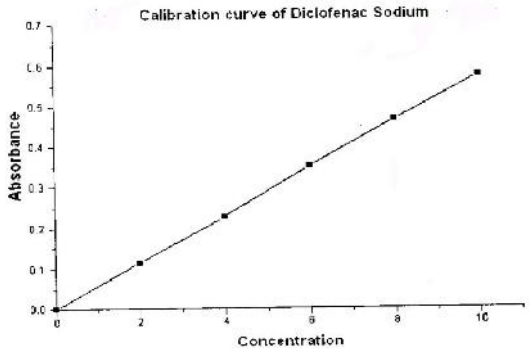


*Fig. 1.* Linearity curve for absorbance of Diclofenac sodium at 276nm against concentration

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was measured at 276nm (Table 2). Linearity curve is obtained (Fig.1).

*Table 2*. Absorbance of Diclofenac sodium at 276nm

| S.No | Concentration(µg/ml) | Absorbance |
|---|---|---|
| 1 | 0 | 0.000 |
| 2 | 2 | 0.115 |
| 3 | 4 | 0.227 |
| 4 | 6 | 0.350 |
| 5 | 8 | 0.465 |
| 6 | 10 | 0.575 |

## Results and Discussion

*Table 3*. Physical Evaluation of Buccal films Of Diclofenac sodium

| S.No | Formulation Code | Colour | Surface texture | Folding Endurance | Area ($cm^2$) | Thickness Mean | Drug Content |
|---|---|---|---|---|---|---|---|
| 1 | F1 | * | Very smooth | ++ | 19.625 | 0.64 | 98.50 |
| 2 | F2 | * | Smooth | ++ | 19.625 | 0.69 | 98.21 |
| 3 | F3 | * | Smooth | +++ | 19.625 | 0.73 | 97.35 |
| 4 | F4 | * | Smooth | ++ | 19.625 | 0.70 | 97.12 |
| 5 | F5 | * | Smooth | +++ | 19.625 | 0.75 | 96.98 |

*White - * Veryflexible- +++ Flexible - + +*

*Table 4*. Swelling Studies of Films

| Formulations | Initial wt of film in mg (W1) at time 0 mins | Final wt of the film (W2)in mg after 5 mins | Swelling Index (W2-W1)/W1 |
|---|---|---|---|
| F1 | 21 | 23 | 0.095 |
| F2 | 28 | 32 | 0.142 |
| F3 | 30 | 35 | 0.166 |
| F4 | 27 | 32 | 0.185 |
| F5 | 29 | 35 | 0.206 |

*Evaluation of buccal films of Diclofenac sodium*

1. *Physical appearance*: Includes visual inspection of films (Table 3).

2. *Surface texture*: It can be evaluated by touching the films (Table 3).

3. *Folding endurance*: It can be determined by number of times, the film could be folded at the same place without breaking (Table 3).

4. *Thickness and size*: The thickness of the film is measured using screw gauge micrometer with a least count of 0.01mm. The maximum probable size for buccal film is 15$cm^2$ but usual range is 1 to 3$cm^2$. The thickness of the film must be limited to a few mm. The shapes comfortable to be used by the patient are either ellipsoidal or circular (Table 3).

5. *Area*: Area of the films was determined (Table 3).

6. *Drug Content*: A film of area 1$cm^2$ was placed in a volumetric flask containing 50ml of phosphate buffer of pH-6.6 and kept aside for some time to release the total drug present in the film and the volume was made up to 100ml with the same buffer. Then the absorbance was measured after suitable dilution at 276nm against drug devoid polymer blank solution in phosphate buffer of pH-6.6 (Table 3), and the content of diclofenac sodium was calculated using standard graph.

7. *Swelling studies*: 1cm2 film of each formulation was accurately weighed placed in a petridish containing 20ml of water. The weight of each film (w2 gm) was determined at 5 and 10 minutes by pressing the film with a tissue paper to remove the excess fluid. The swelling index was calculated by the formula,

Swelling Index = (W2-W1) / W1

Where W1 is initial weight of the film and W2 is weight of the films after particular time of interval (Table 4).

8. *In-vitro evaluation*: *In-vitro* release studies were carried out by using sigma dialysis membrane attached to one end of fabricated open cylinder which acted as donor comportment. Films of 1$cm^2$ area were used for each formulation. The sigma dialysis membrane was previously hydrated by soaking it in the distilled water for 30 minutes after which was fixed to the donor comportment. The film was placed over the dialysis membrane in the donor compartment. The receptor comportment was filled with 100ml of phosphate buffer of pH 6.6.

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*Table 5. In-vitro* release studies of formulations

| S.No | Time | Abs | Con. | Cum% Released | Log Cum% released | Cum % Retained | Log Cum% retained | $(T)^{1/2}$ | Log $(T)^{1/2}$ |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 15 | 0.020 | 0.3428 | 13.49 | 1.1300 | 86.51 | 1.9370 | 3.87 | 0.58 |
| | 30 | 0.027 | 0.4627 | 18.21 | 1.2603 | 81.79 | 1.9127 | 5.47 | 0.73 |
| | 45 | 0.035 | 0.5999 | 23.61 | 1.3730 | 75.39 | 1.8830 | 6.70 | 0.82 |
| | 60 | 0.045 | 0.7713 | 30.36 | 1.4823 | 69.64 | 1.8428 | 7.74 | 0.88 |
| | 90 | 0.058 | 0.9941 | 39.13 | 1.5925 | 60.87 | 1.7844 | 9.48 | 0.97 |
| | 120 | 0.074 | 1.2683 | 49.93 | 1.6983 | 50.07 | 1.6995 | 10.95 | 1.03 |
| | 180 | 0.099 | 1.6968 | 66.80 | 1.8247 | 33.20 | 1.5211 | 13.41 | 1.12 |
| | 240 | 0.123 | 2.1082 | 83.00 | 1.9190 | 70.00 | 1.2304 | 15.49 | 1.49 |
| | 300 | 0.138 | 2.3653 | 93.12 | 1.9690 | 06.00 | 0.8375 | 17.32 | 1.23 |
| F2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 15 | 0.019 | 0.3256 | 12.81 | 1.107 | 87.19 | 1.940 | 3.87 | 0.58 |
| | 30 | 0.025 | 0.4285 | 16.87 | 1.227 | 83.13 | 1.919 | 5.47 | 0.73 |
| | 45 | 0.033 | 0.5656 | 22.26 | 1.347 | 77.74 | 1.890 | 6.70 | 0.82 |
| | 60 | 0.043 | 0.7370 | 29.01 | 1.462 | 70.99 | 1.851 | 7.74 | 0.88 |
| | 90 | 0.057 | 0.9769 | 38.46 | 1.585 | 61.54 | 1.789 | 9.48 | 0.97 |
| | 120 | 0.072 | 1.2340 | 48.58 | 1.686 | 51.42 | 1.711 | 10.95 | 1.03 |
| | 180 | 0.095 | 1.6283 | 64.10 | 1.806 | 35.9 | 1.555 | 13.41 | 1.12 |
| | 240 | 0.119 | 2.0396 | 80.29 | 1.904 | 19.71 | 1.294 | 15.49 | 1.19 |
| | 300 | 0.132 | 2.2624 | 89.07 | 1.949 | 10.93 | 1.038 | 17.32 | 1.23 |
| F3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 15 | 0.018 | 0.3085 | 12.14 | 1.084 | 87.86 | 1.943 | 3.87 | 0.55 |
| | 30 | 0.025 | 0.4285 | 16.87 | 1.227 | 83.13 | 1.919 | 5.47 | 0.73 |
| | 45 | 0.030 | 0.5142 | 20.24 | 1.306 | 79.76 | 1.901 | 6.70 | 0.82 |
| | 60 | 0.041 | 0.7027 | 27.66 | 1.441 | 72.34 | 1.859 | 7.74 | 0.88 |
| | 90 | 0.055 | 0.9427 | 37.11 | 1.569 | 62.89 | 1.798 | 9.48 | 0.97 |
| | 120 | 0.070 | 1.1998 | 47.23 | 1.674 | 52.77 | 1.722 | 10.95 | 1.03 |
| | 180 | 0.093 | 1.5940 | 62.75 | 1.797 | 37.25 | 1.571 | 13.41 | 1.12 |
| | 240 | 0.114 | 1.9539 | 76.92 | 1.886 | 23.08 | 1.363 | 15.49 | 1.19 |
| | 300 | 0.127 | 2.1767 | 85.69 | 1.932 | 14.31 | 1.155 | 17.32 | 1.23 |
| F4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 15 | 0.015 | 0.2571 | 10.12 | 1.005 | 89.88 | 1.953 | 3.87 | 0.58 |
| | 30 | 0.022 | 0.3770 | 14.84 | 1.171 | 85.16 | 1.930 | 5.47 | 0.73 |
| | 45 | 0.027 | 0.4627 | 18.21 | 1.260 | 81.79 | 1.912 | 6.70 | 0.82 |
| | 60 | 0.037 | 0.6341 | 24.96 | 1.397 | 75.04 | 1.875 | 7.74 | 0.88 |
| | 90 | 0.050 | 0.857 | 33.74 | 1.528 | 66.26 | 1.821 | 9.48 | 0.97 |
| | 120 | 0.067 | 1.1483 | 45.20 | 1.655 | 54.8 | 1.738 | 10.95 | 1.03 |
| | 180 | 0.089 | 1.5254 | 60.05 | 1.778 | 39.95 | 1.601 | 13.41 | 1.12 |
| | 240 | 0.110 | 1.8844 | 74.18 | 1.870 | 25.82 | 1.411 | 15.49 | 1.19 |
| | 300 | 0.120 | 2.0568 | 80.97 | 1.908 | 19.03 | 1.279 | 17.32 | 1.23 |
| F5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 15 | 0.012 | 0.2056 | 08.094 | 0.908 | 91.906 | 1.963 | 3.87 | 0.58 |
| | 30 | 0.018 | 0.3085 | 12.145 | 1.084 | 87.855 | 1.943 | 5.47 | 0.73 |
| | 45 | 0.025 | 0.4284 | 16.870 | 1.227 | 83.130 | 1.919 | 6.70 | 0.82 |
| | 60 | 0.034 | 0.5827 | 22.940 | 1.360 | 77.060 | 1.886 | 7.74 | 0.88 |
| | 90 | 0.048 | 0.8227 | 32.389 | 1.510 | 67.611 | 1.830 | 9.48 | 0.97 |
| | 120 | 0.063 | 1.0798 | 42.511 | 1.628 | 57.489 | 1.759 | 10.95 | 1.03 |
| | 180 | 0.084 | 1.4397 | 56.681 | 1.753 | 43.319 | 1.636 | 13.41 | 1.12 |
| | 240 | 0.104 | 1.7825 | 70.177 | 1.846 | 29.823 | 1.474 | 15.49 | 1.19 |
| | 300 | 0.114 | 1.9539 | 76.925 | 1.886 | 23.075 | 1.363 | 17.32 | 1.23 |

A Teflon coated magnetic bead was placed in receptor comportment and the whole assembly was placed in magnetic stirrer and the temperature maintained at 37±0.5c. Buffer was stirred at 50rpm for all formulations. Samples of 5ml were withdrawn at regular intervals, suitably diluted and

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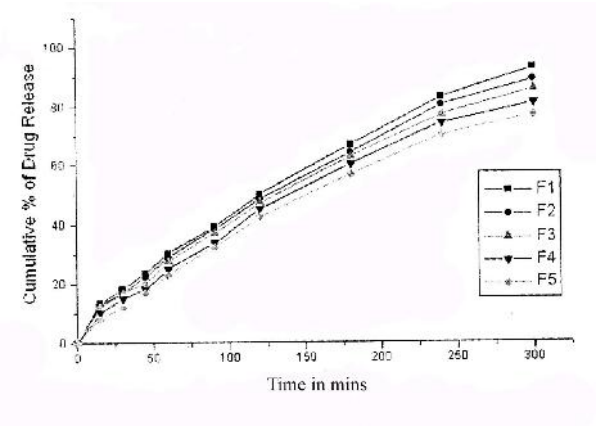


*Fig. 2*. *In-vitro* drug release of formulations

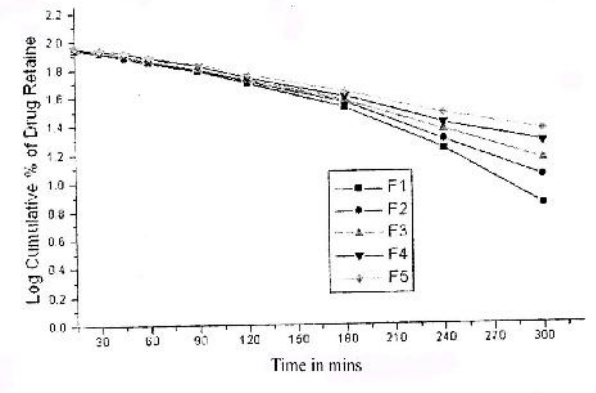


*Fig. 3*. Drug retained Vs Time plots of formulations

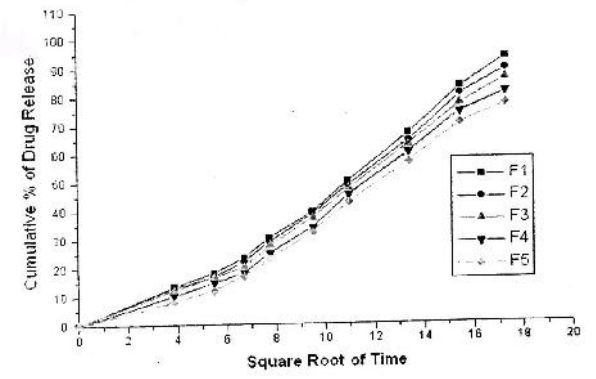


*Fig. 4*. Higuchi plots

absorbance was measured at 276nm (Fig. 2 and 3). The volume of the receptor comportment was maintained constant by replacing equal volume of buffer. The results were tabulated and similarly (Table 5), drug devoid film of same composition was taken and diffusion was carried out in a separate cell.

The thickness of the prepared films ranged from 0.64-0.75mm. The area of the buccal film was found to be constant (19.625). The drug content ranged from 96.98-98.5. The swelling index in the order of F5> F4> F3> F2> F1. The swelling index was found to be in the range of 0.095 to 0.206. Further, the drug content of the films were found to be in the range of 96.98 to 98.5%. The in-vitro release shows that it follows the first order kinetics (Fig.4 and Table 6). This above drug release profile implies that there is a scope to obtain a sustained release for more than eight hours by increasing the concentration.

In the current study, an attempt was made to fabricate and evaluate mucoadhesive buccal films of diclofenac sodium by using various bio-adhesive polymers like HPMC, PVP and Eudragit L-100-55. Five formulations were prepared and evaluated for their physical characteristics such as appearance, surface texture, folding endurance, thickness, area and swelling studies. The in-vitro release studies were carried by using fabricated diffusion cell and dialysis sac was used as a membrane.

## Conclusion

The present study indicates a good potential of erodible mucoadhesive buccal films containing Diclofenac sodium for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The results of the study show that therapeutic level of Diclofenac sodium can be delivered by buccal cavity. It may concluded that the formulation F5 shows good swelling, good flexibility, a convenient residency time and promising sustained drug release, thus seems to be a potential candidate for development of buccal film for effective therapeutic use. The mechanism of drug release was diffusion followed by first order kinetics there is a scope to obtained sustained release for more than 8 hours by increasing the polymer concentration. *In-vivo* studies need to be design and executed.

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*Table 6*. Kinetic values for formulations

| Sl.No | Formulation | First order Equation | | | Higuchi Equation | |
|---|---|---|---|---|---|---|
| | | Slope (n) | First order rate constant (K) | Regression Coefficient (R) | Slope (n) | Regression Co-efficient (R) |
| 1 | F1 | 0.00366 | 0.0084 | 0.9785 | 5.6611 | 0.9873 |
| 2 | F2 | 0.00311 | 0.0071 | 0.9892 | 5.4606 | 0.98734 |
| 3 | F3 | 0.00275 | 0.0063 | 0.9942 | 5.2739 | 0.9870 |
| 4 | F4 | 0.00243 | 0.0055 | 0.9971 | 5.0908 | 0.9839 |
| 5 | F5 | 0.00217 | 0.0049 | 0.9985 | 4.8848 | 0.9826 |

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