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Formulation and evaluation of Buccal mucoadhesive tablets of diclofenac sodium using 2^3 factorial designs

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Diclofenac sodium is an NSAID (Non-Steroidal anti-inflammatory widely used in the treatment of pain, migraine, and inflammation). It has been observed that Diclofenac undergoes extensive first-pass metabolism when administered using conventional dosage forms through the oral route. The aim of this study is to formulate and evaluate pre-compression, post-compression factors and release kinetics of buccal mucoadhesive tablets formulated by a 2^3 factorial method that can prevent the first-pass metabolism of the drug thereby increasing its bioavailability. This formulation increases patient compliance by reducing its dosing frequency. In these formulations, two polymers polyvinyl pyrrolidine (PVP K30) and Chitosan are used in varying proportions. Eight different formulations were prepared by varying concentrations of the polymers. The buccal mucoadhesive tablets formulated have been evaluated for their general appearance, thickness, hardness, weight variation, friability and other *in vitro* tests such as swelling and dissolution studies. The evaluation studies demonstrated that formulation F8 showed better properties as a buccal mucoadhesive formulation compared to other formulations.

Keywords: Buccal tablets, Diclofenac sodium, Drug release, Mucoadhesion, Mucoadhesive tablets, Release kinetics

Diclofenac is an NSAID (non-steroidal anti-inflammatory) drug that is recommended for the treatment of pyrexia, painful and inflammatory rheumatic and non-rheumatic conditions. It is available in various administration forms, including orally, rectally, and intramuscularly[1]. Diclofenac is also used to treat rheumatoid arthritis, menstrual pain, osteoarthritis, dysmenorrhea, ocular inflammation and ankylosing spondylitis. It is completely absorbed orally. Though completely absorbed orally unfortunately it undergoes rapid first-pass hepatic metabolism[2]. Any drug delivery system's goal is to deliver a therapeutic amount of the drug to the desired site of action in the body and to maintain the desired drug concentration. Patients and physicians both agree that tablets are a convenient dosage form[3]. Administering Diclofenac sodium orally leads to significant first-pass metabolism. However, using the buccal route offers several benefits such as bypassing first-pass metabolism, easy administration, and increased patient compliance[4,5]. Thus, the goal of this study is to formulate Buccal Mucoadhesive diclofenac sodium tablets with varying polymer concentrations that can prevent the drug from being extensively metabolized, thereby increasing its bioavailability in systemic circulatio[6]. The adhesion of two materials, at least one of which is a mucosal surface, is commonly defined as mucoadhesion[7]. Since gums, tongues, and swallows are factors that affect buccal drug delivery, mucoadhesive polymers are ideally used[8]. This formulation may also reduce dosing frequency, which may improve patient adherence to the medication[9-12].

Chemicals and Instruments

A gifted sample of Diclofenac sodium standard reference was procured from Mylan Laboratories, Bangalore, Karnataka, India. Acacia gum is manufactured by Finar chemicals (India) Pvt. Ltd., Mannitol, Chitosan and Polyvinyl Pyrrolidine (PVP K30) are manufactured by Molychem, and Magnesium stearate by Kemphasolis used for the formulation. In-house Milli-Q water was used for the dilutions. A pH meter was used for the pH examination and adjustment. The Monsanto hardness tester used for hardness test. A rotary tablet punching machine from Accura was used for tablet punching.

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Materials and Methods

Calibration curve of diclofenac sodium

Preparation of solutions for the Calibration curve

Primary stock: A stock solution of the drug at a concentration of 1 mg/mL was prepared using phosphate buffer (pH 6.8) in a 100 mL volumetric flask. The solution was sonicated for approximately 10 min.

Secondary stock: A stock solution of (1 mg/mL) was prepared using the previous solution to a total volume of 100 mL and then filtered with a No. 41 Whatman filter paper.

Working standard solutions: Various volumes of the sample solution were added to test tubes (0.2 mL - 1.6 mL) and made up to 10 ml with a phosphate buffer (pH 6.8). This resulted in a range of final concentrations of the drug (2, 4, 6, 8, 10, 12, 14, 16 µg/mL) in each test tube.

Determination of absorption maxima: The maximum wavelength (λ_{max}) of Diclofenac sodium was determined by analyzing a 10 µg/mL solution of the drug in a buffer over the range of 200-400 nm using a UV-visible spectrophotometer. A spectrum of the drug in this buffer was also generated as a representation.

Preparation of Calibration curve: Standard solutions of the drug were made using the stock solution, with concentrations of (2-16 µg/mL). These solutions were made using the buffer. The absorbance was obtainedat 276 nm. A calibration curve was plotted by plotting drug concentration (µg/mL) on the x-axis and absorbance on the y-axis. This allowed for the determination of linearity and calculation of the regression equation.

Table 1—2^3 Factorial design

	1	a	b	c	Ab	bc	ac	abc
A	-	+	-	-	+	-	+	+
B	-	-	+	-	+	+	-	+
C	-	-	-	+	-	+	+	+

A: Acacia, B: Chitosan, C: PVP K30

Formulation and evaluation of diclofenac sodium mucoadhesive tablets

Formulation of mucoadhesive tablets by direct compression method

The active ingredient was evenly mixed with polymers and other excipients using a mortar. The resulting mixture was then placed in the die of a tablet compression machine (Tables 1 & 2).

Evaluation of Diclofenac sodium mucoadhesive tablets

Pre-Compression Parameters

Bulk density (Db)

A large funnel was used to measure the volume of powder after it was placed in a graduated cylinder. The bulk density is calculated in g/cc and is represented by the formula Db = M/Vo.

Tapped density (Dt)

A 100 mL measuring cylinder filled with 10g of powder was used to measure the density of the powder after it had been tapped. The volume of the cylinder was measured after it was tapped 100 times from a fixed height. The tapped density is represented in g/cc and was obtained by Dt = M/Vt.

Compressibility index

The formula used for Carr's Index was: $CI = (T_d - B_d) / (T_d) \times 100$

Hausner's ratio

The relationship between the bulk density and tapped density of a powder was calculated by Hausner's ratio (Tapped density/Bulk density). If ratio falls between 1.25 and 1.5, it is an indication that adding a glidant can improve the flow properties of the powder.

Scale of Flowability: Angle of repose (θ) is the maximum angle that can be formed between the surface of a powder pile and a horizontal plane [θ = tan-1(h/r)] (Table 3 & 4).

Total porosity

The total porosity of the powder is determined by calculating the volume taken up by a particular weight of powder (V_{bulk}) and the real volume of the powder mixture (Porosity = $(V_{bulk} - V)/V_{bulk} \times 100$).

Table 2 —Formulation of buccal mucoadhesive tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Diclofenac sodium	20	20	20	20	20	20	20	20
Acacia gum	20	40	20	20	40	40	20	40
Chitosan	0	0	40	0	40	0	40	40
PVP K30	0	0	0	6	0	6	6	6
Mannitol	158	138	118	152	98	132	112	92
Magnesium Stearate	2	2	2	2	2	2	2	2
	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg

Flow rate

The granule flow rate influences die cavity filling and, as a result, the weight of the tablets produced.

Post-compression parameters

Thickness and Diameter

Vernier callipers were used to measure the tablet's thickness and diameter. It is measured in millimetres.

Hardness

Using a Monsanto hardness tester evaluated the hardness of the tablet. The tablet was placed between two jaws, one fixed and one movable. The scale was reset to zero, and the load was gradually increased until the tablet broke. The hardness was measured in Kg/cm^2.

Friability (F)

Friability USP EF-2 was used to assess tablet strength. Pre-weighed tablets were allowed for 100 revolutions before being removed and measured for percent weight loss. The friability% was obtained by [F= (W_{inital}) - $(W_{final})/(W_{initial}) \times 100$].

Weight Variation Test

The USP weight variation test was conducted by individually weighing 20 tablets, was calculated their average weight, and compared the individual weights to the average weight (Table 5). The USP limits for the percentage deviation (PD) of tablets calculated using the formula: $PD = (W_{avg} - W_{initial}) / W_{avg} \times 100$.

Swelling index

Each formulation's tablets were weighed (W1) and transferred in Petri dishes containing 50 mL of pH 6.8 buffer solution (Table 11).

The swollen tablets were removed and reweighed (W2) every 5 min up to 25 min, and the percentage hydration was determined by Swelling index= [(W2-W1)]/W1] × 100.

***In vitro* dissolution studies**

Procedure

The diclofenac tablet release rate was determined by using United States Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle type)[14]. For dissolution testing, 900 mL of buffer was used for 6 min at 37 ± 0.5°C and at 50 rpm. Samples (5 mL) were taken every hour for 6 min, and the sample was replaced (Table 6). The samples were then diluted and analyzed using a UV-Visible Spectrophotometer (UV–1800) to determine the percentage of drug release. Different kinetic models were used to study the release kinetics, including Zero-order, First-order, Higuchi, Korsmeyer, and Hixson-Crowell models (Fig. 1A).

Zero-order equation

The Zero-order release can be described as the release of a constant amount of drug over time (Fig. 1B). It can be represented by the equation Q = Qo + Kt.

First-order equation

The First-order release can be described as the release of a drug at a constant rate over time. It can be represented by the equation Log C = Log Co – Kt. A straight line is drawn between the percent remaining of drugs versus time, indicating first-order kinetics for drug release (Fig. 1C). Adding 2.303 to the slope value will yield the constant 'K'.

Table 3 — Scale of Flowability limit

CompressibilityIndex (%)	Flow character	Hausner's ratio
5-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-27	Very poor	1.46-1.59
>38	Very poor	>1.60

Table 4 — Angle of repose limits

S.No	Flowability	Angle of Repose
1	Excellent	<25
2	Good	25-30
3	Moderate	30-40
4	Poor	>40

Table 5 — Weight variation limits

S.No	Average Weight oftablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324 more	5

Table 6 — *In vitro* dissolution studies

Apparatus	USP XXIV dissolution testingapparatus II (Paddle method)
Dissolution medium	Phosphate buffer pH 6.8
Temperature	37±0.5°C
RPM	50
Vol. Withdrawn and replaced	5 mL every 30 min
λ_{max}	276 nm
Blank solution	Phosphate buffer p^H 6.8
Duration of study	6 min
Dissolution media	900 mL

Higuchi equation

The Higuchi release kinetics is a model used to study the drug release rate that follows a square root of time (Fig. 1D).

It can be represented by the equation F = Kt^1/2.By plotting the cumulative drug released versus the square root of time, a linear relationship is obtained, this indicates that the drug release follows diffusion. The slope of the line is equal to 'K'.

Hixson and Crowell equation

When this model has been used, it is assumed that the release rate is constrained by drug particle dissolution rate rather than diffusion that may occur through the polymeric matrix (% unreleased) 1/3= k t)

Korsmeyer-Peppas equation[10]

The data on release rates was modeled using the equation Mt/M∞ = ktn, where Mt/M∞ is the fraction of drug release, k is the release constant, t is the release time and n is the diffusion exponent that is dependent on the shape of the matrix dosage form (Table 7).

Figure 2 shows the calibration curve for diclofenac sodium. Table 9 shows the pre-compression parameters of diclofenac sodium mucoadhesive tablets. Table 10 shows the post-compression parameters. Table 11 shows the swelling index. Tables 12-14 show the release kinetics of diclofenac sodium buccal mucoadhesive tablets.

Table 7 —Mechanism of drug release based on the value of Korsmeyer-Peppas

N Value	Type of Diffusion
Less than 0.45	Quasi Fickian
0.45	Fickian diffusion
0.45 <n<0.89	Anomalous diffusion or Non-Fickian diffusion
0.89 – 1	Non-Fickian case II
>1	Super case II non-fickian

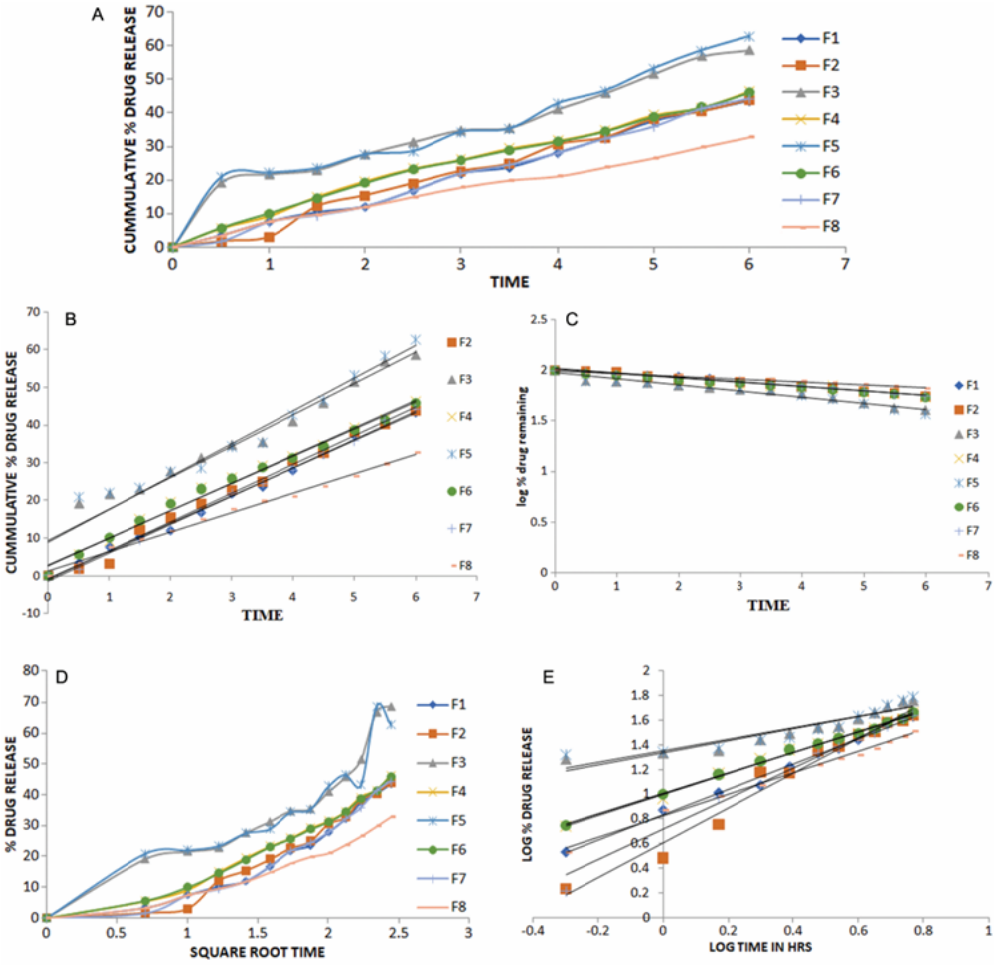

Fig. 1 — (A) Dissolution profiles; (B) Zero order plot; (C) First order plot; (D) Higuchi plot; and (E) Korsmeyer Peppas plot of Diclofenac sodium mucoadhesive tablets

Results and Discussion

In Pre formulation studies, the physicochemical properties of the drug were determined and the melting point was found to be 283-285°C. Using a UV-Visible spectrophotometer the maximum absorbance of Diclofenac sodium was found to be 276 nm. The standard calibration curve of Diclofenac sodium in pH6.8 phosphate buffer solution showed the concentration range as 5-35 mcg/mL the method obeyed beer's law 6.8 phosphate buffer solution showed the concentration with low RSD values ensuring the reproducibility of the method in pH 6.8 phosphate buffer. In order to find the degree of linear relationship, the correlation coefficient was calculated and it was found to be 0.995. To establish the mathematical form of the linear relationship between two variables (concentration and absorbance), the equation obtained was y = 0.0573x + 0.002 as shown in (Fig. 2). Where 'x' is the concentration of Diclofenac sodium (mcg/ mL) and y is the absorbance

Using 2^3 factorial designs8 formulations were prepared.Various pre-compression tests were conducted on all the prepared formulations, such as bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio. The general appearance of formulated mucoadhesive tablets was observed and recorded. All the formulations have a thickness in the range of 9.48 mm to 9.56 mm. The uniformity of tablet thickness was not affected by the polymer used. The average weight of tablets ranged

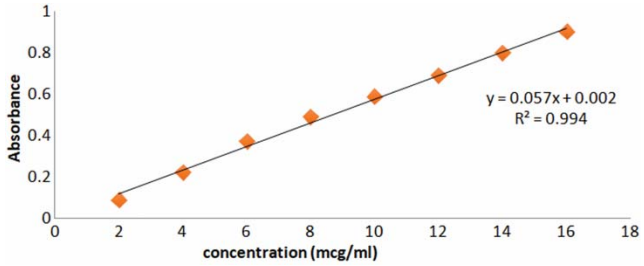

Fig. 2 — Standard calibration curve of Diclofenac sodium. The slope was found to be 0.0573, the correlation coefficient was found to be 0.994

Table 8 — Calibration curve values

Sl. No	Concentration (mcg/ mL)	Absorbance
1	2	0.089
2	4	0.221
3	6	0.371
4	8	0.49
5	10	0.586
6	12	0.689
7	14	0.798
8	16	0.901

Table 9 — Pre-compression parameters

Formulation	Bulk density(gm/ mL)	Tapped density(gm/ mL)	Angle of repose(θ)	Compressibility Index (%)	Hausner's ratio
F1	0.333±0.006	0.373±0.003	22.12	11.95	1.117
F2	0.342±0.005	0.382±0.007	20.22	11.63	1.115
F3	0.338±0.005	0.378±0.005	20.14	11.99	1.118
F4	0.332±0.006	0.337±0.002	20.21	12.90	1.016
F5	0.323±0.001	0.363±0.001	21.13	12.30	1.121
F6	0.340±0.003	0.375±0.0001	20.13	10.27	1.102
F7	0.333±0.005	0.368±0.003	22.84	10.56	1.104
F8	0.340±0.005	0.379±0.004	21.20	11.43	1.112

Table 10 —Post-compression parameters of Buccal mucoadhesive tablets

Formulation	Thickness (mm)	Hardness (Kg/Cm2)	Weight Variation (Gm)	Friability (%)
F1	4.56 ± 0.15	4.1 ± 0.07	0.23 ± 0.01	0
F2	4.48 ± 0.04	4.5 ± 0.04	0.22 ± 0.01	0
F3	4.48 ± 0.05	4.0 ± 0.06	0.22 ± 0.02	1.5
F4	4.49 ± 0.01	4.3 ± 0.05	0.21 ± 0.01	0
F5	4.51 ± 0.04	3.7 ± 0.01	0.24 ± 0.01	1
F6	4.53 ± 0.11	6.9 ± 0.04	0.20 ± 0.02	1
F7	4.56 ± 0.08	3.9 ± 0.02	0.20 ± 0.01	0
F8	4.52 ± 0.01	7.2 ± 0.02	0.21 ± 0.02	0

Table 11 —Swelling index of Buccal mucoadhesive tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	2.3	3.2	2.7	4.8	6.2	5.1	3.5	8.2
10	4.8	4.5	3.8	8.1	8.4	6.9	5.0	15
15	7.88	6.7	5.8	12.2	13.2	7.5	8.2	19
20	11.5	8.2	8.7	17.6	17.5	13.8	12.2	25
25	16.5	11.4	13.2	23.3	22.6	21.1	18.5	30

Table 12 —% Drug Release of Diclofenac sodium Buccal mucoadhesive tablets

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
0.5	3.394	1.737	19.18	5.526	20.92	5.684	1.657	3.39
1	7.578	3.079	21.63	9.158	22.10	10.02	7.421	7.57
1.5	10.263	12.158	22.89	14.921	23.44	14.53	9.394	9.71
2	12	15.395	27.63	19.5	27.55	19.02	12.00	11.92
2.5	16.73	19.023	31.26	23.289	28.89	23.05	16.73	14.92
3	21.78	22.658	34.73	25.894	34.26	25.73	21.78	17.68
3.5	23.60	24.868	35.44	29.210	35.21	28.81	24.39	19.81
4	27.94	30.552	40.97	31.5	42.71	31.26	27.94	21
4.5	32.28	32.684	45.78	34.578	46.57	34.34	32.28	23.68
5	37.34	38.131	51.47	39.158	43.13	38.68	35.76	26.44
5.5	40.32	40.342	66.76	41.368	68.50	41.44	41.13	29.68
6	43.34	43.816	68.57	46.184	62.68	45.86	44.13	32.68

Table 13 — Drug release kinetics of Buccal mucoadhesive tablets

Formulation	Zero Order (R^2)	First Order (R2)	Higuvhi (R^2)	N Value In KorsmeyerPeppas	r^2 value of Korsmeyerpeppas
F1	0.995	0.984	0.901	1.02	0.993
F2	0.990	0.991	0.913	1.32	0.955
F3	0.952	0.961	0.976	0.47	0.911
F4	0.989	0.994	0.956	0.84	0.994
F5	0.947	0.942	0.963	0.47	0.857
F6	0.991	0.995	0.957	0.82	0.998
F7	0.995	0.984	0.947	1.22	0.975
F8	0.993	0.993	0.942	0.86	0.993

Table 14 —Table of rate constants

Formulation	K0	K1	KH	N
F1	0.122	0.001	19.10	1.022
F2	0.127	0.001	20.00	1.325
F3	0.138	0.002	22.78	0.479
F4	0.121	0.001	19.64	0.848
F5	0.148	0.002	23.59	0.471
F6	0.121	0.002	19.43	0.827
F7	0.125	0.002	19.50	1.225
F8	0.086	0.001	13.68	0.864

from 0.20 to 0.24 g. All the tablets showed a high tendency to withstand mechanical strength as the maximum percentage of loss of friability was only 1.5%. All the tablets showed swelling and the swelling index was determined. Formulation F8 showed a high degree of swelling.

From the tests conducted for *in vitro* drug release studies, it was observed that the rate of dissolution for the tablets in all formulations has an increasing pattern of drug release profile. Among all the formulations, it was observed that the tablets in F8 had the highest rate of drug dissolution. The best drug release percentage in the testwasat the 6^{th} h. The rate of drug release for the F8 formulation that showed a high dissolution rate follows zero-order release the n value being 0.86follows non-fickian diffusion.

Conclusion

Diclofenac sodium, a nonsteroidal compound, exhibits pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties by inhibiting cyclooxygenase-1 and cyclooxygenase-2 with relatively equal potency, thereby inhibiting

prostaglandin synthesis. Despite being completely absorbed through the oral route it undergoes extensive first-pass metabolism making it difficult to administer orally. Formulation of buccal mucoadhesive tablets can be an attractive approach to overcome the limitations associated with the oral administration of Diclofenac sodium.

From the above study, we determined that the drug (Diclofenac Sodium) used and the polymers chosen were compatible with each other. The formulations prepared were observed to have some similarities in their general appearance, thickness, weight variation, and their capacity to withstand friability. However, they differed in hardness, *in vitro* swelling, and *in vitro* drug dissolution characteristics. By analyzing the results obtained it was confirmed that Formulation F8 having high concentrations of polymers (PVP-K30 and Chitosan) has shown better results and holds the desired degree of hardness, long residence time, and highest drug release profile. Korsmeyer's Peppas plot indicated the specific mechanism of drug release was diffusion. Formulation F8 was found to follow zero order release kinetics and the mechanism of drug release was found to be non-fickian diffusion. Formulation 8 has the ability to overcome the first-pass metabolism effect by mucoadhesive drug administration.

Conflicts of interest

All authors declare no conflicts of interest.

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