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DESIGN AND EVALUATION OF DICLOFENAC SODIUM BUCCAL MUCOADHESIVE FILM BY SOLVENT CASTING TECHNIQUE

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ABSTRACT: Mucoadhesive buccal patches containing diclofenac sodium were prepared using the solvent casting method. HPMC used as bioadhesive polymer and different ratio of propylene glycol and glycerin also used. FT-IR and UV spectroscopic methods revealed that there is no interaction between Diclofenac sodium and polymers. The patches were evaluated for their physical characteristics like mass variation, drug content uniformity, folding endurance, surface pH, and in vitro drug release, in vitro buccal permeation study. Incorporation of DMSO generally enhanced the release rate. Swelling index was proportional to the concentration of HPMC. Optimized patches (F) showed satisfactory bioadhesive strength. The surface pH of all batches was within ± 0.4 units and thus no mucosal irritation is expected. Patches containing of F5 had higher bioadhesive strength with sustained drug release as compared to patches with other ratios of polymer. Data of *in-vitro* release from patches were fit in to different equations and kinetic models to explain release kinetics. The models used were zero and first-order, Hixon-Crowell, Higuchi and Korsemeyer-Peppas models equation. The optimized patch demonstrated well *in-vitro* results.

INTRODUCTION: The buccal mucosa provides a readily accessible route for transmucosal delivery. The oral cavity is being increasingly used for the administration of drugs, which are mainly designed for the contained medicaments through the oral mucosa into the systemic circulation.

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Mucoadhesion may be defined as state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time [1].

The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids pre systemic elimination in the gastro intestinal tract and liver [2]. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. 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 are easily washed

away and removed by saliva. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively [3]. Buccal mucosa consists of stratified squamous epithelium supported by a connective tissue lamina propia was investigated as a site for drug delivery several decades ago, and the interest in this area for the transmucosal drug administration is still growing. Delivery of drug through buccal mucosa overcomes premature drug degradation within the GI tract, as well as active drug loss due to the first pass metabolism, and inconvenience of parenterals administration. In addition, there is excellent acceptability and the drug can be applied localized, and may be removed easily at any time during the treatment period.

Diclofenac sodium is benzene acetic acid,-[(2, 6-dichlorophenyl) amino] –monosodium salt. Diclofenac sodium is an analgesic and anti-inflammatory. In acute infection, 2-4 drops of diclofenac sodium eye drop is administered for every 15 to 30 min. initially. From this it is clear that this dosage form has several drawbacks such as frequency of administration, loss of drug from tear flow, lachrymal and nasal drainage, patient non-compliance etc.

To overcome this problem, attempt has been made to formulate gel of Diclofenac sodium in the present study using polymer hydroxy propyl methyl cellulose [4].

A few drugs, such as metaprololtartarate, ibuprofen, salbutamol sulphate, diclofenac sodium, diltiazem, isosorbidedinitrate, propranolol hydrochloride, cetylpyridinium chloride, fexo-fenadine hydrochloride and carvedilol have been successfully administered via the buccal route.

Diclofenac sodium is a cyclo-oxygenase inhibitor; analgesic; anti-inflammatory agent. It is used for musculoskeletal complaints, especially arthritis, rheumatoid arthritis, polymyositis, dermatomyositis, osteoarthritis, spondylarthritis, ankylosing spondylitis, gout attacks, and pain management in cases of kidney stones and gallstones. Though it is rapidly absorbed after oral administration, the bioavailability of diclofenac sodium is 50% as it undergoes significant first pass metabolism and will be eliminated from body through urine. The log P (partition coefficient) value for diclofenac sodium is about 4.218. It indicates that diclofenac sodium has sufficient lipophilicity to pass through the buccal membranes. By observing the above point, it is inferred that drug is suitable for formulating into buccal patches.

Materials: Diclofenac sodium was a gift sample (Vasudha Pharma Chem Ltd, Hyderabad, India), Hydoxy propyl methyl cellulose (100cPs) (HPMC) were obtained from Cadila Health Care Ltd., (Ahmedabad, India).Sodium lauryl sulphate and Dimethyl sulphaoxide and Propylene glycol were obtained from S.D. Fine Chemicals Ltd, (Mumbai, India).

Methods:

Drug-Polymer Compatibility: Drug-polymer interaction was observed by IR spectrophotometry. An FTIR study of pure diclofenac sodium and physical mixture of diclofenac sodium and polymers were performed by KBr dispersion method [5] (**fig. 1**).

Calibration curve of Diclofenac sodium with 6.8 Phosphate buffer: In a 100 ml standard flask, stock solution was prepared by dissolving 100 mg of diclofenac sodium in 6.8 phosphate buffer and made up to the volume with 6.8 Phosphate buffer. From this stock solution (1%w/v), serial dilutions were made by withdrawing 1ml, 2ml, 3 ml, 4 ml and 5 ml and transferred individually into 10 ml standard flask and the volume was made up to the mark using 6.8 Phosphate buffer. The absorbance of resulting solutions was measured using shimadzu UV-1601 spectrophotometer at 282 nm and the values are r =0.998, y=0.037x

Preparation of patches: The buccal mucoadhesive films were prepared by using polymer along with the drug and a suitable solvent [6]. The buccal mucoadhesive films of diclofenac sodium were prepared using HPMC 100cPs by casting technique. HPMC polymer (200 mg) was weighed accurately and placed in 3 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 15 minutes for swelling of polymer. The drug solution was weighed and dissolved in suitable solvent (methanol, ethanol).and then the polymer solution was prepared by dissolving the required quantity of HPMC, SLS, propylene glycol, DMSO & glycerin.

To this add 10 ml of distilled water. The drug solution was added to the polymer dispersion and mixes the solution homogeneously by keeping it in a sonicator for 5 mins. The prepared viscous formulation was poured on the Petri dish in room temperature for 2 hrs and followed to evaporate the solvent in hot air oven for 1hrs at 50°C for drying and sudden evaporation. After this period, an inverted funnel was placed over the mould overnight to remove the remaining solvent. The film was removed from the mould, packed in wax paper, and stored in a desiccator. The film goes for further evaluation studies.

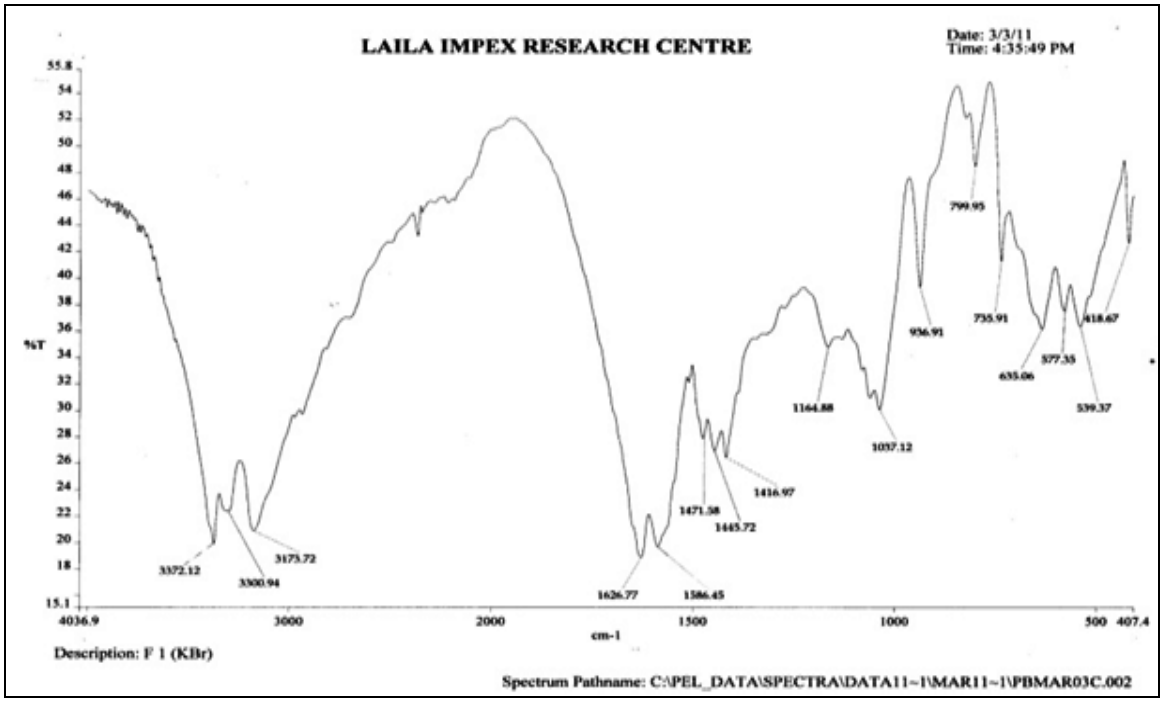

FIGURE 1: FTIR OF DRUG AND POLYMER

Composition of different buccal mucoadhesive formulations containing Diclofenac sodium: Table 1

TABLE 1: COMPOSITION OF BUCCAL MUCOADHEIVE FORMULATION

Formulation code	F1	F2	F3	F4	F5
Diclofenac sodium (gm)	0.1	0.1	0.1	0.1	0.1
HPMC (gm)	1.0	0.5	1.0	0.5	1.0
SLS (gm)	0.02	0.02	-	-	0.02
DMSO (ml)	-	-	0.3	0.3	0.3
Propylene glycol (ml)	1	1	1	1	1
Glycerin (ml)	0.3	0.3	0.3	0.3	0.3
Distilled water (ml)	10	10	10	10	10

EVALUATION OF THE TRANSDERMAL PATCHES [7]: Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

Thickness uniformity of the patches: The thickness of each patch was measured using screw gauge at five different positions of the patch and the average was calculated.

Folding endurance: Folding endurance of the patches was determined (Kevin *et al*., 2008) by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually [7], which is considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the patches for five times.

Uniformity of weight of the patches: Patches sizes of 1 × 1cm^2 were cut [8]. The weights of five patches were taken using Shimadzu balance of sensitivity 0.0001 g (Shimadzu, Tokyo, Japan) and the weight variation was calculated.

Drug content uniformity of the patches: The patches were tested for the content uniformity. A patch of size 1 × 1 cm^2 was cut and placed in a beaker. Ten ml of a 0.1 N hydrochloric acid solution was added [8]. The contents were stirred in a cyclo-mixer to dissolve the film. The contents were transferred in to a volumetric flask (10 ml). The absorbance of the solution was measured against the corresponding blank solution at 285 nm using UV-VIS spectrometer (UV-1601, Shimadzu Corporation, Tokyo, Japan).

Swelling studies of the patches: Weight and area increase due to swelling were measured [6].

Weight increase due to swelling: A drug-loaded patch of 1 × 1 cm^2 was weighed on a preweighed cover slip [9]. It was kept in a petridish and 50 ml of phosphate buffer (pH 6.6) was added. After every 5 min, the cover slip was removed, wiped with tissue paper, and weighed upto 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.

Area increase due to swelling: A drug loaded patch size of 1 × 1 cm^2 was cut and placed in a Petridis. A graph paper was placed beneath the petridish, to measure the increase in the area. After determination of the original film weight [10], the samples were allowed to swell on the surface of agar plate kept in a hot air oven maintained at 37^{o}C. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, % S, was calculated using the following equation: where

$$\%S = \frac{Xt - Xo}{Xo} \times 100$$

***In vitro* Permeation Studies:** The *in vitro* study of Diclofenac sodium permeation through the goat buccal mucosa was performed using a Franz diffusion cell with 15 ml capacity.

Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 ml of simulated saliva pH 6.8 (sodium chloride 4.5g, potassium chloride 0.3g, sodium sulphate 0.3g, ammonium acetate 0.4g, urea 0.2g, lactic acid 3g and distilled water up to 1000ml, adjusting pH of solution to 6.8 by 1 M sodium hydroxide solution).

The receptor compartment (15 ml capacity) contained isotonic phosphate buffer pH 6.8 [11]. The hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm and maintaining the temperature at 37±0.5^{0}C. One ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 224 nm. The graph of % drug permeated v/s time was plotted and flux, permeability coefficient was determined.

Kinetics of Drug Release [12]: To study the study kinetics, data obtained from in vitro release were plotted in various kinetic models.

Zero order equation: The graph was plotted as % drug released Vs time in hours.

$$\mathbf{C = K_0 t}$$

Where, K_0 – Zero order constant in concentration/time; t – Time in hours

First order equation: The graph was plotted as log % cumulative drug remaining Vs Time in hours.

$$\mathbf{Log\ C = log\ C_0 - Kt / 2.303}$$

Where, C_0 - initial concentration of drug; K- First order constant; t- Time

Higuchi kinetics: The graph was plotted as % Cumulative drug released Vs square root of time

$$\mathbf{Q = Kt^{1/2}}$$

Where, K – constant reflecting design variable system; t - Time in hours

Hixson and Crowell erosion equation: To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell rate equation. The graph was plotted by cube root of % drug remaining Vs time in hours.

$$Q_0^{1/3} - Qt^{1/3} = K_{HC} X t$$

Where, Qt – Amount of drug released in time t; Q_0 - Initial amount of drug; K_{HC} – Rate constant for Hixon Crowell equation

Korsemeyer – Peppas equation [13]: To evaluate the mechanism of drug release, it was further plotted in peppas equation as log cumulative % of drug released Vs time

$$M_t / M_\alpha = Kt^n$$

$$\text{Log } M_t / M_\alpha = \log K + n \log t$$

Where, $M_t / M\alpha$ - fraction of drug released at time t; t – Release time; K – Kinetic constant (incorporating structural and geometric characteristics of preparation); n - Diffusional exponent indicative of the mechanism of drug release [14].

If n value is 0.5 or less, the release mechanism follows "Fickian diffusion" and higher values of $0.5 < n < 1$ for mass transfer follow a non- Fickian model (anomalous transport). The drug release follows zero-order drug release and case – II transport if the value is 1. For the values of n higher than 1, the mechanism of drug release is regard as super case II transport. This model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time. The results are tabulated in **Table 3 fig. 5, 6**.

Zero Order Reaction - % Cumulative drug release Vs Time in hrs

Korsemeyer – Peppas equation - log cumulative % of drug released Vs log time

Higuchi kinetics - % Cumulative drug release Vs square root of time

First Order Reaction – Log % Cumulative drug remaining Vs Time in hours

Hixon and Crowell erosion equation- cube root of % drug remaining Vs time in hours

Stability Studies: Optimized medicated films were subjected to short term stability testing. Films were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2 C and 75 ± 5% RH for 1 month as per ICH guidelines [15, 16]. Changes in the appearance and drug content of the stored films were investigated after storage at the end of every week. The data presented were the mean of three determinations.

Interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between diclofenac sodium and the selected polymers. The pure drug and drug with excipient were scanned separately [17].

RESULTS AND DISCUSSION:

Drug Estimation Calibration curves of diclofenac sodium in methanol and phosphate buffer (pH 6.8) solutions were constructed at λmax 282 nm with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 1 – 5 µg/ml. Analysis was done in triplicate.

Drug-Polymer Compatibility: IR spectra of pimozide alone and its combination with polymers are shown in Figure 1**.** An IR spectrum of pure diclofenac sodium shows the peaks 3122.19 cm -1, 2936.09 cm^{-1}, 1505.17 cm –1, and 1154.19 cm^{-1}. These peaks can be considered as characteristic peaks of diclofenac sodium and were not affected and prominently observed in IR spectra of diclofenac sodium along with polymers as shown in the **Figure 1**, which indicated that there was no interaction between diclofenac sodium and polymers.

Evaluation of Patches: (table 2)

Thickness uniformity: All the patches have uniform thickness throughout. Standard deviation of all the patches ranged from -0.0054 to -0.0365.

Weight uniformity: Drug loaded patches (1 × 1 cm2) were tested for uniformity of weight. The patches were found uniform. Standard deviation of the patches ranged from -0.2774 to -0.4324.

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 dummy films and drug-loaded films.

Content uniformity: The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 95.90-96.10%.

Swelling studies: The swelling of the patches were observed in phosphate buffer solution (pH 6.8) and data are shown in Table 2. Swelling was more pronounced in patch F1 which contains HPMC (100 cps). Patches F4 showed least swelling (weight basis). The order of films for their swelling properties is F4 < F3 < F5 <F2 < F1.

Tensile strength: The tensile strengths of patches were in the order of F4 < F3 < F5 < F2 < F1. This indicates propylene glycol produces effective cross-linking. Low swelling and higher viscosity supports this result.

Surface pH: The surface pH of all formulations was the neutral pH and hence no mucosal irritation was expected and ultimately achieved patient compliance.

***In vitro* release:** The release data of diclofenac sodium from all the patches were given in **Figure 2**. A perusal to figure 2 indicated that the drug release was highest in HPMC (F1) and HPMC-DMSO, SLS combinations (F5). At pH 6.8, when compared to F2 and F3, F5, drug release rate is more from F4 may be due to the presence of DMSO+ Propylene glycol. The data of the *in vitro* release were fit into different equations and kinetic models to explain the release kinetics of diclofenac sodium from these buccal patches.

The release kinetics of diclofenac sodium followed zero order from all the patches FI to F5. The better fit (highest R2 values) was observed in case of Korsemeyer Peppas equation than Hixon–Crowell model except formulation-I. Hence mechanism of drug release from the diclofenac sodium patches F2 to F5 followed are diffusion controlled and drug release from F1 followed dissolution controlled.

In the formulation F1 to F5, DMSO was used as permeation enhancer and we observed the response. It was clearly indicated from the fig-F1-98.99% of the diclofenac sodium was released in 12 hrs. When compared to all the earlier formulations, The F1 formulation gave a maximum drug release in 12hrs.

The regression value of films F1 & F5 follows zero order and therefore the release kinetics followed by zero-order

According to Korsemeyer- Peppas model, a value of slope between 0.1 to 0.5 indicates an anomalous behavior.

Fickian diffusion indicates that release mechanism from the all films follows Fickian diffusion. However F1 film follows case –I transport (n<1)

Ageing: Patches that were placed in humidity chamber for short time stability studies were withdrawn every week and analyzed for their drug content. Percentage drug present in the patches were determined spectrometrically. Decrease in the drug content from the patches ranged from 0.952 to 1.497%. It was found that the drug loss is less though the patches were stored for one month. The patches were also observed for their appearance and texture. These properties did not change in patches during the period of study.

Buccal mucoadhesive patches containing diclofenac sodium using HPMC K4-100, DMSO, SLS, and Propylene glycol, glycerin showed satisfactory characteristics without being drastically influenced by ageing.

TABLE 2: EVALUATION OF PATCHES

Formulation	TN (mm)	Swelling		Weight uniformity	Content uniformity	Folding endurance
		% weight increase after 30 min	% area increase after 60 mins			
F1	0.262	431.31	61.60	22.33	96.10	>300
F2	0.199	406.11	59.39	21.80	95.90	>300
F3	0.190	386.07	52.11	19.63	96.06	>300
F4	0.186	291.93	44.09	14.56	96.09	>300
F5	0.261	430.11	60.12	21.89	96.10	>300
F6	0.200	403.09	58.19	20.56	96.09	>300
F7	0.177	384.01	50.09	18.80	96.07	>300
F8	0.161	290.0	43.01	13.89	96.09	>300

TABLE 3: COMPARISON OF FORMULATION F1 TO F5 *IN VITRO* RELEASE STUDIES

Formulation →	F1	F2	F3	F4	F5
Time in hrs ↓	% of drug release± S.D	% of drug release± S.D	% of drug release± S.D	% of drug release± S.D	% of drug release± S.D
0	0	0	0	0	0
0.5	6.55	6.88±	2.8±	2.8±	6.55
1	14.33	15±	7.83±	7.83±	14.33
2	22.5	24.96±	16.17±	14.38±	22.5
4	33.86	37.22±	25.52±	22.39±	33.86
6	50.53	44.12±	35.14±	30.56±	43.99
8	72.81	52.77±	46.23±	41.8±	50.53
10	95.86	75.89±	60.16±	53.89±	82.81
12	98.99	98.56±	98.33±	98.14±	98.15

TABLE 4: COMPARISON OF FORMULATION F1 AND F5

Formulation →	F1	F5
Time in hrs ↓	% of drug release± S.D	% of drug release± S.D
0	0	0
0.5	6.55±0.12	6.55±0.13
1	14.33±0.11	14.33±0.11
2	22.5±0.13	22.5±0.12
4	33.86±0.10	33.86±0.11
6	50.53±0.11	43.99±0.13
8	72.81±0.13	50.53±0.12
10	95.86±0.12	82.81±0.11
12	98.99±0.09	98.15±0.14

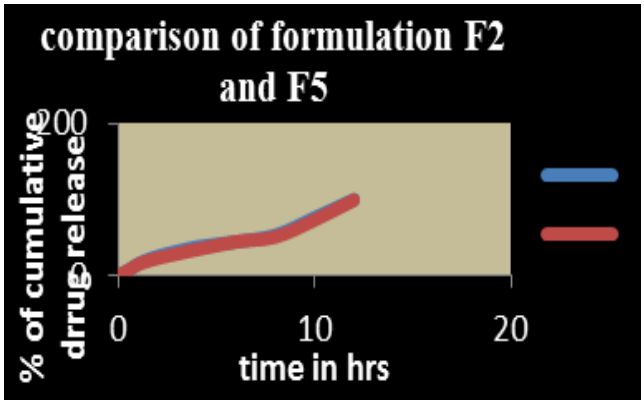

FIG. 2: COMPARISON OF FORMULATION F2 & F3

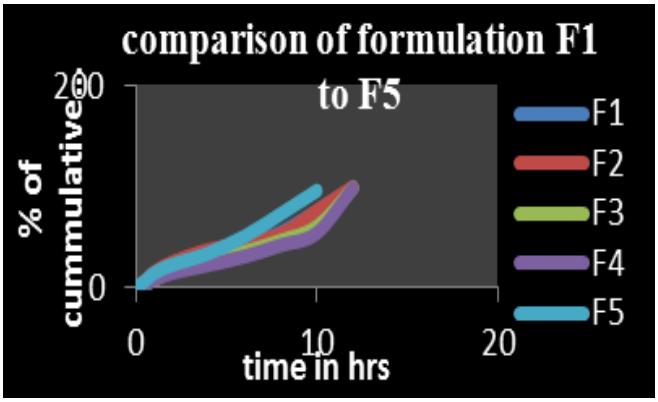

FIG. 3: COMPARISON OF FORMULATION F1 TO F5

TABLE 5: KINETICS STUDY DATA

Time (hour)	% of Cumulative drug release	% cumulative drug remaining	Log% cumulative drug remaining	Square root of time	log time	log % cumulative drug release	Cube root of % drug remaining
0	0	0	0	0	0	0	0
0.5	6.55	93.45	1.9705	0.7071	-0.30102	0.816	4.53
1	14.33	85.67	1.9328	1	0	1.156	4.40
2	22.5	77.5	1.8893	1.4142	0.30102	1.352	4.26
4	33.86	66.14	1.8204	2	0.6020	1.529	4.04
6	50.53	49.47	1.6943	2.449	0.778	1.703	3.67
8	72.81	27.19	1.4344	2.828	0.9030	1.862	3.00
10	95.86	4.14	0.6170	3.162	1	1.981	1.60
12	98.99	1.01	0.0043	3.464	1.0791	1.995	1.003

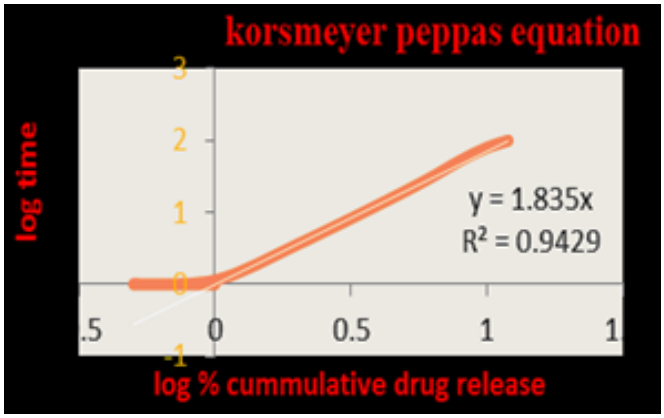

FIG. 4: KORSMEYER PEPPAS EQUATION

FIG. 5: ZERO ORDER RELEASE MECHANISM

CONCLUSION: Good results obtained from *in vitro* release of for diclofenac sodium buccal films. The buccal films release of diclofenac sodium from patches showed a significant improvement. The buccal patches consisting of permeation enhancer demonstrated sustained and controlled release. The drug remained intact and stable in the patches during storage with no significant chemical formulations for diclofenac sodium may be decreased and hence side effects may be reduced. Further work is to establish my further research studies [*in-vivo*].

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