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FORMULATION DEVELOPMENT AND EVALUATION OF DIACEREIN BUCCAL TABLETS

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ABSTRACT

Diacerein (DCN) is a new anti-inflammatory analgesic and antipyretic drug developed specially for the treatment of osteoarthritis. The main objective of the study was to formulate and evaluate bioadhesive buccal tablets to avoid the first pass metabolism in liver. Bioadhesive buccal tablets were prepared by direct compression method using bioadhesive polymers like Gum karaya, Sodium alginate, Carbopol 974P and Carbopol 941NF in different ratios. The physicochemical compatibility of drug and polymers was studied by FT-IR spectroscopy. Prepared tablets were evaluated for permeation study through porcine buccal mucosa, in vitro drug release, bioadhesion strength, swelling index, moisture absorbance, surface pH,ex vivo residence time. Among the prepared formulation containing guar gum (F8) was found to be best formulation which showed the higher drug release, and bioadhesive strength of 2.05±0.42 N (peak detachement force) and 0.5±0.28 mJ (work of adhesion).

KEY WORDS

Diacerein, Bioadesive buccal tablet, ex vivo permeation,in vitro drug release,Bio adhesion strength.

INTRODUCTION

Buccal Delivery involves the administration of drug through buccal mucosal membrane (the lining in the oral cavity).[(1)]The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability.[(2)] A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. Bioadhesive formulations have been developed to enhance the bioavailability [(3,4)] of drugs that undergo substantial first pass hepatic effect and to control the drug release to a constant rate.[(5)] In addition ,it should release the drug in a controlled and predictable manner to elicit the required therapeutic response.[(6-8)] Various buccal mucosal dosage forms are suggested for oral delivery which includes: buccal tablets, buccal Patches and buccal gels.[(9,10)]

Advantages:

- Significant reduction in dose related side effects.
- It provides direct entry of drug into systemic circulation.
- Drug degradation in harsh gastrointestinal environment can be circumvented by administering the drug via buccal route.
- Drug absorption can be terminated in case of emergency.
- It offers passive system, which does not require activation.

- Rapid cellular recovery following local stress or damage.
- Ability to withstand environmental extremes like change in pH, temperature etc.
- The potential for delivery of peptide molecules unsuitable for the oral route.

Disadvantages:

- Once placed at the absorption site, the dosage form should not be disturbed.
- Eating and drinking are restricted.
- There is ever present possibility that the patient may swallow the formulation.
- Drug swallowed with saliva is lost.
- Drugs which are unstable at buccal pH and which irritate the mucosa or have a bitter or unpleasant taste, or an obnoxious odor cannot be administered by this route.

I) MATERIALS AND METHODS

Diacerein was obtained as a gift sample from Aristo Pharmaceuticals Pvt Ltd.,Carbopol 974P,Carbopol 941NF, PVPK30, Gum karaya, Microcrystalline cellulose, Mg. Stearate, Aerosol were obtained as a gift sample from Universal laboratories.

II) EXPERIMENTAL METHODOLOGY

1. Determination of melting point: The melting point of diacerein was determined by Phase equilibrium method.

2. Fourier Transform Infrared spectroscopic studies: FTIR spectra of pure drug was recorded in the range of 450 to 4000 cm-1. Pure drug of Diacerein, Diacerein with physical mixture (excipients) compatibility studies were performed.

3.Preparation of standard graph in phosphate buffer pH 6.8

100 mg of Pure Drug was dissolved in small amount of Methanol (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made upto 100 ml with phosphate buffer pH 6.8. From this secondary stock 1.0, 2.0, 3.0, 4.0, 5.0, ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 10, 20, 30, 40, 50 µg/ml respectively. The absorbance was measured at258nm using a UV spectrophotometer.

III) Evaluation of Pre-Compression Blend :[11-14]

A) Angle of repose: The angle of repose of granules was determined by the funnel method. Angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

Where, θ = angle of repose

h = height of the cone

r = radius of the cone base

B) Bulk density: Density is defined as weight per unit volume. Bulk density ρb, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density was calculated using the formula:

$$\rho b = M/V_0$$

Where, ρb= Apparent bulk density.

M=Weight of the sample.

V=Apparent volume of powder.

C) Tapped Density: The tapped density was calculated, in gm per mL, using the formula:

$$= M/V_f$$

Where, ρ_{tap}= Tapped density.

M = Weight of the sample.

V_f = tapped volume of the powder.

D) Carr's Index: The compressibility index (Carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities.The compressibility index which is calculated using the following formula:

$$\text{Carr's index} = [(\rho_{tap}-\rho b)]/\rho_{tap}] \times 100$$

Where, ρb= bulk density

ρ_{tab}= tapped density

E) Hausner's ratio: It is the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \rho_{tap}/\ \rho b$$

Where, ρ_{tap} = Tapped density.

ρb = Bulk density.

FORMULATION OF BUCCAL TABLET

Then the powder blend was compressed into tablets by the direct compression method using 6mm flat faced punches. The tablets were compressed using a sixteen station Cadmach rotary tablet-punching machine. Composition of the prepared bioadhesive buccal tablet formulations of Diacerein were given in Table 1.

Table 1. Composition of buccal tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diacerein Pure Drug	50	50	50	50	50	50	50	50	50
Gum karaya	25	37.5	50	-	-	-	-	-	-
Sodium Alginate	-	-	-	25	37.5	50	-	-	-
Carbopol 974 P	-	-	-	-	-	-	25	37.5	50
Carbopol 941NF	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
PVPK30	5	5	5	5	5	5	5	5	5
MCC pH 102	107.25	95.25	82.75	107.25	95.25	82.75	107.25	95.25	82.75
Mg. Stearate	2	2	2	2	2	2	2	2	2
Aerosil	4	4	4	4	4	4	4	4	4
Total Weight (mg)	200	200	200	200	200	200	200	200	200

IV). EVALUATION OF BUCCAL TABLETS

A). Weight variation:

The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) X 100

B). Tablet Thickness:

The thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets is calculated and presented with standard deviation.

C). Tablet Hardness:

Hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm^2.

D). Friability:

Tablet strength is measured by using Roche friabilator. Test subjects to number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

Percent friability (% F) was calculated as

$F(\%) = [W_o\text{-}W/W_o] \times 100$

Where, W_0 is the initial weight of the tablets before the test and

W is the final weight of the tablets after test.

E). Assay:

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at258nm using pH6.8 phosphate buffer.

F). *In vitro* release studies:

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 258 nm.

G). Kinetic Analysis of Dissolution Data: [15,16,17]

To analyze the in vitro release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.

H). Swelling Studies:

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.8) solution. At regular intervals (0.5,1, 2, 3, 4, 5 and 6hr), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2**)** (Ritthidej et al., 2002). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Equation**.**

Swelling index = $\frac{(W_2-W_1)}{W_1}$ X 100

I). *In vitro* bioadhesion strength:

Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced force gauge equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK). The peak detachment force was maximum force to detach the tablet from the mucosa.

Force of adhesion = $\frac{\text{Bioadhesion strength}}{1000}$ x 9.8

Bond strength = $\frac{\text{Force of adhesion}}{\text{surface area}}$

J). *Ex vivo* residence time:

The *Ex vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 secs after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 ml of phosphate buffer, pH 6.8, at 37^{0}C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time for complete erosion or detachment from the mucosa was recorded.

***K). Ex vivo* permeation studies through porcine buccal mucosa:**

The aim of this study was to investigate the permeability of buccal mucosa to Diacerein. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption.

L). Tissue permeation:

The experiments were performed in triplicate (n = 3) and mean values were used to calculate flux (J) and permeability coefficient (P).

J = $\frac{(dQ/dt)}{A}$

Where, J is Flux (mg.hrs^{-1}cm^{-2})

dQ/dt = is the slope obtained from the steady state portion of the curve.

A= the area of diffusion (cm^2)

RESULT AND DISCUSSION:

1.Preformulation study:

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients used.

2.FTIR Compatibility Studies:

FTIR spectra of pure drug and formulation with other ingredients were recorded**.** The FTIR Spectra of pure Diacerein drug and polymer was compared with the FTIR spectrum of drug.

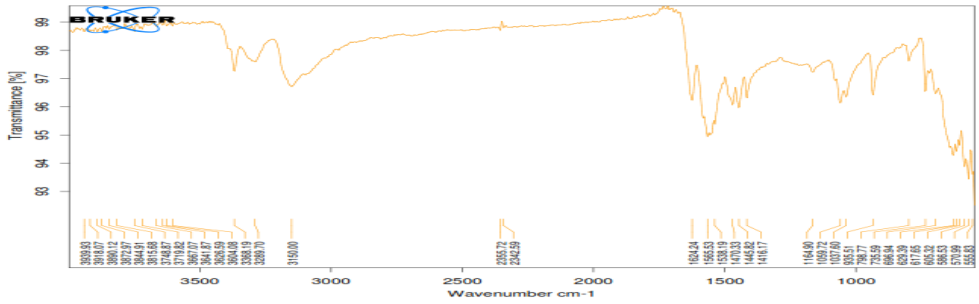

Fig 1: FTIR of pure drug

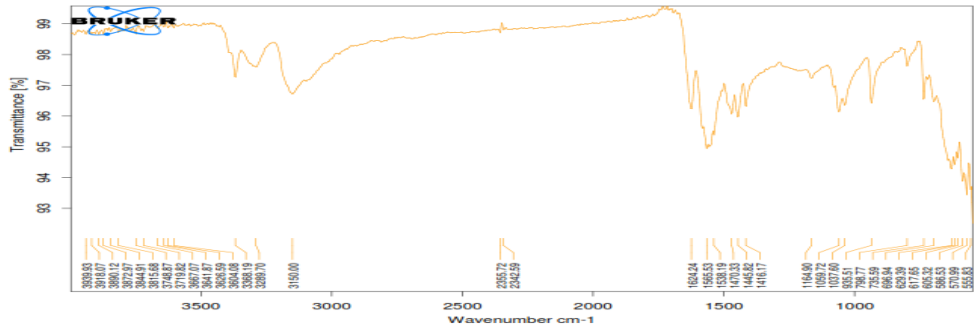

Fig 2: FTIR compatibility studies of optimized formulation

There was no appearance or disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms

that the materials taken for the study are genuine and there were no possible interactions.

Table 2: Standard graph of Diacerein in phosphate buffer pH 7.4

S.No	Concentration (µg/mL)	Absorbance
1	0	0
2	5	0.213
3	10	0.448
4	15	0.684
5	20	0.877
6	25	1.1

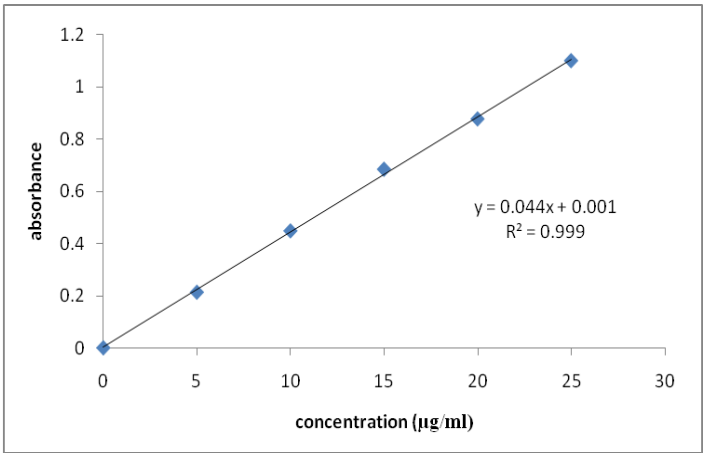

Fig 3 : Standard graph of Diacerein in phosphate buffer pH 7.4

Table 3: *Ex vivo* permeation of Diacerein drug solution through the porcine buccal mucosa

Time (hr)	Cumulative amount of Diacerein permeated
0	0
0.5	19.14
1	23.26
2	30.68
3	38.19
4	46.58
5	56.62
6	68.52
7	78.34
8	88.98
Flux	122.38 µg.hr^{-1}cm^{-2}

The tissue was isolated successfully because no detectable level of phenol red (Marker compound) was observed in the receiver compartment. Hence it did not show any penetration and shows the intactness of the porcine buccal mucosa. The flux was found to be 122.38 µg.hr^{-1}cm^{-2}

III) Characterisation of Precompression Blend:

The precompression blend for Buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index and drug content and shown in the Table 26. Angle of repose was less than 30° and Carr's index values were less than 18 for the precompression blend of all the batches indicating good to fair flowability and compressibility, Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Table 4: Physical Properties of Precompression Blend

Formulation Code	Angle of repose (θ)	Bulk density (g/mL)	Tapped density(g/mL)	Carr's index (%)	Hausner's ratio
F1	26.76±1.2	0.526±1.8	0.612±1.6	14.0±0.02	1.16±0.1
F2	27.54±2.5	0.662±1.2	0.763±1.3	13.23±0.1	1.15±0.05
F3	24.65±2.5	0.695±1.5	0.823±0.8	15.5±0.08	1.18±0.1
F4	22.9±1.4	0.672±1.2	0.742±1.2	12.2±0.1	1.21±0.2
F5	28.3±2.2	0.643±2.1	0.624±0.7	14.2±0.9	1.11±0.2
F6	24.84±0.4	0.654±1.6	0.755±1.4	13.12±1.8	1.12±0.06
F7	28.68±0.8	0.782±1.2	0.869±0.8	11.0±1.2	1.11±0.2
F8	24.68±1.2	0.560±0.5	0.631±1.2	11.25±0.15	1.12±0.08
F9	25.16±0.8	0.628±2.5	0.714±1.6	14.27±0.12	1.17±0.5

Each value represents the mean ±SD (*n* =3).

IV) POST COMPRESSION CHARACTERIZATION OF BUCCAL TABLETS:

Table 5: Physico-chemical parameters of Diacerein buccal tablets:

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm$^{2)}$	Friability (%)	Assay (%)
F1	200.74 ± 0.61	2.37 ± 0.03	5.2±0.14	0.55	99.65 ± 0.44
F2	201.04 ± 0.80	2.34 ± 0.02	5.3±0.29	0.63	99.13 ± 0.75
F3	199.38 ± 0.71	2.36 ± 0.03	5.2±0.49	0.66	99.28 ± 0.92
F4	198.45 ± 0.64	2.36 ± 0.02	5.4±0.17	0.58	98.77 ± 1.00
F5	197.91 ± 1.01	2.21 ± 0.02	5.5±0.28	0.64	98.96 ± 0.44
F6	200.98 ± 0.82	2.34± 0.01	5.9±0.24	0.47	98.81 ± 0.92
F7	201.38 ± 0.80	2.68± 0.02	6.8±0.17	0.66	99.77 ± 0.72
F8	199.04 ± 0.71	2.34± 0.03	6.5±0.49	0.65	99.81 ± 0.44
F9	200.94 ± 0.75	2.22± 0.02	6.0±0.19	0.43	99.15 ± 0.75

Each value represents the mean ±SD (*n* =3).

A) Weight variation:

Acceptable physicochemical properties were observed for the prepared buccal tablets all the formulated tablets passed the weight variation test. The weight variations of all compressed tablets were within the limits as per USP.

B) Thickness:

The thickness of the tablets varied from 2.21 to 2.68 all the batches showed uniform thickness.

C) Hardness:

Hardness of the tablets was found to be good depending upon compression force applied (5.2 – 6.0 kg/cm²).

D) Friability:

Friability was obtained between the ranges 0.55 to 0.67, which was below 1% indicating sufficient mechanical integrity of the tablets.

E) Assay:

The drug content estimation showed values in the range of 98.69±1.00 to 99.81±0.04 which reflects good uniformity in the drug content among different formulations. Assay of all compressed tablets were within the limits as per USP.

F) *In vitro* drug release studies

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Diacerein from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs

Tablets formulated using Gum karaya, Sodium Alginate and Carbopol 974 P alone were eroded faster & dissolved completely within 1-2 hrs. While tablets containing Carbopol 941NF combination with polymers remain intactness and provide slow drug release up to 8 hrs. This might be due to swelling forming nature of Carbopol.

As increase in the polymer concentration, causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusion path and decrease in diffusion coefficient of drug. Therefore, increased in polymers concentration leads to decrease in drug release.

This was observed that there was a reduction in the amount of polymer ensures faster release. This may be attributed due to reduction in strength of gel layer which enhances drug diffusion and water uptake through matrix.

Table 6. *In vitro* cumulative percentage drug release profile of Diacerein formulations with Sodium alginate

Cumulative Percentage Drug Release			
Time (hrs)	**F1**	**F2**	**F3**
0	0	0	0
0.5	38.95	34.76	33.37
1	46.20	41.34	44.79
2	52.89	55.75	50.88
3	63.66	59.45	58.39
4	68	66.89	62.83
5	72.74	72.81	70.87
6	78.18	78.30	76.65
7	83.69	82.62	81.23
8	93.88	89.23	85.54

Table 7: *In vitro* cumulative percentage drug release profile of Diacerein formulations with Gum Karaya

Cumulative Percentage Drug Release			
Time (hrs)	**F4**	**F5**	**F6**
0	0	0	0
0.5	38.95	34.76	33.37
1	46.20	41.34	44.79
2	52.89	55.75	50.88
3	63.66	59.45	58.39
4	68	66.89	62.83
5	72.74	72.81	70.87
6	78.18	78.30	76.65
7	83.69	82.62	81.23
8	93.88	89.23	85.54

Table 8: *In vitro* cumulative percentage drug release profile of Diacerein formulations with Carbopol 974 P

Cumulative Percentage Drug Release			
Time (hrs)	**F7**	**F8**	**F9**
0	0	0	0
0.5	26.42	24.91	31.86
1	44.91	39.82	37.24
2	53.59	44.47	43.15
3	62.87	55.68	52.26
4	69.21	61.81	56.98
5	74.41	66.33	60.6
6	80.18	73.32	64.31
7	86.60	89.51	69.33
8	90.86	96.42	76.48

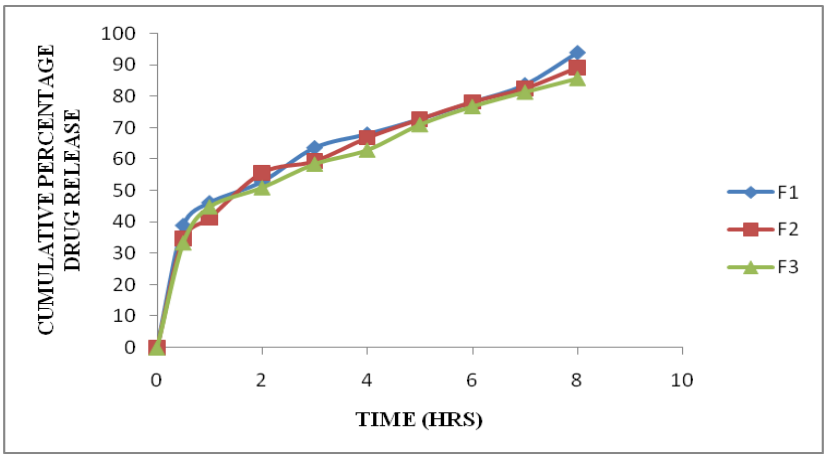

Fig 4: *In vitro* cumulative percentage drug release profile of Diacerein formulations with Sodium Alginate

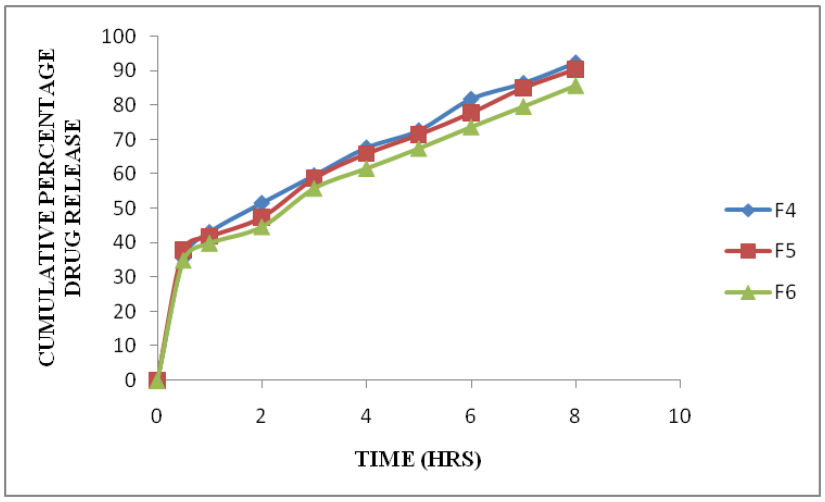

Fig 5: *In vitro* cumulative percentage drug release profile of Diacerein formulations with gum karaya

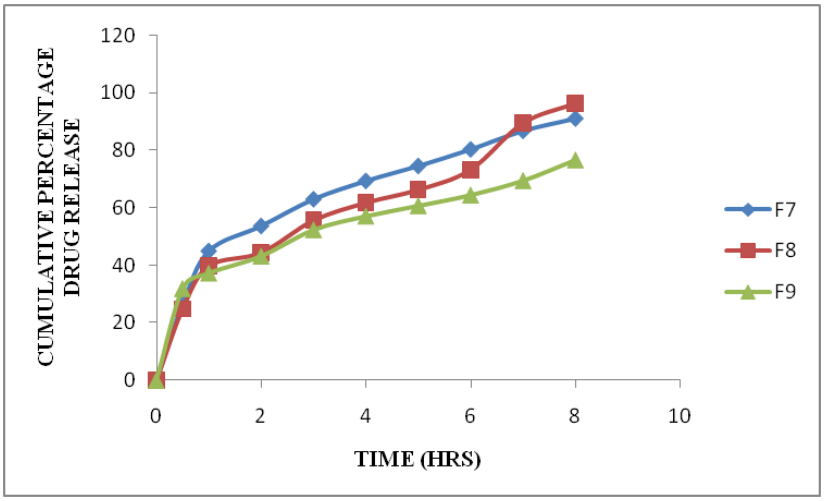

Fig 6: *In vitro* cumulative percentage drug release profile of Diacerein formulations with Carbopol 974 P

From the Dissolution Data, it was evident that the F8 Formulation showed highest drug release 96.42% in 8 hours which consists of Carbopol 974 P, Carbopol 941NF.

I) Ex *vivo* bioadhesive strength measurement:

The values of the bioadhesive strength of Diacerein buccal tablets of different formulations were given in Table. The bioadhesive characters were found to be

affected by the nature and proportions of the bioadhesive polymers used in the formulations.

When the polymer concentration is too low, the number of penetrating polymer chain per unit volume of mucus is small and the interaction between polymer and mucus is unstable. In general, more concentrated polymer would result in longer penetrating chain length and better adhesion.

However, for each polymer, there is a critical concentration, above which the polymer produces an unperturbed state due to significantly coiled structure. As a result, the accessibility of the solvent to polymer decreases and chain penetration of polymer drastically decreased. Therefore, higher concentration of polymer does not necessarily improve and in some cases, actually diminish mucoadhesive properties.

J. *Ex vivo* residence time:

The *Ex vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablets. The *ex vivo* residence time was determined by using specially designed apparatus. As the concentration of mucoadhesive material increased, the residence time increased. This test reflects the adhesive capacity of polymers used in formulations

Table 9: *Ex vivo* residence time, Moisture absorption, Surface pH, Bioadhesive strength values of Diacerein buccal tablets Optimized Formulation.

Formulation code	*Ex vivo* residence time	Moisture absorbance	Surface pH	Bioadhesive strength	
				Peak detachment force (N)	Work of adhesion (mJ)
F1	6Hrs 42 min	30.83± 0.25	6.96±0.16	1.89±0.55	0.47±0.28
F4	7 Hrs 15 min	25.66 ± 0.25	6.86±0.43	2.34±0.02	0.62±0.04
F8	8Hrs 45 min	32.45 ± 0.25	6.99±0.35	2.05±0.42	0.5±0.28

Each value represents the mean ± SD (n=3)

H) Swelling Studies of buccal tablets

Swelling Studies were performed to the selected Formulations (F1, F4, F8).

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drug and proper bioadhesion. The polymeric tablet formulations displayed an increase in weight due to water uptake.

The mucoadhesive polymers used in this study were hydrogels which are swellable upon contact with water and retain large amount of water. The viscosity of polymer affects the swelling index.

The higher swelling index may lead to reduced bioadhesion strength and too low swelling index may not produce sufficient bioadhesion strength. So, the optimum swelling index was produced.

From the results, the highest percentage swelling is to the formulation F8 i.e., 89.2% at the 8 hours.

Table 10: Swelling studies of buccal tablets

% Swelling Index			
Time (hr)	**F1**	**F4**	**F8**
0	0	0	0
0.5	19.2	22.7	23.6
1	24.3	28.4	32.2
2	31.9	33.2	38.3
3	38.6	38.6	45.8
4	44.8	43.7	52.1
5	52.4	49.2	66.4
6	60.4	56.9	71.2
7	69.2	62.7	78.8
8	76.1	68.6	89.2

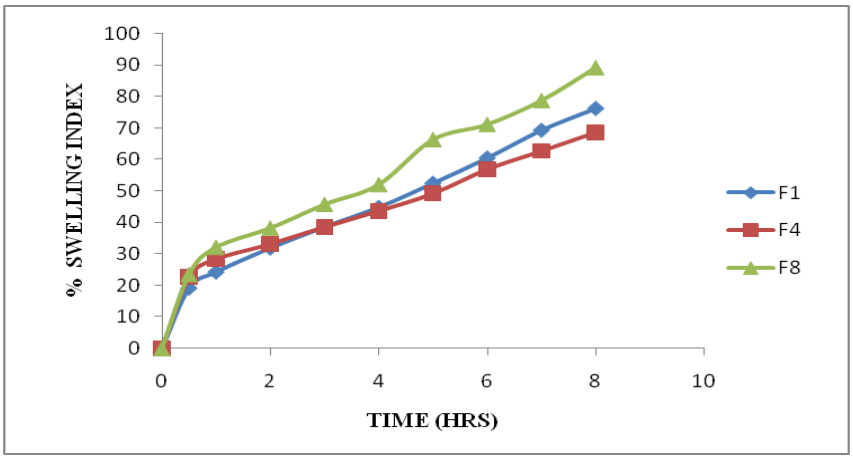

Fig 7: Swelling index of Diacerein buccal tablets

K) *Ex vivo* permeation studies of Diacerein buccal tablets:

Table 11: Drug release of Diacerein *Ex vivo* permeated buccal tablets

Time (hrs)	F1	F4	F8
0	0	0	0
0.5	19.53	11.23	14.53
1	28.43	22.33	29.43
2	36.71	31.47	36.71
3	48.77	42.65	49.77
4	55.98	50.28	55.98
5	60.32	53.24	57.32
6	69.23	64.81	66.78
7	78.48	76.69	77.99
8	87.94	82.8	85.28
FLUX	119.86µghr^{-1} cm^2	111.45µghr^{-1} cm^2	114.15 µghr^{-1} cm^2

indicates units for flux: mg hr^{-1}cm^{-2}

The *ex vivo* permeation studies were conducted for all formulations, the values of flux were given in Table.

Release kinetics:

The optimized formulation such as gum (F8) follows Higuchi order of release kinetics.

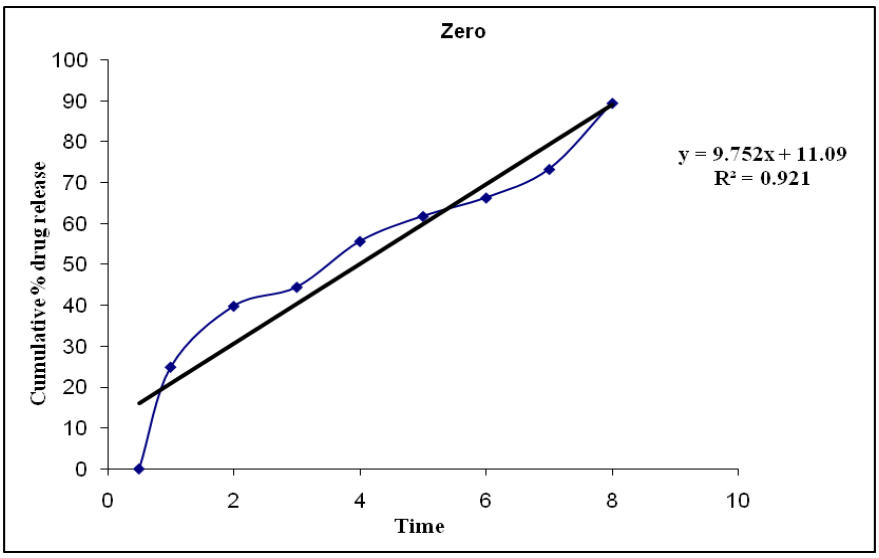

Fig 8: Zero order release kinetics

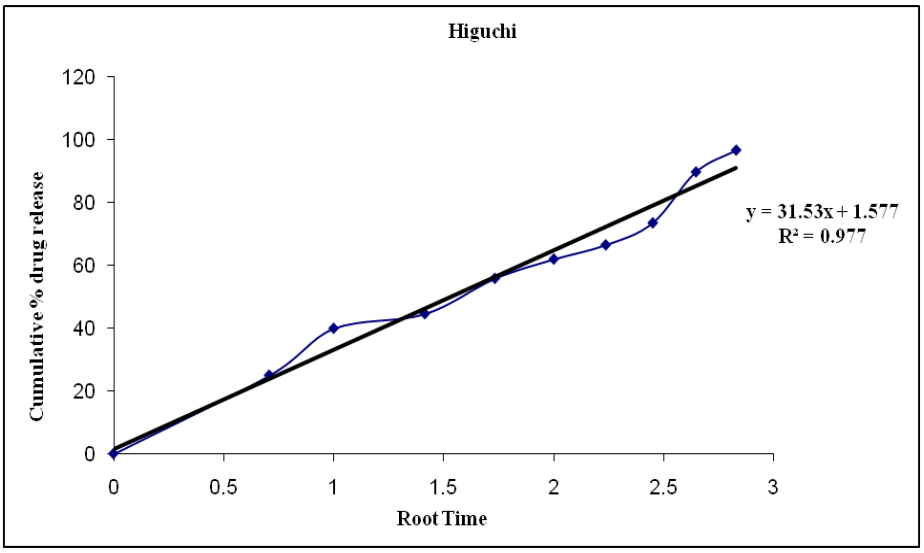

Fig 9: Higuchi release kinetics

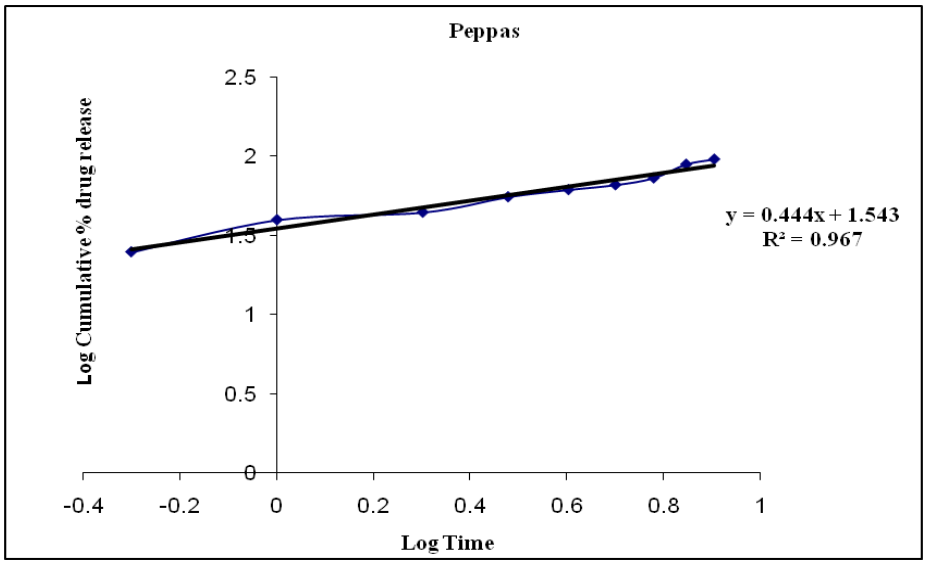

Fig 10: Kors mayer peppas release kinetics

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