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"FORMULATION AND EVALUATION OF BIOADHESIVE BUCCAL TABLET OF DIACEREIN"

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Abstract: The aim of this work was to develop a tablet for the buccal delivery of the poorly water soluble drug diacerein, having extensive hepatic metabolism, which is useful in treatment of osteoarthritis. Buccal tablets containing diacerein were prepared by direct compression method using combination of bioadhesive polymers like carbopol 934P, HPMC, Sodium alginate, SCMC, HPC and PVP K30 in different ratio. Ethyl cellulose used as an impermeable baking layer. Buccal tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, mucoadhesive time, swelling index, *in vitro* drug release. Buccal tablets containing CP and HPMC K4M in the ratio (1:1) had the maximum percentage of *in vitro* drug release (98.86%) in 6 hours along with satisfactory bioadhesive strength (23.5gm). The swelling index of tablet increased with increasing amount of CP. Stability studies on the promising formulation indicated that there are no significant changes in drug content and *in vitro* dissolution, bioadhesive strength and swelling index. The formulation consist of diacerein (50mg), carbopol 934P (30mg), HPMC K4M (30mg), MCC (28mg), sodium saccharin (7.5mg), magnesium stearate (1.5mg), talc (3mg) and ethyl cellulose (20mg) was found as optimum formulation.

Keywords: Valsartan, gellan gum, *in vitro* swelling, *in vitro* drug release

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INTRODUCTION

Buccal drug delivery

There are various routes of drug administration meant for different pharmaceutical dosage forms like parentral, topical and oral route. Among these the later one is the most preferred and convenient route for drug administration. This route however has certain demerits like drug inactivation by the hepatic first pass effect, degradation of drugs by gastro-intestinal tract enzyme. These factors affect the drug absorption and hence cause the poor bioavailability of active drugs which may lead to the formation of therapeutically inactive drug molecule. Advances in emerging trends in pharmaceutical sciences has designed different approaches to avoid first pass metabolism, buccal route seems to be more convenient and beneficial. Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation. A drug administered through the buccal mucosa enters directly in the systemic circulation, thereby minimizing the first-pass hepatic metabolism and adverse gastro-intestinal effect. Buccal cavity possesses ideal characteristics for drug absorption and hence it acts as an excellent site for the absorption of drugs[1].

Bioadhesive buccal tablets

Bioadhesive tablets can be formulated into monolithic partially coated or multi-layered matrices. Monolithic tablets are easy to manufacture by conventional techniques and provide for the possibility of loading large amount of drug. Drug can be incorporated with an absorption enhancer, if required, partial coating of a monolithic tablet affords protection of every face of the tablet, which is not in contact with the mucosa. Such systems allow undirected drug release and avoid drug release into salivary fluids. Multilayered tablets could be of a variety of geometrical arrangements. In case of bi-layered tablets drug can be incorporated in the adhesive layer, which comes in contact with the mucosal surface. This drug containing mucoadhesive layer is then protected from the oral cavity environment by a second upper inert layer, which faces into the oral cavity[2].

Advantages of bioadhesive buccal drug delivery system[6]

- Ease of administration & termination of therapy is easy.
- Permits localization of drug to the oral cavity for prolonged period of time.
- Can be administered to unconscious patients.
- Offers an excellent route to systemic delivery of drugs with high first pass metabolism thereby offering a great bioavailability.

- A significant reduction in dose can be achieved thereby reducing dose dependent side effects.
- It allows for local modification of tissue permeability, inhibition of protease activity in immunogenic responses. Thus selective use of therapeutic agents like peptides, proteins and ionized species can be achieved.
- Drugs which are unstable in the acidic environment of the stomach or which are destroyed by enzymatic or alkaline environment of the intestine can be administered by this route.
- These can be administered to patients with nausea and vomiting, gastrointestinal disease or surgery or swallowing difficulty.

MATERIALS AND METHODS

Diacerein was obtained as a gift sample from Cadila Pharma(Ahmedabad). Carbopol 934P, HPMC K4M, HPMC K_{15}M, Sodium CMC, PVP K30 and HPC wERE obtained as a gift sample from S. D. Fine Chemicals. All other chemicals used were of analytical grade.

EXPERIMENTAL METHODOLOGY

IDENTIFICATION OF DRUG

Determination of melting point

The melting point of diacerein was determined by capillary method.

Fourier transform infrared spectroscopy

FTIR spectra of pure drug was recorded in the range of 400 to 4000 cm^{-1} by KBr discmethod using Perkin elmer, spectrum RX1- FTIR system USA.

ESTIMATION OF DIACEREIN

Preparation of phosphate buffer pH 6.8

Measure accurately 50 ml of the 0.2M potassium dihydrogen phosphate solution using 10 ml measuring cylinder and transfer it in 100 ml volumetric flask. Then accurately measured 22.4 ml final volume.

Estimation of absorption maxima (λ_{max})

10 mg of diacerein was accurately weighed and transferred to 100 ml ofvolumetric flask. The drug was dissolved in phosphate buffer pH 6.8 and the volume was made up to 100 ml to

obtain a stock solution of 100 µg/ml. One ml of this stock solution wasagain diluted with phosphate buffer pH 6.8 up to 10 ml to obtain a solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 400 nm in a double beam UV-Visible spectrophotometer (shimadzu 1800).

Preparation of calibration curve in phosphate buffer pH 6.8

10 mg of diacerein was accurately weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 2 ml DMF and the volume was made up to 100 ml using phosphate buffer pH 6.8 to obtain a stock solution of 100 µg/ml (stock solution I). One ml of this stock solution wasagain diluted with phosphate buffer pH 6.8 up to 10 ml to obtain a solution of 10 µg/ml (stock solution II). From stock solution II aliquots of 2, 4, 6, 8 ml were transferred toa series of 10 ml volumetric flasks. The volume was made up with phosphate buffer pH 6.8 fluid to give 2, 4, 6 & 8 µg/ml of concentration. The absorbances of thesesolutions was measured at 256 nm against blank.

DRUG-EXCIPIENT COMPATIBILITY STUDY

FTIR spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm^{-1} by KBr disc method using FTIR spectrophotometer. FTIR spectra of physical mixture was compared with FTIR spectra of pure drug.

FORMULATION OF BUCCAL TABLET

Preparation of buccal tablets

Bioadhesive buccal tablets containing diacerein were prepared by direct compression method. The ingredients of the core layer were weighed accurately and mixed properly. CP 934P was used as bioadhesive polymer and other polymers were used as release modifier. The mixture was then compressed using 8 mm die by a tablet press. After compression of tablet the upper punch was removed carefully without disturbing the set up and ethyl cellulose for the backing layer was added over the tablet and compressed again[18].

Table 1. Composition of buccal tablets

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Diacerein	50	50	50	50	50	50	50	50	50	50
CP 934 P	30	20	15	12	30	20	15	12	30	20
HPMC K_4M	30	40	45	48	-	-	-	-	-	-
HPMC $K_{15}M$	-	-	-	-	30	40	45	48	-	-
HPC	-	-	-	-	-	-	-	-	30	40
Sodium CMC	-	-	-	-	-	-	-	-	-	-
PVP K 30	-	-	-	-	-	-	-	-	-	-
Sodium saccharin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
MCC	28	28	28	28	28	28	28	28	28	28
Talc	3	3	3	3	3	3	3	3	3	3
Mg-stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
EC (backing layer)	20	20	20	20	20	20	20	20	20	20
Total weight	170	170	170	170	170	170	170	170	170	170

Ingredients (mg)	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}	F_{20}
Diacerein	50	50	50	50	50	50	50	50	50	50
CP 934 P	15	12	30	20	15	12	30	20	15	12
HPMC K_4M	-	-	-	-	-	-	-	-	-	-
HPMC $K_{15}M$	-	-	-	-	-	-	-	-	-	-
HPC	45	48	-	-	-	-	-	-	-	-
Sodium CMC	-	-	30	40	45	48	-	-	-	-
PVP K 30	-	-	-	-	-	-	30	40	45	48
Sodium saccharin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
MCC	28	28	28	28	28	28	28	28	28	28
Talc	3	3	3	3	3	3	3	3	3	3
Mg-stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
EC (backing layer)	20	20	20	20	20	20	20	20	20	20
Total weight	170	170	170	170	170	170	170	170	170	170

EVALUATION OF BUCCAL TABLETS

Pre compression parameters

Bulk density

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density was calculated using following equation.

Bulk density = Weight of powder / Bulk volume

Tapped density

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (Vt) occupied in the cylinder and weight of the blend was measured. The tapped density (ρt) was calculated using following equation.

Tapped Density = Weight of powder / Tapped volume

Compressibility Index (CI)

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 15% has been found to exhibit good flow properties. Tapped and Apparent bulk density measurements can be used to estimate the compressibility of a material.

Carr's index (%) = [(Tapped density - Bulk density) × 100] / Tapped density

Hausner's Ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Hausner's ratio = Tapped density/Bulk density

Angle of repose

Angle of repose is the tan inverse of angle between height of pile of powder and the radius of the base of conical pile. Angle of repose was determined using flowing through funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the following equqtion. Values for angle of repose less than or equal to 30

degrees suggest a free flowing material and angles greater than or equal to 40 degrees suggest a poorly flowing material.

$\theta = \tan^{-1} h/r$

Where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Post compression parameters

Thickness and diameter

The thickness and diameter of the tablet was measured using verniercalipers. Three tablets were selected randomly from individual formulations, thickness and diameter was measured using verniercalipers. It was measured in mm[18].

Weight variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown.

Hardness

The pfizer hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2.[14]

Friability (%F)

Friability of the tablet determined using friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions.Tablets were dedusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage.

% friability=(Initial weight of tablets-Final weight of tablets)/Initial weight of tablets

5) Content uniformity

Twenty tablets were weighted and powdered in a mortar. Accurately weighted a quantity of the powder equivalent to about 10 mg of diacerein dissolved by 2 ml of DMF diluted to 100 ml with phosphate buffer pH 6.8 in 100 ml volumetric flask. It was shaken for 15 minutes and filtered. 1 ml of the filtrate was diluted to 10 ml with phosphate buffer pH 6.8. The absorbance of the resulting solution was measured at λmax 256 nm and the content of diacerein was calculated from the absorbance obtained.

***IN VITRO*EVALUATION OF BUCCAL TABLET**

Surface pH study

The surface pH study for buccal tablets was performed to investigate the possibility of any side-effect *in vivo*. An acidic or alkaline pH may irritate the buccal mucosa, so the surface pH of tablet should be almost neutral. In this method the tablet was allowed to swell by placing it in contact with 1 ml of phosphate buffer pH 6.8 for 2hrs at room temperature. The pH was determined by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1 minute[11].

Swelling index: At first the buccal tablets are weighed individually (W_1) and

then the tablets are placed in an agar gel plates 1% or 2% in a Petri-dish with the core (drug-polymer layer) facing the gel surface, incubated at 37±1°C for up to 6 hrs. At regular intervals of time, the swollen tablets are removed from Petri-dish; the excess water is removed with the help of a filter paper and weighed again(W_2). The Swelling Index (SI) can be calculated using the formula.

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1} \times 100$$

Where W_2= weight of tablet after time at 't'.

W_1 = weight of tablet before placing in the petri dish[18].

***In vitro* drug release study**

The USP dissolution apparatus is used for the drug release study. It can be either a rotating paddle type, where backing layer of buccal tablet is to be attached to a glass disk with adhesive material and the disk is placed at the bottom of the rotating basket type. The dissolution study is to be performed by suitable amount of phosphate buffer pH 6.8, samples at pre-determined

time intervals are taken out and replaced with fresh buffer medium. The samples are filtered and suitable dilution is made and analyzed by an U.V Spectrophotometer[13].

***Exvivo* mucoadhesive strength**

The mucoadhesion strength of buccal tablets can be determined by using a modified balance method. The apparatus constitutes of a two pan balance which has been modified by replacing one pan of the apparatus with a Teflon assembly on which the tablet is stuck. This pan is in turn lowered on to the other Teflon assembly over which the model buccal mucosa has to be tied. The goat buccal mucosa is to be stored in phosphate buffer at room temperature before use. The mucosal membrane is to be excised by removing the underlying connective and adipose tissues and then equilibrated in phosphate buffers pH 7.4, at 37±1°C for 30 min. The tablet is to be stocked to the Teflon arm using cyano-acrylate adhesive and lowered onto the mucosa under a constant weight of 5g for a total contact period of 5 min. The Mucoadhesion strength is assessed in terms of weight (g) required to detach the tablet from the membrane[30].

***Exvivo* mucoadhesion time**

The Ex vivo mucoadhesion time for mucoadhesive buccal tablets was determined modified USP dissolution apparatus. The dissolution medium was composed of 500 ml of phosphate buffer pH 7.4 maintained at 37°C. A segment of porcinebuccal mucosa each of 3 cm length was glued to the surface of glass slab which was then vertically attached to the apparatus. Three tablets of each batch were hydrated using 1.5 ml of pH 7.4 buffer on one side and hydrated surface was brought into contactwith mucosal membrane for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing phosphate buffer pH 7.4. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time necessary for complete erosion or detachment of the buccal tablet from the mucosal surface was recorded[15]

RELEASE KINETICS[7]

In order to understand the mechanism and kinetics of drug release, the results of the in vitro drug release study were fitted with various kinetic models namely zero order (% release vs t), first order (log% unrelease vs t), Higuchi matrix (% release vs square root of time). In order to define a model which will represent a better fit for the formulation, drug release data further analyzed by Korsmeyer Peppas equation, $Mt/M_\infty = kt^n$, where Mt is the amount of drug released at time t and M_∞ is the amount released at time ∞, the Mt/M_∞ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. R^2 values were calculated for the linear curves obtained by regression analysis of the above plots.

STABILITY STUDY

The stability study was carried out on the optimized formulation as per ICH guidelines Q1C. Optimized formulation were packed in rubber stoppered vials kept in stability chamber. The stability study was performed at 40 ± 2 °C / 75 ± 5 % RH for 1 month. At the end of study sample were analyzed for drug content, in vitro drug release, bioadhesive strength and swelling index[9].

***EX VIVO* PERMEATION STUDY**

Ex vivo permeation study of mucoadhesive buccal tablet was carried out on porcine buccal membrane using modified Franz diffusion cell with a diffusion area of 17.35 cm2 and the acceptor compartment volume of 22 ml. A semi permeable membrane was clamped between the donor and acceptor compartments. The water in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer and maintained at 37 ± 5°C. The buccal tablet was placed into the donor compartment and was wetted with 1ml of water. The diffusion was carried out for 8 h. The amount of diacerein permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of water. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically at 256 nm.

RESULT AND DISCUSSION

IDENTIFICATION OF DRUG

MELTING POINT

Melting point of diacerein was found to be 215-220^{o}C which was in the rangeas given in literature, hence the drug could be stated as pure.

Table 2. Determination of melting point

Theoretical range	Practically obtained
217-218^{o}C	215-220^{o}C

FT-IR SPECTRA OF DIACEREIN

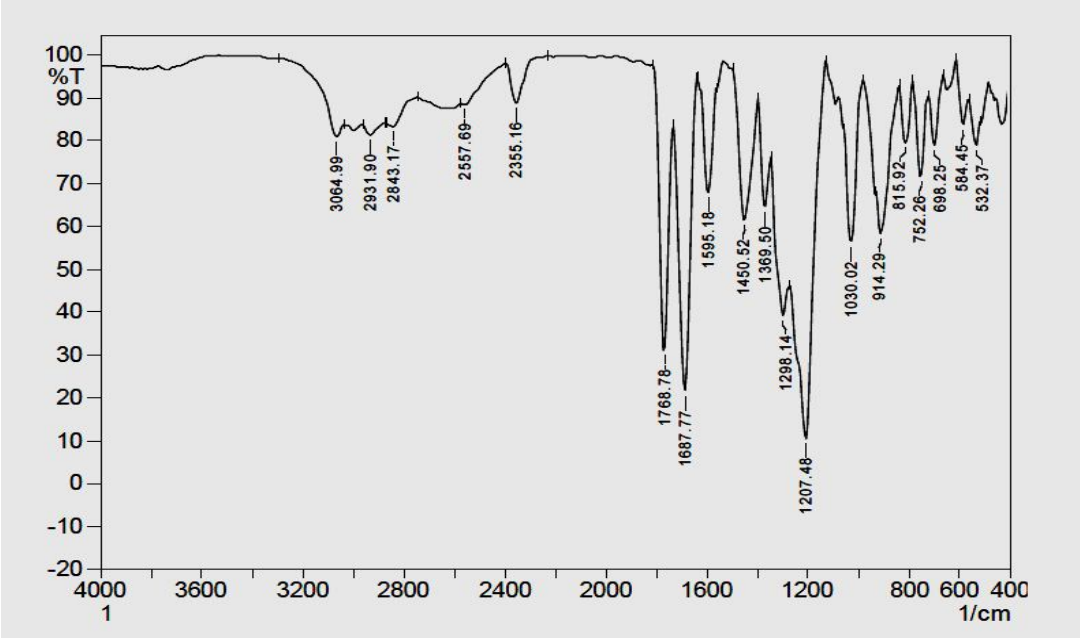

Figure 1 FTIR spectra of diacerein

Table 3. Interpretation of FTIR spectra of diacerein

Functional group	Frequency (cm^{-1})	
	Experimental	Specified in literature
Aromatic ring	1687.77	1600-1700
>C=O Stretching	1768.78	1700-1900
-C-O Stretching	1207.48	1200-1250
O-H Streching	3064.99	2466-3244

ESTIMATION OF DIACEREIN

IDETERMINATION OF ABSORPTION MAXIMA

The UV absorption maxima of diacerein in phosphate buffer pH 6.8 was found to be 256 nm, when scanned between 200-400 nm by UV-visible double beam spectrophotometer.

CALIBRATION CURVE OF DIACEREIN IN PHOSPHATE BUFFER PH 6.8

The calibration curve of diacerein was prepared in phosphate buffer pH 6.8.The linearity data and calibration curve of diacerein in phosphate buffer pH 6.8 has been shown in and Figure

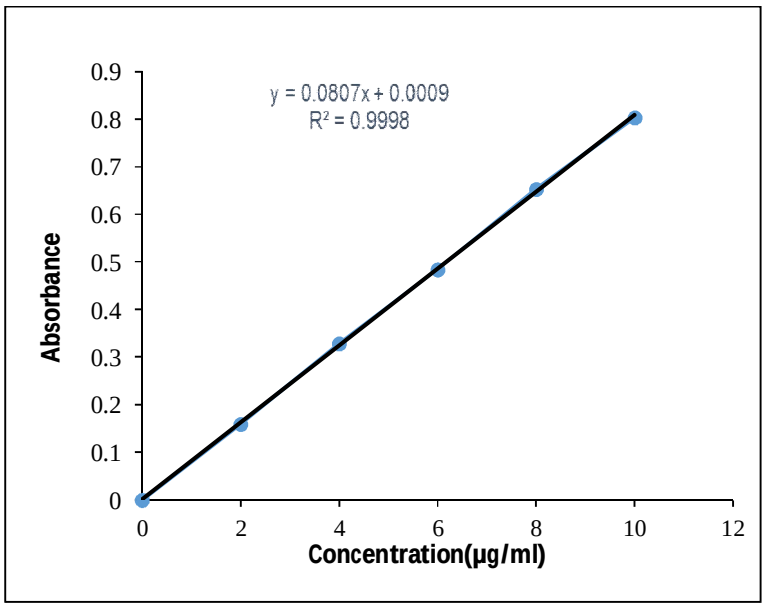

Figure Linearity curve of diacerein in phosphate buffer pH 6.8

EVALUATION OF BUCCAL TABLET

Table 4. Pre-compression parameters

Batch	Bulk density*(gm/ml)	Tapped density*(gm/ml)	Carr's index* %	Hausner's ratio*	Angle of repose*
F_1	0.35 ± 0.01	0.41 ± 0.010	14.63 ± 1.88	1.17 ± 0.01	21.26 ± 1.05
F_2	0.43 ± 0.01	0.50 ± 0.010	14.00 ± 0.77	1.16 ± 0.05	21.12 ± 1.67
F_3	0.36 ± 0.02	0.42 ± 0.150	14.28 ± 1.90	1.16 ± 0.02	20.81 ± 0.72
F_4	0.40 ± 0.01	0.45 ± 0.050	11.50 ± 2.03	1.13 ± 0.05	29.34 ± 0.94
F_5	0.42 ± 0.02	0.46 ± 0.010	8.69 ± 0.95	1.09 ± 0.01	19.59 ± 0.95
F_6	0.44 ± 0.01	0.50 ± 0.020	12.00 ± 1.05	1.13 ± 0.09	21.67 ± 2.21
F_7	0.38 ± 0.02	0.52 ± 0.015	15.55 ± 0.9	1.18 ± 0.04	23.21 ± 0.79
F_8	0.47 ± 0.017	0.57 ± 0.050	17.54 ± 1.45	1.21 ± 0.01	30.00 ± 1.83
F_9	0.45 ± 0.03	0.52 ± 0.010	13.46 ± 0.02	1.15 ± 0.05	22.63 ± 2.07
F_{10}	0.47 ± 0.02	0.57 ± 0.010	17.54 ± 0.11	1.21 ± 0.04	22.89 ± 1.85

F_{11}	0.39 ± 0.05	0.45 ± 0.01	13.33 ± 0.55	1.15 ± 0.02	21.32 ± 2.17
F_{12}	0.45 ± 0.01	0.54 ± 0.05	16.66 ± 0.90	1.2 ± 0.021	26.76 ± 2.80
F_{13}	0.40 ± 0.01	0.46 ± 0.01	13.04 ± 0.57	1.15 ± 0.05	22.05 ± 1.69
F_{14}	0.38 ± 0.02	0.44 ± 0.01	13.63 ± 0.61	1.15 ±0 .55	23.83 ± 1.04
F_{15}	0.44 ± 0.01	0.52 ± 0.05	15.38±0.92	1.18 ± 0.04	22.43 ± 2.19
F_{16}	0.41 ± 0.02	0.48 ± 0.05	14.58 ± 0.53	1.17 ± 0.02	28.33 ± 2.63
F_{17}	0.43 ± 0.01	0.51 ± 0.01	15.68 ± 0.89	1.18 ± 0.03	23.07 ± 1.21
F_{18}	0.35 ± 0.01	0.56 ± 0.02	14.63 ± 0.48	1.17 ± 0.01	23.76 ± 2.07
F_{19}	0.42 ± 0.02	0.51 ± 0.05	17.64 ± 0.14	1.21 ± 0.03	21.93 ± 1.22
F_{20}	0.47 ± 0.02	0.55 ± 0.01	14.54 ± 0.56	1.17 ± 0.05	30.00 ± 1.34

*Values are means ± SD,(n=3)

The results of angle of repose, bulk density, tapped density, carr's index and hausner's ratio indicates that powder blend has good flow property with good compressibilityand suitable for direct compression method.

Table 5. Post-compression parameters

Batch	Hardness* (Kg/cm^2)	Thickness* (mm)	Average weight* (mg)	Friability* (%)
F_1	4.57 ± 0.04	3.05 ± 0.025	170.66 ± 6.02	0.62 ± 0.16
F_2	4.66 ± 0.05	3.05 ± 0.020	167.33 ± 3.51	0.71 ± 0.05
F_3	4.10 ± 0.10	3.02 ± 0.010	171.00 ± 2.64	0.82 ± 0.06
F_4	4.67 ± 0.05	3.06 ± 0.026	164.66 ± 2.08	0.82 ± 0.03
F_5	4.46 ± 0.04	3.07 ± 0.036	168.72 ± 3.04	0.77 ± 0.06
F_6	4.26 ± 0.05	3.02 ± 0.045	170.14 ± 1.66	0.65 ± 0.08
F_7	4.26 ± 0.05	3.02 ± 0.036	174.18 ± 0.80	0.65 ± 0.05
F_8	4.13 ± 0.03	3.00 ± 0.046	167.80 ± 0.98	0.74 ± 0.09
F_9	4.17 ± 0.20	3.05 ± 0.025	173.11 ± 1.07	0.75 ± 0.03
F_{10}	4.57 ± 0.04	3.01 ± 0.041	171.64 ± 2.05	0.76 ± 0.06
F_{11}	4.70 ± 0.05	3.06 ± 0.032	175.02 ± 0.02	0.76 ± 0.04
F_{12}	4.00 ± 0.05	3.06 ± 0.026	164.63 ± 4.21	0.81 ± 0.04
F_{13}	4.35 ± 0.50	3.01 ± 0.051	166.23 ± 3.08	0.64 ± 0.06
F_{14}	4.46 ± 0.01	3.04 ± 0.055	176.68 ± 1.64	0.72 ± 0.03
F_{15}	4.12 ± 0.66	3.05 ± 0.025	176.44 ± 1.97	0.77 ± 0.08
F_{16}	4.47 ± 0.35	3.06 ± 0.028	170.31 ± 0.76	0.55 ± 0.09
F_{17}	4.48 ± 0.86	3.02 ± 0.045	169.14 ± 0.93	0.58 ± 0.01

F_{18}	4.72 ± 0.57	3.03 ± 0.050	166.64 ± 2.52	0.71 ± 0.01
F_{19}	4.16 ± 0.35	3.04 ± 0.051	174.33 ± 1.08	0.66 ± 0.08
F_{20}	4.67 ± 0.04	3.07 ± 0.036	171.12 ± 2.07	0.69 ± 0.04

*Values are means ± SD,(n=3)

Table 6. Evaluation Parameter of Batch F_1 to F_{20}

Batch	Drug content* (%)	Surface pH*	Swelling index* (6 hrs)	Bioadhesive residence Time* (hrs)	Bioadhesive strength (gm)
F_1	99.52 ± 0.70	6.53 ± 0.15	94.2 ± 0.02	8.7 ± 0.70	23.5 ± 1.5
F_2	96.99 ± 0.70	6.23 ± 0.05	86.0 ± 0.02	7.2 ± 0.50	21.7 ± 2.2
F_3	94.37 ± 0.70	6.43 ± 0.05	80.7 ± 0.03	6.5 ± 0.90	18.0 ± 1.3
F_4	99.69 ± 0.96	6.36 ± 0.23	73.2 ± 0.02	6.0 ± 0.60	14.3 ± 1.5
F_5	99.68 ± 1.06	6.60 ± 0.34	91.2 ± 0.01	8.5 ± 0.73	20.6 ± 1.3
F_6	95.52 ± 1.16	6.66 ± 0.25	85.5 ± 0.03	7.6 ± 0.58	17.3 ± 1.1
F_7	95.52 ± 0.70	6.46 ± 0.11	79.5 ± 0.04	6.8 ± 0.57	15.0 ± 1.2
F_8	94.59 ± 0.70	6.56 ± 0.28	72.2 ± 0.10	6.2 ± 0.62	12.2 ± 1.6
F_9	99.69 ± 0.96	6.46 ± 0.05	89.2 ± 0.02	8.3 ± 0.77	21.3 ± 1.2
F_{10}	95.83 ± 0.92	6.43 ± 0.23	84.5 ± 0.05	7.0 ± 0.56	18.6 ± 1.5
F_{11}	96.45 ± 0.96	6.56 ± 0.05	78.6 ± 0.02	6.0 ± 0.94	16.5 ± 1.3
F_{12}	94.65 ± 0.92	6.36 ± 0.05	70.2 ± 0.02	6.0 ± 0.57	13.4 ± 1.6
F_{13}	96.98 ± 0.96	6.13 ± 0.03	88.3 ± 0.03	8.1 ± 0.79	20.5 ±1.4
F_{14}	95.49 ± 0.76	6.27 ± 0.01	83.2 ± 0.02	7.4 ± 0.51	18.4 ±1.3
F_{15}	94.47 ± 0.86	6.39 ± 0.02	77.4 ± 0.01	6.5 ± 0.93	16.4 ± 1.6
F_{16}	93.87 ± 1.02	6.42 ± 0.05	70.3 ± 0.03	6.2 ± 0.69	13.5 ±1.3
F_{17}	95.67 ± 0.84	6.11 ± 0.02	87.3 ± 0.04	8.0 ± 0.81	18.6 ±1.2
F_{18}	97.70 ± 0.76	6.36 ± 0.07	82.7 ± 0.10	7.3 ± 0.51	15.0 ± 1.3
F_{19}	94.06 ± 1.34	6.33 ± 0.03	78.4 ± 0.02	6.6 ± 0.91	12.3 ± 1.4
F_{20}	96.63 ± 1.18	6.11 ± 0.02	69.5 ± 0.05	6.2 ± 0.73	10.0 ± 1.2

*Values are means ± SD,(n=3)

***IN VITRO* DRUG RELEASE STUDY**

CP 934P : HPMC K_4M

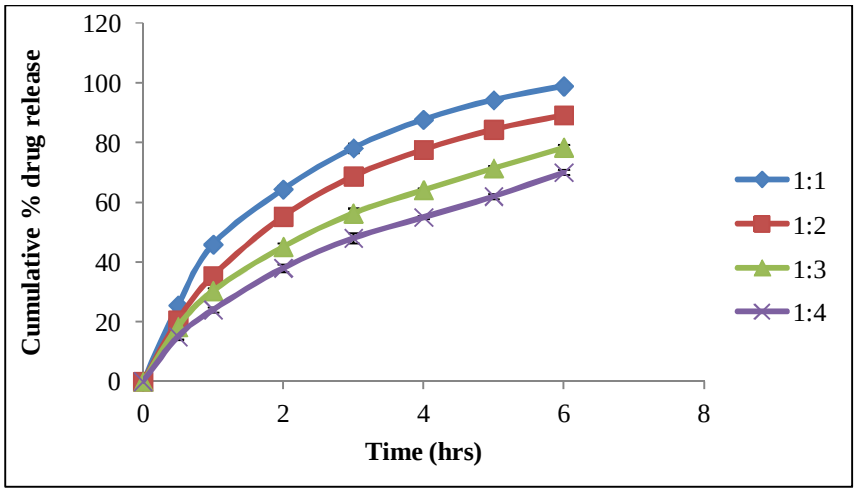

Figure: Comparison of release profile of different batches

CP 934P : HPMC $K_{15}M$

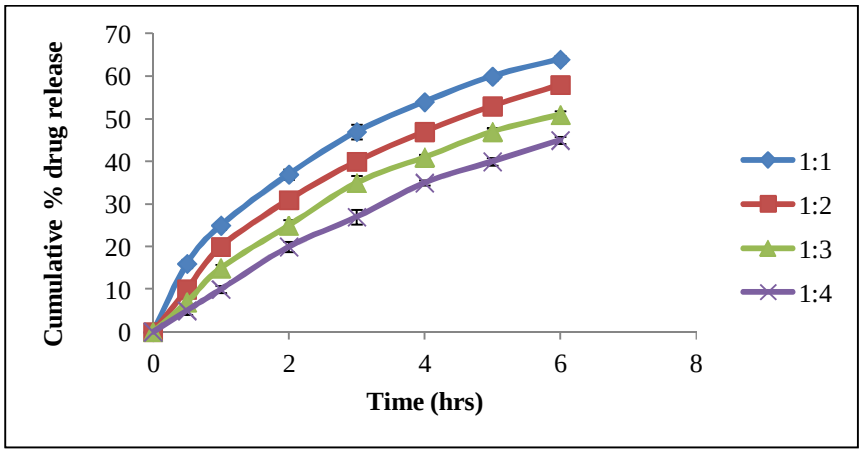

Figure: Comparison of release profile of different batches

CP 934P : HPC

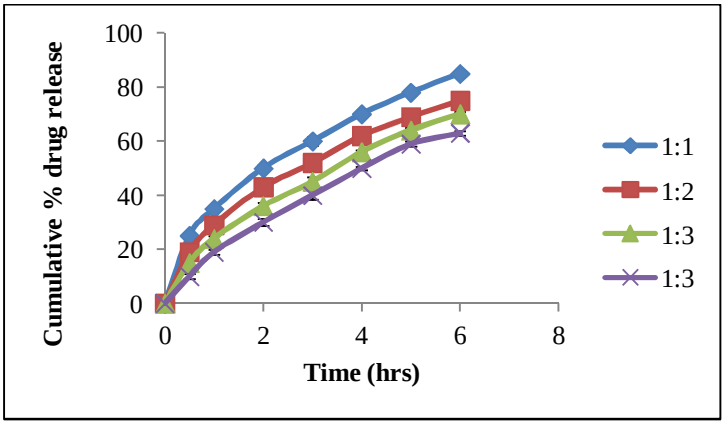

Figure: Comparison of release profile of different batches

CP 934P : Sodium CMC

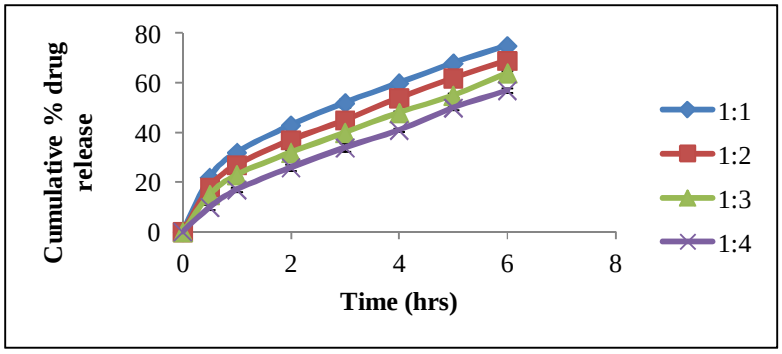

Figure Comparison of release profile of different batches

CP 934P : PVP K-30

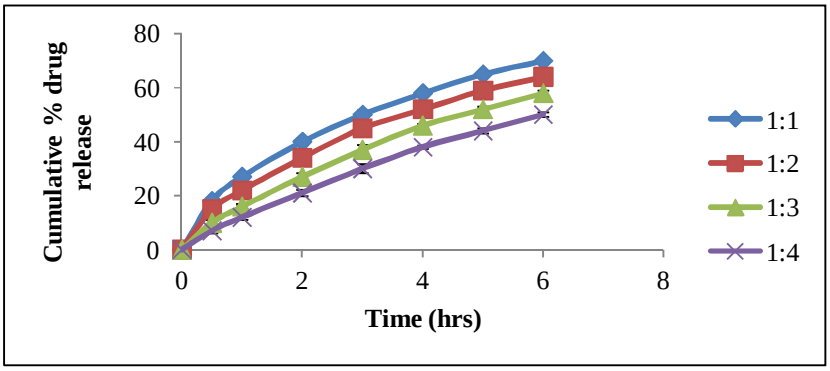

Figure: Comparison of release profile of different batches

From result it was concluded that the *in vitro* drug release, the formulation containing CP and HPMC K_4M is suitable for buccal drug delivery. The release rate of diacerein decreased with increasing amount of HPMC, sodium CMC, HPC and PVP K-30.Carbopol is more hydrophilic than HPMC and Sodium CMC, PVP K-30, and HPC it swells rapidly, therefore decrease in carbopol content may delay in the drug release.

RELEASE KINETICS

The results of curve fitting into the mathematical models are given in Table 3.12. The results indicate the drug release behavior from the formulated buccal tablet of diacerein.

Table 7. In vitro dissolution studies for release kinetics

Batch	Zeroorder	Firstorder	Higuchi	HixonCrowel	KoresmeyerPeppas
	R^2	R^2	R^2	R^2	R^2
F_1	0.8771	0.4928	0.9874	0.9525	0.9886

From result it was concluded that *in vitro* drug release of tablet containing CP and HPMC K_4M followed by Koresmeyer Peppas kinetics model.

STABILITY STUDY FOR OPTIMIZED FORMULATION

Table 8. Results of stability study

Batch F_1	In vitro drug release*	Drug content*	Bioadhesive strength* (gm)	Swelling index*
Initial	98.86±0.891	99.52±0.70	23.5 ± 1.5	94.2±0.02
After 1 months	97.85 ± 0.785	98.12 ± 0.60	23.1 ± 1.2	93.2 ±0.04

*Values are means ± SD,(n=3)

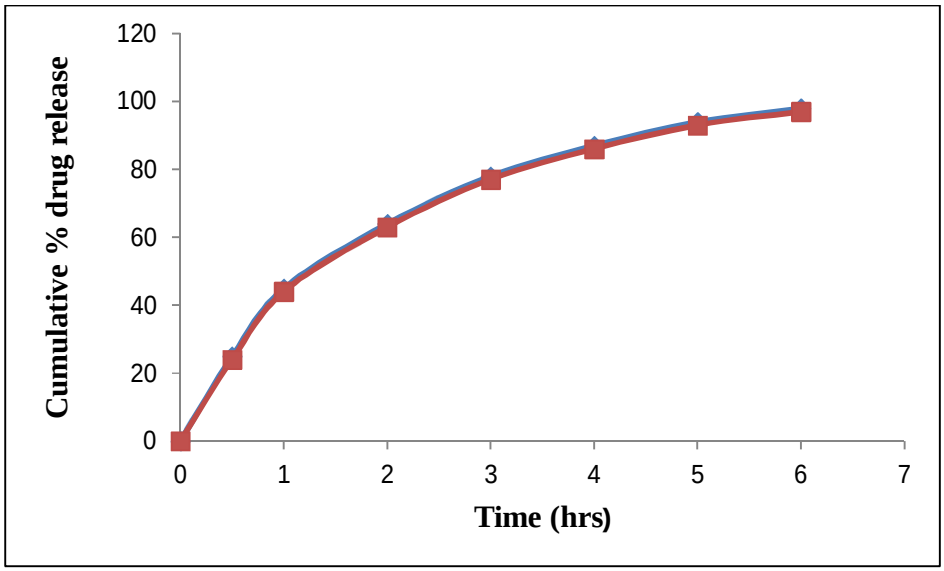

Figure comparison of release profile of stability studies

The stability study was carried out on optimum formulation, and the result indicates that there is no significant change in dissolution profile, drug content, bioadhesive strength and swelling index.

EX VIVO PERMEATION STUDY FOR OPTIMIZED BATCH

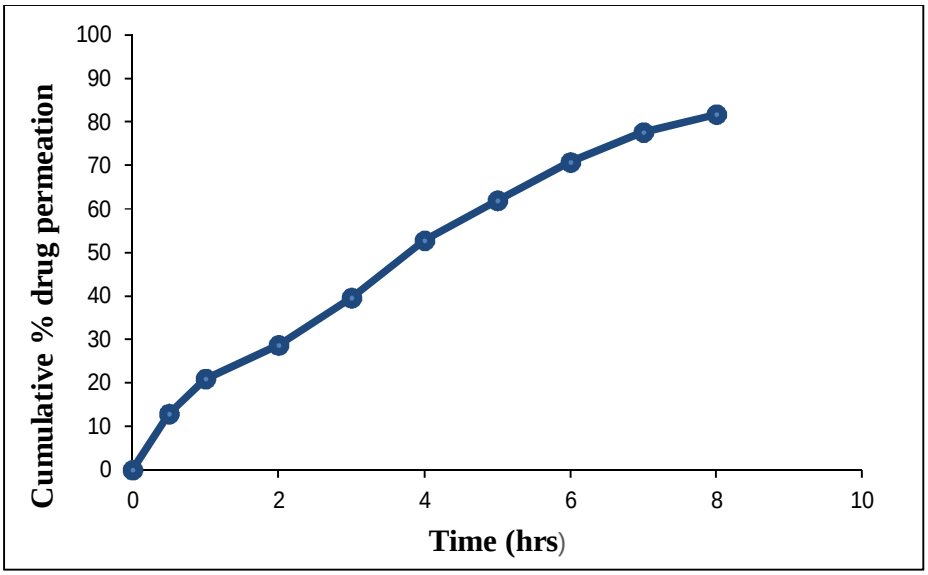

Figure 3. 11 *Ex vivo* drug permeation of optimized batch

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