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Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac by using natural binders

Gwaliory Yash and Tikariya Komal

Dept. Of pharmaceutics, shribherulal pharmacy institute, indore (m.p) India

***Corresponding author: Gwaliory Yash**
Email: ygwaliory@gmail.com

ABSTRACT

The aim of the study is to formulate orodispersible tablet of Aceclofenac for the pain management of rheumatoid arthritis and to improve the efficacy and patient compliance. In the present work, orodispersible tablets of Aceclofenac were prepared by direct compression method using Hibiscus rosasinesis leaves mucilage as natural super disintegrant with a view to enhance patient compliance and to avoid hepatic first pass metabolism and to improve its bioavailability. The prepared batches of tablets were evaluated for hardness, friability, drug content uniformity, wetting time, water-absorption ratio and in-vitro dispersion time. Addition of Drug: β-cyclodextrin inclusion complex leads to improve the dissolution characteristics and solubility of drug at optimum concentration (1:5). It was found that the formulation F5 was found to be optimized formulation from the data obtained. It is observed from the formulation F5 which shown disintegration time 30±1.25 sec. and percentage cumulative drug release shown 95.84±2.08 within 30 minute. The best formulations F5 was analyzed for short-term stability studies on the promising formulation indicated that there are no significant changes in drug content and in vitro dispersion time. The formulation was found to be stable.

Keywords: Orodispersible tablets, Aceclofenac, Natural super Disintegrant, Rheumatoid arthritis, Inclusion complex, In-vitro drug release.

INTRODUCTION

Aceclofenac is an oral non-steroidal anti-inflammatory drug (NSAID) with marked anti-inflammatory and analgesic properties used to treat osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is reported to have a higher anti-inflammatory action or at least comparable effects than conventional NSAIDs in double-blind studies. Aceclofenac potently inhibits the cyclo-oxygenase enzyme (COX) that is involved in the synthesis of prostaglandins, which are inflammatory mediators that cause pain, swelling, inflammation, and fever[1].

Aceclofenac belongs to BCS Class II as it possesses poor aqueous solubility. It displays high permeability to penetrate into synovial joints where in patients with osteoarthritis and related conditions, the loss of articular cartilage in the area causes joint pain, tenderness, stiffness, crepitus, and local inflammation[2].The drug is having poor aqueous solubility 2.10 mg/ml[3].

Aceclofenac is used in the management of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It has a role as an EC 1.14.99.1 (prostaglandin-endoperoxide synthase) inhibitor, a non-steroidal anti-inflammatory drug and a non-narcotic analgesic. . But the major drawback is its poor aqueous solubility[3].

In recent years, there has been increasing interest in the use of bioadhesive polymers to control the delivery of biologically active agents systemically or locally. These bioadhesive systems are useful for the administrative of drugs, which are susceptible to extensive gastro intestinal degradation and first pass metabolism. Bucolic adhesive system appears to be attractive because it avoids significant limitations of traditional routes of drug administration such as poor absorption, enzymatic degradation and first pass metabolism[4].

Buccal delivery necessitates the use of mucoadhesive polymer as their dosage forms should ideally adhere to the mucosa and withstands salivation, tongue movement and swallowing for a significant period of time[4].

The objective of the present study was to formulate a suitable drug delivery system through the buccal mode, for the long term treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

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 gastrointestinal effect. Buccal cavity possess ideal characteristics for drug absorption and hence it acts as an excellent site for the absorption of drugs[5].

MATERIALS AND METHOD

Materials

Aceclofenacwas received as a gift sample fromIpca Laboratory(Ratlam). Carbopol 040 was procured from HIMEDIA (NewDelhi). Xanthan Gum, Acacia, Microcrystaline Cellulose, Magnesium Stearate and talc From SdFine-chem. limited (Mumbai). All other solvent and reagent are used was of analytical grade.

Experiementals
Identification of drug
By uv spectroscopy

In order to ascertain the optimum wavelengths of Aceclofenac, the solution of Aceclofenac in phosphate buffer 6.8 was scanned on UV-Visible Spectroscopy in the range of 200-400 nm against phosphate buffer 6.8 pH as blank[6]. The spectrum of aceclofenac was recorded in fig1.

By melting point determination

Melting point determination of drug was performed using melting point apparatus (BTI-34) Melting point apparatus, Mumbai, India). In this method small amount of drug was filled in capillary tube open from both ends and it was placed along with thermometer in melting point apparatus. The temperature in the heating stand is ramped at user programmable fixed rate until the sample in the tube transition into the liquid state[6]. Melting point of drug sample was recorded in table 2.

By Fourier transform infrared spectroscopy analysis

Identification of Aceclofenac was done by FTIR Spectroscopy. The sample was analyzed by FTIR instrument (IR Affinity-1,(Shimadzu, Japan) was scanned and recorded. The obtained IR spectrum is shown in fig 3,4,5,6 and 7.

Preparation of standard Calibration curve of Aceclofenac

Standard stock solution of aceclofenac was prepared by dissolving 100 mg of drug in 100 ml of phosphate buffer 6.8 (1000 µg/ml) from the above stock solution 10 ml was taken and diluted to 100 ml in phosphate buffer 6.8 (100 µg/ml). From the above solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 ml was taken and diluted upto 10 ml with phosphate buffer 7.4 to get series of 5-30 µg/ml solutions in concentration. Absorbance was noted using UV-VIS Spectrophotometer at 276 nm against blank (phosphate buffer 6.8)[7]. The calibration curves of aceclofenac are shown in fig.8.

Solubility study

Solubility of Aceclofenac was determined in distilled water and various non-aqueous solvents like Methanol, Ethanol, HCl, Chloroform, Phosphate buffer 6.8.

Solubility analysis for aceclofenac was determined in distilled water and various non-aqueous solvents like methanol, ethanol, HCl, chloroform, phosphate buffer 6.8. Ten mg of drug was dissolved in 10 ml of solvent taken in conical flask. For the determination of solute dissolved in each solvent. The solvents were shaken at 25^{o}C for 24 hrs. After shaking, the samples were examined for the presence of any dissolved, suspended particles and clarity[8]. Results are disclosed in the table 10.

Formulation and optimization of mucoadhesive buccal tablet of aceclofenac by using natural binders

Experimental design for optimization

In this present research work aceclofenac mucoadhesive buccal tablets optimization has been done by statistically using 2^3 full factorial designs. In this study, three variables factors were evaluated each at two levels, and investigational were performed at all eight possible combinations. In which three variables was kept at two levels, one is low level and another one is high level.

Formulation anddevelopment of mucoadhesive buccal tablet of aceclofenac

Mucoadhesive buccal tablets of aceclofenac were prepared by direct compression method using tablet punching machine All component ingredients including drug, polymers, binders and excipients were weighed accurately Various batches of aceclofenac buccal tablets were prepared by changing the ratio of Carbopol 934, crosscarmellose sodium, xanthum gum, and acacia. Carbopol 940 was used as polymer, crosscarmellose sodium as super disintegrating agent, acacia and xanthan gum were used as natural binders and microcrystalline cellulose was used as diluent. Magnesium stearate and talc were added to the above blend as flow promoters the prepared blend of each formulation was compressed by using tablet punching machine.

Table 1: Composition of Mucoadhesive buccal tablet

S.No	Name of ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1.	Drug(Aceclofenac)	100	100	100	100	100	100
2.	Carbopol 940P	15	10	5	15	10	5
3.	Acacia	50	55	60	-	-	-
4.	Xanthan gum	-	-	-	50	55	60
5.	Crosscarmellose sodium	5	5	5	5	5	5
6.	Microcrystallinecellulose	20	20	20	20	20	20
7.	MagnesiumStearate	5	5	5	5	5	5
8.	Talc	5	5	5	5	5	5
	Total	**200 mg**	**200 mg**	**200 mg**	**200 mg**	**200 mg**	**200 mg**

Evaluation of mucoadhesive buccal tablet of aceclofenac

Pre compression parameter of mucoadhesive buccal tablet

Bulk characterizations were estimated by Bulk density, Tapped density, Carr's index, and Hausner'sratio. The flow property was determined by Angle of repose. These properties were determined by using the following equations:[9,10]

Bulk Density = Mass (g)/ bulk volume

Tapped density= Mass (g)/tapped volume

Carr's index= Tapped density- bulk density/ tapped density X 100

Hausner's ratio= tapped density/ bulk density

Angle of repose= Tan0=h/r.

The bulk characterization and flow properties were recorded in table 12.

Post compression parameter of mucoadhesive buccal tablet

Appearance

The tablets were visually observed for capping, chipping, and lamination[11].

Dimension (thickness and diameter)

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a vernier caliper. Ten tablets from each type of formulation were used and average values were calculated

Weight variation

For weight variation, 20 tablets of each type of formulation were weighed individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight[12].

Table 2: Specifications of %Weight variation allowed in tablets as per IP.

S. No.	Average Weight	% difference allowed
1	80mgorless	±10 %
2	80mgto250mg	±7.5%
3	Morethan250mg	±5 %

Hardness

For each type of formulation, the hardness value of 10 tablets was determined using Monsanto hardness tester[13].

Percentage friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then deducted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated

asfollows[14].

$$\%F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \quad 100$$

Drug content

The drug content was determined by calibration curve method are as follow:
Ten tablets were taken and amount of drug present in each formulation of tablet was determined. The tablet was crushedina mortar-pestle and equivalent to10mg of drug was dissolved in phosphate buffer pH 6.8 in a 100ml volumetric flask. Volume was made up to100ml. The sample was filtered through filter paper. From this solution 1ml were taken in a 10 ml volumetric flask & diluted with phosphate buffer pH 6.8. Further, 1ml were taken were taken and diluted up to10ml and analyzed for drug content by UV spectrophotometer at 276 nm using phosphate buffer and drug content calculated accordingly[14]. The drug content of various formulations is recorded in table 14.

Swelling test

From each batch, three tablets were individually weighed (W1) and placed separately in petri dishes with 5 mL phosphate buffer of pH 6.8. At the time interval of 1, 2, 4, and 8 h, they were taken out from the petri dish and excess water was removed by using filter paper[57]. The swollen tablets were reweighed (W2) and the percentage of hydration was calculated for each tablet, using the Eq.

Swelling index = (W2 - W1) / W1 X100

Mucoadhesive/bioadhesive strength

A modified physical balance was used to measure the strength of mucoadhesiveness. The apparatus consisted of a double beam physical balance in which the right side has a pan, and the left side of the balance has a string that was hanged and at the bottom of the string was a suctioned glass slide. This was the place where the tablets were placed using an adhesive. The porcine buccal mucosa was placed on top of an inverted 50 mL beaker which was placed inside a 500 mL beaker that was filled with phosphate buffer with pH 6.8 kept at 37 ºC. The buffer amount was just enough so that it reaches the buccal mucosa surface. Exactly five gram of weight was placed on the right pan before putting the porcine buccal tablet in place. The weight was then removed to lower the glass slide with the attached buccal tablet. The tablet was to be in contact with the porcine buccal mucosa membrane and this was not disturbed for 5 minutes. After 5 minutes, weights were added on the right side of the pan to separate the tablet from the membrane. The accumulated weight on the right side was then noted and subtracted with 5 g. The value was taken as the measure for the bioadhesive strength of the tablet[15]. The bioadhesive force was calculated using the formula:

N= W X g/1000

Invitro Drug release study

Invitro drug release study was determined by dissolution test apparatus. Maintained the water level in the water bath up to the specific mark and adjusted or maintained temperature from heater knob. 900 ml of phosphate buffer pH 6.8was poured in dissolution vessel and adjusted temperature between 37±0.5°C. The shaft was positioned in such a way that its axis is within 2 mm of axis of the vessel and lower edge of blade was 23-27 mm from the inside of bottom of vessel. The paddles were lowered down. The tablet was put in each vessel and paddle was rotated at 50 rpm. Withdrawn 5 ml sample at every 5 minutes interval and replaced by equal volume of fresh dissolution medium. Filtered the samples using what man's filter paper and analyzed for drug release of the samples by UV-visible spectrophotometer at λ max 276 nm using phosphate buffer pH 6.8 asblank[16].

RESULT AND DISCUSSION

Identification of drug
Determination of wave length by UV Spectroscopy:

The peak of Aceclofenac was obtained at 276 nm. Which shows that drug is pure as given in the refrence[17]. The UV spectrum of aceclofenac drug is shown in the fig. 1.

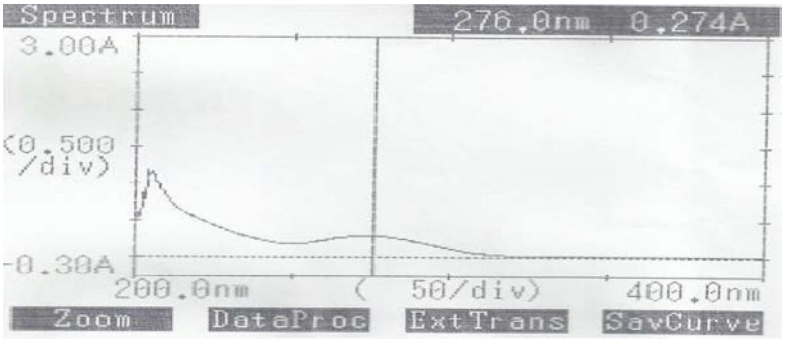

Fig 1: Spectrum of Aceclofenac by UV Spectroscopy

Melting point

The melting point of drug sample was determined by using melting point apparatus. As given in the reference. The melting point of aceclofenacis shown in the table: 2.

Table 3: Melting Point of Aceclofenac

Drug	Observed	Reference
Aceclofenac	149^0C	149-153^0C

Fourier transform infrared spectroscopy

The drug excipient compatibility studies were carried out as per method described in 6.1. The FTIR spectra of aceclofenac, aceclofenac and carbopol 940,aceclofenac + acacia, aceclofenac + xanthan gum, aceclofenac +crosscarmelose sodium+ microcrystalline cellulose (MCC) + talc (T) + magnesium stearate (MS), are given in Fig. 7.7 to Fig. 7.11 respectively. Pure aceclofenac showed absorptions at 2107.1, 1918.1, 1848.6, 1771.5, 1714.6 and 664.4 cm-1 as major peaks. The results revealed no change in the IR peaks of aceclofenac when mixed with excipients compared to pure aceclofenac. Hence, no interaction between the drug and the excipients is inferred.

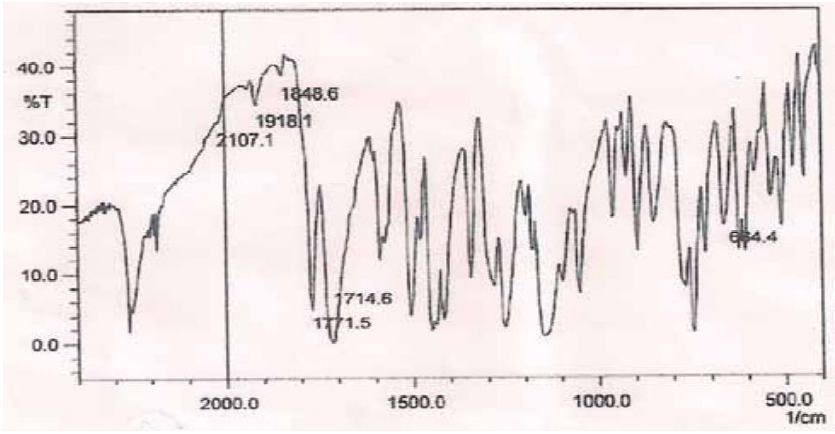

Fig. 2 FTIR spectrum of aceclofenac (ACE)

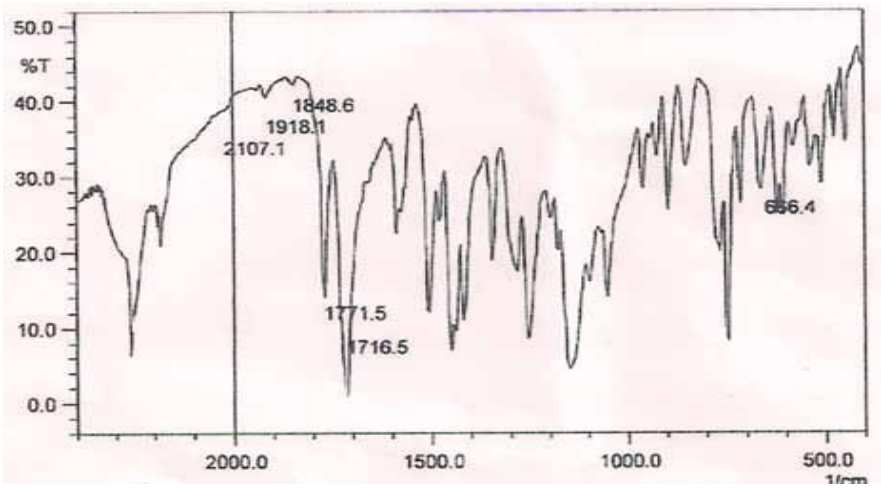

Fig. 3Aceclofenac + Carbopol

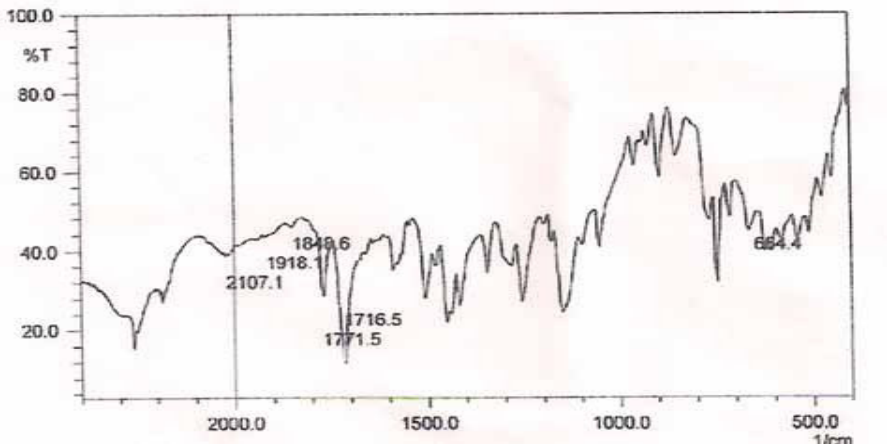

Fig. 4Aceclofenac + Acacia

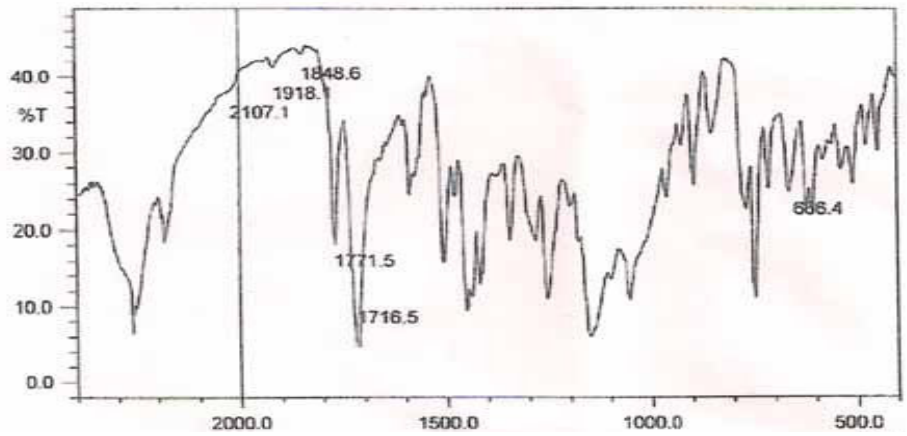

Fig. 5Aceclofenac + Xanthan gum

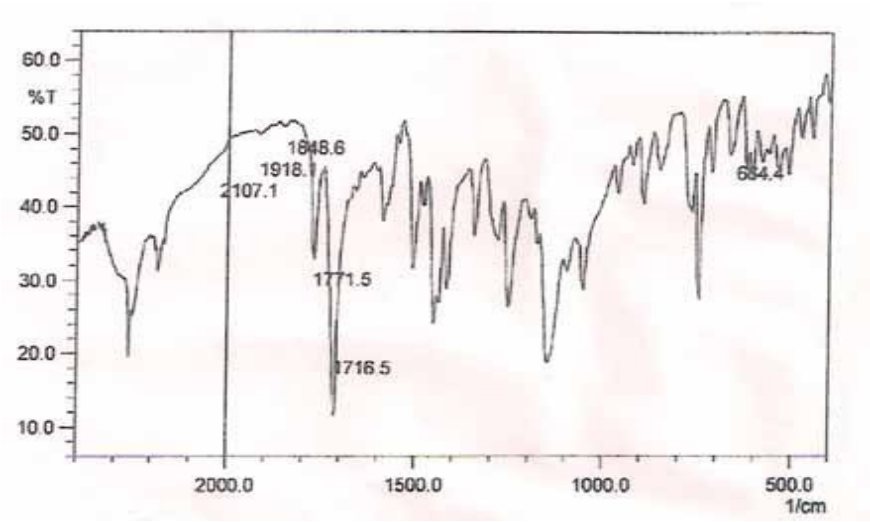

Fig 6. Aceclofenac + Crosscarmellose sodium+ microcrystalline cellulose+ talc+ magnesium stearate

Preparation of standard Calibration curve of Aceclofenac in Phosphate buffer pH 6.8 (λmax 276 nm)

Calibration curve of Aceclofenac was prepared in phosphate buffer pH 6.8 at 276 nm. The absorbance values (mean of three determinations) with their standard deviation at different concentration in the range of 5-30 µg/ml for phosphate buffer pH 6.8 are tabulated. The drug obeys Beer's Lambert law in the concentration range. Linear regression analysis for all calibration curves of Aceclofenac is given in Table.7.4 So, this equation was used for the calculation of the solubility of the drug in different solvent, drug content and drug release.

Table 4: Data of standard calibration curve of aceclofenac in phosphate buffer6.8

S.No.	Concentration (µg/ml)	Absorbance (nm)
1.	0	0
2.	5	0.125
3.	10	0.22
4.	15	0.317
5.	20	0.419
6.	25	0.533
7.	30	0.635

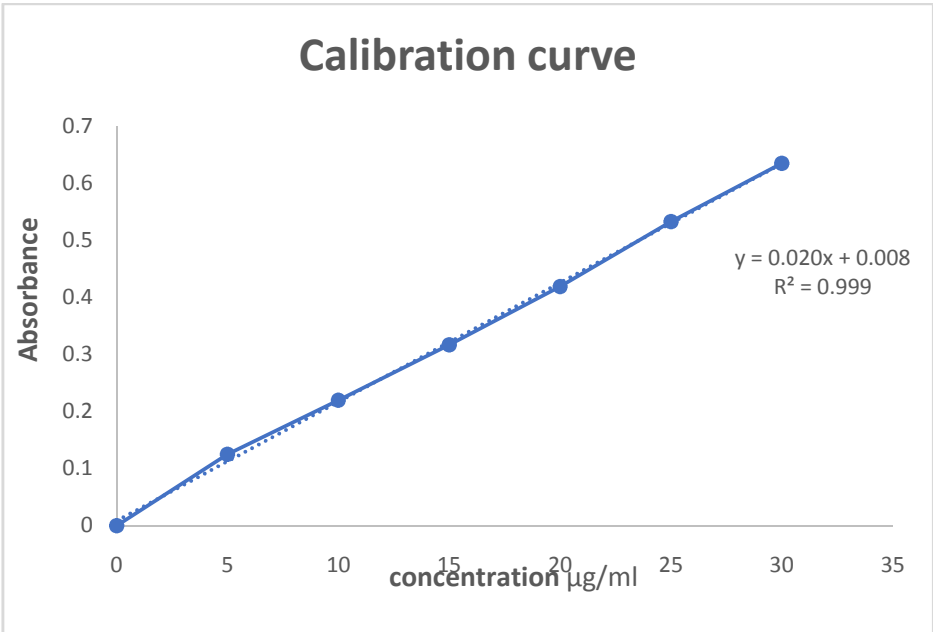

Fig 7: Calibration curve of aceclofenac in Phosphate buffer 6.8.

Determination of solubility of aceclofenac in different solvents

solubility analysis for drug aceclofenac was determined in different solvents. Results are disclosed in the table 10.

Table5:SolubilitydataofAceclofenacindifferentmediums

Solvent (5 ml)	Solubility of drug (5mg)
Distilled water	**Insoluble**
0.1 N HCL	**Slightly soluble**
6.8 pH Buffer	**Slightly soluble**
Ethanol	**Slightly soluble**
Methanol	**Poorly soluble**
Chloroform	**Poorly soluble**
Acetone	**Insoluble**

Evaluation of optimized mucoadhesive buccal tablet of aceclofenac

Evaluation of pre-compression parameters of powder

The bulk density, Tapped density, Hausner's ratio, Carr's index and angle of repose of all the formulations were performed. Results are shown in the table no. 11.

Table6: EvaluationofPrecompressionParametersofpowder

Formulation	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr'sindex(%)	Angle of repose (^{o})	Hausner'sratio
F1	0.314	0.358	14.645	25.446	1.170
F2	0.289	0.368	14.624	29.343	1.166
F3	0.286	0.385	16.323	27.616	1.176
F4	0.335	0.365	13.937	26.946	1.16
F5	0.317	0.383	15.240	25.59	1.176
F6	0.283	0.345	17.360	27.4	1.206

Evaluation of post-compression parameters of mucoadhesive buccal tablet of aceclofenac

The mucoadhesive buccal tablet of aceclofenac was evaluated for post compression parameters like weight variation, hardness, thickness, friability. The results of the studies were shown in below table 12.

Table7: Weight variation, Hardness, Thickness and Friability of Formulation (F1-F6)

Formulation	Weight variation(mg)	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)
F1	210.16	2.6	3.1	0.460
F2	211.75	2.4	3.1	0.750
F3	214	3.0	3.2	0.460
F4	223	2.9	3.3	0.672
F5	232	3.0	4.06	0.346
F6	233	3.0	3.4	0.343

Drug Content

The drug content of all the formulations were found to be in the range of 95± 5%. The drug content of all the formulations are shown in the table no. 13.

Table 8 Drug content of Formulation (F1-F6)

Formulation	Drug Content
F1	94%
F2	96%
F3	95%
F4	97%
F5	99%
F6	98%

Swelling Test

The swelling index of all the formulations are shown in the table no. 14.

Table 9 Swelling Index of all formulations F1-F6

Formulation Code	1 (hr)	2 (hr)	4 (hr)	6 (hr)
F1	30.76	39.23	TabletBreaks	-
F2	25.00	33.42	42.31	44.23
F3	35.96	42.11	54.39	58.33
F4	27.64	43.49	54.14	62.11
F5	41.66	50.71	53.17	54.23
F6	28.63	46.92	55.32	60.21

In-Vitro Bioadhesive Strength

The term bio adhesive implies attachment of a drug carrier system to a specific biological location. In-vitro bioadhesive strength of tablets was measured using modified physical balance. Porcine buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. Bioadhesive studies were performed in triplicate and average strength was determined. From the Mucoadhesive strength, force of adhesion was calculated. The in vitro mucoadhesive strength of all the formulations are shown in the table 15.

Table 10: Mucoadhesive strength

Batch Code	Mucoadhesive Strength(gm)	Force Of Adhesion (N)
F1	8.5	0.83
F2	8.2	0.80
F3	9.2	0.90
F4	9.7	0.95
F5	7.8	0.76
F6	8.0	0.78

In-Vitro drug release

The in-vitro drug release of mucoadhesive buccal tablet of aceclofenac is shown in the table 7.17. The drug released from formulation F1 to F3 were found to be 97.2, 95.7 and 95.2 % for aceclofenac respectively. The drug released from formulation F4 to F6 were found to be 96.4, 95.8, and 96.1% for aceclofenac respectively. The in-vitro drug release was compared with the pure drug.

The release rate of F1 and F3 was found to be more immediate and sustained when compared to other formulations this is due to increase in the concentration of binders.

Table 11: In-Vitro Drug Release

S.No	Time(h)	Pure drug	F1	F2	F3	F4	F5	F6
1	0	0	0	0	0	0	0	0
2	15	6.2	18.71	18.95	19.22	19.16	19.30	20.69
3	30	9.07	37.2	39.5	37.0	39.4	38.6	42.7
4	45	15.1	49.7	45.5	48.6	48.4	43.5	55.5

5	60	26.8	55.7	56.2	58.2	59.5	62.2	67.0
6	90	36.19	74.5	63.4	78.5	76.9	75.1	78.2
7	120	41.01	82	88	85.3	83.4	83.6	89.6
8	150	48.11	92.2	92.3	95.2	93.1	94.3	92.1
9	180	50.12	97.2	95.7	95.2	96.4	95.8	96.1

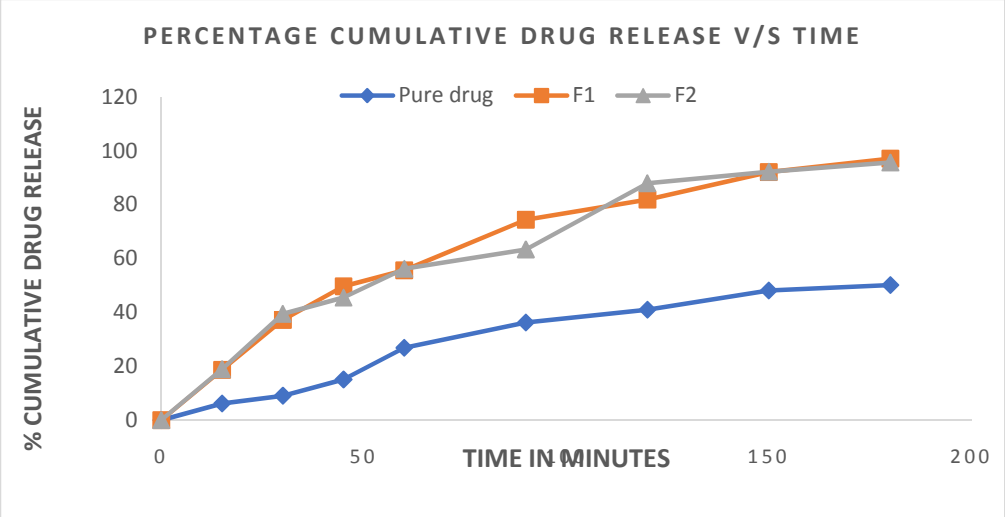

Fig.8 In-Vitro Drug Release of Pure drug, F1 and F2

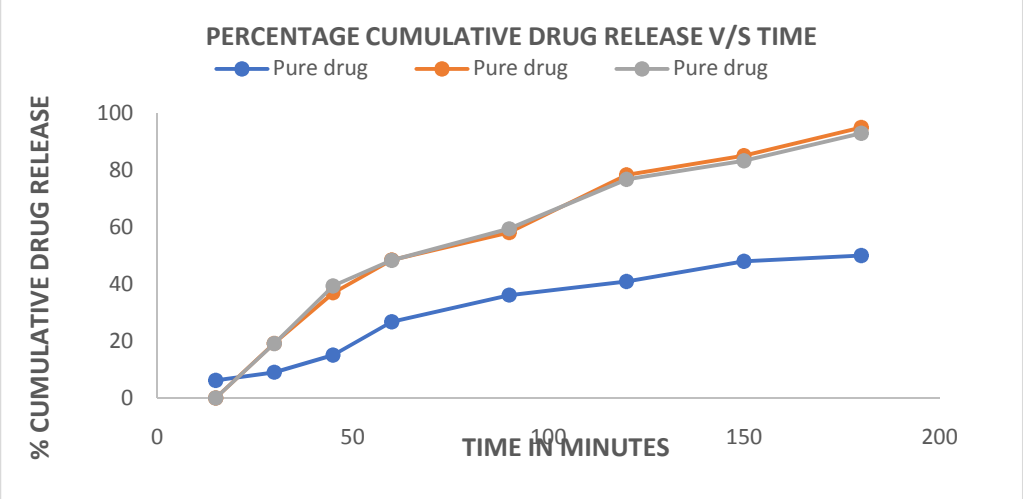

Fig. 9 In-Vitro Drug Release of Pure drug, F3 and F4

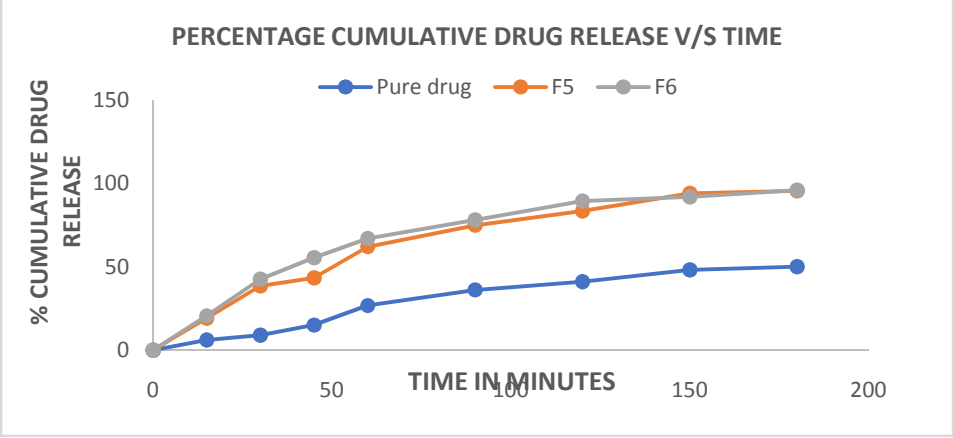

Fig. 10 In-Vitro Drug Release of Pure drug, F5 and F6

CONCLUSION

The study was conducted to formulate and evaluate mucoadhesive buccal tablets of aceclofenac with a sustained release property, to achieve patient compliance for the management of different types of pain. Among 6 different batches, F1 showed sustained and effective drug release, swelling index as well as mucoadhesive strengths. Its physicochemical properties also complied with the pharmacopoeial standards. The results also demonstrate that CP has a major role to increase the mucoadhesive strength. The swelling behavior of the formulation can be optimized by changing the proportion of CP, Acacia and xanthan gum. However higher concentration of xanthan gum can result in abrupt release of the drugs. Therefore acacia can play a significant role to check the swelling behavior and drug release rate. Therefore, the formulation of an aceclofenacmucoadhesive tablet can be an effective alternative route to prevent the first-pass effect and to improve the bioavailability of aceclofenac by using natural binders. It can also enhance patient compliance by fascinating extended release of the drug.

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