Original Research Article

FORMULATION AND EVALUATION OF BUCCAL PATCH CONTAINING ACECLOFENAC

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ABSTRACT

The main objective of the present study was to improve bioavailability of Aceclofenac and decrease the frequency of dosage form administration by sustained release formulation of the drug from the mucoadhesive drug delivery system. Aceclofenac belongs to the drug class known as NSAIDs. It is normally indicated for the treatment of dental pain, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is selective cox-2 inhibitor. It has an extensive and highly variable hepatic first pass metabolism following oral administration having half life of 4 h. The usual dose of Aceclofenac is 100 mg twice daily with systemic bioavailability of 40- 50% due to extensive "first-pass" metabolism and has a narrow absorption window. These characteristics make Aceclofenac a suitable drug candidate for mucoadhesive drug delivery system. Aceclofenac containing mucoadhesive buccal patches were prepared by solvent evaporation method. The buccal patches were formulated using polymers HPMC E-15 and Eudragit RL 100 alone and in combination. The buccal patches were evaluated for weight variation, thickness, folding endurance, content uniformity, swelling index, in-vitro diffusion study, in-vitro residence time and in-vitro Mucoadhesive strength. Among five formulations using factorial approach F2 showed maximum release 92.35% upto 8 h.

***Keywords*:** Aceclofenac, Mucoadhesion, Buccal patch

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INTRODUCTION

The interest in novel route of drug administration occurs from their ability to enhance the bioavaibility of the drugs impaired by narrow absorption windows in the gastrointestinal tracts. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. This route has been used successfully for the systematic delivery of number of drugs candidates. Problems such as high first pass metabolism and drug degradation in the gastrointestinal tract can be circumvented by administrating the drug buccal route. Moreover, buccal drug delivery offers safe and easy method of drug utilization, because drug absorption can be promptly terminated in case of toxicity by removing buccal dosage form from buccal cavity.

Aceclofenac, a new NSAID posses good anti-inflammatory, analgesics and anti-pyretic, used for treatment of treating condition like osteoarthriritis, rheumatoid arthritis, dental pain and other rheumatoid disorder. It is highly protein bound and possesses short biological half life of 4-5 h, which makes it's an ideal candidate for administration by buccal routs the effectiveness of mucoadhesive formulation is greatly determined by the nature the polymer composition used.

The oral route of drug delivery is typically considered the preferred and most patient-convenient means of drug administration. With many drugs the basic goal of therapy is to achieve a steady-state blood or tissue level that is therapeutically effective and nontoxic for an extended period of time.

Sustain release system are considered a wiser approach for the drugs with short half-lives and which require repeated dosing, they are easy to formulate and are irrespective of absorption process from gastrointestinal tract after oral administration. The basic objective of these dosage forms is to optimize the delivery of medications so as to achieve a measure of control on therapeutic effect in the face of uncertain fluctuations in the *in vivo* environment in which drug release takes place.

The advances in the formulation technology of modified release dosage form with sustained release oral dosage form has been widely accepted approach as compared to conventional immediate release formulations of the same drug, over which it provides a prolong release of the drug over extended period of time there by giving the better patient compliance and enhanced bioavailability and resulting blood concentration-time profiles of drugs that otherwise suffer from few limitations.[1]

MATERIALS AND METHODS

Aceclofenac was obtained as a gift sample from Zim Laboratories Limited, Kalmeshwar, Nagpur and Eudragit RS 100 and Eudragit RL 100 were obtained as a gift samples from Evonik Degussa India Private Limited, Mumbai.

Preparation of patch

The buccal patches of Aceclofenac were prepared by solvent evaporation method. The matrix-type controlled buccal drug delivery systems were prepared by using ethanol: dichloromethane (1:1) as solvent for HPMC and ethanol as solvent for E RL 100. For the different batches of formulations the polymer solution in different proportions were mixed and stirred on magnetic stirrer to give homogenous clear solution, drug was added slowly to the polymer solution and stirred thoroughly to obtain a uniform solution. Polyethylene glycol 400 (PEG 400) was added as plasticizer, and Dimethyl sulphoxide (DMSO), as penetration enhancer and stirred. The polymeric solution of drug was poured onto the mercury surface and covered with inverted funnel, then dried at room temperature in a dust-free environment. After 24 h, the patch was cut into 3 cm diameter. The amount of the drug required in the petridish is mainly depends upon the surface area of the petridish.[2]

Table 1. Preliminary batch composition

Batch	Drug (mg)	HPMCE-15 (ml)	Eudragit (mg)	Plasticizer (ml)	Solvent (ml)
P1	120	100	---	0.5	15
P2	120	100	100	0.5	15
P3	120	100	200	0.5	15
P4	120	100	300	0.5	15

In vitro diffusion study

The test was carried out using cellophane membrane. The modified Franz diffusion cell was used for permeation studies, it consists of two compartments, one is donor compartment and another is receptor compartment. The receptor compartment was covered with water jacket to maintain temperature 37°C. The receptor chamber was filled with phosphate buffer solution having pH 6.8. The cellophane membrane was filled over it. The membrane was allowed to stabilize overnight in phosphate buffer. After stabilization, patch was kept on membrane periodically (for 8 h) samples were withdrawn and maintained sink condition. The aliquot were analyzed spectrophotometrically at 274 nm. The drug permeation was correlated with cumulative drug released.[3]

Table 2. Evaluation of preliminary batch

Parameter	P1	P2	P3	P4
Weight variation (mg)	80.75±0.35	81.42±0.40	82.38±0.45	82.92±0.52
Thickness (mm)	0.75±0.40	0.78±0.64	0.80±0.60	0.83±0.55
Surface pH	6.25±0.25	6.22±0.23	6.5±0.18	6.48±0.30
Content Uniformity (mg)	29.58±0.01	29.56±0.01	29.77±0.02	29.86±0.02
Swelling Index (%)	13	20	26	33
Mucoadhesion Time (h)	3.40	3.48	3.50	4.05
Bioadhesive Strength (g)	3.4	3.9	4.6	5.4
Folding Endurance	255	258	260	270

Surface pH study

The surface pH of the buccal patches was determined in order to investigate the possibility of any side effects *in-vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The buccal patch was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min. The experiment was performed in triplicate, and average values were reported.[4]

Content uniformity

Drug content uniformity was determined by dissolving the buccal patch from each batch by homogenization in 100 ml of a phosphate buffer (pH 6.8) for 6 h under occasional shaking. The 5 ml solution was taken and diluted with phosphate buffer pH 6.8 upto 20 ml, and the resulting solution was filtered through a 0.45 µm syringe filter. The drug content was then determined after proper dilution at 274 nm using a UV spectrophotometer.[5]

Folding endurance

Folding endurance of the patch was determined by repeatedly folding one patch at the same place till it breaks. The number of times of patch could be folded at the same patch without breaking gave the value of the folding endurance. This test was done on optimized patches.[6]

Swelling index study

Swelling study of prepared buccal patch was calculated by function of weight increase due to swelling, which was measured for each formulation. A patch from every batch was weighed on a

preweighed cover slip. It was kept in a petridish and 10 ml of phosphate buffer pH 6.8 was added. After 5 h, the cover slip was removed and weighed. The difference in the weights gives the weight increase due to absorption of water and swelling of patch.[7] The percentage weight and swelling ratios were calculated from the average of three measurement using following equation:

$$\%S = (Xt-Xo)/Xo \times 100$$

Where, Xt- weight or area of the swollen patch after time t and Xo- is the original patch weight or area at zero time.

Determination of *in vitro* residence time

The *in vitro* residence time was determined using a USP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.8 phosphate buffer maintained at 37±0.5°C. A goat buccal mucosa, 3 cm length, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was hydrated from one surface using 15µl pH 6.8 PB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch of each batch from the mucosal surface was recorded.[8]

Table 3. Formulations using factorial approach

Formulation	Drug (mg)	HPMC E-15 (mg)	Eudragit RL-100 (mg)	PEG 400 (ml)	E:D (1:1) (ml)
F1	120	225	175	0.5	15
F2	120	150	250	0.5	15
F3	120	250	150	0.5	15
F4	120	175	225	0.5	15
F5	120	200	200	0.5	15

Table 4. Cumulative % drug release in 8 h from formulation F1 to F5

Time (h)	Cumulative % drug release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	7.83	20.83	10.87	14.33	8.87
2	15.66	27.67	19.1	22.45	18.83
3	25.23	40.19	28.83	32.05	28.56
4	30.87	50.83	39.96	43.82	39.59
5	43.83	60.8	52.42	55.1	52.02
6	54.05	74.02	65.69	65.8	61.25
7	65.54	81.54	71.45	74.98	70.34
8	78.54	92.35	80.41	85.56	79.96

Factorial design and drug release kinetics

The objective of present investigation was to optimize the concentration of the polymers which showed sustained release of drug upto 8 h. By using factorial design 2^2 following batches were formulated.

Table 5. R^2 Values

Formulation	Zero-order	First-order	Higuchi	Korsmeyer-peppas
	R^2			
F1	0.9906	0.9433	0.9955	0.5696
F2	0.9972	0.9603	0.9818	0.8287
F3	0.9938	0.9320	0.9947	0.6677
F4	0.9985	0.9511	0.9917	0.7351
F5	0.9985	0.9091	0.9992	0.6439

Measurement of mucoadhesive strength

Mucoadhesive strength of all fabricated buccal patch was measured ex vivo (n=3) on a modified physical balance using the method described by Gupta et al. A piece of porcine buccal mucosa was tied to the open mouth of a glass vial filled completely with isotonic phosphate buffer, pH 6.8. The glass vial was tightly fitted in the center of a beaker filled with isotonic phosphate buffer (pH 6.8; temperature, 37±1°C).The patches were stuck to the lower side of the rubber stopper with glue. The mass (in gram) required to detach the patches from the mucosal surface gave the measure of Mucoadhesive strength (shear stress).[9] The following parameters were calculated from mucoadhesive strength.

Force of adhesion (N) = (Bioadhesive strength (g) × 9.81)/1000

Table 6: Mucoadhesion time for factorial batch

Formulation	F1	F2	F3	F4	F5
Mucoadhesion time (h)	3.02	4	2.5	3.3	3

Table 7: Bioadhesive strength of factorial batch

Formulation	F1	F2	F3	F4	F5
Bioadhesive strength (g)	3.54	5.4	3.08	4.6	4.15

Kinetic assessment

Response 1 R1

Analysis of variance table [Partial sum of squares - Type III]

Table 8. ANOVA for response 1

Source	Sum of squares	df	Mean square	F value	P- value Prob >F
Model	127.58	2	63.79	186.82	0.0053
Linear mixture	94.86	1	94.86	277.83	0.0036
AB	32.71	1	32.71	95.80	0.0103
Residual	0.68	2	0.34		

The Model F-value of 186.82 implies the model is significant. There is only a 0.53% chance that a "Model F-Value" this large could occur due to noise.

R-Squared 0.9947

Adj R-Squared 0.9894

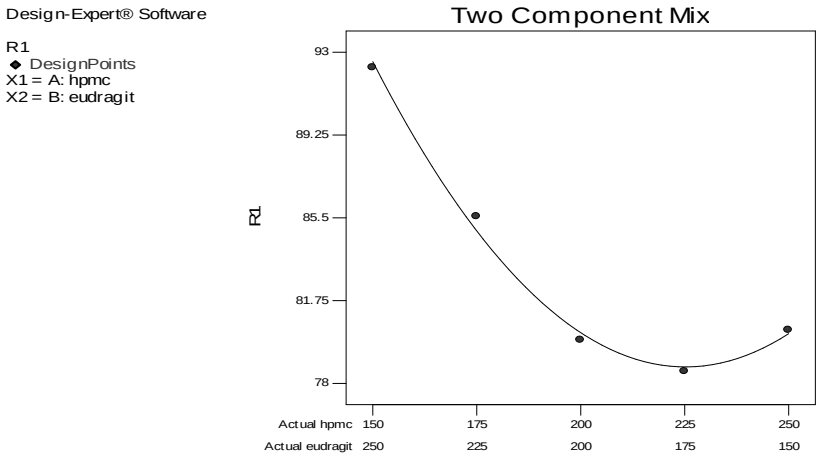

Figure 5. Plot of two component mix for % release

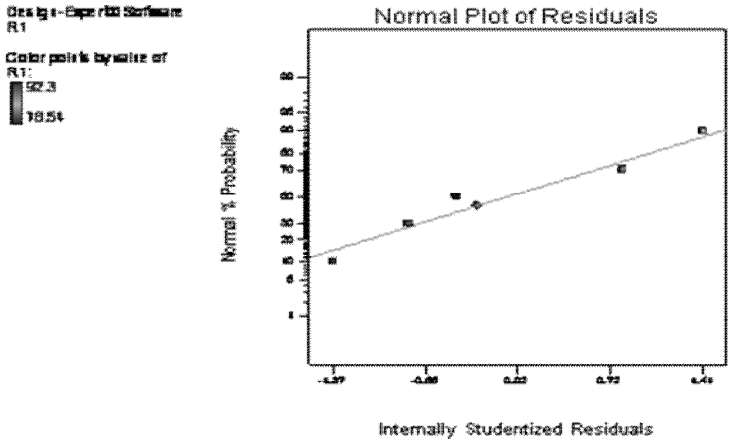

Figure 6. Normal plot of residuals for % release

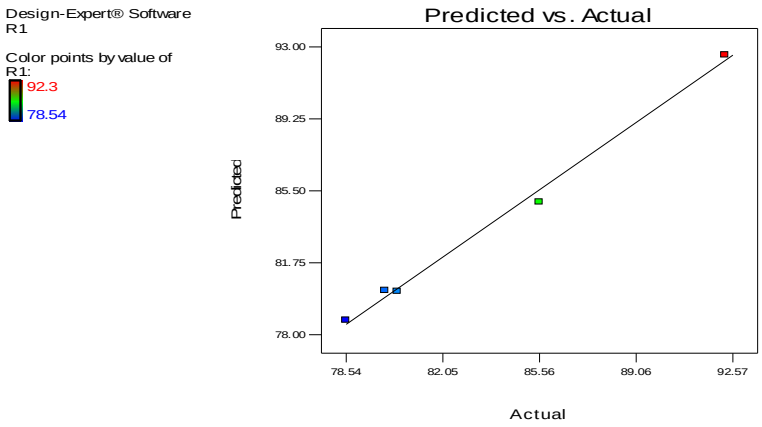

Figure 7. Plot of predicted Vs actual for % release

Response 2 R2

Analysis of variance table [Partial sum of squares - Type III]

Table 9. ANOVA for response 2

Source	Sum of squares	Df	Mean square	F value	P- value Prob >F
Model	1.08	1	1.08	24.81	0.0156
Linear mixture	1.08	1	1.08	24.81	0.0156
Residual	0.13	3	0.043		

R-Squared 0.8921

Adj R-Squared 0.8562

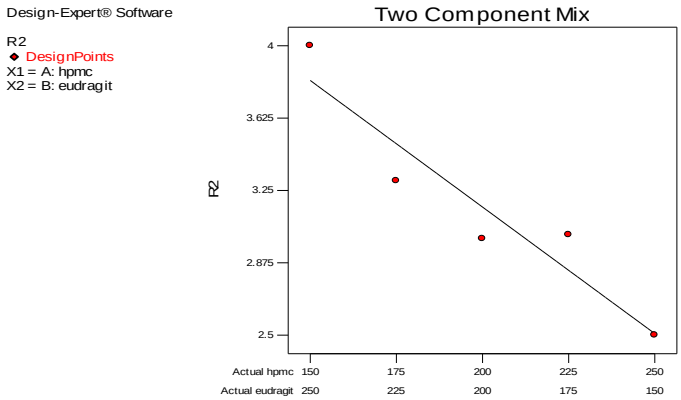

Figure 8. Plot of two component mix for mucoadhesion time

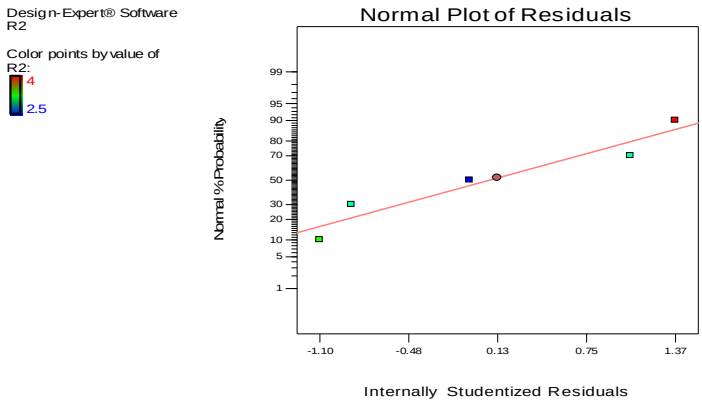

Figure 9. Normal plot of residuals for mucoadhesion time

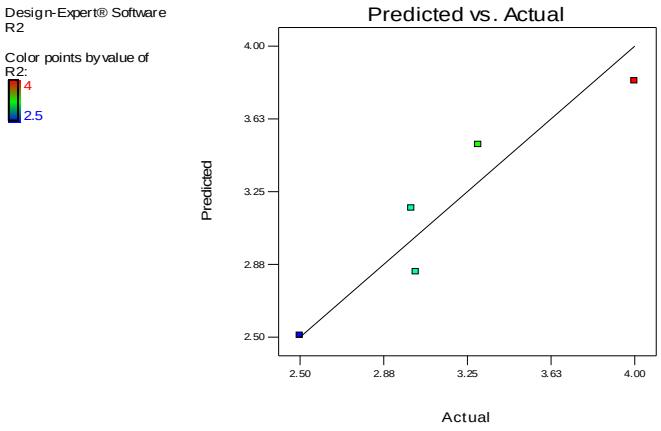

Figure 10. Plot of predicted Vs actual for mucoadhesion time

Response 3 R3

Analysis of variance table [Partial sum of squares - Type III]

Table 10: ANOVA for response 3

Source	**Sum of squares**	**df**	**Mean square**	**F value**	**P- value Prob >F**
Model	3.25	1	3.25	296.08	0.0004
Linear mixture	3.25	1	3.25	296.08	0.0004
Residual	0.033	3	0.011		

The Model F-value of 296.08 implies the model is significant. There is only a 0.04% chance that a "Model F-Value" this large could occur due to noise.

R-Squared 0.9900

Adj R-Squared 0.9866

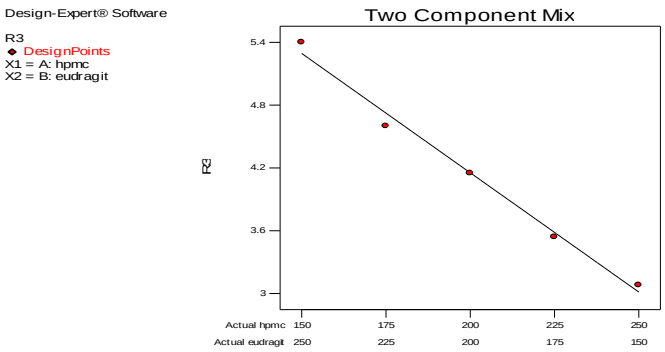

Figure 11. Plot of two component mix for bioadhesive strength

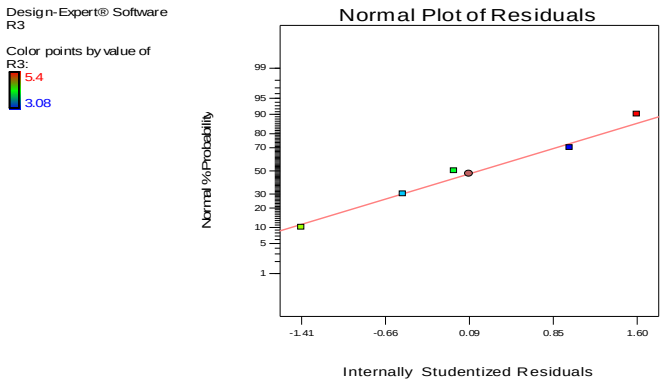

Figure 12. Normal plot of residuals for bioadhesive strength

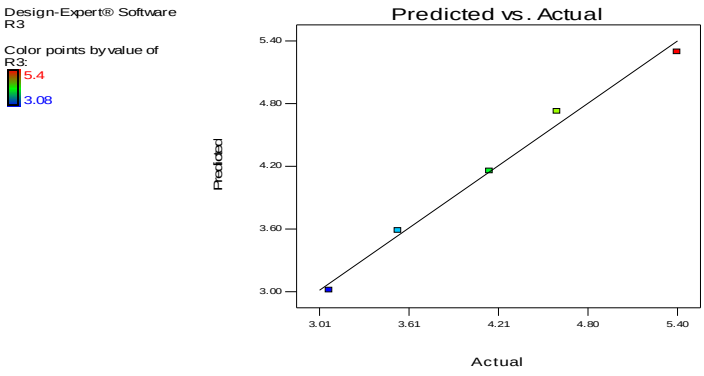

Figure 13. Plot of predicted Vs actual for bioadhesive strength

Stability studies

Stability studies were carried out for optimized batch (F2) of sustained release buccal patches of Aceclofenac. The patches were packed in aluminium foil placed in hot air oven for one month at 45°C. At the interval of 15 days, the patches were withdrawn and evaluated for physical

properties and content uniformity.[10] The results of stability studies are shown in following tables.

Table 11. Stability study of optimized batch F2

Parameters	0 Month	1 Month
Appearance	Transparent	Transparent
Folding Endurance	260	259
Drug content (mg)	29.80	29.74

RESULTS AND DISCUSSION

Any polymer with good swelling property is expected to be a good candidate for bioadhesive application. When bioadhesive comes in contact with aqueous medium they swell and form a gel. The rate and extent of water uptake by a polymer has been reported to be an important factor in determination of its relative bioadhesive strength, uptake of water results in relaxation of originally stressed or twisted polymer chain resulting in exposure of all polymer bioadhesive sites for binding to occur. The faster this phenomenon occurs, more rapidly will be the polymers adhering to its substrate. The swelling is favoured by the protonation and repulsion of free ammonium groups of Eudragit RL 100, thus leading to greater swelling of patch. The results showed that the swelling index (Table 2) of formulation P4 containing HPMC and Eudragit RL 100 is highest. It was observed that there was proportionate increase in swelling of patch as the increase in concentration of polymer.

The results for bioadhesion indicated that the bioadhesive strength (Table 2) of formulation P4 containing HPMC and Eudragit RL100 was more than the other formulations. Here we conclude that HPMC base having good bioadhesive properties in combination with E RL100. Eudragit RL 100 having cationic nature leads to electrostatic interactions between polymer and negatively charged mucous and thus, increase bioadhesive strength. As the concentration of E RL100 increases the bioadhesive strength was found to be increased, may be due to combination of hydrophilic and hydrophobic nature which gains the bond strength with mucosal surface.

The formulation of preliminary batch composition is shown in Table 1. The values of the *in vitro* residence time were reported in the Table 2. Time required for the complete erosion or detachment of buccal patch from the mucosa was found satisfactory. The highest duration (4.05 h) was recorded for formulation P4 containing E RL 100 with HPMC. Patches of formulation P1 containing only HPMC, eroded completely in 3.40 h. This indicated that the water soluble hydrophilic additives dissolved rapidly introducing porosity. The void volume is expected to occupy by the external solvent diffusing into the patch and thereby accelerating the dissolution of the film.

Formulation using factorial approach was indicated in Table 3. The cumulative % drug release in 8 h from formulations F1, F2, F3, F4 and F5 was indicated in Table 4. Formulation F2 showed maximum drug release in 8 h (92.35 %). Mucoadhesion time and bioadhesive strength were performed. F2 showed maximum residence time (4h) and bioadhesive strength of (5.4 g). The studies of drug release kinetics were shown in Table 5. F1, F3, F5 follows Higuchi model while F2 and F4 follow zero-order model. ANOVA was performed for three responses % releases were shown in Table 8, 9 and 10 respectively. The results of mucoadhesion time and bioadhesive strength of factorial batches F1 to F5 were shown in Table 6 and 7 respectively. For validation

study formulation F2 was selected. All parameters weight variation, content uniformity, folding endurance, thickness and surface pH showed close similarity.

CONCLUSION

The mucoadhesive polymers can themselves exert some control over the rate and amount of drug release and thus contribute to the therapeutic efficacy of mucoadhesive drug delivery system. The buccal drug delivery system bypasses the liver and avoids presystemic elimination in the GI tract and liver. The mucosa is relatively permeable with a rich blood supply. Five formulations of HPMC were prepared along with Eudragit RL 100. Among the various polymeric combinations, the combination F2 was found to be most suitable. The formulation F2 comprising polymers HPMC and E RL100 in 3:5 ratios fulfill the requirement of good buccal patch. It showed highest % release 92.35% upto 8 h , mucoadhesion time as well as bioadhesive strength.

Thus from the present study it can be concluded that, buccoadhesive drug delivery system for Aceclofenac with HPMC and Eudragit RL 100 meet the ideal requirement for buccal devices which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability.

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