Original Article

# *Datura stramonium* Leaves Mucilage Aided Buccoadhesive Films of Aceclofenac using $3^2$ Factorial Design with Design-Expert Software

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## ABSTRACT

**Aim and Objectives:** The main motto of this work was to search the additive effect of *Datura stramonium* leaves mucilage in the making of buccoadhesive film by taking Aceclofenac as a model drug. **Materials and Methods:** Nine formulations of buccal films were made using Carbopol 934 P and varying proportions of Ethyl Cellulose and *D. stramonium* leaves mucilage. The films were judged for compatibility studies and physical constraints including Aceclofenac content and discharge. **Results:** Among the films F-9 containing 1:1 of Aceclofenac and ethyl cellulose; and 1:0.5 ratios of Aceclofenac: *D. stramonium* leaves mucilage was found to have good Mucoadhesion time (10.5 ± 0.1h) and Bioadhesive strength (5.5 ± 0.2g). The formulation F2 showed the highest % release i.e., 92.85% up to 8 h. **Conclusion:** The study resolved that buccoadhesive drug delivery system for Aceclofenac with ethyl cellulose aided with *D. stramonium* leaves mucilage meets the ideal requirement for buccal devices is an efficient approach to surpass the hepatic first-pass metabolism and increase bioavailability.

**Key words:** Aceclofenac, Mucilage, Factorial design, Buccal Film, Bio adhesive strength.

## INTRODUCTION

Novel approaches are being emerged for drug administration to augment the bioavailability of the drugs with patient amenability. The buccal route is devoid of gastric irritation and ease of administration.[1] Aceclofenac (ACF) is an NSAID, has anti-inflammatory and analgesics actions.[2,3] It has a t ½ of 4h, which is a faultless match for making controlled release formulation. Mucoadhesive systems are greatly depends on properties of the polymer adopted. The oral route is deliberated as the favorite of many patients as it is convenient for drug administration.[4] Many polymers were tried for making buccoadhesive purposes, which are rare and costly. In the search of new polymer from nature with the bioadhesion properties, the authors are planned to reconnoiter the buccoadhesive films using *D. stramonium* leaves mucilage (ACBF). The aim of this work in making the ACBF is to attain a steady-state blood level that is therapeutically effective and harmless for a protracted time. Controlled discharge systems are measured a cleverer attitude for the short t ½ drugs and those need a continual medicating, as they designed with ease. As ACF causes gastric irritation the novel ACBF are devoid of these issues.

## MATERIALS AND METHODS

### Materials

Aceclofenac (ACF) was from Waksman Selman Pharm. Pvt., Ltd, Anantapur, AP. Carbopol 924 P, Ethyl Cellulose and dichloromethane were of Merck, Hyderabad.

### Methods

#### *Extraction of mucilage*

The extraction was done as described by Ahad *et al.* 2012.[5] The fresh *D. stramonium*

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leaves were washed with water, crushed, placed in water (6 h), boiled for 1h and kept aside for an hour (mucilage released into the water). Later clarified (marc removed). Three times of acetone was added (mucilage precipitated). The separated mucilage parched at 40°C (oven-CEI-248), pulverized, sieved with # 80 (Remi) and preserved in a desiccator (B-3082045 Foxx Life Sciences) at 30°C and 45% RH.

### *Cleansing of the Mucilage*

As described by Hindustan *et al.* 2012, the DSLM was homogenized (Remi-RQ-140/DE) with 5% tri chloroacetic acid, centrifuged (Remi C-852), NaOH was added (neutralization) by drop wise and dialyzed (Nikkison) with distilled water. Later ethanol (95%) was encompassed in the precipitate and washed consecutively with acetone and ether.

### *Drug Excipient compatibility studies*

### *DSC*

ACF and DSLM were taken in a 1:1 ratio and subjected to the analysis. About 10 mg of the mix was taken in the mini pan of DSC and scanned between 50-300°C (Venchal Scientific- 412105- USA).

### *FTIR*

The interactions between ACF with DSLM were examined by FTIR spectroscopy (Bruker) by scanning at 4000-400 $cm^{-1}$ range.

### *Initial risk assessment*

The Quality Target Product Profile (QTPP) is vital in quality by design (QbD) as per ICH Q8 and Q9. In like manner,[6] it is imperious to distinguish the unbiased at the starting time of product development. The QTPP assimilates item product qualities to assurance that the item encounters the base required quality facts.[7] The QTPP and CQAs for the bilayer tablet were strong-minded in light of the past inquiries and literature appraisals.

### *Experimental design*

In this study, 9-run, 2 factors, 3-level full factorial design (FFD) was adopted for making and assessing quadratic response surfaces for optimizing the ACBF[8] with Design-Expert software (11.0.5.0, Stat-Ease Inc.,). The design was utilized for measuring the key, interface and quadratic possessions of independent variables on dependent variables with the resulting quadratic model:

$$Y = B_0+B_1 X_1+B_2X_2+B_{12}X_1X_2+B_1X_1^2 + B_2X_2^2$$

Here Y is the dependent variable, $B_0$, $B_1$ and $B_2$ are the regression coefficients of independent variables and their mutual interactions and $X_1$ and $X_2$ are the independent variables. The dependent variables/responses were the mucoadhesive time (h) and bioadhesion strength (g) for ACBF.[9] The variables and their levels used in the optimization of the ACBF were exemplified in Table 1 and $3^2$ experimental designs were expressed in Table 2. The ingredients in various ACBF were listed in Table 3.

**Table 1: Factors and their levels used in the study.**

| Factors | Levels | | |
|---|---|---|---|
| | −2 | 0 | +2 |
| $X_1$ (EC) | 50 | 75 | 100 |
| $X_2$ (DSLM) | 25 | 37 | 50 |

**Table 2: $3^2$ Experimental design by Design-Expert software.**

| Std | Run | A:EC (mg) | B:DSLM (mg) |
|---|---|---|---|
| 1 | 5 | 50 | 25 |
| 2 | 4 | 75 | 25 |
| 3 | 9 | 100 | 25 |
| 4 | 6 | 50 | 37 |
| 5 | 7 | 75 | 37 |
| 6 | 8 | 100 | 37 |
| 7 | 1 | 50 | 50 |
| 8 | 2 | 75 | 50 |
| 9 | 3 | 100 | 50 |

### *Preparation of ACBF*

The solvent evaporation approach was adopted (ethanol: dichloromethane) in 1:1 proportion to dissolve the polymers with the help of magnetic stirrer (Tarson-4030) and ACF was added slowly till to get a uniform solution. Propylene glycol (plasticizer and penetration enhancer) was added and stirred. Later the combination was poured into the bangles in Petri plates and a funnel was inverted and left for overnight.[10] The formed ACBF was cut into 2.5X2.5 cm.

## Evaluation parameters

## Evaluation of Physical properties

### *Surface pH study*

To examine the acceptability, the ACBF at buccal mucosa was permitted to bulge (in distilled water for 1 h) in glass Petri plates. The surface pH was then distinguished by placing the glass electrode close to the ACBF surface.[11]

### *Content uniformity*

Medication content consistency was appraised by dissolving the ACBF from each group by homogenization in 100 ml of a phosphate buffer (pH 6.8) for 6 h under

**Table 3: Composition of the ACBF.**

| Components | Formulations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F-1 | F-2 | F-3 | F-4 | F-5 | F-6 | F-7 | F-8 | F-9 |
| Aceclofenac (mg) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Ethyl Cellulose (mg) | 50 | 75 | 100 | 50 | 75 | 100 | 50 | 75 | 100 |
| DSLM (mg) | 25 | 25 | 25 | 37 | 37 | 37 | 50 | 50 | 50 |
| Carbopol 934 P (mg) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Propylene glycol (ml) | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| Solvent (ml) | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

periodic shaking.[12,13] Sample (5 ml) was taken, diluted up to 20 ml (pH 6.8), passed (membrane of 0.45 µm) and the medication content was estimated at 203 nm utilizing a UV spectrophotometer.

### *Folding endurance*

The collapsibility of the ACBF was judged by folding it in the same place until it breaks. The point till the ACBF can endure without breach provided this estimation.[13]

### *Swelling index study*

A pre-weighed ACBF in a petri dish (10 ml of PBS of pH 6.8). Every hour the weight gained was assessed until 5 h. The deviation in the weights gives the retention of water and enlargement of the ACBF using this formula.[14]

$$\%\,SI = \frac{X_t - X_o}{X_o} \times 100$$

Where Xt-weight of the ACBF after time, t; Xo- Initial weight of the ACBF

### *Determination of ex vivo residence time*

USP dissolution apparatus with pH 6.8 PBS (900ml) kept at 37±0.5°C is used. A goat buccal mucosa (3 cm length) was stuck to the outside of a glass piece, vertically connected to the apparatus. The surface of the ACBF was hydrated (with 15µl pH 6.8 PBS) and allowed to contact with goat mucosa.[15] The glass piece was vertically placed in the apparatus. The time for complete separation of the ACBF was recorded.

### *Measurement of bioadhesive strength*

The bioadhesive strength of all prepared ACBF was assessed *ex vivo* ($n$=3) using an altered physical balance. A slice of lamb buccal mucosa was knotted to the entrance of a glass vial filled with pH 6.8 isotonic phosphate buffer at 37±1°C. The glass vial was firmly tailored in the middle of a beaker with the same buffer. The ACBF was wedged to the bottom of the rubber stopper with an adhesive. The weight (g) needs to remove the ACBF from the mucosal surface provided the measure of Mucoadhesive strength, as the formula illustrated.[16]

$$\text{Force of adhesion (N)} = \frac{\text{Biodhesive strength (g)} \times 9.81}{1000}$$

### *Statistical optimization*

Design-Expert software was betrothed to calculate the inspiration of independent factors on the responses, which were assessed by contour plot (2D) and response surface plot (3D). Statistical validation of polynomial calculations was done by assessing ANOVA provisions.[17,18] A statistical model was engendered by ANOVA provision to ascertain model abundance and competence. An $F$ value with $p < 0.05$.

## RESULTS AND DISCUSSION

The fresh DSLM was yellowish-green in color, which is used as an aid in buccoadhesive films and its compatibility was assessed.

### Compatibility studies

The DSC assessment summarized that the pure ACF produced a sharp endothermic peak which initiates at 1485.52°C and peak at 155.98°C, represents the purity of ACF, this peak broadens when combined with excipients, which is shifted left (peak at 147.58°C). The DSC observations explore that ACF is devoid of interaction with the excipients (Figure 1).

The ACF pure form spectrum represents typical peaks characteristic FTIR bands at 3316.07 $cm^{-1}$ (secondary amine), stretching at 1171.02 $cm^{-1}$ (phenyl ester) and a vibration at 1718.03 $cm^{-1}$ (carboxylic). Whereas the blend (F-9) showed 3317.08 $cm^{-1}$, 1174.09 $cm^{-1}$, 1719.07 $cm^{-1}$. The specific peaks and stretched in the ACF spectrum were found undisturbed in the spectrum of ACF with excipients (Figure 2).

### Quality Target Product Profile

QTPP was applied for the documentation of CQA (critical quality attributes) and anticipated dosage form. The method used for making the ACBF was strong and

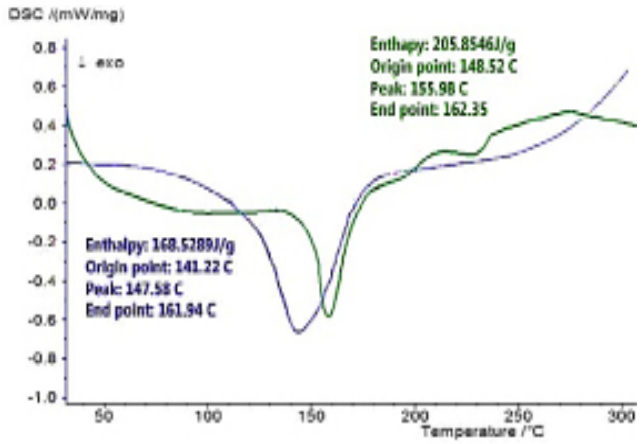


**Figure 1: DSC thermograms of ACF and ACF+ excipient blend.**

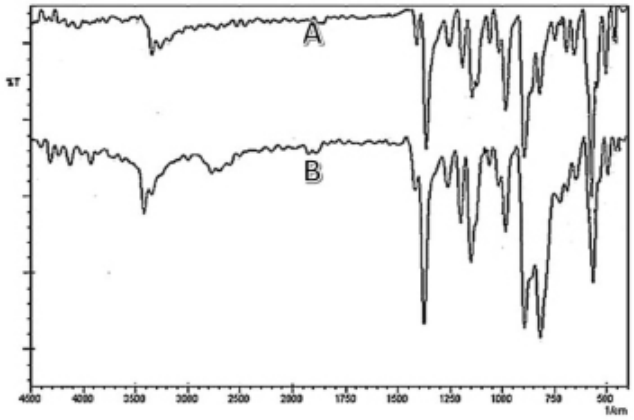


**Figure 2: FTIR spectrum of A) Aceclofenac B) Aceclofenac with excipient blend.**

**Table 4: The physical properties of the films.**

| Formulation | Parameters | | | | | |
|---|---|---|---|---|---|---|
| | Thickness (mm) | Surface pH | Folding endurance | Uniformity in weight (mg) | Swelling index (% in 2h) | Content uniformity (mg) |
| F-1 | 0.13±0.01 | 6.5±0.2 | 74±2 | 175.25±0.26 | 18.1±0.9 | 96.36±1.25 |
| F-2 | 0.11±0.01 | 6.4±0.3 | 90±3 | 200.75±0.81 | 17.2±0.3 | 94.22±2.25 |
| F-3 | 0.12±0.01 | 6.7±0.5 | 95±1 | 225.75±0.25 | 20.4±0.8 | 93.02±1.27 |
| F-4 | 0.18±0.02 | 6.8±0.4 | 79±2 | 187.37±0.95 | 23.2±0.4 | 94.86±1.23 |
| F-5 | 0.17±0.03 | 6.5±0.1 | 89±3 | 212.87±0.28 | 26.4±0.6 | 95.56±4.52 |
| F-6 | 0.16±0.03 | 6.4±0.2 | 96±4 | 237.37±0.64 | 24.7±0.7 | 94.58±1.32 |
| F-7 | 0.23±0.01 | 6.6±0.5 | 87±2 | 201.50±0.39 | 33.2±0.8 | 97.36±1.65 |
| F-8 | 0.22±0.01 | 6.7±0.3 | 76±1 | 226.00±0.78 | 35.6±0.8 | 98.23±1.23 |
| F-9 | 0.21±0.01 | 6.6±0.1 | 98±2 | 251.50±0.84 | 34.3±0.7 | 98.92±2.36 |

Value in mean ±SD

reproducible. Therefore, the product meets the drug product CQA.

## Evaluation parameters

The CQAs (Mucoadhesion time (h) and Bioadhesive strength) of (ACBF) were studied availing QbD to investigate their influence on responses. ACBF was identified. ACBF was made by the solvent casting approach. The polymers used were Carbopol 934P and DSLM. The ACBF were assessed for various physicochemical tests viz., thickness, folding endurance, and surface pH, uniformity in weight, swelling index and content uniformity.

## Physical properties

The thickness of the ACBF was increased slightly based on the concentration of the DSLM concentration (0.11±0.01 to 0.23±0.01 mm). The ACBF were recorded a pH nearer to neutral and extended from 6.4±0.2 to 6.8±0.4. The folding endurance was observed to be good for ACBF with more quantity of EC and ranged from 74±2 to 98±2. The weights of each batch of ACBF were observed to be even and ranged from 175.25±0.26 to 251.50±0.84 mg (as polymer content varied from batch to batch). The swelling index was directly relational to the ACBF with more amount of DSLM and ranged from 17.2±0.3 to 35.6±0.8%. The content uniformity of the ACBF was observed to be uniform ran ranged from 93.02±1.27 to 98.92±2.36 mg. All these values were embodied in Table 4.

The Mucoadhesion time was detected to have an additive effect with increased concentration of DSLM and ranged from 7.5±0.2 to 10.5±0.1h and the bioadhesive strength was also observed to have a similar dependence on the amount of the DSLM and ranged from 3.9±0.1 to 5.5±0.2 g and represented in Table 5, Figure 3 and 4.

## ACF estimation

The calibration curve for ACF estimation in phosphate buffer (pH 6.8) solutions was obtained at $\lambda_{max}$ 203 nm with a UV-VIS spectrometer. Beer's law observed to build the calibration curve was in the range of 0-10 µg/ml (repeated thrice). This data helps in determining content uniformity.

**Table 5: Mucoadhesion time and Bioadhesive strength of the ACBF.**

| Formulation | Parameters | |
|---|---|---|
| | Mucoadhesion time (h) | Bioadhesive strength (g) |
| F-1 | 7.5±0.2 | 3.9±0.1 |
| F-2 | 7.8±0.3 | 4.1±0.2 |
| F-3 | 8.0±0.4 | 4.2±0.1 |
| F-4 | 8.5±0.5 | 4.6±0.2 |
| F-5 | 9.0±0.2 | 4.7±0.1 |
| F-6 | 9.5±0.1 | 4.8±0.2 |
| F-7 | 10.1±0.3 | 5.3±0.1 |
| F-8 | 10.2±0.3 | 5.4±0.3 |
| F-9 | 10.5±0.1 | 5.5±0.2 |

Value in mean ±SD

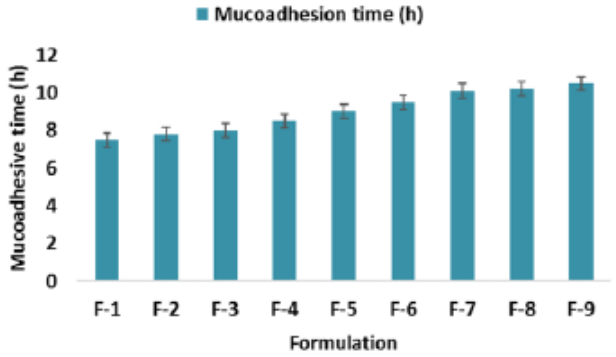


**Figure 3: Mucoadhesive time for the films.**

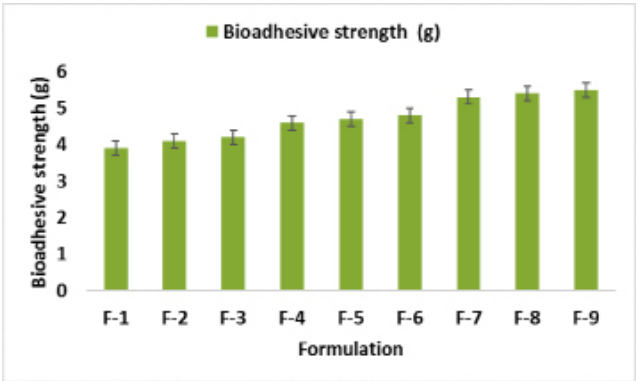


**Figure 4: Bioadhesive strength for the films.**

## *In-vitro* diffusion study

The test was achieved with sheep's buccal mucosa using Franz diffusion cell. The receptor section was maintained at 37±0.5°C with a water jacket. The receptor chamber was packed with PBS of pH 6.8 (5ml). The buccal layer was indorsed to stabilize overnight in the same PBS. Later the ACBF was kept on buccal mucosa for 10 h. Samples were detached at systematic intermissions (sink condition were maintained by replacing the sampling volume with fresh medium) and assessed spectrophotometrically at 203 nm.

The releases kinetics from ACBF was best fitted in Higuchi kinetics. This represents the ACF release tracks the linear kinetic procedure. The dissolution outcome reveals that F-2 shown better ACF release equaled to other ACBF (Figure 5 and 6A-D and in Table 6).

## Drug release kinetics

A $3^2$ randomized full factorial design needs 9 experiments. The responses detected for 9 ACBF concurrently fitted to first order, second order and quadratic models with the Design-Expert 11.0 software and the results of the analysis of variance (ANOVA) for the selected factorial model (Table 7).

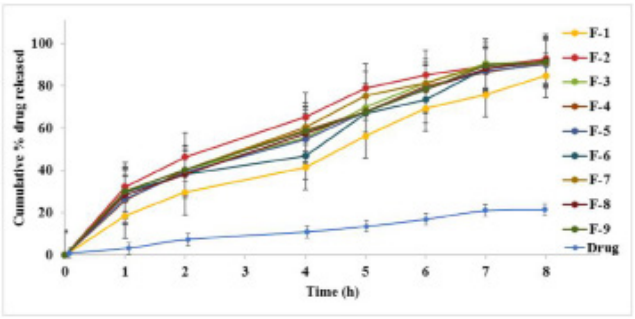


**Figure 5: The cumulative drug release from the Aceclofenac films.**

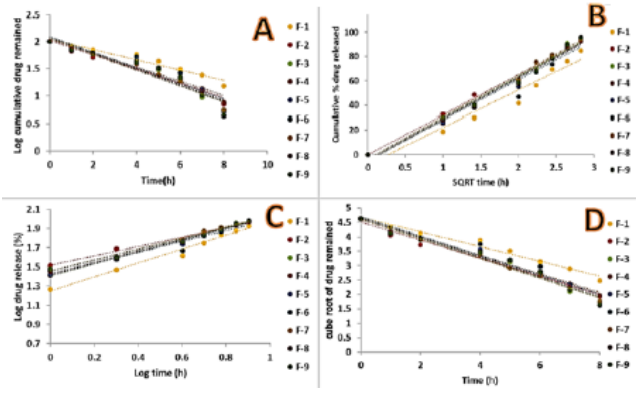


**Figure 6: A) First-order B) Higuchi C) Korsmeyer Peppas D) Hixson Crowell's release kinetics of Aceclofenac films.**

**Table 6: Summary of regression values of various kinetic release models.**

| Formulation | Zero order | First order | Higuchi | Korsmeyer Peppas | Hixson Crowell |
|---|---|---|---|---|---|
| | *R2* | | | | |
| F-1 | 0.9863 | 0.9366 | 0.9494 | 0.9814 | 0.9746 |
| F-2 | 0.9284 | 0.9468 | 0.9929 | 0.9870 | 0.9727 |
| F-3 | 0.9696 | 0.9427 | 0.9806 | 0.9907 | 0.9893 |
| F-4 | 0.9642 | 0.9585 | 0.9901 | 0.9908 | 0.9708 |
| F-5 | 0.9724 | 0.9101 | 0.9818 | 0.9980 | 0.9297 |
| F-6 | 0.9619 | 0.8526 | 0.9540 | 0.9327 | 0.9778 |
| F-7 | 0.9548 | 0.9553 | 0.9911 | 0.9904 | 0.9893 |
| F-8 | 0.9718 | 0.8973 | 0.9840 | 0.9886 | 0.9669 |
| F-9 | 0.9647 | 0.8991 | 0.9859 | 0.9876 | 0.9646 |

**Table 7: Results of ANOVA of measured responses for Mucoadhesion time.**

| Source | Sum of Squares | df | Mean Square | *F*-value | *p*-value | |
|---|---|---|---|---|---|---|
| Model | 9.98 | 5 | 2.00 | 55.13 | 0.0038 | significant |
| $X_1$-EC | 0.6017 | 1 | 0.6017 | 16.62 | 0.0266 | |
| $X_2$-DSLM | 9.37 | 1 | 9.37 | 258.95 | 0.0005 | |
| $X_1 X_2$ | 0.0025 | 1 | 0.0025 | 0.0691 | 0.8097 | |
| $X_1^2$ | 0.0006 | 1 | 0.0006 | 0.0153 | 0.9092 | |
| $X_2^2$ | 0.0006 | 1 | 0.0006 | 0.0153 | 0.9092 | |
| Residual | 0.1086 | 3 | 0.0362 | | | |
| Cor Total | 10.09 | 8 | | | | |

## Diagnostic analysis

### *Diagnostic analysis for mucoadhesive time*

The mucoadhesive time was investigated by diagnostic plots to observe the goodness of fit (Figure 7A–D). The normal likelihood plot of outwardly studentized residuals designated that maximum of the colored points representing the mucoadhesion time was observed around the normal probability line, which certified the normality of residuals and recommended the applicable analysis of response data. The normality hypothesis for residuals was satisfied since the residuals are strategized around the straight line (Figure 7A). The outwardly studentized residuals vs. predicted values plot exposed that the colored points of mucoadhesion time were inside the limits. The random distribution of studentized residuals demonstrated in the plot discloses the postulation of constant variance was true (Figure 7B). The residuals vs. run number plot discovered the variables that may have prejudiced mucoadhesive time through the testing. All the points were lying within ± 4.01 which signposted that there was no faraway observation throughout and steadiness in all the runs (Figure 7C). The predicted vs. actual values plot exposed that the experimentally pragmatic values of mucoadhesive time were in close contact with the prophesied values (Figure 7D).

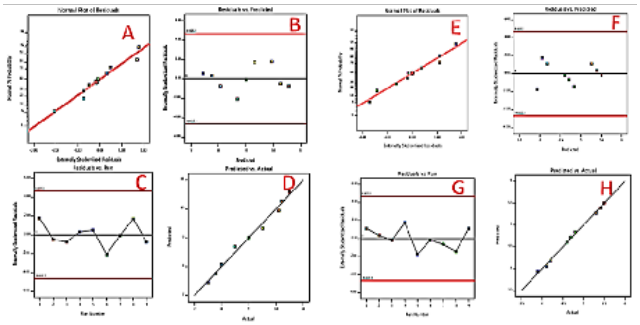


**Figure 7A-H: Plots showing the interaction effect of polymers on Mucoadhesion time, and Bioadhesive strength of prepared films.**

### *Diagnostic analysis for Bioadhesive strength*

The bioadhesive strength was investigated by diagnostic plots to scrutinize the goodness of fit (Figure 7E–H). The normal likelihood plot of superficially studentized residuals specified that most of the colored points indicating the bioadhesive strength were found around the normal probability line, which ensured the normality of residuals and recommended the applicable analysis of response data. The normality assumption for residuals was satisfied since the residuals are plotted around the straight line (Figure 7E). The externally studentized residuals vs. predicted values plot exposed that the colored points of bioadhesive strength lay within the set limits. The random distribution of studentized residuals shown in the plot reveals the postulation of continuous variance was true (Figure 7F). The residuals vs. run number plot discovered the variables which may have prejudiced mucoadhesive time during the study. All the points were lying within ± 4.01 which signposted that there was no outlying reflection throughout and steadiness in all the runs (Figure 7G). The predicted vs. actual values plot expressed that the experimentally observed values of Bioadhesive strength were in close arrangement with the predicted values (Figure 7H).

## ANOVA for Quadratic model

### *ANOVA details of mucoadhesive time*

The ANOVA details of mucoadhesive time were exemplified in Table 7.

The Model *F*-value of 55.13 implies the model is significant. It is only a 0.38% fortuitous that an F-value this large may happen to owe to noise. *P*-values < 0.05

represent model terms are significant. In this case $X_1$, $X_2$ are significant model terms. Values > 0.1 illustrates that the model terms are not significant. The final model in terms of coded factors for Mucoadhesion time was as follows:

$$\text{Mucoadhesive time} = -3.86+1.05\ X_1+7.46\ X_2 -0.40\ X_1X_2+0.06\ X_1^2+1.06X_2^2$$

A positive value signifies a result that favors the optimization, while a negative value designates a converse connection between the factor and the response. The equation in terms of actual factors can be utilized to make forecasts about the response for given levels of each factor. 2D contour plots and 3D response surface plots were shown in Figures 8 (used to study the interaction effects of the factors on the responses).

These types of plots represent the influence of two factors on the response at a time. The contour plot and response surface plot (Figure 5) publicized that an equivalent increase in the Mucoadhesion time of drugs takes place with a rise in the amount of EC and DSLM. The Predicted $R^2$ of 0.8689 is reasonably related to the adjusted $R^2$ of 0.9713; i.e., the difference is <0.2. Adequate Precision procedures the signal to noise ratio. A ratio > 4 is required and the ratio of 20.169 (adequate signal). This model can be utilized to circumnavigate the design space.

### *ANOVA details of Bioadhesive strength*

The ANOVA response 2 i.e., Bioadhesive strength was exemplified in Table 8.

The Model F-value of 849.69 suggests the model is significant. A 0.01% chance that an F-value could happen due to noise. *P*-values<0.05 designate model terms are significant. In this case $X_1$, $X_2$ are significant model terms. Values >0.1represents the model terms are not significant.

The Predicted $R^2$ of 0.9919 is in reasonable contract with the Adjusted $R^2$ of 0.9981; i.e., the difference is < 0.2. Adequate Precision counts the signal to noise ratio. A ratio >4 is desirable and the ratio of 75.368 specifies a tolerable signal. This model can be used to steer the design space.

2D contour plots and 3D response surface plots were shown in Figures 9 (used to study the interaction belongings of the factors on the responses).

The contour plot and response surface plot (Figure 9) shown that an analogous increase in the Bioadhesive strength of ACBF with an upsurge in the amount of EC and DSLM.

## Final Equation in Terms of Actual Factors

$$\text{Bioadhesive Strength} = +0.56+0.91\ X_1+0.13X_2-0.40\ X_1X_2-0.06X_1^2+2.13X_2^2$$

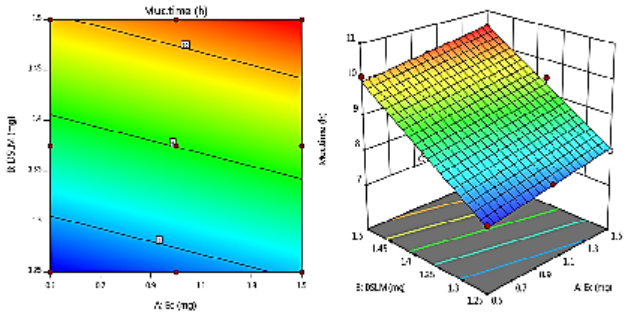

**Figure 8: Contour plot and 3D response plot for Mucoadhesive time.**

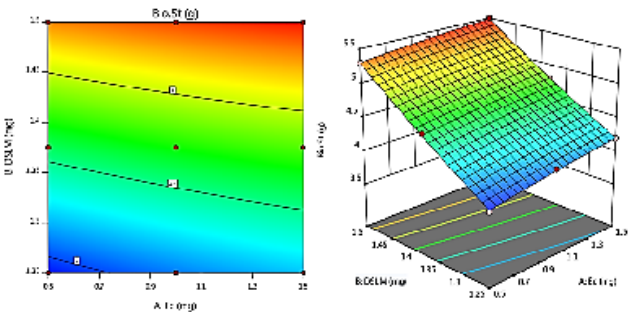

**Figure 9: Contour plot and 3D response plot for Bioadhessive strength.**

**Table 8: Results of ANOVA of measured responses for Bioadhesive strength.**

| Source | Sum of Squares | df | Mean Square | *F*-value | *p*-value | |
|---|---|---|---|---|---|---|
| Model | 2.75 | 5 | 0.5507 | 849.69 | < 0.0001 | significant |
| A-Ec | 0.0817 | 1 | 0.0817 | 126.00 | 0.0015 | |
| B-DSLM | 2.67 | 1 | 2.67 | 4114.29 | < 0.0001 | |
| AB | 0.0025 | 1 | 0.0025 | 3.86 | 0.1443 | |
| $A^2$ | 0.0006 | 1 | 0.0006 | 0.8571 | 0.4228 | |
| $B^2$ | 0.0022 | 1 | 0.0022 | 3.43 | 0.1612 | |
| Residual | 0.0019 | 3 | 0.0006 | | | |
| Cor Total | 2.76 | 8 | | | | |

## CONCLUSION

The mucoadhesive polymers utilize some control on the rate and quantity of ACF release and thus donate to the therapeutic efficacy of the buccoadhesive drug delivery system. The buccal drug delivery system bypasses the liver and evades pre-systemic removal in the gut and the liver. Nine formulations of films were made with Carbopol 934 P and varying proportions of Ethyl Cellulose (EC) and *D. stramonium* leave mucilage (DSLM). Among the various formulations, F-9 containing 1:1 proportion of ACF and EC; and 1:0.5 ratios of ACF: DSLM was noted to have good Mucoadhesion time (10.5±0.1h) and Bioadhesive strength (5.5±0.2g). The formulation F2 showed the highest % release i.e., 92.85% up to 8 h. Thus, from the present study, it can be resolved that buccoadhesive drug delivery system for ACF with EC aided with DSLM meet the ideal requirement for buccal devices which can be an efficient approach to surpass the hepatic first-pass metabolism and increase bioavailability.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

**ACF:** Aceclofenac; **NSAID:** Non-Steroidal Anti-Inflammatory Drugs; **t ½:** Biological half-life; **DSLM:** *Datura stramonium* leave mucilage; **ACBF:** Aceclofenac buccoadhesive film; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transformed-Infrared Spectroscopy; **QTPP:** Quality Target Product Profile; **QbD:** Quality by Design; **CQAs:** Critical Quality Attributes; **FFD:** Full Factorial Design; **PBS:** Phosphate Buffer Saline.

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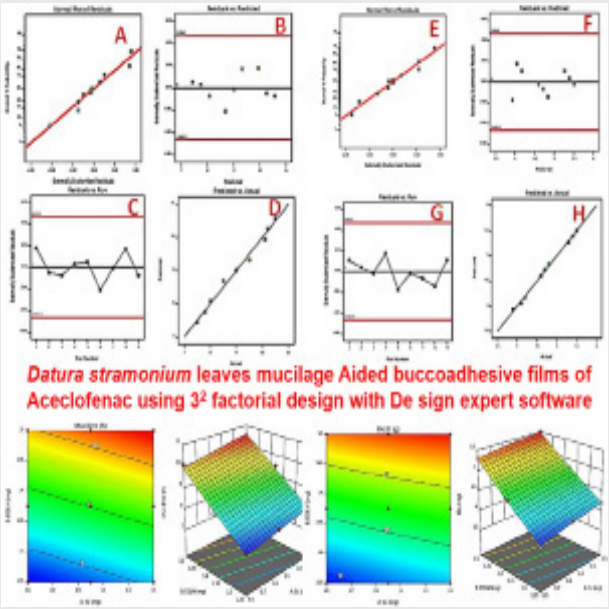
## PICTORIAL ABSTRACT




## SUMMARY

Buccoadhessive films of Aceclofenac (ACF) were made with Carbopol 934 P, Ethyl Cellulose (EC) and *Datura stramonium* leaves mucilage (DSLM). The mucilage from *D. stramonium* was extracted with water. The DSLM was found to be compatible with ACF. 9 different films were made as per $3^2$ factorial design using DSLM and EC as independent variables and mucoadhesive time and bioadhesion strength as dependent variables. The study revealed that all ACBF have good physical constraints. The films (F-9) containing 1:1 proportion of ACF and EC; and 1:0.5 ratios of ACF: DSLM was noted to have good Mucoadhesion time and Bioadhesive strength. The study determined that DSLM has an additive effect as buccoadhesive polymer.

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