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FORMULATION AND EVALUATION OF MUCOADHESIVE VAGINAL TABLET FOR THE TREATMENT OF BACTERIAL VAGINOSIS

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Keywords:

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ABSTRACT: The primary purpose of this study was to formulate a mucoadhesive vaginal tablet of clindamycin phosphate. It developed to achieve an excellent therapeutic effect and patient compliance in the treatment of bacterial vaginosis. The formulation has a sustained-release effect with good mucoadhesion due to mucoadhesive polymers like Polycarbophil and Carbopol 971P NF, which decreases dose frequency. The mucoadhesive vaginal tablets were prepared by the direct compression method. FTIR had employed to study drug excipient incompatibility. The analytical method performed using HPLC. Optimization of the formulation was done by 3^2 full factorial designs using DOE. The mucoadhesive vaginal tablet was evaluated for % swelling index, Muco-adhesive strength, drug content, % drug release, and *ex-vivo* mucoadhesion time. The *ex-vivo* mucoadhesion time of optimized batch was up to 9 h, 97.24% drug content, 88.34 ± 0.97% drug release observed at 8 h. Stability study shows developed mucoadhesive intravaginal tablet was stable at 30 °C ± 2 °C at 65 ± 5% RH (Room temperature) and 40 °C ± 2 °C at 75 ± 5% RH condition after three months. This study may prove potential vaginal formulation of clindamycin phosphate against bacterial vaginosis.

INTRODUCTION: Vaginitis is the most frequent gynecological problem in women of reproductive age groups. It may occur due to vaginal discharge, microbial infection, contact dermatitis, or allergic reaction. The vaginitis is mainly in three types: Bacterial vaginosis, it causes by anaerobic microorganisms. Candidiasis vaginosis is caused by candida microorganisms and is responsible for causing the yeast vaginitis and Trichomoniasis vaginosis, which is caused by protozoan, namely tricho-monas vaginalis. Bacterial vaginosis accounts for 40 - 50 % of vaginal cases, vaginal candidiasis 20 - 25 %, and trichomoniasis 15 – 20 %.

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Normally in the vagina, hydrogen peroxide (H_2O_2) producing by lactobacilli is important in preventing overgrowth of anaerobic bacteria. However, in vaginosis conditions, lactobacilli reduce, therefore decrease the formation of hydrogen peroxide, meanwhile increasing harmful anaerobic bacteria and a rise in pH.

It facilitates adherence of G. vaginalis to the epithelial cells. The problem associated due to bacterial vaginosis is like, occur in childbearing age, early or late miscarriage, preterm labour, preterm delivery, preterm labour rapture of the membrane, low birth weight, increase efficiency of HIV. Increase common incidence due to bacterial vaginosis, so the need for effective therapeutic strategies [1-4]. Antibacterial drugs used for topical delivery, such as clindamycin and metronidazole, have been used effectively to treat bacterial vaginosis. Clindamycin enters very less into the systemic circulation from the intravaginal route [5,] and it has fewer side effects. Also, several reviews or research shows that intravaginal clindamycin is more effective than metronidazole [6].

Several drug delivery systems are used for the local treatment of vaginitis. These include a tablet, suppository, ointment, pH-neutral emulsion, gel, pessaries, ovules, and cream. However, these conventional drug deliveries have some drawbacks, such as short residence time due to the self-cleansing mechanism of the vaginal tract, leakage, and messiness. As a result, this conventional therapy cannot maintain effective drug concentration for a long time and leads to poor patient compliance.

To overcome these drawbacks by a novel drug delivery system in which formulation gives a sustained-release effect for a more extended period and adheres to the vaginal mucosa for a sufficient period. The best formulation to achieve efficacy and patient compliance is to formulate a muco-adhesive vaginal drug delivery system. This system also fulfills specific criteria such as reducing the infection and the dose because it gives local effect at the site of infection, low enzyme activity, avoidance of the first-pass metabolism, and short-term treatment, large region for drug permeation [7-12].

Besides, in the mucoadhesive vaginal tablet added effervescent agent facilitates the dissolution of the tablet in the vaginal cavity, which is difficult as only 6 ml/day vaginal fluid release in the cavity [13]. Also, it adheres to the mucosa. Its ease of storage and handling, administration with the applicator's help, and uniform dosage make a dosage form the preferred choice for formulation.

MATERIALS AND METHODS:

Materials: Clindamycin Phosphate obtained as a gift sample from Sun Pharma, Vadodara, Gujarat, India. Polycarbophil, Carbopol 971P NF, Avicel pH 200, Citric acid, Sodium bicarbonate, Magnesium stearate, and talc were procured from Sigma enriched. All other chemicals were analytical grade.

Methods:

Preparation of Mucoadhesive Tablet: Muco-adhesive tablets were prepared by direct compression technique. The required quantity of polymer, Clindamycin Phosphate, effervescent agents (Citric acid: Sodium bicarbonate at the ratio of 1:3) and other formulation ingredients compressed rotary compression machine, and the tablet mould especially designed using stainless steel and formulated tablet.

Factorial Design and Optimization of Formulation: Based on a literature survey on a mucoadhesive tablet, two independent factors that affect the drug release properties of the muco-adhesive vaginal tablet were considered. Thus, the first attempt was made to evaluate the effect of polymer ratio and effervescent amount on the formulation of a mucoadhesive tablet. A statistical model incorporating interactive and polynomial terms were used to assess the responses. The number of experiments required for the studies depended on the number of independent variables selected. The response was measured for each trial.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_{12} X_1 X_2 + \beta_{11} X_{12} + \beta_{22} X_{22} + \varepsilon$$

Where Y is the dependent variable, β_0 is the arithmetic means the response of the nine-run and β_1 is the estimated coefficient for the factor X_1

The main effect of polymer ratio (X_1) and effervescent amount (X_2) represents the average result of changing one factor from its low to high value.

The interaction terms (X_1X_2) showed how the response changes when two factors are simultaneously changed. The polynomial terms (X_{12} and X_{22}) included investigating non-linearity. A 3^2 randomized full factorial design was utilized in the present study.

In this design, two factors were evaluated. Each at three levels and experimental trials carried out at all nine possible combinations: The Polymer ratio (X_1) and the amount of effervescent (X_2) selected as independent variables. The percentage swelling index (Y_1), Mucoadhesive strength (Y_2), and percentage cumulative drug release at 8 h (Y_3) were selected as the dependent variable [14].

Physical Characteristics of Mucoadhesive Tablet: Mucoadhesive vaginal tablets were evaluated for various physical parameters like appearance, colour, odour and physicodynemic parameters like thickness, hardness, weight variation, friability, %s welling index, and mucoadhesion strength.

Percentage Swelling Index: The swelling behavior of the tablet is described as the water-absorbing capacity determined by using the agar plate. A swelling study was performed on a 2% agar gel plate. Mucoadhesive intravaginal tablets were weighed individually (W_0) and placed in a 2% agar gel plate separately. After a pre-set time, interval of up to 4 h, tables were removed from the Petri plate, wiped with tissue paper, and final weight (Wt) of the swell tablet was noted. The swelling capability is expressed as a swelling index. The following equation calculated it [15-16].

Swelling Capacity (%) = (Final weight-Initial weight) / Initial weight × 100

***Ex-vivo* Mucoadhesion Study:** A modified apparatus used for *ex-vivo* mucoadhesion studies shown in **Fig. 1**. *Ex-vivo* mucoadhesion studies were carried out using goat vaginal mucosa and altered two armed balance. Goat vaginal mucosa fixed to plastic pieces with cyanoacrylate adhesive. A pre-warmed solvent was added into the beaker containing mucosa up to the upper surface of mucosa to maintain mucosal viability.

The mucoadhesive tablet was attached to the upper clamp with adhesive. The beaker was then slowly rained until subtract in contact with the tablet. A preload of 50 gm was placed on the clamp for 5 min so that the adhesive could establish. After this time, the preload removed. Add weight in another pan until mucoadhesive tablet detached from mucosa weight required to detach the tablet from mucosa noted [17-18].

FIG. 1: *EX-VIVO* MUCOADHESION STUDY

Percentage Drug Content: The percentage of drug content was measured to confirm the uniform distribution of clindamycin phosphate in a mucoadhesive tablet. Also, samples were collected randomly from prepared tablets and were crushed individually in a mortar and crushed powder dissolved in 100 ml of mobile phase [Acetonitrile: 25 mM phosphate buffer (40:60)]. Samples were subsequently filtered through a 0.45 µm membrane filter, followed by dilution with the mobile phase. The sample was analyzed by the HPLC method. The analysis performed using a Shimadzu HPLC system composed of an LC-20AT prominence solvent delivery modules, a manual Rheodyne injector with a 20 µL fixed loop, C-18 column, and UV-visible detector. The drug content in each tablet was determined at 210 nm at a flow of 1 ml/min. The content of clindamycin Phosphate was calculated using the calibration curve of clindamycin phosphate (10 – 80 µg/ml) [17].

Modified Dissolution Rate Study: A new simple modified instrument developed for dissolution study, a syringe with 3 ml capacity with an internal diameter of 8.5 mm, was used for this study. One end of the needle was closed, and the tablet was placed in an upright position. The assembly was placed in a water bath at 37 ± 0.5 °C.

The daily production of vaginal fluid is approximately 6 ml/day, and 0.5 to 0.75 ml continuously remains present in the vagina [20]. Therefore to facilitate the dissolution study, 2 ml of simulated vaginal fluid was added to the syringe. At regular time intervals, 0.25 ml of the solution was withdrawn from assembly and replaced with fresh simulated vaginal fluid. The sample was analyzed by the HPLC method [19].

***Ex-vivo* Mucoadhesion Time:** The *ex-vivo* muco-adhesion time was studied using a modified USP paddle apparatus. The simulated vaginal fluid used as a dissolution medium was maintained at 37 °C ± 0.5 °C. A part of the goat vaginal mucosa, 2.5 cm long, was stick on a glass slide vertically attached to the paddle. The mucoadhesive tablet was hydrated from one surface using 20 µl simulated vaginal fluid, and the hydrated surface was brought into contact with the mucosal membrane. The glass slide was vertically attached to the paddle and allowed rotating at 50 rpm. The time required for complete detachment of tablets from the mucosal surface recorded (Mean triplicate determination) [21].

Short Term Stability Study: A stability study of the optimized batch was carried at room condition temperature 30 ± 2 °C and 65% ± 5% relative humidity and accelerated condition 40 ± 2 °C and relative humidity 75% ± 5%. The stability chambers were placed at room condition and accelerated condition, which mentions earlier. Samples were evaluated at 1, 2, and 3 months intervals. Physical stability was observed periodically by evaluating appearance, % swelling index, Mucoadhesive strength, and percent drug content.

RESULTS AND DISCUSSION:

Preliminary Screening of Polymer with and Without an Effervescent Agent by using Swelling Study: Swelling is essential for the assessment of adhesion. This is because adhesion time is less since weak bonds are formed. Optimum water concentration is needed for polymer particles to develop maximum adhesion strength. It was observed that the order of swelling rate was Carbopol 971P NF > Polycarbophil > HPMC K4M in the drug-free formulation. According to the comparison of the corresponding swelling profiles of formulation with and without effervescent agents, it could see that the effervescent resulted in a marked increase in swelling rate. Furthermore, most tablets with 30 mg effervescent showed a higher swelling capacity than tablets without effervescent. The swelling increase could be explained by the excellent disintegration effect of effervescent, which made tablets increase in volume and construct porous channels on the surface and inside of tablets. The porous channels increased contact between polymer particles and water; hence the polymers could be hydrated more easily. Therefore, Carbopol 971P NF and Polycarbophil have a good swelling index and mucoadhesion strength, shown in **Fig. 2**. As a result, further screening was performed by Carbopol 971P NF and Polycarbophil with an effervescent agent. **Table 1** shows optimization by using 3^2 full factorial designs.

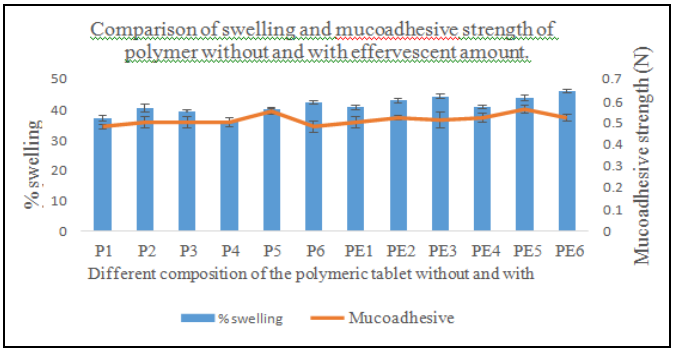

FIG. 2: COMPARISON OF SWELLING AND MUCO-ADHESION STRENGTH OF POLYMER WITHOUT AND WITH EFFERVESCENT MIXTURE BY DIRECT COMPRESSION METHOD

TABLE 1: OPTIMIZATION USING 3^2 FULL FACTORIAL DESIGNS

3^2 Full Factorial Design Layout		
	Independent Variable	
Batch no.	Polymer ratio (Polycarbophil: Carbopol 971P NF) X1	Effervescent amount X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

X_1 = Polymer ratio, X_2 = Effervescent amount

TABLE 2: ENCODED VALUE OF INDEPENDENT VARIABLE FOR OPTIMIZATION OF 3^2 FULL FACTORIAL BATCHES

Level	Polymer ratio (Polycarbophil: Carbopol 971P NF) (50 gm) X1	Effervescent amount (mg) X2
-1	0.25 : 0.75	10
0	0.50 : 0.50	20
1	0.75 : 0.25	30

X_1 = Polymer ratio, X_2 = Effervescent amount

The swelling index of factorial batches showed a linear relationship, as the concentrations of polycarbophil and effervescent agents are directly proportional to the swelling index. The results are shown in **Fig. 3**.

***Ex-vivo* Mucoadhesion Study**: In general, the swelling state of the polymer contributes to its mucoadhesion behavior. It was observed that the swelling rate developed as effervescent applied to the formulation. It increased with increasing effervescence; however, the effervescent led to a significant drop in adhesive strength.

The influence of effervescent on swelling and mucoadhesion was the opposite, mainly due to the tiny bubbles depressed the mucosa-polymer interaction and decreased mucoadhesive strength [22]. The minimum mucoadhesive strength (0.42N) was observed in formulation F9, which could be a lower ratio of Polycarbophil: Carbopol 971P NF and a higher effervescent ratio. On the contrary, with an increase in Polycarbophil: Carbopol 971P NF with the same amount of effervescent, the maximum adhesion strength (0.58N) was obtained for formulation F3. The results are shown in **Fig. 3**.

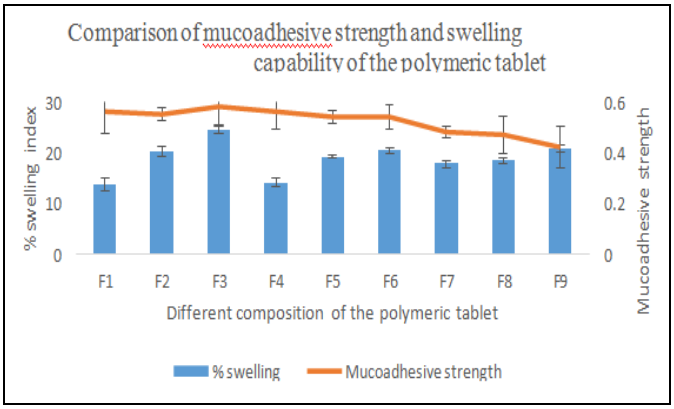

FIG. 3: COMPARISON OF MUCOADHESIVE STRENGTH AND SWELLING CAPACITIES OF F1 TO F9 BATCHES

TABLE 3: DRUG CONTENT OF F1 TO F9 BATCHES

Batch no.	Drug content (%)
F1	96.89 ± 0.58
F2	96.43 ± 0.54
F3	99.25 ± 0.22
F4	98.11 ± 0.55
F5	95.99 ± 0.12
F6	99.32 ± 0.61
F7	96.41 ± 0.46
F8	97.70 ± 0.28
F9	98.48 ± 0.41

Drug Content: The drug content analysis showed that the drug loading is uniform, and there was homogenous drug distribution in the mucoadhesive tablets. The drug content evolution of all factorial batches F1to F9 performed by the HPLC method showed drug content in each tablet, 95.99% to 99.25% of the total amount of the drug added in 300 mg tablets. The F3 batch has the highest drug content. The results showed in **Table 3**.

***In-vitro* Release Study:** The release rate of mucoadhesive clindamycin phosphate tablet was shown in **Fig. 4**. In which the percentage cumulative drug release was given for all factorial batches F1 to F9.

The tablet's release rate continuously increases up to 8 h, in which the F3 batch showed the highest release rate in 8 h. So, it was selected as an optimized batch of factorial design. The result is shown in **Fig. 4**.

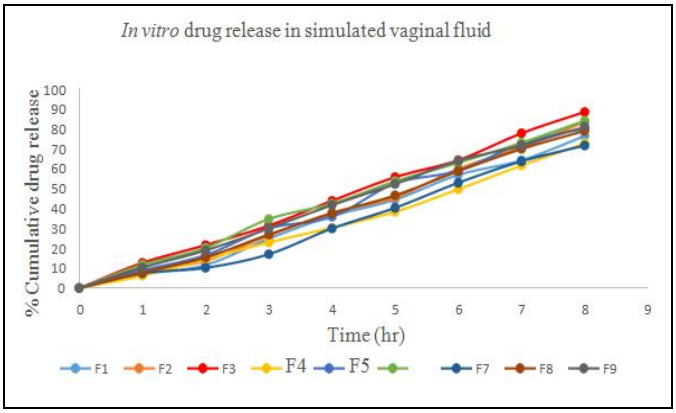

FIG. 4: PERCENTAGE CUMULATIVE DRUG RELEASE OF F1 TO F9 BATCHES

***Ex-vivo* Mucoadhesion Time:** The time for detachment of tablets from the goat vaginal tissue was noted as the mucoadhesion time. Muco-adhesion time change with change in polymer concentration. The F1 to F3 batches showed 8 to 10 hrs, the F4 to F6 batches showed 6 to 8 hrs, and the F7 to F9 batches showed 5 to 6 h. It suggests that a decrease in polycarbophil concentration decreases the time of mucoadhesion.

Statistical Analysis of Full Factorial Design: For optimization 3^2 full factorial design was employed to study the effect of independent variables on dependent variable (Y_1) % swelling index, (Y_2) Mucoadhesion strength and (Y_3) Percentage cumulative drug release at 8 h, All the batches were prepared according to the design and analyzed using the design expert 10.0.0 software. The software itself suggested the quadratic model and gave a model equation for all dependent variables. The ANOVA results and response surface and contour plots generated for each response are presented in **Fig. 5A** to **5D**.

The high value of the correlation coefficient for % swelling index, Mucoadhesive strength, and % cumulative drug release explain a good fit between an independent and dependent variable.

The Full Model For % Swelling Index: Percentage swelling index from the F1 to F9 batches of the mucoadhesive vaginal tablet varied from 13.67% to 24.34%. The polynomial equation for percentage swelling index found to be,

% Swelling Index = +18.61 -0.40*X_1 + 3.11* X_2 -2.25* X_1* X_2 +1.16* X_{12} -1.11* X_{22}

A negative sign for coefficients X_1 and a positive sign for coefficients; X_2 suggest that as the effervescent mixture increased, the % swelling index also increased. The results are shown in **Fig. 5A**.

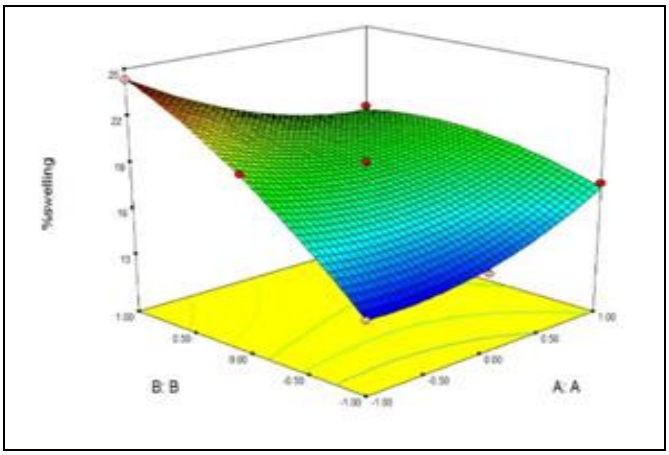

FIG. 5A: RESPONSE SURFACE PLOT FOR % SWELLING INDEX

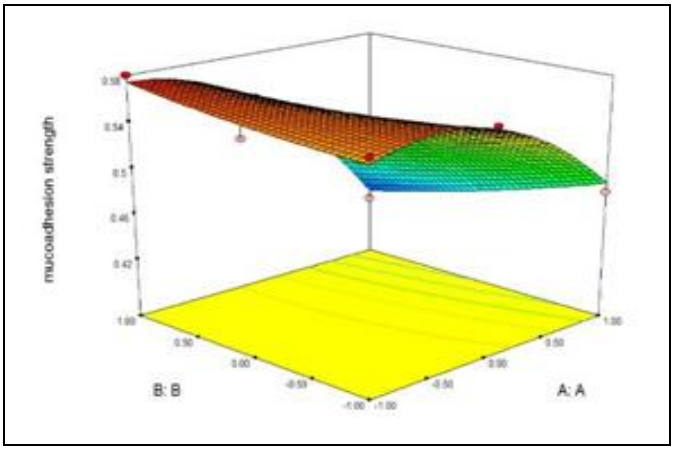

FIG. 5B: RESPONSE SURFACE PLOT FOR MUCO-ADHESION STRENGTH

The Full Model for Mucoadhesive Strength: Mucoadhesion strength from the F1 to F9 batches of the mucoadhesive vaginal tablet was varied from 0.52 N to 0.58 N. Polynomial equation for muco-adhesive strength found to be,

Mucoadhesive strength = +0.54 -0.053* X_1 – 0.010* X_2 - 0.020* X_1* X_2 - 0.037* X_{12} +3.333E-003* X_{22}

A negative sign for coefficients X_1 and a negative sign for coefficients X_2 suggest that as the polymer ratio and the effervescent amount was changed -1 to 1, the mucoadhesion strength decreased. The results are shown in **Fig. 5B**.

The Full Model for % Cumulative Drug Release: Percentage cumulative drug release from the F1 to F9 batches of the mucoadhesive vaginal tablet varied from 71.45% to 88.34%. The polynomial equation for percentage found to be;

% Cumulative Drug Release = +80.10 -2.76* X_1 + 5.48* X_2 - 0.67* X_1*X_2 + 0.96*X_{12}-1.84* X_{22}

A negative sign for coefficients X_1 and a positive sign for coefficients X_2 suggest that as the Polymer ratio was changed -1 to 1, the % CDR decreased, and the effervescent amount was changed -1 to 1, the %CDR increased. The results are shown in **Fig. 5C**.

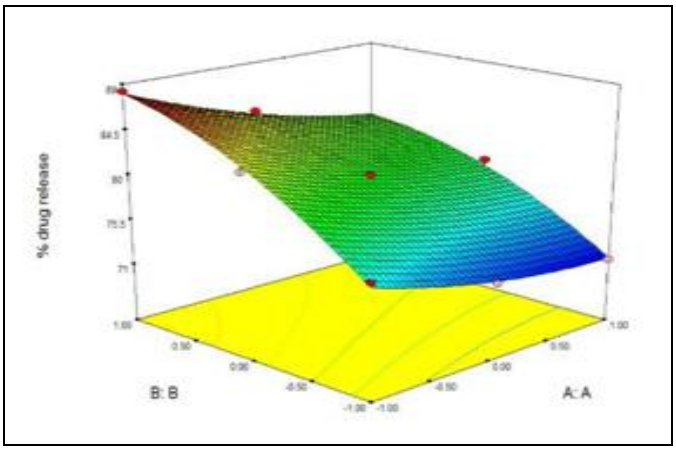

FIG. 5C: RESPONSE SURFACE PLOT FOR % DRUG RELEASE

The Response Surface Model: The response surface plot was used, drawn between polymer ratio (X_1) and effervescent amount (X_2) versus all dependent variables like Mucoadhesive strength, % swelling index, and % cumulative drug release. The plots are drawn by using design expert software. The final batch was selected based on the moderate value of % swelling index and mucoadhesion strength. The controlled manner drug release was also obtained-the checkpoint batch C1 prepared at

level (X_1 = 0.98 and X_2 = 0.97) from the residual model. The model suggests that % swelling should be 24.20%, the mucoadhesion strength should be 0.57 N, and the % cumulative drug release should be 87.94%. The Experimental value of checkpoint batch C1 was 23.08 % swelling index, 0.58 N mucoadhesive strength, and 87.02 % cumulative drug release at 8 h.

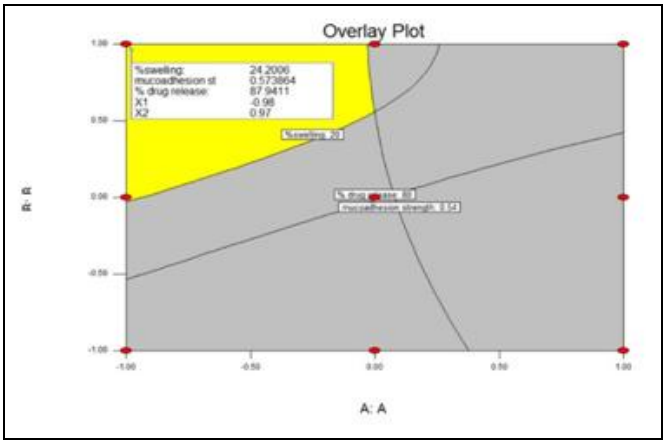

FIG. 5D: OVERLAYPLOT

From the checkpoint, batch results in the $t_{cal} < t_{tab}$ value for all responses at all the level, which suggest that there was no significant difference between the two results. So equations obtained for selected responses are validated in selected ranges of variables. The close resemblance between the observed and predicted response value assessed the robustness of predictions. These values indicate the validity of the generated model. The result is shown in **Fig. 5D**.

Short Term Stability Study: A stability study was performed for the final optimized F3 batch. The stability studies of the optimized formulation for three months found that there was no significant change in % swelling index, mucoadhesive strength, and drug release behavior.

No significant difference in any of above parameter during storage at 30 ± 2 °C temperature and 65 ± 5 % relative humidity (Room temperature), 40 ± 2 °C temperature, and 75 ± 5 % relative humidity (Accelerated) indicated that the developed formulation mucoadhesive vaginal tablet was stable after three months. The result is shown in **Table 4**.

TABLE 4: SHORT TERM STABILITY STUDY

Parameter	% Swelling index		Mucoadhesive strength (N)		Drug content (%)	
	Room temperature	Accelerated	Room temperature	Accelerated	Room temperature	Accelerated
	(30 ± 2°C & 65 ± 5 % RH)	(40 ± 2°&75 ± 5 %RH)	(30 ± 2°C & 65 ± 5 % RH)	(40 ± 2°&75 ± 5 %RH)	(30 ± 2°C & 65 ± 5% RH)	(40 ± 2°&75 ± 5 %RH)
Initial	24.34 ± 0.75	24.34	0.58 ± 0.10	0.58	99.30 %	99.30%
After 1 Month	24.30 ± 0.49	24.22	0.58 ± 0.17	0.57	99.12%	99.05%
After 2 Months	24.24 ± 0.82	24.24	0.58 ± 0.14	0.57	98.80%	98.50%
After 3 Months	24.12 ± 0.67	24.10	0.57 ± 0.10	0.57	98.68%	98.14%

RH = Relative humidity

CONCLUSION: The results of this experiment show that the high swelling due to adding an effervescent agent into the formulation. The mucoadhesion strength and *in-vitro* drug release were dependent on the concentration of polymer and effervescent ratio. Through the experiment optimized the final level of polymers and the ratio of the effervescent agent. The mucoadhesive tablet adheres to the vaginal cavity for a more extended period it proven by *ex-vivo* mucoadhesion time study. Finally, it would conclude that the formulation of clindamycin mucoadhesive vaginal tablets will increase patient compliance; it's better than the pessaries, gel, cream, and tablet.

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CONFLICTS OF INTEREST: Nil

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