QBD Based In-Vitro Functionality Assessment of Developed Foam Based Vaginal Drug Delivery System

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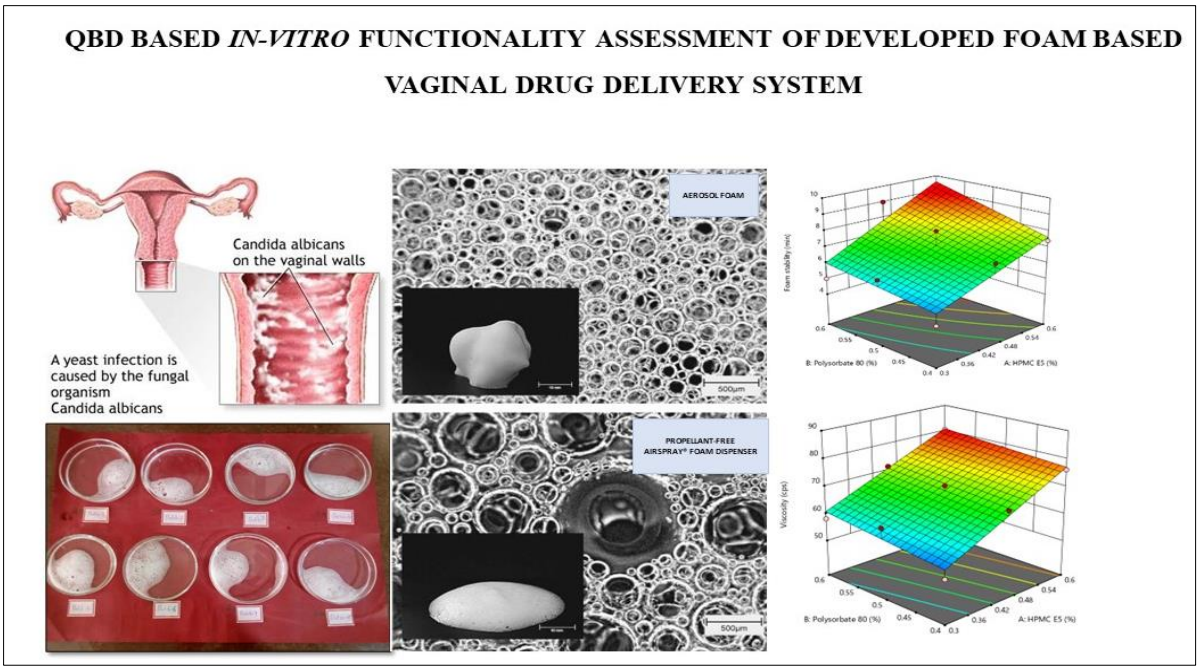
ABSTRACT- Background: ***vulvovaginal candidiasis (VVC) is a yeast infection caused by the fungus Candida at the opening of the vagina. 75% of women suffer from vaginitis at least once in their lifetimes.***
Objective: The present research aims to develop and assess foam- based vaginal formulation for better patient compliance.
Methods: HPMCE5 and HPMCK4M containing mucoadhesive foam formulation of Clotrimazole was prepared by using lactic acid, polysorbate80, lecithin and water. QbD based in-vitro functionality assessment of developed foam based vaginal drug delivery system included viscosity, foam spreadability and foam stability. In vitro drug release was performed and the optimized batch was subjected for stability study.
Result: Clotrimazole was found to be compatible with selected polymers in compatibility studies. 3^2 factorial design was successfully used to optimized foam stabilizers such as 0.51 gm HPMC E5, 0.50 gm HPMC K4M and 0.2 ml polysorbate 80. F4 batch is give a higher Viscosity and drug release due to high concentration of polysorbate 80 and HPMC E5. There was no significant difference found in Drug content and % CDR during stability study.
Conclusion: Optimized foam formulation showed better spreadability with lower surface tension and released the drug within 20 minutes. Subsequently it reduced dosing frequency and provide quick relief.

KEY WORDS: Foam Formulation, HPMC E5, HPMC K4M, QbD, Factorial Design

GRAPHICAL ABSTRACT



1. INTRODUCTION

More than 75% women suffer from vaginitis, once in their lifetime. The fungus Candida is responsible for a yeast infection called vulvovaginal candidiasis (VVC). Pregnancy is an influencing factor for the infection. Women having vaginal candidiasis are more susceptible to HIV(1). Many clinical studies reveals that there is a strong association of Candida, diabetes and preterm birth. Risk factors for VVC are pregnancy, uncontrolled diabetes, use of antibiotics, oral

contraceptive, over use of perfume, use of contraceptive.

Mainly used antibiotics in VVC treatment are clotrimazole, fluconazole, miconazole (2)(3), tioconazole etc(4). Clotrimazole widely used drug in treatment of vulvovaginal candidiasis(5)(6)Marketed formulation of Clotrimazole is available in a form of Tablet, Gel, Cream and Suppositories. While Gel(7), Cream, Suppositories are highly viscous, after application they leaves residue while oral dosage form has main disadvantage to undergo into hepatic metabolism and cause GI side effect. (8)In addition, it is not suitable for the breast feeding and pregnant women, because drug may produce systemic toxicity(9). The semisolid dosage exhibits slow release with limited spreading of base leads to treatment failure. In addition, gel-based formulation is messy to apply and cause leakage of product. Many gel-based products may produce allergic reaction(10).

Above drawback can be overcome by local delivery of clotrimazole using foam-based formulation (11). In this regards, local drug delivery approaches for treatment of vulvovaginal candidiasis have shown to ensure availability of the drug at the site of action, reduce the dose required for treatment, Foam based formulations are generally easier to apply, and spread more easily compared vaginal cream gel (12)Foam based product require negligible mechanical shearing force in order to spread the formulation in vagina. Foam formulation spread eventually over entire vaginal cavity and effectively reaches to the cervix. Uniform coverage of the affected area by foam may lead to success of the treatment (13). The residence time of the foam active pharmaceutical ingredients can be controlled by the use of bio-adhesive polymer. Vaginal foam mainly classified in two categories which include Liquid foam and Solid foam. Propellant free liquid formulation was selected to reduce cost and avoid environmental hazards(14). The range of material was selected based on biocompatibility, foamability and stability(15)(16)

The main objectives of the present research work were screening of bio adhesive polymers and foaming agents. The study was commenced with the characterization of the drug, development of the assay and drug–excipient compatibility study. The current QbD era demands the need of in-depth study(17). Therefore, the concept of design of experiment was adopted to get deeper insight in the formulation. In vitro drug release study was conducted in a clinically relevant medium. The drug release rate of optimized formulation was compared with the commercially available semisolid product. Short-term stability study of optimized batch was performed as per guideline (18)(19)

2. MATERIALS AND METHODS

Clotrimazole (MW: 344.837 g mol^{-1}) provided as a gift sample from Hema pharmaceuticals Pvt. Ltd. Ankleshwar-Gujarat (20–23). HPMC E15, HPMC E5, Hydroxy Ethyl cellulose and HPMC K4M were purchased from Colorcon Asia Pvt. Ltd. Ahmadabad-Gujarat (24,25). Polyvinyl Alcohol, Disodium Hydrogen Phosphate, Potassium dihydrogen phosphate was purchased from Astron Chemicals, Ahmedababd- Gujarat. Polysorbate80(26)] and Lactic acid were purchased from Sd Fine Chemicals Ltd. Mumbai-Maharashtra. Lecithin and methanol were purchased from Chemdyes Corporation, Rajkot-Gujarat. Mucin and Glacial acetic acid were purchased from Himedica Laboratories Pvt, Ltd. Double distilled water used throughout the study and all other reagents were of analytical grade.

The experimental method divided into two parts: The first was preparing and evaluating vaginal foam formulation. The Second was the formulation and evaluation of foam based vaginal tablet.

2.1 Screening of the polymers

Screening of polymer was done on the basis of literature survey. Mainly cellulosic derivatives are used HPMC E5, HPMC K4M, HPMC E15, HEC and PVA were selected as they facilitate the creation of foam with desirable texture and optimum spreading properties. HPMC E5 possess a film - forming property which helps to form uniform layer of active ingredient on the mucous layer. Preliminary screening was carried out to optimize a suitable polymer concentration, to obtain a good polymer-plasticizer system, which was capable of producing films of desirable mechanical property and dissolution characteristics.

2.2 Preparation of vaginal Foam

Vaginal foam formulation was prepared by dividing distilled water in two fractions. Lactic acid, polysorbate 80 and lecithin were dissolved in one part of purified water to get clear solution. The dispersion was agitated at room temperature for 10min. Part 2 was prepared by dissolving lecithin in purified water by agitation at room temperature. Both the solutions were

mixed together by adding preservatives methyl paraben and propyl paraben. It was filled in to container with actuator(27)(28) The prospective material attributes were examined by adopting the concept of DoE(29,30) (31).

2.3 Full factorial design

The formulated foam-based formulation was optimized by using a three level (3^2) full factorial design by using Design-Expert software. The selected independent variables were concentration of HPMC E5 and Concentration of Polysorbate 80. The chosen dependent variables were viscosity and foam stability. A suitable polynomial equation involving the individual main effects and interaction factors was selected based on the estimation of several statistical parameters, such as the multiple correlation coefficient (r^2), adjusted multiple correlation coefficient (adjusted r^2) and the predicted residual sum of squares (PRESS). The linear models were selected as a suitable statistical model for optimized formulation because they had the smallest value of PRESS. PRESS is a measure of the fit of the models to the points in the design. The smaller PRESS value is the indication of best model fits to the given data points.

2.4 Evaluation Parameter

2.4.1. Physicochemical parameters.

pH is one of the most important parameters involved in vaginal formulation. The effect of pH on solubility and stability are the two areas of critical importance(32). The pH of the vaginal formulation should be such that the formulation stays stable at that pH and the same time, no discomfort occurs in the patient when the formulation is administered. The pH range should be between 3.5 and 4.5 for vaginal formulations. A calibrated automated pH meter was used to evaluate the pH of the solution (2ml) triplicate experiments have been conducted(33). The vaginal foam's complex viscosity was measured using an Ostwald viscometer. Density and viscosity were quantified at around room temperature. The Ostwald stalagmometer (number drop method) was used to measure surface tension.(34)

2.4.2. Drug content

In order to achieve dose uniformity, the uniform distribution of active ingredients is necessary. The drug content was measured using pH 4.5 citrate buffer solution. The prepared formulation was diluted in citrate buffer and absorbance was taken in UV double beam spectrophotometer at 263nm(35) Concentration of clotrimazole was calculated as per calibration curve linearity equation.

2.4.3. Foaming tendency and foam stability(36)

The foam capacity test was carried out by transferring 2 ml prepared formulation into 10 ml of water/buffer/SVF in100 ml measuring cylinder. The cylinders were hand shaken for producing foam and measured the foam volume initially and after 15 minutes(37). The foamability of the solution was defined by the Trapped air volume, v0, immediately after shaking (at t=0) and it was characterized by the deforming time, which is defined as a time required for obtaining half of the solution surface free of bubbles were studied.

2.4.4. Average volume per actuation(38)

The weight of spray bottle before and after five successive deliveries of spray were recorded to measure average weight per actuation. The calculation was done by dividing the weight difference by number of deliveries. The experiment was repeated thrice and the average volume was reported.

2.4.5 Dose content per actuation (38)

The drug content of the formulation was determined by mixing 5 successive sprays with simulated vaginal fluid. The solution was filtered through 0.45 µm membrane filter and subjected to spectrophotometric analysis. The drug content was calculated from linear regression equation. Samples from drug-free spray were used as a blank solution during analysis.

2.4.6. *In -vitro* drug release, dissolution and Ex-vivo diffusion study(39)

The study of drug release through the dialysis membrane was studied using Franz diffusion cells. The receptor compartment was filled with 15 ml of citrate buffer. The test was performed at pH 4.0 to guarantee the sink state, and the temperature was maintained at 37 ± 0.5°C. Uniform mixing of the receptor medium was carried out using magnetic agitation. At predefined time intervals, 1 ml aliquots were removed from the receptor compartment, and the samples were analyzed in a UV spectrophotometer at 263 nm. After each sampling, the same amount of fresh dissolution medium was replaced to maintain the sink condition. Each experiment was repeated three times. A graph of the cumulative quantity of drug permeated through the

skin (µg/cm^2) as a function of time (t, h) for formulation was used to measure the permeation data.

2.4.7. Stability Study

The stability testing provides evidence on change in Quality of API or formulations with time under the influence of various environmental factors like temperature, humidity and light(39,40) According to the ICH guidelines, the choice of test conditions was implemented to store and measure the stability of the optimized formulation. The chemical stability of the formulation was assessed at given time point (T0, T10, T20, T30) by the estimation of the physical evaluation of pH, viscosity, foamability, appearance and drug release pattern of optimized batch.

3. RESULTS AND DISCUSSION

3.1 Screening of polymers

Batch B1-B15 of HPMC E15, HPMC E5, HPMC K4M, HEC, and PVA were prepared by using different polymer concentrations and evaluated as shown in table 1. Batches with all the above said polymer gave a colourless and transparent solution, but with the increase in the concentration gel formation was observed.

Table 1: Screening of polymers

Batch	HPMC E15 (g)	HPMC E5 (g)	HPMC K4m (g)	PVA (g)	HEC (g)	Viscosity (cps)	Foaming tendency (ml)	Foam stability (min)	Surface Coverage (cm^2)	PH
B_1	0.20	-		-	-	2.99	2	5	2.1	5.8
B_2	0.25	-	-	-	-	1.82	2.2	4.7	2.45	5.85
B_3	0.30		-	-	-	1.71	2.3	5	2.2	5.66
B_4	-	0.20	-	-	-	1.40	2.9	10	3.4	4.75
B_5	-	0.25	-	-	-	1.76	3.2	9	3.5	4.62
B_6	-	0.30	-	-	-	2.12	4.3	10.5	3.2	4.58
B_7	-	-	0.20	-	-	1.17	4.1	3.5	3.4	4.24
B_8	-	-	0.25	-	-	1.71	4.0	3.2	3.6	4.21
B_9	-	-	0.30	-	-	2.91	2.9	3.75	3.2	4.17
B_{10}	-	-	-	0.20	-	1.51	3.6	4	3.6	5.85
B_{11}	-	-	-	0.25	-	0.95	4.6	3.7	3.9	4.7
B_{12}	-	-	-	0.30	-	1.48	5.0	2.6	4.0	4.5
B_{13}	-	-	-	-	0.20	98.6	-	-	-	5.6
B_{14}	-	-	-	-	0.25	177	-	-	-	5.84
B_{15}	-	-	-	-	0.30	240.6	-	-	-	5.77

HPMC K4M in lower concentration 0.5, 1, 1.5% w/v gave less viscous polymeric solution and adequate mucoadhesion properties. Various evaluation parameters like foam stability, foaming tendency before and after dilution with vaginal fluid (pH 4.5 citrate buffer), and viscosity at room temperature were evaluated. Based on viscosity studies, it was concluded that increase in viscosity can increase retention time and therefor cleansing efficiency can be improved.

Various evaluations of prepared preliminary batches are shown in table 1. Optimum viscosity can facilitate proper actuation, and other parameters like foaming tendency and foaming stability of B4, B5 and B6 batches were better as compared to other batches. Hence, they were selected for further study.

3.2. 3^2 Factorial Design:

The experiment runs with independent variables and the observed responses for the 9 formulations are shown in Table 2. For the response surface methodology involving 3^2 Factorial Design, a total of 9 experiments were performed for three factors at two levels each.

Table 2. Design Matrix of 32 Factorial designs

Batch	Independent variables		Dependent variables	
	X1: Conc. of HPMC E5 (%)	X2: Conc. of Polysorbate 80 (%)	Y1: Viscosity (cps)	Y2: Foam Stability (min)
1	0.45	0.5	70.4	8

2	0.3	0.5	62.1	6
3	0.45	0.6	71.5	9
4	0.6	0.6	80.5	9.1
5	0.45	0.4	68.2	7
6	0.3	0.6	58.2	5
7	0.3	0.4	52.5	4.5
8	0.6	0.5	78.25	8
9	0.6	0.4	76.2	7.4

3.2.1 Contour plots and response surface analysis

Two-dimensional contour plots and three-dimensional response surface plots shows the relationship between the dependent and independent variables. Different graphs show the graphical representation of mathematical models which makes interpretation of results easier. The graphs (contour plot) can be overlapped to define the design space as per the current requirements of FDA for ANDA application.(43) The results of MLR [the value of the correlation coefficient and the coefficients] and ANOVA [Fisher's ratio and P-value] are summarized in Tables 3-8 for the three responses.

3.2.1.1. ANOVA analysis for Response Y1: Viscosity

As shown in ANOVA analysis and fit statistic summary (table 3 & 4), A high correlation coefficient value (0.9437) indicates a good fit between the independent and first dependent variables (Viscosity). The Linear model is significant, with a P-value of 0.0015.

This result demonstrates that at least any selected independent variables statistically influence the viscosity. The mathematical relationship between the selected independent variables and viscosity is shown below:

Viscosity = +68.65 +10.36 * A +2.22 * B -0.3500 *AB

Table 3: ANOVA analysis of response Y1

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	673.74	3	224.58	27.96	0.0015	significant
A-HPMC E5	643.77	1	643.77	80.15	0.0003	
B-Polysorbate 80	29.48	1	29.48	3.67	0.1135	
AB	0.4900	1	0.4900	0.0610	0.8147	
Residual	40.16	5	8.03			
Cor Total	713.90	8				

Table 4: Fit Statistics of Y1

Std. Dev.	2.83	R^2	0.9437
Mean	68.65	Adjusted R^2	0.9100
C.V. %	4.13	Predicted R^2	0.6671
		Adeq Precision	13.3116

The Predicted R^2 of 0.6671 is not as close to the Adjusted R^2 of 0.9100 as one might normally expect. Adequate Precision measures the signal to noise ratio. Contour plot and 3D Response Surface plot are shown in figure 1 and 2 respectively. A ratio greater than 4 is desirable. The ratio of 13.312 indicates an adequate signal. The plot of Viscosity, indicates when Polysorbate and HPMC E5 concentration was increased the Viscosity was gradually increases with up to certain level.

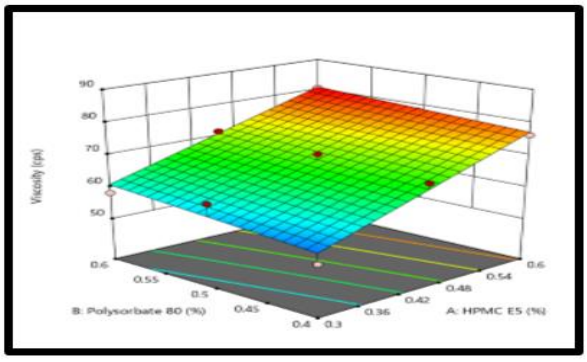


Fig. (1). Contour plot of Y1

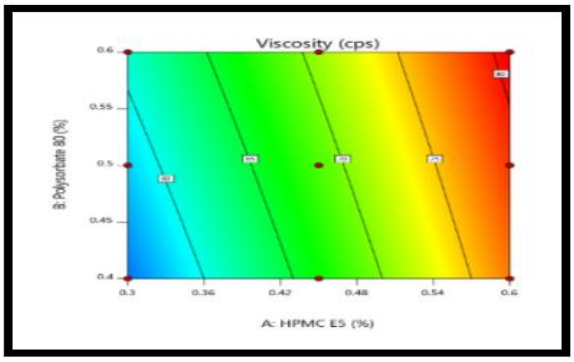


Fig. (2). 3D plot of Y1

3.2.1.2. ANOVA analysis for Y2 Response: Foam Stability

ANOVA analysis and fit statistic summary are shown in table 5 and 6. A negative Predicted R^2 implies that the overall mean may be a better predictor of the response than the current model. In some cases, a higher order model may also predict better. Adequate Precision ratio of 6.661 indicates an adequate signal. The mathematical relationship between the selected independent variables and Foam Stability is shown below:

Foam stability = +7.11 +1.50 *A +0.7000 *B +0.3000 *AB

The plot of foam stability, indicates when HPMC E5 concentration was increased the foam stability was gradually increases with up to certain level. Contour plot and 3D Response Surface plot are shown in figure 3 and 4 respectively.

Table 5: ANOVA analysis of Y2

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	16.80	3	5.60	5.70	0.0453	significant
A-HPMC E5	13.50	1	13.50	13.75	0.0139	
B-Polysorbate 80	2.94	1	2.94	2.99	0.1441	
AB	0.3600	1	0.3600	0.3667	0.5713	
Residual	4.91	5	0.9818			
Cor Total	21.71	8				

Table 6: Fit Statistics of Y2

Std. Dev.	0.9908	R^2	0.7739
Mean	7.11	Adjusted R^2	0.6382
C.V. %	13.93	Predicted R^2	-0.1526
		Adeq Precision	6.6610

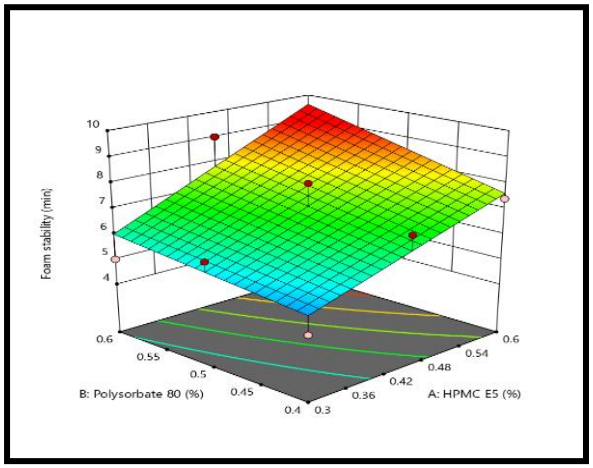


Fig. (3). Contour plot of Y3

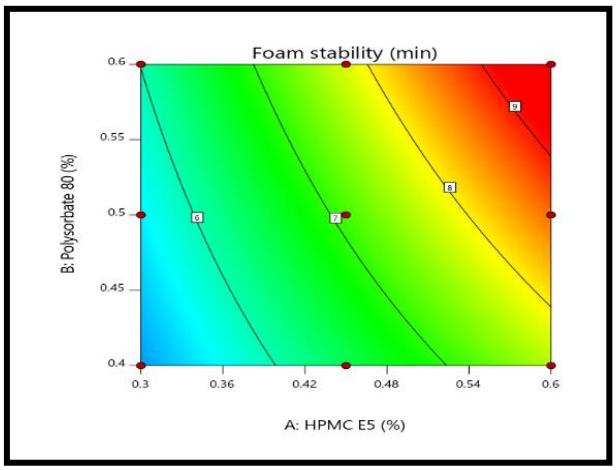


Fig. (4). 3D plot of Y3

3.2.2. Overlay plot:

The overlay plot is the plot which was generated by superimposing the contour plot of all the region and the common region obtained is the overlay plot by which some predicted standard batches which is called Check Point Analysis. The range selected for overlay plot was ±10 as per USFDA criteria.

%PE = predicted- Observed value/ Predicted value × 100

A Checkpoint analysis was performed the role of the derived polynomial equation and contour plots (overlay plots) in predicting the response. From the extensive grid search, values of independent variables were taken at one checkpoint level of the factor. In the region of the design space as shown in Figure. 5 indicates any point selected among the region falls well within the constrains set for the response variables.

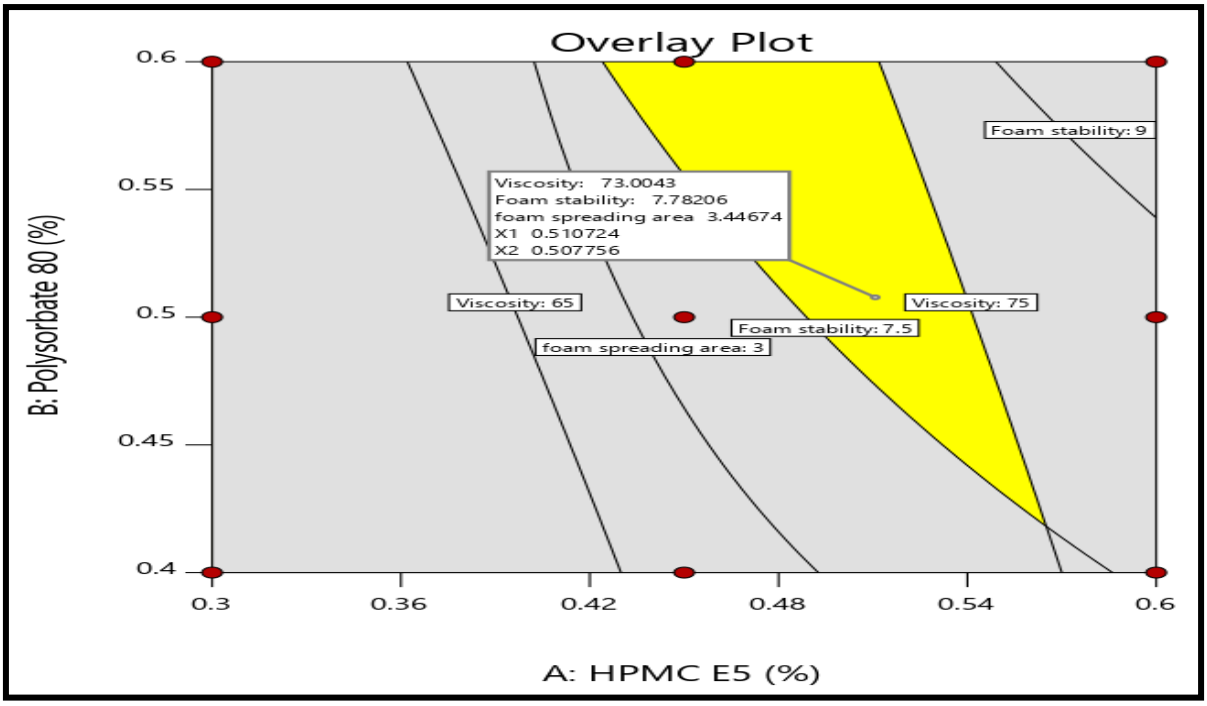


Fig. (5) Overlay plot

The overlay plot indicates that when X1= 0.51, X2=0.50; viscosity and foam stability 73.0 cps and 7.78 min respectively. The % relative error obtained from the checkpoint batch was from 0.66 to 0.79 (Table 7). Hence, a close resemblance between the observed and predicted values assessed the prediction's robustness. Therefore, this value indicates the validity of the generated model.

Table.7 Optimized and checkpoint batches results

Check point Batches	Optimized Batch	Check point Batch 1
X1	0.51	0.49
X2	0.50	0.53
Predicted Y_1 (cps)	73.00	72.35
Observed Y_1 (cps)	72.96	71.69
%Error	0.04	0.66
Predicted Y_2 (min)	7.78	7.79
Observed Y_2 (min)	7.71	7.00
%Error	0.07	0.79

3.3 Physicochemical evaluation of vaginal foam formulation

Table 8 shows the results of evaluation parameters such as viscosity, pH, drug content, foaming tendency, foam stability, average volume per actuation and dose per actuation. The normal physiological pH of vaginal mucosa ranges from 3.5 - 4.5. The measured pH of all formulations was 3.7 - 4.3, within the range of vaginal mucosa. The drug content in the formulated batches ranged from 96.23 ± 0.01 to 99.72 ± 0.01%. It was found to be in acceptable range (95 - 105%) for all the formulation, indicated uniform distribution of drug. For the present formulation the optimum viscosity was required for proper actuation and that can also provide sufficient mucoadhesion at application site. Batch 4 shows optimum viscosity and also other parameters in acceptable range.

3.4. Foamability and Foam stability

As the concentration of HPMC E5 and HPMC K4M increase, due to higher viscosity, foaming tendency reduced. Figure 6 shows that the increase in the concentration of Polysorbate 80 there was increase in the foamability. Foam stability of the solution was measured at t0 and t30 time intervals. Foam stability of all batches at initial and after 30 minutes indicates that increase in the concentration of polymer HPMC E5 and HPMC K4M, increase foam stability.

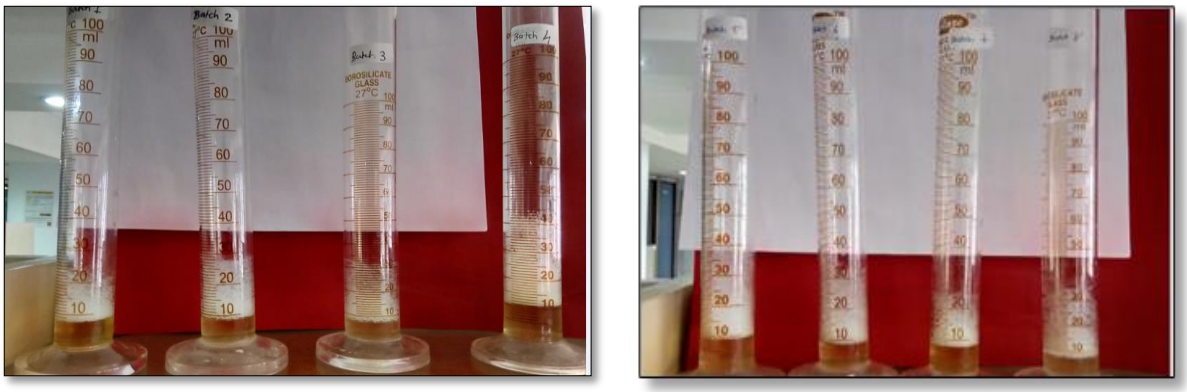


Fig (6) Foaming tendency

Fig (7a) Foam stability at t0

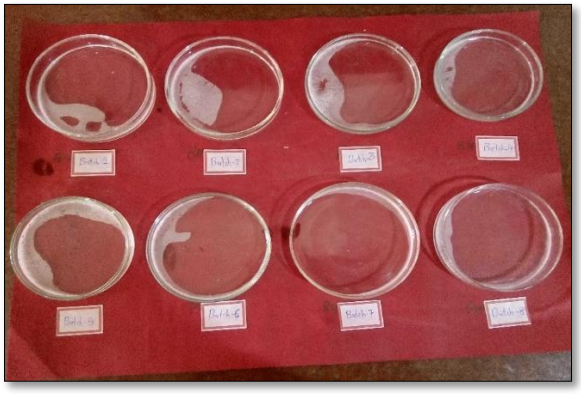


Fig (7b) Foam stability at t30

3.5 Average volume per actuation and Dose per actuation

The average weight per actuation was found be in the range of 0.10 ± 0.01 to 0.42 ± 0.005 ml. The concentration and viscosity of the polymers effect on the actuation of the solution from the container, though there was not much variation in the amount expelled out per actuation indicating the effectiveness of the pump system in delivering reproducible amounts of the formulation per actuation. Batch B4 showed optimum dose per actuation due to lower viscosity imparted by HPMC E5 and HPMC K4M and more concentration of Polysorbate 80 that further increase the foaming tendency. While for other batches, due to the higher viscosity of solution, the proper actuation of solution is hampered and hence, the target of dose per actuation is not met.

Table 8. Foaming tendency, foam stability avg. Volume per actuation and dose per actuation data.

Batch	Drug Content	pH	Viscosity	Foam-ability (ml)	Foam stability (min.)	Avg. vol. per actuation (mg)	Dose per Actuation (mg)
B1	96.52 ± 0.057	3.5 ± 0.32	70.4 ± 0.02	10.8 ± 0.02	7.4 ± 0.03	0.44 ± 0.14	8.13 ± 0.31
B2	97.62 ± 0.002	4.0 ± 0.07	62.1 ± 0.9	18.5 ± 0.08	4.23 ± 0.12	0.12 ± 0.03	7.87 ± 0.12
B3	97.72 ± 0.006	4.3 ± 0.09	71.5 ± 0.07	19.6 ± 0.04	9.7 ± 0.83	0.09 ± 0.07	6.43 ± 0.06
B4	99.72 ± 0.01	4.1 ± 0.02	80.5 ± 0.05	32 ± 0.09	8.9 ± 0.12	0.60 ± 0.02	9.38 ± 0.01
B5	98.23 ± 0.011	4.5 ± 0.08	68.2 ± 0.62	30.5 ± 0.19	7.0 ± 0.05	0.57 ± 0.21	9.0 ± 0.09
B6	96.63 ± 0.28	4.4 ± 0.03	58.2 ± 0.15	25.9 ± 0.02	6.5 ± 0.06	0.46 ± 0.34	9.21 ± 0.05
B7	96.30 ± 0.05	4.2 ± 0.06	52.5 ± 0.26	15.6 ± 0.11	7.4 ± 0.13	0.41 ± 0.07	8.43 ± 0.13
B8	97.65 ± 0.15	4.3 ± 0.13	78.25 ± 0.8	22.3 ± 0.03	8.7 ± 0.31	0.20 ± 0.16	7.46 ± 0.22
B9	96.23 ± 0.01	4.6 ± 0.05	76.2 ± 0.04	23.2 ± 0.07	7.5 ± 0.6	0.18 ± 0.09	6.98 ± 0.5

3.6. In vitro drug release for foam formulation

The drug release profile of clotrimazole vaginal foam preparation showed immediate drug release in 20 min. The drug release study from clotrimazole vaginal foam containing HPMC E5, HPMC K4M, lecithin and Polysorbate 80 clearly indicates that the release of the drug was influenced by the concentration of the polymer and surfactant up to 20 min (fig 8).

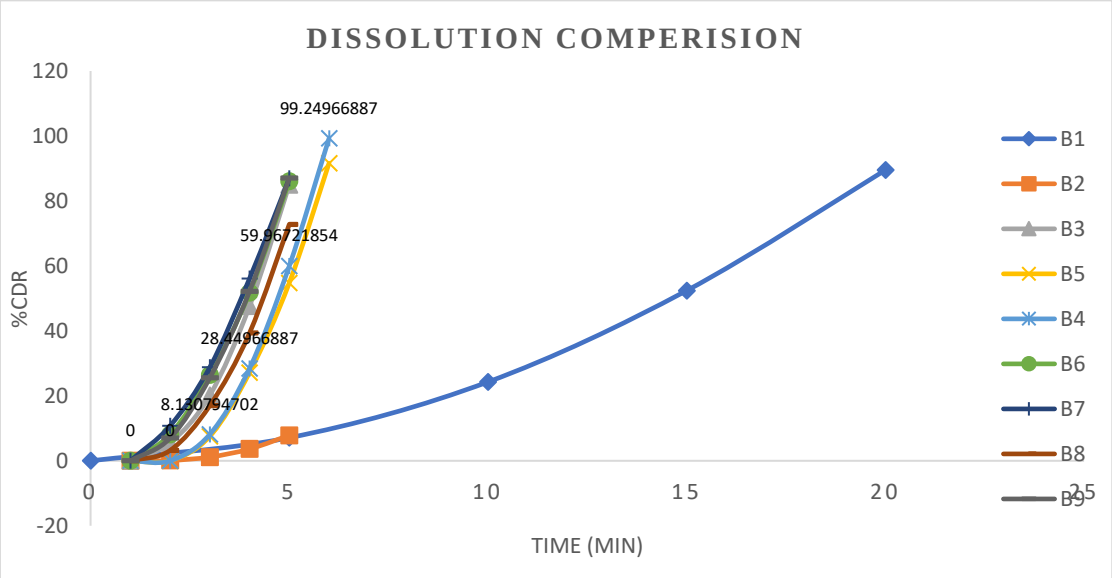


Fig. (8): %CDR of clotrimazole vaginal foam formulation

The viscosity of HPMC E5 was an important factor and affects the release behaviour of the drug from vaginal foam. As concentration of HPMC E5 increased it has led to decrease in drug release rate from clotrimazole vaginal foam. The drug release profile of vaginal foam formulation shown in figure 8. Batch B4 was found to have desired release profile as it was able to provide greater than 99% release up to 20 min.

3.7 stability study

Stability study revealed that there was no significant difference in Drug content and % CDR to be found.

Packing	Glass vials			
Condition	40°C / 75% RH			
Batch	F4			
Test	Initial	10 Days	20 Days	30 Days
Drug Content (%)	98.7 ± 0.15	98.5 ± 0.06	98.38 ± 0.62	98.20 ± 0.08
Appearance	White	White	White	White
Time (min)	Cumulative % Drug Release (at 60 min)			
	0	10 Days	20 Days	30 Days
60	97.65 ± 0.24	97.43 ± 0.31	97.36 ± 0.11	97.16 ± 0.04

CONCLUSION

Clotrimazole Vaginal foam formulation was prepared to treat Vulvovaginal Candidiasis. The major drawback of Clotrimazole is its low solubility. The drug's oral bioavailability is restricted (3%) due to its low solubility. The first step of the research was a preformulation study, which revealed that identification of drug and polymers matched with the reference standard products with specifications. Polymers such as HPMC E5, and HPMC K4M were used to increase viscosity, which leads to increase stability of foam and spreading area. The higher concentration of HPMC E5, and Polysorbate 80 resulted in increase in stability and foamability. Systematic formulation development through concepts of QbD ensure the fulfilment of current requirements of FDA. As per 3^2 factorial design it was concluded that batch containing 0.51 gm HPMC E5, 0.50 gm HPMC K4M and 0.2 ml polysorbate 80 was optimized. Dissolution studies reveals that drug was release within 20 min. Since the development of formulation is cost effective; has better business potential in the formulation performed, and the results revealed that

there was no contact between the drug and the excipients. Optimized batch was selected for stability testing and after 30 days, there was no significant changes observed. The prepared foam formulation potentially may render the treatment more cost-effective and higher patient compliance. Hence, after clinical evaluation and specific regulatory requirements, the developed formulation has good scope for commercial viability and may prove to be a boon to society at a large scale to treat Vulvovaginal Candidiasis.

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