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Factorial Design Approach To Fabricate And Optimize Posaconazole Vaginal Suppository By Using Virgin Coconut Oil

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Abstract

Background*: The aim of the present research work was to fabricate a drug delivery system in the form of suppository using a combination of natural coconut oil, polymers and bases with an intention to enhance the drug action and duration of drug release in vaginal cavity. This may leads to decrease the side effects of drug taken through oral route.*

Results: *The results of the preliminary trial batches prepared by using the hot fusion method resulting in nine different formulations showed good physicochemical characteristics and suppositories conformed to the Pharmacopoeial specifications. Posaconazole vaginal suppository containing natural oil showed prolonged drug release. The optimized formulation (F7) using 3^2 factorial design showed FLT 0.5±0.012%, MT 48.2±0.32 (min) and DC 90.11±0.24 (mg) at 12 h. The stability studies indicated the stability of the formulation during storage.*

Conclusions: *It was concluded that the release profile fitted best to zero-order equation with mechanism of drug release which indicates the drug action is enhanced by vaginal suppository as compared to oral route. Thus, the formulated suppositories have the potential for improved release and antifungal properties.*

Keywords: *Vaginal suppository, virgin coconut oil, beeswax, Factorial design, Drug release, Posacoanzole, Antifungal, ANOVA, polymers, etc.*

INTRODUCTION

Vulvovaginal Candidiasis (VVC) is an opportunistic fungal infection, that in most cases is caused by Candida species with Candida albicans accounting for 85–95%. [1-2] Prescribing anti fungal medications can reduce the chances of a patient acquiring a fungal infection [3]. Suppositories are solid formulations with different shapes and masses adjusted to rectal, vaginal, or urethral administration. They mostly dissolve, melt, or liquefy at body temperature, and they can be formulated to obtain systemic or local action. The bases usually utilized are cocoa butter, glycerinated gelatin, hydrogenated vegetal oils, and a mixture of polyethylene glycols of diverse molecular weights [4, 5]. Vaginal suppositories are commonly used to handle urogenital infections and other local diseases. The vaginal route is efficacious in allowing the efficient transport of some drugs such as progesterone and azoles to the uterus while alleviating systemic side effects [6, 7].

An estimated 138 million women globally experience recurrent VVC annually with associated morbidity of pain, altered self-esteem, poor work performance, discomfort, interference with sexual and affective relations, and mental distress [2, 8-9].

The vaginal route for drug administration has many potential benefits because it has a large surface area for drug absorption, relatively low enzymatic activity, avoids first-pass effects, and has ease of administration [10].

Posaconazole is a structurally related antifungal drug to itraconazole. Posaconazole is a triazole antifungal drug that works by attaching to the heme cofactor on the cytochrome p-450 dependent enzyme sterol 14-demethylase in fungus. This causes the synthesis of ergosterol, a critical component of the fungal cell membrane, to be inhibited, as well as the accumulation of methylated sterol precursors. Posaconazole is very lipophilic (log P 5.5) in nature and has a low water solubility. Posaconazole is effective against a wide variety of fungus and moulds in-vitro, including Aspergillus, Candida, Cryptococcus, filamentous fungi, and endemic mycoses such as coccidioidomycosis, histoplasmosis, and blastomycosis. Importantly, Posaconazole is far more effective against numerous Mucorales species than other azoles, and combining Posaconazole with other antifungal medicines may be beneficial. Hence, Posaconazole is a potential candidate as a single or combination agent to treat fungal infections. [11-13]

Posaconazole is a BCS Class-II medication with a high lipid solubility and low water solubility. Posaconazole is an antifungal medication that comes in a variety of forms, including injections, oral

suspensions, and delayed release tablets. When taken orally, these formulations can cause patient incompliance, bioavailability, site specific administration, poorer stability, constipation, and stomach pain. Hence, preparing Posaconazole loaded nanostructured lipid carriers gel for topical delivery to avoid such side effects of drugs and to improve the bioavailability, patient compliance for different topical fungal infections. [14, 15]

Coconut oil (CO) is obtained from Cocos nucifera Linn (Palmae) [16] and is present in the form of a white paste below 25 ^{0}C; this can provide an advantage for the preparation of vaginal pessaries. Early studies suggest that medium-chain fatty acids (MCFA), commonly found in tropical oils such as coconut oil (CO), are bactericidal for gram-positive and gram-negative bacteria, fungi, protozoa, and viruses [17, 18]. Some studies have reported the efficacy of CO against Candida albicans [19, 20]. CO consists of 99% triglycerides with free fatty acids (less than 0.2%) [21], in addition to lauric acid (C12), caprylic (C8) and capric acids (C10), these components have been reported to exhibit an antimicrobial activity [22].

This study aimed to improve the use, delivery and effect of Posaconazole for the treatment of recurrent vaginal infections. Different bases were used to prepare pessaries, namely, PEG 6000, PEG 4000, Span 60, Tween 60 & PEG 400. These bases were used alone or in conjunction with coconut oil (CO), which is a natural component with many beneficial effects and low side effects, in addition to its availability and low cost. The prepared pessaries were compared based on different physicochemical properties; then the selected pessaries were subjected to evaluation studies, microbiological studies in experimental animals followed by histopathological examination.

MATERIALS AND METHODS

Materials

Posaconazole, Polyethylene glycol 6000, polyethylene glycol 4000, Span 60, Tween 60 & coconut oil (CO) which solidifies below 25 ^{0}C, and melts at around 30 ^{0}C to form a liquid, etc. All Chemicals used were of analytical grade.

Methods

Formulation and Optimization of Posaconazole Vaginal Suppository

The design methodology used considered material attributes to optimize the formulation of the Posaconazole vaginal suppository quality. The expected responses from the formulations were ease of administration, faster release of drug from the base, and meeting quality control requirements. Critical quality attributes of the optimum formulation were that formulation must be solid at room temperature and should melt or disintegrate within 20-30 minutes after administration. The fusion molding method was adopted to formulate suppositories using stainless steel suppository molds. The suppositories were formulated using different concentrations of PEG 6000, PEG 4000, Span 60 Tween 60 & Coconut oil. The effect of formulation factors on product characteristics was evaluated statistically using Sigma Plot software. An optimum mixture design was selected to identify the proportions of PEGs and Span 60 that would yield a fully formed suppository that would remain solid and stable at room temperature. The factors employed for obtaining the suppository formulations from mixture design were PEG 6000 (10%–40%), PEG 4000, and Span 60 (5%–30%), and the evaluated responses were (a) melting time, (b) % Friability and (c) % drug content.

Preparation of Suppository

Suppositories were prepared by the molding method. To obtain Posaconazole vaginal suppository PEGs, Coconut oil & span 60 were melted at 65°C using a water bath, and Posaconazole was dispersed under manual stirring for 2 to 3min. For all suppositories, after final mixing, the blends were cooled to a temperature of 55°C–60°C and poured into a suppository mold. They were then solidified at 24°C (room temperature). The samples were stored in individual aluminum blister packs at room temperature (20°C–25°C) for further analysis. The composition of independent variables for the preparation of the Posaconazole vaginal suppository is shown in Table no. 1.

Table 1: Composition of independent variables for the preparation of the Posaconazole vaginal suppository.

Variables	Actual Values (%)		Coded Values	
	Lowest	Highest	Lowest	Highest
PEG 6000	20	30	-1	+1
PEG 4000	20	30	-1	+1

Span 60	**10**	**20**	**-1**	**+1**

Evaluation

Characterization of Vaginal Suppositories Physicochemical Properties

The physical evaluation was made by a visual examination of the formulation. Color, odor, and characteristics for the presence of bubbles or cracks were reported. The intensity, nature, and color homogeneity of the prepared suppository formulation was observed and recorded. A change in the odor of the suppository is an indication of the degradation process. The shape of the suppositories is verified for consistency [23, 24].

Weight Variation

Weight variation for the prepared suppository formulations was measured as per British Pharmacopoeia (2011). Twenty suppositories of each formulation were weighed to determine the average weight (n=20). Not more than two suppositories varied from the average weight by more than 5%, and no suppository differed from the average weight by more than10% [25].

Friability

Six suppositories were weighed and placed in the chamber of the friabilator (Electrolab EF-2). The friabilator was operated at 25 rpm for 4 min. After completion of the cycle the friability is calculated using formula. [26, 27]

Breaking Point (Hardness)

The breaking strength is a mechanical strength metric that evaluates the suppositories' resistance to mechanical shocks during transit by revealing their brittleness, elasticity, or fragility. It is an iron rod that is pointed on one end and has a plastic disk on the other. A metallic plate and the pointed end of an iron rod are sandwiched by a suppository. Weights are arranged on the disk in ascending sequence until the electric circuit is finished, the bulb illuminates, and the suppository collapses. [28, 29]

Liquefaction time

Liquefaction time was measured using a pipette having a broad opening on one side and a narrow opening on the other; suppository was pushed inside form the broad end side to reach to the narrow end. 5ml of phosphate buffer pH 6.8 was placed inside the pipette, maintained at 37± 0.5℃. A thin iron rod of 30gm is placed on the top of the suppository and the time at which the iron rod just inserts into the suppository is recorded as liquefaction time. This indicates the time taken by the formulation to liquefy under similar pressures found in rectum. [30]

Melting time

The entire suppository is used for the macro melting range test. Each formulation's suppository was put in a beaker with pH 6.8 phosphate buffer and kept at a steady 37±0.5°C. It was documented how long it took for the entire suppository to melt or dissolve in the media. An important factor in the release of the active component is the melting time. [31, 32]

Disintegration time

Six suppositories are used in a standard disintegration test apparatus, and the typical time it takes for a suppository to dissolve in phosphate buffer pH 6.8 is noted. BP 2002 was used to evaluate disintegration. [33, 34]

Drug content

Randomly selected suppository from each formulation was melted in a volumetric flask containing 100ml phosphate buffer pH 6.8; the solution was continuously stirred by using glass magnetic beads. After necessary dilutions and filtration using 0.45µm filter solutions were subjected to UV spectroscopy (Shimadzu UV1800) at 338.80 nm wavelength. [35-37]

In-Vitro dissolution profile

The USP rotating basket dissolution apparatus (Electrolab TDT 06P) was used for the dissolution test. The stirrer was lowered to a height of 1-2 mm from the vessel's bottom after each suppository was put inside. Using a 50 rpm stirrer and 900 ml of phosphate buffer pH 6.8 as the dissolution medium, 5 ml of the aliquot was removed at predetermined intervals and the same amount was replenished with new buffer. The Shimadzu UV1800 was used to perform spectrophotometric analysis on the extracted materials at 338.80 nm. [38, 39]

Factorial Design

The amount of Base (PEG 6000, X1) and the Surfactant (Span 60, X2) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

Y= b0+ b1X1+ b2X2+ b12X1X2+ b11X12+ b22X22, (1)

Where Y is the dependent variable, b0 is the arithmetic mean response of the 9 runs, and bi is the estimated coefficient for the factor Xi. The main effects (X1and X2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X1X2) show how the response changes when 2 factors are simultaneously changed.

RESULT

Suppositories of Posaconazole were prepared by fusion method employing different bases such as PEG 4000, PEG 6000 and Coconut oil. The prepared suppositories were characterized for visual parameters (fissuring, pitting, fat blooming , exudation, migration of active ingredient, length, width, breaking strength, uniformity of weight and friability, melting time liquefaction time, content uniformity and in-vitro release.

Visual Inspection

All the suppositories prepared were evaluated for fissuring, pitting, fat blooming, exudation and migration of active ingredient. The physical appearance of the formulations were checked and compared visually. Absence of pitting, exudation, fat blooming and migration of active ingredient shows that the components of the formulated suppositories were homogenously mixed. The various evaluated parameters summarized in the Table no. 2.

Table 2: Visual Evaluation of formulation F1 to F4

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fissuring	No	No	No	No	No	No	No	No	No
Pitting	No	No	No	No	No	No	No	No	No
Fat blooming	No	No	No	No	No	No	No	No	No
Exudation	No	No	No	No	No	No	No	No	No
Migration of active ingredient	No	No	No	No	No	No	No	No	No

Physicochemical Evaluation

The results of the physicochemical characterization are reported in the following table no. 3 & 4. All the formulations were found to have homogenous drug distribution with content uniformity, weight uniformity and sufficient mechanical strength to withstand abrasives forces which causes disintegration of prepared suppositories.

The width and length of randomly selected suppositories was found to vary from 0.877 cm to 0.895 cm and 1.811 to 1.856 cm for different formulation with good homogeneity and the effect of addition of other excipients were negligible.

Weight variation was determined for randomly selected 20 formulations. The weight of the suppositories varied from 0.716 to 0.976 gm for different formulations of different bases. Each individual suppository did not vary more than 5% from the average weight.

The breaking strength and friability were determined to assess whether the suppositories will be able to endure the mechanical shocks during the packaging, transportation and normal handling. The breaking strength varied from 485.6 gm to 556.4 gm.

Disintegration time was determined using disintegration test apparatus and time ranged from 7 min to 15 min. Addition of plasticizers and surfactants reduce the disintegration time to a smaller extent. The D.T. was well within the limits specified by British Pharmacopoeia.

Liquefaction time was observed in the range of 37 sec to 2 min 30 sec. PEG 4000 suppositories liquefied faster than all the other bases. Melting time was also determined and was seen to vary from 3 min to 50 min.

Drug content was found to homogenous in all the formulations and well within the pharmacopoeial limits. It ranged from 83.22 to 88.55 mg.

Table 3: Physicochemical evaluation of formulation F1 to F4

Parameters	F1	F2	F3	F4
Weight(gm)	0.878±0.003	0.731± 0.001	0.956±0.003	0.716±0.011
Length (cm)	1.818±0.001	1.811±0.002	1.856±0.012	1.821±0.013
Width (cm)	0.878±0.001	0.879±0.002	0.895±0.001	0.878±0.002
Breaking strength (gm)	485.66±2.12	545.6±2.14	545.5±2.13	486.6±2.02
Liquefaction time (min)	2.44±0:112	3.54±0:012	2.14±0:022	3.23±0.013
Melting time (min)	42.13±0.036	52.21±0.036	18.35±0.085	34.18±0.054
Disintegration time (min)	15.32±0.012	17.24±0.11	14.15±0.15	19.35±0.017
Drug content (mg)	84.15±0.001	83.22±0.002	88.55±0.112	83.44±0.123

Table 4: Physicochemical evaluation of formulation F5 to F9

Figure 1: Drug content (%) of formulations F1 – F9

Parameters	F5	F6	F7	F8	F9
Weight(gm)	0.872±0.002	0.878±0.003	0.731±0.001	0.976±0.013	0.899±0.001
Length (cm)	1.822±0.004	1.815±0.002	1.853±0.002	1.847±0.013	1.833±0.002
Width (cm)	0.892±0.003	0.879±0.001	0.877±0.002	0.885±0.001	0.879±0.002
Breaking strength (gm)	556.4±2.12	552.20±2.11	485.6±2.12	478.7±2.10	548.2±2.12
Liquefaction time (min)	2.23±0.024	3.22 ±0.023	3.54±0.012	2.14±0.022	3.45±0.015
Melting time (min)	50.23±0.045	45.10±0:022	47.23±0:045	20.25±0:055	47.23±0:050
Disintegration time (min)	16.20±0.011	14:44±0:017	16:34±0:13	10:35±0:12	15:45±0:017
Drug content (mg)	84.23±0.003	86.15±0.002	84.32±0.001	89.45±0.012	85.31±0.001

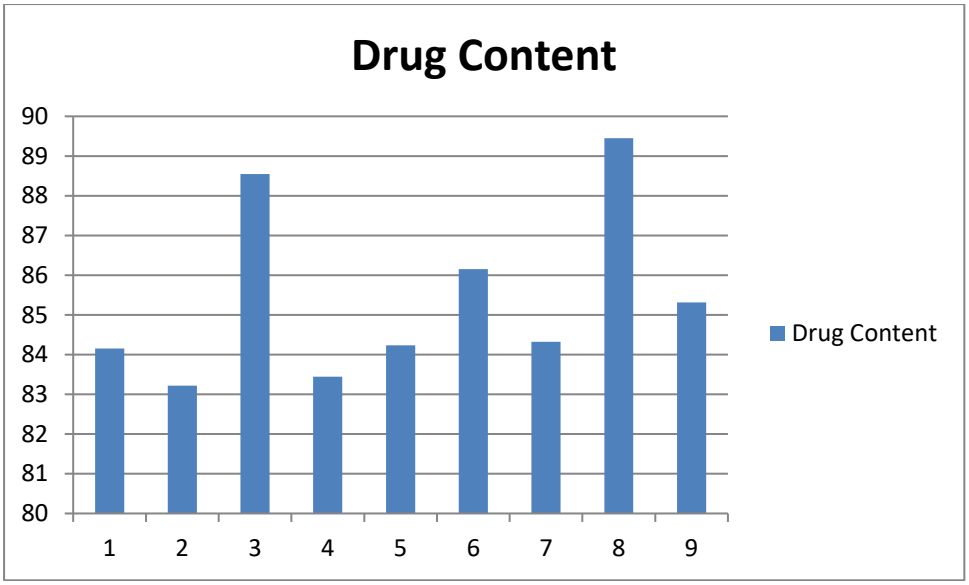

Table 5: Friability testing of formulation

Formulation	Initial weight	Final weight	% Friability
F1	5.347	5.323	0.45
F2	5.368	5.355	0.24
F3	4.311	4.285	0.60
F4	4.342	4.319	0.52
F5	4.388	4.352	0.82
F6	5.220	5.189	0.59
F7	5.355	5.327	0.52
F8	5.420	5.398	0.40
F9	5.485	5.452	0.60

Experimental Design

A 3^2 Randomized full factorial design was used in the present study. In this design 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. The amount of PEG 6000 (X1), and the amount of Span 60 (X2), were selected as independent variables. The melting time, friability test and Drug content were selected as dependent variables.

Table.6. 3^2 Full Factorial Design Layout*

Batch Code	Variable Levels in Coded Form		Response (Y)		
	X1(mg)	X2(mg)	% Friability	Melting Time (min)	Drug Content(mg)
F1	-1	-1	0.42±0.012	35.35±0.38	84.21±0.001
F2	-1	0	0.51±0.011	27.18±0.56	79.6±0.02

F3	-1	+1	0.6±0.013	46.18±0.33	89.27±0.04
F4	0	-1	0.5±0.012	26.38±0.23	78.3±0.13
F5	0	0	0.2±0.011	26.3±0.45	79.32±0.22
F6	0	+1	0.303±0.013	35.42±0.21	85.31±0.12
F7	+1	-1	0.5±0.012	48.2±0.32	90.11±0.24
F8	+1	0	0.205±0.013	36.51±0.56	82.2±0.45
F9	+1	+1	0.112±0.011	45.22±0.42	91.33±0.02

Three batches were prepared using a single base coconut oil and using an different pro portion of Suppository base (PEG 6000) and Surfactant (Span 60). Melted mass of drug, bases and surfactant were prepared by using hot fusion method. The mold were lubricated and melted mass poured into the mold and leave for solidify on ice tray. On the basis of the results obtained in the preliminary screening studies, the batch containing PEG 6000 showed the more drug content release. Hence, it was selected for further studies. The batch was prepared using PEG 6000 at different concentrations to study its effect on melting time. It is worthwhile to note that as the concentration of PEG increased, the rate of melting time is increased. Suppository with lower friability (≤0.5%) may not break during handling on machines and/or shipping. The use of a PEG resulted in increased friability probably due to increased porosity.
The equations for melting time, friability and drug content developed as follows.

Table no. 7. 3^2 factorial design of Melting time (min)

X1	X2	X112	X222	X12	Melting Time(min)
-1	-1	1	1	1	35.35
-1	0	1	0	0	27.18
-1	1	1	1	-1	46.18
0	-1	0	1	0	26.38
0	0	0	0	0	26.3
0	1	0	1	0	35.42
1	-1	1	1	-1	48.2
1	0	1	0	0	36.51
1	1	1	1	1	45.22

Table no. 8. ANOVA of Melting time

	df	SS	MS	F	Significance F
Regression	5	565.9161	113.1832	9.385974	0.047331
Residual	3	36.17629	12.05876		
Total	8	602.0924			

$Y1 (MT) = 23.05 + 3.536X1 + 2.815X2 + 10.40X11^2 + 9.461X22^2 - 3.452X1X2$

The co-efficient of X1 in the Y1 equations has a positive sign, meaning that the melting time with PEG 6000 concentration. The melting time increases with the increasing span 60 concentration, as indicated by the positive sign for the co-efficient of X2 in the Y1 equations. Based on the data, it can be established that increasing the amount of the base and surfactant(X1 & X2) increases the melting time of the dosage form. Furthermore, the Posaconazole suppositories release pattern can be changed by selecting appropriate levels of X1 (PEG6000) and X2 (Span60). The data clearly indicate that the melting time values are strongly dependent on the selected independent variables. The response surface plots exemplified the effects of X1 and X2 on melting time as shown in figure no. 1.

ANOVA was used to identify significant effect, Coefficient of determination R^2=0.93. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). The critical value of F is 0.047, obtained F value (i.e. 9.38) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p<0.05$ i.e. indicates significance at that level of probability (Table). R^2 model found to be significant hence this model has been used for

predictions. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within limit. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model.

Table no. 9. 3^2 factorial design of Friability test(%)

X1	X2	X112	X222	X12	% Friability
-1	-1	1	1	1	0.42
-1	0	1	0	0	0.51
-1	1	1	1	-1	0.6
0	-1	0	1	0	0.5
0	0	0	0	0	0.2
0	1	0	1	0	0.303
1	-1	1	1	-1	0.5
1	0	1	0	0	0.205
1	1	1	1	1	0.112

Table no. 10. ANOVA of Friability test

	df	SS	MS	F	Significance F
Regression	5	0.219516	0.043903	8.022719	0.058468
Residual	3	0.016417	0.005472		
Total	8	0.235934			

$Y2 (FT) = 0.267-0.118X1-0.067X2 + 0.056X11^2 + 0.1008X22^2- 0.142X1X2$

The Co-efficient of X1 in the Y2 equations has a negative sign, meaning that the friability test with PEG 6000 concentration. The friability decreases with the increasing in PEG 6000 concentration The X2 co-efficient shows the positive sign in Y2 equations indicates the increases in friability by increasing the concentration of Span 60. Based on the data, it indicates that increasing the concentration of PEG 6000 leads to decrease in %age friability. Which will help the formulation to avoid breaking while transportation.

ANOVA was used to identify significant effect, Coefficient of determination R^2=0.93. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). The critical value of F is 0.058, obtained F value (i.e. 8.02) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p<0.05$ i.e. indicates significance at that level of probability (Table 7.5). R^2 model found to be significant hence this model has been used for predictions. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within limit. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model.

Table no. 11. 3^2 factorial design of Drug Content(mg)

X1	X2	X112	X222	X12	Drug content
-1	-1	1	1	1	84.21
-1	0	1	0	0	79.6
-1	1	1	1	-1	89.27
0	-1	0	1	0	78.3
0	0	0	0	0	79.32
0	1	0	1	0	85.31

1	-1	1	1	-1	90.11
1	0	1	0	0	82.2
1	1	1	1	1	91.33

Table no. 12. ANOVA of Friability test

	df	SS	MS	F	Significance F
Regression	5	177.7818	35.55636	5.821135	0.088963
Residual	3	18.32444	6.108148		
Total	8	196.1062			

Y3 (DC) = 76.94 + 1.76X1 + 2.21X2 + 5.143 $X11^2$ + 6.048$X22^2$- 0.96X1X2

Basing on this polynomial equation we can conclude that %age drug content increases with increase in concentrations of both factors X1 & X2. The 3D surface model of the factors X1 & X2 i.e, independent variables with dependent variable Y3 is shown in figure 3

ANOVA was used to identify significant effect, Coefficient of determination R^2=0.90. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). The critical value of F is 0.088, obtained F value (i.e. 5.82) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p<0.05$ i.e. indicates significance at that level of probability (Table 7.7). R^2 model found to be significant hence this model has been used for predictions. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within limit. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model. From 3D plots only, the formulation optimization for required response was predicted graphically.

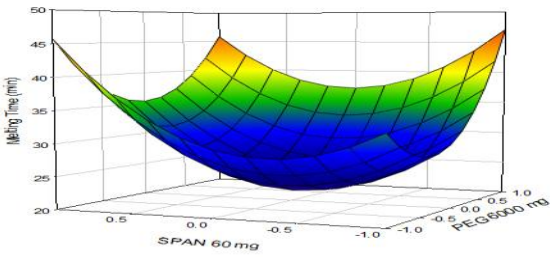

Figure no. 2. Three-dimensional response surface plots relating Melting time

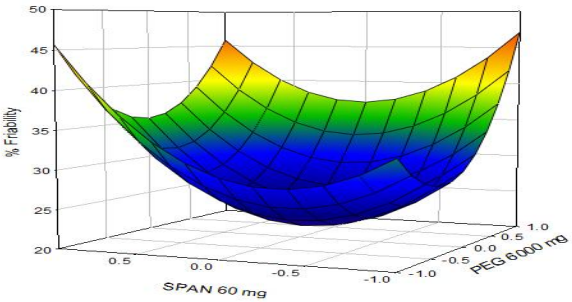

Figure no. 3. Three-dimensional response surface plots relating % Friability Test

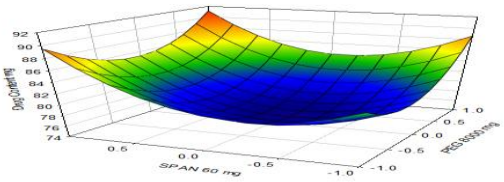

Figure no. 4. Three-dimensional response surface plots relating Drug Content

Suppository each containing 100mg of Posaconazole was formulated by using PEG 4000 & span 60 as given in formula table no. 8.1.

Table no. 13. 3^2 Factorial design Layout of PEG 4000 & Span 60

Batch Code	Variable Levels in Coded Form		Response (Y)		
	X1(mg) PEG 4000	X2(mg) Span 60	Melting point (min)	Friability Test (%)	Drug Content
F1	-1	-1	27.22	0.42	73.25
F2	-1	0	29.2	0.51	88.22
F3	-1	+1	36.11	0.22	76.1
F4	0	-1	50.32	0.401	89.13
F5	0	0	42.3	0.301	92.24
F6	0	+1	47.12	0.113	80.2
F7	+1	-1	26.23	0.522	91.3
F8	+1	0	31.1	0.631	85.1
F9	+1	+1	26.22	0.413	70.4

Polynomial equations were created to describe the relationships for melting time, friability test and drug content. The 3 levels of factor X1 (PEG 4000) at concentrations of 20 mg and 30 mg and the three levels of factor X2 (span 60) at concentrations of 20 mg and 30 mg, were used as the basis of designing the formulation of Posaconazole suppositories. A total of nine Posaconazole vaginal suppositories were developed using chosen pairings of the two variables, X1 (PEG 4000) and X2 (span 60), as per the 3^2 factorial design. In order to find the optimal combination and concentration necessary to produce the desired quick release and dissolution of the drug, these films were assessed to assess the relevance of the combined effects of X1 and X2. The concentration of PEG 4000 was divided into three levels, which were coded as follows: +1= 30 mg, 0=25 mg and -1= 20 mg. Similarly, three levels for the concentration of Span 60 were selected and coded as: +1=30mg, 0= 25mg and -1= 20 mg. The formulas for suppositories are provided in table. Polynomial equations for melting time, Friability test and % drug content were formulated using MS Excel and sigma plot software. Figure no 4-6 Depicts the response surface plot for Melting time, % Friability and % drug content. The impacts of X1 and X2, indicated on the corresponding axes, are displayed in this figure no. 4.

Table no. 14. 3^2 factorial design of Melting time (min)

X1	X2	X112	X222	X12	Melting Time(min)
-1	-1	1	1	1	27.22

-1	0	1	0	0	29.2
-1	1	1	1	-1	36.11
0	-1	0	1	0	50.32
0	0	0	0	0	42.3
0	1	0	1	0	47.12
1	-1	1	1	-1	26.23
1	0	1	0	0	31.1
1	1	1	1	1	26.22

Table no. 15. ANOVA of Melting time

	df	**SS**	**MS**	**F**	**Significance F**
Regression	5	636.1685	127.2337	6.034291	0.084952
Residual	3	63.25534	21.08511		
Total	8	699.4239			

$Y1_{(MT)}$ = 45.68-1.496X1+0.946X2-17.23$X11^2$+1.336$X22^2$-2.225X1X2

The co-efficient of X1 in the Y1 equations has a negative sign, the melting time decreases with the increasing PEG 4000 concentration, as indicated. The co-efficient of X2 in the Y1 equations shows the positive sign that indicates melting time increases on increasing the Span 60 concentrations. Based on the data, it can be established that increasing the amount of the surfactant(X2) increases the melting time of the dosage form whereas increasing the amount of PEG 4000(X1) decreases the melting time. Furthermore, the Posaconazole suppositories release pattern can be changed by selecting appropriate levels of X1 (PEG6000) and X2 (Span60). The data clearly indicate that the melting time values are strongly dependent on the X2 independent variable. The response surface plots exemplified the effects of X1 and X2 on melting time as shown in figure no. 5.

ANOVA was used to identify significant effect, Coefficient of determination R^2=0.90. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). The critical value of F is 0.084 obtained F value (i.e. 6.03) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p<0.05$ i.e. indicates significance at that level of probability (Table 8.3). R^2 model found to be significant hence this model has been used for predictions. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within limit. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model.

Table no. 16. 3^2 factorial design of Friability test (%)

X1	**X2**	**X112**	**X222**	**X12**	**Friability Test (%)**
-1	-1	1	1	1	0.42
-1	0	1	0	0	0.51
-1	1	1	1	-1	0.22
0	-1	0	1	0	0.401
0	0	0	0	0	0.301
0	1	0	1	0	0.113
1	-1	1	1	-1	0.522
1	0	1	0	0	0.631
1	1	1	1	1	0.413

Table no. 17. ANOVA of Friability test

	Df	SS	MS	F	Significance F
Regression	5	0.190949	0.03819	8.179387	0.056976
Residual	3	0.014007	0.004669		
Total	8	0.204956			

$Y2_{(FT)}$ = 0.36+0.069X1-0.0995X2+0.181X112-0.132X222+0.0227X12

The Co-efficient of X1 in the Y2 equations has a positive sign, meaning that the friability test with PEG 4000 concentration. The friability increases with the increasing in PEG 4000 concentration. The X2 co-efficient shows the negative sign in Y2 equations indicate the decreases in friability by increasing the concentration of Span 60. Based on the data, it indicates that increasing the concentration of PEG 4000 leads to increase in %age friability. Which will help the formulation to avoid breaking while transportation. The data clearly indicate that the % friability values are strongly dependent on the selected X1 independent variables. The response surface plots exemplified the effects of X1 and X2 on melting time as shown in figure no. 6.

ANOVA was used to identify significant effect, Coefficient of determination R^2=0.93. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). The critical value of F is 0.056, obtained F value (i.e. 8.17) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p<0.05$ i.e. indicates significance at that level of probability (Table 8.5). R^2 model found to be significant hence this model has been used for predictions. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within limit. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model. From 3D plots only, the formulation optimization for required response was predicted graphically.

Table no. 18. 3^2 factorial design of Drug Content (mg)

X1	X2	X112	X222	X12	Drug Content (mg)
-1	-1	1	1	1	73.25
-1	0	1	0	0	88.22
-1	1	1	1	-1	76.1
0	-1	0	1	0	89.13
0	0	0	0	0	92.24
0	1	0	1	0	80.2
1	-1	1	1	-1	91.3
1	0	1	0	0	85.1
1	1	1	1	1	70.4

Table no. 19. ANOVA of Drug Content

	Df	SS	MS	F	Significance F
Regression	5	503.0712	100.6142	10.20451	0.042234
Residual	3	29.57935	9.859784		
Total	8	532.6506			

$Y3_{(DC)}$ = 92.82+1.538X1-4.496X2-6.461X112-8.45X222-5.937X12

The Co-efficient of X1 in the Y3 equations has a positive sign, meaning that the drug content with PEG 4000 concentration. The drug content increases with the increasing in PEG 4000 concentration The X2 co-efficient shows the negative sign in Y3 equations indicates the decreases in drug content by increasing the concentration of Span 60. Based on the data, it indicates that increasing the concentration of PEG 4000 leads to increases in drug content. The response surface plots exemplified the effects of X1 and X2 on melting time as shown in figure no. 6.

ANOVA was used to identify significant effect, Coefficient of determination R^2=0.94. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). The critical value of F is 0.042, obtained F value (i.e. 10.20) is larger than critical value and so it can be concluded that obtained F value is likely to occur by chance with a $p<0.05$ i.e. indicates significance at that level of probability (Table 8.7). R^2 model found to be significant hence this model has been used for predictions. The relative errors (%) between the predicted and experimental values for each response were calculated and the values found to be within limit. The experimental values were in agreement with the predicted values confirming the predictability and validity of the model. From 3D plots only, the formulation optimization for required response was predicted graphically.

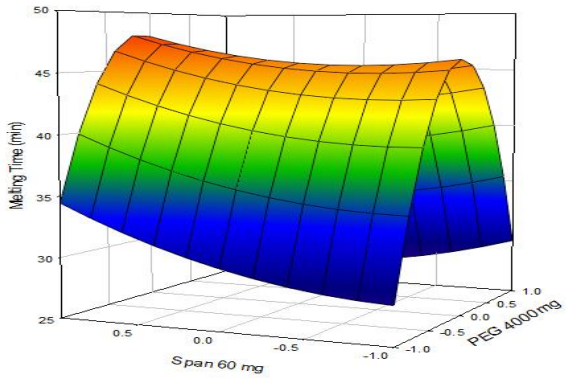

Figure no. 5. Three-dimensional response surface plots relating Melting time

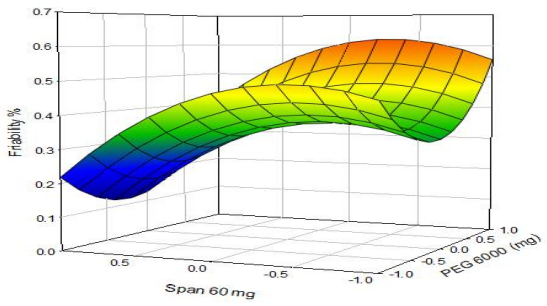

Figure no. 6. Three-dimensional response surface plots relating % Friability

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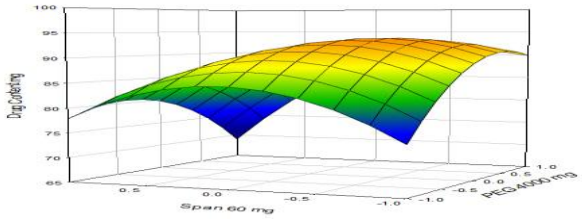

Figure no. 7. Three-dimensional response surface plots relating drug Content

Kinetic Study:

For adequate characterization of drug release rate from suppositories requires the determination of its appropriate release kinetics model. Data obtained from dissolution studies were fitted to Zero-order, First-order, Higuchi and KorsmeyerPeppas' model to determine the kinetics of drug release. The in-vitro data were represented as

Cumulative % drug release versus time

Log cumulative % drug retained versus time

Cumulative % drug release versus square root time

Log % drug release versus log time

Table 20: Zero order release data for formulation (F1-F9)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	28.89	28.14	30.47	27.76	30.89	30.64	32.27	29.96	31.29
10	38.57	46.13	46.14	38.52	40.57	48.63	47.94	40.72	45.97
15	52.89	55.14	52.45	51.37	54.89	57.64	54.25	53.57	54.83
30	69.78	66.44	68.36	62.48	71.78	68.94	70.16	64.68	68.17
45	78.76	74.43	79.35	72.26	80.76	76.93	81.15	74.46	78.19
60	84.98	80.31	87.31	82.02	86.98	82.81	89.11	84.22	86.89

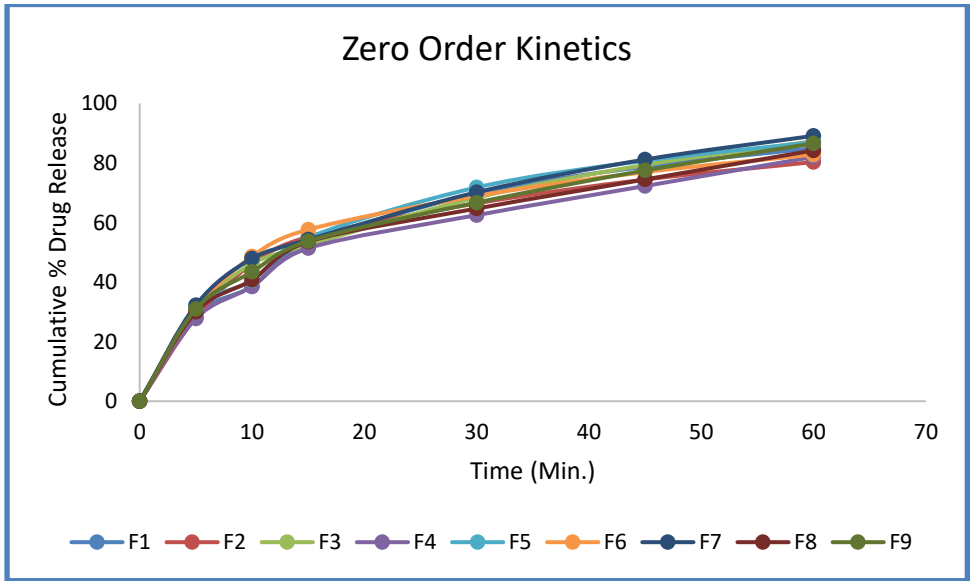

Figure 8: Zero order release profile of all formulations F1-F9)

The formulation F7 showed a better in vitro drug release profile across the membrane when compared to the other formulations. Release kinetics of Posaconazole suppositories. In vitro release data was fitted with various release equations and kinetic models like the Zero-order, First order, Higuchi and Korsemeyer Peppas.

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Table 21: First order release data for formulation (F1-F9)

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	2	2	2	2	2	2	2	2	2
5	1.929	1.904	1.941	1.919	1.939	1.918	1.949	1.925	1.934
10	1.896	1.871	1.899	1.864	1.907	1.886	1.909	1.871	1.881
15	1.843	1.822	1.834	1.802	1.856	1.838	1.846	1.811	1.834
30	1.723	1.741	1.719	1.702	1.739	1.761	1.734	1.728	1.723
45	1.586	1.664	1.664	1.596	1.608	1.686	1.681	1.609	1.651
60	1.461	1.449	1.483	1.458	1.489	1.486	1.508	1.476	1.345

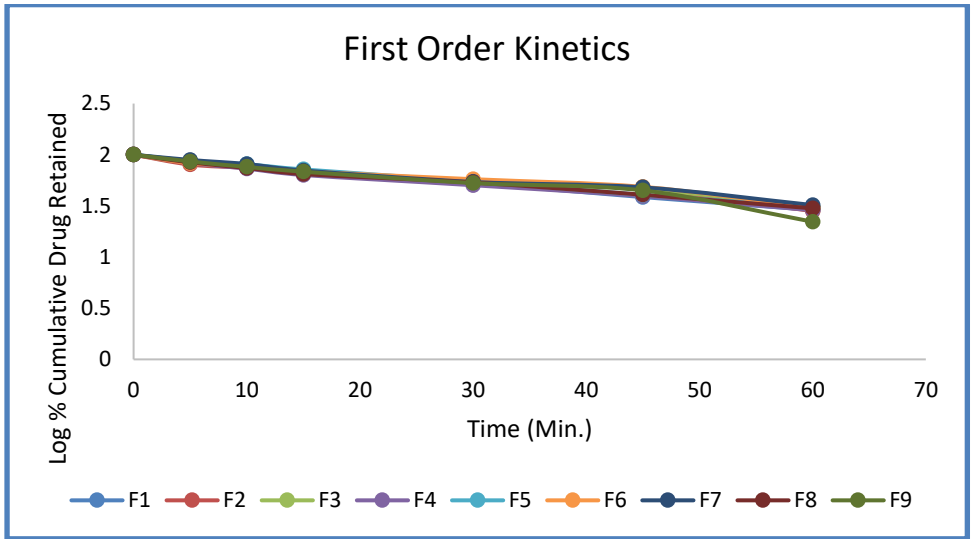

Figure 9: First order release profile of all formulations F1-F9)

Table 22: HiguchiOrder Release data for formulation (F1-F9)

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2.236	28.897	28.145	30.478	27.761	30.897	30.645	32.278	29.961	30.973
3.162	38.578	46.134	46.147	38.523	40.578	48.634	47.947	40.72	43.443
3.873	52.895	55.147	52.453	51.378	54.895	57.647	54.253	53.578	53.781
5.477	69.785	66.441	68.365	62.486	71.785	68.941	70.165	64.686	66.691
6.708	78.765	74.431	79.358	72.269	80.765	76.931	81.158	74.469	77.483
7.746	84.985	80.314	87.314	82.023	86.985	82.814	89.114	84.223	86.563

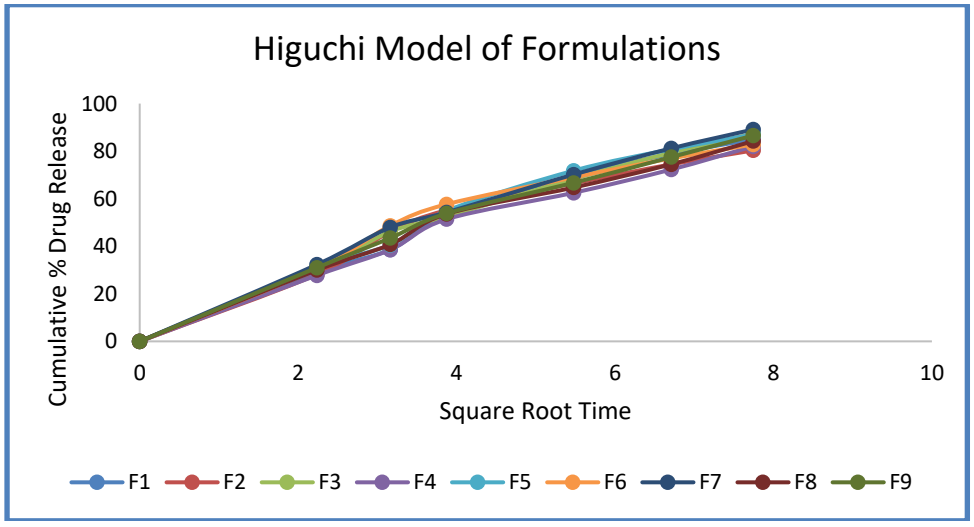

Figure 10: Higuchi model of all formulations F1-F9

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Table 23: Korsmeyer-Peppas model Release data for formulation (F1-F9)

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	2	2	2	2	2	2	2	2	2
0.34	1.929	1.904	1.941	1.919	1.939	1.918	1.949	1.925	1.934
0.5	1.896	1.871	1.899	1.864	1.907	1.886	1.909	1.871	1.881
0.58	1.843	1.822	1.834	1.802	1.856	1.838	1.846	1.811	1.834
0.73	1.723	1.741	1.719	1.702	1.739	1.761	1.734	1.728	1.723
0.82	1.586	1.664	1.664	1.596	1.608	1.686	1.681	1.609	1.651
0.88	1.461	1.449	1.483	1.458	1.489	1.486	1.508	1.476	1.345

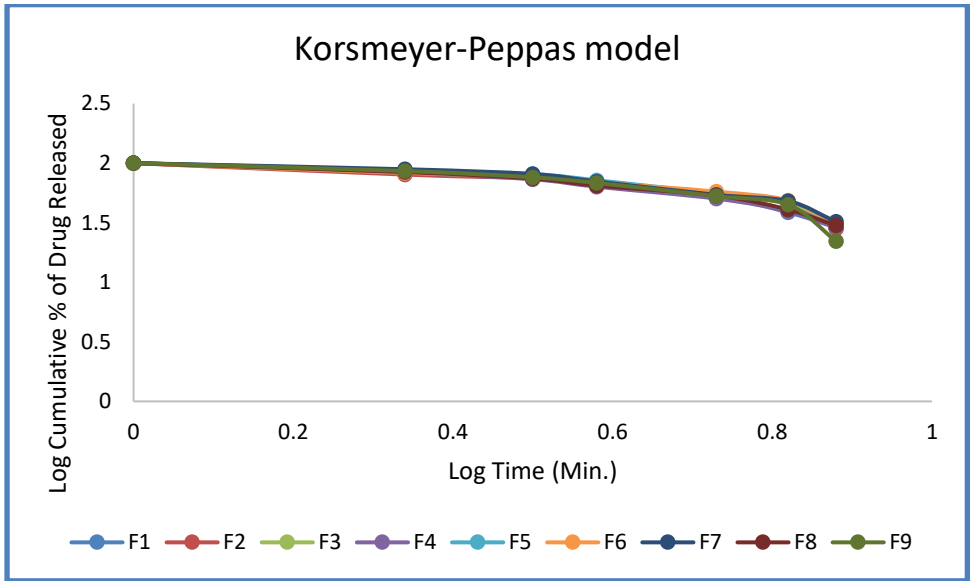

Figure 11: Korsmeyer-Peppas model of all formulations (F1-F8)

Discussion

On summarizing, we can say that on the extent of drug release the PEG 4000 is good in drug release as compared to PEG 6000

On the basis of time duration of drug release bases can be arranged

PEG 6000 < PEG 4000

On the addition of plasticizer PEG 4000 reduces the cumulative percent drug release on whole, but when added at 10% level no change is seen in dissolution time whereas at 30% level the dissolution time reduces by 15 mins.

Surfactants when added, increase the total amount of drug release, however when a fixed percent of surfactants are taken there are differences in the enhancement, which depends on the type and the HLB value of surfactants. The order by which drug release is improved can be give by

Tween 60 < Span 60

On the ability to be used as a carrier in designing of a sustained release bases can be arranged in ascending order

PEG 4000< PEG 6000

Table 24: Fit of various release kinetic models for suppositories of Posaconazole

Code	Zero order	First order	Higuchi	KorsmeyerPeppas
	R^2	R^2	R^2	R^2
F1	0.8384	0.9979	0.9819	0.8074
F2	0.7712	0.9628	0.9547	0.7930
F3	0.8295	0.9809	0.9820	0.8114
F4	0.8402	0.9862	0.9834	0.8564

F5	0.8289	0.9987	0.9796	0.7997
F6	0.7584	0.9672	0.9495	0.7869
F7	0.8202	0.9821	0.9788	0.8045
F8	0.8284	0.9875	0.9799	0.8449
F9	0.8144	0.9514	0.9821	0.7214

The Regression value (R2) of all the 4 mathematical models was compared for the prepared suppository formulations to determine the mechanism of drug release. R2 was found maximum for Higuchi release kinetics which indicated the release of drugs from all the tested formulations followed Higuchi release rate kinetics. Hence, it delivered the drug in a sustained manner for a prolonged period of time.

8.2. Stability studies for the formulation F3

Stability study for the best formulation was done as per the procedure. The pessaries was physically stable at 4±3^{0}c, Room temperature and 40±2^{0}c. The results were tabulated in Table

Table- 25 Stability Testing Physical Parameters

Parameters	**Room Temp. (25±2^{0}C)**	**40±2^{0}C**	**4±3^{0}C**
Visual appearance Initial Final	Solid white	Solid White	Solid White
pH Initial Final	6.9 7.1	6.9 7.0	6.9 6.9
Extrudability Initial Final	+++ +++	+++ +++	+++ +++
Phase separation	Not found	Not found	Not found
Leakage	Not found	Not found	Not found
Nature Initial Final	SmoothSmooth	SmoothSmooth	SmoothSmooth

Conclusion

Posaconazole, a broad-spectrum antifungal agent, is commonly used in the treatment of various fungal infections. The study investigates the development of posaconazole pessaries (vaginal inserts) using coconut oil and surfactants as a delivery system to enhance the antifungal activity and bioavailability of posaconazole. The main goal was to improve the drug's efficacy and local concentration while ensuring ease of application and better patient compliance, Coconut oil is utilized due to its natural emollient properties, which can promote the absorption of the drug, while surfactants such as Tween 60 and Span 60 help in improving the drug solubility and stability. The combination of coconut oil and surfactants in the pessary formulation enhances the release and permeation of posaconazole, making it more effective for treating localized fungal infections. The pessaries were designed t dissolve or melt at body temperature, ensuring controlled release and reducing the likelihood of irritation or discomfort.

The formulation of posaconazole pessaries using coconut oil and surfactants offers promising results in terms of improved drug release, solubility, and antifungal activity. The addition of coconut oil not only contributes to the solubility of posaconazole but also provides a soothing effect on the vaginal mucosa, promoting better patient tolerance. Surfactants further enhance the formulation's stability and the bioavailability of the antifungal agent. This innovative approach has the potential to offer an effective, localized treatment for fungal infections with minimal systemic absorption, which could reduce the risk of systemic side effects commonly seen with oral antifungal therapies. Further studies and clinical trials are necessary to assess long-term efficacy, safety, and patient satisfaction before widespread clinical adoption.

Overall, posaconazole pessaries with coconut oil and surfactants present a novel and effective approach for treating vaginal fungal infections.

REFERENCE

1. Murina F, Lubrano C, Cappelli E, Campo M, Taraborrelli S (2023) The role of female intimate hygiene practices in the management of vulvovaginal candidiasis A randomized controlled open label trial. Health Care Women Int 44(5):689–700
2. 2. Asare KK, Bentil HA, Gyesi E, Amoah S, Bentsi-Enchill F, Opoku YK (2023) Candidiasis profile at the outpatient department of the university of cape coast hospital in the central region of Ghana: a retrospective study. BMC Women's Health 23:1–10
3. A.Böhme,M.Ruhnke,D.Buchheidtetal.,"Treatmentofinva sive fungal infections in cancer patients—recommendations of the Infectious Diseases Working Party (AGIHO) of the Ger man Society of Hematology and Oncology (DGHO)," Annals of Hematology, vol. 88, no. 2, pp. 97–110, 2009.
4. R. A. M.Osmani, P. K. Kulkarni, S. Shanmuganathan et al., "A 32full factorial design for development and characterization of a nanosponge-based intravaginal in situ gelling system for vul vovaginal candidiasis," RSC Advances, vol. 6, no. 23, pp. 18737–18750, 2016.
5. J. E. Norman, N. Marlow, C. M. Messow et al., "Vaginal pro gesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial," Lancet, vol. 387, no. 10033, pp. 2106–2116, 2016.
6. R. P. de Oliveira, J. M. de Oliveira, and C. Caramella, "Special issue on vaginal drug delivery," Advanced Drug Delivery Reviews, vol. 92, p. 1, 2015.
7. S. Shanmugam, Y. H. Kim, J. H. Park et al., "Sildenafil vaginal suppositories: preparation, characterization, in vitro and in vivo evaluation," Drug Development and Industrial Phar macy, vol. 40, no. 6, pp. 803–812, 2014.
8. Gonçalves B, Ferreira C, Alves CT, Henriques M, Azeredo J, Silva S (2016) Vulvovaginal candidiasis: epidemiology, microbiology and risk factors. Crit Rev Microbiol 42(6):905–927
9. Denning DW, Kneale M, Sobel JD, Rautemaa-Richardson R (2018) Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Infect Dis 18(11):e339–e347
10. Mahant S, Sharma AK, Gandhi H, Wadhwa R, Dua K, Kapoor DN (2022) Emerging trends and potential prospects in vaginal drug delivery. Curr Drug Deliv 20(6):730–751
11. Kamble MS, Vaidya KK, Bhosale AV. Solid Lipid Nanoparticles and Nanostructured lipid carriers- an overview. Int J Pharm Chem Sci. 2012;2(4):681–91.
12. Sai L, Zhigui S, Minjie S. An arginine derivative contained nanostructure lipid carriers with pH-sensitive mambranolytic capability for lysosomolytic anti-cancer drug delivery". Int J Pharm. 2012;436(1-2):248–57.
13. Dilip P, Sandipan D. Nanostructured Lipid Carriers(NLC) Based Gel for the Topical Delivery of Aceclofenac: Preparation, Characterization, and In-Vivo Evaluation. Sci Pharm. 2012;80 (3):749–64.
14. Paolino D, Felisa HS, Cosco D. Nanostructured lipid carriers (NLC) for the topical delivery of lutein. Bentham Sci Drug Deliv letters. 2011;80(3):749–64.
15. Spellberg B, Ibrahim AS. Recent advances in the treatment of mucor mycosis. Curr Infect Dis Rep. 2010;12(6):423–9.
16. Santos SS, Lorenzoni A, Pegoraro NS, Denardi LB, Alves SH, Schaffazick SR, et al. Formulation and in vitro evaluation of
17. Kabara JJ, Swieczkowski DM, Conley AJ, Truant JP. Fatty acids and derivatives as antimicrobial agents. Antimicrob Agents Chemother 1972;2:23-8.
18. Skřivanova E, Marounek M, Benda V, Brezina P. Susceptibility of escherichia coli, salmonella sp and clostridium perfringens to organic acids and monolaurin. Veterinarni Medicina; 2006.
19. Bergsson G, Steingrímsson O, Thormar H. In vitro susceptibilities of neisseria gonorrhoeae to fatty acids and monoglycerides. Antimicrob Agents Chemother 1999;43:2790-2.
20. Ogbolu DO, Oni AA, Daini OA, Oloko A. In vitro antimicrobial properties of coconut oil on candida species in Ibadan, Nigeria. J Med Food 2007;10:384-7.
21. Marina A, Man YC, Nazimah S, Amin I. Chemical properties of virgin coconut oil. J Am Oil Chem Soc 2009;86:301-7.
22. Bergsson G, Arnfinnsson J, Steingrı´msson O, Thormar H. In vitro killing of candida albicans by fatty acids and monoglycerides. Antimicrob Agents Chemother 2001;45:3209-12.
23. A. P. Christa, P. T. Biscainoa, R. L. Lourençob, A. B. de Souzab, E. S. Zimmermanna, and A. I. H. Adam, "Development of doxycyclinehyclate suppositories and pharmacokinetic study in rabbits," European Journal of Pharmaceutical Sciences, vol. 142, no. 15, pp. 105141–105141, 2020.
24. S. G. Sudke, S. Singh, and N. S. Bhajipal, "Design of curcumin suppositories for effective treatment of vaginal candidiasis using cow ghee as a suppository base," Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm, vol. 11, no. 4, p. S985, 2017.

25. E. Gomaaa, A. S. Abu Lilaa, A. A. Hasana, and F. S. Ghaz, "Preparation and characterization of intravaginal vardenafil suppositories targeting a complementary treatment to boost _in vitro_ fertilization process," European Journal of Pharma ceutical Sciences, vol. 111, pp. 113–120, 2018.
26. Varshney, H.M., Tanwar, Y.S., 2010. Formulation, physicochemical characterisations and in vitro evaluation of Flurbiprofen Sodium suppositories, Journal of Pharmacy Rsearch, 3(3), 561-565.
27. Varshney, H.M., Tanwar, Y.S., 2010. Designing, release characteristics and in vitro evaluation of Flurbiprofen Sodium suppositories, International journal of Pharmmaceutical and clinical research, 1(1), 31-34.
28. Coben, L.J., and Lieberman, H.A., 2009. Suppositories, in: The theory and practice of industrial pharmacy, Lachman, L., and Lieberman, H.A.(Eds.), CBS Publishers and Distributors, New Delhi, 586-587.
29. Varshney, H.M., Tanwar, Y.S., 2010. Effect of Different Surfactants on the Release Pattern of Coacoa Butter Suppositories Containing Flurbiprofen Sodium, Acta Pharmaceutica Sciencia, 52, 129-136.
30. Sah, M.L., and Saini, T.R., 2008. Formulation development and release studies of indomethacin suppositories, Indian Journal of Pharmaceutical Sciences, 70(4), 498-501.
31. Loyd V. Allen, Jr., Ed., 2008. Quality control of suppositories, in: Suppositories, Pharmaceutical Press, London, pp. 141-142.
32. 34. Singh, K., Shegokar, R., 2010, In-Vitro Release of Paracetamol from Suppocire Suppositories: Role of Additives, Malaysian Journal of Pharmaceutical Sciences, 8(1), 57-71.
33. Abass, H., et.al. , 2012. Metronidazole bioadhesive vaginal suppositories: formulation, in vitro and in vivo evaluation, International journal of pharmacy and pharmaceutical sciences, 4(1), 344-353.
34. Patravale, V., et.al. , 2010. Self micro-emulsifying suppository formulation of β- artemether, AAPS PharmSciTech, 11(3), 1179-1184.
35. Swiader, K., et.al. , 2011. The preparation of suppositories by various methods and evaluation of physicochemical properties, Annales of Marie curie University Lublin, 24(2), 159-167.
36. Swamy, P.V., et.al. , 2009. Design and evaluation of rectal suppositories of carvedilol, International journal of pharmaceutical sciences and nanotechnology, 2(3), 654-660.
37. Baria, A.H., et.al. , 2009. Formulation development and evaluation of sustained release aceclofenac suppository, International journal of pharmaceutical sciences and drug research, 1(2), 71-73.
38. Swiader, K., et.al. , 2011. The preparation of suppositories by various methods and evaluation of physicochemical properties, Annales of Marie curie University Lublin, 24(2), 159-167.
39. Tarimci, N. and Ermis, D., 1995. Ketoprofen Sustain Release Suppositories Containing Hydroxyprooylmethylcellulose Phthalate, International Journal of Pharmaceutics, 113, 65-71.