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Original Article

Formulation and Evaluation of Antifungal Drug Containing Mucoadhesive Tablet for Vaginal Candidiasis

Pranita Sunil Kanojiya, Rita Naresh Wadetwar, Amita Prasanna Godbole

Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Amravati Road, Nagpur, Maharashtra, INDIA.

ABSTRACT

Objectives: Female population frequently seeks medical consultation for the vaginal candidiasis. Voriconazole (VOR) is a BCS class II antifungal drug with low aqueous solubility and hence inclusion complex was formulated using Hydroxypropyl-β-cyclodextrin (HPβCD). The complex was incorporated into mucoadhesive vaginal tablet using Chitosan and Hydroxypropyl Methyl Cellulose (HPMC K100). **Materials and Methods:** A 3^2 full factorial design was employed for sustained release tablet using Design expert® software. **Results:** Scanning Electron Microscopy (SEM) results indicated the complex formation between the drug and HPβCD. The batches showed 39.68±1.2 to 72.31±1.4% of drug release for 4 hr while for 8 hr it was from 77.23±1.5 to 99.82±1.1%. Therefore, the sustained release of drug was achieved for 8 hr. The tablet batches had swelling % from 228.51±12 to 323.11±8% and mucoadhesive strength from 1131.02±49 to 2302.12±55 dyne/cm^2. In the *in vitro* antifungal activity study, a higher zone of inhibition was observed for the inclusion complex-based tablet (34±0.3 mm) as compared to plain drug tablet (25±0.4 mm). **Conclusion:** Therefore, the inclusion complex-based vaginal tablet could be formulated successfully by employing 3^2 full factorial design for increased residence of drug at the vaginal site of infection and for improved therapeutic efficacy.

Keywords: Voriconazole, Factorial design, Inclusion complex, Vaginal Candidiasis, Sustained release, *In vitro* antifungal activity, *In vitro* release.

Correspondence:
Dr. Mrs. Rita N. Wadetwar
Professor, Department of Pharmaceutical Sciences, Rashtrasant Tukaoji Maharaj Nagpur University, Amravati Road, Nagpur-440 033, Maharashtra, INDIA.
Email: rnwadetwar1@gmail.com

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INTRODUCTION

Vaginal Candidiasis is the most frequently occurring infection in the female population. The causative agent for the infection is *Candida albicans* which accounts for 90% of the prevalent vaginal infection. The symptoms of the infection include itching, burning, redness, erythema and inflammation in the vulva and vagina with cloudy white fluid discharge. These manifestations reduce the quality of life due to pain and discomfort.[1]

Voriconazole is a triazole antifungal drug that inhibits 14-α-demethylase enzyme and thus blocks the synthetic pathway of fungal membrane thereby inhibits the growth of the fungal pathogen. The drug is reported to have serious systemic side effect which includes visual defects, dermal reactions and hepatotoxicity. It is a BCS class II drug having poor aqueous solubility and gets precipitated out from the aqueous solution.[2]

Cyclodextrin and their conjugates are currently gaining popularity in the pharmaceutical application due to the potential of forming inclusion complexes with various drug categories to solve the solubility, stability and palatability issues that are very frequently faced during formulation of any dosage form.[3,4] The inclusion complex of class II drugs prepared with HPβCD are used to improve the aqueous solubility as well as stability.[5] The drugs Ketoconazole and Voriconazole are complexed with HPβCD and incorporated in the *in situ* gel and due to which there has been increased drug solubility and improved antifungal activity.[6,7] Voriconazole has been used for the dermal,[8] ocular[9] and nail-plate infections.[10] Hence, it gives the scope to the drug for the usage in the vaginal infections also. Voriconazole when given orally is reported to have systemic effects thus, when given vaginally could act in a better fashion surpassing the side-effects. Recently, Voriconazole loaded NLC,[1] organogel[11] and lipid nanoparticle[12] based gels are reported in the literature for the Vaginal Candidiasis. In such scenario, there was a need to come up with a cost effective formulation that could be easy for scale-up at industrial level and free from the stability issues observed (such as storage condition, availability of high-end equipments and costly excipients) in the case of nanoparticulate formulations.

The conventional vaginal formulations (gels, creams, ointments, solutions, films, and foams) are also often associated with difficulties such as poor retention, leakage from the site (as a

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result of self-cleansing mechanism of the vagina), messiness which can be inconvenient to the patients and also lead to the poor compliance and loss of therapy.[1,13] Vaginal tablet for localized delivery is an appealing option for the efficient therapy due to the complete removal of pathogenic agent, higher drug concentration at the site of infection, reduced administration of the dosage form and minimized side effects. However, the tablets also provide accurate dosing, portable, easy to store, robust, sturdy, easy to administer, economic and large scale industrial production is possible.[13] Clotrimazole,[14] Fluconazole,[13] Curcumin,[15] Itraconazole,[16] Lawsone[17] containing vaginal tablet are formulated for the treatment of Vaginal Candidiasis.

None of the literature has explored the antifungal potential of Voriconazole containing vaginal tablet till date. The common factor found in the former vaginal tablets were the mucoadhesive and the matrix forming polymers. Hence, the vaginal tablet of Voriconazole was proposed using the Chitosan as mucoadhesive polymer and HPMC as matrix polymer and the tablet was studied for the antifungal activity as well as irritation. Therefore, Voriconazole targeted therapy in the form of vaginal tablet may provide higher local drug availability at the therapeutic site and sustain for the desired time with complete fungal bioburden removal. This may decrease the frequency of recurrent Vaginal Candidiasis that is quite common in female patients.

MATERIALS AND METHODS

Voriconazole was generously gifted by Mylan, Hyderabad and hydroxypropyl-β-cyclodextrin HPβCD was procured from Loba Chemie Mumbai. Poloxamer 188 and Poloxamer 407 were procured from Sigma, Mumbai. Soluplus and Kollidone VA 46 were obtained as gift samples from BASF, Mumbai. Sodium acetate, Potassium chloride, Sodium chloride, Albumin, Glacial acetic acid was purchased from S. D. Fine Chemicals India.

Phase solubility study

Different polymers such as Soluplus, HPβCD, Poloxamer 407, Poloxamer 188 and Kollidone VA 64 were used for the phase solubility study. The 5%, 10%, 15%, 20% and 30% of the hydrophilic polymer solutions were prepared in the glass vial and then the excess drug was added in each of the vial separately. Then the vials were stoppered and shaked for 48 hr in an orbital shaker (Remi Instruments Ltd., CIS 24BI, Mumbai). The solution was filtered and analyzed spectrophotometrically (Shimadzu, UV-1200, Japan) at 256 nm.[18] Saturation solubility of the drug and the optimized solid dispersion was performed by the same method mentioned above.

Inclusion complex preparation by kneading method

In this method, the powder mixture of VOR+HPβCD was taken in 1:1 weight ratio and kneaded for 30 min with small amount of ethanol: water 1:1 v/v solution. The resulting wet mass was dried at 45±1°C for 24 hr with the help of hot air oven (Spectra Equipments, Hyderabad). The dried mass was pulverized and screened through the sieve no. 50 then stored in a desiccator till further use.[3,18]

Scanning Electron Microscopy (SEM) study

The surface morphological study of pure VOR, HPβCD and VOR IC were studied by means of SEM analysis employing scanning electron microscope (Hitachi, S-3700N). The double-sided tape was attached over the aluminum stubs and the sample was placed over it. Then the assembled stubs were coated with gold, placed in the vacuum chamber and finally the magnification was adjusted to obtain the image of excellent quality.[4]

Drug content for inclusion complex

The drug content was determined by dissolving VOR IC powder (equivalent to 20 mg of drug) in methanol, filtered through filter paper, and assayed spectrophotometrically at 256 nm. The test was performed thrice and the mean drug content data was presented as mean ± SD.

Design of experiment

The 3^2 full factorial design (Design Expert software version 7) was applied for the optimization of the vaginal tablet by considering the independent variables were HPMC K 100 and Chitosan. The dependent responses were *in vitro* drug release after 4 hr and 8 hr, mucoadhesive strength and swelling %. The three level two factors were kept for the design to get 9 batches.[1,14]

Fourier Transform Infrared (FTIR) spectroscopical study

To study the interaction between the drug and excipients of the tablet formulation, the FTIR study was performed. The samples under consideration were subjected to attrition along with KBr, placed in the cell and then finally scanned from 4000 to 800 cm^{-1} employing FTIR spectrophotometer (IRS Affinity1S, Shimadzu).[17]

Preparation of vaginal tablets

The powder blend amount required for the tablet batches was weighed properly. The compression force of the tablet machine was adjusted to give tablet hardness ranging between 4-8 Kp. The powder blend was added into the die and then was punched using flat face 9 mm round punch using tablet machine (Clit Pilot Press, CPM: 03-10, Ahmedabad) by direct compression method. Each tablet weighed 150 mg with 20 mg equivalent VOR IC.

Evaluation parameters of the tablet

The average weight of the tablet (n=20) was calculated. The hardness test was performed on ten tablets that were selected randomly from each tablet batch and Erweka hardness tester (Erweka, Germany) was used for the hardness measurement. The results were reported as mean ±SD.

Thickness measurement

The thickness of the tablet from all the batches was measured with micrometer gauge and thickness was reported as mean ± SD.

Friability

Twenty tablets were weighed initially (*F*0) and then placed in the friabilator chamber (Icon Instruments, New Delhi) then apparatus was adjusted at 25 rpm and allowed to rotate for 4 min. Then the tablets were removed from the chamber, de-dusted and weighed (*F*1). The loss was calculated from the equation given below:

$$\text{Friability} = \frac{F0 - F1}{F0} \times 100$$

Drug content

The drug content was determined by taking tablet powder, dissolved in the methanol then filtered through filter paper and assayed spectrophotometrically at 256 nm. The test was performed thrice and the mean drug content data was presented as mean ± SD.

In vitro dissolution study

The *in vitro* dissolution was studied using USP type II dissolution apparatus (Electrolab, 80AK, Mumbai). The dissolution flasks were filled with artificial vaginal fluid pH 4.1 as dissolution media (100 mL) and stabilized at 37 ± 0.5°C prior the experiment. The revolution of the paddle was adjusted at 50 rpm. The tablets were added in the flasks and the dissolution was carried out for 8 hr. The samples were removed (5 mL) at appropriate time interval (1-8 hr) and the same volume was filled with the AVF pH 4.1.[22] The samples were then filtered and analyzed spectrophotometrically at 256 nm. The dissolution profile of all the tablet batches along with plain drug tablet were plotted using the dissolution data.[19,20]

Release kinetics

The dissolution data were fitted into the various drug release kinetic models for the estimation of the release mechanism of the drug from the tablet batches. The coefficient value r^2 was calculated from the regression equations and best release fit was predicted from the regression coefficient values.

Scanning Electron Microscopy of Tablet

The morphological study of the intact vaginal tablet surface for the optimized tablet was carried out at 0 hr, 1 hr and 6 hr of the dissolution period and evaluated through the scanning electron microscopy. The tablets were wiped to remove the excess dissolution media and dried at 40°C in oven. After drying, the surface of tablet was properly coated with gold-pallidium sputter and observed using scanning electron microscope (Carl Zeiss, Supra 55, Germany).[21]

Ex vivo mucoadhesion studies

The *ex vivo* mucoadhesive strength was determined by a modified balance method using goat vaginal mucosa obtained from the local slaughterhouse. A weighing balance with two pans was used for this study. One vaginal tissue was attached at the base of the left side pan, another vaginal tissue was fixed on a platform and the tissues were hydrated with the AVF pH 4.1. The vaginal tablet was then applied between the mucosa on the platform and the left side pan bearing the vaginal mucosa and then allowed to make the contact so that the tablet formulation was sandwiched between the vaginal tissues. The preload weight of 10 g for 2 min was applied for the close contact. Then the weight was added on the right pan till the detachment of the vaginal tissue was achieved. The mucoadhesive strength (dynes/cm^2) required to detach the vaginal mucosal tissue from the surface of the tablet was denoted as the mucoadhesive strength. The equation is given as follows:

$$\text{Mucoadhesive strength } \left(\frac{\text{dyne}}{\text{cm}^2}\right) = \frac{g}{A} \times m$$

Where m = weight required for detachment in grams, g = acceleration due to gravity (980 cm/s^2) and A = area of the vaginal mucosa exposed.[13,17]

Swelling study

The swelling studies were performed by means of placing the tablet in 15 mL of AVF pH 4.1 in the petri plate (9 cm) and then removed at specific interval of time from the medium. The initial weight of the tablet was taken as *W0*. Then after swelling, the excess water was wiped with the blotting paper and reweighed and denoted as *Wt* was calculated. The experiment was performed thrice for all the batches. The degree of swelling was calculated by the formula given below:[13]

$$\text{Swelling \%} = \frac{Wt - W0}{W0} \times 100$$

In vitro antifungal activity

The *in vitro* antifungal assay was performed against *Candida albicans* (MCC 1558) by means of agar diffusion method. *C. albicans* strain was cultured on Sabouraud Dextrose Agar (SDA) at a temperature of 37°C. From the cultured colony, one isolated colony was then mixed with sterilized Sabouraud dextrose broth and the turbidity was adjusted to 0.5 McFarland standard with concentration of 10^8 CFU/mL. The molten SDA was filled into the sterile petri dishes and left to solidify. The 100 µL of the *C. albicans* standardized suspension was spread evenly onto the solidified SDA agar. The cups were bored using sterile cork borer. The samples (VOR plain tablet and VOR IC based tablet) were added into the cups with the volume of 1000 µL and left for 15 min and then kept in the incubator at 37°C for 24 hr. The antifungal activity of the dissolution samples (100 µL of AVF pH 4.1 containing VOR IC from the optimized tablet)

were withdrawn for every hour from the dissolution assembly, sterilized and was checked for the optimization of the drug dose. After the incubation period, the zones of inhibition were observed and measured carefully in mm. The experiment was performed thrice and zones were reported as mean±SD.[13]

HET-CAM Test

The Hen's Egg Chorioallantoic Membrane Test (HET-CAM) was performed to check the irritation potential of the prepared vaginal tablet. For this test, the fertilized eggs were incubated at 37.8 ±0.3°C and 58 ±2% humidity for 8 days and then on 9th day the eggs were removed, checked for formation of embryo using LED and then utilized for the study. The wider egg portion was exposed through removing the shell and the test samples (0.1 M NaOH as positive control, 0.9% NaCl as negative control and VOR IC tablet solution) were added. The CAM was observed for 5 min for the signs of irritation such as lysis, hemorrhage or coagulation.[22]

Stability study

The stability study was performed by placing the tablets in glass vials covered with aluminium foil and kept in stability chamber (Remi, SC-6 Plus, Vasai) with humidity condition of 75±5% RH at a temperature of 40± 2°C and 65 ±5% RH at room temperature for 6 months. After the duration of 3 and 6 months, the tablets were checked for weight of the tablet, drug content and *in vitro* drug release.[21]

RESULTS AND DISCUSSION

Solubility study

In the present study, the inclusion complex of VOR was prepared to improve the aqueous solubility of the drug. Initially, the phase solubility study was carried out to choose the suitable carrier for the solid dispersion preparation. Therefore, phase solubility studies were performed using different hydrophilic solubilizers such as Poloxamer 188, 407, Kollidone VA 64, Soluplus and HPβCD. Higher improvement in solubility was achieved with HPβCD as shown in Figure 1. The saturation solubility of the VOR and the VOR IC in AVF pH 4.1 was found to be 0.846±0.11 and 3.442±0.13 µg/mL respectively. Therefore, solid dispersion of drug with HPβCD was prepared by kneading method. The drug content was evaluated and was found to be 19.95 mg in 1:1 weight ratio of VOR IC.

SEM study

From the SEM morphological study, it was evident that the VOR IC was formed. The SEM micrographs are shown in Figure 2. The drug crystals of VOR were prismatic in shape while HPβCD crystals were spherical in shape. The physical mixture had the presence of both the crystals of drug and HPβCD while VOR IC had completely different morphology from the individual components. The particles were irregular in shape with fused homogenous agglomerate having amorphous nature. Therefore, the drug and carrier were completely mixed in a uniform manner. Further the VOR IC was introduced into the tablet formulation.

Critical tablet parameters

The present work displayed the unbeaten development of tablet formulation of VOR IC using HPMC K100 and Chitosan as the matrix polymers. In the preliminary trials, different polymers such as Sodium Carboxy methyl cellulose, Sodium alginate, Guar gum, Carbopol 934 P, Carbopol 940, Chitosan as mucoadhesive agent and HPMC of different grades (HPMC K4M, HPMC E5 LV, HPMC K100) as controlled release agent were tried. The various combinations of the polymers were tried along with VOR IC and many failures were seen and unsatisfactory precompression results were obtained. But the problem was not with polymers and later it was found that VOR IC in higher proportion was the culprit for the poor powder flow. Hence, optimizing the drug dose was an important task. The main challenge was to decide

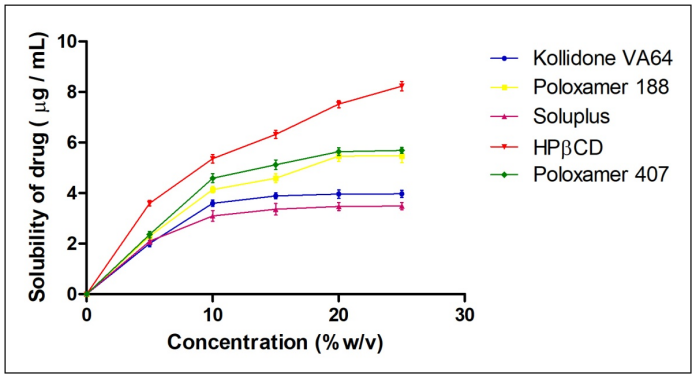

Figure 1: Phase solubility study in aqueous solution of different hydrophilic polymers.

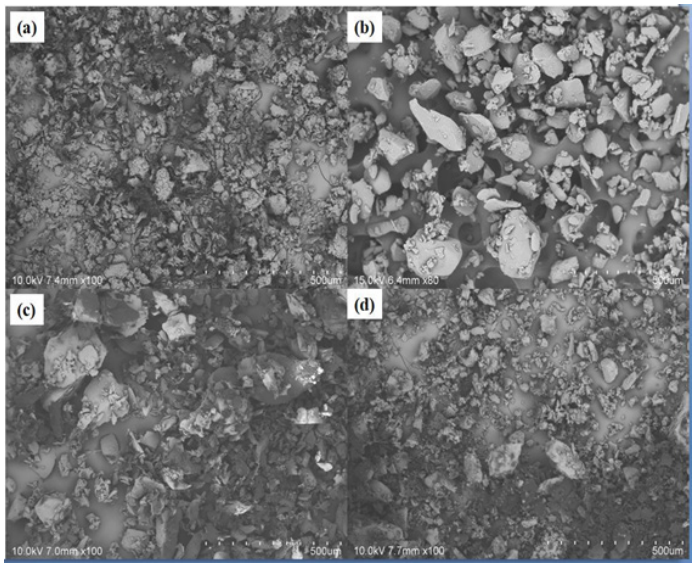

Figure 2: SEM micrographs of (a) Voriconazole, (b) Hydroxy propyl β-Cyclodextrin, (c) Physical mixture and (d) Inclusion complex.

the dose of VOR IC powder. Therefore, the dose required for the sustained release of drug for 8 hr was taken to be 20 mg. This dose was decided on the basis of the antifungal activity of VOR IC from the dissolution of the tablet in AVF pH 4.1 that showed consistent antifungal action with zone of inhibition ~50 mm for every hour as shown in Figure 3. Hence, if 100 µL of AVF pH 4.1 (containing 20 µg of drug) could cover 50 mm then the total surface area of vagina which is 100 cm^2 would require only 400 µg of drug that is necessary for the total vaginal coverage.[23] Thus, the drug dose was taken 5 times higher than the actual dose required, keeping in mind the *in vivo* performance that will vary after encounter of the tablet with the vaginal mucosa and the deep-rooted fungal pathogen. The combination of the HPMC K100 and Chitosan along with the VOR IC (50 mg) showed acceptable flow property and provided the features required for the mucoadhesive and sustained release vaginal tablet having balancing properties of swelling and mucoadhesion. Optimal swelling is vital in determining the mucoadhesion and thus if excess hydration occurs then it can reduce the adhesive force at the tablet and vaginal epithelial surface. The swelling of the tablet should allow proper mucoadhesion and present no breaking of the fragments from the tablet.[24] When HPMC K 100 was used at higher concentration there was faster hydration and the tablet integrity was lost which would not provide the sustained release effect. The reason of the breaking of tablet into fragments was due to the hydrodynamic pressure exerted by the aqueous media on the polymeric network present in the hydrated tablet structure.[24] Hence above the range of HPMC (i.e., greater than 25 mg) no increased dissolution rate or erosion was encountered. It was understood that the hydration of the tablet along with erosion resulted due to the HPMC K100 and was proportional to the concentration of HPMC K100. Hence the amount of HPMC K100 was kept between 20 and 25 mg to avoid the faster hydration. Further the higher concentration of Chitosan resulted in volume addition to the tablet. Hence the polymers concentration was then tapered by keeping in mind that matrix effect of HPMC K100 would be achievable within the range of 20-25 mg and mucoadhesion will be best with Chitosan concentration of 20-30 mg. Hence, through trial and error, the concentration of the HPMC and Chitosan were estimated.

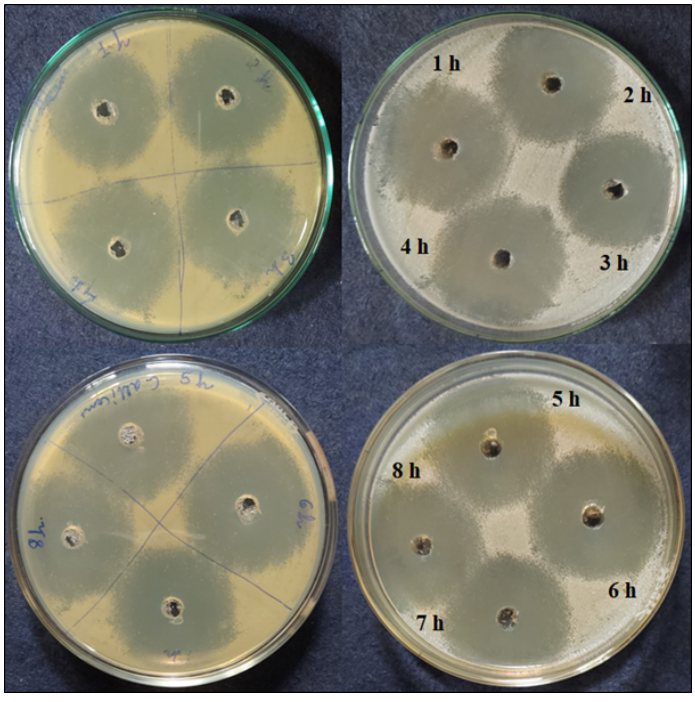

Figure 3: Image showing zone of inhibition shown by 100 µl of AVF pH 4.1 of VOR IC tablet against *Candida albicans* at different time points of dissolution.

Experimental design

To understand the optimal composition of both the polymers that will give the desirable tablet features (like swelling, *in vitro* release and mucoadhesive strength), optimization was carried out by 3^2 full factorial design. The vaginal tablets were prepared with 2 independent factors such as HPMC K100 and Chitosan and the interaction of these factors on the responses such as *in vitro* dissolution after 4 hr, 8 hr, swelling % and mucoadhesive strength were studied. The levels of both the independent variables along with the constraints are given in Table 1.

During the optimization step, constraints were added by setting the high and low limits for each of the dependent variables. The desired drug release after 4 hr and 8 hr were set with the mentioned ranges so that there must be sustained effect for 4 hr and would last upto 8 hr with maximum dissolution. The mucoadhesive strength between the range 1350 to 1675.77 dynes/cm^2 would guarantee the higher residence of the tablet in the vaginal cavity while below 1350 dynes/cm^2 there may be effect of the gravity and chances of expulsion of the tablet from the vaginal cavity and these values were considered after performing the preliminary trials for tablet. The tablets at the selected levels of swelling % showed no breaking and had adequate mucoadhesion in the trials. The swelling % within 250 to 300 would not present dryness of the vagina as confirmed through the swelling studies done from the preliminary trials and also these values are in concordant with the previous literature.[13,24] The tablet composition of all the batches according to the design are given in Table 2.

FTIR study

The interaction and compatibility of the drug and tablet excipients were studied through the FTIR spectroscopy. The results of the FTIR study are illustrated in Figure 4. The IR spectrum of pristine drug VOR showed the characteristic peaks of the groups O-H stretching, aromatic C-N stretch, aromatic C-H stretch, C-F stretch, aromatic C=N and aromatic C-C stretch in the IR region of 3197.98, 1276.88, 2978.09, 1130.29, 1408.04 and 1558.48 cm^{-1} respectively and are correspondent to the previous literature.[7] The IR spectrum of VOR when superimposed with the VOR IC and optimized tablet VT4 IR spectra for the easy characterization demonstrated no significant change of the position of the characteristic peaks of the absorption bands. Though there was

Table 1: Variables of the 3^2 full factorial design for optimization.

Independent variables	Low level	High level	
HPMC K100 (A)	20 mg	25 mg	
Chitosan (B)	20 mg	30 mg	
Dependent variables	Low limit	High limit	Goal
Drug release after 4 hr (%)	50	72.31	In range
Drug release after 8 hr (%)	90	99.82	Maximize
Mucoadhesive strength (dynes/cm^2)	1350	1675.77	In range
Swelling %	250	300	In range

Table 2: Full-factorial design based composition of vaginal tablet batches.

Ingredients	VT1	VT2	VT3	VT4	VT5	VT6	VT7	VT8	VT9
VOR IC	50	50	50	50	50	50	50	50	50
HPMC K 100	20	20	20	22.5	22.5	22.5	25	25	25
Chitosan	20	25	30	20	25	30	20	25	30
MCC PH 102	50	45	40	47.5	42.5	37.5	45	40	35
Aerosil 200	9	9	9	9	9	9	9	9	9
Magnesium stearate	1	1	1	1	1	1	1	1	1

a negligible shift in the characteristic peaks of the drug but there was no major changes observed in the absorption bands of VOR IC and the optimized tablet formulation.

Precompression parameters of the powder blend

The precompression parameters were studied for the powder blend and the results are given in Table 3. The values of all the powder parameters were within the limits and hence allowed to proceed with the tablet compression.

Physical parameters of tablet

The prepared tablets were evaluated for several parameters and the results are given in Table 4. The tablet hardness ranged between 3.1±0.15 to 3.8±0.17 kg/cm^2 for all the batch formulation. The thickness of the tablet batches was observed to be 4 mm. Friability of the tablets were found to be from 0.0035 to 0.0091%. The friability of all the tablets was below the limit of 1% which indicated the robustness and adequate strength of the tablet. The average weight of the tablets ranged between 147.92±1.9 and 149.56±0.8 mg. Weight variation for the tablets were within the limits. The drug content for all the batches were observed between 97.64±2.1 and 99.91±1.6%.

In vitro drug release

The *in vitro* dissolution studies were performed for all the tablet batches according to the experimental design runs. The effect of tablet variables such as HPMC K100 and Chitosan on the release of drug at 4 hr and 8 hr was studied. The dissolution responses are given in Table 5 while the dissolution profiles of the 9 tablet batches are depicted in Figure 5. The plain drug tablet showed lower drug release (51.67%) than VOR IC tablet batches after 8 hr of dissolution.

The dissolution data was modeled into the regression equation after the application of the design expert software for the correlation of the effect of the independent variables on the responses. The equations of regression were used for drawing conclusion after consideration of the magnitude of the coefficient. The positive sign and negative sign of the polynomial equation indicated the increment with increase in the response value and decrement with decrease in response value respectively. Effect of independent factors on *in vitro* dissolution after 4 hr and 8 hr, swelling % and mucoadhesive strength was studied through the polynomial equations.

In vitro dissolution after 4 hr = +54.59-13.69*A-0.11*B (1)

From the polynomial equation, it was concluded that the factors A (HPMC K100) and B (Chitosan) had variable effect on dissolution. For the equation (1), the A and B factors simultaneously decreased the dissolution which suggested that as the concentration of HPMC K100 and Chitosan were reduced then the % drug release was decreased. Majorly, the predominating factor was concentration of HPMC K100 that controlled the release along with lesser contribution from Chitosan. Therefore, both the terms bared the negative sign.

In vitro dissolution after 8 hr
=+95.81-6.72*A+2.18*B-0.85*A*B-10.87*A^2+3.42*B^2(2)

From the equation (2), the factor A decreased the drug release while B with positive sign increased the drug release. The

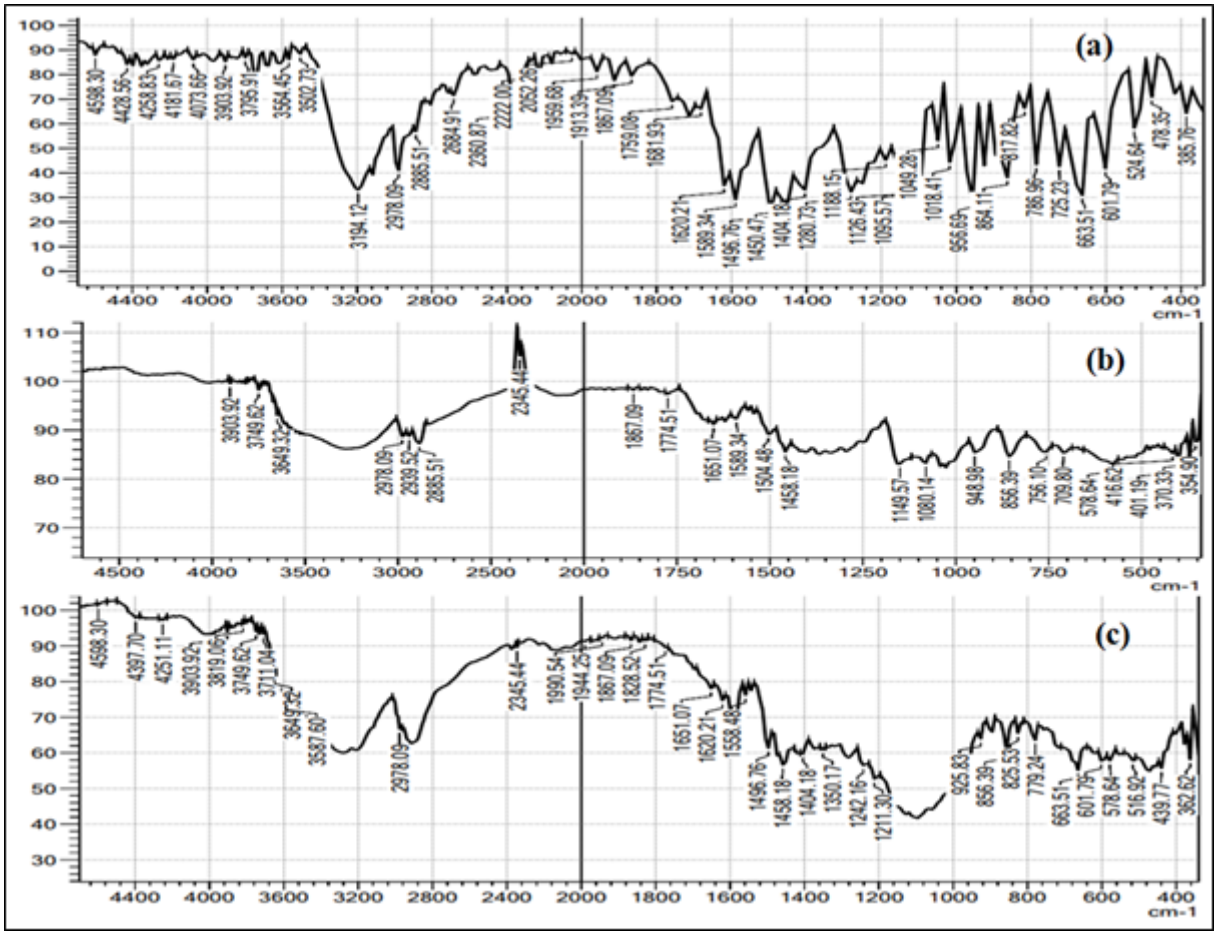

Figure 4: FTIR spectra of (a) pure VOR, (b) VOR IC and (c) Optimized tablet.

Table 3: Precompression parameters for the vaginal tablet powder batches.

Batch code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index	Angle of Repose
VT1	0.3981±0.0008	0.4644±0.0002	1.16541±0.001	14.276±1.3	34.50±2
VT2	0.4126±0.0005	0.4806±0.0003	1.16480±0.002	14.148±1.1	35.56±1
VT3	0.4137±0.0003	0.4827±0.0001	1.16600±0.002	14.294±1.2	36.01±1
VT4	0.4156±0.0002	0.4849±0.0005	1.16674±0.003	14.291±1.0	37.98±2
VT5	0.4155±0.0004	0.4848±0.0003	1.16666±0.003	14.294±1.1	36.74±2
VT6	0.4098±0.0002	0.4782±0.0004	1.16691±0.003	14.303±1.0	36.01±1
VT7	0.4095±0.0003	0.4777±0.0001	1.16654±0.002	14.276±1.0	34.57±1
VT8	0.4200±0.0002	0.4900±0.0002	1.16659±0.004	14.285±1.2	36.20±2
VT9	0.4148±0.0002	0.4839±0.0006	1.16686±0.001	14.279±1.1	36.45±1

interaction of both the factors collectively reduced the drug release. In this case also, factor A had the dominant effect of decrease over factor B for *in vitro* dissolution after 8 hr.

The % drug release after 4 hr ranged from 39.68±1.2 to 72.31±1.4% while drug release after 8 hr ranged from 77.23±1.5 to 99.82±1.1%. The dissolution data were fitted into the various kinetic models as given in Table 6 and the maximum formulation of tablets exhibited the Korsemeyer-Peppas model. The n value of 0.53 to 0.88 suggests anomalous or non-fickian transport while n>0.89 suggests super case II transport. Therefore, from the kinetics of the tablet, it was concluded that the tablets may have more than one release mechanism (transition of the polymer state along with stress release phenomenon). Generally, the hydrophilic matrix polymers such as HPMC when used in formulation give the mechanism through the disentanglement and swelling of the polymer. As the dissolution fluid proceeds towards the tablet

Table 4: Evaluation parameters of the tablet batches.

Batch code	Average weight (mg)	Weight variation (%)	Friability (%)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%)
VT1	147.92±1.9	1.1±0.2	0.0068	4	3.5±0.14	98.23±1.9
VT2	148.46±1.8	1.2±0.3	0.0054	4	3.2±0.12	98.78±1.8
VT3	148.86±1.7	1.3±0.2	0.0061	4	3.8±0.17	97.98±2.0
VT4	148.96±1.8	1.1±0.1	0.0058	4	3.7±0.19	97.64±2.1
VT5	149.56±0.8	1.2±0.1	0.0045	4	3.3±0.11	98.25±1.5
VT6	148.93±1.7	1.2±0.2	0.0091	4	3.4±0.16	99.17±1.4
VT7	149.20±0.6	1.3±0.3	0.0037	4	3.6±0.13	99.86±0.8
VT8	148.80±1.2	1.1±0.1	0.0035	4	3.1±0.15	98.74±1.7
VT9	148.73±0.8	1.2±0.1	0.0064	4	3.3±0.18	99.91±1.6

Table 5: Evaluation of tablet responses.

Batch code	*In vitro* dissolution after 4 hr (%)	*In vitro* dissolution after 8 hr (%)	Swelling %	Mucoadhesive strength (dynes/cm^2)
VT1	62.74±0.9	91.26±2.1	192.62±10	1196.68±51
VT2	55.53±2.0	96.00±1.6	276.59±9	2275.77±42
VT3	72.31±1.4	98.57±0.9	279.32±7	1186.88±52
VT4	49.10±1.4	98.98±0.3	228.51±12	1131.02±49
VT5	52.97±1.1	96.47±1.1	323.11±8	1207.57±45
VT6	52.23±1.6	99.82±1.1	297.58±9	1205.4±43
VT7	43.05±2.1	80.19±1.5	281.5±12	1165.11±46
VT8	39.72±1.5	77.23±1.5	311.23±11	2302.12±55
VT9	39.68±1.2	8.10±1.7	284.45±14	1203.22±30

matrix with a uniform speed, the increment in the thickness of the area occurs due to simultaneous swelling phenomena occuring in opposite directions with time. Hence, it was due to the relaxation of the polymer resulting from the swelling that formed the gel of HPMC polymer. The remaining other tablet batches had anomalous or non-fickian diffusion mechanism of release. Thus, it was concluded that the drug release was due to diffusion and relaxation of the polymer.

Swelling studies

$$\text{Swelling \%} = +318.36+21.39*A+21.52*B-20.94*A*B-21.93*A^2-38.15*B^2 \quad (3)$$

In the equation (3) for swelling %, the factors A and B both individually increased the swelling while the interaction between them caused reduction in swelling as observed from the negative sign. The swelling % profile of all the tablet batches is demonstrated in Figure 6.

Mucoadhesive strength

$$\text{Mucoadhesive strength} = +1546.06-19.81*A+105.45*B+4.48*A*B+68.63*A^2-322.10*B^2 \quad (4)$$

From the equation (4) of mucoadhesive strength, the effect of factor B was much more pronounced that increased the mucoadhesion while factor A lead to decrease in the response with negative sign. The joint effect of the factors caused the enhancement in the mucoadhesion.

Statistical analysis

The design equations are interpreted well by means of the 2D and 3D graphs in the form of contour and response surface plots respectively. These graphs help to analyze the effect of independent variables on the dependent variables. The effect of *in vitro* release after 4 hr, 8 hr, swelling % and mucoadhesive strength was studied through these graphical tools that are projected in Figure 7 and Figure 8. The fit statistics of all the four responses are given in

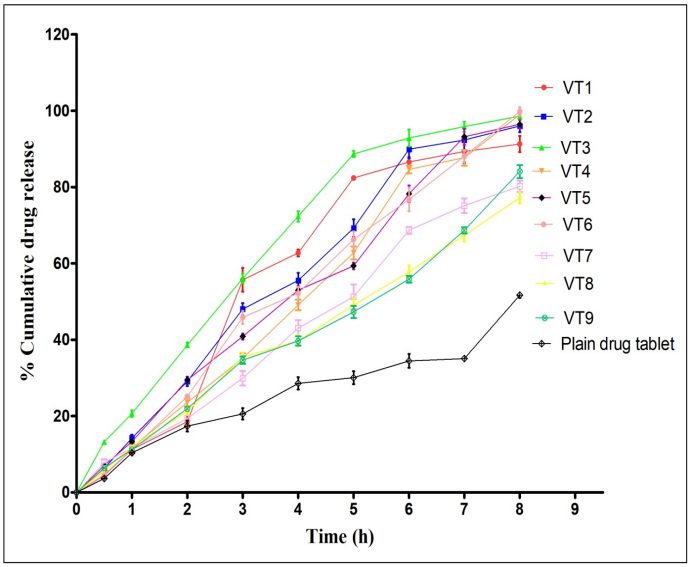

Figure 5: Release profile of vaginal tablet formulations VT1-VT9.

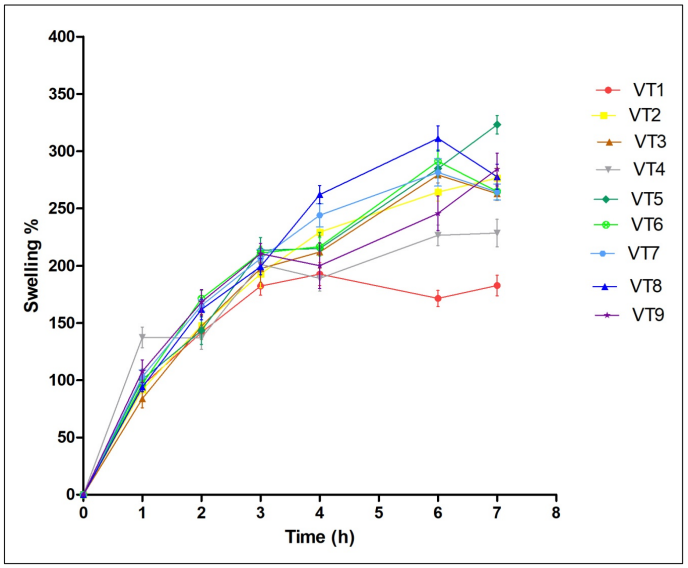

Figure 6: Swelling profile of the vaginal tablet formulation VT1-VT9.

Table 6: Dissolution kinetics analysis for the tablet batches.

Batch code	Zero order	First order	Higuchi plot	Korsemeyer-Peppas plot	
	R^2	R^2	R^2	R^2	n
VT	0.943	0.892	0.894	0.944	0.816
VT1	0.928	0.972	0.949	0.963	1.150
VT2	0.978	0.934	0.982	0.991	0.997
VT3	0.940	0.963	0.977	0.986	0.776
VT4	0.992	0.770	0.962	0.997	1.026
VT5	0.992	0.869	0.974	0.996	0.940
VT6	0.993	0.642	0.986	0.991	1.096
VT7	0.991	0.961	0.959	0.985	0.892
VT8	0.994	0.881	0.980	0.995	0.923
VT9	0.990	0.884	0.940	0.995	0.906

Table 7. The regression and it should have value greateroefficient R^2, predicted R^2 and adjusted R^2 must have a difference less than 2 that indicates the significance of the model. The adequate precision measures the signal to noise ratio and it should have value greater than 4. Thus, in all the models of responses, the difference in R^2 value is less than 2 and the adequate precision is greater than 4.

The ANOVA for the *in vitro* dissolution after 4 hr and 8 hr, swelling % and mucoadhesive strength are presented in Table 8. The results of the ANOVA had *F* value lower than *p* value that indicated that the models were significant. Hence the models were selected for the design space. For the determination of statistical significance, the probability value at the level of 0.05 was kept, that would indicate the rejection of the null hypothesis. The results depicted the factors HPMC and Chitosan has the F ratio higher than the *p* value that meant the significance on the response of *in vitro* dissolution after 4 hr and 8 hr.

SEM study of tablet

The SEM study was carried out to understand the surface tablet morphology along with the drug release mechanism from the matrix. The intact tablet VT4 before undergoing dissolution, tablet after 4 hr and tablet after 6 hr was observed for the SEM as shown in Figure 9. There was intact layer of tablet at the zero hr while in the case of 4 hr there was swelling of the polymers that lead to the formation of pores for the drug erosion. During the 6th hr, there was increment in the pore size as well as number of the pores due to further swelling of the polymers that gave the tablet matrix irregular shape.

Table 7: Fit statistics summary of the response variables.

Fit statistics	Std. Dev.	Mean	C.V. %	R^2	Adj R^2	Pre R^2	Adeq Pre
In vitro dissolution after 4 hr	3.75	54.59	6.87	0.9301	0.9068	0.8079	12.742
In vitro dissolution after 8 hr	1.77	90.71	1.95	0.9835	0.9561	0.8044	16.066
Mucoadhesive strength	46.81	1377.09	3.40	0.9775	0.9401	0.8121	13.501
Swelling %	6.16	278.31	2.21	0.9899	0.9731	0.8983	24.649

C.V.: Coefficient of Variation

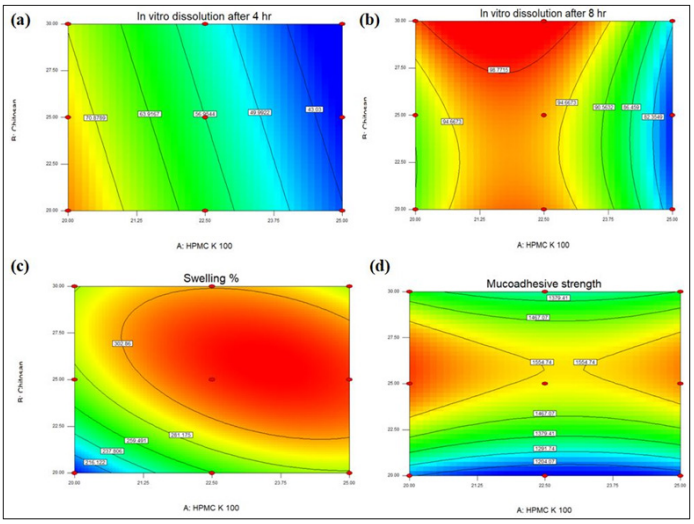

Figure 7: Contour plot for the (a) *in vitro* dissolution after 4 hr, (b) 8 hr, (c) swelling % and (d) mucoadhesive strength.

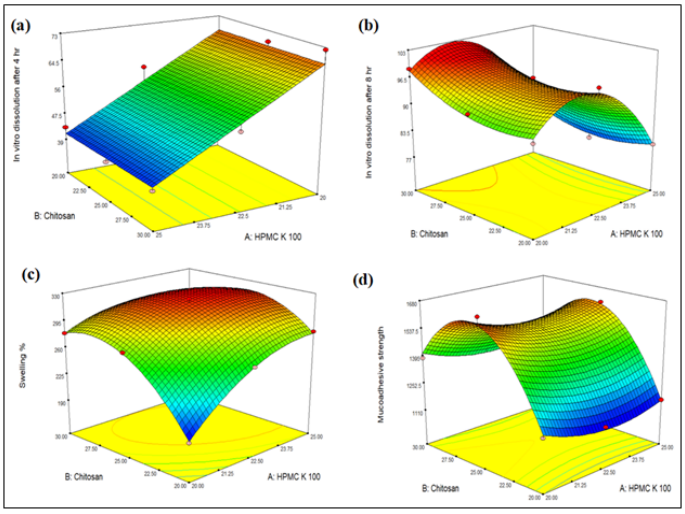

Figure 8: Response surface plot for the (a) *in vitro* dissolution after 4 hr, (b) 8 hr, (c) swelling % and (d) mucoadhesive strength.

In vitro antifungal activity

The antifungal activity against *C. albicans* was studied and the results are shown in Figure 10 with the inhibition zones for plain VOR tablet and VOR IC based tablet respectively. The antimicrobial assay of the prepared tablet was checked using the method of tablet diffusion. As the tablet is required to hydrate, 1000 µL of AVF pH 4.1 was added after the tablet was placed into the agar well before placing the plate for incubation. It was observed that there no compromise in antifungal inhibition potential and also no unconstructive effect was encountered after complexation of VOR with cyclodextrin. Significantly higher zone of inhibition was obtained with the VOR IC based tablet VT4 (34±0.3 mm) as compared to plain drug tablet (25 ±0.4 mm). The blank tablet had no drug hence showed no zone of inhibition.

HET-CAM Test

The HET-CAM assay is performed for understanding the irritant properties of any of the component or the formulation. This test is quite economic and gives the fast result in determination of the irritation. In general, the vaginal formulations should be free from the irritation. The result of the HET-CAM study is presented in Figure 11. The results presented that hemorrhage was encountered that led to blood vessel lysis in the 0.1 N NaOH treated CAM while no such events were seen during the 5 min of exposure in the case of AVF pH 4.1 and VOR IC tablet. The observed images suggested that there was no irritation from the formulated VOR IC tablet solution when applied to the CAM.

Stability study

The stability study was performed to check the variation after exposure to different conditions for 6 months. The parameters studied were weight of the tablet, drug content and *in vitro* drug release. The stability study showed that there was no considerable change in the tablet parameters at both the conditions before and after the storage tenure. The data of the stability study is given in Table 9.

DISCUSSION

The phase solubility study was performed with the different hydrophilic polymers to check the increment in solubility of the VOR and higher solubility was found with the HPβCD. The reason could be the structure aspects that render the hydrophobic interaction of the drug with the internal cavity of the cyclodextrin as a consequence of the hydrogen bonding. Thus, the inclusion complex of VOR was prepared with the HPβCD. The results are concordant with the previous literature.[7] The formation of the VOR IC was confirmed by the SEM studies that showed the complete transformation of the drug crystal after inclusion complex formation. Then the VOR IC was used for the preparation of the tablets. The mucoadhesive as well as sustained-release

Table 8: ANOVA summary of the response variables.

Source	Sum of squares	df	Mean square	F value	*p* value	Remark
ANOVA: *In vitro* dissolution after 4 hr (Linear model)						
Model	1124.30	2	562.15	39.94	0.0003	significant
Residual	84.46	6	14.08	0.9443		
Cor Total	1208.76	8				
ANOVA: *In vitro* dissolution after 8 hr (Quadratic model)						
Model	561.62	5	112.32	47.79	0.0046	significant
Residual	7.05	3	2.35			
Cor Total	568.67	8				
ANOVA: Mucoadhesive strength (Quadratic model)						
Model	2.861E+005	5	57214.35	26.11	0.0112	significant
Residual	6573.14	3	2191.05			
Cor Total	2.926E+005	8				
ANOVA: Swelling % (Quadratic model)						
Model	11150.46	5	2230.09	58.82	0.0034	significant
Residual	113.75	3	37.92			
Cor Total	11264.20	8				

p value <0.05 was considered to have significant terms and values >0.100 indicated the non-significance of the terms.

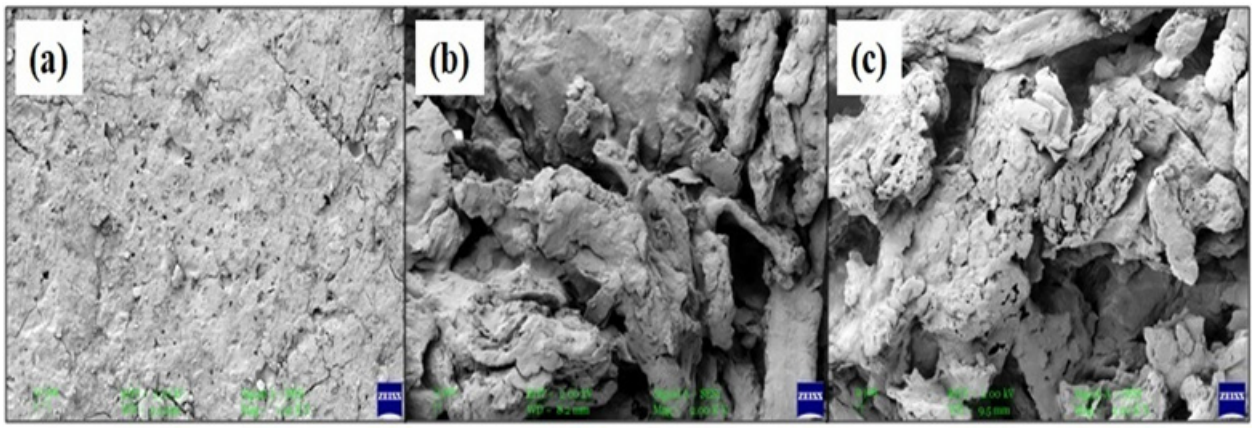

Figure 9: SEM micrographs of optimized tablet batch at 2 µm. Surface morphology of optimized tablet VT4 at (a) 0 hr, (b) 4 hr, and (c) 6 hr.

polymers were desired for the vaginal tablet to prolong the drug action at the target site for a longer period. The pre-compression parameters were studied that paved the path for the feasibility of tablet compression. The micromeritic properties of powder blends were found favorable for the tablet compression as observed from the results of the pre-compression studies. The compatibility of the drug complex with the excipients was analyzed by the FTIR studies. The VOR IC and the tablet excipients exhibited no chemical incompatibility as slight peak shifting was observed. Hence the tablets prepared did not have any untoward drug interaction with the excipients. The post-compression parameters were also studied such as hardness, friability, and thickness. The values were within the desirable limits. The optimization of the tablet was done by the design expert software and the responses were studied by the mathematical equations. The relationship between the factors (Chitosan and HPMC K100) and responses (*In vitro* release after 4 hr and 8 hr, swelling %, and mucoadhesive strength) were studied by the statistical tool such as ANOVA and the results were presented in the form of 3D response surface plot. All the models of the responses were found to be significant with $p<0.5$. The *in vitro* release study was performed to estimate the dissolution of the drug from the vaginal tablet. The inclusion complex got quickly dissolved into the AVF pH 4.1 and helped in the drug dispersion in an effective manner. For any drug to elicit the desired action, the drug must get solubilized first.[17] Thus, the formation of inclusion complex based tablet helped to overcome the dissolution issue. Generally, the hydrophilic matrix polymers

Table 9: Stability study data for the optimized vaginal tablet VT4.

Evaluation parameter	25°C and 65% RH			40°C and 75% RH		
	0 day	3 months	6 months	0 day	3 months	6 months
Weight of tablet	149.1 ±0.5	148.7 ±0.7	148.6±0.7	148.9 ±0.4	148.8 ±0.9	148.6±0.9
Drug content	99.87 ±0.7%	98.92 ±0.6%	98.86±0.6%	99.79 ±0.5%	98.65 ±0.7%	97.54±0.7%
In-vitro release %	98.98 ±0.39%	97.91 ±0.41%	97.84±0.22%	98.88 ±0.19%	97.98 ±0.25%	96.82±0.31%

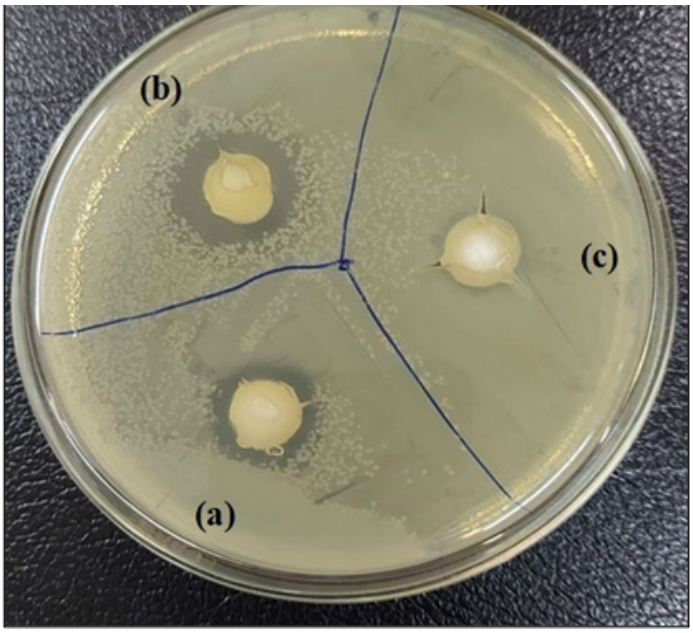

Figure 10: Microbiological assay showing antifungal activity against *Candida albicans* of (a) Plain VOR tablet (25 mm) and (b) Optimized VOR IC tablet (34 mm) and (c) Blank tablet.

such as HPMC when used in the formulation give the mechanism through the disentanglement and swelling of the polymer. The dissolution fluid proceeds toward the tablet matrix with a uniform speed and the increment in the thickness of the area occurs concerning time due to simultaneous swelling phenomena in opposite directions. The tablet formulations were subjected to swelling studies as it is connected directly with the mucoadhesion phenomena. The mucoadhesive polymers get hydrated in the aqueous environment and form a gel layer. If the hydration is excessive then the mucoadhesion potential of the tablet is reduced as a consequence of a cut-throat contest between the mucin chain of the vaginal mucus and water molecules. Since Chitosan and HPMC both are present in the tablet, the swelling was achieved from the contribution of both polymers. The tablet with a high concentration of Chitosan had a higher swelling ratio. Because Chitosan is a pH-sensitive polymer that swells when an acidic environment is provided and in this case AVF pH 4.1 as dissolution media was able to maintain the acidic condition. The mucoadhesive strength of the tablets were evaluated to check the mucoadhesion property by the modified balance method. If the mucoadhesive strength is higher, it can be assumed to have a higher residence time at the vaginal site. The mucoadhesive polymers such as Chitosan along with HPMC K 100 get triggered through the presence of moisture. Due to moisture, there is plasticization of the tablet that allows the mucoadhesive polymer molecules to unwind fully and get attached to the vaginal tissue membrane. Chitosan is a cationic molecule-based polymer and the vaginal epithelium bears the negative charge. Therefore, there is the formation of electrostatic bonding at the polymer-epithelium interface leading to mucoadhesion.[11,24-26] The SEM morphology was studied to understand the drug release mechanism from the optimized tablet during the dissolution experiment. This concluded that as the dissolution proceeded there was a formation of pores on the surface of the tablet. This caused the drug release by the erosion and diffusion mechanism both. In the initial stage, there was erosion followed by diffusion in the later stage. The results of SEM concord with the dissolution kinetic release studies. The antifungal activity of the tablet was evaluated through the microbiological screening assay. The results of the microbiological studies suggested the eligibility of the drug inclusion complex (VOR IC) for improving the antifungal effect. The inclusion complex increased the antifungal activity of the drug which is desirable for the candidal infection. Hence, imparting the drug with good solubility that would allow its enhanced antifungal activity through cyclodextrin was a straight and efficient approach. The smaller zone in the case of the plain drug-based tablet could be due to poor solubility of the VOR that led to decreased fungal inhibition. The drug in dispersed form may exert the antifungal effect promptly and therefore inhibit the fungal bioburden. When the poorly soluble drugs (such as antifungal drugs) are complexed with the cyclodextrins then the anti-fungal action is improved due to higher drug solubility. The results are following the previous literature.[6,27] The smaller zones were obtained due the intact tablet was taken for plain VOR and VOR IC and the reason could be the sustained effect due to the polymers. HET-CAM test is analogues to the vaginal signs of irritation that are lysis, coagulation or hemorrhage when exposed to the irritant substance. The tablet thus can be well tolerated when administered vaginally. The similar results were obtained in

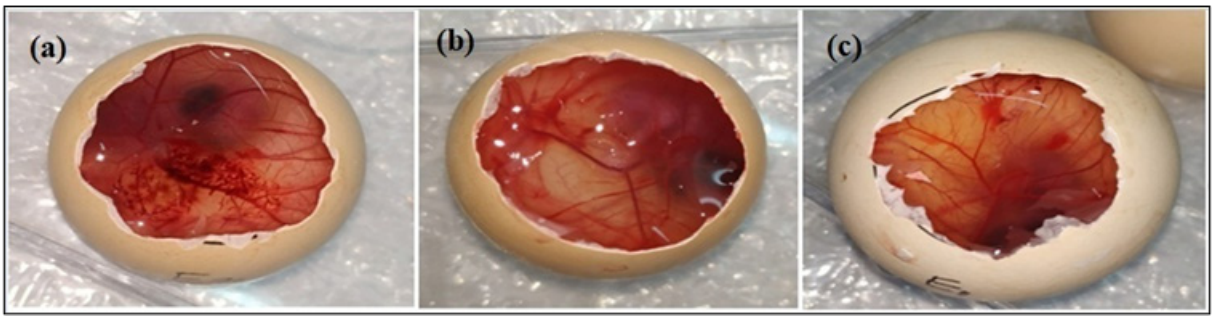

Figure 11: Images showing the vascular effects of samples (a) 0.1 M NaOH (b) Normal saline (0.9% w/v) and (c) VOR IC tablet solution applied on the chorioallantoic membrane over a period of 5 min.

the study with NLC gel of Voriconazole and Lawsone liquisolid tablet.[1,17] The currently available marketed vaginal medicated products (such as Monistat, Candid V etc.)[28] when applied frequently cause sensation of burning, redness and tingling feeling to the female patients during the course of the treatment. This occurs as a result of instant drug release from the medicament that enforces and triggers the immunogenic signal responsible for the allergic episodes.[26] Hence, the VOR IC tablet prepared would be a suitable option as compared to the marketed vaginal products in delivering the drug topically. The tablets were subjected to stability studies for 6 months and after the study duration, there were no significant changes in the tablet weight, drug release, and drug content. Thus, it was concluded that there was no instability in the tablet formulation when subjected to the accelerated testing conditions and can withstand the harsh conditions without any undesirable degradation of drug. The limitations in the formulation of the vaginal tablet are excipients that should be free from irritation, reside for longer time, deliver the drug effectively and do not cause excess hydration in the vagina after application. Hence, careful selection of the excipients that were having GRAS (generally regarded as safe) status was done that would provide the excellent performance through the dissolution, swelling and mucoadhesion. Optimizing the specific amount of the inclusion complex was another challenge in the formulation of the vaginal tablet because as the concentration of the inclusion complex was increased there was compromised flow property of the tablet powder blend. Hence, focus was made on the antifungal activity of the drug inclusion complex that would maintain the sufficient action and desirable killing of the fungal pathogen. Adjusting the concentration of the polymers and excipients was the toughest task as the desirable features were dependant on the same.

CONCLUSION

The present research work offered glorious development of the mucoadhesive vaginal tablet of the antifungal drug Voriconazole using Chitosan and HPMC K 100 as the matrix polymers. The inclusion complex of Voriconazole improved the aqueous solubility of the drug. Thus the desired drug concentrations may be achieved with low drug dose. From the initial trials, it was concluded that the concentration of Chitosan and HPMC K 100 had drastic effect on the tablet dissolution. Therefore, the optimization by 3^2 full factorial design was performed to obtain the optimum batch that could sustain the drug release upto 8 hr. The drug release mechanism was studied for all the batches by the kinetic models that confirmed the Korsemeyer-Peppas plot that prompted the drug release to be anomalous and non-fickian diffusion. The desired tablet formula was predicted by the software and the same was prepared. The mucoadhesion property would allow increased residence of the drug. The tablet was able to sustain the drug release for 8 hr with maximum drug release. The SEM study of the tablets at different interval also confirmed the same. The microbiological assay against *C. albicans* showed higher efficacy of the inclusion complex based tablet than the plain drug tablet.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

VOR: Voriconazole; **HPβCD:** Hydroxy propyl β-Cyclodextrin; **IC:** Inclusion complex; **HPMC:** Hydroxypropyl methyl cellulose; **FTIR:** Fourier transformed infrared spectroscopy; **SEM:** Scanning electron microscopy; **PM:** Physical mixture; **AVF:** Artificial vaginal fluid; **CFU:** Colony forming unit; **RH:** Relative humididty; **GRAS:** Generally regarded as safe.

SUMMARY

Local vaginal delivery is very effective for the treatment of Vaginal Candidiasis. Voriconazole is a BCS class II drug and hence to improve its solubility the inclusion complex of the Voriconazole was prepared. The prepared inclusion complex was added into the mucoadhesive tablet containing Chitosan and HPMC K 100. The FTIR study revealed no incompatibility between the drug and the excipients. The full-factorial design was used to optimize the vaginal tablet. The *in vitro* release after 4 hr, 8 hr, swelling % and mucoadhesive strength was taken as the dependent responses. The ANOVA was applied to get the polynomial equations and fit statistics confirmed that the models were appropriate. The SEM study of the tablet was done to confirm the mechanism of the tablet which illustrated the formation of pores for the drug release with erosion and diffusion mechanism. The antifungal activity against *C. albicans* showed higher zone of inhibition for the inclusion complex based tablet than the plain drug based tablet. The stability study showed no significant change in the tablet properties after storage for 6 months at 25°C and 40°C.

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