RESEARCH ARTICLE

Formulation Development of Mucoadhesive Vaginal Gel of Secnidazole and Voriconazole

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ABSTRACT

Purpose: Over the preceding decades, developing conventional drug delivery in to modified form has acquired importance in the pharmaceutical industry. Vaginal drug delivery system offers localized drug administration of drug and also avoids unwanted side effects of oral drug delivery. Vaginal drug delivery system has significant role in medical practice. Even though VDDS has a lot of advantages over the other routes of administration. The goal of developing the Mucoadhesive Vaginal Gel was to achieve the synergistic effect of voriconazole and secnidazole in the treatment of bacterial and fungal vaginal infections.

Method: Mucoadhesive antimicrobial vaginal gel was optimised using Design expert software using Carbopol 934, HPMC K4M polymers.

Result: Formulation was evaluated for various rheological parameters ,antimicrobial activity, invitro drug release and stability study. The spreadability and pH was found to be 5.5 to 7.4 cm and 4.12. Its compatible with vaginal pH. The selected optimized F8 formulation is the best formulation and the drug ratio is 2:1. and optimum gel viscosity is 1874 cps. antimicrobial study revealed that faster drug release of test formulation was compared to marketed product. It indicates as inhibition zone.

Conclusion: The combination of drugs can serves as better option for treating vaginitis, compared to single drug formulation. Mucoadesion increases contact time of drug with affected area which rendered formulation more effective.

Keywords: Muco-adhesion, Secnidazole, Voriconazole, Vaginal delivery, Vaginitis.

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INTRODUCTION

The vagina possesses a variety of defensive mechanisms for protecting against diseases. The inflammatory condition may arise from any disruption in the defensive systems. There are both infectious and non-infectious causes of vaginitis. Bacteria, fungus, or *Trichomonas* species may lead to infectious vaginitis. Vaginal infections needs to be properly treated to avoid recurrence.

Bacterial vaginosis is an infection of the vagina caused by (anaerobic bacteria) an imbalance in the normal bacterial flora which leads to vaginal epithelium inflammation (Figure 1). The majority of the time, bacterial vaginosis is asymptomatic, recurring, and can raise the risk of STDs.The common causative microbes responsible for bacterial vaginosis are *Klebsiella* spp., *Acinetobacter* spp., *Staphylococcus* spp., *Enterococcus* spp., and group B *Streptococcus*.

Symptoms of BV[(1-3)]

- pH of vagina alters (increases above 4.5)
- Increase in the vaginal discharge
- Burning sensation and fishy smell
- Stomach pain

Vulvovaginal candidiasis is yeast infections, around 90% of which cause by *Candida albicans*.[4]

Symptoms of VVC

- Burning, itching, redness
- Increase vaginal discharge

Advantages of Vaginal drug delivery system[4,5]

- Large surface area
- Rich blood supply
- Permeability to a wide range of compounds [peptides and proteins]
- by-passes first pass metabolism
- High absorption, bioavailability

The objective of present work was to develop formulation that can effectively manage vaginal infections by using secnidazole and voriconazole drugs. It inhibits the growth of *S. aureus* and *C. albicans* which is responsible for Vaginitis.[(6)]

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Bioavailability enhancement with better therapeutic efficacy and patient compliance in the treatment of bacterial and fungal vaginitis can be achieved with this formulation. The aim of this mucoadhesive dosage form was to control the release of a sufficient amount of drug for a long time in vaginal mucosa to treat bacterial and fungal infection.

MATERIALS AND METHOD

Materials

Materials used in this experiment were as follows

Senidazole and voriconazole procured from Glenmark Pharmaceuticals Ltd. R&D Center, Sinnar. HPMC K4M, Carbopol 934 Methyl paraben and Propyl Paraben -Analab Fine Chemicals, Mumbai. PEG 400 - Merck Specialities Pvt. Ltd., Mumbai.

Preparation of the Mucoadhesive Vaginal gel[7,8]

Gel formulations were prepared using polymers Carbopol 934 and HPMC K4M as gelling agents and PEG 400 as a solubility enhancer. Preparation of the mucoadesive vaginal gel (Table 1 and Figure 2).

Preparation of phosphate buffer pH 4.0 (PB pH 4.0)

Both potassium dihydrogen phosphate and disodium hydrogen phosphate weighed 3.01 and 5.04 g, respectively, and were dissolved in distilled water to yield a 1000 mL stock solution. Glacial acetic acid was used to adjust pH.

Standard curve of Secnidazole and Voriconazole using UV-spectrophotometer

Calibration of Secnidazole and Voriconazole

About 10 mg pure secnidazole and voriconazole were dissolved in 100 mL solvent (water/phosphate buffer 4 and ethanol/ phosphate buffer 4 respectively) to get a 100 µg/mL stock solution. Aliquots of 2, 4, 6, 8 and 10 µg/mL were prepared . Calibration of drug was done at 312 and 254 nm, which gave straight line equation.

Drug Excipients Compatibility Study

The compatibility study of drug and excipients was accomplished using FTIR to find out potential interaction. The peak values of pure drug were compared with the physical mixture of drug and excipients.

Physical Appearance

The formulations were inspected visually for physical attributes of formulation like appearance, color, texture etc.

pH Measurement

Using a digital pH metre, the pH of the mucoadhesive vaginal gel formulations was determined, studies were carried out in triplicate, and average values were calculated. About 5 g of the mucoadhesive vaginal gel formulation were diluted using 45 mL of water, the formed solution used for measurement of pH at 27°C.

Spreadability

The spreading diameter of mucoadhesive vaginal gel formulations were determined by placing 1 g of gel between horizontal plates for 1-minute.

Viscosity

A Brookfield Programmable DV-II + Viscometer was used to measure the viscosity (in cps) of mucoadhesive vaginal gel formulations.

Determination of Mucoadhesive Strength

The mucoadhesive strength was determined by using the modified method (Figures 3 and 4). The mucoadhesive

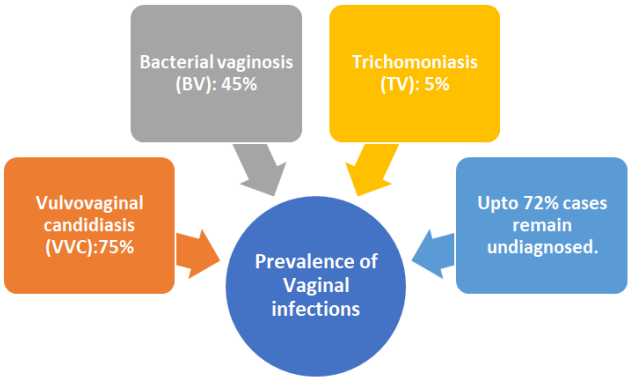

Figure 1: Global prevalence of vaginal infections

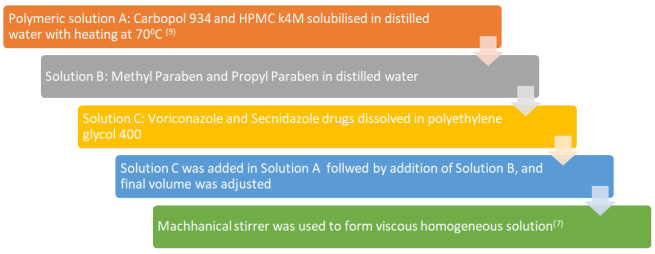

Figure 2: Outline for formulation of vaginal gel

Table 1: Composition of gel

S. No.	*Name of ingredient*	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
1	Secnidazole	2	2	2	2	2	2	2	2	2
2	Voriconazole	1	1	1	1	1	1	1	1	1
3	HPMC K4M	1	1	0.5	1.7	1	1.5	1.5	0.29	0.5
4	Carbopol 934	1.5	0.79	2	1.5	2.20	1	2	1.5	1
5	PEG 400	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

* Methyl Paraben: 0.1%; Propyl Paraben:0.05%; Water: q. s were added in all batches

Quantities are in % w/v

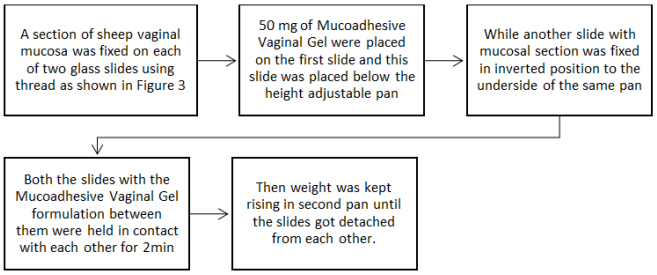

Figure 3: Procedure for determination of Mucoadhesive Strength of formulation

potential of each formulation was determined by measuring the force required to detach the formulation from the sheep vaginal mucosal tissue.

The mucoadhesive force expressed as the detachment stress in dyne/cm^2 was determined from the minimal weight that detached the mucosal tissue from the surface of each formulation.[9]

Mucoadhesive Strength (dynes/cm^2) = mg/A

Where,

m = weight required for detachment in gm,

g = acceleration due to gravity (980 cm/s^2)

A = surface area of mucosa exposed (cm^2)

Percent Drug Content

The drug content of formulation was determined by spectrophotometric analysis. Drug content was calculated using the regression analysis.

In-vitro drug release study

The drug release was estimated using Franz- diffusion cell. Phosphate buffer of pH 4.0 was used as a dissolution medium which was maintained at 37 ± 1ºC and stirred at 50 rpm. The samples withdrawn were evaluated spectrophotometrically.[10]

Antimicrobial Activity

Antimicrobial potential of optimised mucoadhesive vaginal gel formulation was determined using cup plate method, where marketed metronidazole gel and clotrimazole gel were used as reference standard for *S. aureus* and *C. albicans respectively*. About 24 hours fresh cultures of *S. aureus* and *C. albicans* were used as inoculum. In each well 0.16 gm optimised formulation and reference standard were added in inoculated nutrient agar and potato dextrose agar media. After incubation process of 24 and 48 hours, respectively formed zone of inhibition were determined and compared with standard [11]

Stability study

The stability studies of the formulated mucoadhesive vaginal gel were carried out at different temperatures i.e 5 ± 2ºC ; 30 ± 2ºC, RH 65 ± 5% for a period of 3 months. [12, 13]

(A) Modified balance assembly for mucoadhesion test (B) Tissue and vaginal gel contact in the mucoadhesion test

Figure 4: Fabricated apparatus for determination of Mucoadhesive Strength

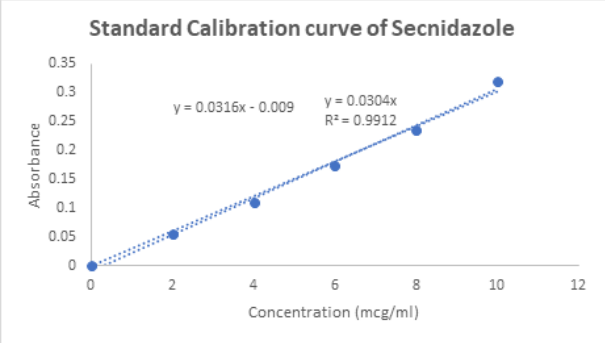

Figure 5: Standard calibration curve of secnidazole

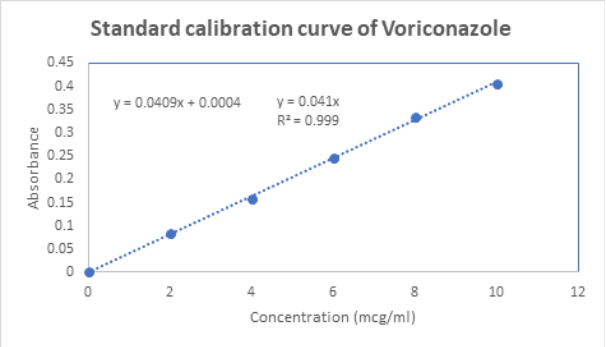

Figure 6: Standard calibration curve of voriconazole

Table 2: pH, spreadability and viscosity

Formulation No.	*pH*	*Spreadability (cm)*	*Viscosity (cps)*
F1	4.08 ± 0.16	6.16 ± 0.057	2039.3 ± 1.15
F2	3.94 ± 0.13	7.46 ± 0.057	773.66 ± 1.15
F3	4.16 ± 0.21	6.43 ± 0.11	1885.3 ± 1.52
F4	4.13 ± 0.28	7.2 ± 0.1	1221.6 ± 2.88
F5	4.12 ± 0.1833	5.4 ± 0.2	3901.6 ± 2.88
F6	3.98 ± 0.13	5.9 ± 0.1	862 ± 2
F7	4.21 ± 0.20	5.43 ± 0.11	4315 ±
F8	4.06 ± 0.16	7.16 ± 0.05	3935 ± 2
F9	4.09 ± 0.24	7.4 ± 0.1	281 ± 1.732

* Readings are taken in triplicate

Table 3: Muco-adhesive strength, Drug Content

Formulation No.	*Mucoadhesive Strength (dynes/cm^2)*	*%Drug content*	
		Secnidazole	*Voriconazole*
F1	1786.26 ± 42.37	97.74 ± 1.359	94.57 ± 3.30
F2	1824.87 ± 58	98.44 ± 1.440	96.89 ± 1.09
F3	1821.55 ± 59.39	96.36 ± 0.839	92.24 ± 3.74
F4	1789.95 ± 57.90	99.653 ± 0.306	93.023 ± 1.22
F5	1781.14 ± 66.37	93.583 ± 1.266	93.026 ± 0.32
F6	1832.4 ± 39	97.05 ± 0.549	89.92 ± 1.33
F7	1814.8 ± 22.6	90.12 ± 2.47	96.12 ± 1.89
F8	1795.36 ± 25	91.16 ± 1.540	89.92 ± 1.64
F9	1835.4 ± 43	93.583 ± 1.916	88.37 ± 0.66

*Readings are taken in triplicate

RESULT AND DISCUSSION

Calibration Curve of Drugs Showing Acceptable Regression Range

UV calibration of secnidazole and voriconazole

The calibration curve of drugs showing acceptable regression range which confirmed linearity (Figures 5 and 6).

Physical appearance

The formulation batches F1-F9 checked visually for physical appearance and also for physical parameters like pH, spreadability, viscosity and mucoadesive strength (Tables 2 and 3).

In-vitro drug release

The %drug release of secnidazole and voriconazole mucoadhesive gel was found to be 98.95 and 100% after 2 hours (Figures 7 and 8).

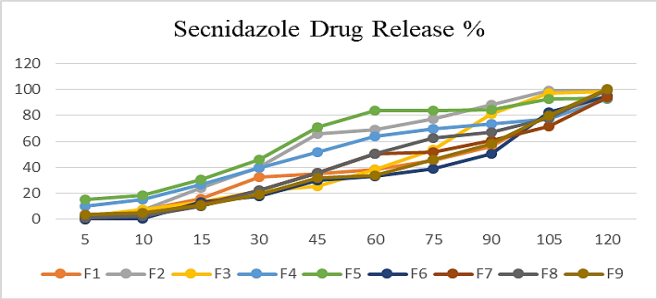

Figure 7: Drug release from mucoadhesive gel from F1-F9

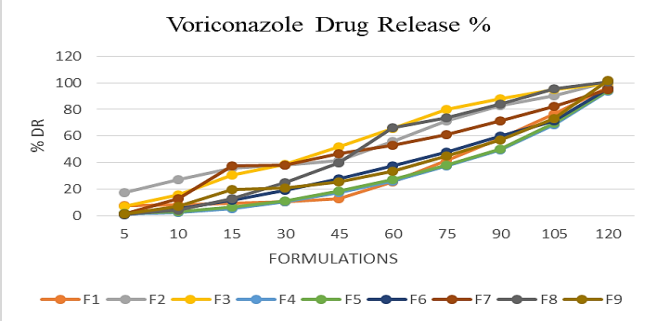

Figure 8: Drug release from mucoadhesive gel from F1-F9

(a) (b)

Figure 9: (a) Determination of antibacterial activity of optimized gel; (b) Determination of antifungal activity of optimized gel

Table 4: Antibacterial and antifungal activity of optimized vaginal gel compared with marketed formulation

Bacterial Species	*Zone of inhibition in (mm)*	
	Optimized formulation	*Marketed metronidazole gel formulation*
S. aureus	15.53 ± 2.30	14.43 ± 2.15
Fungal species	*Zone of inhibition in (mm)*	
	Optimized formulation	*Marketed clotrimazole gel formulation*
C. albicans	15.34 ± 2.24	14.12 ± 2.11

Antimicrobial activity

The antimicrobial activity on selected bacterial and fungal culture is shown in Figure 9 and Table 4. The comparable values of zone of inhibition for optimized formulation were observed to that of marketed formulations.

Stability testing

The stability studies of the formulated gel were carried out at 5 ± 2°C and at a temperature 30 ± 2°C, RH 65 ± 5%for a period of 3 months. This study shows F8 formulation was stable. The samples were analysed for pH, spreadability, drug content at predetermined time interval. The results showed that there was no significant change found in stability after 3 months.

DISCUSSION

The formulation of the gel used in this investigation was made with different concentrations of HPMC K4M, propylene glycol, and carbopol-934. Finalisation based upon evaluation parameters (pH, spreadability, drug content, drug diffusion) results.

HPMC K4M is a good adhesive property. viscosity depends upon the polymer concentration. Concentration of polymer showed positive impact on viscosity of formulated gel. In 2 hours drug release study the time interval increases the %drug release also increases.

Drug release study of various formulations prepared are shown in Figures 3 and 4. It was found that the drug release from mucoadhesive vaginal gel formulation was influenced by varied amount of the polymers added into the gel.

Formulation F8 was found optimized as it showed better results compared to other formulation. The optimised batch of mucoadhesive vaginal gel was evaluated for selected physical parameters, drug release study and mucoadhesive strength.

Based on selected evaluation parameters, the F8 formulation comprising of HPMC (0.29%) and Carbopol 934 (1.5%) was selected as optimized secnidazole and voriconazole mucoadhesive vaginal gel formulation.

The pH of optimised secnidazole and voriconazole mucoadhesive vaginal gel was determined to be 4.12 ± 0.01, which is suitable to minimise the possibility of vaginal irritation. Mucoadhesive gel shown good Spreadability diameter 7.16 ± 0.05 cm in 1-minute. The %drug release of secnidazole and voriconazole mucoadhesive gel was found to be 98.95 and 100% after 2 hours. The optimised secnidazole

and voriconazole mucoadhesive vaginal gel was showed potential antimicrobial activity by cup plate method.

In stability study, formulation shows stability at different temperature conditions i.e 5 ± 2°C and 30 ± 2°C for period of 3 months with no significant change in selected parameters.

CONCLUSION

Secnidazole and voriconazole drugs were successfully formulated in mucoadhesive vaginal gel. The results proved that spreadability, viscosity and %drug released were mainly affected by the concentration of polymers in the formulation. In present study F8 formulation comprises of secnidazole and voriconazole shows the optimum drug release and satisfactory muco-adhesive properties.

Thus, the study proves the mucoadhesive gel showed good mucoadhesion time for more than 5 hours. The present study of secnidazole and voriconazole gel may increase patient compliance as well as effectiveness of topical treatment.

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