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Formulation and Evaluation of Bioadhesive Vaginal Gel for Mixed Vaginal Infections

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ABSTRACT

The objective of our study was to formulate and evaluate bioadhesive gel for mixed vaginal infections. The combination of voriconazole and metronidazole were selected as model drugs for mixed vaginal infections. The bioadhesive gels were prepared with different ratios carbopol934. These bioadhesive gels was were characterized for Fourier transform infrared, content uniformity studies, *in vitro* bioadhesive studies, pH determination, spreadability test, extruability and *in vitro* release study in simulated vaginal fluid. The cumulative percent release of metronidazole from gels was found to be 55.10% and voriconazole was 68.90 % at the end of 7th hour. Among all the formulations F1 was found to be having good spreadability and viscosity with good *in vitro* release characteristics. All the performed experiments confirm the applicability of bioadhesive gels for the local treatment of mixed vaginal infections.

Keywords: Carbopol, Mixed vaginal infections, vaginal gel

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INTRODUCTION

Mixed vaginal infection can be caused due to infection of two or more pathogens in vagina[1].The bacterial vaginosis, vaginal candidiasis and vaginal trichomoniasis are the three common infections. In case, of such mixed vaginal infections, it's impossible for a single drug to cure all the infections. The combination of drugs will be helpful to provide complete treatment and to increase patient compliance. The vagina, as a site of drug delivery, offers certain unique features that can be exploited in order to achieve desirable effects[2].The vaginal route can be used as a favorable site for local and systemic delivery of drugs that can be used specifically for female related conditions the vagina provides a promising site for local infections[3]. Conventional formulations for vaginal delivery includes vaginal tablet, creams, foams, pessaries, gels and vaginal rings that are designed to disperse drug throughout the vaginal tract[4]. These vaginal formulations are required to have a long residence time to complete the treatment drugs. These vaginal formulations are associated with limitations such as poor retention, leakage and messiness there by causing inconvenience for users. This decreases the patient's compliance and they tend to discontinue the treatment. This may be also a major reason for poor acceptability and usefulness of vaginal dosage forms. To avoid these limitations, the bio-adhesive polymers are used in vaginal formulation that adheres to vaginal mucosa for long time[5]. To overcome these limitations, formulations that adhere to vaginal mucosa for a sufficient period of time need to be developed. Bioadhesion and prolonged retention are desirable characteristics can be built in vaginal formulation by the use of bioadhesive polymers. Bioadhesive vaginal gels have several advantages which include wide acceptability, feasibility and low cost. Therefore, in this present work the combination of metronidazole and voriconazole bioadhesive gels were prepared and evaluated for different parameters. The metronidazole is an antibacterial and antiprotozoal drug which is used as a first line drug for vaginal bacterial infections. The voriconazole is an effective antifungal drug which is used for vulvo vaginal candidiasis treatment. The bioadhesive polymer carbopol 934 was used to prepare vaginal gel. The bioadhesive polymer helps the gel to adhere to the vaginal mucosa and deliver the drug slowly.

MATERIALS AND METHOD

Metronidazole was the gift sample obtained from KAPL (Bangalore).Voriconazole was the gift sample from Ranbaxy. Carbopol 934P from loba chemie (Mumbai).All the other chemicals and solvents used in the experiments were of analytical grade.

Preparation of Carbopol 934 Gel

For the preparation, 1% w/w of Carbopol 934 P was dispersed in distilled water containing glycerol and methyl paraben by vigorous stirring. Triethanolamine was added with stirring till a transparent clear gel was formed. The part of plain gel was added to the drug solution with gentle stirring to produce smooth layer of gel. The rest of the gel is added gradually with constant stirring till homogeneous dispersion is obtained[6].Different other concentration of carbopol gels was also prepared in the same procedure. The formulation chart is shown in table number 1.

Table 1: Formulation chart of Bioadhesive gels

Ingredients	F1	F2	F3	F4
Metronidazole	100 mg	100 mg	100 mg	100 mg
Voriconazole	100mg	100 mg	100 mg	100 mg
Carbopol 934	0.5 g	1.0 g	1.5 g	2.0 g
Triethanolamine	1 ml	1 ml	1 ml	1 ml
Glycerol	10 g	10 g	10 g	10 g
Methyl paraben	0.1 g	0.1 g	0.1 g	0.1 g
Water QS	100 ml	100 ml	100 ml	100 ml

Drug excipients compatibility studies

The FTIR spectra of the sample were obtained using FT-infrared spectrophotometer (Spectra 1000, Perkin Elmer Japan.) by KBr pellet method. The position of the peak in FT-IR spectra of pure metronidazole and voriconazole is compared with those in FT-IR spectra of drugs plus excipients.

Determination of drug content in prepared gels

The bioadhesive gel was analyzed for drug content, by taking 100 mg of formulation in 100 ml volumetric flask. The drugs were extracted by adding 20 ml of methanol and water mixture (1:1) was added to volumetric flask and shaken well. Further, the volume was made with the same solution and then diluted to 100 ml with water. The supernatant was filtered and measured. The drug content was determined by simultaneous estimation measuring the absorbance at 256 nm for metronidazole and 320 nm for voriconazole using UV- spectrophotometer (Shimadzu-1601, Japan).

Determination of viscosity

The viscosity of gel was determined by using a Brookfield viscometer DVII model with a T-Bar spindle[7]

pH determination

Weighed 50 gm of each gel formulation were transferred in 10 ml of beaker and measured it by

using the digital pH meter.

Determination of spreadability

Spreadability of all the formulations was determined by an apparatus suggested by Multimeret al[8]

Extrudability study

The closed collapsibletube containing about 20 grams of the gel was pressed firmly at the crimped end and a clamp was applied. The cap was removed and the gel was extrudes until the pressure was dissipated[9]

***In vitro* bioadhesion testing**

The vaginal gels were tested for bioadhesion properties using modified two-armed balance[10].*In vitro* bioadhesion studies were carried out using sheep vaginal mucosa.

***In vitro* diffusion studies of gels:**

The *in vitro* release of metronidazole and voriconazole from different gel base was determined by dialysis method. Prior to diffusion studies, the dialysis tube was soaked overnight in water. The hydrated membrane was used for diffusion study. 1 gm of gel was kept in a dialysis membrane, which was sealed on both sides; the dialysis tube was then placed in glass beaker containing 20 ml simulated vaginal fluid. The release studies were performed at 37□C for different time interval (from 1-7 hr.) 5 ml of recipient solution was withdrawn at 1 hour interval and replaced with an equal amount of fresh media to maintain sink condition. Samples were analyzed for metronidazole and voriconazole by UV-spectrophotometer after appropriate dilution against blank.

RESULTS AND DISCUSSION

The carbopol gel containing voriconazole and metronidazole were successfully prepared. The FTIR studies revealed that there were no interactions between the polymer and the drugs. The FTIR study report is presented in figure 1-3. The IR stretching of pure metronidazole showed 3364,3024,2855,1517 and 720 cm^{-1} wave number as major peaks. The voriconazole showed 3209, 2829, 1181 and 1534 cm^{-1} wave number as major peaks. The results revealed no considerable changes in the IR peaks of metronidazole and voriconazole when mixed with excipients compared to pure metronidazole and voriconazole. The drug content studies show that the drugs were in the range of 96.25 to 98.45.Viscosity of all the four formulations were studied using brookfield viscometer. The viscosity was found to be in the range 38758.30 to93240.01 cps. The viscosities was found to be increased as the concentration of the polymer increased. pH

of the solution was found to be in the range of 6.5 to 6.8.The *in vitro* bioadhesive strength tests was in the range of 5.50±0.98 to 32.82±1.02.As the concentration of polymer increased the bioadhesive strength found to be increased. Spreadability test were studied on all four formulations. This is an important test for all semisolid dosage forms. It helps patient for easy and uniform application of gel to the skin. The *in vitro* drug diffusion studies were carried out and it relieved that as the concentration of polymer increases, the drug release was found to be decreased. F1 was found to release 55.1 % of metronidazole and 68.9 % of voriconazole at the end of 7th hour.

Table 2: Table showing drug content, viscosity, pH, bioadhesive strength spreadability and extrusion.

Spreadability

Formulation No	Drug content	Viscosity in cps	pH	Bioadhesive strength	Spreadability	Extrudability
F1	96.25±0.15	38758.30	6.8	5.50±0.98	12.02	**
F2	98.54±0.9	66440.00	6.9	15.80±1.22	11.56	***
F3	97.0±0.12	78462.37	6.8	24.91±1.08	11.05	**
F4	98.45±0.07	93240.01	6.6	32.82±1.02	10.92	**

*** Excellent

** good

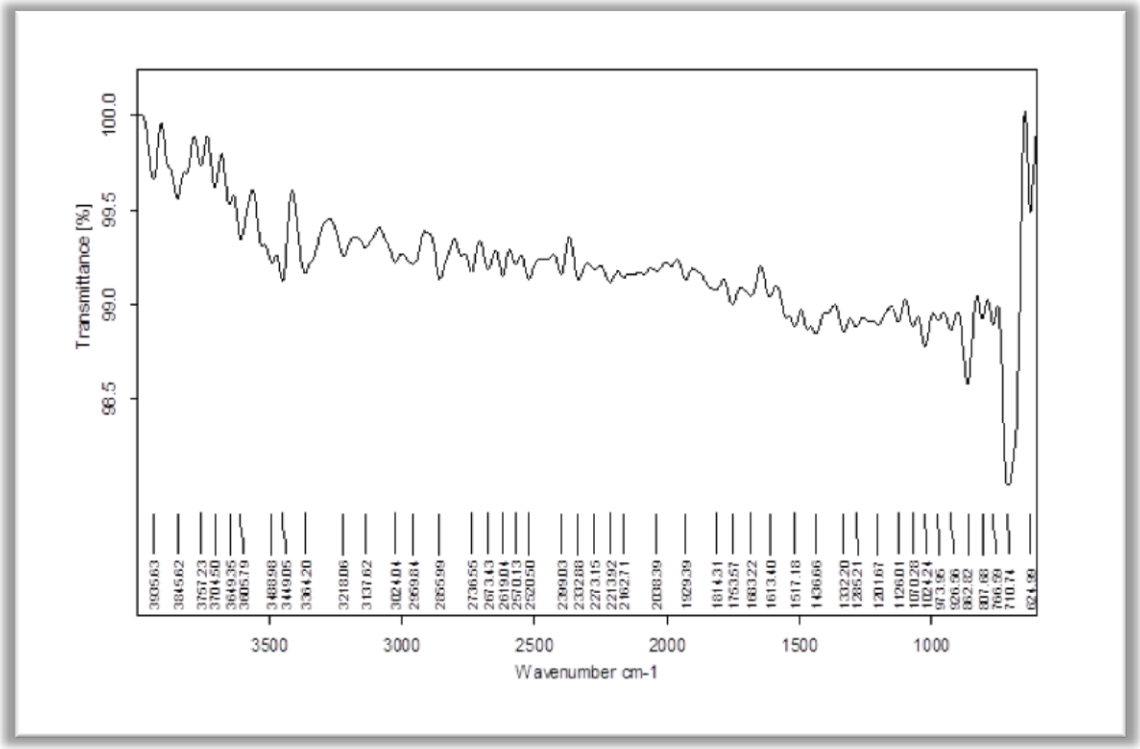

Figure 1: FT-IR spectra of pure drug metronidazole

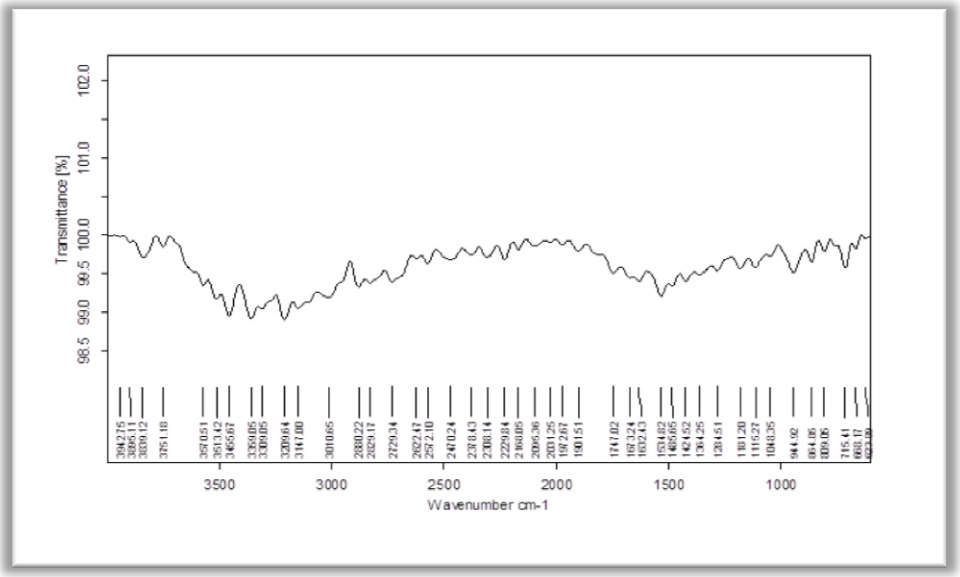

Figure 2: FT-IR spectra of pure drug voriconazole

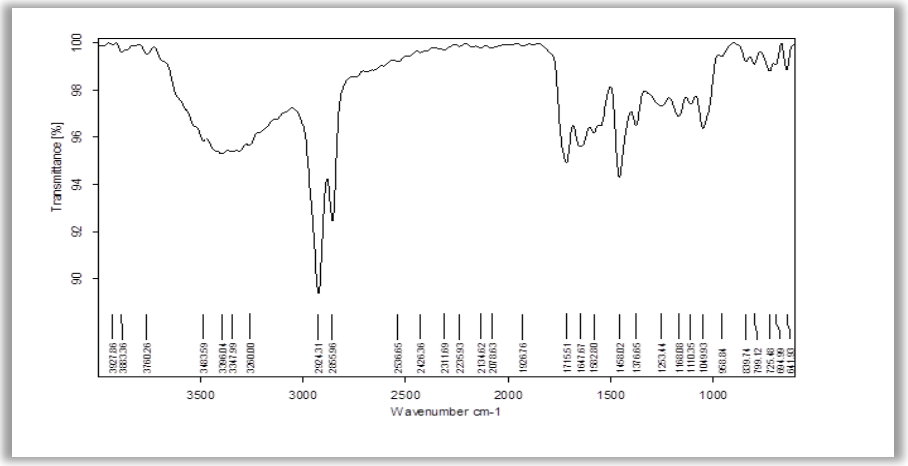

Figure .3: FT-IR spectra of pure drugs and excipients

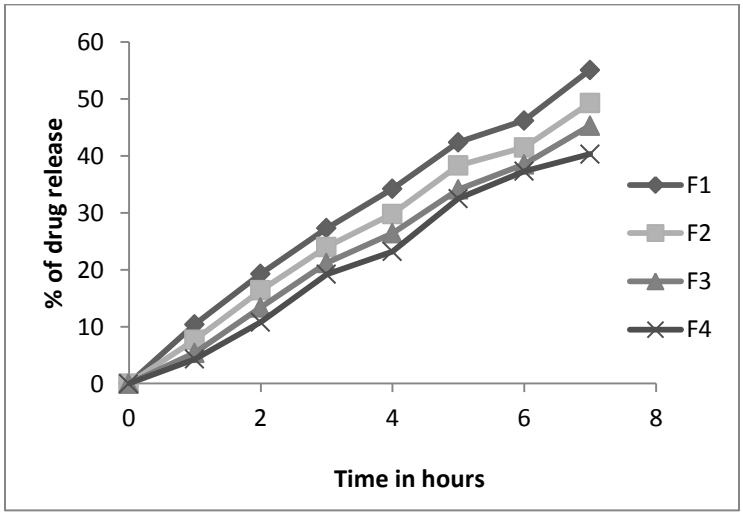

Figure 4(A): *In vitro* release of metronidazole

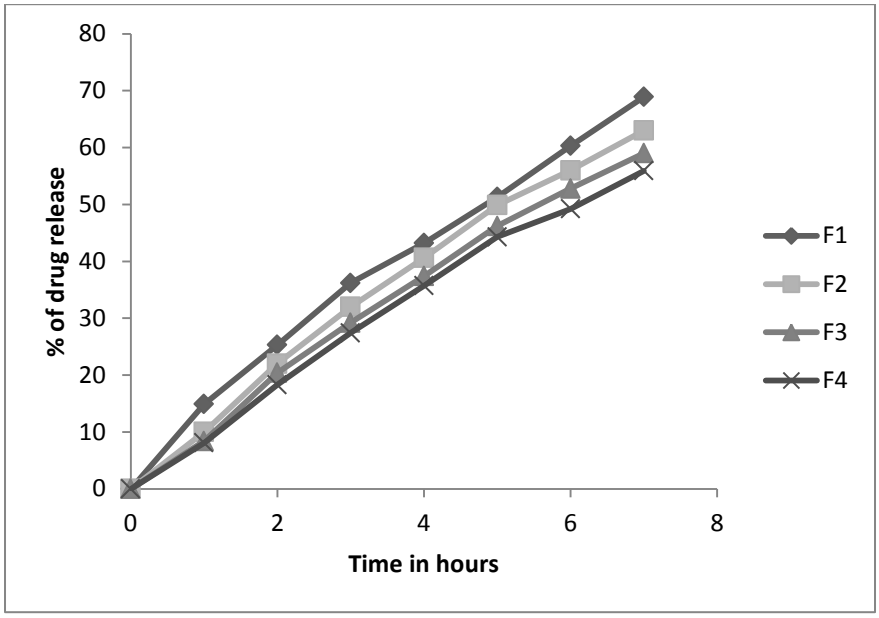

Figure 4(B): *In vitro* release of voriconazole

CONCLUSION

The bioadhesive gels containing metronidazole and voriconazole were prepared successfully and bioadhesive gels were found to be transparent, attractive with all the desired characteristics. Among all the formulations F1 was found to be having good *in vitro* release. From the results it can be concluded that these bioadhesive gels can be a promising dosage form for patients suffering from mixed vaginal infections.

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