# Formulation and Evaluation of Bioadhesive Vaginal Gel for Treatment of Vaginal infections

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**Abstract**

Vaginal infections cause severe inflammation of vagina, itching, thick yellow discharges, odour and irritation. The causes for infection may be an allergic reaction to an irritating substance, a low level of estrogen after menopause etc. Infectious causes of vaginitis include bacterial Infections, Candida infection and trichomonas infection. The aim of the present work is to formulate a gel with a bioadhesive polymer for bioadhesion and retention for extended period of time. The anti fungal drug, Miconazole nitrate gels are formulated using bioadhesive polymers such as carbopol 934, and HPMC in different ratios. The formulated gels were studied for content uniformity, viscosity, bioadhesive strength, effect of flow rate and *in vitro* diffusion studies. It was found that with increase in flow rate, drug release was also increased. It may be concluded that the gel formulation is simple, easy to administer with increased patient acceptance for the treatment of vaginal infections.

**Keywords:** Miconazole nitrate; Bioadhesion; Gels; Vaginal infection; HPMC.

## INTRODUCTION

The term bioadhesive refers to the attachment of a drug delivery system to a specific biological site. This biological site can be epithelial tissue, or even the mucous membrane on the surface of a tissue. A bioadhesive system is defined as a substance that can stick to a biological membrane and remain on it for a long time[3-5].

Local and systemic delivery of drugs through the vaginal route is a desirable site that can be used in conditions related to women. The vaginal cavity is used for local delivery of drugs such as prostaglandins, steroids, antibiotics, antifungals, antivirals, antiprotozoal and spermicidal agents[6-8].

Vaginal infections may be caused by the following conditions: allergy to stimulants, irregular estrogen levels after menopause, foreign particles or other infections. Infectious causes of vaginitis include bacterial infections, Candida infections and Trichomonas

infections. Miconazole nitrate is an effective anti-fungal medication, widely used in the treatment of fungal and yeast infections[2].

## MATERIALS & METHODS

### Preparation of carbopol 934 gel

Required quantity of carbopol 934 was weighed and added to distilled water to get desired concentration of 1%, 1.5%, 2% respectively. The mixture was stirred gently and allowed to soak for 2 hr. Then required quantity of triethanolamine added to form gel. Miconazole Nitrate (1gm) was added and stirred till it gets dissolved[12].

### Preparation of HPMC gel

Required quantity of HPMC was taken and added to distilled water slowly by stirring to get desired concentration of 3.5 %, 4.0 %, 4.5 % respectively. Miconazole Nitrate (1gm) was dissolved in small amount of ethanol. Then above solution was added to polymer solution and stirred to get clear gel[13].

**Table 1. Formulation chart of Bioadhesive Gels**

| Formulation Code | INGREDIENTS | | | | |
|---|---|---|---|---|---|
| | Carbopol 934P% w/w | HPMC % w/w | Triethanolamine % w/w | Glycerol % w/w | Water |
| **F1** | 1 | - | 1 | - | Q.S. |
| **F2** | 1.5 | - | 1 | - | Q.S. |
| **F3** | 2 | - | 1 | - | Q.S. |
| **F4** | - | 3.5 | - | - | Q.S. |
| **F5** | - | 4.0 | - | - | Q.S. |
| **F6** | - | 4.5 | - | - | Q.S. |

*1 g of Miconazole nitrate was used in all formulations.*

**Determination of drug content**

The prepared formulations were analyzed for drug content. The drug content was determined by measuring the absorbance at 272 nm using UV-spectrophotometer.

**Determination of viscosity**

The viscosity of prepared formulations werecarried out by using Brookfield viscometer. The carbopol gel viscosity was measured using spindle No.10 at 100 rpm, which was maintained at $30^{o} \pm 1^{0}$C. The HPMC gel viscosity was measured using spindle No.93 (T- bar spindle) at 6 rpm.

***Invitro* bioadhesion testing**

*Invitro* bioadhesion study was carried out using goat vaginal mucosa and modified two-armed balance. The beaker on one side of the balance was counter balanced by using suitable weights on the other side. A circular piece of goat vaginal mucosa was fixed to the tissue holder with cyanoacrylate adhesive and was immersed in distilled water and temperature was maintained at $37^{0}$C $\pm$ $1^{0}$C. Then the gel was placed on the vaginal mucosa by using a preload of 50 g and kept it aside for 5 min to facilitate adhesion bonding. After preloading time, the preload was removed and the water was allowed to flow into the beaker kept on the other side of the balance at the flow rate of 1 drop / sec until the gel detached from the vaginal mucosa. The weight required to detach gel from vaginal mucosa was noted[14].

***IN VITRO* DRUG RELEASE STUDIES**

The dialysis tube was used for diffusion studies. Pre stabilisation was done by soaking dialysis tube overnight in water. The hydrated membrane was utilised 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 water. 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 hr interval and replaced with an equal amount of fresh water to maintain sink condition. Samples were analyzed for Miconazole nitrate by UV-Spectrophotometer[15].

**Effects of flow rate on release of drug from gels**

The effect of flow rate on release of drug from gels has been carried out.

**RESULTS AND DISCUSSION**

**Drug – Excipient compatibility studies**

The compatibility between the drug and polymer was compared by FT-IR spectra. It was observed that, there was no interaction between drug and polymer (Figure 1, 2 & 3).

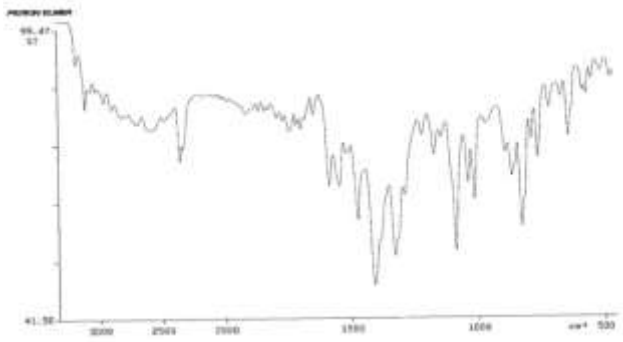

**Figure 1. FT-IR Spectra of pure drug Miconazole nitrate**

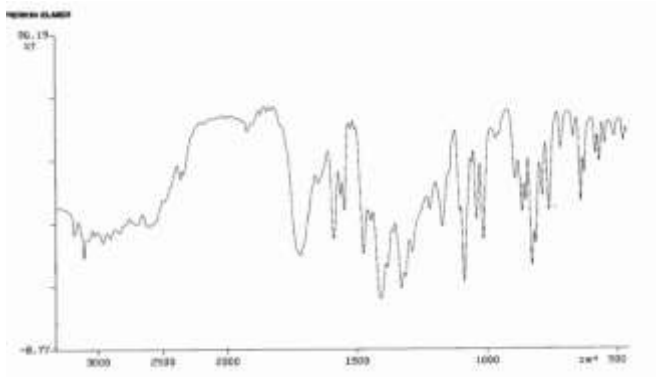

**Figure 2. FT-IR Spectra of drug + Carbopol 934**

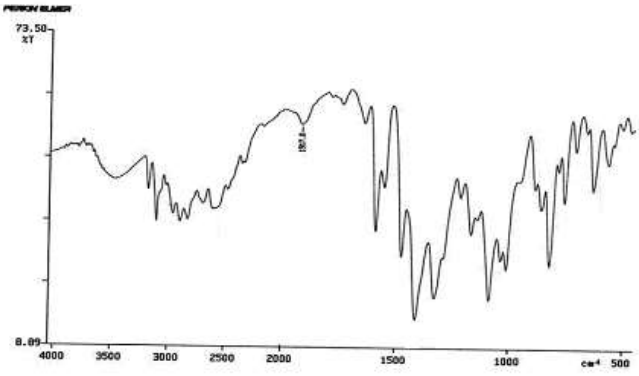


**Figure 3. FT-IR Spectra of drug + HPMC**

**Determination of drug content of gel formulation**

The prepared gel formulations were analysed for drug content and the data is reported in Table 2. It was observed that the drug was uniformly distributed in all the formulations, with small deviation.

**Table 2. Result of drug content (mg/100ml) of gel formulation $F_1$-$F_6$.**

| Sl. No. | Formulation Code | Drug Content (mg/ gm) | | | |
|---|---|---|---|---|---|
| | | Trial I | Trial II | Trial III | Mean ± S.D* |
| 1 | $F_1$ | 19.82 | 20.05 | 19.61 | 19.82±0.24 |
| 2 | $F_2$ | 20.24 | 20.33 | 20.05 | 20.20±0.12 |
| 3 | $F_3$ | 19.93 | 20.26 | 19.81 | 20.0±0.18 |
| 4 | $F_4$ | 19.86 | 19.94 | 20.06 | 19.95±0.20 |
| 5 | $F_5$ | 19.81 | 20.26 | 20.04 | 20.03±0.18 |
| 6 | $F_6$ | 19.62 | 19.74 | 19.91 | 19.75±0.12 |

*Standard deviation, n = 3

**Determination of Viscosity**

The viscosity of all the formulations was determined by using Brookfield digital viscometer DV-II+. The carbopol gel viscosity measurement was carried out using spindle No. 10 at 100 rpm, which was maintained at $30^o \pm 1^0$C. The HPMC and Sodium CMC gel viscosity measurement was carried out using spindle No.93 (T- bar spindle) at 6 rpm, which was maintained at $30^o \pm 1^0$C.

It was observed that with increase in concentration of carbopol 934P, Na.CMC and HPMC, the viscosity also increased.
The data is reported in Table 3.

**Table 3. Results of viscosity studies in (cps) of gel formulation $F_1$ – $F_9$.**

| Sl. No. | Formulation Code | Viscosity in cps | | | |
|---|---|---|---|---|---|
| | | Trial I | Trial II | Trial III | Mean ± S.D*. |
| 1 | $F_1$ | 11498 | 11480 | 11459 | 11479 ±15.93 |
| 2 | $F_2$ | 16890 | 16841 | 16974 | 16901±54.92 |
| 3 | $F_3$ | 22175 | 22151 | 22132 | 22152±17.59 |
| 4 | $F_4$ | 5650 | 5624 | 5638 | 5637±10.62 |
| 5 | $F_5$ | 7689 | 7650 | 7698 | 7679±20.83 |
| 6 | $F_6$ | 9429 | 9490 | 9520 | 9479±37.86 |

| | | | | | |
|---|---|---|---|---|---|
| 7 | $F_7$ | 4145 | 4198 | 4179 | 4174±21.92 |
| 8 | $F_8$ | 6548 | 6539 | 6598 | 6561±25.95 |
| 9 | $F_9$ | 8984 | 8847 | 8942 | 8924±57.3 |

*Standard deviation, n = 3.

***In vitro* bioadhesive testing**

Invitro bioadhesion testing for both blank and drug-loaded gels was evaluated by separation force measurements of the gel from sheep vaginal mucosa. The strong interaction between both blank and drug-loaded formulations with the mucous layer of the tissue helped to increase the contact time and allow localization.

Increasing the concentration of the polymer increased the bioadhesion strength. The effect of hydration on adhesion was observed. Hydration of the mucoadhesion polymer is essential for initiating the mucoadhesion bonding process. Cohesive force is generated when water is absorbed from the space between the mucosa and the polymer; this plays a vital role in establishing an effective mucoadhesion bond.

The mucoadhesive strength of Carbopol gels (F1-F3) was found to be 60-70 g, while HPMC gel formulations (F4-F6) showed maximum mucoadhesive strength of 68-87 g.

The mucoadhesive capacity of the selected formulations followed the pattern of HPMC gel > Carbopol gel. It was observed that with increase in polymer concentration, the mucoadhesive capacity also increased (Table 4 & Table 5).

**Table 4. Results of bioadhesive strength of Formulations F1-F3.**

| **Formulation Code** | **Bioadhesive Strength (gms)** | | | **Mean ± S.D*** |
|---|---|---|---|---|
| | Trail I | Trail II | Trail III | |
| F1 | 62 | 58 | 61 | 60.33±2.08 |
| F2 | 64 | 62 | 65 | 63.67±1.52 |
| F3 | 71 | 69 | 70 | 70.00±1.00 |

* Standard deviation (n=3)

**Table 5. Results of bioadhesive strength of Formulations F7-F9.**

| **Formulation Code** | **Bioadhesive Strength (gms)** | | | **Mean ± S.D*** |
|---|---|---|---|---|
| | Trail I | Trail II | Trail III | |
| F4 | 68 | 69.5 | 67 | 68.17±1.25 |

| | | | | |
|---|---|---|---|---|
| F5 | 74 | 76 | 77.5 | 75.83±1.75 |
| F6 | 86 | 89 | 88 | 87.67±1.52 |

* Standard deviation (n=3)

The results of bioadhesive strength are given in Tables 4 and 5. Formulation F6 showed higher bioadhesive strength compared to all other formulations.

## *IN VITRO* DRUG RELEASE

The data of in vitro release study were quantified using PCP-DISSO-V2.08 software developed by Industry Institute Partnership Cell (IIPC) of Poona College of Pharmacy, Poona. This software was used to determine the percentage of drug release and the release mechanism. It was also used to fit various mathematical models and determine the best model. The results showed that the drug release was found to be first order in all the formulations. The results are shown in Table 9.

From the release data of different formulations, it was observed that the concentration of polymer significantly affected the percentage of drug release. With the increase in polymer concentration, the drug diffusion also decreased accordingly.

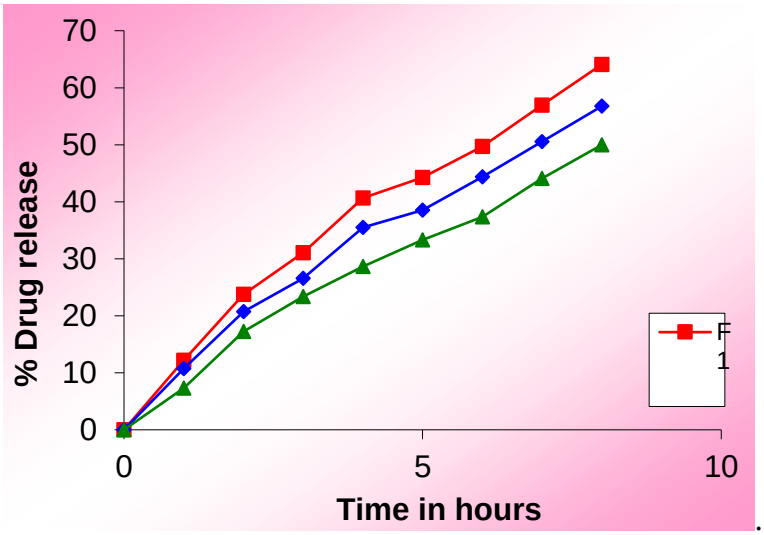


**Figure 4. *In vitro* diffusion profile of gel formulations F1, F2 & F3.**

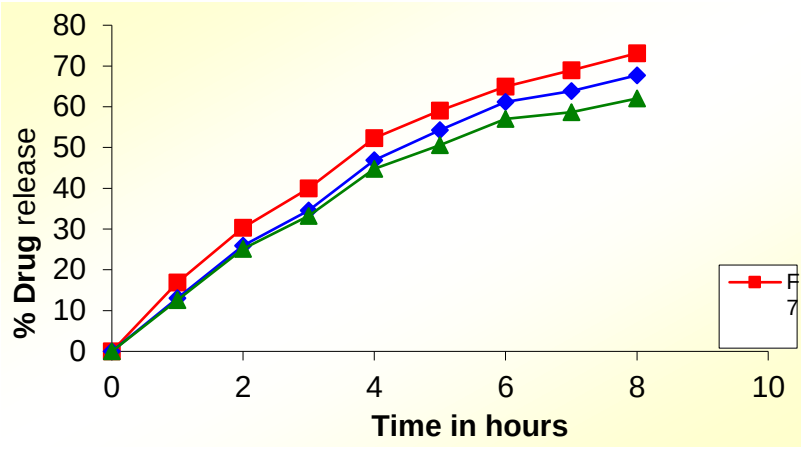


**Figure 5. *In Vitro* diffusion profile of formulations F4, F5 & F6**

**Effect of flow rate on release pattern from gels**

The effect of flow rate on gel was studied to know about the pattern of drug release from the gel. The formulations F3 and F6 were selected for the study based on diffusion studies data. The data obtained is shown in Figure 6 & 7.

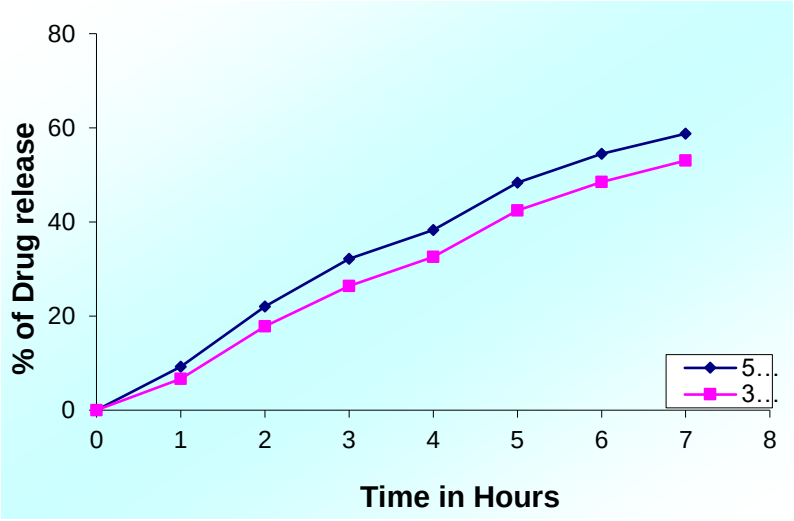


**Figure 6. Effect of flow rate over drug release from carbopol gels.**

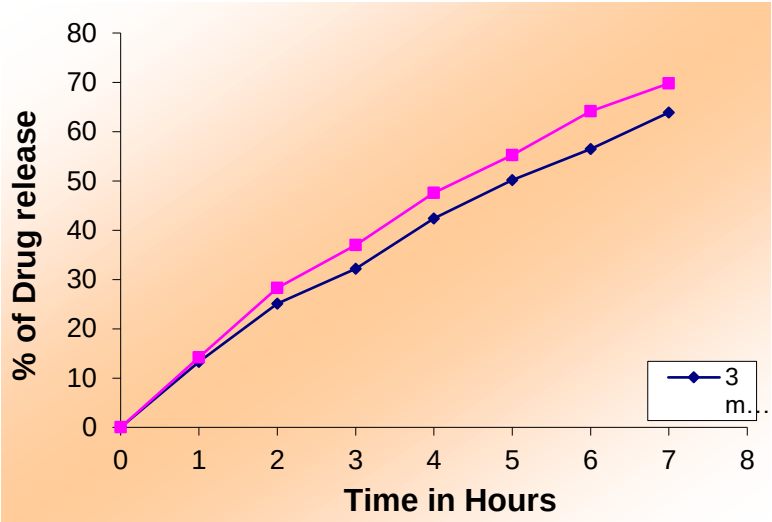


**Figure 7. Effect of flow rate from HPMC gels**

## CONCLUSION

The main objective of the present study was to formulate and evaluate gel based vaginal drug delivery systems containing miconazole nitrate. These formulations were prepared using various bioadhesive polymers such as Carbopol 934 and HPMC in different proportions. The prepared gels were evaluated for various parameters such as compatibility studies, drug content, viscosity, bioadhesive strength, effect of flow rate on drug release and in vitro drug release studies. From the results of the present experimental work, it can be concluded that the use of the gel formulation is easy, simple and comfortable, and patient compliance is also better. Hence, it can be concluded that bioadhesive gel based vaginal drug delivery system is a novel approach for the treatment of vaginal infections.

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