



Formulation Design and Evaluation of Hydrogel-Based Metronidazole Bioadhesive Tablet for Vaginal Candidiasis

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Abstract

Hydrogel-Based Metronidazole Bioadhesive Tablet (HMBT) was prepared as a novel vaginal delivery system to achieve Controlled release of drug from the tablet for vaginal candidiasis. The highly swollen hydrogel were prepared by dissolving chitosan in acetic acid solution containing drug, followed by neutralisation with sodium hydroxide and characterized by SEM, DSC and FT-IR and evaluated for % swelling. The drug loaded hydrogels were incorporated into tablet formulation by dry granulation method using bioadhesive polymers such as HPMC, sodium CMC and guar gum in different ratios. HMBT was tested for drug content, hardness, friability, weight variation, thickness, swelling studies, in vitro drug release, bioadhesive strength, in vivo studies and antifungal activity. The FT-IR and DSC spectra's revealed that there was no chemical interaction between drug and polymers used. SEM revealed that particles of hydrogels appeared small and irregular shaped with large numbers of pores. F3 formulation shows good in vitro release profile with highest bioadhesive strength. From the in vivo study in rabbit it was found that the HMBT hold the tablet for more than 12 hours inside the vaginal tube. It may be concluded from present study that HMBT can be used as a novel delivery system for local therapy of vaginal candidiasis which can controlled the release of drug for prolong period of time.

Keywords : Antifungal activity, Bioadhesive Tablet, candidiasis, Hydrogel, Metronidazole; vaginal.

1. Introduction

The vagina remains a relatively unexplored route of drug delivery in humans despite the potential to be used as a noninvasive route of drug administration [1]. In addition, the vaginal route offers numerous advantages as a localized site for drug de-

livery due to convenient access, prolonged retention of formulations, an extensive region for drug permeation, high vascularization, a relatively low enzymatic activity, the avoidance of gastrointestinal and/or hepatic firstpass metabolism, and the possibility of self-administration of single-dose drug delivery systems that may suffice in releasing drugs over a period of weeks or months and simultaneously provide optimum drug pharmacokinetic profiles [2-4]. Traditionally, the vaginal cavity has been used for the delivery of locally acting drugs such as antibacterial, antifungal, antiprotozoal, antiviral, labor-inducing and spermicidal agents, prostaglandins and steroids [5]. Vaginal candidiasis is

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a common condition and up to 75% of all women suffer at least one episode of this infection during their lifetime. *Candida albicans* j1012 is the most important cause of vaginal candidiasis, accounting for over 80 % of the infection. For the treatment of vaginal candidiasis, local antimicrobial administration of metronidazole has been favoured due to the numerous side effects, toxicity, and teratogenic potential of the systemically applied drugs [6].

Tablet formulations are more likely to be accepted by patients because of the ease of administration. Several vaginal tablets formulations have been developed for the delivery of therapeutic agents. (Metronidazole, Ketoconazole, Clotrimazole, Nystatin, Progesterone, Acriflavine)[5]. During the last three decades, considerable attention has been focused on the development of novel and controlled release drug delivery systems to provide a long-term therapeutic concentration of drugs following a single dose [9]. Bioadhesive vaginal tablet formulations that are capable of delivering the active agent for an extended period at a predictable rate have been recently developed and studied [10]. Many controlled release drug delivery systems are based on hydrogels [9].

Hydrogels are three dimensional hydrophilic polymer networks capable of swelling in water or biological fluids and retaining a large amount of fluids in the swollen state [11]. Hydrogels may undergo a swelling-driven phase transition from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse.

To form stabilizing linkages, hydrogel polymers have functional moieties that allow binding between the chains to prevent gel dissolution. Polymer binding is accomplished either by non-covalent physical associations, such as secondary forces (hydrogen, ionic, or hydrophobic bonding) and physical entanglements, or by covalent cross-linkages [12]. Both methods can sufficiently restrain hydrogel swelling, but

the physical associations are reversible bonds, whereas the covalent crosslinkages between polymer chains are not.

These hydrogels, when placed in an aqueous environment, are able to swell rapidly and retain large volume of water in their swollen structure. These formulations are highly biocompatible. The rate of drug release from these formulations is regulated by controlling cross-linking density. An increase in cross-linking density results in a decrease in both the volume swelling and the rate of drug release [9]. The polymers hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, sodium alginate, and xanthan and guar gums have good stability at pH 3 to 10 and, hence, are good candidates for vaginal delivery systems (pH 4 to 4.5) [13].

The main goal of this research was to design and evaluate a novel hydrogel based metronidazole bioadhesive tablet (HMBT) to achieve controlled release of drug for prolong period of time for the local treatment of vaginal candidiasis.

2. Materials and Methods

2.1. Materials

Metronidazole was a gift from KAPL (Bangalore, India). Chitosan was obtained from Sigma-Aldrich, USA. HPMC, SCMC and Guar gum were obtained from Loba Chemie, Mumbai and all other chemicals used were of analytical grade.

2.2. Simulated Vaginal Fluid pH 4.5

Simulated vaginal fluid (SVF) was prepared from 3.51 g/l Sodium chloride, 1.40 g/l Potassium hydroxide, and 0.222 g/l Calcium hydroxide, 0.018 g/l bovine serum albumin, 2 g/l lactic acid, 1 g/l acetic acid, 0.16 g/l glycerol, 0.4 g/l urea, 5 g/l glucose. The pH of the mixture was adjusted to 4.2 using 0.1M Hydrochloric acid [6].

2.3. Preparation of Chitosan Neutral Hydrogel & Bioadhesive Tablets

Direct therapeutic loading into the hydrogel is accomplished by encapsulation, during which the polymer chains are cross-linked in the presence of the drug. 10 g of chitosan powder was dissolved in 200 ml of 4% w/v of acetic acid aqueous solution containing metronidazole [14] followed by filtration to remove insoluble material. The chitosan solution was then brought to pH 10 by the addition of 10% w/v sodium hydroxide aqueous solution at room temperature. The precipitate was collected by filtration followed by extensive rinse [15] and dried at 50°C for overnight. After drying, crushed the hydrogel and passed through sieve #60. Prepared chitosan hydrogel was incorporated into tablet, containing bioadhesive polymers such as HPMC/SCMC/Guar Gum in combination & different ratio, by dry granulation method. Six formulations were prepared by varying the ingredients as shown in table 1.

2.4. FT-IR Analysis

The FT-IR spectra of the samples were obtained ascertain the compatibility between metronidazole and the se-

lected polymers using FT-Infrared Spectrophotometer (Shimadzu-8400 S, Japan) by KBr pellet method in the wave number range 600-4000 cm^{-1} . The samples were diluted with KBr and then compressed into a tablet, 10mm in diameter and 3 mm in thickness, using a manual tablet presser (Techno search) at 300 kg/cm for 1 min.

2.5. Differential Scanning Calorimetry (DSC) studies

Thermograms of MTZ and MTZ-loaded hydrogel were obtained using a DuPont thermal analyzer 2010. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder samples were hermetically sealed in perforated aluminum pans and heated at constant rate of 10 °C/min over a temperature range of 25 to 300 °C. The system was purged with nitrogen gas at the rate of 100 ml/min to maintain inert atmosphere.

2.6. Hydrogel Swelling Study

The hydrogels were allowed to swell in the SVF pH 4.5 at 37°C for 24 h. From time to time the weight of the hydrogels was checked in an electronic balance after wiping the hydrogel with filter paper. The degree of swelling (Wt) was calculated at

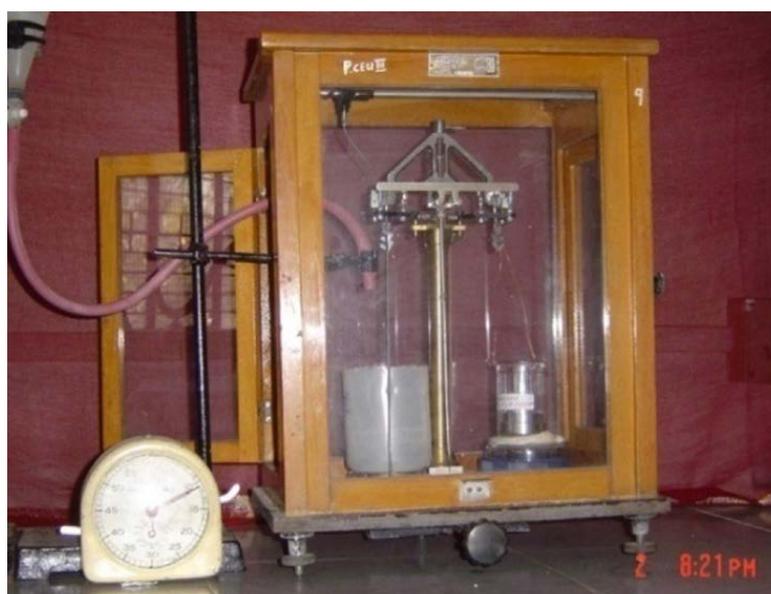


Figure 1. Modified balance for bioadhesion measurement.

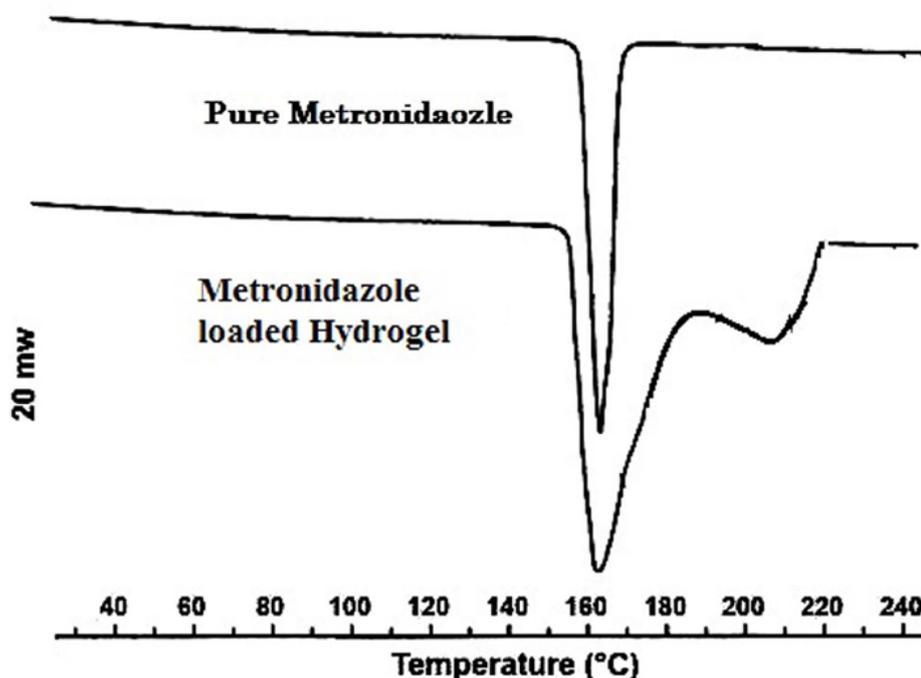


Figure 2. DSC curve of pure metronidazole and metronidazole loaded hydrogel.

different times by means of following expression:

$$W_t = \frac{\text{Weight of swollen hydrogel} - \text{Weight of dry hydrogel}}{\text{Weight of swollen hydrogel}} \times 100 \quad (1)$$

The extent of equilibrium swelling of a hydrogel was reached when the weight of the swollen hydrogel was constant. All the experiments were performed in triplicate and the mean values were taken considering the coefficient of variation within the range [16].

2.7. Drug Content for Hydrogel

100 mg of hydrogel was taken and transferred to 100ml volumetric flask, diluted with SVF. The absorbance of the resulting solution was measured at the maximum at about 320nm using UV spectrophotometer.

2.8. Scanning Electron Microscopy

SEM photographs were taken with a scanning electron microscope Model Joel-LV-5600, USA, at the required magnification at room temperature. The photographs were observed for morphological characteristics of the hydrogel.

2.9. Average Drug Content

Tablets of each formulation were crushed in a mortar to a powder form. A quantity of powder equivalent to 100 mg of Metronidazole was taken and transferred to 100ml volumetric flask, diluted with SVF. The absorbance of the resulting solution was measured at the maximum at about 320nm using UV spectrophotometer [11].

2.10. Tablet Parameters

The bioadhesive tablets prepared were evaluated for various tests like thickness, diameter, average weight, hardness, and percentage friability of prepared tablets [12].

2.11. Tablet Swelling Study

Swelling characteristics of bioadhesive tablets were evaluated dynamic swelling studies. Each tablet was weighed and then placed in 10 ml SVF in a petridish at $37 \pm 0.5^\circ\text{C}$. The tablets were periodically weighed after removing the excess water on the surface with a filter paper:

$$\text{swelling (\%)} = \frac{W_t - W_i}{W_i} \times 100 \quad (2)$$

Where W_t is weight of the swollen tablet at time t , and W_i is initial weight of the

Table 1. Formulation chart of bioadhesive tablets.

Formulation code	Hydrogel containing Metronidazole (mg)	HPMC (mg)	Sodium CMC (mg)	Guar gum (mg)	Magnesium stearate (mg)	Di-calcium phosphate (mg)
F1	300	100	50	-	10	40
F2	300	100	60	-	10	30
F3	300	100	70	-	10	20
F4	300	100	-	50	10	40
F5	300	100	-	60	10	30
F6	300	100	-	70	10	20

*Weight of the each tablet = 500mg

tablet [10].

2.12. Determination of In Vitro Mucoadhesive Strength

The apparatus used for *in vitro* mucoadhesion studies is shown in figure 1. *In vitro* mucoadhesion studies were carried out using sheep vaginal mucosa and modified two-armed balance. Sheep vaginal mucosa was fixed to steel piece with cyanoacrylate adhesive. This was kept in a beaker and prewarmed solvent was added into the beaker up to upper surface of the mucosa to maintain mucosal viability. The tablet compressed was attached to the upper clamp with adhesive. The beaker was then slowly raised until the substrate comes in contact with the tablet. A preload of 50g was placed on the clamp for 5 min (preload time) so that the adhesion could be established. After this time, the preload was removed and water was added into the beaker at a constant rate of 100 drops/min. The addition of water was stopped when mucoadhesive system was detached from mucosa. Weight required to detach the system from mucosa was noted. Experiment was repeated with fresh mucosa in an identical manner [17].

2.13. In vivo X-ray studies

The animal experiment project was cleared and approved by Institutional animal

ethical committee, J.S.S. College of Pharmacy, Mysore. The study was performed on a healthy female rabbit, weighing between 1.5 and 2 kg. F3 was selected as optimized formulation as bioadhesive strength of F3 was good compare to F6 in order to study in vivo performance of the preparation. F3 formulation was modified by using hydrogel loaded with x-ray grade barium sulphate instead of MTZ. The prepared tablet was placed in the vagina of a healthy rabbit. During the study, the rabbit was not allowed to eat or drink. The rabbit was exposed to X-ray examinations and photographs were taken at 1st and 12th h after administration of the tablet.

2.14. In Vitro Drug Release Studies

Release studies were carried out using USP dissolution apparatus I (Basket type). 500 ml of SVF pH 4.5 was used at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ with 100 rpm to mimic the vaginal conditions. 5 ml of the sample was withdrawn at suitable time interval and the same volume was replaced with pre-warmed fresh dissolution media. The sample withdrawn was diluted to suitable volume and analyzed by UV spectroscopy at 320 nm [10].

2.15. In Vtro Antifungal Activity

Antifungal activity of Metronidazole bulk powder, HMBT and placebo tablet was evaluated against *Candida albicans* j1012 by using a cup plate method. A volume of 20 ml of sterilized agar media was dispersed into

Table 2. Evaluation parameter for formulations.

Formulation code	Avg. weight (mg)	Thickness (mm)	Hardness (Kg/ cm ²)	Friability (%)	% Drug content*
F1	498.3	3.3±0.16	5.5±0.66	0.23±0.033	99.1±0.11
F2	499.5	3.44±0.13	6.6±0.38	0.222±0.015	97.5±0.16
F3	500.7	3.35±0.18	6.2±0.81	0.291±0.045	98.6±0.27
F4	502.2	3.29±0.13	4.3±0.31	0.31±0.044	99.5±0.18
F5	498.9	3.4±0.11	4.8±0.45	0.297±0.056	99.5±0.53
F6	501.5	3.36±0.10	5.4±0.16	0.382±0.018	98.6±0.41

three different sterilized petridishes and allowed to solidify. In each petridish a 8mm bore was made using borer at the centre of petridish. Each bore was loaded with equal quantity of the Metronidazole bulk powder, HMBT and Placebo tablet (tablet without the drug). Petridishes were incubated at temperature of 37°C for 24 h to allow the growth of microorganisms to take place. Zone of inhibition produced by the Metronidazole bulk powder and HMBT towards test organism

was measured (mm) in the petridish and photographed.

3. Results and Discussion

Chitosan is a natural polycationic copolymer consisting of glucosamine and N-acetylglucosamine units. It is mostly obtained by deacetylation of chitin derived from the exoskeleton of crustaceans. Chitosan has valuable properties as a biomaterial because it is considered to be biocompatible, biodegrad-

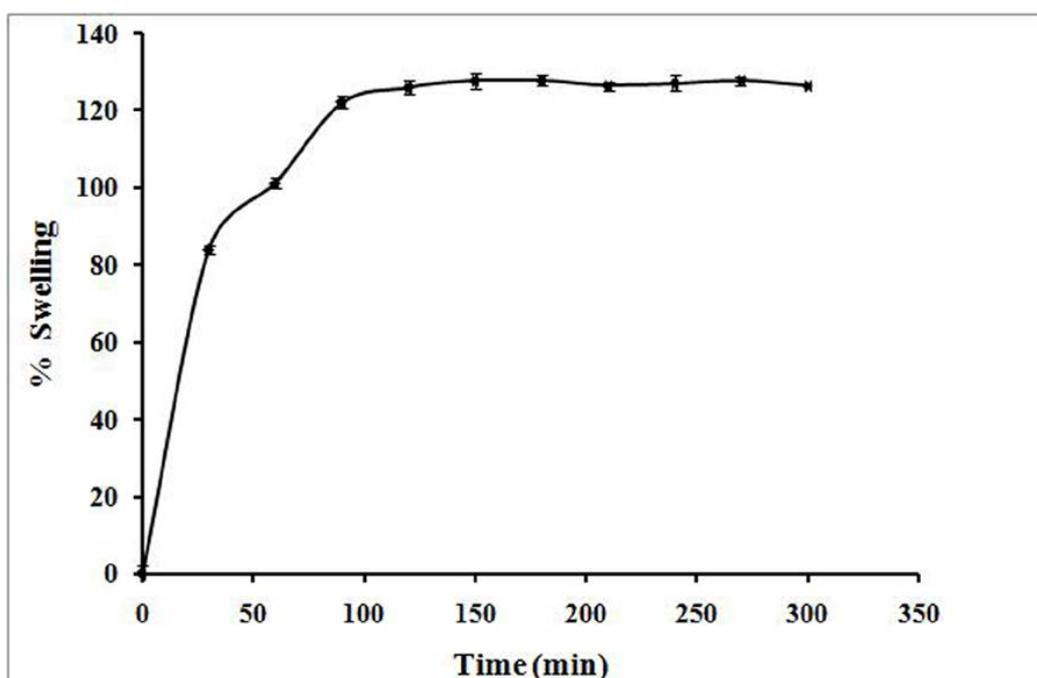


Figure 4. Swelling studies of hydrogel.

Table 3. Zone of inhibition shown by the metronidazole bulk powder, HMBT and placebo tablet for *C. albicans*.

Samples	Zone of inhibition, mm, mean \pm SD (n=3)
Metronidazole bulk powder	18.4 \pm 0.22
HMBT	18.1 \pm 0.76
Placebo tablet	nil

able and non-toxic. The cationic character and the potential functional groups make it an attractive biopolymer for many biomedical and pharmaceutical applications. As pharmaceutical excipients, chitosan has been used in various formulations, like powders, tablets, emulsions, and gels. Furthermore, a controlled release of incorporated drugs can be guaranteed. Chitosan also shows mucoadhesive properties and antimicrobial activity [18].

Chitosan powder was dissolved in acetic acid solution followed by addition of sodium hydroxide aqueous solution gives white gelous material. It was highly swollen hydrogel. The hydrogel formed a gel layer around it when it comes in contact with fluids and leads to controlled drug release from the gel core.

Bioadhesive vaginal formulations that are capable of delivering the active agent for an extended period at a predictable rate have been developed. The prepared hydrogel controlled the drug release by swelling controlled mechanism and also good bioadhesive property, which help to it remain in vagina.

In this study, six formulations of vaginal tablets were prepared using hydrogel containing drug and polymers such as HPMC E 15 LV, SCMC or Guar gum in combination of different ratio. The different polymers of HPMC, SCMC and GG were chosen because of their swelling property and were reported to form a gel layer around the drug core. SCMC with HPMC helps to rapid formation of the viscous gel layer upon hydration and which has been regarded as an essential first step in achieving controlled drug release from tablets. GG helps to maintain the device's in-

tegrity, and due to its swelling property also affects the drug's release profile. The tablets were prepared by direct compression keeping the concentration of the HPMC constant and varying the proportion of SCMC and GG.

Since the swelling behavior of a polymer is essential for its cohesiveness, the water uptake of prepared tablets was tested. All the formulations have shown considerable swelling properties in acidic pH, which is due to the presence of hydrophilic polymers in the formulations. The swelling state of polymer contributes to its bioadhesive behavior and to develop maximum adhesion strength, an optimum water concentration was needed for polymer particles [19]. Polymeric matrices start to swell and build a gel layer around the tablet core when they come in contact with medium which governs the drug release. HPMC, SCMC and GG are readily swellable polymers and shows good mucoadhesion property.

3.1. DSC and FT-IR Studies

DSC and FT-IR were used to detect possible modifications of the physicochemical properties of the drug and/or of the carrier and possible interactions between the components of the formulations. DSC thermograms of MTZ and MTZ - loaded hydrogel (F6) are depicted in figure 2. The DSC thermogram of pure MTZ showed a sharp melting endotherm at temperature 160.52 °C. This melting endotherm was also observed for MTZ -loaded hydrogel (F6) at 161.54 °C, indicating absence of drug and polymer interactions. However, the melting endotherm of F6 was not that much sharp as that of pure MTZ which may be due to the presence of polymers. The IR spectra of

MTZ and drug-loaded hydrogel (F6) were found to be identical and presented in figure 3. The characteristic IR absorption peaks of MTZ at 1265 cm^{-1} (C–O stretch), 2879 cm^{-1} (Aliphatic C–H stretch), 1624 cm^{-1} (C=C stretch) and 1357 cm^{-1} (C–N vibration) were present in drug-loaded hydrogel. Spectra of drug loaded hydrogel showed an extra broad peak which may be due to presence of polymers used in formulation. From the FT-IR peaks, it can be concluded that the peaks of pure drug and formulations were found to be similar indicating that there was no significant interaction between drug and polymer used.

3.2. Swelling Study for Hydrogel

The swelling studies for hydrogels were carried out in SVF pH 4.5. It is shown in figure 4. In acidic environment, chitosan neutral hydrogels showed higher swelling ratio than in basic environment. Hydrogels may undergo a swelling-driven phase transition from a glassy state where entrapped mol-

ecules remain immobile to a rubbery state where molecules rapidly diffuse. In these systems, the rate of molecule release depends on the rate of gel swelling [20]. It was observed that the extent of swelling strongly depends on the extent of cross-linking, at lesser cross-linking density, the network is loose with a greater hydrodynamic free volume, and so that the chains can accommodate more of solvent molecules resulting in higher swelling.

3.3. Drug Content for Hydrogel

The drug content analysis showed that the drug loading is uniform and there was homogenous drug distribution in the hydrogels. The drug content evaluation of different formulations of hydrogels showed that the drug content was in the range of 100-104% of the total amount of the drug added in 300 mg hydrogel.

3.4. Scanning Electron Microscopy

In the SEM photographs of the hydrogels,

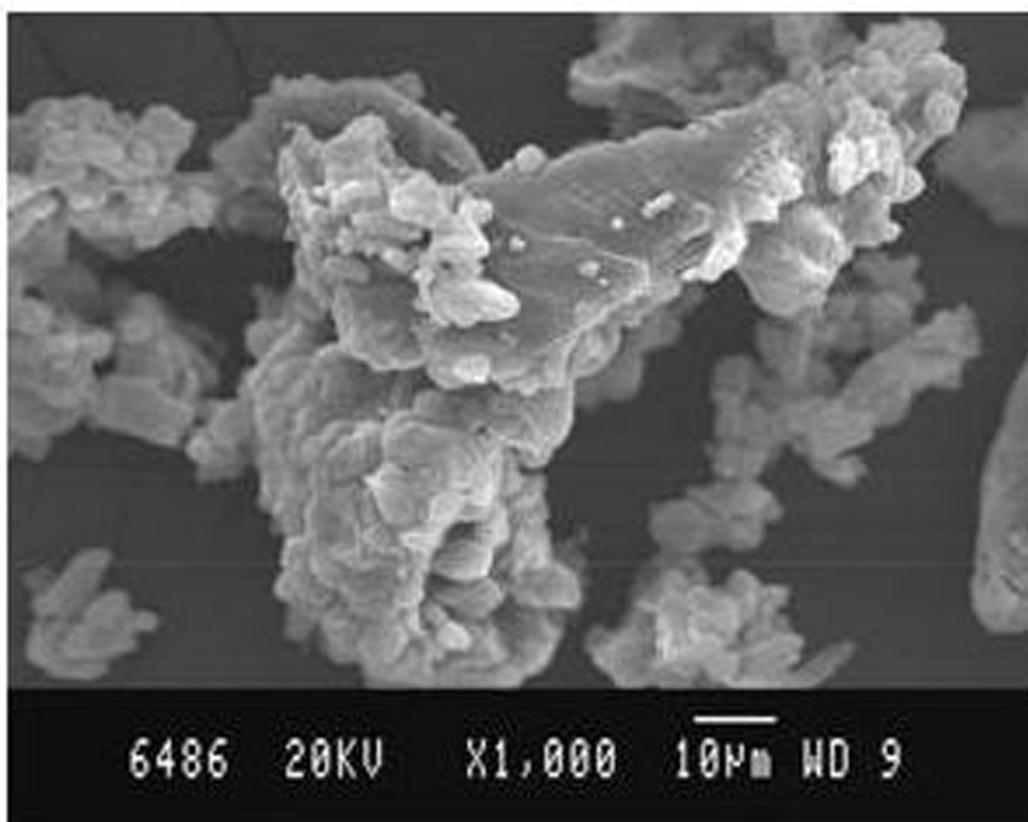


Figure 5. Scanning electron microscopy of hydrogel.

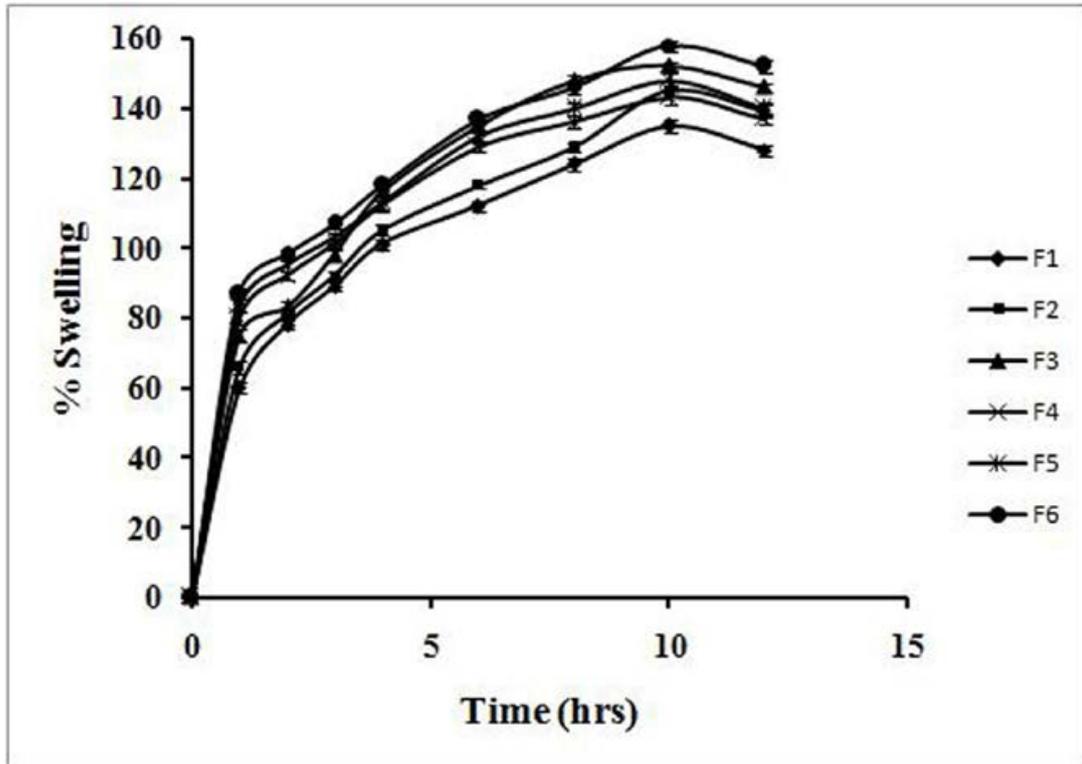


Figure 6. Swelling studies of prepared formulations F1 to F6.

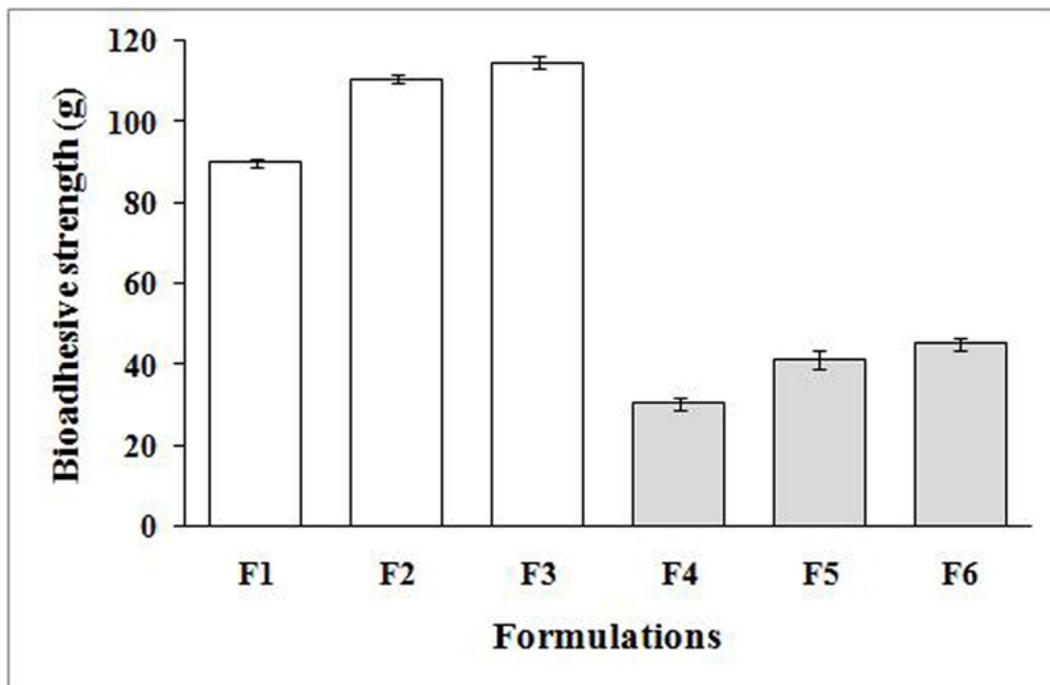


Figure 7. *In vitro* bioadhesion study of prepared formulations F1 to F6.

it can be seen that the particles of hydrogels shown in figure 5 appeared small and irregular shaped. Hydrogel possessed large numbers of pores, indicating that for-

matation of the superporous structure. The morphology of the particles was evident in the packing and flow characteristics of the material.

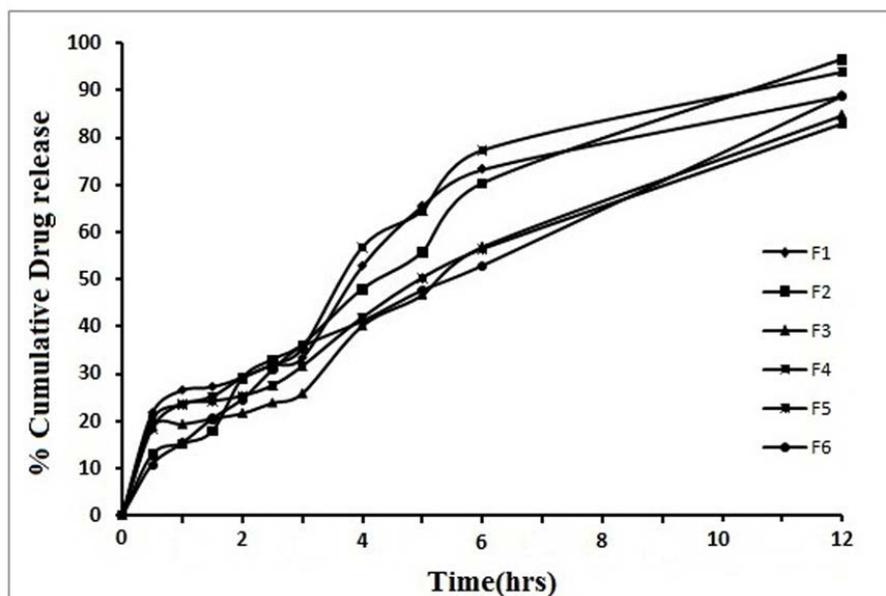


Figure 8. In vitro release profiles of prepared formulations in SVF.

3.5. Tablet Parameters

The tablets prepared were evaluated for various tests and the results obtained are given in table 2. Thickness, average weight, hardness, and percentage friability of prepared tablets were found to be satisfactory. Percentage weight variation, percentage friability and percentage drug content were found to be well within IP limits. The tablets were having an average diameter of 13 mm.

3.6. Tablet Swelling Study

Swelling is an important parameter to be studied before considering mucoadhesion. While some reports showed a direct relation between swelling and mucoadhesion, others did not. [11] The swelling results were expressed in terms of swelling index. The vaginal pH of women in reproductive age is acidic. Therefore, swelling studies were carried out in SVF (pH 4.5). At the initial stage, the swelling occurs very rapidly due to the entry of water via metastable pores in the tablets. This mechanism is known as hysteresis of the swelling that is followed by swelling as a result of diffusion processes. If an intact hydrated layer can establish over the period of study, diffusion may be most important

factor controlling the rate of drug release from the system diffusion. When more swellable polymers were used into the formulations, the release of drug decreased with time. Drug release from hydrophilic matrix could occur by swelling-controlled mechanism. [6]

All the formulations have shown considerable swelling properties in acidic pH, which is due to the presence of the hydrophilic polymers in the formulations. Polymeric matrices start to swell and build a gel layer around the tablet core when they come in contact with medium which governs the drug release. HPMC takes more time in swelling and is able to maintain the integrity of the tablets. SCMC and GG are readily swellable polymers, and as a result the tablets show good mucoadhesion property. The % swelling gradually decreased in all the formulations after 10th hr as the polymer erosion starts to occur. Results obtained are shown graphically in figure 6.

3.7. In Vitro Bioadhesive Strength

In vitro mucoadhesion testing for dosage forms was evaluated by detachment force measurements. Increasing the polymer concentration caused an increase in the mucoadhesive strength. Hydration of the

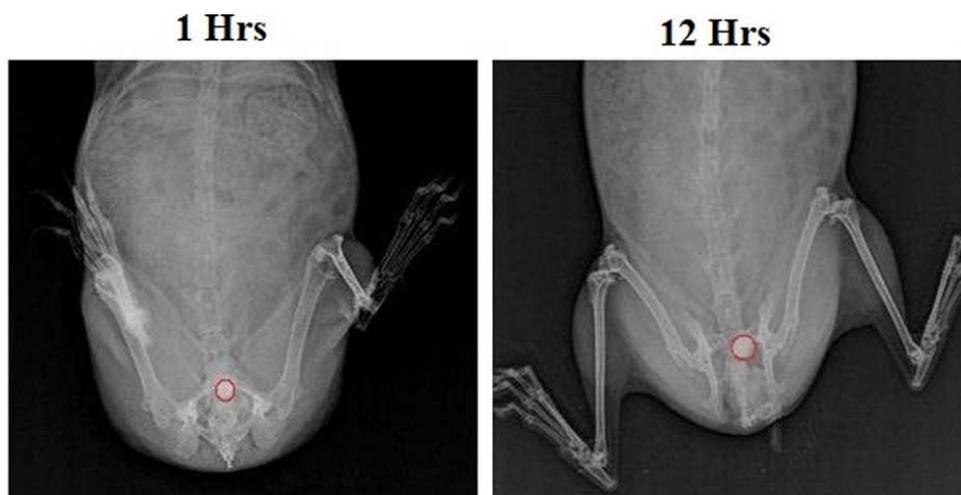


Figure 9. X-ray radiographic images of vaginal cavity at 1 and 12 h after insertion of BaSO₄-loaded optimized F3 HMBT.

mucoadhesive polymer is essential to initiate the mucoadhesive bonding process. The cohesive force arises when water from the space between the mucosa and the polymer is taken up; this plays a vital role in the establishment of an effective mucoadhesive bond. The combination of HPMC with SCMC formulation has shown more mucoadhesive strength than the formulations which is with GG polymer. HPMC is the long chained, non-ionic polymer and the mucoadhesive property could be due to the formation of physical or hydrogen bonding with the mucus components or due to inter-chain bridges between the hydrogel polymer's functional groups and the mucus glycoproteins. F3 formulation was found to have highest bioadhesive strength among all other formulations hence it is selected as optimized formulation. F3 formulation assists the tablet to stay in the vagina and thereby enhance the retention. Results obtained are shown graphically in figure 7.

3.8. *In Vitro* Drug Release Studies

The dissolution studies were carried out by using USP type dissolution apparatus I using SVF pH 4.5 as dissolution medium. All the formulated tablets were tested for their release pattern for a period of 24 hrs. The dissolution data of the individual formulations are shown graphically in the figure 8. Upon

contact with SVF pH 4.5, hydrogels may undergo a swelling-driven phase transition from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. In these systems, the rate of molecule release depends on the rate of gel swelling. The drug release rates are modulated by the rate of water transport and the thickness of the gel layer. The hydrophilic colloid hydrates and this hydrated layer allegedly thereafter slowly dissolves to release the medicament.

The selected polymers such as HPMC, SCMC and GG have shown better mucoadhesive property when they were used in more concentration and thereby release the drug for prolonged period of time. HPMC with SCMC helps to rapid formation of the viscous gel layer upon hydration and which has been regarded as an essential first step in achieving controlled drug release from tablets. The increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the controlled drug release occurred.

The formulations made with single polymer showed burst effect when they come in contact with the fluid. To avoid such a burst effect the combination of polymers were used in different ratios. The selected

polymers have shown better mucoadhesive property when they were used in more concentration and thereby release the drug for prolonged period of time. It was found that, the F3 formulation containing the combination of polymers HPMC and SCMC in the ratio of 1:0.7 have shown better *in vitro* release 85.5% at 12 hrs as well as biadhesive strength which is very essential to remain in the vagina. Also the F6 formulation containing the combination of polymers HPMC and GG in the ratio of 1:0.7 has shown good *in vitro* release 88.8% at 12 h but showed poor bioadhesive strength. Hence F3 was chosen as optimized formulation for *in vivo* studies since F3 has maximum controlled *in vitro* drug release profile and highest *in vitro* bioadhesive strength.

3.9. In Vivo X-Ray Studies

The mucoadhesion and retention property was evaluated in albino rabbit and the X-ray photographic images are given in figure 9. Optimized formulation F3, developed by loading barium sulfate in place of MTZ in a hydrogel was administered to rabbit. The duration of HMBT in vaginal cavity was monitored by radiograms. It was evident from the pictures that the tablets showed swelling, remained intact and adhered to vaginal mucous membrane for over 12 hrs.

3.10. In Vitro Antifungal Activity

The results of antifungal activity of Metronidazole bulk powder, HMBT and placebo tablet evaluated by cup-plate method are shown in table 3. The results were found encouraging. The placebo tablet has not shown any zone of inhibition. Additionally, the zone of inhibition was found with the F3 HMBT formulation. Antifungal study with Sabourad Culture shows that the HMBT was capable to control the growth of *C. albicans* for more than 12 h. HMBT had prolonged drug release and provided better contact with the wells cut in the plate. Microbial activity and *in vitro* safety profile of Metronidazole were not negatively affected by formulating metronidazole into HMBT. Like bulk pow-

der, HMBT effectively inhibited *C. albicans* growth. There was no significant change in antifungal activity of metronidazole.

4. Conclusion

Controlled release can be achieved by incorporating the drug into a release rate controlling carriers like swelling controlled hydrogel and then formulating it as bioadhesive tablet. The release pattern and bioadhesive strengths of different formulations indicate that HPMC & SCMC combination based formulation is better for the vaginal bioadhesive dosage form. *In vivo* studies in albino rabbit reveals the prolong retention of HMBT inside the vaginal tract up to 12hrs. Hence, a novel hydrogel based metronidazole bioadhesive tablet (HMBT) developed can be used to achieve controlled release of drug for prolonged period of time for the local treatment of vaginal candidiasis.

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