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ORIGINAL ARTICLE

Development and Characterization of Mucoadhesive Films Containing Metronidazole for Vaginal Drug Delivery

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ABSTRACT

Objectives: Bacterial vaginosis (BV) is a common disease in women of reproductive age. Metronidazole (MET) is an antibiotic used to treat BV *via* the oral or vaginal route. Vaginal films are dosage forms that combine the properties of solid and gel formulations and increase patient compliance. This study aims to develop and characterize vaginal film formulations containing MET for the treatment of BV.

Materials and Methods: Film formulations were prepared using the solvent casting method with poly(vinyl alcohol), hydroxypropyl methylcellulose K100M, and mixtures of these polymers. Polyethylene glycol 400 was added to the formulations as a plasticizer. The moisture content, average thickness, and weight of the film formulations were examined. Also, the mechanical properties (tensile strength and elongation at break) and *ex vivo* mucoadhesion properties of the films were determined with vaginal tissue. The release of MET from the films was investigated using Franz diffusion cells.

Results: The moisture content of the formulations was found to be less than 10%. It was observed that tensile strength and elongation at break values decreased when MET was loaded onto the films. Mucoadhesion values decreased with MET loading and the work of mucoadhesion values was found to be 0.070±0.053, 0.067±0.039, and 0.150±0.061 for F4, F5, and F6, respectively. The release of MET was found to be 92.7%, 65.5%, and 87.6% for F4, F5, and F6, respectively.

Conclusion: Mucoadhesive films can be used as an alternative dosage form for vaginal delivery of MET in the treatment of BV.

Keywords: Metronidazole, bacterial vaginosis, vaginal drug delivery, vaginal film

INTRODUCTION

Bacterial vaginosis (BV) is a common disease in women characterized by an increase in facultative and anaerobic bacteria by suppressing the normal vaginal flora.[1,2] Various drugs, such as Ampicillin, Penicillin, and Metronidazole (MET), are used to treat BV1. MET is an antibiotic used to treat infections in the digestive, reproductive, and integumentary systems that inhibit nucleic acid synthesis.[3] MET is a preferred agent for treating various diseases with its low cost, acceptable side effect profile, and pharmacokinetic and pharmacodynamic properties.[4,5] MET is associated with low levels of antimicrobial resistance.[6] MET-containing oral or vaginal formulations are commonly used to treat BV. MET is well tolerated and diffuses to all tissues.[7]

Vaginal drug administration is frequently used because of its large surface area, high permeability, ease of self-administration, and both local and systemic effects.[8,9] Different dosage forms, such as gel, suppository, tablet, emulsion, nanoparticle, liposome, and film, are used for vaginal drug administration.[10-14]

Films are solid dosage forms that release active substances by dissolving when placed on a mucosal surface. Film

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formulations have several advantages such as fast and accurate dosing, leakage prevention, ease of use without an applicator, and increased stability.[15] The acceptability of vaginal films over other vaginal formulations, such as gels, foams, and suppositories, has been demonstrated.[15] The solvent casting method, which is based on removing the solvent by pouring the polymer solution on glass, teflon, and plastic, is widely used in the production of vaginal films.[16] Film formulations can be prepared using different polymers such as poly(vinyl alcohol) (PVA), pectin, carrageenan, sodium carboxymethyl cellulose, and hydroxyethyl cellulose, individually or in combinations with different polymers.[17] Hydroxypropyl methylcellulose (HPMC), a non-ionic water-soluble polymer with its swelling and dissolution properties in aqueous media, is frequently used to develop different dosage forms, such as films, gels, nanofibers, and tablets.[13,17-19] PVA is a biodegradable, water-soluble, crystalline, and synthetic polymer used in various industrial and medical applications.[20,21] PVA is a polymer also used in commercial film formulations.[22]

Kawarkhe and Poddar[23] developed film formulations containing MET to be applied vaginally to treat local infections. They investigated the effect of the HPMC and Carbopol ratio and the different plasticizers on film formulation during production. The physical, mechanical, and mucoadhesive properties of the films were evaluated. The solvent casting method successfully produced the optimum film formulation containing MET. Film formulations containing MET have also been developed for buccal administration to treat periodontal diseases.[24]

In our previous work, we developed nanofiber and gel formulations that are containing MET for vaginal use.[25] As an alternative to these formulations, the authors aimed to develop a new, inexpensive, and organic solvent-free dosage form that can be used for vaginal application. For this purpose, mucoadhesive and controlled-release film formulations containing MET have been developed using HPMC, PVA, and mixtures of these polymers. The physical, mechanical, *ex vivo* mucoadhesive, and *in vitro* diffusion properties of the developed films were investigated. In this study, the most suitable vaginal film formulations for MET vaginal administration were evaluated.

MATERIALS AND METHODS

Materials

MET was a generous gift from Abdi İbrahim Pharmaceutical Company, Türkiye. HPMC-K100M was purchased from Colorcon, England. PVA was kindly donated by Wacker Chemical Corporation. Polyethylene glycol 400 (PEG400) was acquired from Merck, Germany. All chemicals and reagents were of analytical grade.

Preparation of vaginal films

HPMC, PVA, or a mixture of the two was used as the film-forming polymer, and PEG400 was used as a plasticizer. To prepare the HPMC film, the polymer was dissolved in distilled water. During the preparation of the PVA film, hot water (80-90 °C) was used. When the polymers were mixed with water, a plasticizer was added to the solution, resulting in a homogeneous mixture. PVA was completely dissolved in hot water to prepare the film containing both polymers. Then, HPMC was added to the PVA solution and mixed until a homogeneous mixture was formed. The ingredients of the formulations and their amounts are shown in Table 1. The films prepared using the solvent casting method were poured into petri dishes. The air in the solutions was removed by sonication. Film formulations were dried in the oven at 40 °C.[26]

Thermal analysis of vaginal films

Thermal properties of MET, polymers, and formulations were characterized using differential scanning calorimetry (DSC) (Shimadzu, DSC-60, Japan). Samples (2-3 mg) were weighed, sealed in aluminum pans, and scanned at a heating rate from 25 to 300 °C.

Weight and thickness of vaginal films

To evaluate the weight homogeneity, three films were cut into 1x1 cm pieces and weighed on a digital scale, and their average weight was calculated. To determine the thickness of the films, random points on the film were measured with a micrometer (Mitutoyo Digital Micrometer, Japan), and the average of these values was determined as film thickness.

Moisture content of vaginal films

The moisture content of vaginal film formulations was evaluated by heating film samples to 130 °C using a moisture analyzer (Sartorius Moisture Analyzer, Germany).

Mechanical properties of vaginal films

(TA.XT. Plus Texture Analyzer, Stable Micro Systems, UK) was used to determine the mechanical characterization of vaginal films. The films were cut to 3x1 cm in size and clamped between the mini tensile grips. Elongation at break and tensile strength of the films were calculated at the point of rupture, while the upper part of the apparatus moved upwards with a fixed lower part. For all formulations, stress-strain graphs were used for measurement parameters such as tensile strength and elongation at break values, and measurements were repeated three times for each film.

Table 1. Content of vaginal film formulations

	Formulation code					
	F1	F2	F3	F4	F5	F6
Content *(w/w)*						
MET	-	-	-	0.05	0.05	0.05
PVA	0.5	-	0.25	0.5	-	0.25
HPMC	-	0.5	0.25	-	0.5	0.25
PEG400	0.5	0.5	0.5	0.5	0.5	0.5
Distilled water	qs 50 g					

MET: Metronidazole, PVA: Poly(vinyl alcohol), HPMC: Hydroxypropyl methylcellulose, PEG400: Polyethylene glycol 400, qs: Quantum satis

Ex vivo mucoadhesion studies of vaginal films

The sheep vagina was used as a model tissue for mucoadhesion studies. Mucoadhesion properties of the films were determined with a texture analyzer equipped with a 50 N load cell. The film formulation was attached to the upper probe of the device with double-sided tape. Vaginal tissue was placed in the inferior attachment. The contact time of the probe used was 60 seconds, the force applied by the probe to the vaginal tissue was 0.2 N, and the experiments were carried out at a speed of 1 mm/s. The force required to separate the films from vaginal tissue was determined as mucoadhesive strength. The work of mucoadhesion was measured using the area under the curve (AUC) of the force-distance graph. The work of mucoadhesion was calculated with the formula (mJ/cm^2)=AUC/(πr^2).[27]

In vitro drug release of vaginal films

Franz diffusion cells were used for the *in vitro* release of MET from vaginal films. *In vitro* diffusion studies were performed with a dialysis membrane (12 kDa, Sigma®, USA). For this study, the film formulation was placed in the donor compartment. The release from the films was sampled at certain time intervals (0.5, 1, 1.5, 2, 3, 4, 6, and 8 h). The samples were withdrawn from the receptor phase (pH 4.5 phosphate buffer) and replaced with fresh buffer. The amount of MET released was determined at 320 nm in an ultraviolet (UV) spectrometer (Cary 60 UV-vis, Agilent Technologies, US). All the release studies were conducted under sink conditions.

RESULTS

Thermal properties of vaginal films

DSC thermograms of MET, polymers, and formulations are given in Figure 1. The characteristic peak of MET was observed around 160 °C, which corresponds to the melting point in the thermogram. According to the literature, pure PVA has a melt peak temperature of 202.7 °C. Similarly, it was found to be 195 °C in our study.

Weight and thickness of vaginal films

The average weight of the films increased with MET loading. In the MET-loaded film formulations, the highest average weight was observed in the F4 formulation (10.0±0.9 mg/cm^2) and the lowest in the F5 formulation (5.1±0.5 mg/cm^2). The difference in vaginal film thickness and MET loading was significant between F1 and F4, while the addition of MET to the other formulations was not found to be significant (p<0.05). The change in the weight of the films with MET loading was found to be statistically non-significant (p>0.05).

Moisture content of vaginal films

It was observed that the moisture content of the MET-loaded films was generally higher. The moisture content of film formulations is less than 10%, as seen in Table 2. F4 formulation containing MET showed a higher percentage of moisture content than other formulations.

Mechanical properties of vaginal films

Vaginal films must have sufficient strength to withstand mechanical effects during manufacture, use, and application.[28] In our film formulations, the presence of the MET changed the mechanical properties. When the mechanical properties of blank and MET-loaded films are examined, it has been found that the addition of MET reduces the tensile strength, as seen in Table 2. The change observed with MET loading was found to be statistically insignificant (p>0.05). The F6 formulation showed higher tensile strength compared to the F5 and F4 formulations containing MET (p>0.05). When the elongation at break values was examined, a significant difference was observed between F1 and F4 with the loading of MET into the films (p<0.05).

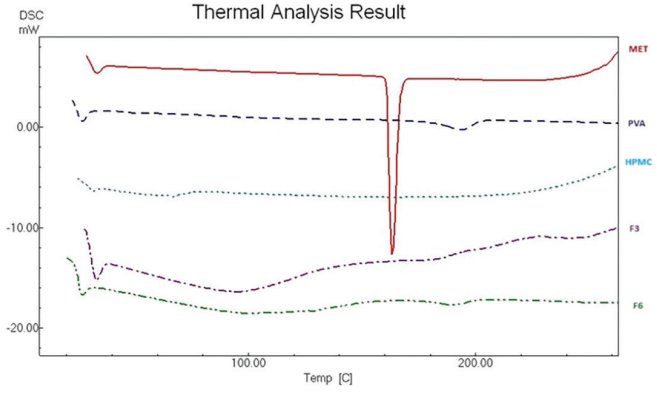

Figure 1. DSC thermograms of MET, PVA, HPMC, F3 and F6 formulations

DSC: Differential scanning calorimetry, MET: Metronidazole, PVA: Poly(vinyl alcohol), HPMC: Hydroxypropyl methylcellulose

Table 2. Different properties of vaginal film formulations

Formulations	Properties				
	Thickness (μm)	Average weight (mg/cm^2)	Moisture content (%)	Tensile strenght (MPa)	Elongation at break (%)
F1	81.7±3.80	6.6±0.40	4	4.68±0.838	239.90±78.749
F2	62.7±1.50	4.9±0.20	4.2	10.96±4.624	121.47±47.626
F3	80.7±4.00	5.4±0.40	7.95	9.779±2.379	88.487±19.673
F4	162.7±38.10	10.0±0.90	8	3.64±0.896	90.687±19.725
F5	46±4.6	5.1±0.50	7.2	7.143±1.881	86.143±17.439
F6	85.3±17.7	7.9±3.1	4.7	7.349±2.680	46.290±20.773

Mucoadhesion studies of vaginal films

The values of the work of mucoadhesion for the film formulations are shown in Figure 2. Mucoadhesion values decreased with MET loading in the formulations. The highest mucoadhesion value of the formulations loaded with MET was observed in formulation F6, prepared with a combination of polymers.

In vitro drug release of vaginal films

The release profiles of MET from the different film formulations were compared. The release profiles of MET were found to be 92.7%, 65.5%, and 87.6% for F4, F5, and F6, respectively (Figure 3). However, approximately 80% of MET release from our formulations occurred within an hour. In our study, the slowest release was observed in the F5 formulation prepared with HPMC.

DISCUSSION

Film formulations were successfully developed using the solvent-casting method. Film formulations were developed with HPMC, PVA, and a mixture of these polymers. The films prepared were transparent, soft, and flexible. This shows that the two polymers can blend completely with the plasticizer to form a new polymer matrix. The formulations developed using HPMC have a more transparent and colorless appearance than those consisting of PVA or polymer mixtures.

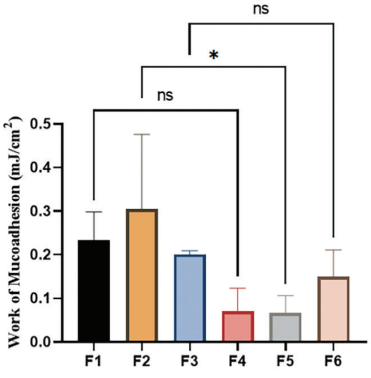

Figure 2. Work of mucoadhesion values of film formulations from sheep vaginal tissue

ns: Not significant, *: $p<0.05$, n=3

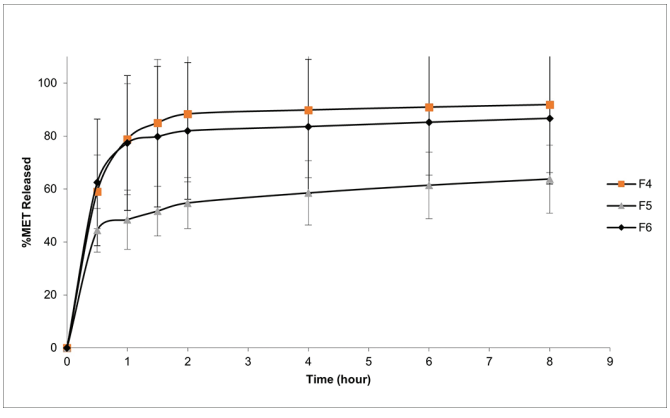

Figure 3. *In vitro* diffusion profiles of F4, F5 and F6 formulations

When DSC analysis was performed, the disappearance of the MET endothermic peak indicated that the drug transformed from a crystalline to a partially amorphous state.[29] The amorphous structure of the drug resulted in increased solubility.[30]

Different thicknesses and weights may be due to the polymer type and amount in the film formulations.

The moisture content of film formulations must be at a certain level so that the formulations are not dry and brittle. Dobaria et al.[30] found the moisture content to be 7.66±0.51% *(w/w)* in the vaginal film formulation they developed to prevent *Candida* infections. The researchers stated that the small amount of moisture content in the films would help them remain stable and prevent them from becoming completely dry and brittle. Cautela et al.[31] found the moisture content of the films containing PVA and pectin to be from 5% to 8.7%. In addition, the moisture content of the commercially available Vaginal Contraceptive Film® (VCF®) (Apothecus, Oyster Bay, NY, USA) was found to be 13.1%. The moisture content of film formulations is less than commercially available VCF®, as seen in Table 2.

Film formulations should have moderate tensile strength and high elongation at break.[32] A decrease in elongation at break values was observed in film formulations prepared with a mixture of HPMC and PVA, relative to the films containing a single polymer. In addition, an increase in tensile strength values was observed in comparison to formulations containing PVA. PEG400 can change the mechanical properties of the film by weakening the intermolecular interactions between polymer chains, with a hydrogen-bonding effect.[32] A suitable vaginal film formulation is recommended to have high tensile strength and an elongation at break value.[33] Akil et al.[15] found that while the tensile strength value of the 0.5 mg dapivirine-containing film was 777.59±19.99 N/cm^2 in the vaginal film formulations, the 1.25 mg dapivirine-containing film's tensile strength was 538.24±57.17 N/cm^2. Increasing the amount of dapivirine changed the films' mechanical properties. Similarly, drug loading changed the mechanical properties of our film formulations. Tensile strength and elongation at break values in our blank film formulations are higher than in the MET-loaded formulations. Higher tensile strength and elongation at break values were obtained in F1 and F4 formulations prepared with PVA.

Retention of vaginal films in the vagina is desirable for therapeutic efficacy and helps reduce frequent dosing.[28] HPMC is a non-ionic polymer, and its mucoadhesiveness is due to physical or hydrogen bonding with mucus components, which can relieve dryness and irritation even if mucus secretions are reduced.[28] With their mucoadhesive properties, the films may help prevent vaginal leakage and will increase the effectiveness of MET by providing better contact of the formulations with the vagina. Notario-Pérez et al.,[16] in their study, prepared film formulations containing zein and HPMC. The film formulation prepared with HPMC remained in the biological sample longer until corrosion was complete. The F6 formulation, prepared with HPMC and PVA, has the highest mucoadhesion value and was expected to remain in the vagina for longer than the other formulations.

The release profiles of MET shown in Figure 3 can be related to the swelling properties of the polymers. Drug release from films occurs by the swelling of the films, which allows gels that can control release.[17] In Kawarkhe and Poddar's[23] study, MET releases were observed over 60 minutes in films prepared with Carbopol and HPMC.

The highest release was obtained in the F4 formulation prepared with PVA (92.7%), while the slowest MET release was obtained from the F5 formulation prepared with HPMC (65.5%). The slow release of MET from our film formulations prepared with HPMC may be due to its high molecular weight or high viscosity. Sudeendra et al.[28] prepared a film formulation using clotrimazole-loaded HPMC, chitosan, and sodium CMC with different types of plasticizers in their study. It was observed that the release of the formulations decreased with the increase in HPMC and sodium CMC ratios. It has been stated that HPMC slows the release by reducing the penetration of water, forming a viscous gel.[28]

CONCLUSION

Film formulations were successfully produced using the solvent-casting method. Mechanical properties and release profiles of the films were investigated. MET-loaded vaginal films are developed for many different purposes and provide various advantages over gel formulations, such as prolonged retention, reduced messiness, and reduced leakage. Film formulations can be a cost-effective dosage form that can be administered vaginally for BV treatment. F6 film formulation, prepared with the combination of PVA and HPMC polymers, showed good mucoadhesive properties and a good drug release profile for vaginal application. More detailed morphological, mechanical, *ex vivo*, and *in vivo* studies are required to determine the optimum film formulation.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

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Footnotes

Authorship Contributions

Concept: F.T.D., Design: F.T.D., Data Collection or Processing: F.T.D., S.S., Analysis or Interpretation: S.S., FTD., Literature Search: F.T.D., S.S., Writing: F.T.D., S.S.

Conflict of Interest: The authors declare no conflicts of interest.

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