

The physicochemical properties of mucoadhesive polymeric films developed as female controlled drug delivery system

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Received 30 June 2005; received in revised form 15 November 2005; accepted 16 November 2005

Available online 10 January 2006

Abstract

To develop an efficient female controlled drug delivery system (FcDDS) against sexually transmitted diseases (STDs), the polymeric films containing sodium dodecyl sulfate (SDS) were prepared with various compositions of Carbopol 934P, hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG). The physicochemical properties of mucoadhesive polymeric films, such as tensile strength, contact angle, swelling ratio and erosion rate in a vaginal fluid stimulant (VFS), were characterized. In addition, the drug release profile of SDS from the films and mucosal residence time were evaluated using a simulated dynamic vaginal system. It was demonstrated that the films made of Carbopol, HPMC and PEG were colorless, thin and soft and had proper physicochemical properties for FcDDS. An increase in Carbopol content elevated tensile strength and swelling ratio but decreased the contact angle, erosion rate and the SDS release rate from the films. The films containing 0.25% (w/v) PEG as well as 0.75% (w/v) of combining Carbopol and HPMC remained on the vaginal tissue for up to 6 h. The films containing the ratio of Carbopol:HPMC:PEG = 1.5:1.5:1 and 1:2:1 seem to be optimal compositions for FcDDS, as they showed good peelability, relatively high swelling index and moderate tensile strength, and achieved the target release rate of SDS for 6 h.

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Keywords: Mucoadhesive polymeric films; Female controlled drug delivery system; Carbopol; Hydroxypropyl methylcellulose; Physicochemical properties

1. Introduction

Sexually transmitted diseases (STDs) caused by human immunodeficiency virus (HIV), human simplex virus (HSV), human papillomavirus (HPV) and other pathogens continue to be a major health threat around the world. It is estimated that about 19 million STD infections occur annually in the United State (Weinstock et al., 2004). According to the World Health Organization (WHO), as of 2003, 19.2 million women were living with HIV/AIDS worldwide, accounting for approximately 50% of the 40 million adults infected with HIV/AIDS. Biologically, young women are more susceptible to STDs than men because of substantial mucosal exposure and sex without condom use. Consequently, complications of STDs are greater and more frequent among women, and serve as a significant cause of reproductive health morbidity (Risbud, 2005).

For the protection of women against STDs, various types of preventive tools have been developed. The immunological vac-

cine for AIDS has been investigated, but it is several years away from clinical application. Under these situations, the mucoadhesive formulations containing microbicides or prophylactic agents seem to be an alternative choice to control and prevent the rapid spread of STDs (Harrison, 2000). Sodium dodecyl sulfate (SDS) is an efficient microbicidal agent. SDS, which denatures membrane proteins of cells and pathogens, is an alkyl sulfate surfactant derived from an organic alcohol. SDS at very low concentrations completely inactivates HIV, HPV and HSV after a brief exposure at physiologic temperatures (Kreb et al., 1999). SDS is also of low intrinsic toxicity to skin and mucous membranes (Piret et al., 2000). In vivo toxicity study assessed using the rabbit vaginal irritation test has demonstrated that an exposure of vaginal mucosa to SDS at concentrations of up to 5% (w/v) was neither toxic nor broke vagina homeostasis (Kreb et al., 1999).

Conventional vaginal formulations, such as tablets and creams, have been limited in use because of leakage, short resident time and poor patient compliance, and insufficient therapeutic effects. Mucoadhesive formulations can circumvent these limitations (Vermain and Garg, 2000). In our previous studies, a gel base mucoadhesive female controlled drug delivery sys-

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tem (FcDDS) containing SDS were developed and their efficacy in protection against SDS was demonstrated (Wang and Lee, 2002, 2004). Vaginal films made of Carbopol and HPMC have several advantages over vaginal gels, such as portability, convenient application, long retention time, easy storage and improved stability of drug at the extreme condition (Garg et al., 2005). PEG, a hydrophilic excipient, is commonly used as a plasticizer in the preparation of vaginal suppositories.

The physicochemical properties of mucoadhesive formulations are characterized in various aspects. A contact angle is used as an indication of initial degree of wetting. The lower value of contact angle means the higher degree of wetting and hydrophilicity. It was also reported that contact angles were closely correlated to the work of adhesion, which represents strength of mucoadhesiveness of the film containing Carbopol (Li et al., 1998). The swelling capability of the polymer was also reported to be crucial for its bioadhesive behavior (Chen and Cyr, 1970) and has a great impact on their stability and release profiles of incorporated drugs (Mortazavi and Smart, 1993). The extent and rate of the water uptake flux are affected by the degree of cross-linking and chain length of the mucoadhesive macromolecules (Smart, 1999). The adhesiveness increases with the degree of hydration, but which is not an unlimited process. An excessive swelling causes a leakage in cohesiveness of formulations and leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface (Peh and Wong, 1999).

In this study, vaginal polymeric films which are composed of various ratios of Carbopol 934P, hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG) and containing SDS are developed. We herein examined physicochemical properties and SDS release profiles of mucoadhesive films to find the most suitable formulation for female controlled drug delivery system against STDs.

2. Materials and methods

2.1. Materials

Carbopol 934P was a gift from B.F. Goodrich (Cleveland, OH) and Dow Chemical Company (Midland, MI), respectively. PEG 400, mucin and ^{14}C -labeled SDS (0.1 mCi/ml) were pur-

chased from Sigma (St. Louis, MO). All other reagents and solvents were of analytical grade.

2.2. Preparation of polymeric films

Polymeric films composed of various ratios of Carbopol, HPMC and PEG were prepared (Table 1). A 3% (w/v) SDS in citrate buffer solution (pH 4.0) was loaded in each polymer. ^{14}C -labeled SDS (0.5 $\mu\text{Ci/ml}$) was added for evaluation of drug distribution uniformity and SDS release profile.

Carbopol–HPMC solutions were first prepared and PEG was subsequently added to the solution. A 1% (w/v) polymeric solution was allowed to stir for 10 h and kept until all the air bubbles entrapped were removed. Then, 40 ml of each polymer solution was poured into a Petri dish and dried in the oven at 60 °C for 24 h. The films were carefully peeled off and stored in a stability chamber at 25 °C under 60% RH until next use.

2.3. Vaginal fluid stimulant (VFS)

Vaginal fluid stimulant was prepared using the method previously reported (Lee et al., 2002). Mucin was dissolved separately in distilled water and added to the solution containing the rest of the components (NaCl, KCl, sodium acetate (CH_3COONa), urea, albumin, lactic acid, amino acids and glycerol). The final pH of VFS was adjusted to pH 4.0 using 5% acetic acid or 1 M sodium hydroxide.

2.4. Film thickness

The thickness of each film was measured at five different locations (center and four corners) using a micrometer screw gauge (Fowler co., Japan) and a mean value of five locations was used as a film thickness.

2.5. Determination of drug content in the films

To ensure the uniformity of distribution of SDS in a film, a content uniformity test was performed. One square centimeter of samples representing five different regions (center and four corners) within the film were cut, weighed and dissolved in VFS. Content of ^{14}C -SDS was analyzed by Liquid Scintillation Counter (a model LS-6500, Beckman Coulter, Fullerton, CA).

Table 1
Physical properties of the polymeric films made of various compositions

Compositions (Carbopol:HPMC:PEG)	Thickness (μm) ^a	Tensile strength (N/mm^2) ^b	SDS content (mg in 1 cm^2) ^a	Weight (mg in 1 cm^2) ^a	Physical characteristics of film
2:1:1	220 ± 16	9.73 ± 0.70	22.80 ± 1.70	286.44 ± 12.05	Colorless, homogeneous surface, soft, easy to peel
1.5:1.5:1	223 ± 41	10.26 ± 0.42	24.20 ± 2.42	305.25 ± 22.62	Colorless, homogeneous surface, soft, easy to peel
1:2:1	220 ± 21	12.67 ± 0.44	25.22 ± 1.84	310.23 ± 14.70	Colorless, homogeneous surface, soft, easy to peel
1.2:0.8:2	241 ± 16	3.71 ± 0.43	25.58 ± 3.43	318.38 ± 16.22	Colorless, homogeneous surface, soft, hard to peel
1:1:2	236 ± 11	4.85 ± 0.59	22.53 ± 2.59	294.16 ± 18.21	Colorless, homogeneous surface, soft, hard to peel
0.8:1.2:2	230 ± 6	5.18 ± 0.87	23.33 ± 3.87	288.04 ± 12.17	Colorless, homogeneous surface, soft, hard to peel
2:2:0	N/A	N/A	N/A	N/A	Too brittle

^a Values are expressed as mean ± S.D.; $n = 5$.

^b Values are expressed as mean ± S.D.; $n = 3$.

2.6. Measurement of tensile strength

The polymeric film was cut into a narrow strip with a width of 10 mm and 30 mm in length. The film was placed between the higher and the lower grip of a Chatillon Digital Force Gauge (a model DFM-10, John Chatillon and Sons, Greensboro, NC) mounted on a test stand (a model LTC, John Chatillon and Sons, Greensboro, NC), aligning the long axis of the specimen and the grip with an imaginary line by joining the points of attachment of the grips to the machine. The two grips were kept at a distance of 10 mm in a same plane, and the hand wheel attached to the lower grip was rotated gradually until the film ruptured. The load at the moment of rupture was recorded and tensile strength was calculated using the following equation:

$$\text{tensile strength } (\sigma) = \frac{\text{force or load } (F)}{\text{MA}}$$

where F is the maximum load in Newton and MA is the minimum cross-sectional area of the film specimen in square millimeter.

2.7. Measurement of the contact angle

An NRL contact angle goniometer (a model 100, Ramé-Hart Instrument Co., NJ) is used to measure the contact angle of the polymeric films. The light source was switched on and the goniometer was adjusted to the path of the light. The specimen film was cut into around 50 mm × 30 mm in size. The adjustable scale on the goniometer was set horizontal. The specimen film was placed on the mechanical stage and height adjusted such that the specimen was exactly at the same height as the horizontal scale in the goniometer. VFS drop of 50 or 100 μl was settled on the test surface by using a microburette for 10 s. The shadow of each drop was considered as the arc of a circle. The contact angle was measured directly by adjusting the movable scale to the tangent at the point of contact.

2.8. Swelling study

VFS (pH 4.0) was used as a medium for film swelling studies. Plastic weighing boats with pores in the bottom was used as a container. Each film sample with 10 mm × 10 mm of surface area was weighed and placed in a preweighed container. The weight boat containing the film sample was then submerged into 25 ml VFS in a Petri dish. At predetermined time intervals, the weight of the swelled film was measured. The swelling index was calculated using parameter $(W_t - W_0)/W_0$, where W_t is the weight of film at time t and W_0 is the weight of film at time zero.

2.9. Film erosion study

The polymeric films were cut into a size of 10 mm × 10 mm. The erosion degree of the polymeric film was determined by placing the polymeric film in 25 ml of VFS (pH 4.0) on 20 rpm of Orbital Shaker (a model OR-100, Daigger, IL). At predetermined time intervals, a sample was removed and completely dried in the oven at 60 °C for 24 h to determine its weight. Percentage remaining was calculated by using parameter

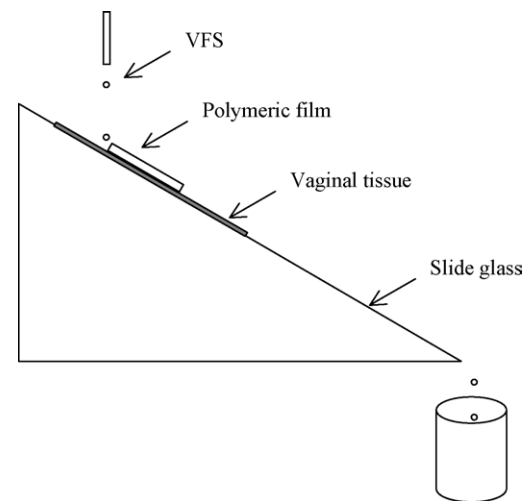


Fig. 1. Simulated dynamic vaginal system used for drug release and mucoadhesive tests.

$100 - (W_p - W_s) \times 100/W_p$, where W_p and W_s are the original weight of the film and the weight of the dry film after erosion, respectively.

2.10. In vitro release profiles of SDS

A simulated dynamic vaginal system (Fig. 1) was prepared by assembling a slide glass and a flow rate pump. Isolated porcine vaginal tissue, obtained from a slaughterhouse, was cleaned, deprived of the connective tissue with surgical scissors with special care to maintain integrity of mucosa, and stored at $-20\text{ }^\circ\text{C}$ until further use. Before the experiments, porcine vaginal tissue was thawed in normal saline containing 0.1% (w/v) sodium azide as preservative. The porcine vagina was cut into pieces with 5 cm × 5 cm in size. The vaginal membrane was mounted with the mucosa side up on a glass slide (30° angle slope). The polymeric film with 1 cm × 1 cm in size was mounted on the mucosal membrane. VFS (pH 4.0) was applied on the films with a flow rate of 5 ml/h. At predetermined time intervals, the perfused VFS was collected into a receptor beaker placed under the slide glass for 6 h. Residence time of the films on the mucosa was also measured using the same system. The amount of released ^{14}C -SDS was analyzed by Liquid Scintillation Counter.

3. Results

3.1. Preparation and physical characteristics of the films

Polymeric film formulations containing various ratios of Carbopol:HPMC:PEG, loaded with 3% (w/v) SDS, were prepared and their physical properties, such as thickness, uniformity of drug content and weight variation, were examined (Table 1). Homogeneous films are translucent, colorless, thin and soft, and no spot or stain was found on the films. The average thickness of the films ranged from 220 to 241 μm. The differences in the thickness and weight between batches were within an acceptance range. In peelability, the films containing 0.25% (w/v) PEG (C:H:P=2:1:1, 1.5:1.5:1 and 1:2:1) were easily taken off

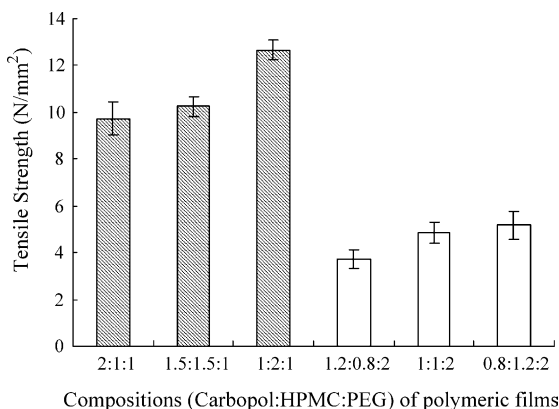


Fig. 2. Comparison of tensile strength of polymeric films. Each data point represents the mean \pm S.D. of three replicates.

from the Petri dish, while the films containing 0.5% (w/v) PEG (C:H:P = 1.2:0.8:2, 1:1:2 and 0.8:1.2:2) attached more strongly to the bottom of Petri dish after dry. The films without PEG were easily peeled off, but too brittle to perform further tests. Without HPMC, the films were not homogenous and showed a cloudy surface. An assessment of drug content at five different places in each film revealed that SDS was distributed evenly throughout the films regardless of the polymer ratios.

3.2. Tensile strength

In producing polymeric films that are intended as a dosage form for intravaginal drug delivery, the films should possess sufficient strength to withstand mechanical damage during production, handling and application. The tensile strength is defined as the maximum stress (σ) sustained by the material. As shown in Table 1 and Fig. 2, tensile strength varied according to the compositions of the formulation. Among tested variables, the PEG concentration seems to be the most prominent factor in determining tensile strength. The films containing 0.25% PEG showed higher tensile strength than those containing 0.5% (w/v) PEG. Tensile strength was also affected by the ratio of Carbopol to HPMC, even though the degree of change is less than that caused by PEG concentration. As the ratio of Carbopol to HPMC concentration decreased, tensile strength increased. The highest tensile strength was observed with the film which has a composition of Carbopol:HPMC:PEG (C:H:P)=1:2:1.

3.3. Contact angle measurement

A contact angle is used as an indication of degree of wetting. The higher value of contact angle means the less degree of wetting. It was also reported that contact angles are correlated to the work of adhesion, which represents strength of mucoadhesiveness (Li et al., 1998). As shown in Fig. 3, the degree of contact angle decreased as Carbopol concentration in the films increased. The film with the highest concentration of Carbopol (i.e., the composition of C:H:P = 2:1:1) showed the lowest contact angle, which means having high wetting capability and work of adhesion.

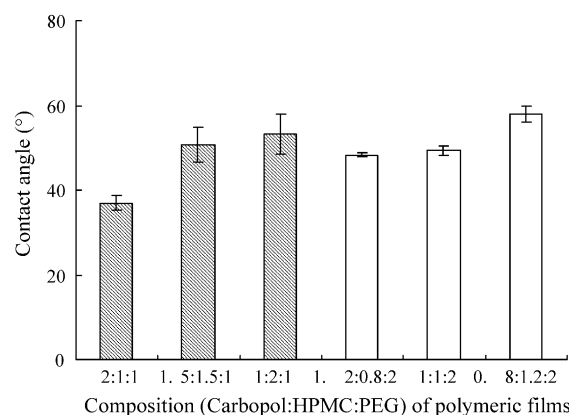


Fig. 3. Measurement of contact angle of polymeric films. Each data point represents the mean \pm S.D. of three replicates.

3.4. Swelling capability study

The effects of various compositions on the swelling index of the film are shown in Fig. 4. The films were not dissolved nor eroded, indicating that the cohesiveness of the polymers is sufficient to guarantee the stability of the system. The films were rapidly swelled within 30–45 min and thereafter gradually reached a plateau. Films containing 0.25% (w/v) PEG showed higher swelling index than those containing 0.5% (w/v) PEG. As the concentration of Carbopol in the film increased, the swelling index increased. At 1.5 h, a film with 0.5% (w/v) Carbopol (C:H:P = 2:1:1) swelled about eight times, whereas 0.2% (w/v) Carbopol film (C:H:P = 0.8:0.2:2) swelled about three times. Since Carbopol is used as a cross-linking agent, it is expected that it can retain more water and higher swelling degree as its concentration increases.

3.5. The erosion profile of the films

The erosion test of the mucoadhesive films was conducted to evaluate the resistance force of the films in VFS. The fast erosion of the films in VFS may pose the problems, such as unexpected burst release of drug and short residence time on the

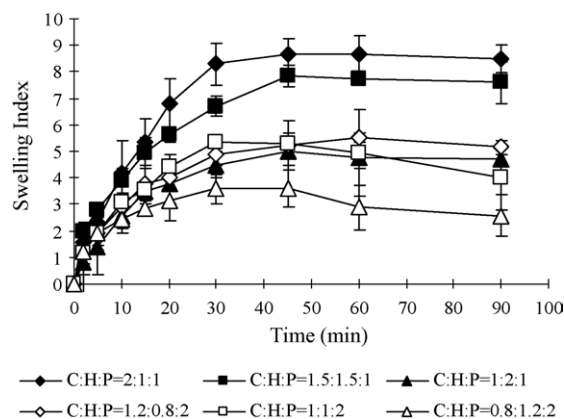


Fig. 4. Swelling index of polymeric films. A film of 1 cm \times 1 cm in size was cut and immersed in VFS (pH 4.0). Each data point represents the mean \pm S.D. of three replicates.

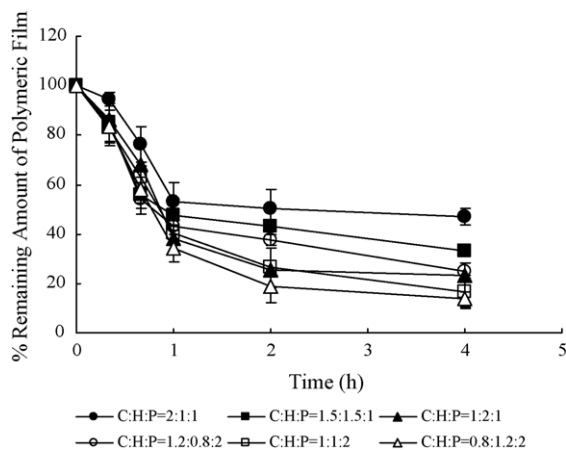


Fig. 5. Erosion degree of polymeric films. A film of 1 cm \times 1 cm in size was cut and immersed in VFS (pH 4.0) on 20 rpm of a shaker. Each data point represents the mean \pm S.D. of three replicates.

vaginal mucosa. The remaining percentage of the films expressed as a function of time is shown in Fig. 5. The films were eroded quickly within 1 h and then gradually increased before reaching a plateau. At 4 h, the film made of C:H:P = 0.8:1.2:2 was eroded up to 86%, whereas the film made of C:H:P = 2:1:1 was eroded only up to 53%. Even though higher concentrations of Carbopol showed greater swelling capability, the erosion rate of the films decreased as Carbopol content in the film increased.

3.6. SDS release profile

The release rate of SDS from the films was described as a function of time as shown in Fig. 6. The simulated dynamic vaginal system used in this study mimics the physico-dynamic conditions of the vagina. The percentage amount of the total SDS released from the films gradually increased as a function of wearing time. In all formulations, the burst release of SDS from the films was observed within first 2 h, and then gradually increased up to 6 h. About 46, 54 and 74% of the total SDS loaded in the film were released within 6 h from mucoadhesive films made of C:H:P = 2:1:1, 1.5:1.5:1 and 1:2:1, respectively.

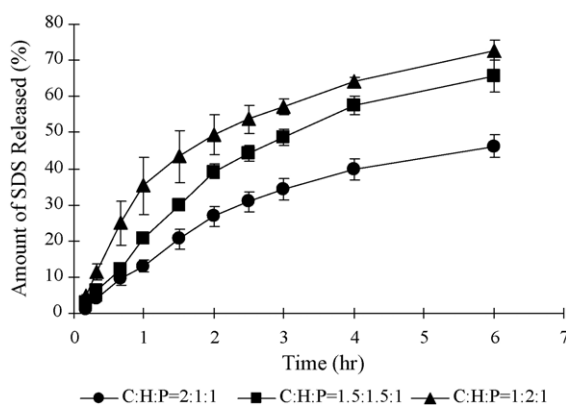


Fig. 6. The release profile of SDS from the polymeric films. The polymeric film with 1 cm \times 1 cm in size was mounted on the mucosal membrane. VFS (pH 4.0) was applied on the films with a flow rate of 5 ml/h. Each data point represents the mean \pm S.D. of three replicates.

As the ratio of Carbopol to HPMC concentration in the formulation increased, the SDS release rate from the film decreased, indicating the SDS release rate from the polymeric film can be controllable by the ratio of Carbopol to HPMC concentration.

3.7. The residence time

The time required for the complete removal of the polymer film from the vaginal tissue varied with the compositions in the films. The films (0.25%, w/v, PEG) containing more Carbopol and HPMC than PEG remained on the porcine vaginal mucosa for up to 6 h, but the films (0.5%, w/v, PEG) containing less Carbopol and HPMC than PEG were removed from the tissue within less than 4 h. The results of this study indicated that the concentration of Carbopol and HPMC is an integral factor in residence time of the mucoadhesive formulations.

4. Discussion

Polymeric films, which were made of Carbopol, HPMC and PEG and containing SDS as the major microbicidal agent, were fabricated and examined for their physico-dynamic properties to find the most suitable composition for FcDDS. Carbopol and HPMC were selected as the main ingredients because they were proven to have good properties as gel based FcDDS (Wang and Lee, 2002, 2004). Carbopol, which is consisted of acrylic acid backbone and small amounts of polyalkenyl polyether cross-linking agents, is commonly used for the preparation of vaginal gel formulations because of its polarity and bioadhesive properties. HPMC is proven to have good mucoadhesiveness and can relieve the dryness and irritation even in the case of reduced mucus secretions. Carbopol and HPMC have good water solubility and the co-polymer film made of these polymers fastly dissolves in water and is biocompatible for vaginal delivery. A plasticizer, PEG, which makes a film soft, elastic and flexible, was added as a film-forming agent.

Peelability is one of the important considerations in the manufacture processes and the film without PEG was excluded from the experiments because it was too brittle to conduct further analysis. Hydrophilicity and swelling index increased as Carbopol content in the film increased. It was previously observed that Carbopol uptakes more water than HPMC (Nafee et al., 2004) and an addition of Carbopol enhances the swelling rate of the tablet formulation (Mohammed and Khedr, 2003). This may explain our observations that Carbopol increased the swelling index and decreased contact angle of the polymeric films.

Since drugs from the films are released by both diffusion and erosion, the rate of erosion of the system was examined. Even though higher concentrations of Carbopol showed greater swelling capability, the erosion rate of the films decreased as Carbopol content increased, implying that Carbopol is able to not only increase the degree of the hydration and mucoadhesiveness, but also maintain the morphology of the films in the vaginal cavity. Since the cross-linked network in Carbopol enables the entrapment of drugs in the hydrogel domain, the films made of Carbopol hydrogels are neither water-soluble nor eroded. Since HPMC is a linear hydrophilic polymer which does not have a

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