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Effects of intrinsic variables on release of sodium dodecyl sulfate from a female controlled drug delivery system

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Abstract

The release profile of sodium dodecyl sulfate (SDS), a potent microbicide, from a female controlled drug delivery system (FcDDS) made of Carbopol 934P and hydroxypropyl methylcellulose (HPMC) was evaluated using a newly developed in vitro Simulant Vaginal System (SVS). The major parameters involved in the release profiles of SDS were categorized as: (1) formulation variables (total loading weight of intravaginal delivery systems, SDS loading doses in intravaginal delivery systems); (2) intrinsic variables (vaginal fluid secretion rate, vaginal fluid pH); and (3) extrinsic variables (inserting position). In most conditions, about 70% of the loading dose of SDS was released from FcDDS within 6 h of application. The release profile showed that concentrations needed for complete human papilloma virus (HPV) inactivation could be obtained within 10 min after the application. It was demonstrated that intrinsic variables (i.e., the rate and pH of vaginal fluid) played an integral role in determining the release profile of SDS, while loading dose of SDS in FcDDS did not significantly affect the percentage of the total amount of SDS released. It can be concluded that FcDDS can be exploited as a controlled delivery device for prevention against sexually transmitted diseases.

Keywords: Sodium dodecyl sulfate; Carbopol 934P; Female controlled drug delivery system; Vaginal fluid simulant; Release profile

1. Introduction

A female controlled drug delivery system (FcDDS) containing sodium dodecyl sulfate (SDS) as a microbicide was evaluated as an intravaginal delivery system for prevention of sexually transmitted diseases (STD). Carbopol 934P gel, which can adhere to and remain on the vaginal mucosa for up to 24 h, has been an excellent carrier for spermicide/microbicide (Robinson and Bologna, 1994). Hydroxylpropyl methylcellulose (HPMC) was used as a viscosity enhancer for the FcDDS (Kumar and Himmelstein, 1995). Based on our previous study, the combination of 1.5% Carbopol and 1.5% HPMC was chosen as the optimal

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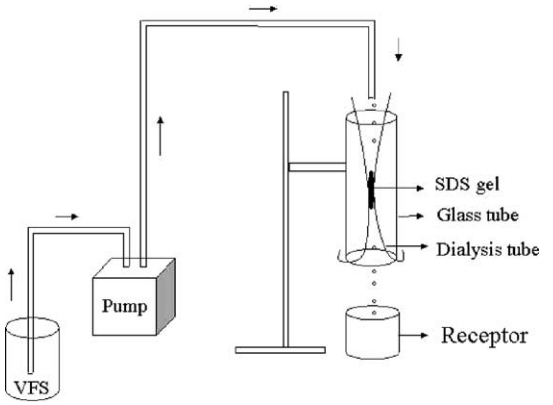

Fig. 1. Simulant Vaginal System (SVS) for the study of SDS release from FcDDS.

gel base for the delivery of SDS (Wang and Lee, 2002).

Since the biological mechanisms underlying the effect of physiological conditions on the drug release profiles and the pharmacological efficacy are complex, the release profiles of SDS from FcDDS should be monitored and quantified using a system which more closely mimics in vivo status. A Simulant Vaginal System (SVS), which was intended to simulate the human vaginal cavity, was developed to obtain the release profiles of SDS from FcDDS with various conditions. As shown in Fig. 1, SVS was equipped with a dialysis tube, which was placed inside a glass tube and loaded with FcDDS with various conditions. Vaginal fluid simulant (VFS) (∼5 ml/h) was applied on top of FcDDS with varying flow rates, which were chosen based on the physiological secretion rate (Hunter and Nicholas, 1959).

As the pharmacological efficacy of the delivery system strongly depends on the initial loading conditions of intravaginal formulations and physiological variables at the loading sites, there are a number of parameters that need to be considered in interpreting the drug release profiles and the pharmacological efficacy. The major parameters that may affect the release profile of SDS from FcDDS are summarized in Table 1. The factors can be categorized as follows: (1) formulation variables (total loading weight of intravaginal delivery systems, SDS loading doses in intravaginal delivery systems), which are adjustable during the formulation development process; (2) intrinsic variables (vaginal fluid secretion rate, vaginal fluid pH), which cannot be manipulated directly in a real situation; and (3) extrinsic variables (inserting position and inserting time before intercourse), which can be manipulated externally by customers. The degree of contribution of each variable to overall release profile was determined.

The modified Higuchi equation $Q = (2ADC_s t)^n$ was used to examine the release profile of SDS from FcDDS, in which Q is the percentage of drug released from the FcDDS at time t (in hours), n is the diffusion exponent, A is the total concentration of drug in the system, D is the diffusion coefficient of the drug in the system, and C_s is the solubility of drug in physiological buffer (Higuchi, 1963; Toddywala and Chien, 1990). Diffusion in multicomponent mixtures is usually approximated by defining one single diffusion coefficient for each solute, where the diffusion coefficient

Table 1
Factors affecting the release profile of SDS from FcDDS

Factors	Condition	Description
SDS concentration (%)	3, 5	The concentration of SDS at the application site needs to achieve the minimum effective concentration required for HPV inhibition within 2 min of initial application (Howett et al., 1999; Piret et al., 2000).
Loading weight of gel (g)	1.8, 3.0	The loading weight of SDS gel will examine the volume effects on the rate of drug release from FcDDS (Kim et al., 1992).
Flow rate of VFS (ml/h)	3, 5	The flow rate of VFS will reflect the physiological secretion rate (30–60 mg/day) of vaginal mucus at the different phases of the menstrual cycle (Ruel-Gariepy et al., 2000).
pH of VFS	4.0, 5.5, 7.4	Normal pH range of vaginal secretion is 3.0 ∼ 5.5. Menstrual and cervical secretions and semen act as alkalizing agents to increase vaginal pH (Hunter and Nicholas, 1959; White and Aitken, 1989).
Site of application (cm)	5, 10, 15	The inserting position in the vaginal cavity will affect the rate of drug release and the time required to achieve the effective microbicidal concentration at the application site (Ceschel et al., 2001).

rates the concentration gradient of the solute to its flux (Fick's law). Measurements of diffusion coefficient are typically used to predict and model the kinetics of several in vivo, medical, and pharmaceutical applications.

From the above equation, the following equation was derived: $\ln M_t/M_\infty = n\ln(2AC_sD) + n\ln t$, in which M_t/M_∞ is the percentage of the total drug released from the FcDDS at time t (in hours), n is the diffusion exponent, and K ($n\ln(2AC_sD)$) is the constant apparent release rate (% h^{-1}) (Ritger and Peppas, 1987). The values of n and K derived from the release profiles of SDS from FcDDS under various combinations of variables were compared and the contribution proportion of each variable on the release profiles was examined.

2. Materials and methods

2.1. Materials

Carbopol 934P and HPMC were obtained from BF-Goodrich (Cleveland, OH) and Dow Chemical Company (Midland, MI), respectively. SDS, ^{14}C-labeled SDS (0.1 mCi/ml), and mucin were obtained from Sigma chemical company (St. Louis, MO). All other reagents and solvents were of analytical grade.

2.2. Preparation of Carbopol–HPMC gel containing SDS

Carbopol–HPMC gel formulation containing SDS was prepared by mixing two separately prepared solutions of Carbopol and HPMC. A proper amount of SDS (the ratio of ^{14}C-labeled SDS and SDS was 1:5,000) was added into citrate buffer solution (pH 4.0) and stirred constantly until totally dissolved. One hundred grams each of Carbopol–HPMC gel containing various conditions described in Table 1 was prepared. The batch size of the gel was optimized by adjusting concentrations of a gel, conditions, and instrumentation of gelation process, viscosity, surface tension, and porosity (Wang and Lee, 2002).

2.3. Preparation of VFS at various pH values

The VFS 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, glycerol). The final pH was adjusted to pH 4.0, pH 5.5, and pH 7.4 using 5% acetic acid or 1 M sodium hydroxide.

2.4. Solubility of SDS in various buffer solutions and FcDDS

An excess amount of SDS was added to 10 ml of citrate buffer (pH 4.5) in screw-capped glass vials and subsequently agitated in a shaker at 25 °C for 24 h. After equilibration, a portion of the mixture was withdrawn and centrifuged at 12,000 rpm for 5 min. The supernatant was diluted and the concentration of SDS was determined by HPLC. The same procedure was repeated for determination of solubility of SDS in phosphate buffer (pH 7.4), VFS, and Carbopol–HPMC gel, respectively.

2.5. HPLC analysis of SDS

The HPLC system for analyzing SDS consisted of a pump (Waters 510, Milford, MA), an Octyl Ultrasphere Beckman column (250 × 4.6 mm i.d., dp = 5 μm), an RID-10A differential refractometric detector (Shimadzu, Kyoto, Japan), and an integrator (Waters). The mobile phase consisted of acetonitrile–water (55:45, v/v) and tetraethyl–ammonium bromide (2×10^{-2} mol/l). The flow rate of the mobile phase was 1.0 ml/min. The retention time of SDS was around 7.5 min.

2.6. In vitro release study of SDS from FcDDS

SVS, which simulates the hydrodynamic condition of vaginal cavity, is shown in Fig. 1. A dialysis tube (3.5 kDa cut-off) with a diameter and a length of 2.5 and 20 cm, respectively, was used as a base of the simulating vagina mucosa. The bottom of the tube was closed with a clamp and vaginal fluid simulant was added on the gel (i.e., FcDDS) loaded in SVS. The system was equilibrated with VFS for 30 min and VFS was removed by opening the clamp. The soaked dialysis tube was inserted into a modified glass tube with a diameter and a length of 2.5 and 15 cm, respectively. The bottom of the dialysis tube was opened and tied to the glass

tube, while the top of the dialysis tube remained open. FcDDS containing various concentrations of SDS (3 and 5%) or with varying gel weights (1.8 and 3.0 g) was loaded into the dialysis tube at various distances (5, 10, and 15 cm) from the bottom of the tube. VFS was dropped on top of FcDDS at various flow rates (3 and 5 ml/h) adjusted by a low-flow rate pump. The flow rates of VFS were chosen based on the reported human cervical secretion rates (Hunter and Nicholas, 1959).

The perfused VFS was collected into a receptor beaker placed under the glass tube for 6 h and the amount of ^{14}C–SDS released from the tube at predetermined time intervals was determined using a scintillation counter.

2.7. Statistical analysis

Data were expressed as the mean ± standard deviation (S.D.). The difference in mean values of solubility and the percentage of total amount released determined under the experimental conditions was statistically analyzed by a one-way analysis of variance (ANOVA) with pair wise multiple comparisons using the Student–Newman–Keuls method. P values ≤ 0.05 were considered to be statistically significant.

3. Results

3.1. Solubility of SDS in various buffer solutions and Carbopol–HPMC gel

The solubility of SDS in citrate buffer (pH 4.5), phosphate buffer (pH 7.4), VFS (pH 4.0), and Carbopol–HPMC gel was determined. The solubility of SDS in Carbopol and HPMC gel was 88.4 ± 8.8 mg/ml, which was much lower than that in VFS (176.3 ± 9.8 mg/ml). There was no significant difference in the solubility of SDS among the buffer solutions with two different pH values (172.4 ± 10.2 mg/ml for pH 4.4 and 165.1 ± 11.6 mg/ml for pH 7.4) and VFS (pH 4.0).

3.2. Effect of loading dose on the release profile of SDS from FcDDS

To evaluate the effect of the loading dose on the release rates of SDS from FcDDS, the release profiles of SDS from Carbopol–HPMC gel with two SDS concentrations (3 and 5%) were plotted as a function of time. As shown in Fig. 2, the percentage of the total SDS released from FcDDS gradually increased as a function of wearing time. In both conditions, the burst release of SDS from FcDDS was observed within the first hour. The release rate of SDS gradually increased for the next 3 h, and then reached the plateau. In both 3 and 5% SDS formulations, about 70% of the total SDS loaded in the FcDDS was released within 6 h, indicating that the loading dose of SDS had no statistically significant effect on the release rate of SDS from FcDDS. Different from the conventional drug release profile, in which the most common procedure for identifying an optimal release behavior of such polymer-based systems has been on dose levels, externally added VFS seemed to eradicate the effect of the loading concentration on the release rate of SDS from FcDDS.

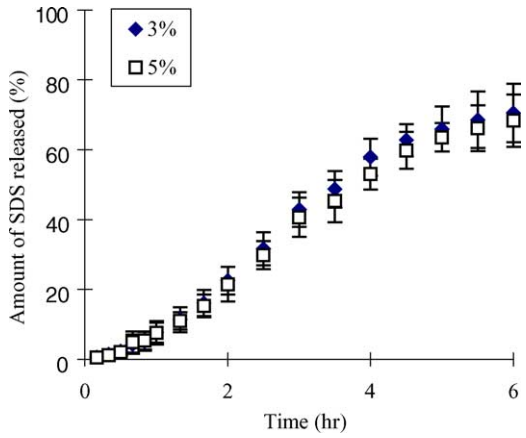

Fig. 2. Effects of the SDS concentration on the release profile of SDS from FcDDS (dose: 3 and 5%; weight: 1.5 g; flow rate: 3 ml/h; pH of buffer: 4.0; insertion position: 10 cm).

3.3. Effect of loading weight of the gel on the release profile of SDS from FcDDS

Two weights (1.8 g of 5% SDS gel and 3 g of 3% SDS gel) of FcDDS were loaded on the SVS and the effect of loading weight of the gel on the release profile of SDS was evaluated (Fig. 3). The release rate and the percentage of the total SDS released from 1.8 g gel (3 ml/h) were much greater than those from the 3 g gel (3 ml/h). Since the total loaded amounts of SDS in the gels were same (0.09 g of SDS) in both gels, 1.8 g of the 5% gel had a higher concentration of SDS than

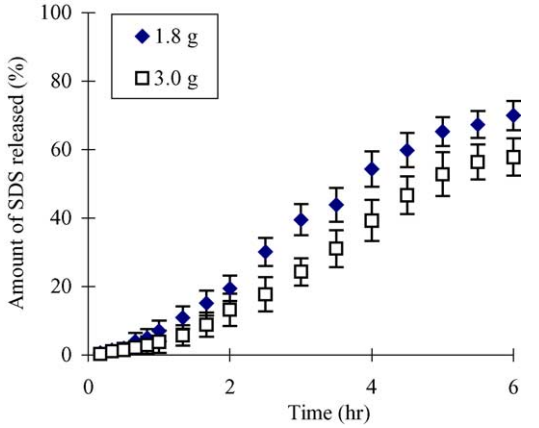

Fig. 3. Effects of the loading weight of gel on the release profile of SDS from FcDDS (dose: 5 and 3%; weight: 1.8 and 3.0 g; flow rate: 3 ml/h; pH of buffer: 4.0; insertion position: 10 cm).

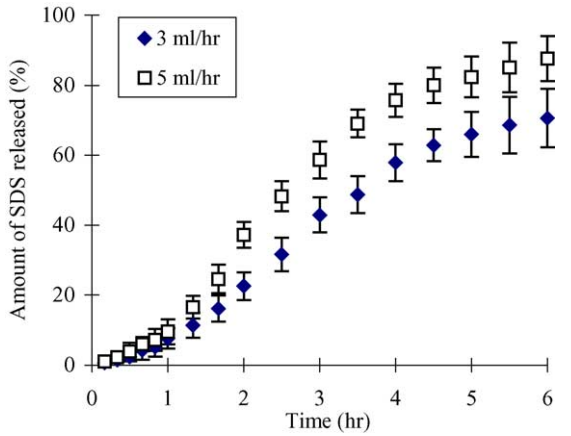

Fig. 4. Effects of the flow rate of VFS on the release profile of SDS from FcDDS (dose: 3%; weight: 1.5 g; flow rate: 3 and 5 ml/h; pH of buffer: 4.0; insertion position: 10 cm).

3 g of the 3% gel. Therefore, under the same physiological conditions, the release rate of SDS from the lower weight formulation (1.8 g gel) was much greater than that of the 3 g gel. This indicated that there was a volume effect of gel on the release rate of SDS from FcDDS.

3.4. Effect of flow rate of VFS on the release profile of SDS from FcDDS

The effect of the flow rates (3 and 5 ml/h) of VFS added on top of gel on the release rate of SDS is shown in Fig. 4. The release rate of SDS with a VFS flow rate of 5 ml/h was much greater than that with a flow rate of 3 ml/h. As the rate of VFS added into FcDDS increased (i.e., a higher flow rate), the release rate of SDS increased, indicating that a higher flow rate influences a driving force of drug release from the gel formulation. After 6 h, the percentage of the total SDS released from FcDDS with a VFS flow rate of 5 ml/h was about 20% greater than that with a VFS flow rate of 3 ml/h. The results of this study have clearly demonstrated that the secretion rate of VFS has an integral role in determining the release profiles of SDS from FcDDS.

3.5. Effect of pH of VFS on the release profile of SDS from FcDDS

The effect of pH of VFS on the release profile of SDS from FcDDS was evaluated using VFS with various pH values. The release rate of SDS in the presence of VFS (3 ml/h) with pH 4.0 was much greater than that in the presence of VFS (3 ml/h) with pH 7.4, as shown in Fig. 5. There were differences in the release rate of SDS between VFS of pH 4.0 and 5.5. The total percentage of SDS released from FcDDS in the presence of VFS with pH 5.5 was reduced by about 20% as compared with that in the presence of VFS with pH 4.0. The physicochemical characteristics of the Carbopol–HPMC gel may account for the differences in the release profiles of SDS among VFS with different pH values. As the

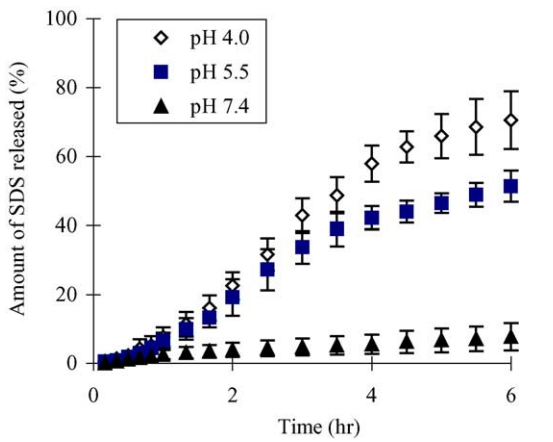

Fig. 5. Effects of the pH of VFS on the release profile of SDS from FcDDS (dose: 3%; weight: 1.5 g; flow rate: 3 ml/h; pH of buffer: 4.0, 5.5, and 7.4; insertion position: 10 cm).

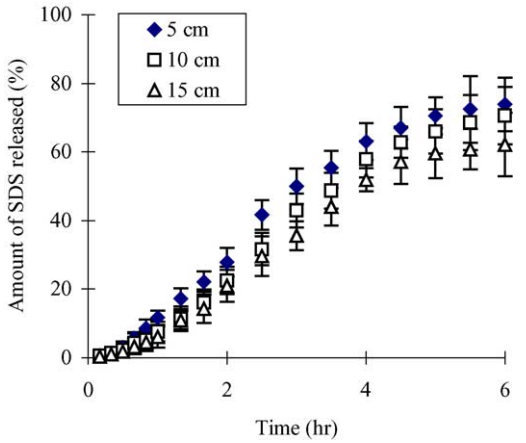

Fig. 6. Effects of the insertion position on the release profile of SDS from FcDDS (dose: 3%; weight: 1.5 g; flow rate: 3 ml/h; pH of buffer: 4.0; insertion position: 5, 10, and 15 cm).

pH of the gel increases from 4.0 to 7.4, the viscosity of the Carbopol–HPMC gel increases and the gel system becomes more resistant to external pressure. VFS with pH 7.4 significantly reduced the release rate of SDS from FcDDS, achieving about 8% SDS released from the total amount loaded in the system for 6 h. The pH of VFS prominently affected the release rate of SDS from FcDDS.

3.6. Effect of insertion position on the release profile of SDS from FcDDS

The effect of an insertion position of FcDDS in the vagina cavity on the release rate of SDS is shown in Fig. 6. The insertion position refers to the distance between the loaded site of the gel and the bottom of the tube. The gel starts moving downward as the fluid is gradually added on the gel, which may also take place in vivo situation. The release rate of SDS from FcDDS at the insertion position of 5 cm (3 ml/h) was greater than that at 15 cm (3 ml/h), but which was not significantly different. Even though it was expected that the shorter distance might expedite the release rate of SDS from the FcDDS into the receptor compartment, this was not clearly demonstrated in this system.

3.7. Analysis of release profile

The kinetic data of drug release profile were examined to determine whether they fit the following equation, $\ln M_t/M_\infty = \ln K + n\ln t$ (Ritger and Peppas, 1987). The values of n and K derived from SDS release profiles from FcDDS under various combinations of variables were determined. Since most of the SDS release profiles reached a plateau within about 4 h, at which about 60% of the total SDS loaded was released, the release profile from 0 to 4 h was used for the calculation of the release flux and values of n and K. As shown in Table 2, the experimental condition of VFS with pH 7.4 at a flow rate of 3 ml/h produced the n value of 0.59, which is close to the standard n value of the Higuchi equation ($n = 0.5$). When VFS with acidic pH (4.0 or 5.5) was added on top of FcDDS, the n values increased up to 1.52. The apparent release rate was 2.56% h^{-1} under the experimental conditions of pH 7.4 VFS at a flow rate of 3 ml/h, while the apparent release rate varied within a range of 5.76–7.38% h^{-1} as the pH of VFS was changed from neutral to acidic pH (5.5 or 4.4). The apparent release rate significantly increased from 7.38 to 8.38% h^{-1} as the flow rate of VFS was changed from 3 to 5 ml/h. The observed variation from the Higuchi

Table 2
Diffusion exponents and K values of SDS released from FcDDS under various conditions

Variables	Conditions	n	K (% h^{-1})	R^2
Effect of loading weight	5%, 1.8 g, VFS pH 4.0, 3 ml/h, 10 cm	1.45	7.20 a	0.9938
	3%, 3.0 g, VFS pH 4.0, 3 ml/h, 10 cm	1.43	5.85 a	0.9931
Effect of VFS flow rate	3%, 1.8 g, VFS pH 4.0, 3 ml/h, 10 cm	1.46	7.38 b	0.9952
	3%, 1.8 g, VFS pH 4.0, 5 ml/h, 10 cm	1.52	8.36 b	0.9932
Effect of VFS pH	3%, 1.8 g, VFS pH 4.0, 3 ml/h, 10 cm	1.46	7.38 c	0.9952
	3%, 1.8 g, VFS pH 5.5, 3 ml/h, 10 cm	1.41	5.76 c	0.9909
	3%, 1.8 g, VFS pH 7.4, 3 ml/h, 10 cm	0.59	1.77 c	0.9938

There are significant differences between numbers with the same letter (a–c) ($P < 0.05$).

equation indicated that the erosion of the polymer matrix driven by externally added VFS on the gel was the major force that shaped the release profile of SDS from FcDDS.

3.8. Implication of SDS release rate on the pharmacological efficacy of FcDDS

According to reported physiological data, about 0.5–0.75 g mucus is present in the vagina at any time in healthy women of reproductive age. Based on the maximum vaginal secretion rate (5 ml/h) and the maximum volume of mucus in the vagina (0.75 ml) (Hunter and Nicholas, 1959), the concentration of SDS in the mucus upon being released from FcDDS could be calculated. The target SDS concentration in the vaginal mucus within 10 min after loading of FcDDS was about 0.04%, which is much greater than the required SDS concentrations to achieve total inactivation of human immunodeficiency virus (HIV)-1 and HIV-2, which are 0.025 and 0.0125%, respectively. These criteria were used to evaluate the pharmacological efficacy of FcDDS. Most formulations including that tested under VFS with pH 7.4, which had the lowest release rate among tested conditions, met the minimum concentration required for the pharmacological activity within 10 min of insertion in vagina, indicating that FcDDS is well controllable device for an intravaginal delivery of SDS against pathogens of STD.

4. Discussion

A female controlled drug delivery system in a form of Carbopol gel has been developed as an intravaginal delivery system to prevent the onset of sexually transmitted disease including human immunodeficiency virus and human papilloma virus (HPV). FcDDS is a mucoadhesive formulation, whose adhesiveness is controlled by Carbopol concentration. It was reported that higher viscous bioadhesive polymer gel enhanced the duration period of mucosa contact, while the release rate of a drug molecule from polymer-based gel remained as fast as it is in water (Upadrashta et al., 1993). The ability of Carbopol gel to attach to lymphocytes also makes them a site-specific drug delivery system for AIDS prophylaxis (Maguire et al., 2001), since human immunodeficiency virus is known to attack the lymphocytes during the transmission.

FcDDS was loaded with sodium dodecyl sulfate, an alkyl sulfate surfactant derived from an organic alcohol (Howett et al., 1999), which functions as a protein denaturant at low concentrations and as a surfactant at high concentrations (Piret et al., 2000; Krebs et al., 2000). It denatures and unfolds both monomeric and subunit proteins. Like other microbicide, SDS is a detergent that dissolves the fatty coating that holds those viruses together. SDS is a potent microbicide against human immunodeficiency virus, human papilloma virus, and herpes simplex virus (HSV) at concentrations comparable to those used for N-9 (Krebs et al., 1999; Piret et al., 2000). Even though HPV is coated with tightly packed proteins that some microbicide like nonoxynol-9 (N-9) cannot dissolve, SDS acts as a denaturing agent that separates those proteins apart (Krebs et al., 2000). SDS, even at very low concentrations (<0.025%), completely inactivated HSV, HIV, and HPV upon its brief exposure to them at body temperature (Piret et al., 2000). Total HSV-2 inactivation was achieved with SDS concentrations between 0.0125 and 0.025%, and total HIV-1 inactivation was achieved with SDS concentrations as low as 0.025% (Howett et al., 1999). SDS is reported to be of low intrinsic toxicity to skin and to mucous membranes (Krebs et al., 1999).

Due to difficulties in monitoring intrinsic factors in the closed system (i.e., vaginal cavity), the drug release profiles from FcDDS should be evaluated with a proper testing device. We have developed a “Simulant Vaginal System” that closely mimics the physico-dynamic conditions of the vagina and was used to properly predict drug release profiles and pharmacological efficacy based on the intrinsic variables (i.e., pH and vaginal secretion rate). FcDDS made of Carbopol and HPMC containing SDS achieved the effective concentration against STD pathogens within 10 min after application, which makes FcDDS as a fast-responsive prevention device against STD, and maintained a controlled release rate of SDS for up to 6 h under the normal physiological conditions.

The release profiles of drugs from a polymer matrix system usually follow the Higuchi equation. In our study, the n value for the release profile of SDS from FcDDS upon addition of VFS at pH 7.4 was 0.59, which is close to that fit the Higuchi equation, but the release profiles of SDS from FcDDS under the conditions other

than pH 7.4 did not fit the Higuchi equation. This can be explained by the viscosity changes in FcDDS upon exposure to VFS with various pH and flow rates. The viscosity of the Carbopol–HPMC gel increased significantly, when the pH value of the gel was changed from acidic to neutral. When VFS with pH 7.4 was added on top of the FcDDS, the viscosity of FcDDS kept increasing; this subsequently increased the adhesion force of FcDDS to and retention time of FcDDS at the simulated vagina mucosa. Under the higher adhesion force within the FcDDS, the release profile of SDS from FcDDS well fits the Higuchi equation. When VFS with pH 4.0 or 5.5 was added on top of FcDDS, the viscosity of FcDDS decreased as did the adhesion force of FcDDS to a mucosal surface. When the adhesion force was less than a critical value, part of the gel began to diffuse out of the SVS, causing a rapid release of SDS from FcDDS, and the release profile did not follow the Higuchi equation any more.

5. Conclusion

FcDDS was evaluated as a potential preventive device against STD. SVS, as an in vitro simulated model, was developed to investigate the effects of various parameters on the percentage of the total SDS released from FcDDS. The release profiles of SDS from FcDDS are greatly affected by the vagina flow rate and its pH, while the loading dose of SDS in FcDDS had no statistically significant effect. FcDDS should be subsequently adjusted to accommodate the effects of the intrinsic variables before being made available for clinical application. From the release profile, we found that concentrations needed to achieve total HIV-1 and HSV-2 inactivation could be obtained within 10 min after the application of FcDDS. Therefore, FcDDS containing SDS can be exploited as a well-controlled intravaginal system for prevention of STD. Confirmation of a modeling-based examination of delivery systems will lead to an efficient preventive strategy against STD with a high degree of confidence and at a high level of functional integration.

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