# Microbicide Dosage Forms

**L. C. Rohan, B. Devlin and H. Yang**

**Abstract** Microbicides are topically applied, user controlled dosage forms that are being developed to prevent the transmission of HIV during coitus. Early candidates focused on coitally dependent dosage forms such as gels and creams. More recent development has focused on broadening the coitally dependent options through the introduction of films and fast dissolving tablets. Additionally, it has become important to have longer acting products to minimize the burden of user compliance and thus vaginal rings have been developed providing sustained delivery of antiretroviral drugs. This chapter discusses the history of microbicides along with a detailed description of coitally dependent products, gels, films, tablets diaphragms, as well as coitally independent dosage forms such as vaginal rings and the introduction of a new technology, electrospun fibers.

## Contents



L. C. Rohan (✉) · H. Yang
Department of Pharmaceutical Sciences, School of Pharmacy,
University of Pittsburgh Magee Women's Research Institute,
Pittsburgh, PA, USA
e-mail: rohanlc@upmc.edu

B. Devlin
International Partnership for Microbicides, Silver Spring, MD, USA
e-mail: bdevlin@ipmglobal.org

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## 1 Microbicide Products

Microbicides are products that can be applied vaginally or rectally to protect the user from acquiring HIV and, possibly, other STIs. Many variables can impact the in vivo effectiveness of any given microbicide product such as the anti-HIV activity (efficacy of the product), the user's willingness and ability to use the product as instructed (acceptability and adherence), the safety of the formulation, and HIV 'dose'-related variables (Morrow and Hendrix 2010). The appropriate drug-delivery strategy for each microbicide drug candidate will depend upon many variables such as the physicochemical characteristics and pharmacokinetic profile of the candidate, its mechanism of action against HIV-1 transmission, its dosing regimen, delivery route, and patient acceptability (Buckheit et al. 2010). Microbicide products can be classified as coitally dependent or non-coitally dependent. Coitally dependent microbicides are applied immediately before and/or after intercourse, whereas coitally independent products are applied and provide sustained protection over time.

During the past two decades, the majority of microbicide product development has focused on vaginally applied products. However, receptive anal intercourse (RAI) is practiced by both MSM and women around the world (Kalichman et al. 2009; Chandra et al. 2011). In fact, a US national survey found that 36 % of female responders aged 25–44 had ever had anal sex with an opposite-sex partner (Chandra et al. 2011). Development of a microbicide that is effective and safe in both mucosal compartments (vaginal and rectal) should be considered (Minces and McGowan 2010). Rectal microbicide research is currently in the early phase of clinical development. Aside from a number of studies designed to investigate the behavior of placebo products in the rectum, a few studies have evaluated rectally applied microbicide products contacting antiretrovirals. These studies are focused on the drug safety and acceptability evaluation for rectal use, such as of tenofovir gel (McGowan et al. 2013) and UC781 (Ventuneac et al. 2010).

## 1.1 History of Clinically Evaluated Microbicides

### 1.1.1 Early Generation Microbicides: Nonspecific or Moderately Specific

Initial products developed as vaginal microbicides contained agents which did not directly affect the life cycle of the HIV virus. These nonspecific antiretroviral microbicides were surfactants/detergents (Weber et al. 2005). Three surfactants were tested clinically as microbicides. These were products containing nonoxynol 9 (N-9) (gel, sponge and film), SAVVY® or C31G gel, and sodium lauryl sulfate (SLS) gel.

Acidifying agents help to restore or maintain the protective acidic pH of the vagina. Acidifying agents clinically assessed for safety and effectiveness against male-to-female HIV-1 transmission include BufferGel and Acidform. Both BufferGel and Acidform are acid-buffering bioadhesive vaginal gels. BufferGel was found to be well tolerated, but not effective for the prevention of HIV-1 vaginal transmission in a Phase II/IIb trial (Abdool Karim et al. 2011). Acidform vaginal gel was found to have favorable formulation properties (Garg et al. 2001). However, no clinical effectiveness trials pertaining to the prevention of male-to-female vaginal transmission of HIV-1 have been reported for Acidform.

The next microbicide candidates evaluated were primarily macromolecular linear anionic polymers (Balzarini and Van Damme 2007). Their anti-HIV mechanism of action centered on their ability to block viral entry into cells (Weber et al. 2005). These agents carry negative charges, which result in a charge interaction with viral envelope proteins blocking the binding of the virus to target cells. Such microbicide candidates include Carraguard® gel, cellulose sulfate gel, cellulose acetate phthalate gel, VivaGel®, and PRO2000 gel. In a Phase III study of Carraguard it was found to be safe but ineffective against vaginal transmission of HIV (Skoler-Karpoff et al. 2008). Cellulose sulfate was also found to be ineffective, while the PRO2000 showed an increased risk of HIV infection (Tao et al. 2008).

This early work in microbicide product development provided a number of lessons: nonspecific agents, e.g., surfactants, are unlikely to provide protection against HIV transmission and may increase HIV infection risk; moderately specific agents, e.g., some polyanions have little effect but are safe; and product adherence is crucial for protection. These lessons led to an emphasis in the field for evaluation of specific or antiretroviral containing microbicide products.

### 1.1.2 Specific Microbicide Products

Due to the clinical failure of early microbicide candidates development efforts in the field have now shifted to antiretroviral microbicide candidates that directly and specifically act against the HIV life cycle, namely specific antiretroviral products (ARVs). The two classes of ARVs being most widely evaluated are entry inhibitors

and reverse transcriptase (RT) inhibitors (Balzarini and Van Damme 2007). Evaluation of other classes such as HIV integrase inhibitors is also beginning to emerge (Reeves and Piefer 2005).

The majority of antiretrovirals under current clinical investigation are reverse transcriptase inhibitors (RTIs). Tenofovir is the most widely studied RTI microbicide candidate to date. Several Phase I studies demonstrated the safety and pharmacokinetics of tenofovir (Mayer et al. 2006; Beigi et al. 2011; Keller et al. 2011). A Phase IIb trial (CAPRISA 004) to assess the safety and effectiveness of tenofovir 1 % gel in the prevention of male-to-female HIV transmission was performed in South Africa (Abdool Karim et al. 2010). The results of this trial showed that tenofovir gel use was associated with an overall 39 % decrease in HIV-1 acquisition, which is statistically significant. Additionally, among women with high gel adherence, the tenofovir gel reduced HIV infection by 54 % in comparison to placebo gel (Abdool Karim et al. 2010). The results of CAPRISA 004 have paved the way for future vaginal microbicide trials by providing proof-of-concept for antiretrovirals as microbicides for HIV prevention. The Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial is a Phase IIb five-group study examining the safety and efficacy of daily oral tenofovir disoproxil fumarate, oral Truvada® (a fixed dose combination of tenofovir disoproxil fumarate and emtricitabine), oral placebo, tenofovir 1 % vaginal gel and placebo vaginal gel in HIV-negative women in Malawi, South Africa, Uganda and Zimbabwe (also called MTN 003). This daily-use regimen of a vaginal microbicide (topical PrEP) and oral PrEP differs from the coitally dependent regimen utilized in CAPRISA 004 and earlier microbicide efficacy trials. In September 2011, it was recommended that the VOICE participants randomized to oral tenofovir be discontinued from this group due to futility. In November 2011, VOICE discontinued use of tenofovir gel as it concluded from an interim evaluation that the gel was "not effective in preventing HIV in the women enrolled in the VOICE trial."

Tenofovir is not the only antiretroviral that is being clinically tested. Formulations of UC781 and dapivirine, both non-nucleoside RTI (NNRTIs), have been clinically evaluated. Early-phase trials of these NNRTI formulations looked to assess short-term safety, tolerability, acceptability, and PK of these products (Neurath et al. 1999; Jespers et al. 2007; Schwartz et al. 2008b; Nel et al. 2009a, 2010a, b). To date, early-phase clinical trials have found RTIs to be generally safe and well tolerated. Additionally, a Phase I safety and PK trial of a dapivirine/maraviroc (NNRTI/CCR5 co-receptor antagonist) IVR was conducted (MTN-013/IPM 026). Studies involving the delivery of specific antiretroviral agents in vaginal polymeric quick-dissolving films and tablets are also planned or ongoing.

Although the potent antiviral activity of a microbicide candidate is essential, the formulation or delivery system plays a key role in developing these candidates into practical dosage forms with safety, acceptability, and effectiveness in clinical application. Different formulations are being evaluated for vaginal delivery of microbicide candidates including gels, rings, films, tablets, and suppositories. In this chapter microbicide dosage forms (gel, film, vaginal ring and tablet) will be discussed in detail.

## 1.2 Vaginal Drug Delivery

Vaginal drug delivery systems can be designed to achieve topical or systemic effect. The earliest record of vaginal product use was in Egypt in 1850 BC (O'Dowd 2001). Numerous records also show the application of vaginal formulations in Greece and Rome from the Middle Ages, and later Renaissance, through modern day. Modern vaginal administration of drug was fully recognized in 1918 after Macht reported drug absorption in vagina (Macht 1918). Since then, many chemicals or therapeutics have been administered vaginally, especially steroids, prostaglandins, and antimicrobials.

The major advantages of the vaginal route of administration for systemic drug delivery are the avoidance of hepatic first-pass metabolism (thus increasing drug exposure), and reducing gastrointestinal side effects, and decreasing hepatic side effects such as those seen with steroid application (Vermani and Garg 2000). The rate and extent of drug absorption and blood drug concentration after intravaginal administration are dependent on formulation factors, vaginal physiology, age, and menstrual cycle. Most drugs in vaginal formulations are indicated for the treatment of topical conditions such as vaginitis and other vaginal infections, and include antimicrobials (Bradshaw et al. 2012), labor inducers (Seeras 1995; Seeras et al. 1995), spermicides (Iyer and Poddar 2008), and sexual hormones for postmenopausal symptoms (Rad et al. 2006). Vaginal preparations are traditionally used for local treatment, however, systemic effects via the vaginal route can also be achieved (Alexander et al. 2004; Song et al. 2004). Vaginal drug delivery systems include a large variety of dosage forms such as foams, creams, gels, ointments, pessaries, tablets, capsules, films, tampons, vaginal rings, and douches. Generally, these dosage forms can be classified into solid, semisolid, and liquid formulations. For microbicide products these dosage forms can be further categorized with regard to their coital dependence for use as shown in Fig. 1.

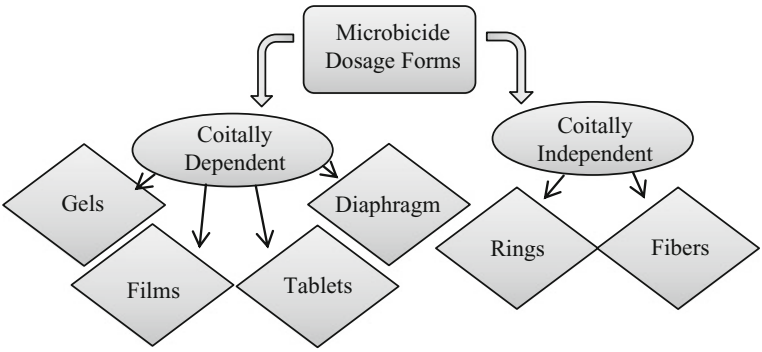


**Fig. 1** Types of microbicide dosage forms

# 2 Coitally Dependent Dosage Forms

## *2.1 Gels*

### 2.1.1 What are Gels?

Gels are defined as semisolids in which suspensions of (small) inorganic particles or (large) organic particles are interpenetrated by a liquid (aqueous or non-aqueous). The majority of vaginal products marketed fall into this category. Familiarity of users with gel dosage forms for vaginal drug delivery as well as their ability to provide lubrication during sexual intercourse is an advantage of this dosage form. Gels present a number of additional features which contribute to their wide use as vaginal preparations such as consistency, good spreadability, bioadhesion, acceptability, feasibility, and generally low manufacturing cost. The main disadvantages associated with vaginal gel products are messiness and leakage (Hussain and Ahsan 2005). The preponderance of microbicide gel products evaluated to date are hydrogels, or aqueous gels. The application of hydrogels for biomedical use dates back to 1960 when Wichterle and Lim developed a cross-linked poly (hydroxyethyl methacrylate) (pHEMA) (Wichterle and Lim 1960). Since that time the use of hydrogels in the biomedical and pharmaceutical field has been widespread.

### 2.1.2 Microbicide Gel Product Components

Vaginal gels being developed as microbicides most commonly employ water soluble polymers as gelling agents. Generally, gels are manufactured by the addition of polymers and other excipients to water with continuous mixing. Cellulose derivatives like hydroxyl ethyl cellulose (HEC) and poly acrylic acid derivatives like Carbopol 974P are the most commonly used polymers due to their generally recognized as safe (GRAS) status, cost effectiveness, and safety profile. The universal placebo gel used as a placebo control in a large number of microbicide clinical trials consists of 2.7 % w/w HEC as the gelling agent. Another common practice in the formulation of gel products is to include preservatives to avoid bacterial growth within the product upon storage. A combination of methyl paraben and propyl paraben is one of the most widely utilized preservative systems in microbicide products currently being evaluated. Many vaginal gels also contain cosolvents, humectants (such as glycerin, polyethylene glycol, and propylene glycol), buffering agents, and acidifying agents to improve aesthetic aspects of the product and to also aid in solution of the drug substance and stability. In addition to traditional gels, nonaqueous/lipid gels (Politz et al. 1994; Forbes et al. 2011), thermoreversible gels (Roy et al. 2001; Escobar-Chavez et al. 2006), and bioresponsive gels (Gupta et al. 2002; Chen et al. 2012) are being developed. A silicone

hydrogel preparation was developed as a microbicide product for the delivery of the CCR5 antagonist, maraviroc. This product resulted in a high concentration of maraviroc in plasma, vaginal fluids, and vaginal tissue in rhesus macaques (Forbes et al. 2011).

### 2.1.3 Historical Overview of Microbicide Gel Products

Gels have been historically the most common drug delivery formulation for microbicides. In clinical studies conducted to date, gel products have been applied as a single daily dose or as a single dose before and/or after sexual intercourse. Early clinical trials for nonspecific microbicide drug candidates utilized the gel formulation platform. The first gel tested as a microbicide was the marketed contraceptive product which contained N-9. Other gel products evaluated were SAVVY® (C31G gel), a sodium lauryl sulfate gel, cellulose sulfate, Carraguard®, acidifying agents (BufferGel and Acidform), VivaGel, and PRO2000. Although many of the gels were found to be safe, to date no nonspecific microbicide drug containing gel clinically tested has been found to be effective.

Gel dosage forms containing specific microbicide drug candidates have also been evaluated. A number of these candidates tested are viral replication inhibitors. A tenofovir gel product was found to be both safe and effective, resulting in an overall statistically significant 39 % decrease in HIV-1 acquisition in the CAPRISA 004 Phase IIb clinical trial. However when this gel was tested in the VOICE Phase IIb clinical trial utilizing a varied dosing regimen the gel was found not to be effective in preventing HIV. A third trial which utilizes the same dosing regimen as the CAPRISA trial is ongoing. Other non-nucleoside reverse transcriptase inhibitor microbicide drug products which have been studied include UC781 and dapivirine.

#### *Evaluation of Microbicide Gels*

There are several critical product assessment tools which are utilized to evaluate potential microbicide gel products. Of central importance are the evaluations of gel safety, anti-HIV activity, and physical and chemical characterization including stability assessments. It is known that gel characteristics can change over time and upon exposure to certain environmental conditions. These product changes may result in variation of gel product in vivo performance (Gallagher et al. 2003). Critical characteristics of gels might include API content and uniformity, pH, osmolarity, and viscosity.

Safety is essential for a microbicide gel product. The failure of clinical trials of nonoxynol-9 (N-9) and cellulose sulfate gels highlights the importance of safety considerations in microbicide gel product development. Results from clinical trials indicate that minor perturbation of the vaginal membrane could significantly increase the susceptibility of women towards HIV infection. The excipients, pH,

and the osmolality of a vaginal microbicide gel could have profound effects on the vaginal environment and epithelium which could lead to toxicity or enhanced infection (Turpin 2011). Irritation caused by gels could also compromise patient adherence to the products. In addition to consideration of the effect of a microbicide gel product on the vaginal epithelium, it is also important to consider its effect on the innate microflora. The acidic pH environment of the vagina is maintained by the microflora, specifically *Lactobacillus* species, and increased vaginal pH can result in enhanced susceptibility to HIV infection. Thus, a safe microbicide should not have any toxic effects on innate vaginal lactobacilli (Martin et al. 1999). Additionally, it has been shown that hyperosmolality of products is associated with mucosal irritation and tissue damage in the slug mucosal irritation model (Adriaens and Remon 2008). In a phase I trial unacceptable vulvo-vaginal side effects were observed with use of a hyperosmolar vaginal microbicide product (Lacey et al. 2010). Furthermore, some commonly used gel excipients such as glycerin and disodium EDTA were shown to increase the susceptibility of mice to HSV-2 infection in a dose-dependent manner. In the same mouse model, propylene glycol and polyethylene glycol-8 also increased HSV-1 susceptibly by >10 times (Moench et al. 2010). These reports indicate that the selection of excipients and their concentration in microbicide gels can have a profound effect on the safety of a microbicide product. Formulation excipients or excipient combinations may lead to not only irritation and toxicity but also enhanced infection.

Several models have been utilized to evaluate bioactivity of microbicide drug candidates as described by Shattock and Herrera (2013). Most cell-based models for activity are limited in their usefulness due to the requirement of significant dilution of the gel product because of its high viscosity. The most widely used model is an ex vivo challenge model in which vaginal, cervical, or colorectal tissue is exposed to the gel product and subsequently challenged with HIV virus.

Evaluation of gel product drug release is an important product performance and quality control assessment. A simple, reliable, and reproducible release rate method can guide formulation development and monitor manufacturing reproducibility and product stability. The FDA published SUPAC-SS guidance details release testing for active pharmaceutical ingredients from semisolid dosage forms after certain post approval changes (FDA 1997). Several in vitro models have been applied to evaluate drug release from gels such as the Franz cell diffusion system, the enhancer cell, and flow through cell apparatuses. Generally, drug release from semisolid preparation from Franz cell and Enhancer cell are the same once the data are standardized by surface area (Kumar 1993; Fares and Zatz 1995). The Franz cell diffusion system is one of the systems recommended by the FDA for evaluating drug release from topical gels for vaginal use (Shah et al. 1989; Siewert et al. 2003). The Franz cell system was utilized to compare two formulations (3.0 % hydroxyethyl cellulose (HEC) formulation and a 0.65 % Carbopol) for IQP-0528, a NNRTI being evaluated for use as a microbicide product. Diffusion-controlled release of IQP-0528 was observed for both gel formulations (Mahalingam et al. 2011).

Rheological testing is normally conducted for microbicide semisolid products because these properties may be critical to the success of the product. Specifically, the viscosity of the product can be monitored to assess product stability (Tamburic and Craig 1996) and can also impact product performance in vivo. Once a microbicide gel is applied to the vagina, these preparations will be diluted by vaginal fluid and during coitus will be further diluted with semen and exposed to shear forces through coital activity. Thus, the viscosity changes under these conditions should be evaluated. Owen et al. evaluated the rheological properties of several gel formulations using vaginal or cervical fluid simulant (Owen et al. 2003). The dilution of gels with vaginal or cervical fluid simulant may reduce the anti-HIV activity performance. Sassi et al. reported that hydrogel products of UC781 maintained greater activity against HIV-1 as compared to liposomal products after dilution with vaginal/cervical fluid simulant (Sassi et al. 2008).

Currently, most hydrogel microbicide gels are coitally dependent products, which could provide anti-HIV activity by forming a physical barrier after application. If a physical barrier to virus entry is a desired characteristic of a microbicide, then it is important that complete coating of the vaginal mucosa surface is achieved to obtain maximum barrier function. In one study it was predicted that a gel layer thickness of 150 μm was needed to reduce HIV transport in an in vitro model (Lai et al. 2010). Mahalingam et al. presented a preclinical algorithm for use in design of gel products with specific mechanical properties using biomechanical modeling of gel spreading. Their model presents relationships between gel composition and spreadability (Mahalingam et al. 2010). Furthermore, coital activity as well as dilution with fluids can impact the vaginal coverage achieved by a particular semisolid formulation.

*Gel Applicators*

Microbicide gels are semisolid formulations, generally with high viscosity, and an applicator is required to vaginally apply semisolid products. Several types of applicators have been utilized for microbicide administration. Applicators can be refillable or disposable. Most applicators are made of high density polyethylene/polypropylene (HDPE) or low density polyethylene/polypropylene (LDPE). Two important considerations for vaginal applicators are compatibility with the microbicide product and the potential for vaginal trauma, epithelial damage, and irritation from applicator use. Such damage could lower patient compliance or result in reduced natural barrier function, both of which could potentially lead to microbicide product failure. Therefore, it is essential that applicators are adequately evaluated to determine their suitability for use with microbicides.

## 2.2 Films

### 2.2.1 The History and Background of Polymeric Thin Films

Thin polymeric films are solid dosage forms which consist of an active agent incorporated into a polymeric matrix. When applied to a mucosal surface the film disintegrates and releases the active drug agent. Oral thin films were first introduced in the 1970s. In 2001, Pfizer introduced the Listerine® Strip to freshen breath and by 2006, nine oral thin films were marketed worldwide. The initial thin films that were marketed were for consumer or cosmetic products. In 2010, the first prescription oral thin film drug product (Zuplenz) was introduced in the United States. Over the years this dosage form has become widely used.

The first vaginal film introduced was the contraceptive vaginal film. In 1973, an article published in the journal Contraception evaluated C-Film (Lichtman et al. 1973). C-Film was a water soluble film measuring 2″ × 2″ inch which contained the nonionic spermicide nonylphenoxypolyethoxyethanol (Nonyl-9) and was designed to be placed in the vagina 30 min prior to sexual intercourse for protection from unwanted pregnancy. Vaginal film formulations of nonoxynol-9 (N-9) (Mauck et al. 1997a, b, c; Roddy et al. 1998) and some feminine hygiene products are also commercially available. Apothecus Pharmaceutical Corporation in New York, USA currently markets three vaginal film products, the Vaginal Contraceptive Film (VCF), VCF Lubricating Film, and Vaginal Scented Film.

In addition to vaginal films being used for the delivery of the contraceptive agent N-9 (Mauck et al. 1997a, b, c; Roddy et al. 1998), polystyrene sulfonate (PSS), an antimicrobial contraceptive agent, was formulated in a vaginal film (Garg et al. 2005). The PSS films were colorless, transparent, thin, soft, and tough, and found to rapidly dissolve in physiologic fluid in in vitro studies. Several other pharmacologically active agents have been developed as vaginal films. Metronidazole (Kawarkhe and Poddar 2010) and clindamycin phosphate (Dobaria and Mashru 2010) were formulated into vaginal film dosage forms as treatment for bacterial vaginosis (BV). The antifungal drugs clotrimazole (Sudeendra et al. 2010) and itraconazole (ITR) (Dobaria et al. 2009) were both formulated as vaginal films for treatment of vaginal candidiasis. A film formulation was studied which contains s-nitrosoglutathione, an endogenous NO donor, for use in female sexual arousal disorder (FSAD) (Yoo et al. 2009).

A number of drug candidates being evaluated for their use in HIV prevention have also been formulated as film dosage forms, including several with nonspecific action against HIV such as sodium dodecyl sulfate (SDS) (Yoo et al. 2006) and cellulose acetate phthalate (Neurath et al. 2001, 2003) cellulose acetate 1,2 benzenedicarboxylate (Trifonova et al. 2006) and the nucleoside reverse transcriptase inhibitor zidovudine (AZT) (Chatterjee et al. 2010), the non-nucleoside reverse transcriptase inhibitors UC781 (Yang et al. 2008), dapivirine (Akil et al. 2011), and the pyrimidinedione IQP-0528 (Ham et al. 2012) and the gp120 inhibitor RC-101 (Cole et al. 2010; Sassi et al. 2011). A number of other anti-HIV agents

are being formulated as vaginal films including small molecule drugs, proteins, peptides, monoclonal antibodies, and probiotics.

### 2.2.2 Vaginal Film Features

Vaginal films can be used to deliver drug candidates with a broad range of chemical attributes. Both hydrophilic and hydrophobic drug candidates can be successfully formulated into film dosage forms (Table 1). Furthermore, highly susceptible entities such as biomolecules and bacteria can be incorporated. One of the limiting factors for this dosage form is the amount of active agent which can be put into the film. Generally, the active agent does not constitute greater than 50 % of the dry weight of the film product (Vondrak and Barnhart 2008; Hariharan and Bogue 2009). Extremely low concentrations of active agents are also difficult to manufacture in this dosage form due to the difficulty in achieving content uniformity. Thin polymeric films designed for microbicide vaginal use commonly are $1'' \times 2''$ or $2'' \times 2''$ in size (Table 1).

Vaginal films can deliver drug agents to the vagina in order to achieve either topical or systemic effects. This dosage form is dependent upon the fluids in the vaginal vault for disintegration and subsequent dissolution and distribution of the drug. In order to achieve successful delivery, a number of commonly used excipients are incorporated in addition to the active agent. The primary component of a vaginal film is generally a water soluble film forming polymer. A number of polymers have been utilized in this capacity such as cellulose based polymers, poly vinyl alcohol, and Pullulan to name a few. Many film products incorporate combinations of polymers to achieve acceptable attributes. In addition to the base polymers, vaginal thin films use plasticizers to enhance flexibility and reduce brittleness. Commonly used plasticizers include glycerol, propylene glycol, phthalate derivatives, and polyethylene glycol. Other excipients that may be incorporated into the film dosage form are disintegration agents, buffers, stabilizers, fragrance, and coloring agents.

**Table 1** Size and dosing level for published microbicide films

| Film size (inch) | API | Percentage of w/w (dry film) | Reference |
|---|---|---|---|
| $\sim 1 \times 1.5$ | IQP-0528 (pyrimidinedione) | 0.05–0.1 | Ham et al. (2012) |
| $2 \times 1$ | Dapivirine | 0.52–1.36 | Akil et al. (2011) |
| $2 \times 1$ | EFdA (4′-ethynyl-2-fluoro-2′-deoxyadenosine) | 0.8–1 | Zhang et al. (2012) |
| $2 \times 2$ | Tenofovir | 10 | Agashe et al. (2012) |
| $1 \times 1.3$ | RC-101 (retrocyclin analog) | 0.04–0.8 | Sassi et al. (2011) |
| $2 \times 2$ | Nonoxynol-9 (N-9) | 28 | Roddy et al. (1998) |
| $1 \times 1$ | Polystyrenesulfonate (PSS) | 57 | Garg et al. (2005) |
| N/A | Cellulose acetate phthalate (CAP) | 40 | Neurath et al. (2001) |

### 2.2.3 Manufacturing Processes

Thin film dosage forms are manufactured using two methods. The major method used is aqueous solvent casting. This method involves casting a viscous polymer solution onto a substrate. The polymer solution is dried to a solid film and the film is removed from the substrate, cut, and packaged. Hot melt extrusion can also be used to manufacture thin films. This process has the advantage that the polymer, drug, and excipients can be processed without requiring solvent use. This results in a rapid manufacturing process which is compatible with drugs that are susceptible to hydrolytic degradation. The disadvantage of this manufacturing process is the requirement for high temperature and high shear.

### 2.2.4 Evaluation of Vaginal Films

Vaginal films should undergo a range of chemical, physical, and mechanical testing in order to adequately characterize them for pharmaceutical use. Chemical assessments of thin films generally include swelling index, bioadhesion properties, moisture content, disintegration time, dissolution and drug release, and drug content uniformity. Physical tests generally include film weight, size, appearance, and thickness. Mechanical testing may include tensile strength, puncture strength, elongation at break (film deformation), Young's modulus (stiffness), tear resistance, fold endurance, and bioadhesive strength. In addition to standard testing for films several additional in vitro assessments are required for vaginal microbicide products. Drug release and disintegration are critical evaluations for prediction of in vivo efficacy for film products. It is important to determine these parameters when considering biorelevant conditions such as decreased pH and low fluid volume. It is also essential that these products are nontoxic and retain bioactivity. Preliminary toxicity assessments can be conducted in either a cell based or ex vivo tissue model, but more extensive assessments are necessary to support clinical trials (see chapter by Holt and Nuttall 2013). Compatibility with the innate microflora should also be established.

*Acceptability*

Drug product efficacy can be directly correlated to user compliance and acceptability. The film formulation of N-9 has been evaluated for acceptability in a broad range of international and domestic studies (McGowan et al. 2013). Women who utilized the film noted a lack of lubrication provided by the film but were less likely to report "messiness" as compared to that experienced with gel products (McGowan et al. 2013). Another study evaluating foaming tablets versus N-9 film for contraception over 28 weeks found that the film compared favorably in terms of acceptability to foam tablets. Several recent studies have been conducted to assess film acceptability. The first was the Product Acceptability Study (PAS II)

conducted by International Partnership for Microbicides which compared a tablet, film, and softgel placebo product (Nel et al. 2011). The study was a marketing study in that the primary objective of the study was to assess consumer opinions of, and preferences between, the test products in order to gain insight for continuing product development. The outcome of the study showed that films would be an acceptable microbicide product dosage platform. The second study involved a focus group evaluation conducted at the University of Pittsburgh (Fan et al. 2011). In this study, questionnaires and focus groups were used to explore women's preferences for vaginal film physical characteristics. Results from this study indicated that women most frequently preferred vaginal films to be $2'' \times 2''$ square size, smooth, thin, and translucent. Driving these preferences were six major themes: ease and accuracy of use, desire for efficacy, discretion, film disintegration, intravaginal comfort and minimal impact on intravaginal homeostasis, and freedom to continue sexual activities unimpeded.

## *2.3 Tablets*

Although tablets are primarily used for the treatment of HIV/AIDS in oral form, vaginal tablets are a dosage form of choice for some microbicide developers that encounter issues with drug delivery from rings or stability concerns with gels. A tablet is a dosage form comprising active pharmaceutical ingredient(s) and excipients, usually in powder form, that are blended and compressed into solid formed shapes. For vaginal delivery the typical shapes are double convex (Fig. 2) or ovule (Fig. 3c) to allow for easy insertion. The excipients in a vaginal tablet can include diluents, binders or granulating agents, disintegrants, glidants, and lubricants. Diluents act as a dispersant to the API to allow uniform distribution of drug throughout the granulation. The binder ensures that the adhesion of the API and other excipients is adequate to enhance compression. Disintegrants ensure the tablet will break apart once it reaches the vaginal fluid. A glidant acts as a flow aid for the granulation which allows the powder to flow freely from the bulk blend into the cavities of the tableting equipment during manufacturing. Finally, the lubricant

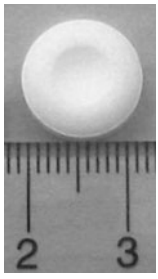


**Fig. 2** Image of CONRAD bi-convex tenofovir fast dissolving tablet

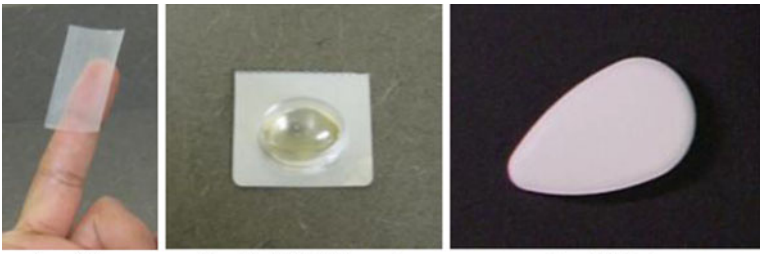


**Fig. 3** Comparison of dosage forms assessed in PAS II study

coats the granulation which prevents the tablets from sticking to the tablet tooling during the compression operation. Oftentimes, a polymer coating is applied to the tablets at the end of the manufacturing process to make the tablets visually more attractive, but also to make the tablet smoother and easier to insert into the vaginal tract. The polymer coating can also control the release of the API from the tablet core and extend the tablet shelf life by protecting it from the environment.

The drug delivery from vaginal formulations can be aimed at three different areas, i.e., surface, within mucus layers, and systemic. Microbicide vaginal tablets are developed with the intention of surface and mucus layer penetration with minimal or no systemic absorption (Garg et al. 2010). As such, in vitro performance of vaginal tablets often focuses on mucoadhesive properties of the formulations and the methodologies designed to examine these effects (Baloglu et al. 2011).

The International Partnership for Microbicides (IPM) developed a combination tablet containing the NNRTI dapivirine (TMC120) and a gp120 inhibitor DS003 (Gupta et al. 2011). This formulation utilized standard solid dosage form excipients (Table 2) and direct blend methodology, followed by standard tableting techniques to produce an ovule-shaped tablet. A placebo version of this tablet

**Table 2** Composition of dapivirine and DS003 vaginal tablet

| Ingredients | Functionality | Percentage of composition (w/w) |
|---|---|---|
| Dapivirine | API | 0.125 |
| DS003 | API | 0.25 |
| Polyethylene oxide | Swelling agent | 7.5 |
| Crospovidone | Disintegrant | 15 |
| Mannitol | Filler/flow aid | 10 |
| Colloidal silicon dioxide | Lubricant | 2 |
| Sodium bicarbonate | Effervescent | 3.5 |
| Tartaric acid | Acidifier | 3.3 |
| Microcrystalline cellulose | Diluent | 10 |
| Compressible lactose | Diluent | 47.325 |
| Magnesium stearate | Lubricant | 1 |

(Fig. 3c) was then placed into a Product Acceptability Study (Nel et al. 2011) (PAS II) where it was compared against a placebo film (Fig. 3a) and softgel formulation (Fig. 3b). The PAS II was designed to be conducted in two markets within each of four countries: Burkina Faso (Bobo-Dioulasso and Ouagadougou), Zambia (Lusaka and Chipata), Mozambique (Maputo and Beira), and Tanzania (Dar es Salaam and Morogoro). The countries and locales were selected on the basis of four factors: (1) Feasibility of conducting the study in the country (i.e., approval by an ethics review committee, logistics, etc.); (2) Areas where there is a significant need for microbicide products; (3) The extent to which countries represent a diversity of cultural norms regarding the use of vaginal products and lubricants; and (4) Whether IPM was conducting, or planned to conduct, microbicide clinical trials and/or HIV incidence studies in the country. In each country, the researchers interviewed women from urban center and rural or peri-urban settings. The outcome of the study showed that the film and softgel capsule had the most potential. Targeted end-users' reactions to the tablet were comparatively negative enough to conclude that the particular formulation utilized in the study was not as good a candidate as the other options presented. Conversely, Panacea Biotec (New Delhi, India) developed a microbicide Praneem polyherbal vaginal tablet (Joshi et al. 2005) and 95 % of the women reported that the product was easy to use and did not affect sexual pleasure (Joglekar et al. 2006). This disparity in acceptability results could demonstrate that tablet composition plays an important role in user preference.

In addition to direct blend methodology for making tablets such as the dapivirine/DS003 tablet, product developers can employ a technique called dry granulation. Using this approach, APIs are blended with excipients, compressed into large pellets called slugs, and ground down to uniform particles before being blended with lubricants and compressed into tablets. For other API blends that lack flow, cohesion, or lubricating properties (Gohel and Jogani 2005), a process called wet granulation is utilized. With this approach a fluid binding solution is added to the blended API and excipients, wet mass sifted, dried, and ground to produce uniform particles. These granules are blended with a lubricant and compressed on tableting equipment. An alternate method of tablet manufacture is the production of a fast dissolving dosage form whereby drugs are trapped or dissolved within the matrix of the fast dissolving carrier material (Virley and Yarwood 1990; Seager 1998). CONRAD (Arlington, VA) is currently developing fast dissolving tablets containing tenofovir alone (Clark et al. 2011, 2012) and a combination tablet containing tenofovir and emtricitabine. These bi-convex tablets are derived from a fast dissolve oral technology developed by Aptalis Pharmaceutical Technologies (Seattle King County Department of Public Health 2000). These tablets are prepared on standard tableting equipment and comprise excipients commonly used in other vaginal products.

Tablets are the most commonly used dosage form (Sam and Fokkens 1997) outside the microbicide field due to their inexpensive manufacturing costs, ease of dosing, potential for high drug loading, and stability compared to aqueous-based dosage forms like liquids and gels. Although there has not been significant

development effort on tablets in the microbicide field until recently, they do offer the potential for an inexpensive, discreet, portable product that has no environmental waste. Among the many factors to consider, developers need to formulate to ensure the tablet adequately disintegrates upon use to avoid unwanted particulate discharge.

## 3 Coitally Independent Dosage Forms

### *3.1 Vaginal Rings*

Vaginal rings (VRs) are torus-shaped polymeric drug delivery devices designed to release drugs in the vagina in a controlled fashion. The size of VRs generally ranges from 54 to 58 mm in diameter with cross-sectional diameters from 4.0 to 8.4 mm (Johansson 2000; Roumen et al. 2001). VRs do not require a healthcare professional for insertion and can be managed by the user for easy insertion and removal when needed. The concept of a vaginal ring for sustained drug administration was first described in a 1970 patent application (Duncan 1970), and since then a wide range of drugs and ring designs have been evaluated. Estring® was the first ring product to reach market in 1992, a silicone elastomer reservoir device providing constant release of 17-$\beta$-estradiol daily over 3 months for the local treatment of menopausal urogenital atrophy. Two other rings have also reached market; Organon's NuvaRing®, delivering the contraceptive steroids etonogestrel and ethinyl estradiol over 21 days, and Warner Chilcott's Femring® (Menoring® in the UK), releasing an estradiol prodrug, estradiol-3-acetate, continuously over 3 months. A number of VRs are also currently in development in the microbicide field, as single agents or in combination with other microbicides or hormonal contraceptives. Intended to be worn continuously, such coitally independent microbicide rings are being developed to maintain effective vaginal microbicide concentrations over many weeks or months, thereby overcoming issues around timing of product application, user compliance, and acceptability associated with more conventional semisolid formulations (Malcolm et al. 2010). IPM is in Phase III clinical trials with a dapivirine loaded VR. They are also developing dapivirine in combination with maraviroc, and dapivirine with a hormonal contraceptive. Population Council is developing a thermoplastic ring containing MIV-150. CONRAD is developing thermoplastic ring containing tenofovir and a combination ring containing tenofovir and levonorgestrel. This list is not exhaustive and it is important to note that multiple developers are studying microbicides or multi-prevention products in VRs.

The most basic design of the VR is a matrix formulation whereby API is dispersed throughout the polymeric matrix and typically the drug release rates are proportional to the amount of API loaded and the surface area of the VR. A second type of VR is a reservoir or core design where the API is loaded into core and over-molded with a separate polymer sheath. In this case the sheath often controls

the diffusion of API out of the reservoir. A third design is a pod insert design whereby tablets or pods containing API are inserted into VRs to improve loading and control release of drug from the VR (Moss et al. 2012). Lastly, there are novel approaches to ring designs such as multi-segmented rings and hydrogel vaginal rings (Han et al. 2007; Saxena et al. 2009). The most effective choice of polymer for a given microbicide depends on the solubility of the drug in the polymer, and on whether the drug has a low enough molecular weight to diffuse through the polymer (Fetherston et al. 2010). The latter is also affected by the degree of cross-linking within the polymer under study. The focus in this section will be on the primary polymeric systems utilized to design these different ring types, namely elastomers and thermoplastics, and the following subsections describe them in more detail.

### 3.1.1 Silicone Elastomer Rings

Silicone elastomers are formed by the cross-linking of functional linear siloxanes and are the most common material used in manufacturing VRs, via injection molding (Fetherston et al. 2010). A VR fabricated from this hydrophobic elastomeric polymer can be self-inserted high into the vagina, where it is held in place due to its shape and inherent elasticity (Woolfson et al. 1999). There are several kinds of curing systems but only two of which have been explored in the microbicide field to date, the platinum catalyzed cure and the tin condensation cure system.

For the platinum catalyzed cure, the elastomer is thermally cured via an addition-cure (platinum catalyzed) reaction and the resulting elastomer consists of cross-linked dimethyl and methyl-vinyl siloxane copolymers and reinforcing silica. Elastomers featuring this type of cure system are supplied as two-part kits: one part contains the catalyst, the other a silicon hydride-functional cross-linker and an inhibitor to provide working time once the two parts have been mixed. A major advantage of addition cure rubber is that the cure reaction produces no by-products (2009).

Tin condensation systems involve hydroxyl functional polymers and alkoxy-functional cross-linking compounds. The alkoxy functional cross-linker first undergoes a hydrolysis step and is left with a hydroxyl group. This hydroxyl group then participates in a condensation reaction with another hydroxyl group attached to the polymer. The reaction can proceed without the assistance of the tin catalyst, but the presence of the catalyst boosts the rate of reaction (Reilly and Bruner 2004). Condensation systems can be advantageous due to their ability to cure at room temperature which may be of benefit should an API be temperature sensitive. However, the main disadvantage of condensation systems is the long cure time which increases manufacturing time and, hence, cost. An additional complication for developers that incorporate API into a tin catalyzed silicone system is that API may migrate to the surface of the ring during the extended curing process and create a “burst effect” upon release in vitro and in vivo.

In the early development of the dapivirine VRs, IPM developed reservoir and tin-catalyzed condensation cure rings before the final platinum catalyzed ring

containing 25 mg dapivirine matrix ring. The tin catalyzed VR showed the burst effect due to the redistribution of dapivirine that was dissolved in propanol which was released during the condensation reaction and consequently deposited on the surface of the ring. As a result a platinum cure silicone was employed which was a complete cure and contained no by-products. Dapivirine is well suited for delivery via VR, as evidenced by the favorable safety and pharmacokinetic data generated to date (Nel et al. 2009b). Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month and Phase III efficacy and safety trials (The Ring Study and ASPIRE) are underway.

### 3.1.2 Thermoplastic Rings

Thermoplastic elastomers have a long history in the biomedical device arena and are an important material class from which FDA approved intravaginal devices have been constructed (Creatsas et al. 2001; Thyssen et al. 2001; Foran 2003; Novak et al. 2003). The most commonly used thermoplastic elastomers used for intravaginal ring formulations are poly(ethylene vinyl acetate) (EVA) and segmented polyurethane (PU) (Malcolm et al. 2010).

NuvaRing® is one of the first thermoplastic hot melt extruded combination rings on the market (Kiser et al. 2012). It was developed by Organon, approved in Europe and USA and releases etonorgestrel (120 μg/day) and ethinyl-estradiol (15 μg/day) for 3 weeks′ continuous use followed by 1 week off (Novak et al. 2003). NuvaRing® comprises EVA which is copolymer of vinyl acetate and ethylene that varies from 10 to 40 % vinyl acetate content. NuvaRing® is a thermoplastic reservoir VR fabricated from two different grades of EVA (van Laarhoven et al. 2002a, b) and is comprised of coaxial fibers whereby the hormone is dissolved or dispersed in a core polymer. The release from these coaxial fibers depends directly on the concentration gradient over the rate limiting membrane (van Laarhoven et al. 2002a, b). Particle Sciences (Bethlehem, PA) initiated the development of a dual purpose EVA ring containing UC781 and levonorgestrel CONRAD (Loxley et al. 2011) before the development of UC781 was discontinued.

Polyurethanes are thermoplastic elastomers consisting of linear segmented block copolymers of which there are many types. They are formed by a reaction between a polymeric diol (e.g., polytetramethylene oxide or polyethylene oxide) and an aliphatic or aromatic isocyanate. Aromatic isocyanates have potential toxic side effects (Szycher 1988), therefore aliphatic isocyanates have been chosen for VR manufacturing in the microbicide field. Polyurethanes are starting to be utilized for intravaginal applications (Gupta et al. 2008; Johnson et al. 2010, 2012) for formulating microbicides such as pyrimidinediones, dapivirine, MIV-150, and tenofovir, either alone or in combination. The particular advantage of polyurethane VRs is their ability to swell in aqueous environments which enables the incorporation of hydrophilic compounds (such as tenofovir) that were previously very challenging to formulate into a VR.

## 4 Other Dosage Forms

There are other dosage forms such as ARV-loaded SILCS diaphragm (Schwartz et al. 2008a), hydrogel vaginal rings (Han et al. 2007; Saxena et al. 2009), and electrospun fiber meshes containing drugs that are currently under development within the microbicide field. The following section describes a small portion of these unique drug/device combinations to demonstrate some of the creative approaches taken to supply the HIV prevention field with options for novel dosage forms and multi-prevention technologies.

### *4.1 Electrospun Fibers*

Electrospinning is a technique that applies electrostatic forces to form micro- or nanoscale polymer fibers that can be fabricated into meshes of varying geometries. The diversity and number of polymers that can be electrospun should enable a correspondingly large number of active agents to be encapsulated for sustained delivery (Pham et al. 2006; Greiner and Wendorff 2007; Mauck et al. 2009). As such, electrospinning is an elegant method to deliver combination drug therapies because polymers can be selected based on their drug compatibility as well as their degradation or dissolution rates. In addition, controlling processing parameters (applied voltage, polymer flow rate, capillary-collector distance), nozzle configuration (single, multijet, coaxial), and choice of materials (non-degradable, biodegradable, water-soluble) allows great versatility and flexibility to design topical prevention strategies. The University of Washington has begun development of an electrospun drug-eluting matrix uniquely designed for the geometry and physiology of the vagina, which provides chemical and physical barrier methods for HIV-1 prevention and contraception. This vaginal drug delivery platform could potentially be used to prevent other STIs or RTIs alone and in combination, for intravaginal delivery of nanoparticles, or be designed for rectal drug delivery.

Electrospinning has been used to fabricate controlled-release systems to deliver small molecule drugs (Jiang et al. 2005; Cui et al. 2006; Huang et al. 2006; Luong-Van et al. 2006; Stitzel et al. 2006; Taepaiboon et al. 2006; Feng et al. 2010; Okuda et al. 2010), proteins (Reilly and Bruner 2004; Wei et al. 2006; Zhang et al. 2006; Chiu et al. 2007; Jin et al. 2008; Maretschek et al. 2008; Fletcher et al. 2009; Ionescu et al. 2010), and nucleic acids (Liang et al. 2005; Cao et al. 2010; Kim and Yoo 2010; Wang et al. 2010). Drug release kinetics from the electrospun matrix can be finely tuned by controlling the nanofeatures (size, geometry, architecture) as well as physicochemical properties of the materials (polymer wetting, swelling, and dissolution as well as drug-polymer interactions). Electrospinning also presents a novel method for delivering combination drug therapies by assembling a composite matrix from component electrospun matrices that are individually

coated or embedded with a single active agent (Reilly and Bruner 2004; Kidoaki et al. 2005, 2006). Based on these qualities, electrospun nanofibers are uniquely positioned to have a significant impact on the development of contraceptive microbicides for dual-protection against sexual HIV-1 transmission and pregnancy.

In addition to the design of the drug-eluting properties, electrospun fiber meshes must also be engineered to withstand a complicated loading environment that includes anisotropic multiaxial tension, compression, and shear forces that arise during application and coitus. Randomly deposited nanofibers produce scaffolds that exhibit isotropic mechanical properties primarily reflective of their polymer composition and, given the large number of polymers that can be used for electrospinning, a wide range of mechanical properties are achievable (Duncan 1970). However, fiber alignment also significantly influences mechanical properties of nanofibrous scaffolds and can alter the stiffness or elasticity of scaffolds electrospun from otherwise identical polymer compositions (Theron et al. 2001; Ayres et al. 2006; Courtney et al. 2006; Nerurkar et al. 2007). Random scaffolds exhibit a relatively linear stress-strain response in the regime before the material yield point and then extend linearly after this point. In contrast, aligned scaffold tested in the fiber direction have a sharper increase in stress with increasing deformation, whereas the same scaffolds tested in the transverse direction exhibit a much lower stress–strain profile (Duncan 1970). Another factor that can affect the mechanical properties of nanofibrous scaffolds are the number of fiber–fiber cross-links that are introduced by controlling solvent deposition and evaporation at the grounded collector, or the use of chemical cross-linking agents (Kidoaki et al. 2006; Tan et al. 2008). Therefore, a large number of factors can be employed to impart specific mechanical properties to electrospun fiber meshes intended for topical prevention strategies. This technology has recently been applied to develop a combination anti-HIV and contraceptive product (Ball et al. 2012).

## *4.2 SILCS Diaphragm*

Contraceptive diaphragm technology has been available since the late nineteenth century (2000). Although the device design and composition has changed significantly over time, the diaphragm still offers a female-controlled, non-hormonal, barrier method for prevention of pregnancy. PATH (Seattle, WA), along with research partner CONRAD, developed one such device called the SILCS diaphragm that improved upon earlier versions of the diaphragm by making it more comfortable and easier to use. Patent protection was sought and awarded on the first generation of this diaphragm in 1998 (Austin et al. 1998). Subsequently, it was recognized that the polymeric construction (thermoplastic spring core and overmolded silicone elastomer membrane) made this device a viable candidate for incorporation of HIV microbicides into this core. The drug loaded core can be viewed as a vaginal ring that allows permeation of drugs from the thermoplastic core through the silicone sheath layer while the diaphragm itself acts a barrier

contraceptive. Queen's University Belfast (QUB) has developed prototypes of this multi-prevention device using UC781 (Major et al. 2010) dispersed in polyoxymethylene (POM) copolymer. Additionally, QUB initiated development of dapivirine-loaded POM spring cores of the SILCS contraceptive diaphragm (Major et al. 2012). These devices could offer women a coitally dependent, non-hormonal contraceptive along with HIV prevention.

## 5 Conclusion

A multitude of dosage forms and devices are being evaluated for the delivery of microbicide drug candidates. These formulations offer both coitally dependent and coitally independent mechanisms for HIV prevention. A number of advantages and disadvantages exist with each product type. It is critical that any microbicide product be safe, effective, and acceptable to the user. Ultimately, it will most likely be advantageous to offer drug candidates in a variety of platforms since a user's product compliance will vary based on preference, circumstance, and economic situation.

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