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Review

Multipurpose prevention technologies: Products in development

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ABSTRACT

Multipurpose prevention technologies (MPTs) are broadly defined as products capable of simultaneously addressing multiple sexual and reproductive health needs including unintended pregnancy, STIs including HIV-1, and other reproductive tract infections. MPTs have been discussed for a few decades but little product development has occurred. With the recent proof-of-concept that a topically applied antiretroviral (ARV) can effectively reduce sexual transmission of HIV-1 (tenofovir 1% gel) the impetus to develop MPTs is gaining momentum. Products currently in development are broadly categorized as either long-acting or on-demand. Long-acting MPTs include intravaginal rings (IVRs) and long-acting injectable products. Several IVR MPTs are under development including one designed to release tenofovir to prevent transmission of HIV-1 and levonorgestrel (LNG) to prevent unintended pregnancy over a 90-day period. Another MPT IVR under development is designed to release the ARV dapivirine and LNG for 2 months. Long-acting injectable pre-exposure prophylaxis (PrEP) formulations of rilpivirine (TMC278) and GSK1265744 have entered clinical evaluation and could form the basis of long-acting injectable products for HIV-1 prevention and prevention of unintended pregnancy. On-demand products include TFV 1% gel (HIV-1/HSV-2 prevention), a zinc/carrageenan zinc gel (HIV-1/HSV-2 prevention), and the SILCS diaphragm administered with TFV 1% gel. Significant technical, funding, and regulatory hurdles must be overcome to develop most MPTs; however, the significant reproductive health benefits to many women around the world should provide motivation to overcome these hurdles. This article is based on a presentation at the "Product Development Workshop 2013: HIV and Multipurpose Prevention Technologies", held in Arlington, Virginia on February 21–22, 2013. It forms part of a special supplement to Antiviral Research.

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1. Introduction

Unplanned pregnancies account for nearly half of all pregnancies worldwide and lead to almost 100,000 maternal deaths per year as a result of unsafe abortions and complications of pregnancy and delivery (World Health Organization, 2007). The needs for technologies that address both HIV-1 infections and unplanned pregnancy overlap in many low income countries and urban regions of the world (Friend, 2012; Malcolm and Fetherston, 2013; Thurman et al., 2011). While transmission of HIV-1 is of considerable concern, other sexually transmitted infections (STIs) such as HSV-2 and HPV are highly prevalent in the developing and developed world. The imperative to address unmet needs in contraception and prevention of sexual transmission of HIV-1 has recently spawned significant research and development. At the same time, it has been recognized that combining approaches to address unplanned pregnancies and STIs offers a unique opportunity to reduce cost, potentially improve user adherence, and ultimately improve the sexual reproductive health of women overall.

This review focuses on recent efforts to create products designed to simultaneously prevent unintended pregnancy and STIs, often referred to as multipurpose prevention technologies (MPTs). There are several reviews written on MPTs from both technical and strategic development perspectives (Berer, 2006; Brady, 2003; Feldblum et al., 2007; Friend, 2012; Friend and Doncel, 2010; Harrison et al., 2013; Holt et al., 2010; Thurman et al., 2011). The development of MPTs is intimately tied to development of microbicide products (also known as topical pre-exposure prophylaxis, PrEP). The recent findings of the Phase IIb trial known as VOICE showed that women were poorly adherent to all dosing regimens (once-daily topical tenofovir gel or oral Truvada® and Viread®) which led to an inability to demonstrate effectiveness (Marrazzo et al., 2013). This finding reinforces the need to provide products women are willing and eager to use. In addition to combining prevention technologies to improve adherence, the specific nature of the products can be tailored to make them more appealing to women. For instance, development of simple on-demand products used around the time of sex or longer acting dosage forms (from several days to several months) may lead to improved user adherence compared with products required to be taken once-daily on a continuous basis. Data from on-going clinical trials will shed more light on women's user preferences.

2. Background

The overall framework for development of MPTs has been broadly defined as products that simultaneously address multiple sexual and reproductive health needs including unintended pregnancy, STIs including HIV-1, and other reproductive tract infections. The need for MPTs conceptually has been known for some time. For instance, Wasserheit published a review in 1992 on the contribution of other STIs to sexual transmission of HIV-1 (Wasserheit, 1992) wherein she concluded that STI treatment should be coupled to HIV-1 prevention. This opinion was expanded on in 1999 (Fleming and Wasserheit, 1999). Also published in the 1990s were papers discussing dual protection approaches addressing unintended pregnancies and STIs (Cates and Stone, 1992; Cates, 1993, 1996). It was known at that time that barrier methods, in particular, male condoms were effective at preventing unintended pregnancies and transmission of HIV-1 (Davis and Weller, 1999; Feldblum et al., 1995). However, the considerable nonuse of both male and female condoms (Mansour et al., 2010) has reduced their potential contribution in preventing the spread of HIV-1 to women, particularly in the developing world.

Despite these early papers, there was little progress in MPTs due primarily to the inability to prevent transmission of HIV-1 itself let alone develop a product that also prevents unintended pregnancy. With the results from the proof-of-concept study demonstrating effectiveness of the anti-retroviral (ARV) microbicide product [tenofovir (TFV) 1% gel] (Abdool Karim et al., 2010) in the CAPRISA 004 study, the ability to develop MPT products has a basis for further investigation. In addition, there have been advances in vaginal drug delivery systems that permit the administration of 2 (or more) drugs simultaneously (Friend, 2012; Johnson et al., 2010). In the following discussion, products are divided into 2 main product categories: long-acting (sustained release) and on-demand (peri-coital). While once-daily products used for prophylactic purposes are feasible from a development perspective, it is unlikely women will consistently use such products thereby diminishing their effectiveness.

There are a number of approaches to developing MPTs such as barrier devices (e.g., diaphragms), combinations of drugs and devices, and drugs that potentially demonstrate dual indications, and combination of 2 (or more) drugs each with its own indication. This review will cover products currently under development. Most, but not all, recent activity has focused on development of products indicated for the prevention of transmission of HIV-1 and prevention of unintended pregnancy.

3. Sustained release MPTs

As summarized in a recent paper (Harrison et al., 2013), there has been an on-going planning initiative to prioritize development of MPTs. A conclusion of this initiative was that the leading dosage form for MPTs, (independent of indications) is the intravaginal ring (IVR). IVRs are a relatively advanced drug delivery system that can release a variety of compounds from a month to potentially 1 year (Friend, 2011; Kiser et al., 2012; Malcolm et al., 2012; Woolfson et al., 2000). IVRs have been used successfully for contraception (Brache and Faundes, 2010; Brache et al., 2013) and have been explored extensively for the delivery of microbicides. It is believed that adherence to longer acting products will be higher than once-daily or on-demand drug administration although evidence supporting this assumption in the area of microbicides or MPTs is lacking. This assumption however is supported by a large amount of data from other women's healthcare products that show a general trend of increasing compliance/adherence as the dosing interval is decreased (Kruk and Schwalbe, 2006).

In general, IVRs are well accepted by women. In a study with 3 different placebo rings of varying mechanical properties, all were found to be acceptable to nulliparous and parous women (Roumen et al., 1990). NuvaRing®, a contraceptive IVR, has been found to be preferred over oral contraceptives (Novák et al., 2003). In an international study involving 1950 women, there was a high level of user and partner acceptability for NuvaRing. In a study involving men and at-risk women using an IVR for HIV-1 prevention, several themes have been identified: risk of covert use and discovery by male partners was a concern, but overall most participants were open to using an IVR for HIV-1 prevention (Smith et al., 2008). Results from a recent study to assess ring adherence in sub-Saharan Africa suggest that counseling is required to overcome concerns about the use of IVRs for HIV-1 prevention (Montgomery et al., 2012; van der Straten et al., 2012).

3.1. IVRs under development as MPTs

The primary focus on IVR MPTs has been the co-delivery of drugs for the prevention of transmission of HIV-1 and the prevention of unintended pregnancy. The two lead microbicides are TFV, a

nucleotide reverse transcriptase inhibitor and dapivirine (DPV), a nonnucleoside reverse transcriptase inhibitor (NNRTI). Both are in Phase III clinical studies, one as an on-demand vaginal gel (TFV) and the other (DPV) as 1 month IVR formulation. Both drugs are under investigation in the form of IVRs combined with the contraceptive progestin levonorgestrel (LNG). In addition, work has been performed with IVRs capable of releasing two different antiviral agents potentially capable of preventing transmission of HIV-1 (TFV) and HSV-2 (acyclovir, ACV).

3.1.1. TFV/acyclovir IVR

Efforts at developing an IVR that could prevent transmission of 2 STIs, namely HIV-1 and HSV-2, have been investigated. There is an inter-relationship between HIV-1 and HSV-2 in that HIV-1 transmission is enhanced in women infected with HSV-2 (Renzi et al., 2003; Reynolds et al., 2003; Wald and Link, 2002). Thus the ability to treat or prevent HSV-2 transmission along with prevention of HIV-1 transmission could have considerable health benefits. ACV is widely used to treat HSV-2 infection. While not proven clinically, it is being investigated as a potential microbicidal agent to prevent transmission of HSV-2.

A pod-based IVR has been developed capable of releasing TFV (see Section 3.1.2 for a description of this drug as a microbicide) and acyclovir (ACV) and evaluated under in vitro conditions and in vivo in rabbits and sheep (Moss et al., 2012). The system was capable of sustained release of both drugs over a 28-day period. Daily release rates were estimated based on residual drug content of the used devices: rabbits, 343 ± 335 μg/day (ACV) and 321 ± 207 μg/day (TFV); sheep, 174 ± 14 μg/day (ACV) and 185 ± 34 μg/day (TFV). Mean drug levels in sheep vaginal samples were as follows: secretions, 5.25 ± 7.31 μg/ml (ACV) and 20.6 ± 16.2 μg/ml (TFV); cervicovaginal lavage fluid, 118 ± 113 ng/ml (ACV) and 191 ± 125 ng/ml (TFV); tissue, 173 ng/g (ACV) and 93 ng/g (TFV). An in vitro–in vivo correlation was established for both drugs and will allow the development of future formulations delivering target levels for prophylaxis and therapy. Since both drugs are relatively low potency it is unclear if sufficient amounts of either drug released from the pod-based IVR would be efficacious; co-release of more potent compounds would potentially be effective using this IVR design.

TFV and ACV have also been formulated into a matrix-type polyurethane (PU) IVR (Kelly et al., 2011; Livingstone et al., 2011). Depending on the chemical structure of the PU used, release of both TFV and ACV could be controlled over a 28 day period as demonstrated by in vitro release testing and in vivo assessment in sheep. Due to its design, this IVR releases these water-soluble drugs in a non-linear manner with decreasing release rates over time in contrast to the pod system which is designed to release drugs at constant rate. However, matrix and reservoir (described below) are capable of delivering more drug over a given period of time than the pod-based due to differences in total drug loading.

3.1.2. TFV/LNG IVR

The development of TFV as a microbicide was initially as a topical vaginal gel. Development of TFV as a topically active HIV-1 prevention product was started around 1995. Gilead Sciences initiated development of TFV gel but soon transferred development to NIH and continued to provide support for some product development activities. TFV gel was moved through Phase II development, with funding primarily from NIH. In 2006, Gilead licensed the use of TFV for prevention of sexual transmission of HIV-1 to CONRAD (a division of the Obstetrics and Gynecology Department at Eastern Virginia Medical School) and the International Partnership for Microbicides. CONRAD since has been primarily responsible for its on-going development with funding from the United States Agency for International Development (USAID).

LNG has an established track record of safety and efficacy in oral contraceptives and is well suited for incorporation into controlled-release devices due to its low molecular weight, hydrophobicity, and physical stability. LNG has been approved for non-oral controlled-release delivery via subcutaneous implants (Norplant®, Norplant II®, Jadelle®) and intrauterine systems (Mirena® and Skyla™). The mechanism of action of LNG is a combination of ovulatory dysfunction shown by serum estradiol and progesterone levels, which occurs in one-half to two-thirds of users depending on plasma LNG concentration, changes in the endometrium, and changes in cervical mucus that reduce sperm penetration and motility, which occur in users regardless of ovulatory pattern (Landgren et al., 1982; Lewis et al., 2010; Mandelin et al., 1997; Rose et al., 2009).

The development of a LNG IVR began in 1972 sponsored by the World Health Organization (WHO) (Benagiano et al., 2008). This reservoir IVR (Burton et al., 1979, 1978) was made of polysiloxane elastomer with an outer diameter of 55.6 mm and a cross-section of 9.5 mm, and it released 20 μg LNG/day. Contraceptive efficacy was demonstrated in a large multicenter trial of 1005 women in which the pregnancy rate was 3.6% after 1 year of use (Brache et al., 2000; Koetsawang et al., 1990a,b,c). A confirmatory trial among 1710 women in the UK yielded a 1-year pregnancy rate of 5.1% (Sahota et al., 1999). While 20 μg LNG/d has been shown to be effective when released from an IVR, it is unclear if a lower dose could provide the same level of contraceptive efficacy.

TFV has been developed as a 90-day reservoir IVR (Johnson et al., 2012). This IVR is composed of hydrophilic polyurethane (PU) tubing filled with a TFV/glycerin/water paste. A hydrophilic PU was found to provide the target release rate of ~10 mg/d over a 90 day period under in vitro conditions. The TFV IVR released TFV at a constant rate over 90 days in sheep as determined by vaginal tissue, vaginal fluid, and plasma levels that were near or exceeded those measured following once-daily administration of TFV 1% gel over 28 days (Johnson et al., 2012). In vivo release of TFV from the IVR in female sheep was estimated at about 17 mg per day on average. A similarly designed IVR has recently been

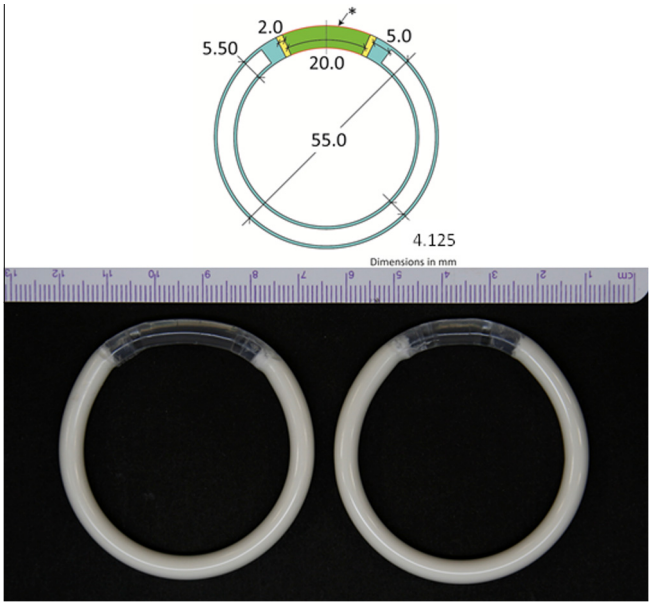

Fig. 1. Schematic (top) and images (bottom) of TFV/LNG (20 mm and 10 mm) IVR. TFV-loaded segment shown in white and blue; LNG-loaded segment shown in green and is coated with a thin (80–100 μm) rate-controlling membrane (labeled with *) and capped with 2-mm wide PU caps (yellow), to prevent drug diffusion between drug-loaded segments. Dimensions are shown in mm units.

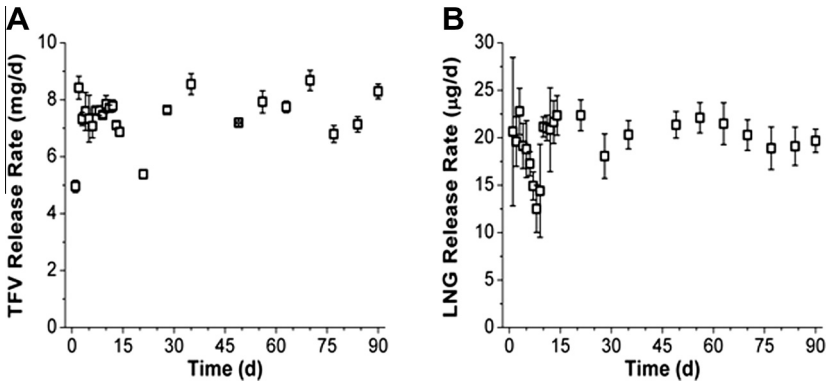

Fig. 2. In vitro release of (A) TFV and (B) LNG for 90 days from TFV/LNG IVR prototypes using polyurethanes, with 20 mm length, 5.5 mm OD diameter co-axially extruded LNG segments. RCM thicknesses of LNG segments were measured between 74 and 85 µm. All data represent $N = 5$, mean ± SD (Clark et al., 2013).

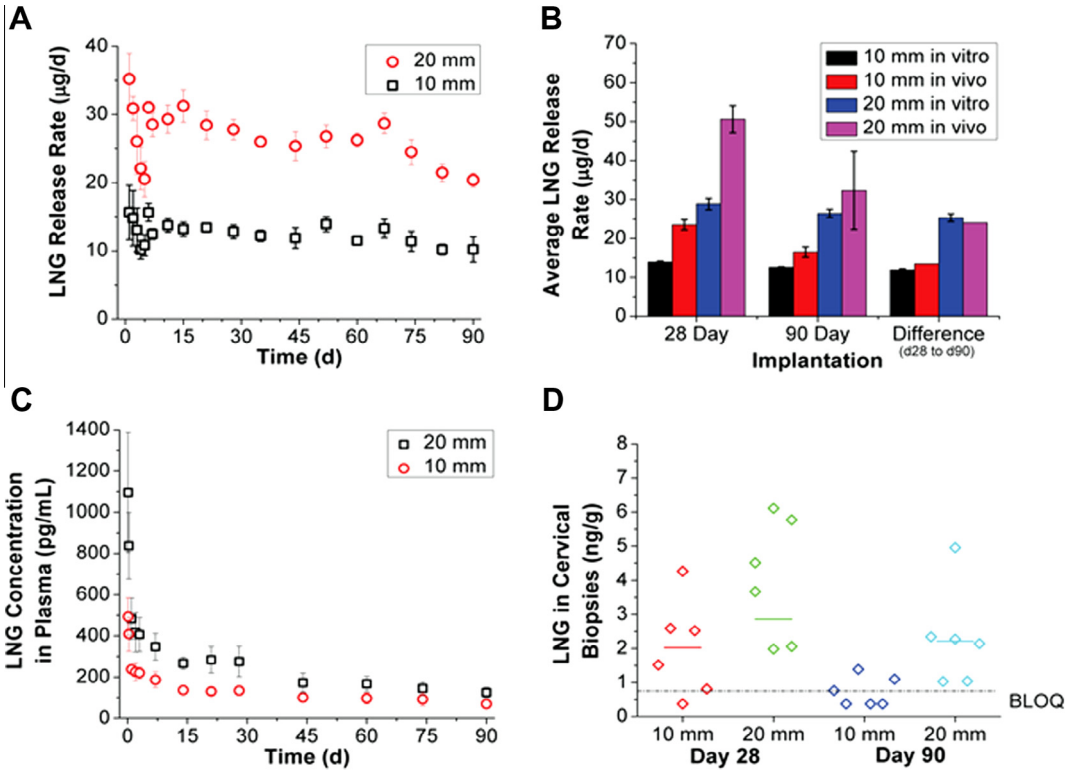

Fig. 3. Pharmacokinetic (PK) testing of end-capped 10 or 20 mm PEU-1/PEU-2 LNG segments in New Zealand white rabbits. (A) Parallel in vitro release data for the same LNG segment lot used in the study and (B) comparison with in vivo data for the 28 and 90 day study groups. A subtraction of the mean LNG recovery between study groups was performed to directly compare in vitro and in vivo behavior from day 28 to day 90. (C) Plasma LNG levels measured during the rabbit PK study for 10 and 20 mm LNG segment implantations. (D) Individual LNG levels determined from extractions of terminal cervical biopsies. Some samples in the 10 mm study groups were below quantification (BLOQ: <0.750 ng LNG per g tissue). BLOQ data points are graphed as LOQ/2 (0.375 ng/g). In vitro data represents $N = 5$, mean ± SD and in vivo data represents $N = 6$, mean ± SD (Clark et al., 2013).

shown to release tenofovir disoproxil fumarate (TDF) in a manner that provides complete protection against multiple vaginal simian-HIV challenges (Smith et al., 2013).

The same approach to controlling the release of TFV over 90 days is the basis for the design of a 90 day TFV/LNG IVR. The challenge in developing an IVR releasing 2 drugs with considerably different release rates and physicochemical properties was addressed by developing a segmented ring. The segmented IVR was first used in the field of microbicides to control the release of TFV and DPV (Johnson et al., 2010). This system was composed of 2 polyurethane segments each of which was a matrix capable of releasing both drugs over 28 days.

To control the release of LNG at a relatively constant rate over 90 days, a reservoir-type IVR segment was constructed from two hydrophobic PUs; a low-modulus PU LNG used for the LNG-containing core and a high-modulus PU used for the thin (80–100 µm) rate-controlling membrane (RCM). The key features of the TFV/LNG IVR are shown in Fig. 1. The LNG segment is prepared by coaxial extrusion in a manner similar to that used to prepare NuvaRing®. The target release rates for this delivery system are 10 or 20 µg LNG/d and about 8–10 mg TFV/d which are nominally reached by using segments of the same compositions but 2 different lengths. The lower dose of LNG is being investigated to determine if it is effective, which would lead to a reduction in

systemic side effects. To obtain these LNG release rates, mathematical modeling and experiments were performed leading to the selection of an 80–100 μm thickness for the RCM. The in vitro release of TFV and LNG from full IVRs is shown in Fig. 2. Release of TFV and LNG were essentially constant over 90 days at rates of approximately 8 mg and 20 μg per day, respectively. The tissue concentrations of TFV from the IVR were similar to those observed when 4.0 ml of TFV 1% gel was administration once daily over 30 days (Johnson et al., 2012).

Release of LNG from IVR segments has been studied in rabbits and sheep. Concentrations of LNG in rabbit plasma and cervical tissues plus relevant in vitro release data are shown in Fig. 3a. Average in vitro release rates were 12.6 and 26.4 μg/day from 10 mm to 20 mm length LNG segments respectively over 90 days. Comparisons of in vitro and in vivo release rates for the various study groups are shown in Fig. 3b. As expected, a near 2-fold difference was observed in average in vivo release rates between the 10 mm and 20 mm segment groups (Clark et al., 2013). LNG plasma levels were sustained over 90 days following a short burst period. The TFV/LNG IVR is expected to enter clinical evaluation shortly.

3.1.3. Dapivirne/LNG IVR

Another MPT IVR under development is designed to release dapivirine (DPV) and LNG. DPV (TMC120), is a potent NNRTI investigated by Janssen (Tibotec) as a potential HIV-1 treatment, but development was discontinued due to its poor oral bioavailability. DPV demonstrates potent, dose dependent inhibitory effects against a broad panel of HIV-1 isolates from different clades (Fletcher et al., 2009). It has shown an EC_{50} of 1 nM (CME T cells) (Van Herrewege et al., 2004) and 15 nM with cell-free virus (MO-DC and CD4+ T cell co-cultures) and 3 nM with cell associated virus (Terrazas-Aranda et al., 2007). While DPV has been formulated as a gel and an IVR, the DPV IVR was moved ahead into late stage clinical evaluation (Rosenberg and Devlin, 2012). A history of the development of this product and the various iterative IVR designs tested has been reviewed recently (Malcolm et al., 2012). The dosage form chosen for clinical advancement was a matrix ring design composed of silicone elastomer. The IVR releases DPV over a 1 month period, after which the woman removes the ring and inserts a new one. The DPV IVR is currently in Phase III clinical testing in 2 separate trials. The first trial, called ASPIRE, is being conducted by the Microbicide Trials Network in several sub-Saharan countries. The study intends to enroll around 3500 women with completion expected in early 2015. The second trial, called the Ring Study (IPM-027) is a similar study and intends to enroll 1650 women. The Ring Study is also expected to end early 2015.

The DPV/LNG IVR under development is a silicone-based system designed to release both drugs over a 60 day period. This product is in an early stage of development. Unlike the TFV/LNG IVR, the daily release rate of LNG from the DPV/LNG IVR is targeted at higher release rates (35 and 70 μg/day). While these doses should be effective based on expected plasma concentrations compared with implantable products, they will lead to higher systemic levels and an overall anovulatory effect which is often associated with break through bleeding. Under in vitro release test conditions, it is possible to control the release of both drugs depending on the design (reservoir vs. matrix) being studied but to date target release rates of both drugs from the same device have yet to be attained (Fetherston et al., 2013).

3.1.4. Dapivirine/SILCS contraceptive diaphragm

An alternative microbicide/contraceptive MPT approach is based on barrier devices such as diaphragms. Diaphragms act by blocking sperm from passing the vagina into the uterus by physically blocking the cervix. Recently, the SILCS diaphragm has been developed as a single-size, easy-to-fit and-remove, reusable cervical barrier (Coffey et al., 2008; Pentlicky et al., 2013; Schwartz et al., 2008). The device is composed of a contoured thermoplastic

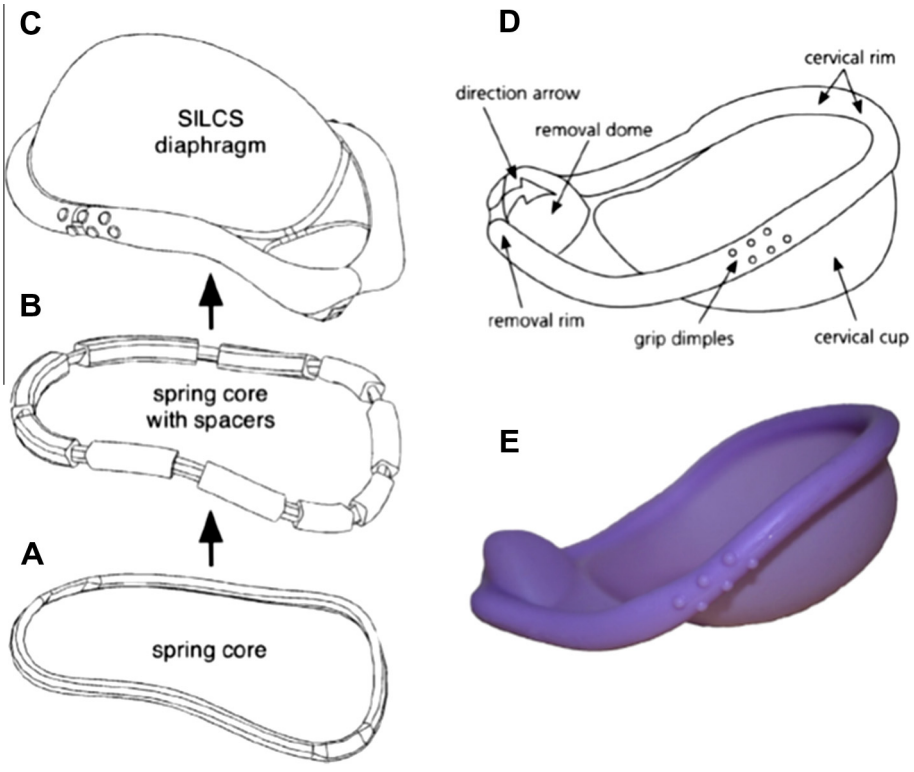

Fig. 4. The SILCS diaphragm device. A through C shows the three step injection molding process used to manufacture first the spring core, the spring core with spacers and the final overmolded device. D: device features, and E: is a photograph of an actual device. Reprinted with permission (Major et al., 2013).

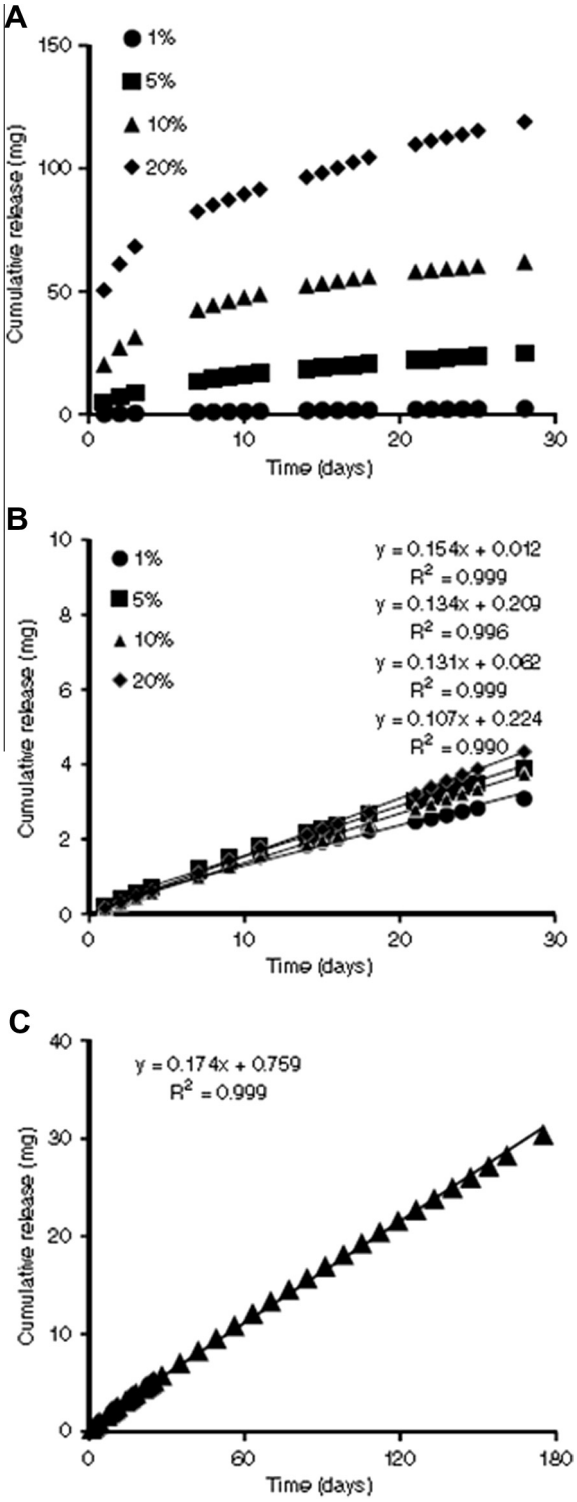

Fig. 5. Mean cumulative release versus time profiles for spring cores (A) and full diaphragm devices (B) containing various concentrations of DPV. Panel C shows the extended release profile out to 175 days for a 10% w/w-loaded diaphragm device. These in vitro release studies were performed in mixed isopropanol/water (1:1) at 37 °C. Reprinted with permission (Major et al., 2013).

(nylon 6–6) spring encased in a silicone barrier sheath (Fig. 4). The SILCS diaphragm has been modified to incorporate DPV to create a drug/device MPT (Major et al., 2013). To better accommodate DPV, the nylon spring was replaced with polyoxymethylene (POM) copolymer with the same shape and mechanical properties. Springs were prepared by co-mixing DPV and POM and melting/extruding into a mold. The DPV-loaded springs were then over-molded with silicone elastomer. Release of DPV from springs and from full diaphragms is shown in Fig. 5. DPV release from the springs showed typical matrix device release kinetics (high initial release followed by declining release over time). When the DPV-loaded spring was over-molded with the silicone sheath, reservoir-like drug release was observed with no dependency on drug loading. In vitro release of DPV was assessed from the entire device over 175 days. Near zero-order release was observed over this time (Major et al., 2013). Diaphragms traditionally are not used continuously (they are typically removed within 8 h after ejaculation). The long-term stability of the DPV-loaded SILCS diaphragm needs to be confirmed. Thus, there are some questions remaining to be addressed to better assess the viability of an ARV-releasing diaphragm and if developed further the SILCS diaphragm containing DPV would be used as a on-demand MPT (see below).

3.1.5. Long-acting injectable MPTs

An element promoted as a desired attribute of microbicide products is the ability for women to control their use. Unfortunately user control can confound efficacy assessments when women choose not to use these products in clinical trials. As seen in several of these trials, women appear in general unlikely to use a once-daily product as a preventative tool, particularly for HIV-1. Reducing user control should result in increased adherence. Long-acting injectable and implantable contraceptives have been available for many years. However, no such long-acting ARV product has been developed for either treatment or prevention of HIV-1. There are now products in development that, if combined with an appropriate long-acting hormonal contraceptive, could largely remove the issue of adherence.

Two ARVs are currently being developed as long-acting injectable formulations. The first is based on an approved oral product rilpivirine (RPV; an NNRTI). A nanosuspension formulation of RPV is being developed for both HIV-1 treatment and prevention (Baert et al., 2009; van 't Klooster et al., 2010). Studies in animals have demonstrated elevated and sustained RPV plasma concentrations in rats and dogs for 3 week and 3 months, respectively. The RPV injectable is promising as a potential prevention modality based on RPV concentrations in vaginal tissues and cervicovaginal fluids observed in human trials (Abraham and Gulick, 2012). A second drug in development for HIV-1 treatment and prevention is the integrase inhibitor GSK1265744 (744). 744 has a long plasma half-life (30 h) suggesting less frequent dosing may be possible compared to other injectable formulations (Min et al., 2009). Like RPV, 744 has been formulated as a nanosuspension and tested in a human PK study (Spreen et al., 2012) and a rectal challenge study in macaques (Andrews et al., 2013). Results from these studies of the long-acting 744 preparation show that potentially effective plasma concentrations are maintained for at least 1 month and that parenteral administration of 744 protects against rectal transmission of SHIV-1.

A key issue in creating an injectable, long-acting MPT that protects against HIV-1 transmission and unintended pregnancy is matching the duration of action. Clinical data of long-acting ARV formulations support a 1 month duration and suggest reaching 3 months is a possibility. Currently parenteral contraceptives have a 3 month minimum duration whereas implants release drug for years. Due to the irreversibility of injectable nanosuspensions, the ARV may require a lead-in period of oral dosing to assure no adverse events are observed. The potential for eliminating adherence issues encountered with user-controlled products is sufficient to accelerate development of injectable long-acting MPTs.

4. On-demand MPTs

The second approach to development of MPT products assumes administration around the time of sex (as opposed to once-daily administration which appears difficult for women to adhere to). These products can be vaginal gels, tablets, or films. While conceptually interesting, less work has been performed to date investigating these dosage forms as MPTs compared to long-acting formulations. An attempt to create a dual protection product (HIV-1 prevention and emergency contraception) is an interesting example of an on-demand MPT. This work involved combining LNG with Carraguard (carrageenan) gel. While Carraguard was shown to be ineffective as a microbicide (Skoler-Karpoff et al., 2008) the approach did confirm it is possible to administer LNG vaginally with effectiveness being similar to oral LNG used for emergency contraception (EC) (Brache et al., 2007, 2009; Sitruk-Ware et al., 2007). It is unclear how long after sexual intercourse a microbicide can be applied and still be effective. The window of administration will most likely be narrower than that for LNG, which is effective as an EC even when administered several days after sexual intercourse.

While Carraguard as originally formulated was ineffective as a microbicide, it has been modified to include zinc acetate (ZA). The mechanism of action of ZA with carrageenan is unclear but could be based on competition of Zn^{2+} with Mg^{2+} in the active site of HIV reverse transcriptase (Fenstermacher and DeStefano, 2011). In a recent study, this zinc/carrageenan gel was found to be safe and effective against SHIV-1 and HSV-2 transmission in macaques and mice, respectively (Kenney et al., 2013). Results from these animal models suggest the zinc/carrageenan gel could provide protection against transmission of both HIV-1 and HSV-2.

TFV 1% gel will be an MPT product that prevents HIV-1 (Abdool Karim et al., 2010) and HSV-2 (Tan, 2012) assuming the results from CAPRSA-004 are confirmed in the on-going Phase III study (FACTS-001). The 51% reduction of HSV-2 transmission was surprising but subsequent studies have provided some insight into TFV's mechanism of HSV-2 inhibition (Andrei et al., 2011; Vibholm et al., 2012). Should a similar reduction in HSV-2 transmission be found in the on-going Phase III trial of TFV 1% gel, the product could also be indicated for prevention of transmission of HSV-2.

The SILCS diaphragm is also being investigated along with a microbicide gel to create an MPT product. The idea is relatively simple in that at the time of diaphragm insertion, a dose of microbicide gel (e.g., TFV 1% gel) would be placed on the device thus providing protection against transmission of HIV-1 and blocking sperm from the uterus. Couples have found this method of gel administration acceptable (Frezieres et al., 2012). Vaginal distribution of BufferGel® as a model microbicide gel administered on one side of the SILCS diaphragm, both sides, or gel alone showed similar spreading patterns immediately after insertion and 6 h following simulated coitus (Pentlicky et al., 2013). The SILCS diaphragm and TFV 1% gel are to be examined clinically shortly in a collaboration with PATH (Seattle, WA) and CONRAD.

5. Challenges

There are a number of issues facing the development and regulatory approval of MPTs. A few products represent insignificant challenges in terms of their development and manufacturing (viz., TFV 1% gel and the zinc/carrageenan gel). However, most others MPTs represent significant technical challenges due to added complexity of delivering 2 drugs often with dissimilar dose requirements and physicochemical properties. Thus more complicated devices such as the segmented IVR or the pod-based IVR are being developed. These dosage forms can be prototyped on small scale but there will be added costs during development, scale-up, and manufacturing. These costs however will be offset to some extent by distributing across 2 indications using a single product and over long durations of use (up to 3 months in the case of the TFV/LNG IVR).

The second major area that remains unclear is the regulatory pathway for approval of MPTs as traditionally, Phase III studies for both indications are required by regulatory authorities. The only potential MPT product in late stage clinical testing is TFV 1% gel, wherein data are being collected for both HIV-1 and HSV-2 prevention in the on-going Phase III clinical trial (FACTS-001). Registering the TFV 1% gel for 2 indications would be relatively straight forward. Approval for the HIV-1 prevention indication for a DPV/LNG MPT IVR without preforming another Phase III HIV-1 prevention trial might be possible if the 28-day DPV IVR is shown to be effective and the release rate of DPV in vivo over 60 days is above or at that demonstrated with the 28 day ring in the on-going Phase III studies. In this case, the efficacy data from the 2 current clinical trials could support HIV-1 prevention but a Phase III contraceptive efficacy study would be required. This approach towards regulatory approval could constrain the design and delivery targets to a point that it may be challenging to control LNG release over 60 days. In terms of TFV it is likely that a TFV IVR would need to be found to be effective in at least one Phase III clinical trial since it is unlikely that therapeutic equivalence can be shown between TFV 1% gel administered on-demand and 90 days of continuous TFV release from an IVR.

The need to perform large efficacy trials is a challenge due to the current limitations in funding available for MPTs. While there have been several published reports extolling the benefits of MPTs, relatively little funding is available for product development beyond early stage proof-of-concept studies. This funding has come almost exclusively from USAID. The Gates Foundation has shown interest in funding development of MPTs, but has yet to make any significant investments in existing or proposed MPT approaches. The National Institute of Allergy and Infectious Diseases (NIAID) is expanding funding to include development of MPTs but only using licensed contraceptive methods. Demonstrating efficacy in HIV-1 prevention studies is critical to the further development of MPTs.

Another challenge is the lack of marketing data for vaginal gels, IVRs, and injectable ARVs. There is little if any history of use of these types of products and it will require a considerable social marketing effort to inform and educate women about these novel products.

Despite these challenges and undoubtedly some failures along the way, MPTs have strong potential to become a reality. The reproductive health benefits that would be gained from the availability of a portfolio of MPT products are too significant and therefore require continued investment.

6. Conclusions

Development of MPT products is gaining increasing importance as the need to protect women against STI transmission and prevent unintended pregnancy persists world-wide. IVRs are currently regarded as the most suitable technology for MPT development due to their potential for increased user acceptance and adherence over on-demand products. Several approaches are in or about to enter clinical trials that could ultimately become MPTs. These include TFV 1% gel (HIV-1/HSV-2), the SILCS diaphragm with TFV 1% gel (HIV-1/contraception), and TFV/LNG IVR (HIV-1/contraception). Also in preclinical development is the DPV/LNG IVR (HIV-1/contraception) and zinc/carrageenan gel (HIV-1/HSV-2). Regulatory strategies will vary with each MPT but could in some cases

require performance of Phase III clinical trials for each indication. Funding for MPT development is currently limited and will need to increase substantially as the most promising products enter clinical testing.

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