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Review

Advances in microbicide vaginal rings

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ABSTRACT

Vaginal ring devices capable of providing sustained/controlled release of incorporated actives are already marketed for steroidal contraception and estrogen replacement therapy. In recent years, there has been considerable interest in developing similar ring devices for the administration of microbicidal compounds to prevent vaginal HIV transmission. 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 semi-solid formulations. In this article, an overview of vaginal ring technologies is presented, followed by a review of recent advances and issues pertaining to their application for the delivery of HIV microbicides. This article forms part of a special supplement on presentations covering intravaginal rings, based on the symposium "Trends in Microbicide Formulations", held on 25 and 26 January 2010, Arlington, VA.

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1. Introduction

The concept of sustained/controlled drug delivery to the human vagina using vaginal ring devices was first described in a 1970 patent (Duncan, 1970) and a number of related publications

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Table 1
Marketed intravaginal rings and microbicide rings in/entering clinical development.

Ring [type[a]]	Status	Company/Organisation	Indication	Elastomer type	Active(s) [loading]	Release Rate [duration]
Estring® [R]	Marketed worldwide	Pharmacia	ERT[b]	silicone	estradiol [2 mg]	7.5 μg/day / [3 months]
Nuvaring® [R]	Marketed worldwide	Organon	Contraception	EVA copolymer	etonogestrel + ethinyl estradiol [11.7/2.7 mg]	120/15 μg/day [21 days]
Femring® [R]	Marketed worldwide	Warner Chilcott	ERT[b]	silicone	estradiol acetate [12.4 or 24.8 mg]	50/100 μg/day as the acetate [3 months]
Progering® [M]	Marketed Peru and Chile	Silesia	Contraception	silicone	progesterone [1 g]	variable [3 months]
Fertiring® [M]	Marketed Peru and Chile	Silesia	Contraception	silicone	progesterone [1 g]	variable [3 months]
dapivirine [M]	Phase II	IPM[c]	HIV microbicide	silicone	dapivirine [25 mg]	variable [28 days]
dapivirine + maraviroc [M]	Preclinical	IPM[c]	HIV microbicide	silicone	dapivirine [25 mg] + maraviroc [100 mg]	variable [28 days]
Versaring-a [P]	Preclinical (IND 108536)	Auritec Pharmaceuticals	Herpes prophylaxis	silicone	acyclovir [60 mg]	200 μg/day [3 months]

[a] R - reservoir; M – matrix; P - pod.
[b] estrogen replacement therapy.
[c] International Partnership for Microbicides.

(Mishell et al., 1970; Mishell and Lumkin, 1970), following the discovery that a range of molecules, including steroids, could be released from silicone elastomer in a predictable manner (Dziuk and Cook, 1966). Consequently, the early focus for vaginal ring technology was the development of steroid-releasing silicone elastomer rings for contraception, reflecting concerns over burgeoning global population in the developing world and the need to improve family health by controlling conception rates. However, a number of development issues, largely concerned with the choice and safety of the progestin compound, seriously hindered contraceptive ring development to the extent that the first ring did not reach market until 1992 (Pharmacia & Upjohn's estrogen replacement therapy product Estring®) (Fig. 2-A, Table 1). Two other major ring products, Nuvaring® and Femring®, have since reached market (Fig. 2-B and C, Table 1).

The most recent HIV/AIDS statistics make grim reading - 33.4 million living with HIV/AIDS; 2.7 million new infections in 2008; 2.0 million deaths in 2008; 25 million deaths since 1981; 14 million AIDS orphans in Africa (UNAIDS, 2009). Despite almost thirty years of scientific endeavour, a safe and effective preventative HIV vaccine has yet to be developed, although encouraging data have recently emerged (Rerks-Ngarm et al., 2009). Meantime, there is a growing interest in alternative HIV preventative strategies, most notably 'vaginal microbicides'. These are chemical compounds that, when formulated appropriately and applied to the vagina before intercourse, have the potential to either prevent or reduce HIV transmission via a number of well established mechanisms mostly associated with viral entry and replication. The reader is directed to several articles providing overviews of the current status and issues relating to development of HIV microbicides (Lederman et al., 2006; Klasse et al., 2008; Hendrix et al., 2008; Morris and Lacey, 2010). In this article, we provide an overview of conventional vaginal ring technologies before reviewing recent scientific and clinical advances in the development of HIV microbicide-releasing rings.

This paper forms part of a group of seven reviews covering presentations from the Trends in Microbicide Formulations Workshop that was held on 25–26 January, 2010 in Arlington, Virginia, USA. The other articles discuss the preclinical evaluation of anti-HIV microbicides (Doncel and Clark, 2010), gel, film, and tablet formulations (Garg et al., 2010), clinical evaluation of microbicides (Morrow and Hendrix, 2010), the prevention of mucosal transmission (Hladik and Doncel, 2010), dual protection (Friend and Doncel, 2010) and novel approaches to microbicide delivery and safety assessment (Whaley et al., 2010).

2. Vaginal rings

Vaginal rings are flexible, torus-shaped, elastomeric drug delivery devices that provide long-term, sustained or controlled release of substances to the vagina for either local or systemic effect. In this context, 'sustained release' refers to release of an active over a prolonged time period; 'controlled release' specifically refers to constant rate of release of an active according to zero-order kinetics. They are designed to be self-inserted and removed, and are positioned in the upper third of the vagina, generally adjacent to the cervix (Barnhart et al., 2005) (Fig. 1). Although the exact location of ring placement is not critical for clinical efficacy, it may have implications for comfort in some women.

The simplest design of vaginal ring contains solid drug dispersed throughout the polymeric matrix (a 'homogeneous' or 'matrix' ring), such that drug release rates are proportional to both the drug loading and the surface area of the device. Release from these matrices is via a permeation mechanism, involving (i) dissolution of the solid drug within the polymer, (ii) diffusion of the solubilised drug molecules though the polymer network, and (iii) partition of the drug from the polymer into the surrounding vaginal fluid/tissue. Drug at the surface of a matrix ring is released first, creating a drug depletion zone through which other solubilised drug molecules must diffuse in order to be released. As time progresses, the thickness of the drug-depletion zone increases with simultaneous decrease in the surface area of the inward moving boundary layer. Therefore, the daily amount of drug released decreases with time as the drug close to the surface of the ring becomes exhausted and the diffusional pathway for the remaining drug increases. Release kinetics are referred to as 'root time kinetics' (proportional to $t^{0.5}$), and are confirmed when the corresponding cumulative drug release versus root time plot is linear.

'Sandwich' and 'core' vaginal ring designs (also referred to as 'shell' and 'reservoir', respectively) were developed to provide con-

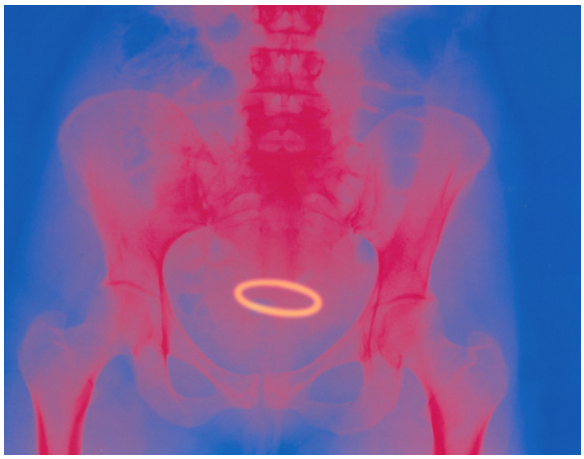

Fig. 1. A – X-ray image showing vaginal ring in position close to the cervix.

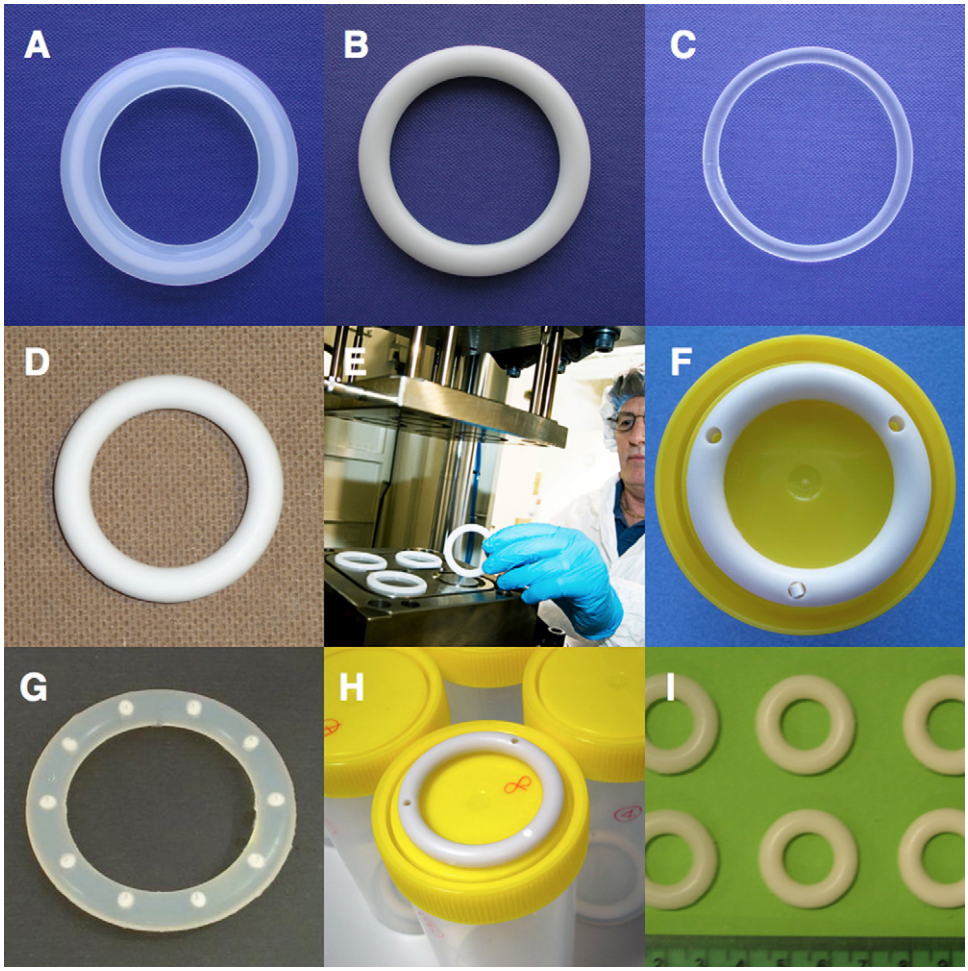

Fig. 2. A – Estring®; B - Femring®; C - Nuvaring®; D – Progering/Fertiring®; E – manufacture of dapivirine matrix ring; F – tablet insert ring; G – coated pod insert ring; H - lyophilised rod insert ring; I – macaque-sized silicone elastomer rings.

stant daily release rates, resulting in linear cumulative release versus time profiles, and conforming to zero order release kinetics. The sandwich design consists of a narrow drug-loaded polymer layer located below the surface of the ring and positioned between a non-medicated central core and a non-medicated outer membrane. Positioning the drug-loaded layer close to the external ring surface provides relatively high release rates; the small volume of the layer also reduces drug loading. Core-type rings comprise drug-loaded core(s) encapsulated by a non-medicated polymer membrane. Several individual, small drug-loaded cores of various lengths may be incorporated into the same core ring, thereby allowing multiple drug administration at pre-determined and independent release rates. As with the sandwich design, release rates can be modified by changing the thickness of the rate-controlling membrane.

A large number of clinical studies have reported the high user acceptability of vaginal rings (Dieben et al., 2002; Brache et al., 2000; Ayton et al., 1996; Barentsen et al., 1997; Roumen et al., 2001; Roumen et al., 1990; Vartiainen et al., 1993; Roumen and Dieben, 1999; Novak et al., 2003; Casper and Petri, 1999; Weisberg et al., 1995; Faundes et al., 1981; Nachtigall, 1995; Gilliam et al., 2010; Schafer et al., 2006; Fine et al., 2007; Brucker et al., 2008). Of particular significance is the strong preference for rings over semi-solid systems (Ayton et al., 1996; Barentsen et al., 1997). In a recent study comparing experiences with three different devices that could be used to administer a microbicide, both users and their male partners gave preference to the vaginal ring (53%) over a vaginal gel applicator (36%) and a diaphragm (11%) (Hardy et al., 2007). The authors suggest that the preference is attributed to the fact that ring insertion is unrelated to the coital act and therefore does not interfere with the spontaneity of intercourse.

2.1. Silicone elastomer vaginal rings

The excellent biocompatibility of silicone elastomers, and particularly polydimethylsiloxane (PDMS) systems, has led to their use in a wide range of medical and drug delivery devices (Mashak and Rahimi, 2009). Historically, vaginal rings have been fabricated most commonly from PDMS elastomers, although thermoplastic polymers are emerging as alternative materials (Malcolm, 2008). Although various types of silicone elastomer are commercially available with different chemical crosslinking mechanisms (Colas; Mashak and Rahimi, 2009), medical grade materials are limited to addition-cure and condensation cure systems. For example, Estring® is manufactured from a two-part addition-cure silicone elastomer, while Femring® is manufactured using a three-part condensation cure system (elastomer base, crosslinking agent and crosslinking catalyst). Unlike condensation-cure systems, addition-cure silicone elastomers do not produce an alcohol by-product during curing (crosslinking), and therefore are less inclined to produce large day one burst effects (Woolfson et al., 2003) and variable release upon storage.

The potential for sustained release of HIV microbicides from silicone elastomer rings was first established for nonoxynol-9 (Malcolm et al., 2003a), a surfactant-type first-generation microbicide candidate whose development was discontinued when clinical evaluation of gel formulations showed damage to the vaginal

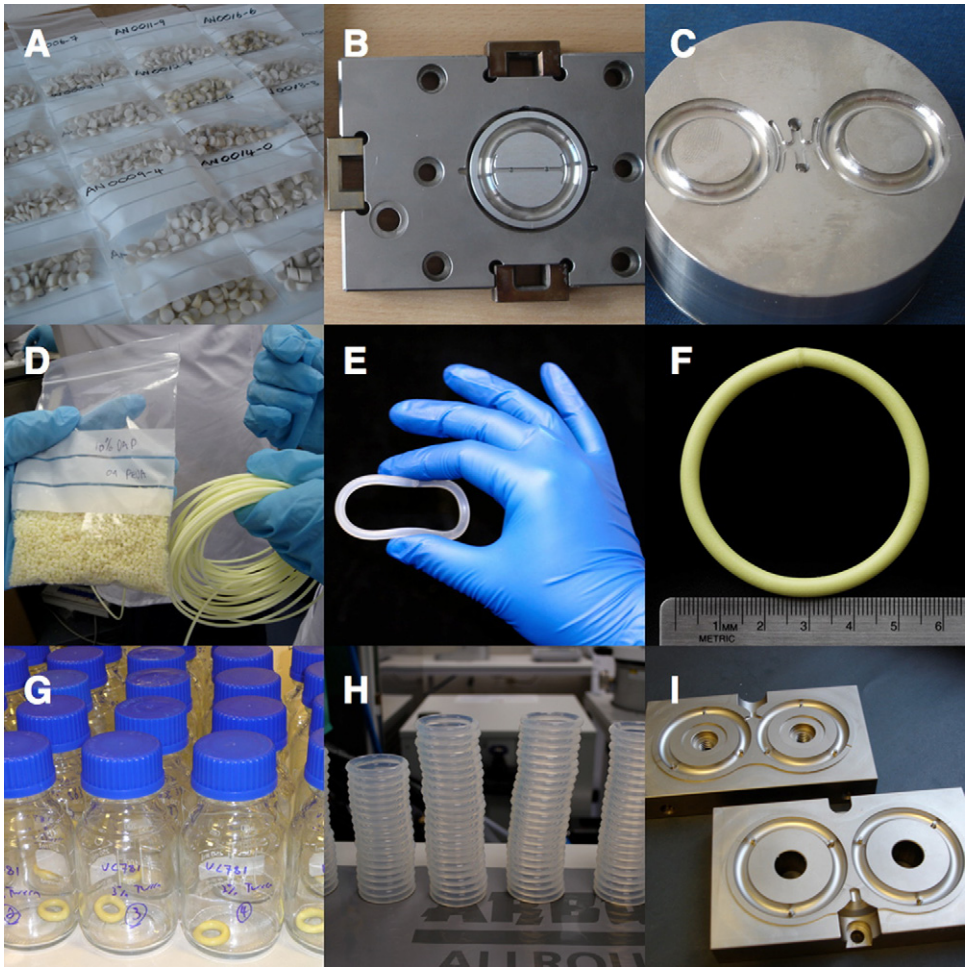

Fig. 3. A – ring sections prepared for residual drug content extraction; B – injection mold for manufacture of human-sized silicone elastomer ring; C - injection mold for manufacture of macaque-sized silicone elastomer rings; D – microbicide + thermoplastic extrudate; E – polyurethane ring; F - polyether-based polyurethane (Tecophilic HP-60D-20) ring containing 5% UC781 and 20% tenofovir; G – UC781-loaded macaque rings for release testing; H – placebo silicone elastomer rings; I – injection molds for manufacture of rod/tablet-insert ring holder.

mucosa and increased viral transmission (Stafford et al., 1998; Van Damme et al., 2002). Subsequently, vaginal rings for prevention of HIV transmission have focused exclusively on delivery of potent, small molecule, antiretroviral compounds, whose physicochemical characteristics (diffusion and solubility) are conducive to potentially effective release rates (Malcolm et al., 2003b). The non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine (formerly known as TMC120) has been extensively tested in silicone elastomer vaginal rings (Malcolm et al., 2005; Woolfson et al., 2006; Bell et al., 2007; Romano et al., 2009; Nel et al., 2009). A reservoir-type ring device containing 400 mg dapivirine has been shown to provide continuous and controlled *in vitro* release over the 71-day study period. Based on the observed daily release rate (140 mcg/day) and the total dapivirine loading within the device, this ring formulation is capable of sustaining release of dapivirine at this rate for between one and four years. Details on clinical development of dapivirine vaginal rings are presented in Section 3 of this article.

In order to facilitate efficacy testing of microbicide vaginal ring products against mucosal HIV transmission, smaller silicone elastomer rings have been developed for use in non-human primates. Non-medicated silicone elastomer vaginal rings having an overall diameter of 25 mm and cross-sectional diameter of 5 mm were shown to provide optimal fit and no mucosal irritation in pig-tailed and Chinese rhesus macaques (Promadej-Lanier et al., 2009) (Figs. 2-I and 3-C). A number of pharmacokinetic studies in macaques fitted with similar microbicide-releasing silicone elastomer vaginal rings are ongoing.

2.2. Thermoplastic vaginal 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 (Thyssen et al., 2001; Creatsas et al., 2001; Foran, 2003; Novak et al., 2003). The most commonly used thermoplastic elastomers in this application are poly(ethylene vinyl acetate) (pEVA) and segmented polyurethane (PU). Intravaginal devices from this class are manufactured by injection molding or continuous hot-melt extrusion (Neves, 2008; Crowley et al., 2007; Repka et al., 2008). The drug is compounded into molten polymer using melt mixing and then forced by melt extrusion screws or hydraulic pumps into a mold or through an extrusion die (Fig. 3-D). In extrusion, the polymer rod is cut to length and end-joined together either using butt welding, overmolding, solvent welding or biomedical grade epoxies to form the final ring (Grewell, 2007).

The only intravaginal thermoplastic ring currently on the market – the contraceptive NuvaRing® (Fig. 1-C, Table 1) – is made from pEVA, a copolymer of vinyl acetate and ethylene that varies from 10 to 40% vinyl acetate content. NuvaRing® is a thermoplastic reservoir IVR fabricated from two different grades of pEVA (Van Laarhoven et al., 2002b). As the mole fraction of vinyl acetate increases the poly-

mer crystallinity is reduced, the Young's modulus decreases and the drug permeability within the matrix increases. Because of these properties it is possible to produce via co-extrusion a reservoir device comprising a softer higher vinyl acetate mole fraction pEVA in the interior that promotes drug permeation and contributes the majority of the ring's mechanical properties, and a more crystalline pEVA (i.e. lower vinyl acetate fraction) on the exterior that serves as a rate-limiting membrane to control drug release.

Polyurethanes are another well-established and highly flexible class of elastomeric polymer. There are many subtypes of polyurethanes and the reader is referred to a number of reviews and books on the subject (Krol, 2008; Vermette, 2001; Szycher, 1988; Holden, 2004). Polyether urethanes are being evaluated for fabrication of intravaginal devices (Johnson et al., 2010; Gupta et al., 2008) (Fig. 3-E and F), wherein the network is formed by reaction between a polymeric diol such as polytetramethylene oxide (PTMO) or polyethylene oxide (PEO), a chain extender, and an aliphatic isocyanate. Many of the polyurethane medical devices on the market are prepared using aromatic isocyanates since they have superior physical properties and are less expensive than aliphatic isocyanates (Szycher, 1988). However, under improper processing and storing conditions aromatic isocyanates can hydrolytically break down into aniline derivatives, a known chemotype of toxic carcinogens, mutagens, and teratogens (Szycher, 1988). Consequently, concern over aniline derivatives causing potential reproductive toxicity is the motivation for selecting aliphatic isocyanates for intravaginal use. Other additives present in most commercially available polyurethanes include a catalyst to promote the polymerization reaction (e.g. tin octanoate, dibutyltin), antioxidants (BHT and Irganox) to prevent oxidation of the polyether, and extrusion lubricants to help with the flow of the polymer melt in the production of the device (Vermette, 2001, Krol, 2008). Because polyurethanes are constructed from two components and can be mixed together in various ratios a wide variety of material properties can be readily achieved with PUs that are not readily available in other elastomer systems. These include polymers with varying degrees of crystallinity and hydrophobicity that can have an impact on material and drug release properties and therefore on the types of drugs that can be formulated in this class of materials (Vermette, 2001).

Release of water-soluble actives from hydrophobic polymers, such as silicone and pEVA, is often poor, creating a need for elastomeric systems to deliver water-soluble antiretroviral microbicides like tenofovir. Water swellable PUs are an interesting class of thermoplastic elastomer that have received relatively little attention in the drug delivery field. Milligram quantities per day of the water-soluble antiretroviral tenofovir have been released from hydrophilic water swellable polyurethanes composed of a mixture of PEO (water swellable domain) and PTMO (hydrophobic domain) (Johnson et al., 2010) (Fig. 3-F). When the device is placed in an aqueous environment the polymer imbibes water, the drug is dissolved and then diffuses through the water swellable polymer network. The advantage of this system is that high drug loadings can be achieved (greater than 20 wt% of the device). The disadvantage is that the release patterns are complicated by the interplay between the swelling and a variable diffusion coefficient of the drug in the polymer at different states of hydration (Siepmann and Peppas, 2001).

In constructing a vaginal ring from thermoplastic materials there are a number of considerations that must be taken into account, including drug stability, the physical stability of the drug, and the mechanical properties of the device. Typical processing temperatures for creating polymeric elastomeric devices range from 130 to 190 °C (Szycher, 1988). Clearly, it is important for antiretrovirals incorporated within the device to be stable under these conditions, at least for several minutes while the drug is being compounded into the polymer melt and then processed to form the final device. All antiretrovirals examined to date have been able to survive conditions of 170 °C range for several minutes, including dapivirine, UC781, IQP-0528, IQP-0532, maraviroc, tenofovir, BMS-793 and several other small molecule antiretrovirals being considered as topical microbicides [unpublished data].

Another important consideration is the high solubility of hydrophobic drug substances in the polymer matrix, which is often more pronounced at the high melt extrusion temperatures. This creates an amorphous dosage form that is potentially thermodynamically unstable and from which the drug may undergo an amorphous to crystalline transformation. This phenomenon has been observed in two ways; first, drug crystals can form at the surface/air interface of the ring. Second, spherical drug crystallites can form within the polymer matrix upon cooling (post-extrusion), a phenomenon also observed after NuvaRing® manufacture (Van Laarhoven et al., 2002a). Both of these physical changes tend to occur at high drug loading (>10 wt%). This amorphous to crystalline transformation also occurs in hot melt extrusion products used to orally deliver highly insoluble drugs (Patterson et al., 2007; Bruce et al., 2009). A number of approaches have been used to minimize formation of crystals from amorphous dosage forms including the use excipients and surface coatings (Bruce et al., 2010).

2.3. Novel vaginal ring designs

A number of novel vaginal ring types have been developed to overcome obstacles associated with more conventional designs and construction materials, particularly the limits placed on the permeation of high molecular weight and/or relatively hydrophilic HIV microbicide candidates through conventional vaginal rings constructed from hydrophobic silicone and pEVA. By using the ring body as a holder for insertion and retention of alternative solid dosage forms, these permeation obstacles might be overcome. However, major manufacturing difficulties associated with the complex multi-component design of these new devices may limit their clinical development in the short-term.

2.3.1. Coated pod-insert vaginal rings

Oak Crest Institute of Science (OCIS) in collaboration with Auritec Pharmaceuticals is developing a unique intravaginal ring platform based on technology developed for the Vitrasert intraocular implant which was FDA approved for the treatment of AIDS-related CMV retinitis and releases ganciclovir into the eye for eight months. The technology platform is based on a polymer coated solid core of drug incorporated into a silicone elastomer ring and exhibiting pseudo-zero order release kinetics. Drug cores are coated with layers of semi-permeable polylactic acid polymer. Coated drug pods are incorporated into silicone rings and the drug is released through a delivery window in the silicone ring, with the release rate determined by the window diameter (Fig. 2-G). The amount of drug released from each ring can be adjusted by changing the amount and composition of the polymer coating of the drug core, the size of the drug delivery window and the number of drug pods in each ring. Vaginal rings containing tenofovir provide in vitro daily release rates spanning 2.5 orders of magnitude (10–4000 μg/day for tenofovir). The modular nature of the rings also makes the release of multiple drugs of varying solubilities relatively trivial. To date, *in vitro* release of tenofovir and acyclovir from the same ring segments has been demonstrated. *In vivo* studies have demonstrated sustained release of tenofovir over 14 days in rabbits and 28 days in macaques in the micro-molar range with no local inflammation or altered vaginal flora. In rabbits, vaginal tissue tenofovir levels at sacrifice were 3597 ± 1678 ng/g. In the macaques, vaginal biopsies proximal and distal to the inserted rings at days 7 and 21 measured tenofovir levels at 76 ± 54 μg/g, over

100 times the IC 50 of tenofovir (2 μM). The data demonstrates feasibility of a one-month tenofovir microbicide ring for women.

2.3.2. Rod and tablet-insert vaginal rings

Similar to the pod-insert vaginal ring, rod and tablet-insert vaginal rings comprise one or more polymeric solid dosage forms (lyophilised polymer gel rods and directly compressed tablets, respectively) inserted into a silicone elastomer ring (Fig. 2-F and H). While the ring acts primarily as a retainer for the solid dosage inserts, it may also be used to load and deliver other microbicide candidates compatible with conventional permeation-controlled release mechanisms. The lyophilised inserts are prepared by freeze-drying microbicide-loaded aqueous gel formulations. This technology is potentially useful for the production of solid dosage inserts containing peptide and protein-based microbicide candidates, since it does not involve high temperatures and the dried product serves to stabilise the active molecule. The gel is slowly reconstituted *in vivo* upon imbibing vaginal fluid, leading to sustained release. Similar lyophilised tablets have recently been reported for the formulation of dapivirine (Woolfson et al., 2010). The compressed tablet insert strategy makes use of ubiquitous direct compression tabletting technology to manufacture conventional sustained release solid dosage forms. In unpublished work, these insert-type rings provided sustained release of various protein molecules over up to seven days.

2.3.3. Multi-segment vaginal rings

Multi-segment IVRS are non-isotropic devices that have two or more segments each loaded with one or more drugs that are connected to each other using the methodologies described above in the section on elastomeric vaginal rings (Johnson et al., 2010). This type of drug delivery device offers several advantages including individual control of the release rate of the encapsulated drug substance and the ability to separate the drug molecules if cross reactivity exists between them. Disadvantages include the requirements for significantly more sophisticated manufacturing scheme than what is required for single segment vaginal rings.

2.3.4. Biosoluble and hydrogel vaginal rings

Given the regulatory constraints, very few polymer materials apart from silicone elastomer and pEVA have been considered to date for fabrication of vaginal rings. Matrix-type rings constructed from styrene-butadiene block copolymers have previously evaluated for sustained release of 17β-estradiol for treatment of post-menopausal symptoms (Vartiainen et al., 1993). The use of polymers that control drug release by mechanisms other than permeation might be useful for the delivery of hydrophilic and/or large molecular weight actives. Vaginal rings constructed from biosoluble acacia gum and a nonbiodegradable hydrogel of 2-hydroxyethyl methacrylate and sodium methacrylate and designed to provide sustained release for up to 28 days have been reported for the simultaneous release of combination antiretroviral HIV microbicides, and combinations of microbicides with non-hormonal contraceptives (Han et al., 2007; Saxena et al., 2009).

2.3.5. Microbicide-releasing SILCS diaphragm

The SILCS diaphragm is a "one-size-fits-all" barrier contraceptive device that is inserted vaginally to cover the cervix (Fig. 4) (Yang et al., 2007; Schwartz et al., 2008). Developed by the Program for Appropriate Technology in Health (PATH) and the Contraceptive Research and Development Program (CONRAD), the device comprises a thermoplastic nylon spring core and an overmolded silicone elastomer sheath, and as such has a similar structure to that of a reservoir-type vaginal ring. PATH are currently developing a microbicide-releasing variant of the SILCS diaphragm, where the microbicide compound is loaded into a spring core component constructed from a thermoplastic material with a lower processing temperature than nylon. Such a diaphragm would represent an important advance for the field by providing both contraception and microbicide delivery functions within a single device.

Fig. 4. Contraceptive SILCS diaphragm, comprising a thermoplastic spring core overmolded with silicone elastomer sheath. Microbicide-releasing formats are being developed where the microbicide is loaded within the spring core, similar to the design of a reservoir-type vaginal ring.

3. Clinical developments

To date, the only microbicide candidate to be evaluated clinically in a vaginal ring formulation is dapivirine, a non-nucleoside reverse transcriptase inhibitor that has also been evaluated clinically as a gel formulation (Nel et al., 2009a) (Fig. 2-E). Initial clinical studies involved reservoir ring configurations, evaluated in slightly different trial designs and involved different dapivirine drug loadings (200 mg or 25 mg) within the ring cores (Romano et al., 2009). Both rings were generally safe and well tolerated with similar type and frequency of adverse events observed in both the placebo and dapivirine groups. Dapivirine levels were assessed in plasma and vaginal fluids at multiple time points, and in cervical tissue after 7 days of ring use. Plasma levels were <50 pg/mL and fluid levels measured at the cervix, introitus, and near where the ring was inserted were >1,000 fold above the EC50 of the drug for both ring types. Levels of drug associated with the tissue biopsies were similar for each ring and were >1000× EC50. Therefore, similar levels and distribution of drug were obtained with the reservoir rings, independent of the drug load.

A subsequent study was conducted comparing matrix and reservoir rings each containing 25 mg of dapivirine (Nel et al., 2009b). This was a double blind, placebo controlled study that involved a 1:1:1 randomization of reservoir ring to matrix ring to placebo ring for 28 days of use in eight women per arm. Again, all rings were found to be equally well tolerated and safe with similar frequency and type of adverse events in all groups. Although the drug distribution was consistent between the matrix and reservoir groups, the levels of dapivirine measured in all compartments was higher in the matrix group. Plasma levels in the reservoir group were consistent with those observed in the previous seven-day trial with the reservoir ring. However, peak plasma levels with the matrix ring were as high as 1–2 ng/mL. The dapivirine levels measured in vaginal fluids were significantly higher in the matrix group than in the reservoir group, with peak differences being 1–2 orders of magnitude greater at specific time points in the matrix group. Thus, the vaginal fluid level profiles seen with the two different rings in this trial were consistent with the differences observed upon in vitro analysis of drug release of these two ring types. Although the reservoir ring appears capable of a more consistent level of drug release over 28 days both in vivo and in vitro, the matrix ring is able to deliver larger quantities of drug per unit mass of drug loaded.

4. Manufacturing scale up

With demonstrated safety and drug delivery from the Phase I-II safety studies, planning for Phase III efficacy evaluation and product launch are the logical next steps. At this stage, the focus should be on maintaining acceptable product quality, minimizing the cost of goods, and the manufacturability and throughput of the process. Since material produced at this stage will be used for both pivotal clinical trials as well as commercial product launch, it is essential that the drug product meets the marketing profile characteristics prior to the start of the efficacy trials and is manufactured in a manner consistent with international quality and regulatory standards. The key factors to consider when preparing to scale up a manufacturing process are: regulatory strategy, formulation and dosage form finalization, projected forecast demand, manufacturing capability, raw material suppliers, and equipment needs.

4.1. Regulatory strategy

Prior determination of the regulatory strategy for approval of the drug product is necessary as it will determine all aspects of final product development, including the requirements for the manufacturing process and its control. The drug product manufactured will have to comply with cGMP standards, but there may be differences in the specific regulatory requirements when dealing with the FDA, EMEA or other regulatory and governing agencies. Therefore, it is important to understand the intended regulatory strategy and requirements early in order to avoid unnecessary costs and delays to the development timeline. Lastly, the regulatory strategy will also define the preclinical work required to support the Phase III trial and eventual product launch, and could include biocompatibility studies, extractables/leachables assessments and other ICH and ISO requirements.

4.2. Formulation and Dosage Form

Typically, the Phase II stage of clinical evaluation defines the dose at which efficacy is likely achieved. Unfortunately, this approach is not feasible with a microbicide since the trial size for such a proof of concept is essentially equivalent to that required for full demonstration of efficacy (Van de Wejgert and Jones, 2006). In addition to dose (i.e., drug(s) quantity loaded into the ring), configuration of the ring (matrix, reservoir, insertion type) and polymer type (silicone elastomer, pEVA, polyurethane, etc) needs to be defined. Based on the safety and drug distribution data obtained from Phase I/II trials, the final dose and as well as ring configuration and chemistry are finalized for advancement into Phase III/product launch. It is sometimes necessary to adjust the formulation prior to Phase III, either to increase/decrease dose level or to adjust the excipient ratio or inclusion. However, such modifications may require additional preclinical or clinical bridging studies. Lastly, the container closure system should be selected and evaluated prior to the Phase III trial so that all supporting studies may be representative of the final intended product.

4.3. Projected Forecast Demand

Since microbicide efficacy trials are necessarily quite large (e.g. the phase III study of the Carraguard microbicide gel involved more than 6,000 women; Skoler-Karpoff et al., 2008), a manufacturing scale-up relative to phase I/II is typically required for phase III. In the case of a vaginal ring study, more than 100,000 units may be required over a three year trial. Importantly, some estimation of post trial ring needs is also necessary so that the phase III manufacturing process is consistent with achieving the commercial launch demands as well. If the phase III process were to be smaller than what is implemented for commercial launch, regulatory agencies could require bridging studies to establish the uniformity between the phase III process and a large commercial process. This could add significant time and cost to the program. Therefore, accurate projections for phase III and product launch are critical components of the product planning effort

4.4. Manufacturing Capability

Unfortunately, vaginal rings are not a common dosage form and therefore contract manufacturers of rings are not readily available to the microbicide field. Consequently, it is anticipated that an investment in phase III/launch scale manufacturing would be required at an appropriate contract manufacturing organization, preferably with the proper experience in related ring technologies and in phase III pharmaceutical manufacturing. It is not likely that such a manufacturing organization would have access to the equipment needed for microbicide vaginal ring production. Such equipment is often custom made to meet typical pharmaceutical requirements. Therefore, there can be significant costs associated with equipment procurement and lengthy timelines required for fabrication. The specific types of equipment required include mixers for compounding of excipients and drug substances, fluid or solid phase feeding systems, injection molders and moulds, or extrusion equipment. Ultimately, these systems need to be fully integrated, and partnered with inspection and packaging systems.

4.5. Raw Material Suppliers

At the Phase III stage, it is important to have multiple raw material suppliers qualified. In the case of vaginal rings, this includes proper quality audits and agreements with suppliers of both the excipients (e.g., silicone elastomer) as well as the drug substance. It is important to avoid reliance on single sources for these materials so as to mitigate the risk of interrupted supply of material during a trial or after commercial launch. At present, suppliers of potential ring polymer materials are extremely limited and this represents a significant risk to the development of microbicide vaginal rings from a cost and supply perspective.

5. Concluding Remarks

Despite the fact that vaginal rings are already marketed for other clinical indications, it will be apparent from the preceding discussion that there are many major challenges ahead for microbicide-releasing vaginal rings. Demonstration of proof-of-concept of the HIV microbicide strategy would serve as a huge incentive for continuing with vaginal ring research and development programmes. After a number of Phase III clinical set-backs based on early generation microbicide candidates, the microbicide field has been reinvigorated by the results of the CAPRISA 004 tenofovir gel trial, announced in July 2010 at the Vienna AIDS Conference. The results have demonstrated proof-of-concept for HIV microbicides, and has provided the foundation for the development and testing of advanced formulations, such as vaginal rings, with the potential to offer increased user compliance, adherence, acceptability and ultimately clinical efficacy.

Appendix A. Panel discussion on intravaginal rings for the formulation of HIV microbicides

Panel members: Joe Romano (International Partnership for Microbicides), Patrick Kiser (University of Utah), Tom Smith (Auritec Pharmaceuticals), Karl Malcolm (Queen's University Belfast)

Henry Gabelnick: Tom, what delivery duration can the pods in the IVRs provide?

Thomas Smith: It depends on the level of drug needed, and then it's simply a question of release rate time and duration. There is also a physical restriction.

Gustavo Doncel: Tom, after insertion of the Vitrasert® implant, is the concentration of ganciclovir different in the different ocular tissues?

Thomas Smith: We looked at drug concentrations in the vitreous, retina, cornea and lens and found that the ganciclovir levels in the vitreous were predictive of the levels in the other tissues. In the vitreous, the ganciclovir levels were approximately 1 to 1.5 log units above what was needed.

David Friend: The two most advanced microbicide dose forms are gels and rings. Joe, do you think it would be prudent to conduct the next proof-of-concept study with a ring rather than a gel?

Joseph Romano: We suspect that compliance with gels and oral tablets is a potential challenge to obtaining proof-of-concept for these formulations. The real advantages of the ring are the sustained release and the assumption that there will be fewer compliance issues, so it seems wise to conduct a study to attempt to demonstrate proof-of-concept for the ring.

David Friend: So, the added risks and costs are outweighed by the potential?

Joseph Romano: Yes. The risks, complexities and costs are higher in terms of reaching the point of running a clinical trial with rings.

Participant: What are the risks associated with a ring?

Joseph Romano: The risks are not related to safety. The rings themselves do not cause harm and the drugs in the rings are being studied intensively. The risks are primarily related to product readiness: finding a partner, implementing scale-up, and the investment required.

Jim Turpin: Regarding the earlier discussion on using solvents to create sink conditions, what should we be using as our measurements of release for rings? Is there consensus on an assay?

Karl Malcolm: For the release of certain types of compounds from rings, solvents can be used to create sink conditions for in vitro release, and good in vitro/in vivo release correlations can be achieved. More animal model PK studies conducted in parallel with human studies are needed to allow correlation of animal and human data.

Thomas Smith: I am at the opposite extreme. Because I cannot test everything in animals, I depend greatly on in vitro release data. My colleagues and I spent years developing a flow through dissolution system that mimics sink conditions to allow in vitro release of low solubility drugs like UC781.

Patrick Kiser: There are a few different ways to approach this. For screening, the one phase method is a good starting point; more sophisticated methods can be used later. The flow through system is also a good system. Stirring-based models are another approach. The best approach will likely be different for different systems.

Karl Malcolm: The issue is really that the in vivo system is a dynamic one and the flow through dissolution system speaks to that. It would be great if a model that even more closely mimics the in vivo system could be developed.

Henry Gabelnick: Rings have been made for a number of years now, often with fairly hydrophobic drugs. I think that the flow through dissolution system is one of the better ways to create sink conditions, but there are a number of other ways to solubilize drugs. The bottom line is that we would like to see changes that can be correlated with what occurs in humans. UC781 PK studies in women are underway. If the drug levels in women are not high enough, in vitro release testing will be repeated, the rate of release will be increased and the new formulation will be tested in women.

Karl Malcolm: How do you know that the drug level is high enough?

Henry Gabelnick: The upper limit is known from systemic administration. The optimal amount will not be known until an efficacy study is completed.

Thomas Smith: Karl, I was surprised to hear that you are moving forward with the matrix ring. The reservoir ring data seemed quite promising.

Karl Malcolm: Yes, but if the aim is to provide proof-of-concept, it makes sense to deliver as much drug as possible. Matrix rings provide greater release rates than reservoir rings.

Thomas Smith: I'm not sure about that; there may be excess toxicity with higher drug levels.

Joseph Romano: If we had a fast, easy, inexpensive way to manufacture reservoir rings at scale, we probably would have chosen to move forward with the reservoir ring. We are moving forward with the matrix ring because that is what is available to us.

Patrick Kiser: I would argue that there might be a good biological reason, as long as the drug is found to be safe, to have a burst at the beginning of the dose.

Thomas Smith: With ganciclovir, there is no evidence that a burst is necessary.

Karl Malcolm: The first ring that we developed for IPM was a reservoir ring and I believe it released 70 micrograms of drug per day. We think we can release drug from that ring for 1 year and that would only release 50% of the loading of the drug, so a burst at the beginning is possible.

Thomas Smith: According to my calculations, that ring was likely releasing about 10 micrograms per day.

Karl Malcolm: No, that particular ring released between 60 and 70 micrograms per day.

Thomas Smith: That's the release into alcohol. If there were 25 milligrams in the ring to start and 300 micrograms were released over a period of 30 days, the release rate was approximately 10 micrograms per day. Those are spectacular results. I think we've been deluded by this cancer model of, the more drug, the better. I think you showed that 10 micrograms per day is plenty for that drug. That is, unless a study shows that amount not to be effective.

Joseph Romano: We are trying to determine if it is effective. The next study IPM is undertaking will test a dapivirine reservoir ring with slightly different chemistry that releases drug levels between the levels released with the matrix and reservoir rings. The plan is to determine if there are inhibitory levels of drug in the fluids. Tissue will also be biopsied and challenged with virus ex vivo. The aim is achieve drug levels that are high enough to provide protection but not so high that they cause resistance.

Henry Gabelnick: Going back to the example of contraception, the initial hormone levels were much higher than needed. When side effects were seen, the doses were titrated down until an effective dose with minimum side effects was achieved. With microbicides, we do not necessarily have that luxury, but we cannot let the perfect be the enemy of the good. We must make educated guesses to move these products forward.

Joseph Romano: Regarding toxicity, the oral dose of dapivirine was quite high at 300 mg. The dapivirine ring has a total of 25 milligrams that is released during a 30-day period. The oral dose studies did not show any toxicity, so toxicity is not a major concern with the dapivirine ring. Resistance, however, is a concern.

Sandra Klein: I think there is a need to develop biorelevant dissolution tests for vaginal delivery systems. The flow through dissolution system is good for certain drugs, but not for all drugs or dosage forms. There is no one-size-fits-all system.

Gustavo Doncel: We use a system similar to the flow through dissolution system to test drug release from rings and tissue concentrations. The system is a hybrid between testing in vitro and in animal models and humans as it uses a reconstructed epithe-

lium instead of a silicone membrane. The system has proven useful for screening candidate microbicides as it has shown differences in drug tissue levels with different dosages and different ionization processes. Tom, do pKa and ClogP values correlate with your flow through dissolution system?

Thomas Smith: Yes, and perhaps even more so because our system is a true diffusion system.

Gustavo Doncel: Patrick, does the ClogP range of 2–4 also apply to your system?

Patrick Kiser: In terms of absorption, yes. However, it really depends on the material. For the hydrophobic polyurethanes, ClogP of 2–4 is applicable, but it is not applicable for the hydrophilic polyurethanes.

Gustavo Doncel: I'm asking because UC781, for instance, does not release well from silicone systems but it does release well from some of the polyurethanes and it releases even better from ethylene vinyl acetate copolymer (EVAc).

Patrick Kiser: In the case of UC781, I think that the release has more to do with the lattice energy of UC781. In the systems that I am developing, UC781 is solubilized in the solution so it is mobile. In Karl's system, the drug changes from a crystal state to solubilized drug before it is released from the ring. ClogP really has nothing to do with the lattice energy of the drug.

Gustavo Doncel: So, the bottom line is that release is system-dependent.

Kirti Valia: I have been working with transdermal administration for more than 20 years and I have found that the only way to achieve consistency is to use PBS buffer. I would recommend not using alcohol because the results produced may be misleading.

Karl Malcolm: We don't use buffers at all for in vitro release testing of rings because vaginal fluid has no appreciable buffering capacity.

Marcus Krumme: Regarding the dissolution tests, there are two types: quality control and development. For quality control, the tests run quickly and the aim is to distinguish between a good and bad product. I was surprised to see the long dissolution times that were reported for the quality control method. For development, the aim is to be able to correlate in vitro and in vivo data, so using a biorelevant method is more of an issue.

Karl Malcolm: Rings are different than films. Rings are diffusion-controlled systems, so when diffusion-controlled assays are used, the release time cannot be condensed.

Jim Turpin: Joe, is the industrial infrastructure in place to produce hundreds of thousands of rings each year? Are there enough raw materials available?

Joseph Romano: There are enough raw materials to make approximately 1 million rings per year. Even more rings could probably be made if needed, but there probably is not enough material to make 10 or 100 times that amount. The problem is that there are only a few companies in the field. More players are needed to address capacity.

Gustavo Doncel: If a Phase III trial shows a ring to be effective, are there funds available to manufacture all of these rings?

Karl Malcolm: The manufacturing scale-up is a huge challenge.

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