Abstract—Contraceptive diaphragms offer a female-controlled barrier method that enhance a woman’s ability to prevent pregnancy. Incorporation of antiretroviral HIV microbicides into such devices may also provide protection against HIV infection. The paper gives a brief outline of the work being conducted by PATH, CONRAD and QUB on the development of a microbicide-releasing SILCS diaphragm. The design, engineering and manufacturing challenges that have been encountered will be discussed, as well as the potential impact such a device could have in the developing world.

I. INTRODUCTION

Diaphragm contraception was first developed in the late 1800s with the advent of the Mensinga diaphragm, which was constructed from vulcanized rubber. Over the years, the size, shape and material of construction have changed and a number of different types of diaphragm are available. Devices can now be produced from latex, silicone rubber and natural rubber and are able to take different forms to match anatomical variations between women, depending on the spring system incorporated into the design.

Arcing spring devices are the most widely used diaphragm type as they are readily fitted at the cervix and are suitable for use in a wide range of women. Coil and flat spring devices can both be inserted using applicators; the former are suited for women with a deep pubic arch and the latter for women with a shallow pubic arch. Wide rim diaphragms are available with arcing or coil springs and create a better seal at the cervix when compared to other diaphragms.

The SILCS diaphragm has been developed to overcome a number of shortcomings with these current diaphragm devices and most importantly to better meet user requirements. Since 1994, PATH has worked on a female controlled barrier device undertaking a number of iterative rounds of user evaluation, each one informing the design and development process. The team has created a diaphragm that has easier insertion and removal, easier fit and increased comfort compared to traditional diaphragms. The SILCS diaphragm has also been designed as a one-size-fits-most device and does not require clinician fitting.

The development of the present SILCS diaphragm has involved many years of design to match the user identified requirements. The original spring-core for the SILCS diaphragm prototype was of a metal spring construct overmolded by a silicone sheath similar to traditional diaphragm devices. The metal spring-core benefitted from excellent bending dynamics and has been extensively tested in the clinic. However, manufacture of the metal spring-core SILCS diaphragm was expensive and there was high reject rate due to part-to-part variations and overall poor tool fit. A decision was made to switch to a polymer spring-core that would be easier and cheaper to manufacture.

For initial studies an elliptical cross-section spring was designed. Sections of the ellipse were altered to match the bending of the metal spring-core and to also reduce stress. Finite element analysis (FEA) was used to assess part stiffness and the design was rapid prototyped with a selective laser sintering (SLS) process using a polyamide resin. Extensive mechanical testing allowed for part evaluation and design refinement. The final polymer spring-core could then be manufactured in an injection molding process.

Material selection for the thermoplastic spring-core was limited to injection molding grade resins meeting the following requirements: high melting; FDA approved; high flexural modulus; semi-crystalline (improved fatigue) and high elongation. Nylons 6/6, 6/12, PET, PBT, polyketone and polyacetal resins were identified as possible candidates and
were extensively tested. A nylon 6,6 grade was identified as
the resin that produced the desired mechanical performance
of the polymer spring-core. The switch to the polymer
spring-core brought increased design flexibility and
significant cost savings in terms of device manufacture and
capital equipment cost.

Since 1998, the SILCS diaphragm prototypes have been
evaluated in two clinical Phase 1 post-coital test (PCT)
evaluations and two user acceptability studies. The PCT
clinical studies indicated that SILCS diaphragm prototypes
used in conjunction with a spermicide (2% N-9) performed
well, reducing the average number of progressively motile
sperm per high powered field (HPF) to 0. User acceptability
studies evaluating the ease of handling, comfort, fit, stability
and acceptability of SILCS diaphragm prototypes during use
in a range of women with different fits and of different BMI
sizes were conducted, and compared with those from the
Ortho All-Flex® diaphragm. The studies indicated no
adverse events and women reported ease of use and better
comfort and fit. At the end of a 2004-2005 study 19 of 20
couples stated they preferred the SILCS devices..

II. MICROBICIDES

Although, the SILCS diaphragm addresses the need for a
female controlled barrier contraceptive method, it will not
protect protection against sexually transmitted infections,
such as HIV. Female controlled HIV prevention methods,
including gels, tablets and intravaginal rings (IVRs), are
already being extensively investigated®. IVRs have long
been used as an effective means of sustained, controlled
delivery of therapeutic drugs to the vagina.45 IVRs are
commercially available for the sustained delivery of steroid
molecules for either contraception (Nuvaring®) or estrogen
replacement therapy (Estring®, Femring®).5,6 The former
device is fabricated from poly ethylenevinylacetate (PEVA),
and the later from silicone elastomer.

Intravaginal rings overcome the many disadvantages
associated with other conventional semi-solid vaginal
delivery systems, including poor user acceptability, leakage
and short vaginal retention time. Like diaphragms, IVRs can
be used discreetly by the woman during intercourse.58 Drug
delivery to the vagina occurs via permeation-controlled
mechanisms wherein the drug dissolves in and diffuses
through the polymeric material(s). In matrix-type ring
devices the drug is homogeneously dispersed throughout
the polymeric carrier; For reservoir-type devices the drug is
homogeneously dispersed in a polymeric core encased
within an outer metering polymeric sheath, and providing
constant daily release over longer periods.

Vaginal microbicides are drugs applied vaginally to
prevent or decrease the likelihood of viral infection by
STIs10. An IVR capable of sustaining the delivery of a
potent HIV microbicide for several weeks or months (i.e.
coitally-independent) would make an ideal female-controlled
strategy for women to protect themselves against infection.
Several groups and organizations worldwide are actively
pursuing the development of such ring devices. However,
IVRs do not provide a barrier contraception. Uniquely, a
microbicide-releasing SILCS diaphragm has the potential to
combine barrier contraception and antimicrobial functions in
a single device.

III. MICROBICIDE-RELEASING SILCS DIAPHRAGM

Although it is theoretically possible to incorporate the
active agent within the sheath layer, there is a concern that
the barrier properties could be compromised, particularly as
the active is released to leave holes within the sheath. The
most practical location for incorporation of an HIV
microbicide in a SILCS diaphragm device is within the
polymeric spring core component, which is subsequently
overmolded with the silicone elastomer sheath. In this way,
the microbicide-loaded SILCS is analogous to a reservoir-
type IVR, in that the active agent must permeate the non-
medicated layer in order for release to occur into the
surrounding vaginal environment. The microbicde release
rate will depend on several parameters, including the
physicochemical characteristics of the drug molecule and the
polymeric sheath. Silicone elastomers and thermoplastic
PEVA show excellent drug permeation properties and are
already approved for use in a number of medical and drug
delivery devices. We propose that effective microbicde
release could occur from a diaphragm device comprising a
thermoplastic spring core overmolded with a silicone
elastomer sheath.

Fig. 2. A simple model drug-loaded SILCS diaphragm, comprising a
PEVA rod inserted into a silicone elastomer tube section, sealed by
silicone end caps. The device is then placed in a 10 ml vial for in vitro
release studies.

A. Preliminary Investigations

Model diaphragm devices were constructed comprising
PEVA rods (1 cm length) loaded with the lead candidate
microbicide UC781 inserted into a medical grade silicone
elastomer tube (6.5 cm length, outer diameter 4.87 mm and
inner diameter 2.64mm.) (Fig 2). The inserted core remained
in contact with the luminal surface of the silicone elastomer
tube thereby allowing the permeation of drugs from the
thermoplastic core through the silicone sheath layer. The model devices were placed in a glass vial ensuring that the two sealed ends were located above the level of the release medium (10 mL of 1:1 isopropanol:water). Cumulative release of 3.25 mg over 14 days into the isopropanol:water medium was achieved. Results from the studies demonstrated that the concept of providing sustained release of a microbicide compound from a SILCS diaphragm is a valid.

B. Drug-loaded Spring-core Development

The current SILCS diaphragm spring-core is manufactured from nylon 6,6 and although this material provides the requisite mechanical performance to match the metal spring-core it is processed at temperatures exceeding 500°F. However, this high processing temperature is a major obstacle for development of a microbicide-releasing SILCS diaphragm since such high temperatures are detrimental to drug stability during processing and injection molding. Therefore, alternative thermoplastic materials were required having lower processing temperatures. Although lower melting thermoplastics, such as PEVA, have been shown to provide good drug elution properties, they do not provide the necessary mechanical performance of the spring-core that is critical for in vivo function and user acceptability of the device. Hence, polyacetal (or polyoxymethylene) resins, having processability at temperatures below 400°F and its similar mechanical performance to nylon, were selected for replacement of the nylon 6,6 material.

Polyoxymethylene is a semi-crystalline material synthesized from trioxane. To increase thermal stability a POM copolymer is formed by the incorporation of a more stable cyclic acetal as a co-monomer, such as dioxolane. The oxygen atoms along the polymer backbone make POM copolymer highly polar. POM exhibits three major thermal relaxations: (i) -123 to -53°C (ii) -43 to -3°C (iii) 147 to 157°C. Although highly crystalline, the lower temperature relaxations allow for high chain mobility and the possible diffusion of drug molecules at body temperature.

In vitro drug release studies were conducted to understand the drug elution properties of the POM copolymer. Microbicide-loaded spring cores were prepared by compounding UC781 at 1, 5 and 10% w/w loadings into the thermoplastic using a Thermo Haake Minilab Twin-Screw Compounder (365°F, 50 rpm), followed by spring-core manufacture on a Morgan Industries Injection Press (374°F, 60 psi). The drug-loaded spring-cores were placed into individual 250 mL flasks containing 60 mL of isopropanol:water (1:1) medium. The flasks were placed in an orbital shaking incubator (60 rpm; throw 25 mm, 37°C, Infors AG CH-4103). Daily sampling with complete replacement of the release medium was performed for fourteen days. The cumulative release over 14 days of 1.12, 6.37 and 30.81 mg for 1, 5 and 10% drug loaded spring-cores respectively (Fig. 3). The spring-core weighed 1.1g. In this study the spring-core represents a matrix device and therefore release is characterized by a high initial burst of drug in the first few days followed by a decline in release until a steady daily release is obtained. Clearly, POM copolymer is a good candidate material since it has similar mechanical properties to nylon 6,6 and is shown to have sufficient drug elution properties.

C. Drug-loaded Diaphragm Production

The next step was to fabricate entire SILCS diaphragms from nylon 6,6, POM copolymer and drug-loaded POM copolymer spring-cores and to directly compare the mechanical performance of each. In vitro release was also performed on the drug-loaded SILCS diaphragms. Spring-cores were manufactured and shipped to a third party vendor that has been previously contracted to manufacture the SILCS diaphragm. The vendor was able to successfully manufacture nylon 6,6 and POM copolymer spring-core SILCS diaphragms. However, drug loaded spring-cores were unable to be used to produce SILCS diaphragms as silicone elastomer curing issues were encountered during overmolding, attributed to poisoning of the addition-cure platinum catalyst. The likely reason for this poisoning is due to the presence of sulfurous byproducts caused by the degradation of the UC781 drug (C₃₇H₁₈CINO₅S) during processing. The processing temperature for POM copolymer was deemed too high for UC781 and therefore use of this microbicide candidate has been discontinued. Alternative microbicide candidates with enhanced thermal stability at the required processing temperatures are now being actively investigated.

Mechanical tests to measure the two basic properties of the nylon and POM spring-cores (the force required to compress the diaphragm in the short axis and the materials ability to rebound under stress). The spring-core was placed between two tensile clamps spaced 65 mm apart in an Instron Universal Tensile Tester with 100N Load Cell. The spring-core was compressed 40 mm at 10 mm/min whereupon the load was held for five minutes.
The Force (N) to compress the spring-core 40 mm was recorded for each material. The change in Force (N) recorded as a percentage was used as a value for compression relaxation (%), which is taken as a measure of shape formation under compression i.e. the lower the change in Force (N) the greater potential to shape form. No significant differences between the nylon and POM copolymer SILCS diaphragms were observed (Figure 4).

This mechanical test was also conducted for various microbicide-loaded spring-cores only (no overmolded silicone sheath) and no significant effects on mechanical performance were observed up to 10% w/w drug loadings.

**IV. CONCLUSION**

PATH has successfully responded to meet a much needed requirement in female healthcare - a female controlled barrier method that is acceptable for most women. Moving forward the SILCS diaphragm also has the potential to give women the ability to protect themselves against HIV protection. The iterative design process has meant that the SILCS diaphragm has been able to firstly meet the requirements of the end user and also aid the requirements of the production team. The spring-core design has progressed from the beginning of the project, moving from a traditional metal spring rim to an innovative thermoplastic contoured spring-core. In developing for the new microbicide-releasing SILCS diaphragm, the spring-core has changed material and incorporated a drug, while maintaining the requisite mechanical performance. New microbicide drug candidates are presently being assessed and lead candidates will be incorporated into intact SILCS diaphragms in the near future. New overmolding facilities are being installed in QUB for in-house research and production. New user acceptability studies are planned for the POM copolymer SILCS diaphragms in 2010, with an animal pharmacokinetic study of microbicide-releasing SILCS diaphragms planned for 2011. An application to USFDA for market approval of the SILCS diaphragm as a contraceptive will be submitted in 2010-2011.

**REFERENCES**


