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Review

Advances in development, scale-up and manufacturing of microbicide gels, films, and tablets

Sanjay Garg[a,*], David Goldman[b], Markus Krumme[c], Lisa C. Rohan[d], Stuart Smoot[e], David R. Friend[f,1]

[a] School of Pharmacy, University of Auckland, 93 Grafton Road, Grafton, Auckland, New Zealand
[b] MedCrystalForms LLC, 10819 Gilroy Road, Hunt Valley, MD 21031, United States
[c] LTS Lohmann, 21 Henderson Way, West Caldwell, NJ 07006, United States
[d] Magee Women's Research Institute, 204 Craft Way, Pittsburgh, PA 15231, United States
[e] DPT Laboratories, 3300 Research Plaza, Brooks City-Base, TX 78235, United States
[f] CONRAD, 1911 N. Fort Myer Drive, Suite 900, Arlington, VA 22209, United States

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ABSTRACT

Vaginal HIV microbicides are topical, self administered products designed to prevent or significantly reduce transmission of HIV infection in women. The earliest microbicide candidates developed have been formulated as coitally dependent (used around the time of sex) gels and creams. All microbicide candidates tested in Phase III clinical trials, so far, have been gel products with non-specific mechanisms of action. However, recently, research is focusing on compounds containing highly potent and specific anti-retrovirals. These specific anti-retrovirals are being formulated as primary dosage forms such as vaginal gels or in alternative dosage forms such as fast dissolve films and tablets. Recent innovations also include development of combination products of highly active antiviral drugs such as reverse transcriptase inhibitors and entry inhibitors, which would theoretically be more effective and would reduce the possibility of drug resistance. In this article, an overview of recent advances in the microbicide gel, film, and tablet formulations and issues pertaining to scale-up, formulation, and evaluation challenges and regulatory guidelines have been presented. This article forms part of a special supplement covering presentations on gels, tablets, and films from the symposium on "Recent Trends in Microbicide Formulations" held on 25 and 26 January 2010, Arlington, VA.

Contents

* Corresponding author. Tel.: +64 9 923 2836.
E-mail addresses: s.garg@auckland.ac.nz (S. Garg), dfriend@conrad.org (D.R. Friend).
[1] Tel.: +1 703 276 3906.

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1. Introduction

Dosage form composition and performance can be as critical as the active ingredient for biological efficacy of vaginal and rectal microbicides. Vaginal dosage forms available around the world include creams, gels, tablets, capsules, pessaries, foams, ointments, films, tampons, rings, and douches. While the majority of vaginal drugs so far have been in the form of gels, there is a growing interest in alternative dosage forms such as rings, tablets, and films.

As the microbicide field progresses through generations of active compounds, diverse formulation options are needed to accommodate varying physical characteristics and delivery modalities. Simultaneously, better understanding and advances in quality, scale up issues, and regulations also affect the effort and investment required in designing new microbicide products. While the majority of product development and scale up issues with microbicide tablets, films, and gels are similar to other pharmaceutical products, there are some unique challenges because of site of delivery, prophylactic nature of product application, and diversity in sex and hygiene practices across the developing world.

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), the prevention of mucosal transmission (Hladik and Doncel, 2010), intravaginal rings (Malcolm et al., 2010), clinical evaluation of microbicides (Morrow and Hendrix, 2010), dual protection (Friend and Doncel, 2010) and novel approaches to microbicide delivery and safety assessment (Whaley et al., 2010).

2. Gels

Vaginal gels (broadly known as semisolids) are commonly used to formulate microbicides. Early microbicide drugs were themselves water-soluble gel forming polymers so there was little choice but to prepare aqueous gels. More recently, small molecule compounds, specifically reverse transcriptase inhibitors (RTIs) (Klasse et al., 2008) are being investigated as microbicides.

Vaginal gels are used in a range of commercial and prescription medications to provide local and systemic drug delivery (Das Neves and Bahia, 2006). Vaginal gels are typically developed empirically using mechanical/physical properties of other semisolid products as a guide. A more rational approach would be to design a gel product addressing the key elements of effectiveness, safety, and reliability for effective delivery of microbicides. This approach relies on gaining an understanding of the underlying composition–property–performance relationships of vaginal gels to optimize physical and drug delivery properties (Ndesendo et al., 2008). A unique element in this approach is the use of biomechanical flow models relating gel rheologic properties, gel volume, vaginal forces acting on the gel, and vaginal geometry to predict and measure spreading along the vaginal canal (Lai et al., 2008; Szeri et al., 2008).

2.1. Rational design of a vaginal microbicide gel

The overall design elements considered critical for a vaginal microbicide gel are (1) formulation composition, (2) gel properties (e.g., pH), (3) intravaginal deployment and retention, (4) drug delivery, (5) acceptability, and (6) pharmacodynamics (i.e., efficacy). The following is an example of using these elements to rationally design a vaginal microbicide gel. The objective of this effort was to design three distinct gels: a spreading gel (SG), an intermediate spreading gel (ISG), and a bolus gel (BG). The SG was designed to behave in a manner similar to gels, that once administered, spread throughout the vagina (~100% of the vagina is quickly coated with gel). An example of such a gel is the universal placebo (UP) (Schwartz et al., 2007). The ISG was designed to spread less than the UP (30–50% of the vagina). The BG was designed to spread very little after administration by remaining as a bolus in the fornix. These gels were prepared using a drug combination containing the nonnucleoside reverse transcriptase inhibitor (NNRTI) UC781 (Van Herrewege et al., 2004) and the nonnucleotide reverse transcriptase inhibitor (NtRTI) Tenofovir (TFV) (Mayer et al., 2006).

An objective function was designed to serve as a Mixed Design of Experiments (MDOE) response factor, which was constructed as a piecewise continuous function of area, A: it has different analytical forms for $A \leq A_{max}$ and for $A > A_{max}$, which give equal results at $A = A_{max}$. The domain of the function is defined from zero to unity such that when its value, termed the score (S), equals 1, the gel fully meets the performance requirements. A simple form of the objective function based upon this result and the criterion that its value $S = 1$ when $A = A_{max}$ is:

$$S = \left(\frac{A}{A_{max}}\right)^2 \quad \text{for } 0 < A \leq A_{max}$$

The two primary polymers used to create these gels were hydroxyethylcellulose (HEC) and Carbopol 974P. HEC creates low yield stress gels and therefore flows with little applied force. In contrast, Carbopol forms high yield stress gels requiring an applied force to flow. These two polymers were used in a MDOE design to limit the number of experiments required to assess (1) predicted spreading properties, (2) in vitro release as assessed by in vitro release tests (IVRT) and (3) in vitro permeability using vaginal tissue (EVT) (Fig. 1). All gels contained micronized UC781 (0.1%) as a suspension and TFV (1.0%) in solution at a pH of 5.2. Using the results from the MDOE, optimal compositions of a SG, ISG, and BG were defined. Graphically, these data are shown in Fig. 2. The color scale indicates the gels S: red to white indicating a score closer

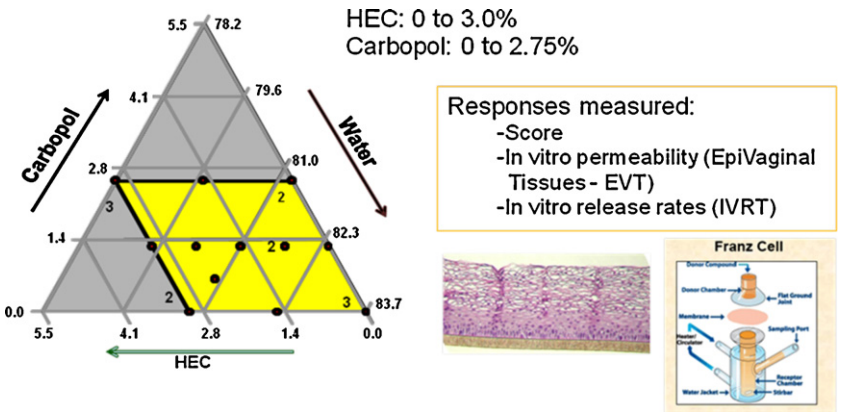

Fig. 1. On the left is shown a phase diagram of the MDOE. Each red dot represents the composition of the specific gels prepared and tested. The responses measured using the MDOE were S, IVRT data and permeability in EVT. Also shown is a cross-section of EVT and a diagram of a Franz cell used to collect IVRT data.

to 1 (desired) and blues indicating a score closer to 0 (undesired). The optimum SG composition was a 3.0% HEC/0% Carbopol 974P. The model predicted a BG composition of 3.0% HEC/2.75% Carbopol 974P but since this gel exhibited impractically high viscosity, the BG composition was 2.0% HEC/1.7% Carbopol 974P while the ISG composition was 2.5% HEC/0.6% Carbopol 974P.

The gels were also assessed for their ability to release drug using validated IVRT methods for UC781 and TFV. Despite the wide range in gel compositions (0% HEC/0% Carbopol 974P to 3.0% HEC/2.75% Carbopol 974P) there were no meaningful differences in the amount of drug released over the time course of the experiments (8 h). The amount of UC781 and TFV accumulating in vitro in the EVT (EpiVag^{TM} Tissue, MatTek Corp.) was also used to verify the ability of the SG, ISG, BG to deliver each drug into tissues. EpiVag is a human 3-dimensional vaginal–ectocervical tissue produced from normal (non-transformed), human-derived vaginal–ectocervical epithelial cells. It is a multi-layered tissue composed of a basal layer and multiple non-cornified layers (see Fig. 1). Accumulation of UC781 and TFV was at or close to maximum for the SG, ISG, and BG compositions.

The SG, ISG, and BG compositions were evaluated for delivery into vaginal tissues and plasma of rabbits following intravaginal administration of 1.0 mL of each gel type. There were no statistical differences in tissue after seven days of once daily vaginal administration (gels were introduced via a tube about 8 cm into the rabbit vagina). The median amount of UC781 in rabbit vaginal tissues after 7 d ranged from 0.1 to 10 μg/g tissue and median tissue concentrations of TFV were 1.0 to a little over 100 μg/g of tissue. Plasma concentrations of UC781 were independent of gel composition. The mean steady state concentrations after the last dose were around 0.4 ng/mL (UC781) and 30 ng/mL (TFV). The MDOE approach to optimization of three different types of gel permitted the definition of specific compositions of HEC/Carbopol 974P. Despite the predicted differences in vaginal coating (and viscosities) of the three gels, verification studies confirmed all three should deliver UC781 and TFV into the ectocervical and vaginal tissues in vivo. These studies are being verified by pharmacokinetic and efficacy studies in macaques and acceptability and imaging studies in women (both using pre- and post simulated coitus).

In addition to rheologic properties of vaginal gels, they must be safe. Product safety goes beyond identification of active ingredients (Wilkinson et al., 2002) to include osmolarity (Dezzutti, 2008) of topical microbicide gel formulations. If a gel is excessively hyperosmotic there is the potential to cause irritation leading to an inflammatory response. Each dissolved ingredient in a topical microbicide gel contributes to the osmolarity of the product, so the effect of the overall composition of the formulation must be considered in addition to the impact of each individ-

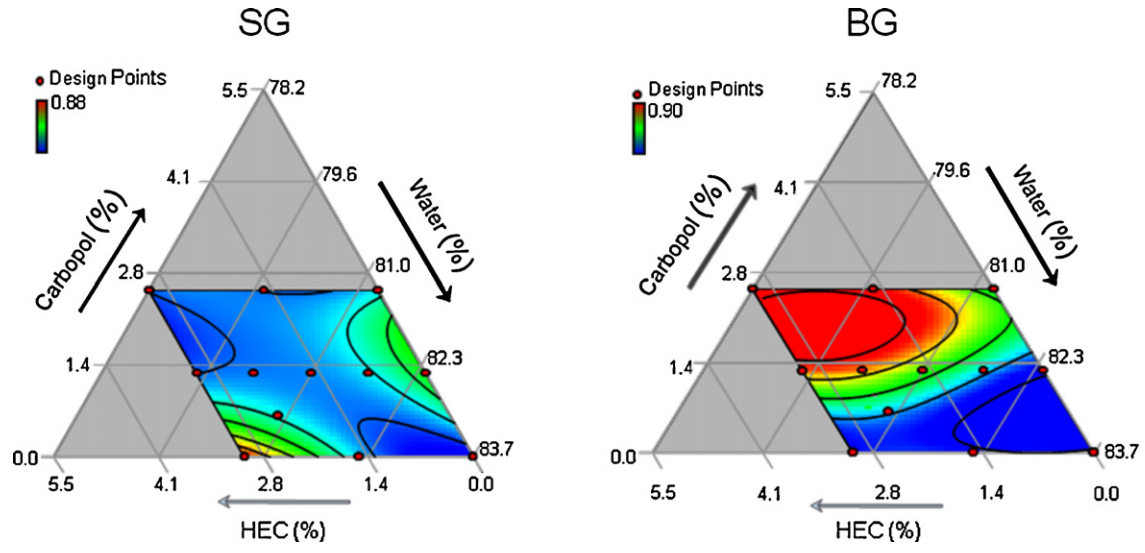

Fig. 2. S derived from MDOE. Left panel shows results for a SG. In this case, the optimum S is observed at 3.0% HEC/0% Carbopol 974P. The right panel shows results for a BG. In this case, the best BG is obtained in the range of 1.5–3.0% HEC and 1.4–2.75% Carbopol 974P.

ual ingredient. All the gels described above have an osmolality of <1000 mOsm/kg.

2.2. Scale-up of vaginal gels

During scale-up of gel manufacturing, the balance of physicochemical properties in the formulation must be maintained, and all components of the formulation must be uniformly distributed in a large-scale batch. It has been common in the past to demonstrate uniform distribution of the active ingredient as part of process scale-up and validation. Recent guidelines (see Section 5) make it clear that regulatory agencies expect a clear demonstration of the understanding of the effects of individual raw material characteristics and process parameters on product quality. Critical quality attributes associated with this profile might include API content and uniformity (related to dose volume and route/frequency of administration), pH, osmolarity (may relate to irritation), and viscosity (relates to route of administration).

Manufacture of semi-solid products is usually a matter of dispersing solid materials in the carrier medium (water). The dispersal of aqueous polymers may require different measures depending on the scale at which the product is prepared. The objective is to meet the same set of critical quality attributes no matter whether 50 or 50,000 doses are being prepared. These quality attributes may require process modification and may highlight process steps critical in a large-scale batch manufacture not typically identified as critical in a small batch.

Scaling up from laboratory bench-top batches to commercial scale requires an understanding of the properties of the product that are affected by the scale of manufacture. Solubility is not directly affected by scale, but solubility may have different effects in a small batch compared with a large batch. Dispersions of aqueous polymers are usually easily in small sizes (up to several 10s of kgs). When large batches (up to or exceeding 1000 kg) are being prepared, addition of the dried polymer powder or granules can lead to incomplete hydration if the material is not added with appropriate precaution. Understanding complete hydration conditions when preparing small-scale batches will help demonstrate evolution of the process, and allow documentation of the effects of individual unit operations on critical product characteristics. Such documentation can establish a basis for post-approval process changes.

2.3. Challenges with vaginal gels

Gels are relatively simple to develop compared with intravaginal rings and thin films. A critical issue is stability of the API(s) in aqueous gels. If the drug is unstable in water, it may require formulation in a solid dosage form. A second issue is packaging costs. Clinical studies evaluating vaginal microbicide gels typically use pre-filled, single dose applicators. The cost of these applicators, even in bulk, is relatively high (US$0.10–0.12 per applicator). Alternatives include reusable applicators or single use paper applicators filled immediately prior to use from a tube containing the gel. Finally, filling single dose applicators at high speed with highly viscous gels can be challenging due to the inability of the gel to flow. Increasing the temperature and application of external pressure can improve the flow characteristics of some gels.

3. Films

Film dosage forms are thin strips of polymeric water-soluble substances which dissolve when placed on the vaginal mucosal surface to release the active ingredient. Fig. 3 describes the evolution of this dosage form from confectionary use to its current application as a vaginal delivery system. Thin films are convenient dosage forms which can be administered without an applicator. Other advantages include portability, easy storage, discreet use, no product leakage, and low unit dose cost. Finally, as solid dosage forms, thin films can be used to stabilize drugs susceptible to degradation in aqueous environments.

3.1. Thin film formulations

Typically film formulations are comprised of the active pharmaceutical ingredient (API), water soluble polymers, plasticizers, fillers, color, and flavor (Hariharan and Bogue, 2009; Rathbone et al., 2008). Polymers used should be non-toxic; non-irritant; devoid of leachable impurities; possess good wetting and spreadability; exhibit sufficient peel, shear, and tensile strength; and inexpensive to manufacture and package. Polymer choice and polymer molecular weight can significantly impact properties of the film such as mechanical strength and disintegration time. Thin film formulations usually include plasticizers to provide flexibility and ensure acceptable texture. To enhance the fast dissolving property of the film, disintegration agents can be used.

3.2. Film formulation assessment

In vitro assessments for thin film formulations include physical, chemical, and mechanical testing. Physical tests generally include film weight, size, appearance, and thickness. Mechanical testing may include tensile strength, % elongation, Young's modulus (stiffness), tear resistance, fold endurance, and peel strength. Chemical assessments of thin films generally include swelling index, bioadhesion properties, moisture content, disintegration time, dissolution and drug release, and drug content uniformity. The development of successful algorithms which begin with confirmation of mechanical and physical film properties and move forward to assessments of toxicity and bioactivity must be utilized. Modulation of specific thin film product physical and chemical attributes is expected to alter in vivo drug release and pharmacokinetics. Currently no model linking these parameters to in vivo outcomes exists. However, such models are currently under development.

3.3. Application of films to vaginal delivery

Thin film dosage forms are being used as vaginal formulations. One vaginal film product currently marketed is the Vaginal Contraceptive Film (VCF) which contains the spermicidal agent Nonoxynol-9 (N-9). Vaginal films have also been investigated as delivery systems for other drugs such as antifungals, and antibacterials. In a recent study, the antifungal drug itraconazole (ITR) was formulated in a bioadhesive vaginal film for treatment of vaginal candidiasis (Dobaria et al., 2009). Vaginal bioadhesive films were developed containing clindamycin phosphate for treatment of bacterial vaginosis (BV) (Dobaria and Mashru, 2010).

3.4. Application of films to microbicide delivery

Thin film dosage forms have been investigated for use as delivery systems for vaginal microbicides. Polystyrene sulfonate (PSS), an antimicrobial contraceptive agent, was formulated in a vaginal film to be used as a microbicide product (Garg et al., 2005). The bioadhesive strength of PSS developed films was shown to be significantly greater than the currently marketed vaginal films, VCF and Ortho-Options Vaginal Contraceptive Gel.

Neurath et al. (2003) developed cellulose acetate 1,2-benzenedicarboxylate (CAP) in a vaginal film as a microbicide product. The microbicidal activity of the developed CAP film was assessed in vitro and found to be dose dependent with activity against HIV-1, HSV-1 and HSV-2.

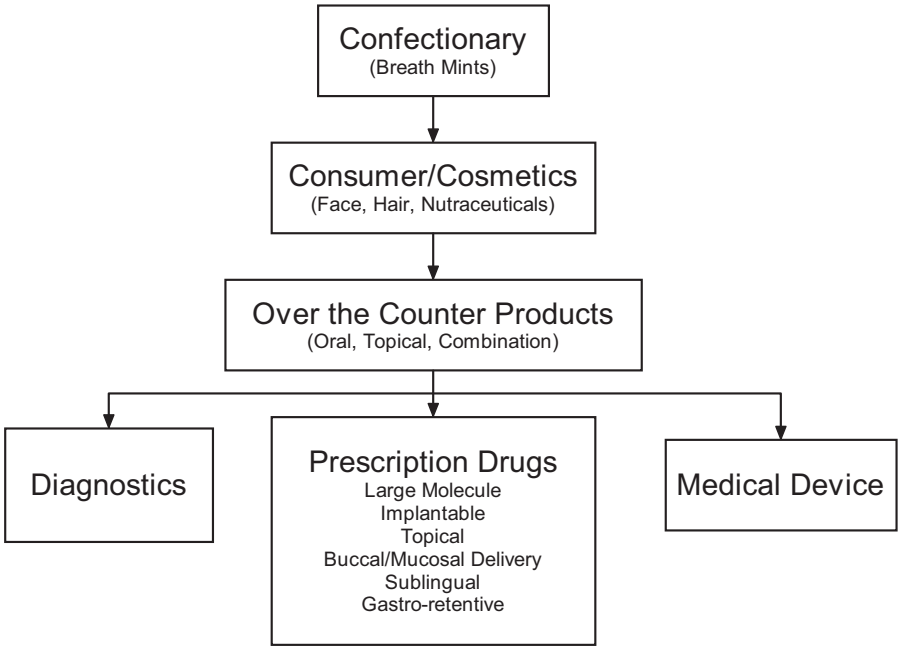

Fig. 3. The evolution of thin film dosage forms.

Other agents evaluated in films as microbicide candidates include nonoxynol-9 (Mauck et al., 1997; Roddy et al., 1998), and sodium dodecyl sulfate (SDS) (Yoo et al., 2006). More recently, thin films (Fig. 4) are being studied for use as a vaginal delivery platform for specific anti-HIV agents such as replication and entry inhibitors (Akil et al., poster presentation, AAPS Annual Meeting and Exposition, 2009).

3.5. Film – product development considerations

It is crucial that vaginal films be developed properly to ensure that they can be manufactured on a large scale.

Films are unique because they combine two technologies in one formulation: solid dosage forms and gels. Films begin as solid dosage forms, two advantages of which are exact dosing and the absence of growth-promoting agents. After hydration, the gel coats the mucosal lining. Another advantage of this dosage form is low packaging volume per dose: films are small and light enough to be convenient for the user as previously noted. Different formulation principles allow for PK modulation. The film manufacturing process is unique, making it difficult to manufacture similar products. From an industry perspective, this is an advantage, but from a development perspective, manufacturability presents a challenge since few companies can manufacture this dosage form.

Fig. 4. Vaginal microbicide film.

Films can be formulated for potent compounds (up to 40 mg). Small molecules are typically easier to manufacture into films, but it is possible to formulate larger molecules (biopharmaceuticals). The API should be non-irritating to vaginal mucosa in high concentrations. Typically, heat sensitivity of the API is not a critical factor.

3.6. Types of films

Basic film types include: fast disintegrating films (flash release films that release molecules or flash dispersal films that release particles); nondisintegrating mucoadhesive films (these can be combined with fast disintegrating films to control residence time); and medium disintegrating mucoadhesive films.

3.7. The manufacturing process

Parameters to consider during product development include: hydration rate in a limited volume of body fluids; release mechanism (primarily diffusion after hydration); system design (single or multiple layers); system size; local tolerability; film moisture content; packaging requirements; and mechanical properties under tropical conditions (e.g., WHO Zones IVa and IVb).

Films can be designed to provide a burst of drug resulting in rapid delivery to vaginal mucosa or to provide a burst followed by sustained release.

The manufacturing process includes the following steps: preparation of coating mass; coating on a process liner; multi-stage drying; cutting or die-cutting of individual dosage forms; and packaging in blister packs, pouches, cards, or dispensers.

3.8. Packaging

Films can be packaged in single or multiple dose packages. Single dose packaging provides primary stability of the product and avoids potential fusing of some multidose packaging formats. Single dose packaging uses more pouch stock per dose as compared with multidose packaging. It is possible to combine single dose units into a dispenser. Also, unit dose packaging is best for demanding climate

zones. Multiple dose packaging is more expensive to develop but is less expensive to manufacture in large quantities and, for this reason, may be more realistic for developing countries. With multiple dose packaging, the secondary package needs to provide shelf life stability; in-use stability is also critical.

3.9. Important factors to consider for microbicide vaginal films

Film dissolution profile and drug release are important issues to consider when applying thin film technology to vaginal microbicide delivery. Drug distribution achieved in the vagina using this dosage form must be evaluated. Additionally vaginal fluids (Cone, 2009; Sassi et al., 2008) and microflora may impact drug delivery from films.

Vaginal films can be designed for immediate or controlled release by optimizing the polymeric composition of the film, using different types of films (single layer vs. multiple layers), or combining thin film technology with other drug delivery strategies. Thin film dosage forms can be used for delivery of more than one active agent simultaneously and can be combined with other delivery strategies. A study by Ham et al. (2009) investigated the combination of the film dosage form with a nanoparticle delivery system for vaginal delivery of PSC-RANTES, a CCR5 chemokine receptor inhibitor.

3.10. Acceptability

Although data regarding vaginal film acceptability is scarce, the few published studies which incorporated film product acceptability indicate vaginal films are preferred over other dosage forms due to their advantages of portability, ease of application, ease of storage and handling. Studies have shown that film formulations are more likely to be accepted by women than are other vaginal formulations, such as gels, foams, or suppositories (Elias and Coggins, 2001; Raymond et al., 1999, 2005; Steiner et al., 1995).

3.11. Challenges with microbicide vaginal films

Additional information is needed to develop successful products. A model for mucosal irritation and an understanding of the histological implications of drug products are needed. For vaginal administration, there is a need for a better understanding of hydration and dissolution in limited volumes (e.g. 1 mL) of vaginal fluids. Proper API selection is crucial as is a clear understanding of the therapeutic action of the drug. Should an applicator be required to administer vaginal films, applicator design for films and determining how an applicator will be cleaned will be essential elements of the successful development of multi-use applicators.

4. Tablets

To ensure compliance, a vaginal microbicide formulation should be aesthetically appealing, easy to apply, available at a reasonable cost, and in a form which is acceptable to the users. About 40% of the vaginal formulations available in Indian market are tablets, indicating their acceptance in India probably due to climatic and cost considerations (Garg et al., 2002).

Conventional vaginal tablets available around the world consist of anti-infective agents, hormones, plant extracts, and Lactobacillus spores. Some of the commonly used drugs in the form of tablets include clotrimazole (Canesten®-6, Candid-V6®, Clomax-V7), miconazole, tinidazole, neomycin (Candizole-T™), and povidone iodine (Betadine®) (Du et al., 2007; Hoffman, 1995; Larsson and Kjaeldgaard, 1980). A number of microbicide candidates formulated as tablets include cellulose sulfate, ACIDFORM, polystyrene sulfonate, dapivirine, DS003, tenofovir and UC781. Praneem polyherbal tablets (Panacea Biotec, New Delhi, India) are the only example of a vaginal microbicide tablet which is in Phase II clinical trials in India (Joglekar et al., 2006; Joshi et al., 2005).

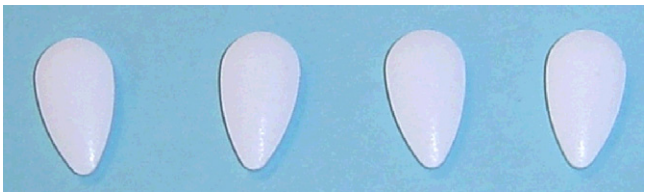

Fig. 5. Vaginal tablets.

4.1. Advantages of tablet as vaginal dosage forms

Tablet formulations offer several advantages including portability, precise dosing, ease of storage, handling and administration, feasibility of large scale production, and low cost. Tablets also offer the potential for improved stability of drugs at extremes of temperature and humidity. In addition to the active ingredient, tablets contain excipients functioning as diluent, binder, disintegrant, lubricant, antiadherent, and glidant.

Tablets can be designed with additional characteristics such as bioadhesion, sustained release, and rapid dispersion with the help of specific excipients (Baloğlu et al., 2006; El-Gindy et al., 2003; Gursoy and Bayhan, 1991). Thus, tablet dosage forms can be used to address the issues of leakage and messiness that can be associated with conventional vaginal gel formulations. Fig. 5 shows the shape of a typical vaginal tablet.

4.2. Performance evaluation

Tablets are generally evaluated by various pharmacopoeial quality control tests such as assay, weight variation, dissolution, and disintegration; non-pharmacopoeial tests including size, shape, color, viscosity, pH, osmolarity of dispersion, hygroscopicity, insoluble content, microbial purity, and bioadhesion.

Though pharmacopoeias cover a range of vaginal formulations, some of the tests are incapable of simulating in vivo conditions. For example, the disintegration test for vaginal dosage forms as per British Pharmacopoeia (2007) require 4 L of water as disintegrating fluid, however the vaginal cavity usually contains very small volume of fluid. Several studies (Kryger et al., 1983; Yamaguchi and Tanno, 1986; Yamaguchi et al., 1990) recommend modifications of compendial methods to improve in vitro/in vivo correlations.

There are no compendial tests to measure the release rate pattern from vaginal preparations. A number of methods including (1) modified USP dissolution apparatus (Ahmad et al., 2008; El-Kamel et al., 2002; Wang and Tang, 2008), (2) beaker or flask method (Genc et al., 2000; Valenta et al., 2001; Woolfson et al., 2006), (3) dialysis tubing method (Kale et al., 2008), (4) permeation cell method (Lee and Chien, 1996), (5) modified BP and EP disintegration test apparatus (Gursoy and Bayhan, 1991) have been reported to better simulate the physiological conditions of the vagina.

The drug delivery from vaginal formulations can be aimed at three different areas, i.e. surface, within mucus layers, and systemic. Microbicides vaginal tablets are developed with the intention of surface and mucus layer penetration with minimal or no systemic absorption. In vitro–in vivo correlations are very well established for oral tablets. However, in case of vaginal tablets, studies are yet to be conducted to establish this link. The release of the drug is a function of the drug's physico chemical properties such as solubility, particle size, lipophilicity, ionization. Formulation design will also have an impact on the bioavailability of the drug in terms

of disintegration time of the tablet, dispersion and retention of the drug in the vagina. With the advent of novel concepts in drug delivery systems leading to fast disintegrating and bioadhesive tablets, the tablets can be designed to disperse rapidly and have a longer residence time in the vaginal cavity. However, currently there is no clinical data to support the biological efficacy of such tablets.

4.3. Fast dissolve tablets

Fast dissolve tablet formulations have been commercially available for several years as orally administered products that dissolve or disperse in the mouth and has been previously reviewed (Fu et al., 2004). Uses of the fast dissolve tablets vary depending upon specific goals and needs of the product. These purposes may include local delivery at the site of administration (e.g. vaginal, rectal), for systemic absorption, avoidance of first-pass metabolism (oral), patient or care provider convenience, and improved targeting to the site of action (e.g., uterus). Depending on the specific aims desired, formulation of fast dissolve tablets requires different approaches. In general, a fast dissolve tablet should release the API in such a way that complete or near complete dissolution is achieved at the site of administration. Other properties such as taste masking, local tolerability, patient convenience, permeability, and residence time at the local site may also be important considerations in the design of a formulation. The site of administration also influences aspects important to drug delivery such as the amount of moisture available, the area of the absorptive surface, permeability, and residence time.

When developing a specific product the degree of risk or difficulty of formulation varies depending upon the API properties and the dose to be administered. For instance API's with high water solubility, good permeability, and low dosage represent the limited risk, whereas API's with low water solubility, low permeability and high dosage can represent a comparatively higher degree of risk. Rapid in vivo dissolution rate is an important goal during the formulation of fast dissolve tablet products. The inherent solubility of the API in the biological fluids is important for the in vivo dissolution of the product. The solubility performance may be modified by the physical form of the API and formulation effects. Formulation design will impact disintegration time of the tablet, API dispersion, spreading/coating properties, and self-emulsification, all of which affect bioactivity of the product.

When selecting technologies to enhance dissolution rate of the API from vaginal tablets, it is important to consider ease of manufacturing, product stability, local tolerability of the formulation constituents, performance properties, among other aspects. Several technologies are successful in accelerating dissolution rate. The technologies modify API solubility by different means such as form modification (salts, hydrates, solvates, co-crystal, and amorphous forms), particle size reduction, engineered nanoparticles, and co-processed materials (co-crystallization). These approaches produce different outcomes with respect to altering the API's dissolution properties. The formulation scientist needs to take into consideration the anticipated benefit against possible development difficulties associated with stability of the drug product or difficulty in manufacturing at commercial scale including cost of goods.

In a case example, an approach to improve progesterone dissolution by improving water dissolution rate and controlling particle size was investigated. In this case, a freeze drying process for bench scale was investigated; this process can be scaled up using a spray granulation process for larger scale manufacturing. Screening of solubility enhancing excipients is done through a semi-empirical method, first identifying excipients with a high potential to form loose complexes or associations through stereospecific bonding (H-bonding, π-bonding, van der Waals) with the API. The API and excipients are co-crystallized and tested through a screening cascade to identify materials with dissolution rate enhancement and/or contribute to improvement of particle size or dispersion qualities. Co-processing of the excipients with the API via co-crystallization (Goldman, 2005) increases the interactions between the materials, allowing effects to be obtained with a minimum amount of excipient which helps improve drug loading and reduces the physical size of the dosage form.

4.4. Formulation challenges

The following are some of the typical challenges in the development of microbicides tablets:

- Lack of a "gold standard": Microbicides, being new formulations, are not currently official in any pharmacopoeia, thus setting regulatory standards for their evaluation is a challenging exercise.
- Difficulty in ensuring content uniformity, especially with low dose actives: As these tablets are high in weight (1.0–1.2 g), ensuring content uniformity of low dose actives can be challenging.
- Difficulties in composition optimization: ideally vaginal tablets should disintegrate rapidly and form smooth, homogenous, viscous and bioadhesive dispersions. Achieving these goals may be difficult with tablet compositions containing relatively large amounts of excipients in the limited amount of vaginal fluid available.
- Formulation for animal studies: the tablets for human use cannot be used in animals because of size, making it difficult to establish correlation between animal and human studies.
- Combination products, compatibility, and analysis: If there is more than one active drug in the formulation, establishing the compatibility of the actives of drugs and with excipients and establishing a combined method of analysis of the APIs will present more challenges compared with tablets prepared with one API.

5. Regulatory guidelines

The US Food and Drug Administration (FDA) has outlined expectations for formulation and product development in a revised guidance document (2009a) derived from the International Committee on Harmonization's Q8 guidance on Pharmaceutical Development. This, in turn, should be viewed in the larger context of the Q9 guidance on Risk Assessment and the Q10 guidance on Quality Systems. Together, they outline elements of freedom to pharmaceutical developers – as well as restated expectations of responsibility. The guidance explicitly does not apply to products in clinical trials, but since it applies to the data package submitted with a New Drug Applications (NDA) or Common Technical Document (CTD), consideration of the guidance and its implications should be considered during Phase 3 clinical trials, if not earlier.

In the Annex, the Q8 guidance presents developers of new drug products with the freedom to outline how *Material Attributes* and *Process Parameters* are linked to *Critical Quality Attributes* (*CQAs*) and, in turn, how CQAs are linked to the *Quality Target Product Profile*. The Quality Target Product Profile (QTPP) is a "prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product." The FDA's (and other regulatory authorities) expectation is that the QTPP will be organized according to key sections in the product's labeling.

Following this guidance, developers identify links between CQAs (such as viscosity, pH, density, or content uniformity) and the QTPP. For a vaginally or rectally administered topical microbicide, a QTPP might include the following:

- Dose volume
- Intended route of administration
- Low/no irritation
- Once-daily administration

Critical quality attributes associated with this profile might include API content and uniformity (relates to dose volume and route/frequency of administration), pH, osmolarity (may be related to irritation), viscosity (relates to route of administration).

The Q8 guidance also outlines the connection of critical process parameters to product characteristics. Topical microbicide gels are, most often, aqueous solutions of drug products that have materials added to modify the flow characteristics, of the finished dosage form.

FDA's "Pharmaceutical cGMPs for the 21st Century" (2009b) (out of which grew the Q8/Q9/Q10 guidance) outlines a flexible approach to controlling production of pharmaceutical products than characteristic of the agency's approach in the past. With this new freedom comes the expectation that an NDA submission will document a higher level of understanding about the relationship of process parameters and raw material characteristics to intended product properties than expected in past submissions. Developers who work in preparation of clinical supplies with knowledge of this expectation will facilitate submission of this information when their product is submitted for regulatory approval.

6. Discussion

Over the past few years, there have been many changes in microbicide product development. Microbicide formulation is an important link between the inherent efficacy of an API and its therapeutic effectiveness. Once limited largely to gel formulations intended coitally-associated use, the formulation requirements microbicide products is expanding to include a greater emphasis on "coitally-independent" approaches including slow-release intravaginal rings, pre-loaded physical barriers, and a variety of innovative longer lasting topical formulations such as quick dissolve polymeric films, bioadhesive vaginal tablets, and soft gel capsules. There are several issues which need to be addressed independent of the formulation type. These issues include (1) balance between residence of active formulation in situ and systemic toxicity, (2) accuracy of dose, (3) ease and cost of manufacturing, (4) shelf life, (5) side effects, and (6) acceptability in different user population. Each formulation has advantages and disadvantages for researchers, trial participants, and users. Hence, research is currently focused on designing drug delivery systems to ensure potency and efficacy plus acceptability to maintain adherence. The FDA is currently revising its guidelines for microbicides according to scientific and clinical changes in the microbicide field.

7. Conclusion

Although early microbicide formulations were mainly gel products, new technologies are being developed for vaginal delivery to prevent transmission of HIV-1. The use of thin film dosage forms has expanded greatly over recent years and provides an alternative strategy for vaginal drug delivery. A small number of studies have been conducted which demonstrate the successful application of the film dosage form to microbicide drug delivery. The application of films in this area can be extended by combination with other drug delivery strategies to achieve effective delivery of anti-HIV drugs to the vagina. The tablets provide an efficient delivery platform for microbicide drug candidates and if designed properly, can be tailored to achieve desired QTPP. The specifics of the formulation and development strategy need to be consistent with clinical requirements and specific drug delivery requirements of the dosage form. Appropriate formulation of HIV-1 microbicides is essential to ensure product safety, efficacy, and acceptability.

8. Panel discussion

S. Smoot: It seems that a common theme stressed by the manufacturers is the importance of keeping the manufacturing process in mind from the start of the formulation process. What do those working on the formulations think about this?

D. Friend: We try to bring manufacturers in as early in the formulation process as we can. At CONRAD, our formulations are usually developed at universities and manufactured elsewhere, so we try to bridge that gap early on.

M. Mitchnick: Does the audience have any questions for the panelists?

A. Stone: Films and tablets depend on the existence of sufficient fluid in the vagina, but the amount of fluid can vary tremendously from woman to woman based on age, hormone use, state of arousal, etc. A formulation could work fine in the laboratory but then could be highly variable in a Phase I trial in women. Do we know how FDA would handle a situation like this where there would be high variability in the effectiveness of a microbicide? If tenofovir (TFV) is shown to be effective in gel form, will FDA require bridging studies to reformulate TFV into a tablet?

D. Goldman: Our first clinical trial was with a gel formulation; the same product was later made in tablet form and no bridging studies were required. With respect to the amount of fluid present in the vagina, with our formulations, if there is less fluid, the drug concentration is higher and the drug is more effective.

S. Garg: Any dosage form will have different dilution and dissolution behavior with different fluid volumes. Performance of the dosage form must be evaluated to determine distribution.

M. Krumme: In my experience, variability is much less with films than with tablets. Secondly, based on Florian's presentation, it appears that impregnating the upper millimeter of the epithelium is adequate for providing protection.

L. Rohan: I agree that there is still much to learn about distribution and localization; we are working to address this. Also, several people mentioned modifying existing in vitro analyses. After in vivo data become available, we can determine if the in vitro data were, in fact, predictive of what occurred in vivo.

M. Mitchnick: There is now a fair amount of PK data on rings and drug distribution in vaginal tissue and plasma. Rings release drug in one specific area, but it appears that small hydrophobic molecules can move around quite easily.

K. Malcolm: Given that the means of distributing the microbicide is not built into solid dosage forms, how can we be sure that the drug is going to be effectively distributed throughout the vaginal tract?

M. Mitchnick: To truly answer that question, these formulations needed to be tested in women.

R. Cone: With a solid dosage form that dissolves quickly, there will be high localized concentrations of drug. Even if a drug is generally recognized as safe, this does not mean it is safe in high concentrations. As far as I know, there are no animal models for testing the toxicity of solid dosage forms; this is something that is needed.

G. Doncel: As a follow-up to that, some of the speakers raised the issues of mucosal toxicity and possible enhancement of irritation. What types of models have the speakers used to test these solid dosage forms for these effects?

D. Goldman: For our vaginal tablet, we used the rabbit irritation model.

R. Cone: The first 3 cm of the rabbit vagina is squamous epithelium like the human vagina, so location of the tablet placement is important.

L. Rohan: Film toxicity has been studied in monkey models and in excised tissues.

S. Garg: My approach is to calculate the amounts of active and inactive ingredients delivered with each dose. I use FDA-approved inactive ingredients; these should not cause toxicity.

G. Doncel: A word of caution about substances that are generally recognized as safe by FDA: this simply means that the substance is not significantly irritating and does not cause burning and itching. HIV infection involves a different type of toxicity. Simply recruiting CD4- or CCR5-positive cells and activating them might result in an enhancement of HIV transmission.

K. Malcolm: Regarding Markus's previous comment about delivering drug only to the superficial layers of the submucosal tissue, the reality is that if drug penetrates the tissue, it is likely to reach the blood as well.

M. Krumme: It is molecular weight and polarity-dependent. Working with a larger molecule would limit systemic exposure, but with a small molecule that penetrates well, there is no stopping it.

K. Malcolm: I suspect that with large molecules, there would not even be drug in the tissues because of the size of the molecules and ionization.

R. Shattock: There is no scientific evidence that drug merely penetrating the epithelial surface is sufficient to provide protection. Ideally, we would test which of the following provides the best protection: the drug delivered to the epithelial surface, the drug locally in the tissue and the drug reaching the systemic compartment.

L. Rohan: With PSC-RANTES, the explant challenge model showed much greater protection with the formulated particles compared to the unformulated particles.

M. Callahan: Regarding the discussion on the need for bridging studies, FDA has indicated that bridging studies are needed for the transition from the HTI applicator to multi-dose and paper applicators. These studies are intended to show that the same amount of product is delivered with the different applicators.

D. Friend: CONRAD began developing gels using the HTI applicator and later learned that this applicator would be too expensive for the developing world, so the lesson here is that it is wise to consider the cost of materials early in the development process.

G. Doncel: I wanted to second Robin's earlier comment. We do not know, especially with RTIs, if a microbicide is needed at the surface of the epithelium or if it needs to go deeper. Regarding Dr. Goldman's comment about not being required to conduct a bridging study for the gel to tablet, I'm not sure that this decision could be made based on animal PK data. How was that requirement avoided? Also, did the animal PK data for the tablets predict the human PK data?

D. Goldman: Actually, in effect, a bridging study was conducted because all of the studies were Phase I studies. The correlation between the animal and human PK data was not very good. The release and absorption rates in the humans were higher than in the animal models, with the release rate six times higher in humans and the absorption rate two times higher in humans.

S. Klein: Lisa, you had mentioned that sometimes cyclodextrins are used in films. Cyclodextrins can enhance the solubility of UC781 or stabilize formulations but there are reports in the literature of cyclodextrins having negative impacts on mucosal barriers. Are there any studies on the impact of cyclodextrins on the vaginal mucosa?

L. Rohan: The effect of cyclodextrins on the membrane is a function of the type and concentration of the cyclodextrin used. Itraconazole is a product intended for vaginal use that consists of 50% cyclodextrins; it has not shown toxicity.

G. Doncel: Cyclodextrins may not show toxicity at high concentrations, but that does not mean that they are safe to use in a product aimed at preventing HIV.

M. Krumme: Anything that increases the permeability of the tissues will increase potential tissue irritation. There is no generalizable answer for any excipient; each one needs to be evaluated.

J. Hanes: Something can be nontoxic and still increase susceptibility to a virus. In my work with mouse models, there is no evidence of toxicity at a time when the animals become far more susceptible to herpes.

M. Krumme: The other side of this coin is that increased tissue permeability could allow for more drug penetration.

Participant: A question for the panel members: Is there any golden rule for formulating water insoluble microbicides in gel, tablet, or film forms?

D. Friend: UC781 has poor water solubility. We have formulated it as a suspension in a gel that achieves concentrations both in vitro and in vivo that should be effective.

Karl Malcolm: You could also get effective UC781 uptake in the tissue by formulating it at a pH of 11. I'm not suggesting that that is a solution. My point is that we need to pay more attention to the physicochemical characteristics of the drug molecules that we are working with.

D. Friend: I agree. In many cases, we are working with drugs that were abandoned for other uses. We have not designed drugs to be microbicides. This could be done, but it would be time consuming and expensive and honestly, at this point, impractical.

K. Malcolm: Now that we have moved on to anti-retrovirals, there are a lot of drugs to choose from. It is just a matter of obtaining permission to develop them as microbicides.

D. Friend: At CONRAD, we are constantly working to acquire rights to other drugs. In the short-term, this is the most viable approach.

R. Gandour: With CONRAD's support, I am working to design a UC781 prodrug that will address some of the less desirable physicochemical characteristics, including as low water solubility.

K. Malcolm: There are advantages to this approach, but one downside is that you are developing a new drug entity and there are many steps involved in obtaining approval for a new drug.

R. Gandour: That is true.

I. Zalenskaya: What was the UC781 uptake in the tissue? What was the ratio between the amount applied and the amount found in the tissue?

D. Friend: Several percent of the UC781 was absorbed in the tissue after a few hours; the vast majority was unabsorbed.

I. Zalenskaya: Does UC781 permeate through the tissue?

D. Friend: The EpiVaginal model is used to determine tissue levels. In most instances, UC781 does not permeate all the way through the tissue. This is consistent with human PK data that shows low levels of UC781 in the tissue when the single entity UC781 gel (0.1% and 0.25%) is applied vaginally.

G. Doncel: The important point is that the concentrations seen in the tissue were orders of magnitude higher than the IC90 for the compound.

A. Stone: The discussions at this meeting and at several meetings that I have recently attended have focused on the use of anti-retrovirals as microbicides. Anti-retrovirals might prove to be effective microbicides but it is likely, particularly in the beginning, that their use will be restricted to people who have tested negative for HIV. If this is the case, anti-retrovirals will not be everything we had hoped for in a microbicide because a key element is protecting women in countries that do not have testing infrastructure in place. I think we should also focus on the formulation of non-anti-retroviral microbicides.

I. Zalenskaya: I am new to this field. Is anything known about the mechanical distribution of microbicides in the vagina?

M. Mitchnick: Imaging techniques have been used to determine the distribution of gels in the vagina. In addition, PK data for gels and rings show drug in the vagina, in the tissue and in the plasma. For the most part, if the molecules are applied in the vagina, they will distribute. With molecules that distribute within the tissue itself, it does not appear that 100% or even majority coverage of the epithelium is needed.

D. Katz: Is it correct to say that a film begins as a semi-solid dosage form, goes through a phase change that depends on water availability, and then becomes a liquid or gel? How dependent is the phase change on vaginal moisture? What is the final dose form? This is important because the final dose form will affect drug delivery and distribution.

M. Krumme: That is a pretty accurate description. A film begins as a solid form and transforms into a semi-solid. The chemistry can be altered to affect drug delivery (e.g., drug can be delivered for a few seconds up to many hours).

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