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Non-aqueous silicone elastomer gels as a vaginal microbicide delivery system for the HIV-1 entry inhibitor maraviroc

Claire J. Forbes [a], Deborah Lowry [a], Leslie Geer [b], Ronald S. Veazey [c], Robin J. Shattock [d], Per Johan Klasse [e], Mark Mitchnick [b], Laurie Goldman [b], Lara A. Doyle [c], Brendan C.O. Muldoon [a], A. David Woolfson [a], John P. Moore [e], R. Karl Malcolm [a,*]

[a] School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK
[b] Particle Sciences, Bethlehem, PA, USA
[c] Tulane National Primate Research Center, Tulane University Health Sciences Center, Covington, LA 70433, USA
[d] Medical School Building, St Mary's Campus, Imperial College, London, W21PG, UK
[e] Department of Microbiology and Immunology, Weill Medical College of Cornell University, New York, NY 10021, USA

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ABSTRACT

Aqueous semi-solid polymeric gels, such as those based on hydroxyethylcellulose (HEC) and polyacrylic acid (e.g. Carbopol®), have a long history of use in vaginal drug delivery. However, despite their ubiquity, they often provide sub-optimal clinical performance, due to poor mucosal retention and limited solubility for poorly water-soluble actives. These issues are particularly pertinent for vaginal HIV microbicides, since many lead candidates are poorly water-soluble and where a major goal is the development of a coitally independent, once daily gel product. In this study, we report the use of a non-aqueous silicone elastomer gel for vaginal delivery of the HIV-1 entry inhibitor maraviroc. In vitro rheological, syringeability and retention studies demonstrated enhanced performance for silicone gels compared with a conventional aqueous HEC gel, while testing of the gels in the slug model confirmed a lack of mucosal irritancy. Pharmacokinetic studies following single dose vaginal administration of a maraviroc silicone gel in rhesus macaques showed higher and sustained MVC levels in vaginal fluid, vaginal tissue and plasma compared with a HEC gel containing the same maraviroc loading. The results demonstrate that non-aqueous silicone gels have potential as a formulation platform for coitally independent vaginal HIV microbicides.

1. Introduction

The latest global report by UNAIDS estimates that 33 million people worldwide were living with HIV/AIDS at the end of 2009, with 2.6 million new infections during that year [1]. In the worst affected areas of sub-Saharan Africa, the high rate of infection is still a very serious problem, with heterosexual intercourse the dominant mode of transmission and women accounting for almost half of the new infections [1,2]. There is an urgent need for effective ways to prevent the sexual transmission of HIV-1 to women. With no effective vaccine in sight, the emphasis is on the development of prevention strategies based on systemic (oral pre-exposure prophylaxis; PrEP) or vaginal administration (HIV microbicides) of antiretroviral (ARV) drugs [3–8]. The promising outcomes of the recent CAPRISA and iPrEX trials of vaginally and orally delivered reverse transcriptase inhibitors (RTIs) support these concepts [9,10].

To date, aqueous semi-solid polymeric gels, exemplified by hydroxyethylcellulose (HEC) and Carbopol®, have been the formulation strategy of choice for HIV-1 microbicide candidates, due to their low cost, ease of manufacture, low mucosal toxicity and long history of use for vaginal drug administration [11–13]. However, such aqueous gels also suffer from several disadvantages, including the need to include preservatives to inhibit microbial growth. However, a greater problem is that a substantial number of the lead microbicide candidates progressing through the clinical pipeline are highly hydrophobic, with water solubilities in the low mcg/mL range [14–16]. In such cases, aqueous gel formulations commonly contain the active microbicide component in a dispersed format, rather than as a true solution [17]. That scenario has adverse implications for the absorption of the compound and its antiviral activity.

Poor retention of the active compound within the vagina is a further problem associated with conventional aqueous gels [18,19]. These gels rapidly become diluted in the vaginal fluid, resulting in reduced viscosity, leakage from the vagina, and a subsequent rapid decline in local drug concentrations [19–21]. In order to overcome the poor retention and be effective, the gel must be applied soon before every act of sexual intercourse (i.e. a coitally-dependent strategy

* Corresponding author. Tel.: +44 28 9097 2319.
E-mail address: k.malcolm@qub.ac.uk (R.K. Malcolm).

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[22]), with adverse implications for adherence to recommended protocols. A better strategy, particularly for women at high risk of infection via regular contact with multiple sex partners [23], would be the use of a microbicide gel that could be administered independently of coitus (e.g. once a day), and that maintained sufficiently high vaginal concentrations of the microbicide between applications. There is, therefore, a need for alternative vaginal gel systems that are optimized for formulation, retention and delivery of hydrophobic drug molecules, including a large number of lead candidate microbicides.

In this study, we report for the first time on the development and testing of non-aqueous silicone elastomer gel formulations for use in the vaginal delivery of HIV-1 microbicides. Non-medicated silicone elastomer gels are presently used as medical device lubricants, personal (sexual) lubricants, and in a wide range of cosmetic applications (where they are regulated as medical devices). They are now being developed and marketed for external topical (i.e. skin) drug delivery applications. To our knowledge, they have not been studied previously for vaginal drug administration. The gel selected for testing in this study, available commercially under the brand name Silky Touch® (Dow Corning), comprises a lightly cross-linked polydimethylsiloxane (ST-Elastomer 10) mixed with cyclomethicone, a small molecule cyclic silicone [24] (Fig. 1). Other elastomeric silicone systems, in the form of vaginal rings, are already used for effective controlled / sustained delivery of active compounds to the vagina [13,25–28], including ARV-based microbicides [25–27]. We postulated that a silicone gel formulation might provide release and site-retentive characteristics that are intermediate between an aqueous gel and a silicone elastomer vaginal ring.

Maraviroc (MVC; Fig. 1) was selected as a model hydrophobic microbicide compound (experimental log P = 4.37; unbuffered water solubility ~1 mg/mL at 20 °C). It is a licensed ARV drug that inhibits the entry of HIV-1 into cells by binding to the CCR5 co-receptor and preventing its interaction with the viral Env complex [29]. MVC is currently being evaluated in a silicone-based intravaginal ring, both as a single compound and in combination with dapivirine, for its suitability as an HIV-1 microbicide [28]. It has potent antiviral activity *in vitro*, with a MIC_{90} value of 2 nM against a panel of diverse HIV-1 Env-pseudoviruses [30]. When formulated as an aqueous 2.2% HEC gel and applied vaginally, MVC provided dose-dependent protection (mM range) against a single high-dose challenge with the SHIV-162P3 test virus [31]. The extent of protection was also time-dependent, in that the longer the interval between the administration of the gel and the challenge virus, the more likely it was that the animal became infected. The half-life of protection was ~4 h [31]. These results reinforce the perception that traditional, water-based vaginal gels may not be developed successfully as coitally-independent products.

We hypothesized that a non-aqueous silicone elastomer gel formulation containing MVC would allow vaginal fluid and tissue levels of MVC to be sustained over a longer period of time compared with the previously tested 2.2% w/w HEC maraviroc gel [31]. Accordingly, we compared the mechanical, rheological and *in vitro* retention properties of the silicone elastomer gel with the HEC gel. The gels were also compared for mucosal irritancy in the slug model and tested for local and systemic pharmacokinetics in rhesus macaques.

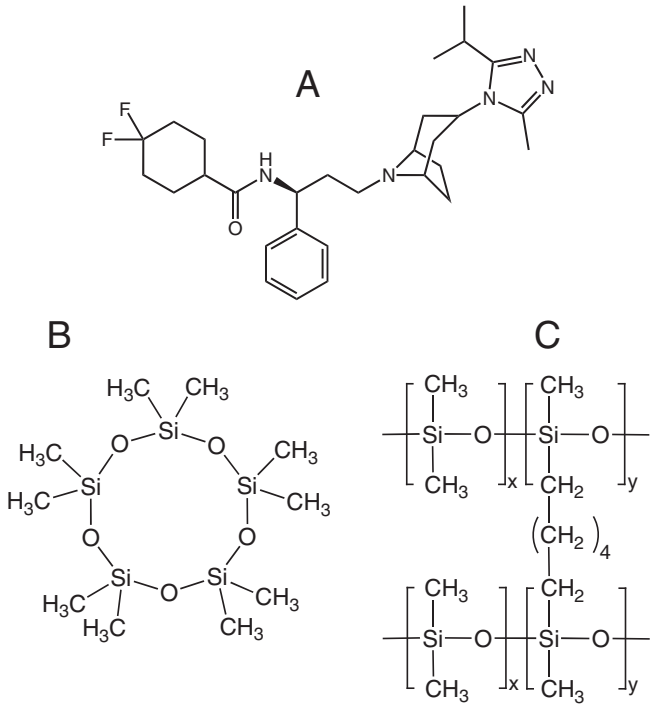

Fig. 1. Chemical structures of the HIV-1 entry inhibitor maraviroc (A), cyclomethicone (B) and ST Elastomer 10 (C). The active silicone elastomer gels used in the study are comprised of a mixture of all three components.

2. Materials and methods

2.1. Chemicals

ST-Elastomer 10 and cyclomethicone, used in the preparation of the silicone elastomer gels, were kindly donated by Dow Corning® (Midland, USA). MVC was supplied by Pfizer® Ltd (Surrey, UK). Hydroxyethylcellulose (HEC), (Natrosol® 250 M-Pharm) was obtained from Aqualon Hercules (Wilmington, USA), sodium chloride from Sigma Aldrich® (St. Louis, MO, USA), potassium chloride and potassium dihydrogen orthophosphate from AnalaR® VWR (West Chester, Pennsylvania, USA) and disodium hydrogen orthophosphate from Fisher Scientific (Loughborough, Leicestershire, UK). All other materials and solvents were supplied by Sigma Aldrich® and were used as received.

2.2. Preparation of HEC and silicone elastomer gels

Non-aqueous silicone elastomer gels were prepared by mixing the requisite weights of ST-Elastomer 10 and cyclomethicone [24] with micronized MVC in a SpeedMixer™ (DAC 150 FVZ-K, Synergy Devices Ltd., UK) for 1 min at 3000 rpm. Aqueous HEC gel (2.2% w/w) was prepared by addition of HEC to phosphate buffered saline with stirring for 2 h (motorized overhead, propeller stirrer), followed by addition of micronized MVC and adjustment of the pH to 7.3 (the pK_a of MVC). This base HEC gel formulation was similar to that used in a previous macaque challenge study [31]. The maraviroc component is present in a dispersed state within both gels.

2.3. Rheological assessment of gels

Continuous flow rheological assessment of the gels was carried out using a TA Instruments AR 2000 Rheometer fitted with a 40 mm diameter steel parallel plate. The gel sample was transferred to the base plate of the rheometer, followed by lowering of the plate to produce a gap depth of 1000 μm. Excess gel was removed before initiating the test. Flow rheology was conducted at 37 °C in continuous ramp mode with the shear stress increased from 0 to 200 Pa over 60 s (40 sampling points). Viscosity was determined by applying the Power Law [32] on the linear portion of the resulting log-log plot of viscosity against shear rate.