On-demand, self-administered fast-dissolving insert for prevention of HIV, HSV, and HPV infections

Microbicides are a potential discreet prevention method for empowering millions of women worldwide to protect themselves against incurable sexually transmitted infections (STIs) including HIV, herpes simplex virus (HSV), and human papillomavirus (HPV). For nearly three decades, much work on microbicide delivery systems has focused on sustained-release dosage forms. However, an urgent and unmet need remains for many women who have infrequent sex and concerns about the side effects and health risks of long-term products.

To overcome the disadvantages of current self-administered microbicide delivery systems, including gel leakage and insoluble particulates, we adapted a technology previously developed in our laboratory for creating fast-dissolving inserts (FDIs) for vaginal or rectal use. This technology produces fast-dissolving tablets or FDIs by freeze-drying aqueous solutions of drug with stabilizing excipients directly in blister packaging. To test the feasibility of our FDI technology for administering microbicides vaginally, we chose two potent antiviral agents: griffithsin (GRFT) and carrageenan (CG). GRFT is an algae-extracted protein with an excellent safety profile and potent activity against STIs including HIV, while CG is a polysaccharide derived from red seaweeds that has also demonstrated safety and activity against HPV. The combination of GRFT with CG has reportedly demonstrated synergy against HSV infections. Combining these two potent antiviral agents in a self-administered FDI creates an attractive multipurpose prevention option against STIs.

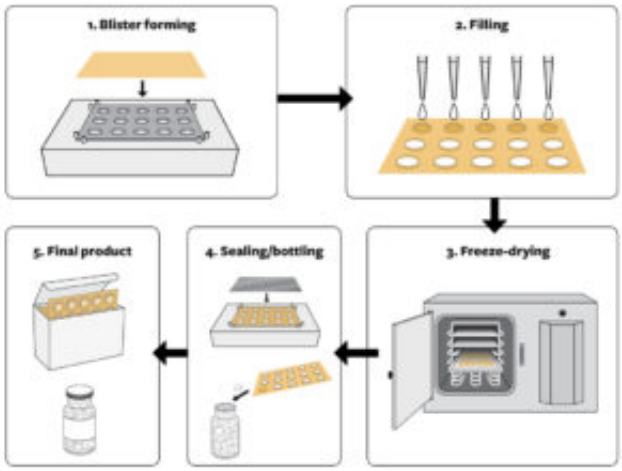

Fig. 1. Freeze-drying-in-blister technology for developing GRFT-CG vaginal fast-dissolving inserts (FDIs).

Using the freeze-drying-in-blister process, we have successfully developed an FDI containing

GRFT and CG that disintegrates in less than 60 seconds in simulated vaginal fluid with desirable post-disintegration characteristics and maintains thermostability during storage. FDIs for human applications are about 9 mm by 17 mm, with a smooth surface and rounded edges for comfortable insertion, and can fit the reported range of vaginal cavities, from widths of 2.1 to 6.5 cm and posterior lengths from 8 to 15 cm.

Using fiber-optic imaging, we showed FDIs disintegrated completely in the presence of minimal fluid in the vaginal region of macaques and formed a gel without any insoluble particulates present. Preclinical efficacy, pharmacokinetic, and safety studies of GRFT-CG FDIs demonstrated significant protection against simian-human immunodeficiency virus (SHIV), HSV-2, and HPV (Derby et al., 2018). A vaginal FDI that could be administered at the time of sex and dissolves quickly in the vagina to release and maintain targeted levels of antiviral agents would provide a dosage form that is on demand and coitally dependent. The FDI combines the ease of insertion of a compact solid dosage form with rapid formation of a soft, viscous semi-solid gel with favorable mucoadhesive and spreading properties.

The lead microbicide candidate FDI formulation of GRFT-CG consisting of 1.5 wt% CG, sucrose, mannitol, and dextran 40 met the evaluation criteria for appearance, disintegration time, and drug stability. The sensitivity of GRFT to oxidation under mild conditions has presented regulatory challenges for its development as a microbicide. However, by formulating GRFT in a low moisture content FDI (~1%), we are able to suppress oxidation compared with the aqueous gel formulation and thereby generate a stable product. The FDIs are robust with good handling properties and maintain the stability of GRFT and CG under elevated temperature and humidity conditions for up to six months. These results are important for use and storage of FDIs in tropical conditions prevalent in many regions with high HIV and HPV incidence rates.

The results from our evaluation warrant further investigation of user acceptability, safety, pharmacokinetics and pharmacodynamics, and human clinical studies of the GRFT-CG FDI as a pre-coital, on-demand vaginal dosage form. A self-administered topical multipurpose microbicide FDI could extend coverage to the most vulnerable populations, improve adherence, and decrease global HIV and STI incidence.

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Publications

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