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Controlled-release system for intra-vaginal delivery, for the prevention of vaginal infections. Phase I safety data available

Introduction

In healthy conditions the vagina is colonized by symbiotic microorganisms, in particular lactobacilli, that protect against vaginal infections. The acidity of a healthy vagina of a woman of child-bearing age (pH about 3.8 - 4.5) is due to the degradation of secreted glycogen/glucose to lactic acid and acetate by lactobacilli. This acidic environment prevents the growth of many pathogenic microorganisms, including bacteria, protozoa and viruses. However, any imbalance in this vaginal ecosystem may result in overgrowth of pathogenic microorganisms, resulting in vaginal infections, such as bacterial vaginosis, vaginal candidiasis and trichomoniasis (a sexually transmitted disease).
Current treatment options rely on antibiotics, anti-mycotic or anti-parasitic drugs but suffer from problems of resistance and frequent recurrence. Alternative treatment options consist in the application of acidic compounds (lowering the pH) or naturally occurring vaginal bacterial strains. However, most currently available products make use of gel-like formulations requiring frequent applications, requiring a lot of effort and commitment of the patient. It would be very advantageous to provide a controlled-release product for delivery of active ingredients, in particular organic acids, which can be applied only once every few days or even every few weeks.

Technology

Researchers at Ghent University have developed an intra-vaginal delivery system for the controlled release of one or more organic acids, such as lactic acid. This intra-vaginal delivery system consists of a combination of ethylene vinyl acetate (EVA) copolymers and carboxylic polymers, for example methacrylic acid - methacrylic ester copolymers.

Applications

Intra-vaginal delivery device for the controlled release of organic acids. This delivery device may be in any suitable form, for example vaginal pessaries or vaginal rings. A vaginal ring is inserted in the vagina and the vaginal wall holds it in place, where it may remain over the complete period of organic acid release. A vaginal ring may be manufactured by extrusion or injection molding and typically has a diameter of 50-55mm and a cross-section of 4mm.

Advantages

- Controlled release of active ingredients avoids frequent application
- Standard manufacturing methods and low-cost materials allow cost-efficient production
- Low mucosal irritation results in good tolerance and safety
- Broad action mechanism (lowering pH) minimizes risk of resistance
- Long-term use reduces risk of recurrence
- Using lactic acid, regarded as safe
- Likely to be classified as medical device with approval based on phase 2 data

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Status of development

Lab tests have demonstrated that carboxylic acid-containing polymers with lactic acid (5% or 10%) lower the pH of a solution for more than 10 consecutive days.

As a prototype we produced a vaginal ring matrix system consisting of a mixture of ethylene vinyl acetate and methacrylic acid-methyl methacrylate copolymer loaded with 150 mg DL-lactic acid with an L/D-lactic acid ratio of 1:1.

Preclinical safety assessment was performed by use of the Slug Mucosal Irritation test, a non-vertebrate assay to evaluate vaginal mucosal irritation, which revealed no irritation

Clinical safety was evaluated in a phase I trial with six healthy premenopausal volunteering women, with the investigational drug left in place for 7 days. Colposcopic monitoring according to the WHO/CONRAD guidelines for the evaluation of vaginal products, revealed no visible cervicovaginal mucosal changes. No adverse events related to the investigational product occurred. Total release from the intravaginal ring over 7 days was estimated through high performance liquid chromatography at 37.1 (standard deviation 0.9) mg DL-lactic acid.

Partnership

Ghent University wishes to partner with pharmaceutical or medical device companies who will apply the controlled release formulations in products for vaginal delivery of organic acids. The Laboratory of Pharmaceutical Technology is willing to provide support for product development. Exclusive license rights can be considered.

Intellectual property

PCT patent application WO2013010915: “Intravaginal Delivery System”
National patent applications in Europe, China, Hong-Kong, Japan
Granted patent in US: US9,168,303

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Keywords

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