

INTRAVAGINAL RING DEVICES

FIELD OF THE DISCLOSURE

[001] The present disclosure is in the field of women's health. More specifically, the disclosure is directed to intravaginal ring (IVR) devices for use in non-hormonal contraception. The IVR devices are comprised of a non-segmented or segmented ring that is made with an uncoated thermoplastic polymer that encircles a curved non-resorbable barrier, wherein the ring has minimal distortion to its ring structure due to the absorption of vaginal fluid or from humidity that occurs in the storage of the device before its use as compared to intravaginal devices made with a copolymeric silicone matrix.

BACKGROUND OF THE DISCLOSURE

[002] Applicant has discovered that intravaginal ring devices made with a copolymeric silicone matrix become distorted due to humidity or when used in a subject for a period of time resulting in an IVR device that may not fit properly in a subject, resulting in an intravaginal device that may not function as well as a non-distorted device. The present disclosure relates to new intravaginal ring devices that have ring components and or ring shapes that reduce or eliminate ring distortion over time that occurs with intravaginal ring devices made with a copolymeric silicone matrix enabling a better fit and more comfort for subjects using the device.

SUMMARY OF THE INVENTION

[003] In an aspect of the disclosure, disclosed herein are intravaginal ring devices that have a flat, circular or oval ring made with a non-segmented or segmented uncoated thermoplastic elastomer, excluding copolymeric silicone. The ring may contain one or more non-hormonal spermistatic agents; and, the ring encircles a curved, non-resorbable polymeric barrier which is attached to the ring. When inserted into a subject the ring covers the cervix.

[004] In some embodiments the flat, circular or oval intravaginal ring is made with a segmented uncoated thermoplastic elastomer.

[005] In some embodiments, the number of segmented ring sections is two.

[006] In some embodiments the flat, circular or oval intravaginal ring is made with a non-segmented uncoated thermoplastic elastomer.

[0007] In some embodiments, the uncoated thermoplastic elastomer of the flat, circular or oval intravaginal ring is selected from one or more of styrene-butadiene block copolymer, ethylene vinyl acetate copolymer, poly(methyl methacrylate), poly(butyl methacrylate), poly(vinyl chloride), nylon, soft nylon, poly(ethylene terephthalate) (PET), poly(ethylene), poly(acrylonitrile), polychlorotrifluoroethylene (PCTFE), poly(ethylene-vinyl esters), poly(ethylene-vinyl acetate), poly(vinylchloride-diethyl fumarate), poly(esters of acrylic and methacrylic), poly(amides), poly(vinyl chloride), PTFE (polytetrafluoroethylene) poly(urethane), polypropylene or other poly(olefins).

[0008] In some embodiments, the uncoated thermoplastic elastomer for the flat, circular or oval intravaginal ring is selected from one or more of ethylene vinyl acetate copolymer (EVA), polyurethane, or polyethylene terephthalate (PET).

[0009] In some embodiments, the uncoated thermoplastic elastomer for the flat, circular or oval intravaginal ring is EVA.

[0010] In some embodiments, the flat, circular or oval intravaginal ring has a polymeric barrier mesh that is comprised of one or more of polyolefin, nylon, and/or silk. In some embodiments, the polyolefin of the polymeric barrier mesh is polypropylene or polyethylene. In some embodiments, the polymeric barrier mesh is a mono- or multi-filament polymer. In some embodiments the polymeric barrier mesh has pores that range in size from about 100 to about 150 μ M.

[0011] As used herein term “about” is used to mean approximately, roughly, around, or in the region of. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 20 percent up or down (higher or lower).

[0012] In some embodiments, the flat, circular or oval intravaginal ring device has a removal tab that aids in removing the ring after insertion. In some embodiments the removal tab has a diameter of about 10 mm in length.

[0013] In some embodiments, the flat, circular or oval intravaginal ring contains one or more spermiostatic metals and/or metal salts. In some embodiments, the salts are selected from one or more of ferrous sulfate, ferrous gluconate, iron amino acid chelates, copper sulfate, copper gluconate, copper amino acid chelates, or copper oxide.

[0014] In some embodiments, the flat, circular or oval intravaginal ring contains ascorbic acid.

[0015] In another aspect of the disclosure, the flat, circular or oval ring device is resistant to shape distortion due to absorption of vaginal fluids and/or fluids contained in the packaging used to store the device before use.

[0016] In some embodiments, the flat, circular or oval ring intravaginal device absorbs less water or simulated vaginal fluid as compared to an intravaginal ring made with a copolymeric silicone matrix in which both rings contain equivalent amounts and composition of nonhormonal spermistatic agents and or ascorbic acid.

[0017] In some embodiments, the amount of absorption of simulated vagina fluid by the flat circular ring intravaginal device is about 95% less, 90% less, 85% less, 80% less, 70% less, 60% less, 50% less, 40% less, 30%, 20% less, 10%, less, 5% less, 4% less, 3% less, 2% less or 1% less as compared to an intravaginal ring made with a copolymeric silicone matrix in which both rings contain equivalent amounts and composition of nonhormonal spermistatic agents.

[0018] In some embodiments, the amount of simulated vaginal fluid absorption of the flat, circular ring intravaginal device is from about 1%-95% less, or any ranges in between about 1%-95% less as compared to an intravaginal ring made with a copolymeric silicone matrix in which both rings contain equivalent amounts and composition of nonhormonal spermistatic agents.

[0019] In some aspects of the disclosure, disclosed herein are intravaginal ring devices that are a saddle-shaped, oval ring made with a non-segmented or segmented uncoated thermoplastic elastomer, excluding copolymeric silicone. The saddle-shaped intravaginal ring contains one or more non-hormonal spermistatic agents; and, the saddle-shaped oval ring encircles a curved, non-resorbable polymeric barrier which is attached to the ring. When inserted into a subject, the saddle-shaped oval ring covers the cervix.

[0020] In some embodiments, the thermoplastic elastomer of the saddle-shaped, oval ring intravaginal device is selected from the group of one or more of styrene-butadiene block copolymer, ethylene vinyl acetate copolymer, poly(methyl methacrylate), poly(butyl methacrylate), poly(vinyl chloride), nylon, soft nylon, poly(ethylene terephthalate) (PET), poly(ethylene), poly(acrylonitrile), polychlorotrifluoroethylene (PCTFE), poly(ethylene-vinyl esters), poly(ethylene-vinyl acetate), poly(vinylchloride-diethyl fumarate), poly(esters of acrylic and methacrylic),

poly(amides), poly(vinyl chloride), PTFE (polytetrafluoroethylene) poly(urethane), polypropylene or other poly(olefins).

[0021] In some embodiments, the uncoated thermoplastic elastomer for the saddle-shaped, oval ring intravaginal device is selected from one or more of ethylene vinyl acetate copolymer, polyurethane, or PET.

[0022] In some embodiments, the saddle-shaped, oval ring intravaginal device has a polymeric barrier mesh that is comprised of one or more of polyolefin, nylon, and/or silk. In some embodiments, the polyolefin is polypropylene or polyethylene. In some embodiments, the polymeric barrier mesh is a mono- or multi-filament polymer. In some embodiments the barrier has pores. In some embodiments the barrier has pores that range in size from about 100-150 μM .

[0023] In some embodiments, the saddle-shaped, oval ring intravaginal device contains one or more spermistatic metals and/or metal salts. In some embodiments, the salts are selected from one or more of ferrous sulfate, ferrous gluconate, iron amino acid chelates, copper sulfate, copper gluconate, copper amino acid chelates, copper oxide.

[0024] In some embodiments the saddle-shaped, oval ring intravaginal device contains ascorbic acid.

[0025] In some embodiments, the saddle-shaped, oval ring intravaginal device absorbs less simulated vaginal fluid or water as compared to an intravaginal ring made with a copolymeric silicone matrix in which both rings contain equivalent amounts and composition of nonhormonal spermistatic agents and ascorbic acid if present.

[0026] In some embodiments, the amount of simulated vaginal fluid absorption of the saddle-shaped, oval ring intravaginal device is about 95% less, 90% less, 85% less, 80% less, 70% less, 60% less, 50% less, 40% less, 30%, 20% less, 10%, less, 5% less, 4% less, 3% less, 2% less or 1% less as compared to an intravaginal ring made with a copolymeric silicone matrix in which both rings contain equivalent amounts and composition of nonhormonal spermistatic agents.

[0027] In some embodiments, the amount of water absorption of the saddle-shaped, oval ring intravaginal device is from about 1%-95%, or any ranges in between about 1%-95% less as compared to an intravaginal ring made with a copolymeric silicone matrix in which both rings contain equivalent amounts and composition of nonhormonal spermistatic agents.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The Figures illustrate exemplary modes of aspects and embodiments of the disclosure. However, the scope of the invention is not limited to the specific embodiments disclosed in these Figures, which are for purposes of illustration only, since alternative embodiments can be utilized to obtain similar results.

[0029] Figure 1 is a perspective view of an intravaginal ring device of the disclosure with a curved polymeric barrier, and flat circular ring.

[0030] Figure 2 is a side view of the intravaginal device of Figure 1 also showing the rounded or curved cross section of the ring.

[0031] Figure 3 is a perspective view of an intravaginal ring device of the disclosure with a saddle-shaped ring and curved polymeric barrier.

[0032] Figure 4 is a side view of the intravaginal ring device of Figure 3 also showing the rounded or curved cross section of the saddle-shaped ring.

[0033] Figure 5 is a perspective view of an intravaginal ring device of the disclosure with a segmented ring, curved polymeric barrier and removal tap.

[0034] Figure 6 is a side view of the intravaginal device of Figure 5 also showing the rounded or curved cross section of the ring.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0035] Disclosed herein are intravaginal ring (IVR) devices. In some embodiments, the intravaginal ring devices include a flat, circular or oval ring made with a non-segmented or segmented, uncoated, thermoplastic elastomer, excluding copolymeric silicone. The ring encircles a curved, non-resorbable polymeric barrier which is attached to the ring; and wherein the ring covers the cervix.

[0036] In other embodiments, the IVR devices disclosed herein are a saddle-shaped oval ring made with a non-segmented or segmented uncoated thermoplastic elastomer. The ring encircles a curved, non-resorbable polymeric barrier which is attached to the ring; and wherein the ring covers the cervix when inserted into a subject.

[0037] As used herein thermoplastic elastomers are copolymers or a mix of polymers that have thermoplastic and elastomeric properties and exclude silicone polymers.

[0038] Thermoplastic polymers suitable for IVR devices disclosed herein include polymers and copolymers that are capable of being softened by heating and hardened by cooling through a temperature range characteristic of the polymer, its crystalline melting or glass transition temperature, and in the softened state they can be shaped by flow into systems by molding or extrusion. Thermoplastic polymers suitable for the present purpose are permeable to non-hormonal spermistatic agents, ascorbic acid, antimicrobials, antifungals, and absorb a low amount of vaginal fluid when inserted into a subject.

[0039] Examples of thermoplastic polymers that can be used to make the disclosed IVR devices include, without limitation, ethylene vinyl acetate copolymer, poly(methyl methacrylate), poly(butyl methacrylate), poly(vinylchloride), nylon, soft nylon, poly(ethylene terephthalate) (PET), poly(ethylene), PCTFE (polychlorotrifluorethylene), poly(ethylene-vinyl esters), poly(ethylene-vinyl acetate), poly(vinylchloride-diethyl fumarate), poly(esters of acrylic and methacrylic), poly(amides), poly(vinyl chloride), poly(urethane), polypropylene, and other poly(olefins). These polymers and their physical properties are known to the art and they can be synthesized according to the procedures disclosed in Encyclopedia of Polymer Science and Technology, Vol. 15, pages 508 to 530, 1971, published by Interscience Publishers, Inc., New York; Polymers, Vol. 17, 938 to 956, 1976; Technical Bulletin SCR-159, 1965, Shell Corp., New York; and references cited therein.

[0040] In some embodiments, the rings of the disclosed IVR devices contain one or more spermistatic metals and/or metal salts. The salts can be selected from one or more of ferrous sulfate, ferrous gluconate, iron amino acid chelates, copper sulfate, copper gluconate, copper amino acid chelates, copper oxide.

[0041] In some embodiments, the rings of the disclosed IVR devices contain ascorbic acid.

[0042] In some embodiments, the IVR devices contain antimicrobials and/or antifungal agents.

[0043] In some embodiments, the IVR devices do not absorb as much vaginal fluid from the subject using the device as compared to a intravaginal ring devices made from a copolymeric silicone matrix.

[0044] The ability of the IVR devices of the present disclosure to absorb less vaginal fluid or water as compared to vaginal rings made of polymeric silicone can be

tested *in vitro* using fluids such as water or simulated vaginal fluid. Example 4 provides a method for testing the absorption of simulated vaginal fluid by IVR devices.

[0045] In some embodiments, the IVR devices disclosed herein have less distortion than intravaginal ring devices made from a copolymeric silicone matrix when used in a subject for a period of time of about 14-days to about three-months or when stored in packaging that is susceptible to humidity before use. Thus, the disclosed rings will maintain their shape longer than intravaginal ring devices made from a copolymeric silicone matrix, resulting in a better fit, performance and comfort in subjects using the disclosed devices.

[0046] In some embodiments, the devices can be used for greater than at least 14 days.

[0047] In some embodiments, the intravaginal ring devices disclosed herein are non-resorbable in the subject.

[0048] In some embodiments, the polymeric barrier of the intravaginal devices disclosed herein is a mesh comprised of one or more of polyolefin, nylon, and/or silk. In some embodiments, the polyolefin is polypropylene or polyethylene. In some embodiments, the polymeric barrier is a mono- or multi-filament polymer. In some embodiments the polymeric barrier has pores that range in size from about 100-150 μM .

[0049] The pore size can be measured microscopically.

[0050] Examples are provided below to facilitate a more complete understanding of the invention. The following examples illustrate the exemplary modes of making and practicing the invention. However, the scope of the invention is not limited to specific embodiments disclosed in these Examples, which are for purposes of illustration only, because alternative methods can be utilized to obtain similar results.

EXAMPLES

EXAMPLE 1: FLAT RING

[0051] The barrier mesh of the ring device illustrated in FIG. 1 is prepared by extruding poly(propylene), nylon, or poly(ethylene), multi- or monofilaments and using a 3D knitting machine and a warp knit pattern to create a spherical cap shape.

The spherical cap shape has an outer diameter of about 50 mm (millimeters) and a height of about 15 mm.

[0052] Alternatively, sericin-free silk fibroin multi- or monofilaments are knitted using a 3D knitting machine and a warp knit pattern to create a spherical cap-type shape where the portion of the sphere is cut off by a saddle, instead of a plane (FIG. 3). The spherical cap shape has an outer diameter of about 50 mm (millimeters) and a height of about 15 mm.

[0053] The intravaginal contraceptive ring device illustrated in FIG. 1 is prepared using poly(ethyl-co-vinyl acetate) (EVA), about 500 (milligrams) mg of ferrous gluconate and about 400 mg of ascorbic acid which are dissolved together in approximately 10 mL of a nonpolar solvent such as dichloromethane in a scintillation vial. Next, the polymeric mixture is prepared by adding about 4000 mg of EVA to the solution, and mixing the EVA/drug compositions using a rotary shaker. The resulting mixtures are then solvent cast in dry ice using ethanol as the solvent. The solvent is allowed to evaporate overnight, and the dry EVA/drug mixtures are then ground into powders. The EVA/drug powders are placed into an injection molding unit. The injector is heated to approximately 80° C. The barrier mesh is held in a stainless-steel mold using an insert molding fixture, then the molten EVA/drug compositions are extruded into a stainless-steel mold, creating a finished device with an outer diameter of about 55 mm and a cross-section of about 4 mm.

[0054] Alternatively, the intravaginal contraceptive ring device illustrated in FIG. 1 is prepared using polyurethane or polyethylene terephthalate as the ring material and copper gluconate and ascorbic acid as the spermistatic agents using a process similar to that described above.

EXAMPLE 2: SADDLE RING

[0055] The barrier mesh of the ring device illustrated in FIG. 3 is prepared by extruding poly(propylene), nylon, or poly(ethylene), multi- or monofilaments and using a 3D knitting machine and a warp knit pattern to create a spherical cap-type shape where the portion of the sphere is cut off by a saddle, instead of a plane (FIG. 3). The spherical cap shape has an outer diameter of about 50 mm (millimeters) and a height of about 15 mm.

[0056] Alternatively, sericin-free silk fibroin multi- or monofilaments are knitted using a 3D knitting machine and a warp knit pattern to create a spherical cap-

type shape where the portion of the sphere is cut off by a saddle, instead of a plane (FIG. 3). The spherical cap shape has an outer diameter of about 50 mm (millimeters) and a height of about 15 mm.

EXAMPLE 3: FLAT RING WITH REMOVAL TAB

[0057] The barrier mesh of the ring device is prepared using the process from Example 1 above.

[0058] The intravaginal contraceptive ring device illustrated in FIG. 5 is prepared using poly(ethyl-co-vinyl acetate) (EVA). About 250 (milligrams) mg of ferrous gluconate are dissolved in approximately about 5 mL of a nonpolar solvent such as dichloromethane in a scintillation vial. Next, the polymeric mixture is prepared by adding about 2000 mg of EVA to the solution, and mixing the EVA/drug composition using a rotary shaker.

[0059] A semi-circle of EVA/ascorbic acid is prepared using the process described above. The two semicircles are then welded together into a full circle with an outer diameter of about 55 mm and a semi-circular cross-sectional geometry.

[0060] EVA is then placed into an injection molding unit. The mold is circular with an outer diameter of about 55 mm with a removal tab protruding from one side of the circle, and has a semi-circular cross-sectional diameter of about 4 mm. The injector is heated to approximately 80° C, then the molten EVA/ferrous gluconate is extruded into a stainless-steel mold. The two ring halves are then welded together with the barrier mesh in the middle to create the finished device.

[0061] Alternatively, the intravaginal contraceptive ring device illustrated in FIG. 5 is prepared using polyurethane, or polyethylene terephthalate as the ring material and copper gluconate and ascorbic acid as the spermistatic agents using a process similar to that described above.

EXAMPLE 4- Measurement of Absorption of Synthetic Vaginal Fluid

[0062] The IVR device of the present disclosure is weighed with an analytical balance. It is then submerged in about 100mL of simulated vaginal fluid (SVF) for 14-35 days at 37°C-for making simulated vaginal fluid see, for example, Rastogi R. et al., (2016), "Engineering and Characterization of Simplified Vaginal and Seminal Fluid Simulants", *Contraception*, 2016, 93(4):337-346. The ring is then removed from the simulated vaginal fluid, patted down with a Kimwipe, then weighed again. The ring is then placed in a vacuum oven to remove any water absorbed. The

ring is kept in the vacuum oven and dried until it is at a constant weight. That final dry weight is recorded.

[0063] The same process is performed with the comparator ring. The water absorption is quantified by subtracting the wet ring weight from the dry ring weight to get the weight of water absorbed per ring. The weight of water absorbed by the comparator ring is divided by the weight of water absorbed by the comparator ring to quantify the percentage less water absorption.