United States Patent

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[54] **MEDICATED DEVICES AND METHODS**
19 Claims, 4 Drawing Figs.

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[51] **Int. Cl.** **A61m 7/00**
[50] **Field of Search** 128/130, 131, 128, 129, 334, 270, 156, 268, 260, 1; 424/15, 27, 28; 264/337; 260/75, 858; 3/36

[56] **References Cited**

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2,017,596	1/1936	Hoffman	424/28
2,423,475	7/1947	Rice et al.	424/28
3,442,266	5/1969	Krejci et al.	128/130
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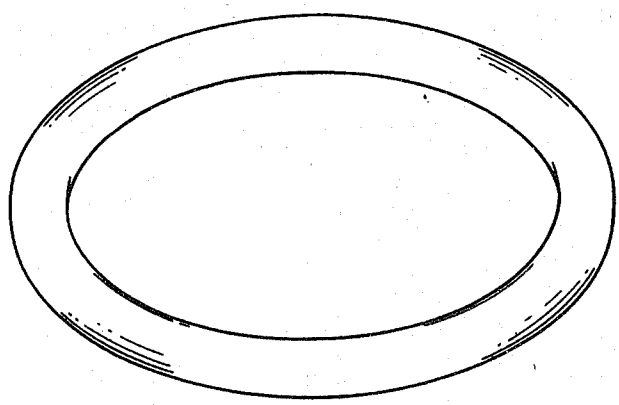
ABSTRACT: An improved resilient annular device for intravaginal placement and retention as required and formed of a compatible nonabsorbable polymeric substance such as an organopolysiloxane, nylon, natural or synthetic rubber, dacron, teflon, polyurethane and polyethylene and containing an effective amount of a medicament which is capable of passage through the drug-permeable polymeric material. The device is useful to provide a readily inserted, readily retained and readily removable source of continued medication for sustained beneficial effects in female mammals, human and animal.



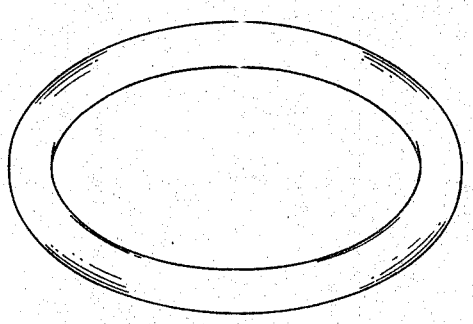


figure 1

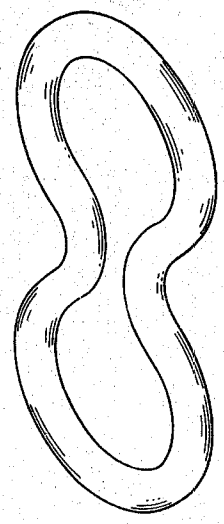


figure 2

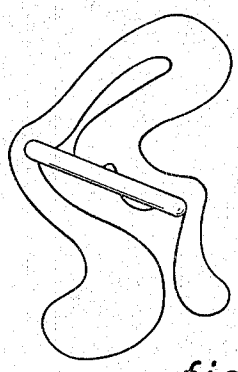


figure 3

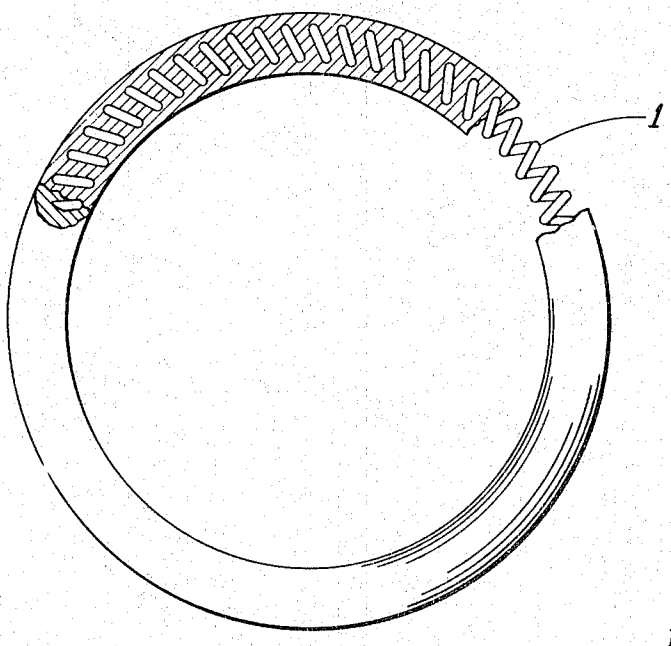


figure 4

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MEDICATED DEVICES AND METHODS

BRIEF SUMMARY OF THE INVENTION

This invention relates to pharmaceutical devices and methods of their use, more particularly to such a device for intravaginal placement in the form of a resilient medicated ring comprised of a compatible nonabsorable polymeric material and an effective amount of a diffusible medicament. The invention relates also to methods of providing continuous medication during a predetermined medication period via the vagina in female mammals, human and animal, for example dogs, sheep, cattle, horses, and rats.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a prospective view of a tangible embodiment of the concept of the invention.

FIG. 2 is a prospective view showing how the annular device is compressed for ease of insertion into the vagina.

FIG. 3 is a sectional view showing the correct placement of the annular device in the human vagina.

FIG. 4 is a sectional view of a device containing tensing means in the form of a coiled endless steel spring positioned within the device.

DETAILED DESCRIPTION

It has been found that the device according to this invention provides sufficiently resilient characteristics so that upon tensing for ready manual or mechanical insertion in the vaginal tract there will be relative ease of handling. Upon release of tension, the device will resume the annular form necessary for providing retentive contact within the vaginal area. Proper retention is obtained upon placement in the vagina in accordance with FIG. 3 and when properly placed, the ring fits securely and comfortably between the rear wall of the vagina and the upper edge of the pubic bone. In that position the medicated device can be readily inserted and is readily retained during the desired period of continued medication. When it is desired that medication cease, the ring is readily removed in a reverse fashion to insertion.

As aforesaid, the resilient annular device is formed of a compatible drug-permeable polymeric material. As used herein, the word "compatible" means compatible both with the environment of the vaginal tract in that there is no breakdown of the annular tensile nature of the device due to the contents of the vagina, nor is there any absorption of the polymeric material itself, only the medication being absorbed for local and systemic effects in the female mammals. Likewise, there is no deleterious action on the sensitive tissue in the area of placement in the vaginal tract. Widely varying types of polymeric material are suitable in providing these compatible, nontoxic and nonabsorbable properties, for example organopolysiloxane of the linear type converted to rubber by heat curing (vulcanization). These linear organopolysiloxanes are known as the conventional type, for example dimethyloplysiloxane. Likewise suitable are those known as the RTV type which are converted to the rubbery state at room temperature in the presence of a catalyst. U.S. Pat. No. 3,279,996 describes various conventional silicone rubbers which may or may not contain fillers, such as silica, to enhance tensile strength and the other physical properties of the cured rubber. This patent also describes commercially available RTV silicone rubbers. Other patent literature shows the preparation of conventional silicone rubbers, illustratively U.S. Pats. Warwick, No. 2,504,137; Konkle et al., No. 2,890,188; and other patents set forth in the U.S. Pat. to Long et al., No. 3,279,966. Other suitable nontoxic, nonabsorbable, compatible, drug-permeable polymeric materials are, for example, nylon, a polyamide resin made by polymerization of the hexamethylenediamine salt of adipic acid; dacron, a synthetic fiber made by E. I. DuPont de Nemours and Co. from teraphthalic acid and ethylene glycol; teflon, a tetrafluoroethylene polymer manufactured by E. I. DuPont de Nemours and Co.; polyurethane elastomer prepared according to known methods from polyisocyanate and polyhydroxyl material. The polyhydroxyl materials, for example polyesters, polyethers and the like, are reacted with isocyanates to yield rubberlike products for use as millable gums or in casting systems or as thermo processable resins. See U.S. Pat. Nos. 2,871,218 and 3,015,650. Another exemplary polymer is polyethylene, prepared by polymerization of ethylene, usually prepared from natural gas or the cracking of crude oil. Modern Plastics Encyclopedia for 1968, Sept. 1967, Vol. 45, No. 1*a*, McGraw-Hill, New York, New York, U.S.A. describes the preparation of the aforesaid suitable plastic materials, especially in reference to their molding qualities, compression molding temperatures, and compression molding pressures. Details on the aforesaid polymers are given in the plastic properties chart of the aforesaid Encyclopedia, pages 29 through 46, inclusive. In reference to the nonabsorbability and nontoxic nature of the aforesaid polymeric material, U.S. Pat. No. 3,272,204 refers to the use of vinyon N, nylon, orlon, dacron, teflon, and the like as nonabsorbable, reinforcing strands for the preparation of prostheses. Such strands have the advantage that they do not become a part of the body tissues. So it is with the improved resilient annular device of the present invention, which is particularly advantageous because of its ready insertion and ready retention but does not become or form any part of the tissue of the female mammal utilizing the device, for example human and animal, such as dogs, cattle, and horses. In this respect, the present annular device, with its medication contained therein for continued medication as desired, is greatly superior to implantates, which of necessity are placed within the actual body tissues, such placement often requiring at least minor surgery for both insertion and removal, especially if encapsulated.

As aforesaid, the device, properly sized and fitted, is useful to provide a readily inserted, readily retained, and readily removable source of continued medication for local and systemic effects. Subject to the property of being capable of passage through the polymeric material, a wide range of medication is suitable for use in this improved device for both local and systemic effects. Suitable drugs are digitoxin, triiodothyronine, isoproterenol, atropine, histamine, nitrogen mustard, vitamin B_{12}, pyrimethamine, hormonal substances, i.e., estrogenic substances, progestational substances, androgenic substances, e.g., estradiol, progesterone, androstenedione, testosterone, cortisol, medroxyprogesterone acetate, melengestrol acetate, chlormadinone, and the like. In this connection, both in vivo and in vitro methods of determination of passage of the drug by diffusion through the drug-permeable polymeric material are available. See Dziuk, P. J. and Cook, B., Passage of Steroids Through Silicone Rubbers, Endocrinology, 78:208, 1966; U.S. Pat. No. 3,279,996; Folkman and Edmonds, Circulation Research 10:632, 1962; Folkman and Long, J. Surg. Res. 43:139, 1964; Powers, J. Parasitology 51:53 (April 1965), No. 2 Section 2. An in vitro method of test utilizes polymeric material, e.g., polysiloxane tubing which is loaded with the particular drug and plugged at the ends with polysiloxane cement. After allowing about 48 hours for setting or curing, the filled link of tubing is placed in, for example, 50 ml. of normal saline in a suitable container and shaken at approximately body temperature for about 24 hours. Spectroscopic analysis of the liquid, for example by the isonicotinic hydrazide method for medroxyprogesterone acetate, shows that the drug is capable of permeating through the silastic into the saline material, in which it can be demonstrated by the in vitro test. For in vivo testing, placement of a suitable size device containing a known amount of medicaments, e.g., medroxyprogesterone acetate in a polysiloxane, molded-plastic ring and retention in the vagina of the monkey for a period of about 2 months shows that the initial content of the drug is appreciably reduced. As stated supra, the amount of medication in each of the annular devices is that sufficient for bringing about the desired physiologic effect, for example, the amount sufficient for controlling fertility. Given in ranges of active ingredients, suitable amounts for individual drugs in

the device are as follows: digitoxin, 5 to 50 mg.; triiodothyronine, 1 to 10 mg.; isoproterenol, 100 mg. to 2 Gm.; atropine, 10 to 250 mg.; histamine, 1 to 10 mg.; nitrogen mustard, 50 mg. to 2 Gm.; vitamin B_{12}, 0.5 to 100 mg.; pyrimethamine, 50 mg. to 1 Gm.; estradiol, 0.5 to 100 mg.; progesterone, 50 mg. to 2 Gm.; androstenedione, 50 mg. to 2 Gm.; testosterone, 50 mg. to 2 Gm.; cortisol, 100 mg. to 2.5 Gm.; medroxyprogesterone acetate, 50 mg. to 2 Gm.; melengestrol acetate, 50 mg. to 2 Gm.; chlormadinone, 50 mg. to 2 Gm. The amount of any additive medication, for example locally effective antimicrobial agent, is calculated on the basis of the known amounts useful in similar vaginal applications. Other principal active medicaments are, for example, antiulcer and antisecretory agents, for example methscopolamine, 75 mg. to 2 Gm.; anticoagulant, for example diphenadione, 75 mg. to 1 Gm.; hypocholesteremic agent, for example 3-methyl-5-isoxazole carboxylic acid, 200 mg. to 2 Gm.; appetite depressant, for example D-amphetamine, 100 mg. to 2 Gm.; tranquilizers and sedatives, thiothixene and haloperidol, 50 mg. to 2 Gm.; hypoglycemic agent, 1[[p-[2-(5-chloro-o-anisamido)ethyl]phenyl]sulfonyl]-3-cyclohexylurea, 100 mg. to 2.5 Gm.; hypotensive agent, mecamylamine, 100 mg. to 1.5 Gm.; antibacterial and antimalarial agents, 7-deoxy-7(S)-chlorolincomycin, 2 to 7 Gm., N-demethyl lincomycin, 2 to 7 Gm., 4'-pentyl-N-demethyl-7(S)-chlorolincomycin, 1 to 5 Gm.; antihypertensive agent, for example angiotensin amide, 100 mg. to 2 Gm.; glucocorticoid, for example dexamethasone, 10 to 250 mg.: prostaglandins, for example PGE_1, PGE_2, PGA_1 as antiulcer and antisecretory agents and for inhibition of blood platelet stickiness, 0.5 to 10 mg. The aforesaid amounts are ranges of active ingredients to be included in the annular device, the exact amount depending upon the age, condition of the patient, and the particular effect desired. These amounts are calculated to provide predetermined daily release dosages as follows: for the cardiac stimulant digitoxin, 0.1 to 0.2 mg.; for the metabolic stimulant triiodothyronine, 5 to 100 mcg.; for the bronchodilator isoproterenol, 5 to 30 mg.; for the antianemia agent vitamin B12, 10 to 300 mcg.; for the antimalarial pyrimethamine, 1 to 5 mg.; for the estrogen estradiol, 1 to 500 mcg.; for the progestogen progesterone, 0.1 to 20 mg.; for the androgens androstenedione and testosterone, 0.1 to 10 mg.; for the glucocorticoid cortisol, 5 to 50 mg.; for the progestogens medroxyprogesterone acetate, melengestrol acetate, and chlormadinone, 0.01 to 10 mg.; for the methscopolamine, 3 to 20 mg.; for the diphenadione, 3 to 5 mg.; for the 3-methyl-5-isoxazole carboxylic acid, 10 to 30 mg.; for d-amphetamine, 5 to 30 mg.; for thiothixene, 2 to 30 mg.; for haloperidol, 2 to 15 mg.; for the hypoglycemic cyclohexylurea compound, 5 to 50 mg.; for the mecamylamine, 2 to 10 mg.; for the antibacterial, antimalarial lincomycin compounds, 250 to 500 mg., 250 to 500 mg. and 125 to 300 mg., respectively; for the angiotensin amide, 0.7 to 30 mg.; for the dexamethasone, 0.2 to 2 mg.; and for the prostaglandins, 1 to 10 mcg.

Especially beneficial progestational substances for use in this invention include, for example, norethynodrel, norethindrone, medroxyprogesterone acetate, chlormadinone acetate, dimethisterone, and ethynodiol diacetate. Useful estrogenic substances for combination with these progestogens include, for example, ethinyl estradiol and 3-methyl ether of ethinyl estradiol. The dosages of these progestational substances, whether used alone or in combination with the estrogenic substances, are those effective for control of fertility.

The use of the nonabsorbable, nontoxic plastic material, for example an organopolysiloxane or other rubbery-type resilient material, will not induce a significant tissue reaction at the site of placement in the vaginal tract of the female mammal. Exemplary uses of such a device would be inhibition of fertility (contraceptive purposes), facilitation of reproduction, for example pregnancy salvage and inhibition of premature labor. Other uses are for the treatment of pathologic conditions of the reproductive tract, for example synivaginitis, endometriosis. These devices are constructed in such a way that they are retained in the vagina for periods of a day up to several months and can be readily inserted and removed, for example in the case of the human female patient. The device, due to its unique shape and size, does not obstruct the os uteri as do diaphragms. The medication for release as desired can be introduced into hollow cavities in the ring forming a tubular device, or directly introduced into the plastic material itself while the device is being manufactured as by molding. The drug can be the individual drug or mixed with suitable compatible physiologic material, for example in the case of a progestogen an estrogen can be included. Likewise, a locally effective antimicrobial agent, for example an antibiotic such as neomycin, nystatin and polymyxin can be included within the polymeric material. The improved device of this invention possesses numerous advantages over, for example, the intrauterine devices, which the uterus rejects in some cases. Moreover, nonprofessional placement of the present inventive device is possible in comparison with the intrauterine devices. Unexpected advantages for the improved device as such are ease of placement, ease of retention, ease of removal, relative freedom of infectious conditions, and ease of dosage over a wide range. As aforesaid, the amount of drug incorporated into the inventive device is that sufficient to bring about the local and/or systemic effect, for example an effective amount for control of fertility, probably by inhibition of ovulation. The medicated device of the present invention provides more uniform and constant serum levels of drug during the predetermined period of time for which the beneficial physiologic effects are desired. This is in marked contrast to fluctuations that occur with other treatments, for example oral treatment. In the practice of this invention, low circulating levels of medicament can still be highly effective in target tissues while not accumulating in the nontarget tissues. For example in the case of estradiol, the uterine tissue is the target in contrast to the heart, muscle, liver and like tissues, which are nontarget tissues.

Depending upon the anatomy of the particular species involved, the improved ring device will vary in size, for example in the case of the human from about 70 mm. diameter to about 80 mm. diameter, these dimensions being overall dimensions; the diameter of the actual ring itself will be in the neighborhood of about 5 to 10 mm. In the case where an endless helical spring or flat spring structure is used for additional tensing property, the diameter of this metallic part of the ring will vary with that of the device itself. Overall dimensions of the improved medicated ring for use in other species are approximately as follows: for sheep and swine, 20 to 65 mm.; for dogs, 5 to 50 mm.; for cats, 5 to 30 mm.; for cattle, 50 to 100 mm.; and for horses, 50 to 150 mm. These dimensions are overall dimensions. As will be apparent, the actual diameter of the ring itself varies with the overall size and with the particular species. Suitably the annular devices may incorporate a tab for assistance in removal. The polymeric materials are, as disclosed in the aforesaid Modern Plastics Encyclopedia, those that are suitable for molding in manners known to those familiar with this art. Those polymeric materials, for instance the organopolysiloxanes, which are in a liquid state or paste state, can be directly mixed with the drug, for example melengestrol acetate or medroxyprogesterone acetate, and the semifluid material placed into the mold for compression molding with the addition of a catalyst, for example stannous octoate. In case the device is to contain a spring structure for tension properties, this is usually centered in the semifluid material while it is in the mold and thereafter covered by additional drug-containing polymeric material for the compression molding.

An additional, in vivo, technique for determining the suitability of the polymeric material for use in the preparation of the inventive device is as follows: 150 mg. of medroxyprogesterone acetate was well mixed with 615 mg. of polysiloxane elastomer 3H2 382 (Dow Corning Company) to prepare resilient containers approximately 4 cm. long and 0.48 cm. in diameter. Different dosages of the drug are ob-

tained by cutting the required length of the material. The material is sterilized and can be inserted subcutaneously into the scapular region of normally cycling female rats. Daily records of vaginal cytology, which reflect the release of the medroxyprogesterone acetate, are made for periods of 2 to 6 weeks at dosages of 18.75 mg. for 6 weeks in four animals, 37.5 mg. for 2 weeks in four animals, and 56.25 mg. for 2 weeks in four animals. Cycling is prevented in the otherwise normally cycling female rats. This shows that the active medicament is released by diffusion through the drug-permeable polymer and exerts its physiological effect via the vaginal tract. In addition to the in vivo data in the rats, it was found by measuring the final content of the medicament in the silastic material that average total releases of 4.4 mg., 5 mg. and 5.2 mg. occurred from elastomeric carrier material of 0,5, 1.0 and 1.5 cm. in size, respectively.

The following examples illustrate the manner and process of making and using the inventive annular device, but are not to be construed as limiting.

EXAMPLE 1

An annular device was prepared of organopolysiloxane elastomer containing 170 mg. of medroxyprogesterone acetate. The ring was placed in accordance with the technique of this invention in the vaginal tract of a monkey and allowed to remain there for 63 days. At the end of this time, the residual content of the medicament in the ring was found by analysis to be 132 mg., showing that a sufficient amount for control of fertility was released from the ring during its retention within the vaginal tract.

EXAMPLE 2

Resilient devices are prepared, each to contain 2 Gm. of medroxyprogesterone acetate, 3 drops of stannous octoate as catalyst, and q.s. silastic elastomer, medical grade 382 (Dow Corning Company).

12.85 Gm. of medroxyprogesterone acetate are thoroughly mixed into 92.15 Gm. dimethylpolysiloxane elastomer, medical grade 382 (Dow Corning Company). 21 Gms. of this mixture plus 3 drops of catalyst, stannous octoate, is incorporated into each mold designed to prepare a device of an outside diameter of about 80 mm. The two halves of the mold are tightened down by the use of wing nuts and the mold is allowed to cure in an oven of 40 to 50° C. for 1 to 2 hours. Each so prepared ring weighs about 17 Gm. and contains about 2 Gm. of the medroxyprogesterone acetate. Placement of a ring in the vaginal tract of the human female supplies an effective amount of medroxyprogesterone acetate for the control of fertility by inhibition of ovulation. Measurement of basal body temperature shows that ovulation did not occur during a 4 week test period.

Similar rings are prepared with other molds designed to give outside diameters of 70 and 75 mm., respectively. Although these annular ring structures will cure at room temperature in the presence of the catalyst, for convenience and speed of handling, they are cured at temperatures of from about 40 to about 70° C.

EXAMPLE 3

Tensing means are added to the devices prepared as in Example 2 by positioning within the first half of the mold an endless helical spring having a diameter of about 8 mm. and weighing approximately 4.8 Gm. The upper half of the mold is then sealed down with the use of the wing nuts and the device compression molded in a like manner at about 45° C.

EXAMPLE 4

Polyurethane rubber-type annular devices are prepared by polymerizing two equivalents of methylene bis isocyanate, one equivalent of 3,000 molecular weight polyether triol and one equivalent of 1,4-butanediol. Parts by weight are 250 of the isocyanate, 1,000 of the triol and 45 of the butanediol. At the time of mixing, melengestrol acetate to provide 2 Gm. per individual ring is added to the mixture. The mixture of drug and elastomer is then heat cured in the mold at about 100° for 1 hour to provide resilient annular devices for placing in the vaginal tract.

EXAMPLE 5

Likewise, medicated annular devices containing an effective amount of the drug which can permeate through the polymeric substance are prepared from nylon, natural rubber, synthetic rubber, dacron, teflon, and polyethylene and are useful in the same manner in providing continued sustained medication over desired predetermined periods of times in the vaginal tract of the female mammals.

The manner and process of making and using the invention is not limited to the aforesaid examples, for the other desirable medicaments as heretofore listed can be incorporated into devices prepared from the various polymeric substances to provide sustained medication over predetermined periods of time. As aforesaid, depending upon the particular species in which the device is to be used, the size of the device will vary to provide close anatomical contact with the vaginal or like tract of the female mammals. The relationship between the daily amount of medication to provide a beneficial physiologic effect and the amount initially placed in the inventive annular device has been set forth for the individual drugs concerned, and within this concept the amount of drug is varied for the particular polymer, depending upon the permeability rate and the amount required for the physiological effect. Devices so prepared are likewise beneficially effective in providing the desired medication via the vagina.

Although an annular shaped device is preferred because of simplicity in manufacture and ease in fitting, insertion and removal, other shapes which will fit anatomically, will stay in place and still allow for ease of insertion and removal can be used, such as oval or elliptical shapes. The device does not have to be in one plane if a closer anatomical fit is desired.

I claim:

1. A medicated annular device in the form of a resilient individual ring which releases medication for systemic effects during intravaginal use in a female mammal consisting essentially of a medicament-permeable, compatible, nonabsorbable, resilient, polymeric substance and a systemically effective amount of a diffusible medicament for providing to a said female mammal sustained systemic medication for a predetermined period of time.

2. The resilient individual ring of claim 1 wherein the polymeric substance is a polysiloxane or polyurethane elastomer.

3. The resilient individual ring of claim 2 wherein the polysiloxane is convertible to a rubbery state by heat curing or by room temperature in the presence of a catalyst.

4. The resilient individual ring of claim 2 wherein the polysiloxane is an organopolysiloxane

5. The resilient individual ring of claim 4 wherein the organopolysiloxane is dimethylpolysiloxane.

6. The resilient individual ring of claim 1 which is a tubular ring.

7. The resilient individual ring of claim 1 which contains tension providing means.

8. The resilient individual ring of claim 1 wherein the diffusible medicament is effective for systemic inhibition of fertility of said female mammal.

9. The resilient individual ring of claim 5 wherein the dimethylpolysiloxane is convertible to a rubbery state at room temperature in the presence of a catalyst and the diffusible medicament is medroxyprogesterone acetate.

10. A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female mammal, which consists essentially of retainably positioning within the vaginal tract of a said female

mammal for said predetermined period of time a resilient individual ring according to claim 1.

11. A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female human, which consists essentially of retainably positioning within the vaginal tract of a said female human for said predetermined period of time a resilient individual ring according to claim 2.

12. A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female human, which consists essentially of retainably positioning within the vaginal tract of a said female human for said predetermined period of time a resilient individual ring according to claim 3.

13. A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female human, which consists essentially of retainably positioning within the vaginal tract of a said female human for said predetermined period of time a resilient individual ring according to claim 4.

14. A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female human, which consists essentially of retainably positioning within the vaginal tract of a said female human for said predetermined period of time a resilient individual ring according to claim 5.

15. A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female mammal, which consists essentially of retainably positioning within the vaginal tract of a said female mammal for said predetermined period of time a resilient individual ring according to claim 6.

A method of providing a predetermined amount of systemically effective medicament for a predetermined period of time to a female mammal, which consists essentially of retainably positioning within the vaginal tract of a said female mammal for said predetermined period of time a resilient individual ring according to claim 7.

17. A method of providing a predetermined amount of systemically effective fertility-inhibiting medicament for a predetermined period of time to a female mammal, which consists essentially of retainably positioning within the vaginal tract of a said female mammal for said predetermined period of time a resilient individual ring according to claim 8.

18. A method of providing a predetermined amount of medroxyprogesterone acetate for a predetermined period of time to a female human, which consists essentially of retainably positioning within the vaginal tract of a said female human for said predetermined period of time a resilient individual ring according to claim 9.

19. The method of claim 10 wherein the ring is removed at the end of said predetermined period of time.