United States Patent [19]

Zaffaroni

[11] 3,905,360

[45]*Sept. 16, 1975

[54] **INTRAUTERINE DEVICE FOR GOVERNING THE REPRODUCTIVE PROCESS**

[75] Inventor: **Alejandro Zaffaroni,** Atherton, Calif.

[73] Assignee: **Alza Corporation,** Palo Alto, Calif.

[*] Notice: The portion of the term of this patent subsequent to Dec. 8, 1992, has been disclaimed.

[22] Filed: **July 23, 1973**

[21] Appl. No.: **381,404**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 194,222, Nov. 1, 1971, abandoned.

[52] **U.S. Cl.** **128/130**

[51] **Int. Cl.²** **A61F 5/46**

[58] **Field of Search** 128/260, 130, 127; 424/19

[56] **References Cited**

UNITED STATES PATENTS

3,200,815	8/1965	Marguilies	128/130
3,279,996	10/1966	Long, Jr. et al.	128/272 X
3,306,286	2/1967	Ahmed	128/130
3,382,869	5/1968	Rigney et al.	128/130
3,561,438	2/1971	Canel	128/130
3,598,115	8/1971	Horne, Jr.	128/130
3,699,951	10/1972	Zaffaroni	128/130
3,777,015	12/1973	Zaffaroni	128/130

OTHER PUBLICATIONS

C. C. Chang and F. A. Kincl, "Sustained Release . . . of Steroid Hormones"; *Fertility and Sterility;* Vol. 21, No. 2; February, 1970, pp. 134–139.

F. A. Kincl et al., "Sustained Release Hormonal Preparations," *Steroids;* 11(5): May, 1968, pp. 673–680.

D. A. McGinity et al., "Effect of Local Application of Progesterone on the Rabbit Uterus," *Endrocinology;* 24: 829–832 (1939).

E. R. Garrett et al., "Evaluation, Control, and Prediction of Drug Diffusion Through Polymeric Membranes III," *J. Pharm. Sci.;* 157: 1401–1409, Aug., 1968.

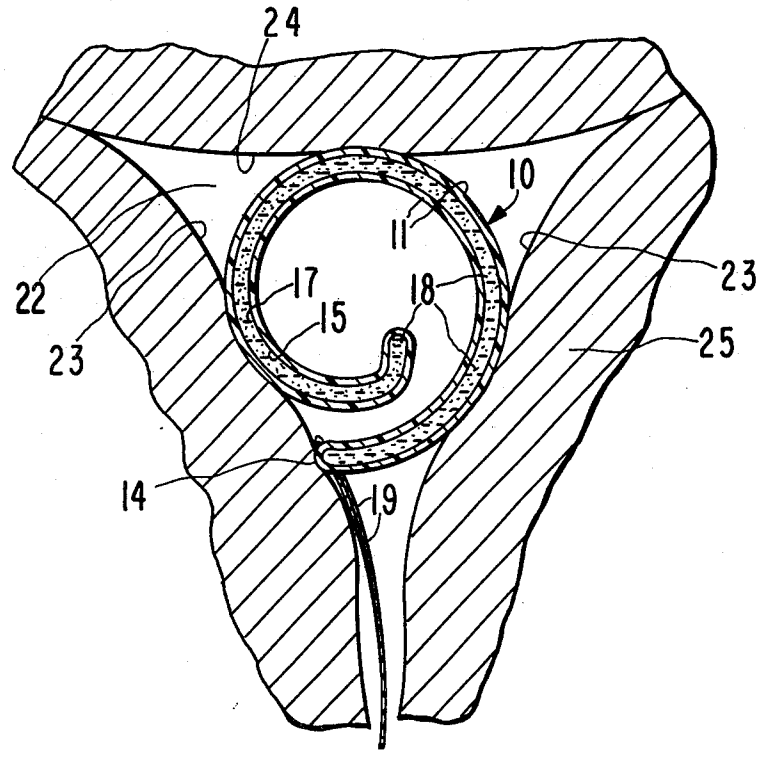
P. Kratochvil et al., "Sustained Release . . . of Various Steroids," *Steroid;* 15(4):505–511, April, 1970.

Primary Examiner—Richard A. Gaudet
Assistant Examiner—J. C. McGowan
Attorney, Agent, or Firm—Paul L. Sabatine; Edward L. Mandell; Steven D. Goldby

[57] **ABSTRACT**

An intrauterine contraceptive antifertility delivery device for administering an antifertility agent at a controlled rate for a prolonged period of time is comprised of a shaped body having two free ends with one end moving around the other end while receded from it. The body is comprised of a wall surrounding a reservoir containing an antifertility agent. The reservoir is formed of a liquid carrier permeable to the passage of the agent and in which the agent has limited solubility. The wall is formed in at least a part of a release rate controlling material permeable to the passage of the agent, but the rate of passage of the agent through the wall is lower than the rate of passage of the agent through the carrier so that release by the wall is the release rate controlling step for releasing the antifertility agent from the shaped intrauterine contraceptive antifertility delivery device.

6 Claims, 6 Drawing Figures



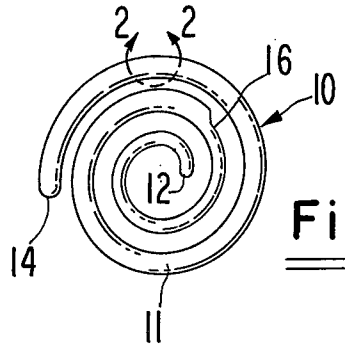


Fig.1

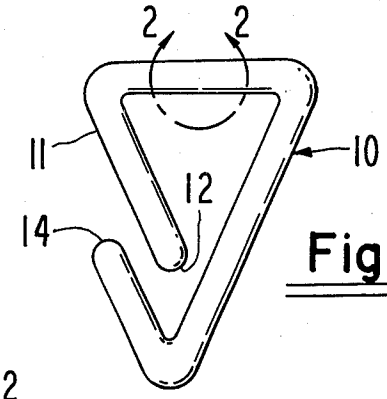


Fig.3

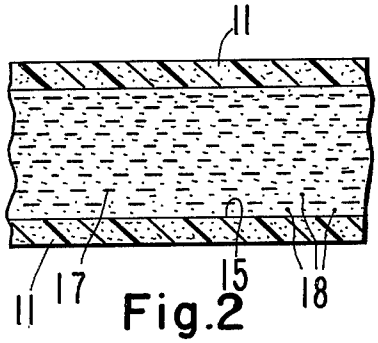


Fig.2

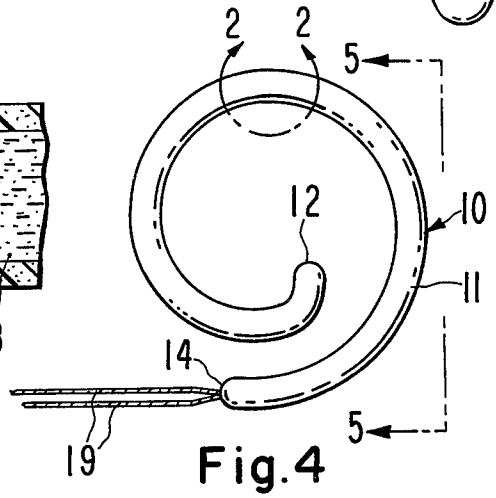


Fig.4

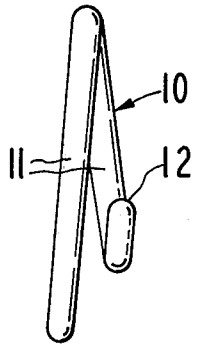


Fig.5

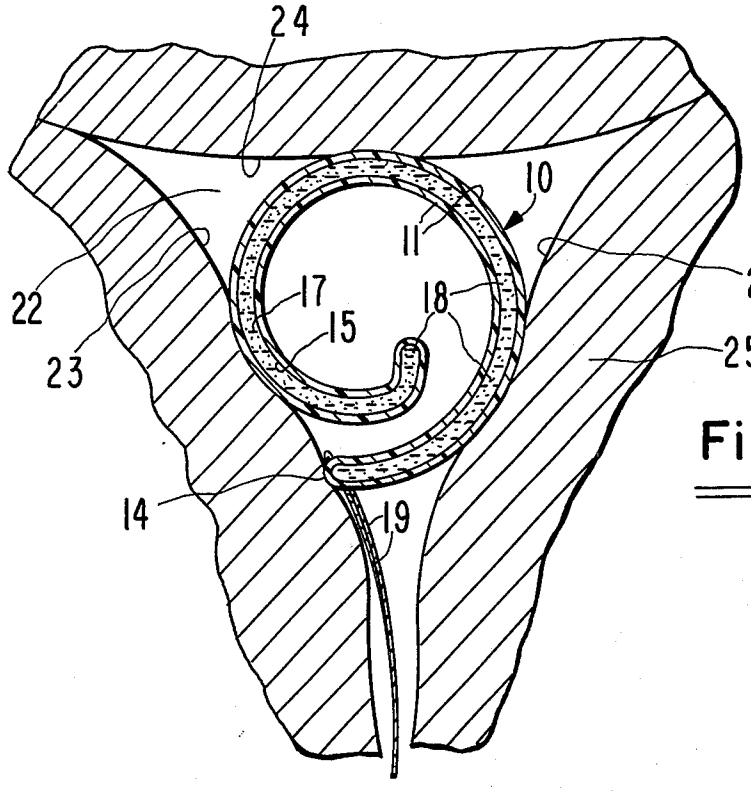


Fig.6

INTRAUTERINE DEVICE FOR GOVERNING THE REPRODUCTIVE PROCESS

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of copending patent application U.S. Ser. No. 194,222 filed on Nov. 1, 1971, and assigned to the same assignee of the present patent application, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the invention

This invention relates to a novel and useful intrauterine contraceptive antifertility delivery device for releasing an antifertility agent at a controlled rate for a prolonged period of time. The device is comprised of a wall having two free ends with one end moving around the other end while receding from it, and a reservoir defined by the inner surface of the wall. The reservoir is comprised of an antifertility agent in a liquid carrier permeable to the passage of the agent and in which the agent has limited solubility. The wall of the device is comprised in at least a part of a release rate controlling material permeable to the passage of the agent. Both the carrier and the wall are permeable to the passage of the agent, as by diffusion, but the permeability of the wall to the agent is lower than the permeability of the carrier to the agent. Accordingly, the release of antifertility agent through the wall is the release rate controlling step for releasing the agent from the intrauterine contraceptive antifertility devices of the invention.

2. Description of the prior art

Intrauterine contraception devices formed of an integral, solid filamentary body in one of several well known configurations have become an increasingly popular method of birth control. One of the most notable configurations formed in accordance with the prior art practice that is relatively inexpensive to manufacture and does not require the daily attention of the host is the open or the winding type configuration as described in U.S. Pat. No. 3,200,815. While, as with other types of prior art devices, one of the purposes of the patent is to provide an intrauterine contraceptive device that is essentially free of the disadvantages of spontaneous expulsion, pain/bleeding and pregnancies, the actual medical history of this kind of device has seen a high frequency of these disadvantages associated with their use. For example, in U.S. Pat. No. 3,457,915 the disadvantages are described as follows: "The coil of Margulies (U.S. Pat. No. 3,200,815) is more easily expelled and induces considerable bleeding." This high incident of spontaneous expulsion is also acknowledged in U.S. Pat. No. 3,353,533, and in *Report to the Pathfinder Fund*, Report No. 5, August 1970. The report also classified coil or spiral devices of the kind described in U.S. Pat. No. 3,200,815 as large or small, and listed the unacceptable disadvantages associated with the use of these devices as follows: frequency of spontaneous expulsion for a large spiral device 17 percent, for a small spiral device 28 percent, the incident of undersirable pain/bleeding for a large spiral device as 17.7 percent and for a small spiral device as 19.1 percent. The report recorded the complication of unwanted pregnancy for a large spiral device as 1.3 percent and for a small spiral device as 2.8 percent. Thus, the medical history of this device with its high incidents of spontaneous expulsion and pain/bleeding has resulted in the device being classified for its relative effectiveness as "poor." *Biomechanics of the Female Reproductive System and the Development of Intra-Uterine Contraceptive Devices* by Waibel, E. M., Thesis, 1970, Massachusetts Institute of Technology. Another serious disadvantage of the prior art spiral device is the presence of a substantially straight follower adapted to extend from the body of the spiral through the cervical canal. That is, in position, the follower passes from the uterine cavity through the cervical canal, the internal os and into the vagina. In the uterus the follower acts to stimulate uterine motility and in the canal it irritates the internal os. This stimulation and irritation contribute to the high frequency of spontaneous expulsion associated with the device. High removal rates attributed to abnormal pain/bleeding have also been reported for other open type intrauterine contraceptive devices, such as the open ring device. One other disadvantage reported for the prior art devices in *J. Am. Med. Assoc.*, Vol. 212, pages 765 to 769, 1970 is the occurrence of endometritis. Generally, this inflammatory response of the endometrium is attributed to use and presence of solid, polyethylene intrauterine contraceptive type devices. The prior art attempted to overcome those disadvantages by using several techniques. One technique used was to design and manufacture a large number of intrauterine devices of varying sizes and assorted configurations for use in all types of uterine cavities. However, this attempt has not been successful because of the large, natural variations in size and contour of the uterine cavities that makes it impossible to effectively design a device that will avoid unduly distending some uterine cavities while not being subjected to spontaneous expulsion and pain/bleeding in other uterine cavities. The use of a range of sizes also in inappropriate because of the lack of a reliable technique for determining the size of the uterine cavity which increases the possibility that the wrong choice will be made on inserting the device.

Another attempt by the prior art consists in using a capsule containing a progestational agent that is releasable therefrom in the uterus for reducing uterine contractility and expulsion of the device, and seemingly the incidents of pain/bleeding and endometritis. However, this approach, as with previous approaches, has been fraught with problems. One problem for this kind of device is its unpredictable release pattern for the progestational agent that inherently prevents it from becoming a reliable birth control device with a continued ability to overcome the mentioned disadvantages. This pattern arises from the use of a solid carrier with the progestational agent mixed therein, which carrier is often unable to self release the agent. When the agent does leave the carrier, the carrier contracts to fill the space and recedes from the inner wall of the device, so that the progestational agent is no longer available to the wall for its release from the device in a uniform and reliable pattern. A similar problem is encountered in devices filled with milled crystals of a progestational agent. *Amer. J. Obstet. Gynecol.* Vol. 101, pages 564 to 568, 1968; and, *Fertility and Sterility, Vol.* 21, pages 201 to 210, 1970.

OBJECT OF THE INVENTION

Accordingly, it is an immediate object of this invention to provide an intrauterine contraceptive device for the administration of an antifertility agent which device

overcomes the aforesaid disadvantages associated with the prior art intrauterine contraceptive devices.

Still another important object of the invention is to provide an intrauterine contraception device for releasing an antifertility agent at a controlled rate for a prolonged period of time.

Yet still another object of the invention is to provide a reliable and easily used intrauterine contraceptive device suitable for continuously administering controlled quantities of an antifertility agent within the uteri of various sizes and contours while substantially remaining free of the tribulations of the prior art.

It is also an object of the invention to provide an intrauterine contraceptive device that can be inexpensively fabricated in mass quantities and essentially painlessly and simply inserted through the normal cervical canal.

Another object of the invention is to provide an intrauterine contraceptive antifertility dispensing device with improved properties for substantially lessening the incident of expulsion, pain/bleeding and endometritis.

Other objects, features, and advantages of the invention will be apparent to those skilled in the art from the detailed description of the invention which follows, taken in conjunction with the drawings, and the accompanying claims.

SUMMARY OF THE INVENTION

This invention concerns, in its broadest aspects, a novel intrauterine contraceptive antifertility delivery device comprising a wall enclosing a reservoir. The wall has two free, closed ends with one end moving around the other while receding from it. The wall is comprised of a flexible, release rate controlling material permeable to the passage of an antifertility agent. The reservoir is defined by inner surface of the wall and it is comprised of an antifertility agent and a liquid core, which core is permeable to the passage of the antifertility agent and having limited solubility therefore. Both the wall and the liquid core are permeable to the passage of the agent, as by diffusion, but the permeability of the wall to the passage of the agent is at a lower rate than through the liquid core. Since the permeability of the wall to the passages of the antifertility agent is lower than the permeability of the liquid core to the passage of the agent, the passage of the agent through the wall is the rate determining step for releasing the agent from the intrauterine contraceptive antifertility dispensing device.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not drawn to scale, but rather are set forth to illustrate various embodiments of the invention, the drawings are as follows:

FIG. 1 is a side, elevational view of a spiral shaped intrauterine contraceptive device of the invention;

FIG. 2 is a cross-sectional view of the intrauterine contraceptive device of FIG. 1 through 2-2 depicting the reservoir of the device;

FIG. 2 is a side elevational view of an intrauterine contraceptive device of open triangular shape as manufactured according to the invention;

FIG. 4 is a side illustration of a singularly curved intrauterine device of the invention;

FIG. 5 is a perspective view of the intrauterine contraceptive device of FIG. 4 illustrated through 5—5 depicting an intrauterine contraceptive device having a spatial design;

FIG. 6 is a side, fragmentary view of a uterine cavity showing an antifertility releasing intrauterine device positioned in the uterus.

In the specification and the drawings, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further discussed elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, which are examples of various intrauterine contraceptive antifertility devices of the invention, and which examples are not to be construed as limiting the invention, one embodiment of a novel intrauterine contraceptive device is indicated in FIG. 1 by the number **10.** Intrauterine contraceptive device **10** can be generically defined as the path of a point in a plane moving around a centered point while continuously receding from it. In device **10** the points comprise two free ends **12** and **14** with end **14** receding from end **12** to define a spiral in a substantial area in one plane. Device **10** is made of a flexible material and it can be lengthened into a straight strand by the use of light force or by threading it through a hollow pencil-like instrument. While the spiral is deformable to a straight strand, it retains its memory and returns when free to define a spiral in one plane having a substantial area relative to the cross-section of a strand and preferably having a total curvature in excess of 360°. The spiral's ability to temporarily deform to a straight strand conveniently aids in its insertion into a uterus, while the spiral's memory insures its return to a spiral shape in the uterus. End **12** of spiral **10,** in this embodiment, is the inserting or leading end, and it has a slightly reduced diameter from **12** to **16** to assist the spiral's memory to start spiraling immediately on its release in the uterus. Generally, spiral **10** can be manufactured in different sizes to accomodate all uteri; for example, spiral **10** can have a radius of about 1 cm to 2.5 cm from end **12** to end **14,** and its length when deformed into a substantially straight line will be about 7 cm to 18 cm.

Spiral **10** is comprised of a wall **11** surrounding a reservoir **15,** not shown in FIG. **1,** but illustrated in FIG. **2** in cross-section through **2—2** of FIG. **1.** Wall **11** of FIGS. **1** and **2** is formed of an antifertility release rate controlling material and reservoir **15** is defined by the inner surface of wall **11.** Reservoir **15** is comprised of an antifertility carrier **17** containing an antifertility agent **18,** or a mixture of antifertility agents. Carrier **17** is a liquid carrier, a description of which is presented later in this disclosure, and it is permeable to the passage of antifertility agent **18,** as by diffusion, or by convection, or by an occurrence of both. Wall **11** is also permeable to the passage of the antifertility agent **18,** as by diffusion, but the rate of passage of the antifertility agent through wall **11** is lower than the rate of passage of the antifertility agent through the carrier **17.** In operation, carrier **17** serves as a reservoir by supplying dissolved antifertility agent **18** to wall **11** as molecules move through the carrier to bathe the inner surface of wall **11.** Antifertility agent **18** present at the antifertility carrier/wall interface dissolve in and migrate through wall **11,** ultimately reaching the outer surface of wall **11**

for release in the uterine cavity. As antifertility agent 18 leaves carrier 17, undissolved agent present in reservoir 15 dissolve in carrier 17 to maintain a constant supply of dissolved antifertility agent in the carrier for continuously supplying it at substantially the same rate to wall 11. Wall 11 operates to effectively control the rate of release of antifertility agent throughout the useful period of birth control by the device. Thus, a zero order antifertility release rate can be obtained.

Wall 11 is made from a material that can have uniform properties across all its dimensions, or it can be microporous, or it can be a material possessing both of these properties. When wall 11 is made from the former material, that is, a material that is substantially imperforate, molecules of antifertility agent 18 dissolve in and diffuse through wall 11 by the process of diffusion. When wall 11 is made from the latter material, that is, a material having microporous properties, molecules of antifertility agent 18 diffuse through a liquid phase, not shown, present in the minute pores, pinholes or cracks, for example, by absorption of uterine fluids by a hydrophilic microporous material, as by diffusion. When wall 11 is made from a material having both of these properties, antifertility agent 18 can be released by intrauterine device 10 through wall 11 by a concurrent operation of both of these mechanism, that is, by diffusion through wall 11 and by diffusion through liquid in the pores of wall 11. In the specification, the permeation mechanism of drug release through the drug release rate controlling material is generically described as "by diffusion" for both types of materials used to fabricate wall 11. The permeability of wall 11 to the diffusion of antifertility agent is always lower than the permeability of liquid carrier 17 to the diffusion of antifertility agent 18 and accordingly, passage through wall 11 thus acts as the rate limiting step for agent 18 release from intrauterine contraceptive device 10.

FIG. 3 illustrates another intrauterine contraceptive device for administering an antifertility agent according to the invention. In FIG. 3, device 10 is comprised of a wall 11 with an end 14 moving around an end 12 to define a substantial area in one plane. Device 10 is designed with rounded, non-traumatising ends and inner corners of a triangular configuration, and it is made from a material having a high elastic memory for preserving its shape. Thus when device 10 is straightened into a strand for insertion into a uterine cavity, it will return to its original shape therein. Device 10 can be fabricated into assorted sizes and thicknesses for adaption to a variety of uteri by having its dimensions correspond to those of uteri having a cross-sectional area of from 4.5 cm^2 to 11 cm^2.

Intrauterine contraceptive device 10 of FIG. 3 is comprised of a wall 11 permeable to the passage of an antifertility agent as, by diffusion. Wall 11, as seen through section 2—2 of FIG. 2 surrounds a reservoir 15 comprised of a carrier medium 17 containing an antifertility agent 18. Carrier medium 17 can be a liquid, gel, sol or the like, and a description thereof is presented later in the disclosure. The carrier medium confined in the reservoir serves several purposes for effectively releasing drug from the device. First, it is permeable to the passage of an antifertility agent so that it can migrate to wall 11. Secondly, the carrier contacts and bathes the inner surface of wall 11 for facilitating antifertility agent transfer from the carrier to the wall so that molecules can dissolve in and migrate through the wall to the outer surface thereof. Thirdly, the carrier acts as a constant source of antifertility agent as it has a limited, or varying degree of solubility for the antifertility agent or a mixture of agents. The carrier is formulated to contain both dissolved and undissolved antifertility agent and to act as a constant source of antifertility agent, because as dissolved agent transfers from the carrier to the wall, undissolved agent dissolves in the carrier to insure a constant and uniform supply of agent until essentially all the agent has been released by the device. This mechanism of continually replenishing the agent enables the device to achieve a uniform release rate for the device throughout its use.

Wall 11 of the intrauterine contraceptive device 10 is formed of a release rate controlling material to continuously meter the flow of an effective amount of an agent from the reservoir for release within the uterus. Wall 11 thus has two memory functions; first, it has an elastic memory for retaining the shape of the device, and secondly the material forming the wall has a memory for releasing the agent at a controlled rate throughout the device's history. The rate of drug release through wall 11 of FIG. 3 is lower than the passage of the agent through the carrier, so that the former is the rate controlling step for agent release from the device.

FIG. 4 is an intrauterine contraceptive device 10 for use in administering an antifertility agent within a uterus. Device 10 is shaped like an open ring with a pair of free ends 12 and 14 respectively. End 12 of device 10 is the lead or inserting end and it bends inwardly towards the center of the ring. The band acts as the device's memory for curving a straightened device to its original, predetermined shape. Device 10 measures about 3 cm in diameter and it has a double thread 19 attached to its trailing end 14. Device 10 is easily removed from the uterus by pulling on threads 19. Threads 19 can be any suitable material, for example, nylon, surgical thread having a thickness of about 0.005 to 0.010 inches and the like. Device 10 of FIG. 4 is substantially planar with a curvature of about 360°, or larger, for example, a multiple curvature of 540°, 720° or the like, and it is manufactured with a reservoir containing a liquid carrier and an antifertility agent as described and seen through cross-section 2—2 of FIGS. 1, 2 and 3. The invention also provides intrauterine contraceptive antifertility devices, not shown, that possess the features of the open ring device of FIG. 4 in combination with the features of the spiral device of FIG. 1, for example a device comprised of a small spiral like leading end and an open ring trailing end, a device comprised of part spiral and part open ring with the part spiral occupying a small area than the area occupied by the open ring, and the like.

FIG. 5 is an intrauterine contraceptive device 10 similar to device 10 of FIG. 4 as seen through 5—5 of FIG. 4, except that in FIG. 5 device 10 is substantially spatial while in FIG. 4 device 10 is substantially planar. In FIG. 5, device 10 is comprised of a hollow body having a leading end 12 and a trailing end, not shown, integrally formed with wall 11. Wall 11 surrounds a reservoir, not shown, formed on the hollow space defined by the inner surface of wall 11 as described for FIG. 2 through cross-section 2—2 of FIGS. 1, 2 and 3. In device 10, the trailing end can extend upwardly and around or it can curve upwardly and outwardly around the leading end in a configuration to form a coil, a helix, or the like spatial device.

In FIG. 6 there is graphically depicted an intrauterine contraceptive antifertility delivery device **10** prepared according to the spirit of the invention. Device **10** is of open ring configuration and it is adapted to be located within the uterine cavity **22** and it contacts the sides **23** as well as the fundus uteri **24** of uterus **25.** A thread **19** is attached to the trailing end **14** of device **10** for manually removing device **10** from uterus **25.** Device **10** is comprised of a wall **11** surrounding a reservoir **15.** Reservoir **15** is comprised of a liquid core **17** containing an antifertility agent **18.** Liquid core **17** is permeable to the passage of antifertility agent **18,** as by diffusion or convection, and it possesses limited solubility for agent **18.** Wall **11** is formed of an antifertility release rate controlling material permeable to the passage of an antifertility agent, but the rate of agent **18** passage through the wall is lower than its rate of passage through the liquid core. Thus, wall **11** of device **10** acts as the rate limiting carrier for releasing antifertility agent **18** for the device to the uterine cavity **22** at a constant and uniform rate for producing the desired result.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the practice of the present invention, it has now been found that the intrauterine contraceptive device of this invention provides many important advantages over the prior art. One advantage of the device is the ease of construction of the antifertility delivery device by standard manufacturing techniques into devices acceptable to the uterine cavity. A more important advantage of the claimed intrauterine contraceptive device is to provide devices having a reservoir containing a liquid carrier or a mixture of liquid carriers permeable to the passage of an antifertility agent and having limited solubility for an agent or a mixture of agents, and where the carrier simultaneously releases drug and dissolves replacement drug to maintain a constant supply of drug for release by the intrauterine contraceptive device.

Another important advantage of the invention resides in the intrauterine contraceptive device's memory to effectively control the rate of release of an antifertility agent from the device by providing a zero order rate of agent release and also this memory ability to act in concert with the device's memory to substantially maintain the device's shape throughout the major portion of the device's medical history. Another important advantage of the intrauterine contraceptive devices of this invention is their improved property for uniformly and continually releasing antifertility steroid agents while simultaneously decreasing the incident of spontaneous expulsion, menorrhagia, metrorrhagia and endometritis and decreasing menstrual flow.

The above advantages and objects are achieved by the unique construction and operation of the intrauterine contraceptive device and its ability to transfer antifertility agent to a recipient. In construction, the device can be viewed as a single unit constructed device comprising two structures acting in combination for effective antifertility administration to a host. One structure pertains to a wall comprising the device and formed of an antifertility release rate controlling material permeable to the passage of the agent and the other structure relates to a reservoir comprising a liquid carrier phase formed of a material permeable to the passage of an antifertility agent and having limited solubility for the agent. The materials forming the wall and the carrier phase comprising the device are chemically and structurally different within a single device and the rate of antifertility release through the wall is lower than the rate of passage in the carrier phase.

These two structures, comprising the unit intrauterine contraceptive device, operate to effectively transfer antifertility agent from the device by first transferring the agent from the carrier to the wall, and secondly, by transferring the agent through the wall to a uterus. The transfer of agent through the wall can occur by two different processes or transfer mechanisms. These transfer processes are the diffusion of an agent through a uniform material, and by diffusion of an agent through the media present in the micropores of a material, as hereinafter described. Thus, for example, an agent can be transferred from the carrier to the wall and then through the wall by diffusion to the recipient, or the agent can be transferred from the carrier to the wall and then through the media in micropores of the wall by diffusion to the recipient. With the contraceptive devices of this invention, an antifertility agent can be transferred by using a combination of these mechanisms for transferring the agent through the wall. Thus, by fabricating devices having different kind of walls made from different materials, the device can provide for transfer of an agent through the wall by either diffusion in a substantially homogenous material or by diffusion through the media in a microporous wall. The wall of the delivery device is made from a material that has a lower agent release rate than the rate of passage of the agent through the carrier phase to ensure that release kinetics of the device are controlled by the release rate of agent through the wall. Thus, by choosing the wall, a zero order release of an antifertility agent or a time release pattern of an agent to the body site can be achieved.

In the diffusion process, the wall is formed of an antifertility agent release rate controlling material that is permeable to the agent to permit passage of the agent by diffusion through the material at predetermined rates. In this process, the agent dissolves and equilibrates in the wall surface, and then diffuses in the direction of lower chemical potential. At the second boundary equilibrium is again established. When the boundary conditions on both sides of the wall are maintained constant, a steady state flux of the agent will be established which can be described by Fick's Law of Diffusion. The rate of passage of the agent through the wall material is generally dependent, in the case of diffusion, on the solubility of the agent therein as well as on the thickness of the material. This means that selection of appropriate materials for fabricating the wall will be dependent on the particular agent to be used. By varying the composition and thickness of the wall, the dosage rates per area of the device can be controlled for this material acts to meter the diffusion of the agent from the reservoir. In the devices of this invention, the materials comprising the wall are chemically and/or structurally different than the material comprising the carrier of the reservoir. The carrier of the reservoir is permeable to the passage of the agent, but the rate of diffusion or passage through the wall is lower than the rate of diffusion or passage through the carrier, so that the rate of passage of the agent through the wall is the rate release controlling step for the device. Thus, through this invention, devices of the same surface

area, functioning by diffusion, can give different dosages of the agent by varying the characteristics of wall to give controlled administration of the agent.

In the devices of the invention, when the wall is formed from a release rate controlling microporous material that is permeable to the agent, the agent transfer mechanism is by diffusion through a medium contained in the micropores of the material at a controlled and predetermined rate. That is, in this material, the rate of passage or the rate of agent release through the wall is governed by diffusion of the agent through a diffusive medium present in the pores, microholes and cracks of the material forming the wall. The diffusive medium, in one embodiment, is a liquid phase comprised of a solution, a colloidal solution, a suspension, or a sol, and the solution can be polar, semi-polar or non-polar. In these diffusive media, the agent can have different degrees of solubility, such as fully soluble, partially soluble and the like, to act in cooperation with the material for achieving a controlled release rate.

The diffusive medium can be added to the microporous material by methods well known to the art, for example, by immersion of the material in a bath containing the medium to let the medium partially fill or fully saturate the micropores of the material. Another method for charging the micropores with a diffusive medium is to first add to the reservoir a diffusive medium, or a mixture of diffusive media so that the medium can flow from within the reservoir into the pores and remain therein to permit diffusion of later added agent, but not its solubilizing limited carrier, to pass therethrough. The media suitable for the immersion purpose are those well known to the art such as water, glycerin, ethylene glycol, propylene glycol, castor oil, olive oil, alcohols of 2 to 10 carbon atoms, halogenated hydrocarbons having 2 to 20 carbon atoms, aldehydes, and ketones having 4 to 10 carbon atoms, syrups, and the like. Additionally, the medium can be emulsifying and suspending agents such as methyl cellulose mixed with water, mixtures of propylene glycol monostearate and oils, gum tragacanth and water, assorted waxes and the like. Representative mediums are set forth in *Remington's Pharmaceutical Science*, pages 246 to 269 and 1338 to 1380, 1970, published by Mack Publishing Company, Easton, Pa.

In another embodiment, the medium can be added to the pores and cracks of the material forming the wall by locating the wall in a fluid environment, for example, by contacting the device with a body tissue, for example, the mucous membranes of the uterus, that can make available its intracellular and/or extra/cellular fluid for subsequent transfer into the micropores of the wall for functioning as a medium for the drug. In another embodiment, the pores can be filled with plasticizer by immersing the wall in a plasticizer solvent composition, and removing the solvent in vacuo after the filling of the pores. Exemplary plasticizers suitable for employment of the present purpose are the commercially available plasticizers conventionally used for the manufacture of polymeric materials such as diethyl adipate, di-isobutyl adipate, di-n-hexyl adipate, di-iso-octyl adipate, di-n-hexyl azelate, di-2-ethylhexylazelate, ethylene glycol dibenzoate, acetyl tri-n-butyl citrate, epoxidized soy bean oil glycerol monoacetate, diethylene glycol dipelargonate propylene glycol diluarate, iso-octyl palmitate, triphenyl phosphate, and the like.

The materials comprising the wall are chemically and/or structurally different than the materials comprising the carrier. Both of the materials are permeable to the passage of the antifertility agent but the rate of flow through the wall is lower than the rate through the carrier. Thus, the rate of passage of the agent through the wall is the rate release controlling step for the device. Generally, for the practice of this invention, the ratio of the agent release rate through the carrier of the reservior to the agent release rate through the wall should be from 100:1 to 2:1 and preferably from 10:1 to 2:1.1 Of course, the invention is not limited to these release rates as the invention comprises lower or higher release rates from the carrier and lower and higher rates through the wall with the release rate of the wall lower than the release rate of the carrier. Thus, the invention provides that devices of the same surface area, activated by diffusion, can give different dosages of a drug by varying the characteristics of the wall material to give controlled administration of an antifertility agent; *Encyclopedia of Polymer Science and Technology*, *Vol.* 9, pages 794 to 807, 1968.

For either of the above discussed mechanisms, diffusion through a homogenous material, or diffusion through a medium present in the micropores and cracks of a material, the transfer or rate of release of the antifertility agent through the wall is at a lower rate than the rate of release of the agent from the carrier of the reservoir for administration to the receptor site. Thus, the passage of the agent through the wall is the release rate controlling step for the agent delivery system. In addition, because the reservoir serves to transfer antifertility molecules to all areas of the wall, the wall of the delivery device housing the reservoir remains substantially at the thermodynamic activity corresponding to that of the agent until substantially all of the agent has been released from the reservoir. Ordinarily, one would expect migration of antifertility agent from the reservoir to cease when sufficient agent has entered the wall to establish an equilibrium; however, when the delivery device is in situ, molecules are continuously removed from the outer surface of the wall. For optimum results, the rate of release of the agent through the wall should be less than the rate of clearance of migrated agent from the external surface of the device. This ensures that the agent administration rate is dependent on the rate of release of the agent through the wall which can be controlled, rather than upon clearance of the agent from the device in vivo, which can vary. Thus, in contrast to previously proposed intrauterine contraceptive delivery devices, the rate of release of the agent from the device of the invention can remain essentially constant until the intrauterine contraceptive device has substantially completed its useful function.

The term "reservoir" as used in the specification and the accompanying claims generally refers to a "carrier" or to a "medium containing the antifertility agent", that constantly bathes the inner surface of the release rate controlling wall and supplies agent thereto. That is, the reservoir is comprised of a carrier material containing dissolved agent, and/or undissolved agent, and/or mixture of both, and it is a material that is permeable to the passage of the agent as by diffusion or convection. The carrier medium used for the purpose of the invention is a liquid, and it can be inorganic or organic, and of naturally occurring or synthetic origin. Exam-

ples of carriers comprised within the terms liquid are, for example, solutions, immiscible liquids, emulsions, gels, sols, jellies, colloids, oils, syrups, suspensions, dispersions, liquid pre-cured polymers, liquid polymers, liquid plasticizers, liquid thixotropic agents, polar solvents, semipolar solvents, nonpolar solvents, liquid-like mediums, mixtures thereof, and the like. Further, for the purpose of this invention, the terms liquid and the examples thereof are deemed as functional equivalents and they can be generically termed "liquid core".

The carrier medium comprising the reservior, also has in addition to the properties described supra, limited solubility for the contained antifertility agent or for a mixture of agents. By limited solubility is meant that the agent is soluble in given amounts in the carrier, that is, it comprises varying concentrations of the agent dissolved in the carrier. Essentially, there is also an excess amount of undissolved drug present in the carrier. These varying limited solubility concentrations include solubilities such as, soluble, sparingly soluble, slightly soluble, vary slightly soluble, and almost practically insoluble. Generally, on a weight basis at 25°C, the amount of and design of the device, the particular agent, the length of time the device is used, and the rate of release of desired agent from the reservoir. That is, there is no critical upper limit on the amount of undissolved agent incorporated in the reservoir, since it serves as a reserve source of agent for replacing released agent by dissolving in the carrier to make the agent continually available from the carrier to the wall during the history of the device, or until the device is no longer used. The lower limit will depend on the activity of the particular agent and the time span of its release from the device. Generally, the amount of undissolved drug initially present in the reservoir will range from about 90 percent by weight to about 99.9 percent by weight, of the total amount of agent present in the reservoir.

The materials suitable for fabricating the wall of the intrauterine device are generally those materials capable of forming walls, with or without micropores, through which the agent can pass at a controlled rate of release by diffusion. Such materials are referred the agent dissolved in a carrier that is termed a soluble carrier is about 1 part of agent to about 10 to 25 parts of carrier, the amount of agent dissolved in a carrier that is sparingly soluble for the agent is 1 part of agent to about 25 to 100 parts of carrier, from 100 to 1000 parts of carrier for 1 part of agent when the agent is slightly soluble in the carrier, from b **1000** to 10,000 parts of carrier for 1 part of agent when the agent is very slightly soluble in the carrier, and from 10,000 to 15,000 parts of carrier for 1 part of agent in a carrier that is almost practically insoluble for the drug. Hence, the term limited solubility comprises a range of solubility of the agent in a carrier of 1 part of agent to about 10 to 15,000 parts of carrier on a weight basis at 25°C. The above ranges are set forth to aid in defining the invention, and they should not be considered as limiting as other ranges at higher or lower temperatures are embraced within the above presentation are also included herein. The amount of undissolved antifertility agent incorporated in the reservoir will vary depending on the type of materials to in this specification and the appended claims as "release rate controlling materials". Suitable materials for forming the wall are naturally occurring or synthetic materials, preferably materials that are biologically compatible with body fluids, and uterine tissues, and essentially insoluble in body fluids with which the device will come in contact. The use of rapidly dissolving materials or materials highly soluble in natural body fluids is to be avoided since dissolution of the wall of the device would affect the constancy of the drug release, as well as the capability of the system to remain in place for certain uses for prolonged periods of time.

Exemplary naturally occurring or synthetic materials suitable for fabricating the wall are release rate controlling materials such as poly(methylmethracrylate), poly(butylmethacrylate), plasticized poly(vinylchloride), plasticized nylon, plasticized soft nylon, plasticized poly(ethylene terephthalate), natural rubber, poly(isoprene), poly(isobutylene), poly(butadiene), poly(ethylene), poly(tetrafluoroethylene), poly(vinylidene chloride), poly(acrylonitrile), cross-linked poly(-vinylpyrrolidone), poly(trifluorochloroethylene), poly (4,4'-isopropylidene diphenylene carbonate), and the like. Also, by way of non-limiting example, copolymers such as ethylenevinylacetate, vinylidene chloride acrylonitrile, vinyl chloride diethyl fumarate and the like. Examples of other materials include silicone rubbers, especially the medical grade poly(dimethylsiloxanes), and siliconecarbonate copolymers; modified insoluble collagen, cross-linked insoluble poly(vinylalcohol), cross-linked partially hydrolyzed insoluble poly(vinylacetate), and surface treated silicone rubbers as described in U.S. Pat. No. 3,350,216. Other polymeric membranes that are biologically compatible and do not adversely affect the drugs can be used.

Additionally, other materials permeable to the passage of the anti-fertility agent that are suitable for the present purpose include copolymers such as acrylonitrile dithioglycidol, acrylonitrile ethylene oxide, poly(-vinyl butyral) comprised of 11 percent to 45 percent free hydroxyls, anisotropic permeable microporous membranes of ionically associated polyelectrolytes, the microporous polymers formed by the coprecipitation of a polycation and a polyanion as described in U.S. Pat. Nos. 3,276,589; 3,541,005; 3,541,006; 3,546,142; and the like; treated aliphatic polyamide membranes as in U.S. Pat. Nos. 2,071,253; 2,966,700; 2,999,296; and the like; vinylidene chloride vinyl chloride copolymer 40/**60** and 10/**90**; vinyl chloride acrylonitrile copolymer 80/**20**, **75/25**, **50/50** and the like; vinylidene chloride acrylonitrile copolymer 60/**40** and 12/**88**; water insoluble natural gums, and the like. Also, materials such as regenerated cellulose diacetate, cellulose triacetate, poly(urethanes), poly(arylenes), poly(carbonates) and the like. Materials having a pore size of several hundred microns or larger, or down to several angstroms or smaller. For example, the wall can comprise regenerated insoluble, nonerodible cellulose, poly(electrolytes) with a pore size of 7 to 50A, epoxy resins, poly(olefins), poly(vinylchlorides) with a pore size of about 50A or less to 150 microns or larger as conventionally made by leaching out incorporated salts, soap micelles, starch or the like materials to give a microporous membrane. Also, the materials that can be used include those materials having homogenous properties and microporous properties, such as cross-linked gelatinous membranes; and the like.

The carrier used to form the reservoir containing the anti-fertility agent is comprised of materials of naturally occurring or synthetic origin, of the inorganic or

organic types that do not adversely affect the agent, or the mixture of agents contained therein and which are permeable to the passage of the agent. Generally, the carrier used does not substantially diffuse from the reservoir, but if the carrier does diffuse from the reservoir, for example, if the carrier is an aqueous medium, it would be replaced by a corresponding amount of medium diffusing inward from the exterior of the device when the device is positioned in an aqueous type environment. Representative liquid carriers include ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, dipropylene glycol, thiodiethylene glycol, ethylene glycol monomethyl ether, ethylene glycol mono-n-butyl ether, ethylene glycol diethyl ether, propylene glycol mono-propyl ether, liquid polyethylene glycols having a molecular weight of 200, 300, 400 and 600, 1,3-butylene glycol; solvent system like ethyl acetate-ethyl alcohol-water 10:83:7; isobutyl acetate-isobutyl alcoholwater 24:46:30; mixed binary liquid systems such as methanol:water, ethyl alcohol:water, n-amyl alcohol; ethyl acetate; mixed tertiary liquid systems such as n-butyl acetate-butyl alcohol-water 27:27:46; esters such as liquid methyl propionate, methyl isobutyrate, butyl stearate, dibutyl fumarate; fats and oils of plant, animal and marine origin such as almond oil, babassu oil, corn oil, eucalptus oil, cottonseed oil, olive oil, palm oil, peanut oil, rapeseed oil, soybean oil, tung oil, whate oil, herring oil; saturated, unsaturated, straight and branched chain liquid fatty acids such as caproic, lauric, arachidic, oleic, linoleic, etc.; liquid prepolymers; emulsions of the single phase and two phase types such as oil in water, water in oil, lipophilic-liquid-inhydrophilic-liquid emulsions with or without suspending ingredients; emulsions of castor oil in aqueous solution of pigskin gelatin, emulsion of gum arabic, water and ethyl cellulose, halogenated hydrocarbons having 2 to 10 carbon atoms, aldehydes and ketones having 4 to 10 carbon atoms, syrups, and the like. Other carriers include silicone oil, medical oil, sterile water; saline; dextrose; dextrose in water or saline; condensation products of castor oil and ethylene oxide combining about 30 to about 35 moles of ethylene oxide per mole of castor oil; liquid glyceryl triester of a lower molecular weight fatty acid; oils with emulsifiers such as mono- or di-glyceride of a fatty acid, or a phosphatide, e.g., lecithin, and the like; aqueous media in the presence of a suspending agent for example, sodium carboxymethylcellulose; sodium alginate; poly(vinylpyrrolidone); and the like, alone, or with suitable dispensing agents such as lecithin; polyoxyethylene stearate; and the like, carriers such as acetamide; N,N-dimethyl acetamide, N-(2-hydroxyethyl) acetamide, and the like. The carrier can also contain adjuvants such as preserving, stabilizing, or wetting agents, and the like.

The rate of release of an agent through various materials can easily be determined by those skilled in the art by standard procedures. In this manner, particular materials used as the device wall as the drug release rate controlling barrier for release of drug from the reservoirs can be selected. Various techniques, such as the transmission method, the sorption desorption method, and the like, can be used as measurers of permeability. One technique that has been found to be eminently well suited is to cast or hot press a film of the material to a thickness in the range of 2 to 60 mils. The film is used as a barrier between a rapidly stirred (e.g., 150 r.p.m.) saturated solution of the drug and a rapidly stirred solvent bath, both maintained at constant temperature (typically 37°C). Samples are periodically withdrawn from the solvent bath and analyzed for drug concentration. By plotting the agent's concentration in the solvent bath versus time, the permeability constant P of the material is determined by Fick's First Law of Diffusion.

$$\text{Slope of plot} = \frac{Q_1 - Q_2}{t_1 - t_2} = P\,\frac{AC}{h}$$

wherein

Q_1 = cumulative amount of drug in solvent in micrograms at t_1

Q_2 = cumulative amount of drug in solvent in micrograms at t_2

t_1 = elapsed time to first sample i.e. Q_1

t_2 = elapsed time to second sample i.e. Q_2

A = area of membrane in cm^2

C = initial concentration of drug

h = thickness of membrane in cm.

By determining the slope of the plot, i.e.

$$\frac{Q_1 - Q_2}{t_1 - t_2}$$

and solving the equation using the known or measured values of A, C, and h, the permeability P constant in cm^2/time of the material for a given drug is readily determined.

Using the above technique, the permeability constant P of the antifertility progesterone from isotonic solution through different materials into isotonic solution at 37°C was found to be:

Membrane	Permeability Constant (cm^2/hr)
Poly(dimethylsiloxane)	8.0×10^{-2}
Poly(ethylene)	4.7×10^{-4}
Ethylene vinyl acetate copolymer 9% vinyl acetate	3.8×10^{-3}
Silicone-polycarbonate copolymer, General Electric MEM 213	12.6×10^{-3}

Using the above technique and data to design a device of the invention of release the antifertility agent progesterone, one would employ poly(ethylene) as the release rate controlling material as the wall if a slow rate of release is desired, and the cured poly(dimethylsiloxane) membrane as the wall if a faster rate of release is desired. If a faster rate of release than the rate of release through poly(ethylene) but slower than the rate of release through poly(dimethylsiloxane) is preferred for progesterone, either the copolymer ethylene vinyl acetate or the silicone polycarbonate can be used as the release rate controlling material. The poly(ethylene), the poly(dimethylsiloxane), the ethylene vinyl acetate copolymer and the silicone-polycarbonate copolymer are commercially available products. The poly(dimethylsiloxane) used above is commercially available Silastic 340 of the Dow Corning Co., and the poly(ethylene) is low density with a melt index of 0.85. These examples and like examples can be used to determine the rate of drug release through different drug

release controlling materials by easily ascertained standard techniques known to the art as recorded in *J. Pharm. Sci.*, Vol. 52, pages 1145 to 1149, 1963; ibid. Vol. 53, pages 798 to 802, 1964; ibid. Vol. 54 pages 1459 to 1464, 1965; ibid. Vol. 55, pages 840 to 843 and 1224 to 1239, 1966; *Encyl. Polymer Sci. Technol.*, Vol. 5 and 9, pages 65 to 82 and 794 to 807, 1968; the references cited therein, and the like.

The rate of solubilization, or the rate at which the antifertility agent will go into solution is quantitatively governed by physico-chemical principles. For an example, a particle of an agent dispersed in a solvent is surrounded by a thin layer of solvent having a finite thickness *l* in cm. This layer is considered as an integral part of the agent and it is characteristically referred to as the "stagnant layer". The stagnant layer remains a part of the surface of the agent, moving wherever the agent moves. Using Fick's First Law of Diffusion, the rate of solution is the rate at which a dissolved agent diffuses through the stagnant layer for supplying agent to the reservoir's inner wall. The driving force behind the movement of the agent through the stagnant layer is the difference in concentration of the agent, C_1, in the stagnant layer at the surface of the agent and the concentration C_2 on the farthest side of the stagnant layer. The difference in concentration C_1–C_2 determines the rate at which agent is solubilized in the carrier. Hence, if the carrier on the farthest side contains its optimum concentration because of a low release by the agent release rate controlling wall, the rate of solubilization of new agent will be low. Correspondingly, as agent leaves the carrier, new agent is solubilized to establish a steady state within the carrier.

The rate of diffusion of the antifertility agent in a solubilizing limiting carrier is broadly determined by measuring the rate an agent transfers from one chamber through a sintered glass filter of known pore size and thickness into another chamber at atmospheric pressure and room temperature about 25°C, or body temperature 37.5°C, and calculating from the obtained data the agent's transfer rate. The method is carried out by adding to a first conical flask equipped with a ground glass stopper and a stirring bar, a measured amount of carrier and simultaneously, the agent in the same carrier is added to a second conical flask similarly equipped while keeping the level of the carrier in the two flasks the same. Next, the flasks are stirred, and samples drawn at various time intervals for analysis. The measured rate of agent transport through the sintered glass filter, and the concentration difference of the agent in the two flasks is then calculated. These procedures are known to the art in *Proc. Roy. Sci. London*, Ser. A, Vol. 148, page 1935; J. Pharm. Sci., Vol. 55, pages 1224 to **1229**, 1966; and references cited therein. The diffusion coefficient of an agent can also be experimentally determined by using the above apparatus and references, or similar apparatus and procedures as described in *Diffusion in Solids, Liquids and Gases*, by W. Jost, Chapter XI, pages 436 to 488, 1960, Revised Edition, Academic Press Inc., New York.

Also, according to Fick's Law, the rate of an agent's solution is directly proportional to the area of the agent, A in cm^2, as exposed to carrier and inversely proportional to the length of the path through which the dissolved agent molecule must diffuse. Then, the rate of solution of the agent is given by

$$R, = DA/l\ (C_1 - C_2)$$

wherein R is the rate of solution, D is a proportionality constant called diffusion coefficient in cm^2/sec, and C_1, C_2, and *l* are as previously defined. See *Remington Pharmaceutical Science*, 14th Ed., pages 246 to 269, **1970**, Mack Publishing Company.

The solubility of the anti-fertility agent in the release rate controlling material comprising the wall of a device broadly is determined by preparing a saturated solution of a given antifertility agent and ascertaining, by analysis, the amount present in a definite area of the material. For example, the solubility of the agent in the wall is determined by first equilibrating the wall material with a measured saturated solution of the agent at a known temperature and pressure, for example 37°C and one atmosphere. Next, agent is desorbed from the saturated wall material with a suitable solvent for the agent. The resultant solution for the agent then is analyzed by standard techniques such as ultraviolet, visible spectrophotometry, refractive index, polarography, electrical conductivity and the like, and calculating from the data the concentration, or solubility of the agent in the material.

The solubility of an agent in a liquid core can be determined by various art known techniques. One method consists in preparing a solution, for example, a carrier plus agent and ascertaining by analysis the amount of agent present in a definite quantity of the carrier. A simple apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature and pressure, for example 37.5°C and one atmosphere. The carrier and agent are placed in the tube and stirred by means of a motor driven rotating glass spiral. After a given period of stirring, a definite weight of the carrier is analyzed and the stirring continued for an additional period of time. If the analysis shows no increase of dissolved substance after the second period of stirring, the ressults are taken as the degree of solubility of the agent in te carrier. Numerous other methods are available for the determination of the degree of solubility of an agent in a liquid carrier. Typical methods used for the measurement of solubility are chemical analysis, measurement of density, refractive index, electrical conductivity, and the like. Details of various methods for determining solubilities are described in United States Public Health Service Bulletin No. 67 of the Hygienic Laboratory; *Encyclopedia of Science and Technology*, Vol. 12, pages 542 to 556, 1971 McGraw-Hill, Inc.; *Encyclopaedic Dictionary of Physics*, Vol. 6; pages 545 to 557, 1962, Pergamon Press, Inc.; and the like.

Using the procedures and formulas above described, one skilled in the art can design an intrauterine contraceptive antifertility dispensing device according to the invention by ascertaining the properties of the wall and carrier forming material and then fabricating the intrauterine contraceptive device by selecting a carrier in which the agent has limited solubility and which is permeable to the agent but at a higher rate than the permeability of the wall, For example, by using the permeability coefficient, which is determined by using the above procedures and formulas, and which permeability coefficient is defined as the product of the diffusion coefficient, D_W, of the agent in the wall and a distribution coefficient, K, which is a ratio of the solubility of the agent in the wall to the solubility of the agent in the sat-

urated solution, the selection of materials for forming the wall and the carrier can be made for making aa device according to the invention. For purposess of comparing the permeability of the wall to that of the liquid carrier, it is convenient to define the permeability as follows: $P_w = PC = D_wS_w$ wherein P, C and D_w have the meaning as above described and S_w is the solubility of the agent in the wall. The permeability of the carrier to the agent can similarly be defined as $P_c = D_cS_c$ wherein D_c and S_c are the diffusion coefficient and the solubility of the agent in the liquid core carrier. The solubility, S_c, can be determined by cited methods. The diffusion coefficients of the antifertility agent in liquid carriers will be in the range of 10^{-6} to 10^{-5} cm^2/sec. The diffusion coefficient of the antifertility agent in the wall will be in the range of 10^{-10} to 10^{-8} cm^2/sec. Thus, a selection of carrier materials such that $P_c > P_w$, preferably $P_c \geq 5\ P_w$, is ascertained for preparing an intrauterine contraceptive anti-fertility delivery device. The symbols used herein have then conventional meaning, for example, the symbol ">" means greater than and the symbol " ≥ " means greater than or equal to.

In the specification and the accompanying claims, the phrase "anti-fertility agent" and the term "agent" are used interchangeably and they broadly include progestational substances, estrogenic substances and mixtures thereof, that have anti-fertility properties. These substances can be of naturally occurring or synthetic origin and they generally possess a cyclopentanophenanthrene nucleus. The term progestational substance as used herein embraces "progestogen" which term is used in the steroid art to generically describe steroids possessing progestational activity, and the former also includes "progestins", a term widely used for synthetic steroids that have progesteroid effects. The active anti-fertility agent that can be used to produce the desired effects in female mammals, including humans and primates that are able to maintain the reproduction process, include without limitations: pregn-4-ene-3,20-dione (also known as progesterone); 19-nor-pregn-4-ene-3,20-dione; 17-hydroxy-19-nor-17α-pregn-5(10)-ene-20-yn-3-one; dl-11β-ethyl-17-ethinyl-17-β-hydroxygon-4-ene-3-one; 17α-ethinyl-17-hydroxy-5(10)-estren-3-one; 17α-ethinyl-19-norestosterone; 6-chloro-17-hydroxypregna- 4,6-diene-3,20-dione; 17β-hydroxy-6α-methyl-17-(1-propynyl)androst-4-ene-3-one; 9β,10α-pregna-4,6-diene-3,20-dione; 17-hydroxy-17α-pregn-4-en-20-yne-3-one; 19-nor-17α-pregn-4-en-20-yne-3β,17-diol; 17-hydroxypregn-4-ene-3,20-diene; 17-hydroxy-6α-methylpregn-4-ene-3,20-dione; 17-hydroxy-pregn-4-ene-3,20-dione; 17-α-hydroxyprogesterone; mixtures thereof, and the like.

The term estrogenic and estrogenic anti-fertility agents as used herein also includes the compounds known as estrogens, and the metabolic products thereof that possess anti-fertility properties or are converted to active anti-fertility agents in the preselected biological environment. Exemplary estrogenic compounds include β-estradiol, β-estradiol 3-benzoate, 17-β-cyclopentanepropionate estradiol, 1,3,5(10)-estratnene-3,17β-diol dipropionate, estra-1,3,5(10)-triene-3,17-β-diol valerate, estrone, ethinyl estradiol, 17-ethinyl estradiol-3 methyl ether, 17-ethinyl estradiol-3-cyclopentoether, estriol, mixtures thereof, and the like.

Additionally, the above progestational and estrogenic agents can be in the form of their pharmacologically accepted derivatives, such as their hydroxy or keto groups can be in a derivative form for the present purpose. The progestational or estrogenic derivative used should easily convert to the parent agent upon its release from the device by biological activities such as enzymatic transformation, pH assisted hydrolysis in uteri, tissue and metabolism and the like. The derivative can also be used to control the solubility of the agent in the liquid core and to assist in metering the agent from the device. Suitable derivatives include without limitation, esters with pharmaceutically acceptable acids such as acetate, glucuronate, benzoate, propionate, butyrate, valeroate, hexanoate, heptanoate, maleate, citrate, succinate, tartrate, fumarate, malate, ascorbate, sulphate, phosphate and the like; eithers such as lower alkoxy-tetrahydropyran-yl, unsubstituted tetrahydropran-yl, silyl moieties, trifluoromethyloxy, cyclopentyl enol ethers and other functional groups such as ureido, and the like.

The degree of solubility of various progestational and anti-fertility agents in various liquid cores, is ascertained by using the above techniques. Typical examples of solubilities are as follows: 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione acetate practically insoluble in water; 17β-hydroxy-6α-methyl-17-(1-propynyl)-androst-4-3n3-3one slightly soluble in acetone; 9β,10α-pregna-4,6-diene-3,20-dione slightly soluble in distilled water; 17-hydroxy-17α-pregn-4-en-20-yn-3-one slightly soluble in alcohol and slightly soluble in vegetable oil, 19-nor-17α-pregn-4-en-20-yne-3β-17-dioldiacetate sparingly soluble in fixed oil, 17-hydroxy-6α-methylpregn-4-ene-3,20-dione acetate sparingly soluble in methanol, 17-hydroxy-19-nor-17α-pregn-4-en-20yn-3-one sparingly soluble in vegetable oil, 17-β-estradiol sparingly soluble in vegetable oil, ethinyl estradiol soluble in various vegetable oils, and the like.

The amount of agent present in the reservoir, whether dissolved, partially dissolved or undissolved is generally non-limited and it is an amount equal to or larger than the amount of an agent that on its release from the device is effective for being about the agent's anti-fertility effect. For example, the amount of agent present in the reservoir of an intrauterine device when the device is used for a predetermined period of time to achieve an anti-fertility effect in a potential child-bearing worman is for pregn-4ene-3,20-dione for a year supply wherein a year is 400 days, and the rate of release from the device is 25 μg/day is 10 mg in the reservoir, at the same rate of release for 2 years a reservoir supply of 20 mg and for 3 years 30 mg. If the rate of release for the same progestational agent is 100 μg/day and the length of the year is as before, the reservoir concentration for 1 year is 40 mg, for 2 years 80 mg and for 3, years 120 mg. The amount of progestational agent present in the reservoir for a 1 year, 2 year and 3 year device is 80 mg, 160 mg and 240 mg respectively when the rate of release is 200 μg/day. Of course, for shorter periods or longer periods smaller amounts or larger amounts will be present in the reservoir, and the amount will also vary relative to the degree of activity of the progestational agent. Generally, the intrauterine contraceptive device will contain from about 0.1 mg to 10 g of a progestational agent for releasing it at a controlled rate of from about 5 micrograms to 300 micrograms of agent, or larger amounts per day. Of course,

devices containing different amounts of agent for use for different time periods such as week, month, and the like, are also readily made by the invention.

The reservoir comprising the liquid core and the agent is fabricated by standard techniques. For example, in one embodiment the liquid can be mixed with the agent in solid, semi-solid, or liquid forms at the time of mixing, and then distributed therethrough by conventional methods, such as ballmilling, calendering, stirring, shaking, rollmilling, and the like. The liquid core is then charged into the lumen formed from release rate controlling material and sealed therein. In another embodiment the liquid core and the agent are mixed and then charged into a highly permeable tube that is positioned within a drug release rate controlling material. Alternatively, the tube can be coated with the release rate material, or a prepolymer can be case around the tube and finally cured into a release rate controlling material. The wall material forming the antifertility dispensing device and having the reservoir contained therein can be formed to a given intrauterine contraceptive device's design by molding, casting, pressing, extruding, drawing, rotational molding, compression and transfer molding, or like standard processes of manufacture. also, depending on the material used to form the wall, a monomers may be cured at this stage of manufacture. The ability to design and shape the wall into a device of highly reproducible shapes of controllable composition, readily results in fabrication of intrauterine contraceptive devices with controlled characteristics and thus overcomes a significant disadvantage of previously described devices. Other standard procedures, as described in *Modern Plastics Encyclopedia*, Vol. 46, pages 62 to 70, 1969, well known to those skilled in the art can be used to fabricate the drug delivery device of the invention.

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, drawings, and the accompanying claims.

EXAMPLE 1

An intrauterine anti-fertility dispensing device shaped like a spiral and comprising a reservoir comprised of a liquid core containing an anti-fertility agent and permeable to the passage of the agent is surrounded by a wall of an anti-fertility release rate controlling material permeable to the agent is manufactured as follows: first, a reservoir comprised of a liquid core consisting of 11% by weight of progesterone and 10% by weight of barium sulfate in a mixture of 3 parts by weight of Dow-Corning Silastic 382 elastomer resin liquid silicone oil and 1 part by weight of Dow-Corning 360 medical grade fluid silicone oil are throughly mixed in a standard laboratory v-blender to yield a liquid core. The progesterone is sparingly soluble in the liquid co re. Next, an aliquot of the liquid core is injected into a section of medical grade polyethylene tubing having an outside diameter of 0.110 inches and an inside diameter of 0.070 inches and the ends of the tubing heat sealed with a standard, hand heater. The filled polyethylene tubing, about 10 cm in length, then is placed into the lower half of a two piece spiral shaped mold, the upper half is placed thereon, and the mold electrically heated to yield a spiral shaped anti-fertility device. The device will release 25 to 30 micrograms of progesterone per day for controlling fertility in an adult woman weighing from 35 kg to 90 kg.

EXAMPLE 2

An intrauterine contraceptive anti-fertility administrating device having the shape of an open circle with one end extended around the other end and receded from it with the wall of the circle formed of a release rate controlling material permeable to the passage of the agent and surrounding a reservoir comprised of a liquid core containing the agent is fabricated as follows: first, a section of medical grade polyethylene tubing is washed with methanol for at least 72 hours, rinsed with water, and then air dried. Next, a core material is prepared as a homogenous mixture consisting of 11% by weight of progesterone, N.F., 10% by weight of barium sulfate, U.S.P., 19.5% by weight of Dow-Corning 360 Medical Fluid, a water white polydimethylsiloxane fluid, and 59.25% by weight of Dow-Corning Silastic 382 Medical Grade Elastomer, a fluid polysiloxane polymer by thoroughly blending the ingredients for about 10 to 12 hours. Next, the core material is injected into precut lengths of the washed polyethylene and the devices formed by placing the filled polyethylene in a mould having a female portion containing a cavity which corresponds to the shape of the device. When the mold is closed, the male portion of the mold forms the top of the device. The clearance between the male member and the female member is sufficiently small, so that closing the molds and applying heat thereto forms the predetermined device. The device contains 20 mg of progesterone for releasing it at a rate of 25 μg/day for 2 years.

EXAMPLE 3

An intrauterine contraceptive anti-fertility device comprised of a release rate controlling wall permeable to the passage of an anti-fertility agent and surrounding a reservoir comprised of an agent and a liquid core for releasing the agent is manufactured as follows: a liquid carrier is prepared by intimately contacting and blending in a rotating mill 25% by weight of progesterone and 10% by weight of barium sulfate with a mixture comprising 3 parts by weight of Dow-Corning 382 elastomer resin, low molecular weight prepolymer liquid silicone and 1 part by weight of Dow-Corning 360 medical fluid silicone oil to yield a liquid carrier. The liquid carrier is permeable to the progesterone and the progesterone is sparingly soluble therein. Next, the liquid carrier is injected into a length of ethylene vinyl acetate copolymer tubing comprised of 9% by weight of vinyl acetate and having an inside diameter of 0.075 inches and an outside diameter of 0.110 inches. The ends of the tubing are heat sealed and the tubing is then formed into a device in a heated mold. The device is shaped in open circle design with one end extended around the other, and also receded and raised above it. The device releases 90 to 100 micrograms of progesterone per day.

EXAMPLE 4

Following the procedure set forth in Example 1, a reservoir comprised of a liquid core containing aqueous poly(vinyl pyrrolidone) and progesterone housed within a poly(ethylene) barrier is prepared by generally following the example. The progesterone is sparingly soluble in the aqueous poly(vinyl pyrrolidone) and

both the poly(vinyl pyrrolidone) and the poly(ethylene are permeable to the passage of the steroid, but the rate of passage is lower for the poly(ethylene). The poly-(ethylene) barrier has a thickness of 50 microns, and it releases about 33 micrograms per square centimeter per day of progesterone to a progesterone receptor site.

EXAMPLE 5

An intrauterine contraceptive anti-fertility delivery shaped like a spiral device and comprised of a liquid carrier of aqueous carboxymethylcellulose containing progesterone laminated between two poly(ethylene) half tubes, sealed at their perimeters, and having a thickness of 50 microns is prepared according to the procedure of Example 1. The steroid is sparingly soluble in the carrier, and both the carrier and the poly-(ethylene) are permeable to the passage of the steroid, with the rate of passage for the former higher than the rate of passage of the latter. The use of this device results in a controlled rate of release of progesterone over a prolonged periodd of about 1 year at the rate of 33 micrograms per sq. cm. per day.

EXAMPLE 6

Repeating the general procedure as described in Example 1, an intrauterine contraceptive device is made of a permeable, release rate controlling wall of ethylene vinylacetate copolymer of 91% ethylene and 9% vinyl acetate of about 50 microns thick and surrounding a reservoir comprised of progesterone in water is made by substituting the ingredients of this example for those set forth above. A drug delivery device made according to this procedure will release about 230 micrograms of progesterone per sq. cm. per day.

EXAMPLE 7

The general procedure as described in Example 1 is followed in this example except that the anti-fertility steroid is β-estradiol. The device has a release capacity of 50 μg/day for a 100 to **130** lb. woman in need of fertility control.

In Table 1, immediately below, the rate of release obtained with an intrauterine contraceptive device shaped like an open ring and having a wall of ethylene vinyl acetate copolymer with 9% vinyl acetate and a reservoir comprising liquid core of silicone oil and progesterone is measured and compared with the rate of release obtained for an intrauterine device shaped like a "T" with the upright of the T made of cured silicone tubing filled within its lumen with dry, powdered progesterone. The release rates for these delivery devices is determined by agitating each device in separate isotonic saline baths at 37°C, and determining the optical absorbance of the test saline solution at 248 nm using 10 cm cells in a double-beam ultraviolet spectrophotomer with isotonic saline in the reference cell. The concentration of progesterone in the test solution is determined by comparing the absorbance value at 248 nm with the values obtained at 248 nm for various known progesterone concentrations in isotonic saline. The results are expressed in micrograms per day for devices of like surfaces. In the table, Run 1 and Run 2 indicate the release rate obtained for duplicate devices.

TABLE 1

RELEASE RATES OF INTRAUTERINE DEVICES

Time Days	Release Rate μg/day Open Ring — liquid core Run 1	Run 2	Release Rate μg/day "T" device — dry Run 1	Run 2
Start			687	727
1			485	497
2	139	131	415	415
3	134	118	330	320
9			215	134
10	97	93		
15			173	121
18	99	95		
20	88	85		
21			193	150
24	100	82		
30	104	89		
31	100	88		
35	99	90		

It will be understood to those versed in the art in the light of the present specification, drawings and accompanying claims that the invention makes available to the art both a novel and useful intrauterine contraceptive anti-fertility delivery device for administering an anti-fertility agent to produce the desired effect; and, that the rate of release from the device can be controlled to produce these effects, while simultaneously lessening or overcoming the undesirable effects frequently associated with the prior art methods. It will be further understood to those versed in the art that different embodiments of this invention can be made without departing from the spirit and the scope of the invention. Accordingly, it is to be understood that the invention is not to be construed as limited, but it embraces all equivalents inherent herein.

I claim:

1. An intrauterine device for the administration of an antifertility agent at a controlled rate for a prolonged period of at least one month, said device consisting essentially of;

a. a reservoir comprising dissolved antifertility agent and undissolved replacement antifertility agent selected from the group consisting of progestational and estrogenic steroids in a liquid core material permeable to the passage of agent, the replacement agent present in an amount sufficient to maintain the dissolved agent in an amount substantially equal to the amount of dissolved agent originally present in the core during said prolonged period, said reservoir surrounded by;

b. a shaped wall having two free closed ends with one end extended around the other end and receded from it with a radius of about one centimeter to two and one-half centimeters to define the device adapted for insertion and placement within a uterus, said wall formed of a release rate controlling permeable to the passage of agent with the permeability of the wall to the agent lower than the permeability of the core to the agent; and,

c. said device when placed in the uterus releasing dissolved agent from the reservoir in a contraceptively effective amount by metered passage through the wall, the agent so released being replaced by the continuous dissolving of replacement agent in the core material.

2. An intrauterine device according to claim **1** wherein the end extended around the other end formed a spiral and the wall is formed of a member selected

from the group consisting essentially of homogenous and microporouss materials, and the liquid core is an oil.

3. An intrauterine device according to claim 1 wherein the end extended around the other end formed an open ring with the wall formed of a member selected from the group consisting essentially of homogenous and microporous materials, and the liquid core is an oil.

4. An intrauterine device according to claim 1 wherein the liquid core is a mixture consisting essentially of an oil, a prepolymer and the agent.

5. An intrauterine device according to claim 1 wherein the substantially spatial device is formed by the one end extended around the other end, receded and raised above, and the liquid core is a mixture consisting essentially of an oil, a prepolymer and the agent.

6. An intrauterine device according to claim 1 wherein the end extended around the other end and receded from it formed a member selected from the group consisting of a substantially planar and spatial device.

* * * * *