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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 10-135-578

TÍTULO SOLICITADO: SISTEMA INTRAUTERINO PARA SUMINISTRAR
UNA SUSTANCIA Ó PRODUCTO TERAPÉUTICO
DIRECTAMENTE DENTRO DEL ÚTERO DE UN
PACIENTE Y MÉTODO PARA SU FABRICACIÓN.

PUBLICACIÓN: Gaceta 631 de 22/08/2011, número de publicación
1060.

SOLICITANTE: BAYER SCHERING PHARMA OY.

APODERADO: JESÚS MARIA MÉNDEZ BERMÚDEZ.

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN.

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, sociedad constituida y vigente de conformidad con las leyes colombianas, con domicilio en Cali, Valle, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente **10-135-578**, por no cumplir con lo dispuesto por los artículos 14, 16, 18 y 20 (d) de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **LAFRANCOL S.A.**, legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

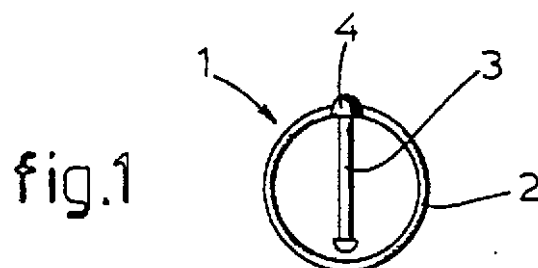
III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite, que se refiere a un sistema intrauterino para una inserción durante un tiempo prolongado en una cavidad uterina, incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

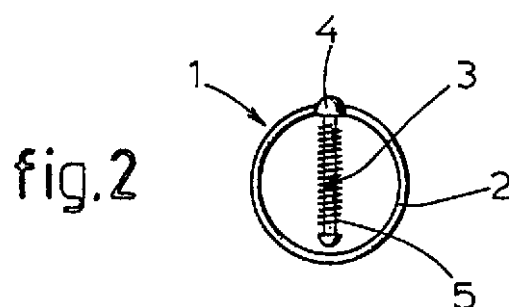
En primer lugar, y ante la reivindicación textual de un método para suministrar una sustancia terapéuticamente activa a un mamífero hembra, específicamente en la reivindicación 17, es importante indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."*

En segundo lugar, y refiriéndonos específicamente a la carencia de novedad y nivel inventivo de la solicitud, podemos citar varias anterioridades en donde se exponen dispositivos intrauterinos que comprenden en esencia las mismas características técnicas reveladas por la solicitud colombiana en cuestión, veamos:

La patente de los Países Bajos NL 8601570 publicada el 18 de enero de 1988 revela:



(...)



(...)

La patente europea EP 0872751 publicada el 28 de octubre de 1998 revela:

The present invention relates to a pharmaceutical product for application to the uterus mucosa, which carries a drug comprising a peptide having the luteinizing hormone releasing hormone (hereafter referred to only as 'LH-RH') action, an LH-RH antagonist or the like on an intrauterine contraceptive device (hereafter referred to as 'IUD') and is adjusted to be able to administer the drug over a prolonged period of time while taking a contraceptive measures by being fitted in the uterus or the like.

(...)

A means for controlled release which employs a container provided with pores in its peripheral wall instead of the foregoing semi-permeable membrane.

A closure-type means for controlled release which comprises a container accommodating a drug and covered with a closure formed from a biodegradable or soluble high polymer, and

A pulse-type means for controlled release which comprises a plurality of small chambers arranged in series and accommodating a drug, a partition wall of each chamber being made of a biodegradable or soluble high polymer.

(...)

Example 3

500 mg of leuporelin acetate was dissolved in 50 g of water to prepare an aqueous solution. Meanwhile, 4.5 g of copolymer of butyric and glycolic acids having a molecular weight of about 18,500 (PBGA) was dissolved in 10 g of dichloromethane. This solution was added to the above aqueous solution to prepare a W/O emulsion.

Next, this emulsion was vacuum dried in a casting mold and compression molded to a desired shape of IUD. The obtained pharmaceutical product for application to the uterus mucosa continued to release leuporelin acetate in the uterus over a period of at least one month.

(...)

A pharmaceutical product 1 for application to the uterus mucosa according to a second embodiment of the present invention as shown in Fig. 2 comprises a drug 2 enclosed in a diffusion controlled film 5 made of a high polymer material such as, for example, a copolymer of ethylene and vinyl acetate and then supported by silicon elastomer 6 or the like to be formed into an IUD 4.

The drug 2 carried on the IUD 4 gradually passes through the diffusion controlled film 5 and diffuses to be absorbed through the uterus mucosa. Since the transmission and diffusion of the drug decrease after a predetermined period of time has elapsed, this IUD 4 is removed from the uterus and a new IUD 4 is fitted if the administration is continued.

(...)

40 The IUD 4 may take the shape of the modification shown in, for example, Fig. 3 or other shapes as far as they don't cause any abnormality to the living body when fitted.

(...)

FIG. 1

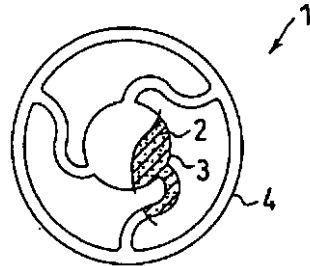


FIG. 2

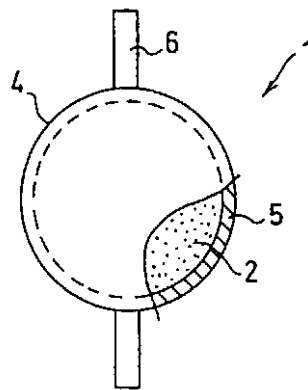
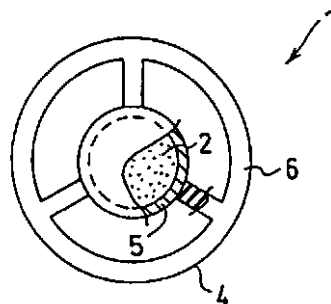
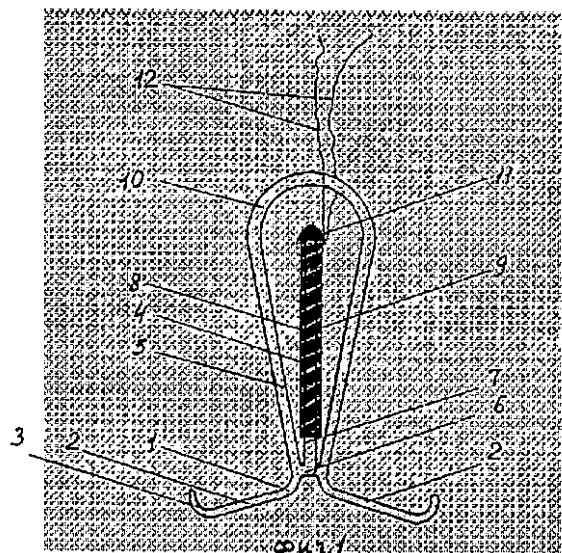
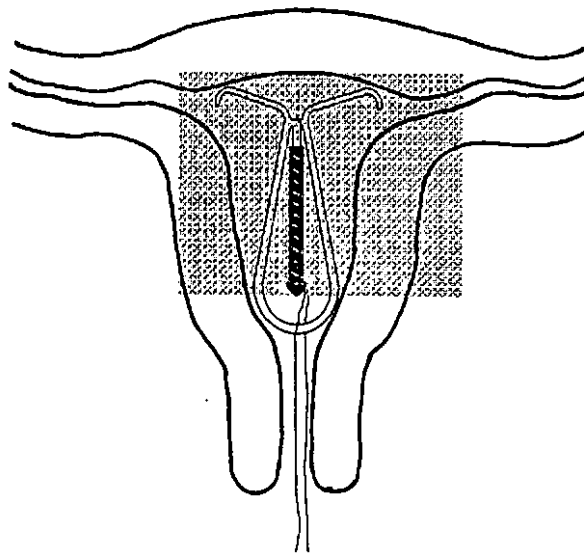


FIG. 3



La publicación internacional WO 9629026 publicada el 26 de septiembre de 1996 revela:





(...)

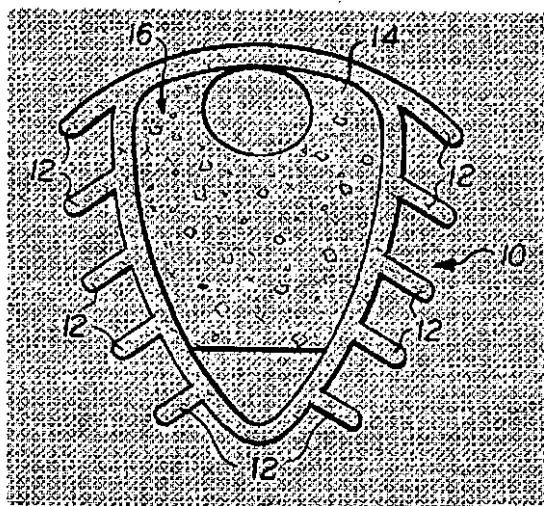
(57) Abstract

The proposed intrauterine contraceptive device comprises a horizontal strip (1) with two legs (2) at least one of which has a curved end (3); a coil (4); and a loop (5) joined to the horizontal strip (1) and provided with a thickened base (6). The legs (2) of the straight section of the horizontal strip (1) are configured at an acute angle to the horizontal plane and symmetrically in relation to the vertical axis; both are provided with curved ends (3), the curve being in the form of a circular section, the coil (4) takes the form of a polyethylene strip and is situated inside the loop (5) on an anchoring element (7) connected to the base (6) of the horizontal strip (1) and coaxial with the vertical axis of symmetry of the intrauterine contraceptive device. The legs (2) of the horizontal strip (1) are at an angle of between 5 and 30° to the horizontal. The coil (4) is provided with a coating (8) of refined copper which is applied to the outer surface of the polyethylene strip by plasma deposition. The lower part of the loop (5) is springy and is at least twice the length of the anchoring element (7). The free end of the anchoring element (7) is provided with a spherically curved section (11) and serves as the base for securing locating threads (12).

La patente americana US 3834378 publicada el 10 de septiembre de 1974 revela:

An intrauterine device composite is provided which comprises a plastic matrix, such as a copolymer of ethylene and vinyl acetate, having a particulate material selected from the group consisting of metals such as copper, zinc, silver, platinum, or cadmium, and metal salts dispersed within the matrix. The particulate preferably includes both a metal and a salt, such as a sulfate, thereof, although solely a salt or a metal particulate may be utilized. In addition, a radio-opaque particulate such as barium sulfate is preferably also dispersed within the composite. The particulate material preferably comprises between 0.1% to 50% by weight of the composite, and the matrix preferably has a water permeability or rate of water vapor transmission of at least 0.3 grams/100 square inches/24 hours/mil at 25° C.

(...)



(...)

Preferably, the intrauterine device 10, as shown and preferred in the FIGURE, is a composite formed of a plastic material such as a copolymer of ethylene and vinyl acetate, polyvinyl acetate, polyethylene, polypropylene, polyvinyl chloride, nylon, or silicone rubber, such as disclosed in co-pending patent application, Ser. No. 775,729. Most preferably, the plastic material is a copolymer of ethylene and vinyl acetate, such as UE 632, manufactured by United States Industrial Chemical Corporation, which contains 13-15% vinyl acetate by weight. As shown and preferred, in addition, the

(...)

Preferably, the intrauterine device 10, as shown and preferred in the FIGURE, is a composite formed of a plastic material such as a copolymer of ethylene and vinyl acetate, polyvinyl acetate, polyethylene, polypropylene, polyvinyl chloride, nylon, or silicone rubber, such as disclosed in co-pending patent application, Ser. No. 775,729. Most preferably, the plastic material is a copolymer of ethylene and vinyl acetate, such as UE 632, manufactured by United States Industrial Chemical Corporation, which contains 13-15% vinyl acetate by weight. As shown and preferred, in addition, the plastic matrix of which the intrauterine device 10 is preferably constructed, has dispersed therein particulate material. Most preferably, the particulate is dispersed throughout the plastic matrix. The particulate material preferably includes a metal and a salt thereof, although it may comprise solely a metal or a salt. By way of example, metals which are satisfactory for purposes of the present invention are copper, zinc, silver, platinum, or cadmium. Most preferably, copper particulate is preferred. By way of example, metal salts which are satisfactory include salts of copper, zinc, silver, platinum, or cadmium. The salt is preferably a sulfate, carbonate, nitrate, acetate or phosphate. Most preferably, the salt is a sulfate of the metal particulate.

(...)

In addition to the presence of a particulate or a metal and a salt thereof in the preferred composite, a radio-opaque particulate material may also be dispersed

(...)

In order to form the intrauterine device composite, conventional techniques may be utilized. Once such preferred conventional technique requires intimately admixing particles of the desired plastic with finely ground particulate metal and particulate metal salts at a sufficiently high temperature for a sufficient time in order to obtain a homogeneous-like phase. The resultant impregnated plastic having the particulate material dispersed throughout is then molded under heat and pressure in a conventional manner to readily form any desired configuration such as the shield configuration 10 illustrated in the FIGURE.

(...)

1. An intrauterine device having a body structure encompassing an area which can be contained within a normal uterus, made from a composition enabling flexing to conform to the uterine cavity comprising a plas-

tic matrix, and a particulate material comprising at least one non-magnetic metal selected from a group consisting of copper, zinc, silver, platinum and cadmium, and at least one salt of a metal selected from said group, said particulate material being dispersed within said plastic matrix; and said particulate material comprising between 0.1% to 10% by weight of the composition of said device.

2. An intrauterine device having a composition in accordance with claim 1, wherein said particulate material comprises a metal and a salt of said metal.

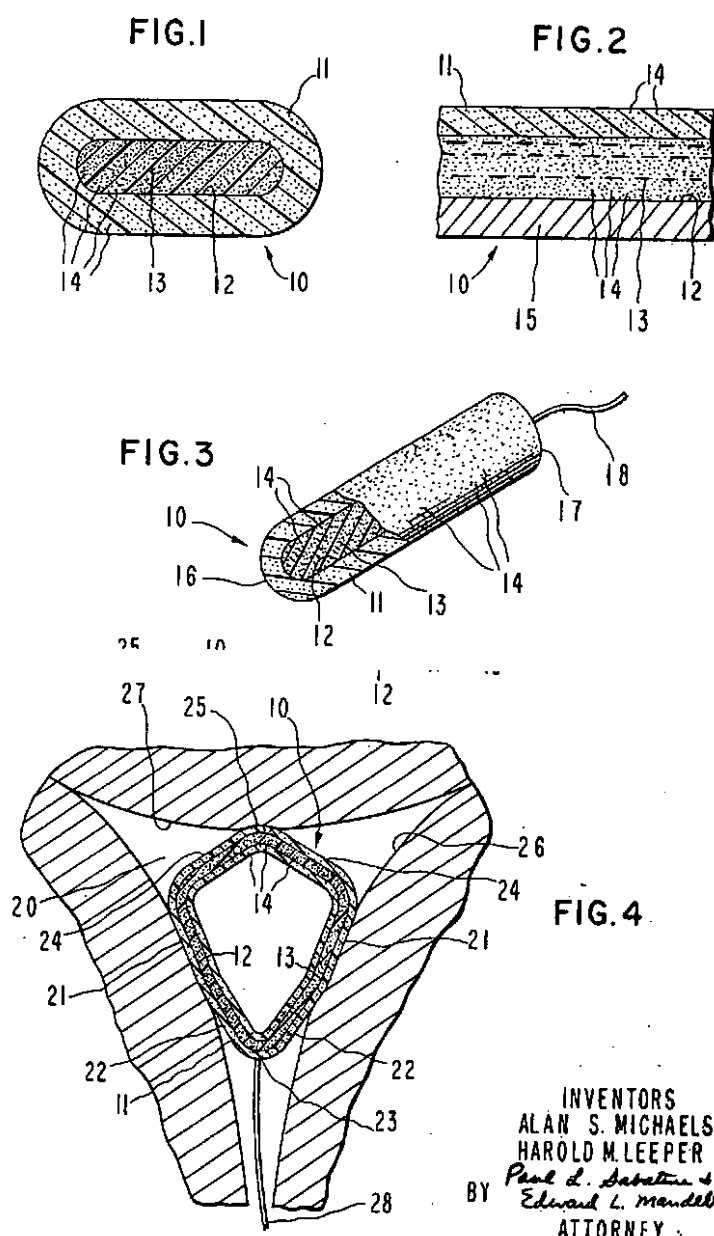
(...)

5. An intrauterine device having a composition in accordance with claim 1, wherein said material comprising the plastic matrix is a copolymer of ethylene and a vinyl monomer material.

Finalmente, la patente americana US 3938515 publicada el 17 de febrero de 1976 revela:

A polymeric wall adapted to release drug at a controlled rate for a prolonged period of time from a reservoir comprising a drug and a carrier which is permeable to the drug and saturated therewith during said prolonged period of time, to a body environment or a drug receptor site, the wall comprising a mixture of a polymer which is biologically compatible with said environment or site and maintains its integrity while in contact therewith, has a glass transition temperature between ambient temperature and 150°C, a crystallinity of 5% to 95%, or is rubbery, and is permeable to the drug but at a rate less than that of the carrier and as a minor constituent a polymeric additive such as a polyester prepared from a glycol and a dibasic acid, polyethylene glycol, chlorinated polyethylene or copolymers of ethylene and vinyl esters or vinyl esters or vinyl halides, the amount of additive being sufficient to make the permeability of the wall to the drug substantially different than the permeability of the polymer to the drug but still less than the permeability of the carrier to the drug.

(...)



(...)

permeability to drugs, and (3) polymers which are rubbery, and whose glass transition temperatures are below room temperature, i.e. about 20°C. In the latter category these rubbery polymers may be thermoplastic or thermosetting in nature. Such polymers are commercially available and include polyvinyl chloride, polyvinylidene chloride, polyvinyl fluoride, polyvinylidene fluoride, polyvinyl acetate, polyvinyl butyral, polystyrene, cellulose acetate, cellulose nitrate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, polyurethane, butadiene/acrylonitrile copolymer, chlorinated natural rubber, styrene/butadiene copolymer, ethylene/propylene copolymer, ethylene/vinyl acetate copolymer, ethylene/vinyl chloride copolymer, polyethylene, polypropylene and polyalkyl acrylates in which the alkyl group is of 2 to 4 carbon atoms.

(...)

The term "reservoir" as used in the specification and the accompanying claims generally refers to a "drug", a "drug carrier" or to a "medium-containing drug", that constantly bathes the inner surface of the drug release rate controlling wall and supplies drug thereto.

(...)

The wall material forming the device and having the reservoir contained therein can be formed to a given drug 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 tubes, rods, discs, films, rings and other highly reproducible shapes of controllable composition, readily results in fabrication of drug delivery devices with controlled characteristics and thus overcomes a significant disad-

(...)

Como se puede apreciar claramente en las anterioridades expuestas, las características correspondientes a sistemas intrauterinos que comprenden un deposito y un marco cerrado y flexible, de forma poligonal circular, ovalada, angular, triangular o elíptica, en donde el marco es un polímero flexible; en donde el depósito consiste de un núcleo envuelto en una capa de polímero; en donde además dicho dispositivo intrauterino tiene elementos que mejoran su detección dentro del útero como por ejemplo un metal inerte particulado que sirve como material radio-opaco; y en donde finalmente dicho dispositivo puede ser obtenido por moldeo por inyección, extrusión o compresión; corresponden, todas estas, a características técnicas descritas con anterioridad para dispositivos del mismo tipo.

En otras palabras, y teniendo en cuenta la información expuesta con anterioridad, existen los suficientes lineamientos técnicos, para qué una persona medianamente versada en la formulación de productos farmacéuticos, pudiese obtener un dispositivo intrauterino con todas las mismas características que las reivindicadas por la solicitud colombiana en trámite.

Por todo lo anterior, le solicito Señor Superintendente, que analice los argumentos citados con el rigor y detenimiento habituales y que decrete, además de la negación de la solicitud en comento, el archivo del citado expediente.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20 literal d) de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Copia de todos los documentos citados en el acápite de Fundamentos de la Oposición.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Lafranco S.A.
2. Poder para actuar (copia auténtica reposa en el expediente 08-095-718).
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta

ciudad. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

United States Patent [19]

Lerner et al.

[11] 3,834,378

[45] Sept. 10, 1974

[54] INTRAUTERINE DEVICE

[75] Inventors: Irwin S. Lerner, Greenwich, Conn.;
Hugh J. Davis, Baltimore, Md.;
Thad J. Earl, Defiance, Ohio

[73] Assignee: A. H. Robins Company,
Incorporated, Richmond, Va.

[22] Filed: Feb. 26, 1973

[21] Appl. No.: 336,066

Related U.S. Application Data

[63] Continuation of Ser. No. 88,538, Nov. 12, 1970,
abandoned.

[52] U.S. Cl. 128/130, 424/14

[51] Int. Cl. A61F 5/46

[58] Field of Search 128/130, 131; 424/14, 16,
424/22

[56] References Cited

UNITED STATES PATENTS

3,306,286	2/1967	Ahmed	128/130
3,563,235	2/1971	Zipper	128/130
3,633,574	1/1972	Lerner	128/130

Primary Examiner—Richard A. Gaudet

Assistant Examiner—G. F. Dunne

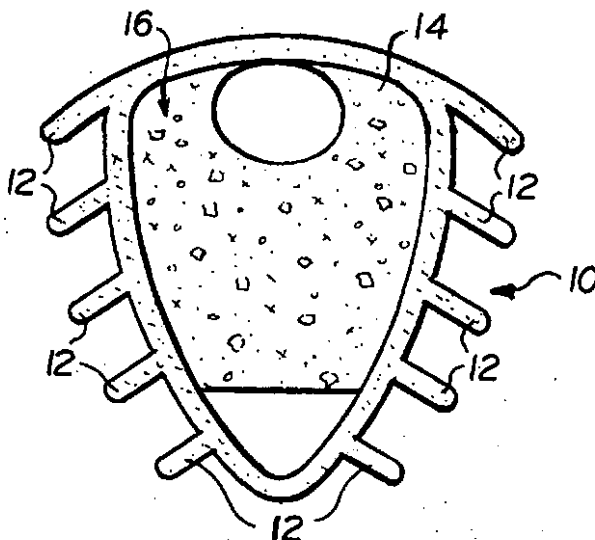
Attorney, Agent, or Firm—Strauch, Nolan, Neale, Nies
& Kurz

[57]

ABSTRACT

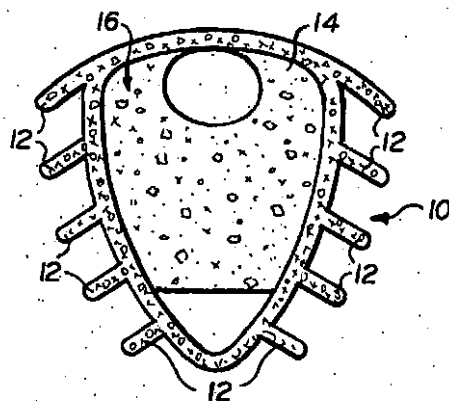
An intrauterine device composite is provided which comprises a plastic matrix, such as a copolymer of ethylene and vinyl acetate, having a particulate material selected from the group consisting of metals such as copper, zinc, silver, platinum, or cadmium, and metal salts dispersed within the matrix. The particulate preferably includes both a metal and a salt, such as a sulfate, thereof, although solely a salt or a metal particulate may be utilized. In addition, a radio-opaque particulate such as barium sulfate is preferably also dispersed within the composite. The particulate material preferably comprises between 0.1% to 50% by weight of the composite, and the matrix preferably has a water permeability or rate of water vapor transmission of at least 0.3 grams/100 square inches/24 hours/mil at 25° C.

17 Claims, 1 Drawing Figure



PATENTED SEP 10 1974

3,834,378



INVENTORS

IRWIN S. LERNER
HUGH J. DAVIS
THAD J. EARL

BY

Hubbell, Cohen & Stiefel

ATTORNEYS

3,834,378

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INTRAUTERINE DEVICE

CROSS REFERENCE TO RELATED APPLICATION

This application is a continuation of application Ser. No. 88,538 filed Nov. 12, 1970 and now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to intrauterine device composites and more particularly to such composites comprising a plastic matrix having a particulate material dispersed therein.

2. Description of the Prior Art

Prior art intrauterine devices have utilized structures including a metal wire in order to obtain improved results. Such prior art devices have involved the use of a plastic T-shaped device having a fine copper wire wrapped about the upper end of the stem of the T, a silkworm gut wrapped in a bronze wire, and a copper loop having a silkworm gut tail. These prior art intrauterine devices, however, are bulky, difficult to insert, and are not necessarily well tolerated within the uterine cavity. Moreover, whenever any beneficial effect has been observed, a substantial quantity of time has been required before such beneficial effects occur, resulting in a lag time between insertion of the device and achievement of the benefits thereof. In addition, in intrauterine devices employing a wire wrapped about a T-stem, the wire tends to dissolve and break up thus minimizing its long range effectiveness. Furthermore, such prior art devices have a relatively low surface area for the metal which, thereby, also minimizes their effectiveness. Due to these disadvantages, prior art intrauterine devices have not achieved the wide spread usage enjoyed by oral contraceptives. The present invention overcomes these disadvantages of the prior art.

SUMMARY OF THE INVENTION

An intrauterine device composite is provided which comprises a plastic matrix having a particulate material dispersed within the matrix. The particulate material is selected from the group consisting of metals and metal salts and comprises between 0.1% and 50% by weight of the composite. The particulate preferably includes both a metal and a salt, such as a sulfate thereof, although solely a metal or a salt particulate may be utilized. In addition, a radio-opaque particulate, such as barium sulfate, is preferably also dispersed within the matrix. The plastic matrix preferably has a water permeability or rate of water vapor transmission of at least 0.3 grams/100 square inches/24 hours/mil at 25° C.

BRIEF DESCRIPTION OF THE DRAWING

The FIGURE is a diagrammatic illustration exemplary of an intrauterine device composite in accordance with the preferred embodiment of the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

For purposes of illustration, an intrauterine device of the type commonly termed a "shield," such as described in co-pending application, Ser. No. 775,729, filed on Nov. 14, 1968, now U.S. Pat. No. 3,633,574, generally referred to by the reference numeral 10, is

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shown. The shield device 10 disclosed in co-pending application, Ser. No. 775,729, preferably has a contour which conforms to the mid-range of the uterine cavity, and has a plurality of lateral fins 12-12 which promote retention and permit accommodation to uterine contractions and variations in uterine shape extending outwardly from a central membrane portion 14. As disclosed in co-pending application, Ser. No. 775,729, the central membrane portion 14 increases endometrial surface contact, as well as precludes bowel strangulation in the event of perforation. However, the present invention is not limited to the shield type of intrauterine device, but rather is applicable to all types of intrauterine devices, the shield type 10 only being shown and described by way of example.

Preferably, the intrauterine device 10, as shown and preferred in the FIGURE, is a composite formed of a plastic material such as a copolymer of ethylene and vinyl acetate, polyvinyl acetate, polyethylene, polypropylene, polyvinyl chloride, nylon, or silicone rubber, such as disclosed in co-pending patent application, Ser. No. 775,729. Most preferably, the plastic material is a copolymer of ethylene and vinyl acetate, such as UE 632, manufactured by United States Industrial Chemical Corporation, which contains 13-15% vinyl acetate by weight. As shown and preferred, in addition, the plastic matrix of which the intrauterine device 10 is preferably constructed, has dispersed therein particulate material. Most preferably, the particulate is dispersed throughout the plastic matrix. The particulate material preferably includes a metal and a salt thereof, although it may comprise solely a metal or a salt. By way of example, metals which are satisfactory for purposes of the present invention are copper, zinc, silver, platinum, or cadmium. Most preferably, copper particulate is preferred. By way of example, metal salts which are satisfactory include salts of copper, zinc, silver, platinum, or cadmium. The salt is preferably a sulfate, carbonate, nitrate, acetate or phosphate. Most preferably, the salt is a sulfate of the metal particulate.

Preferably, the particulate metal in the intrauterine device composite 10 is at least 0.1% by weight of the overall composite. The metal salt is, preferably, at least 0.5% by weight of the overall composite. In addition, the preferred overall content of metal plus metal salt in the composite should not exceed 50% by weight of the overall composite, thereby providing a preferred range of total particulate, by weight, in the overall composite of between 0.1% to 50% by weight.

The requisite amount of particulate material, which is biologically active, is preferably related to the water permeability or rate of water vapor transmission of the plastic matrix, which is biologically inert. The greater the permeability of the plastic, the less the requisite amount of active particulate that need be present. Conversely, the lower the permeability, the greater the requisite amount of active particulate that should preferably be present. Preferably the water permeability or rate of water vapor transmission of the plastic is at least 0.3 grams/100 square inches/24 hours/mil at 25° C.. If desired, better results may be obtained with a water permeability of at least 5 grams/100 square inches/24 hours/mil at 25° C.. Most preferably this rate is at least 10 grams/100 square inches/24 hours/mil at 25° C..

In addition to the presence of a particulate of a metal and a salt thereof in the preferred composite, a radio-opaque particulate material may also be dispersed

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therein. Preferably, this radio-opaque material is a salt of an alkaline earth metal, such as barium. Most preferably, this salt is barium sulfate.

In order to form the intrauterine device composite, conventional techniques may be utilized. Once such preferred conventional technique requires intimately admixing particles of the desired plastic with finely ground particulate metal and particulate metal salts at a sufficiently high temperature for a sufficient time in order to obtain a homogeneous-like phase. The resultant impregnated plastic having the particulate material dispersed throughout is then molded under heat and pressure in a conventional manner to readily form any desired configuration such as the shield configuration 10 illustrated in the FIGURE.

The resulting intrauterine device composite consists of a plastic matrix having the particulate material dispersed throughout the matrix. This is illustratively shown by the particulate, generally referred to by the reference numeral 16, shown in the FIGURE. Most preferably, the intrauterine device composite comprises a plastic matrix of a copolymer of ethylene and vinyl acetate having a particulate of copper and cupric sulfate dispersed throughout the matrix, with the percent by weight of the copper and cupric sulfate particulate being between 0.5% to 10% by weight of the composite, and the water permeability of the plastic being at least 10 grams/100 square inches/24 hours/mil at 25° C.

The presence in the water permeable plastic matrix of the biologically active metal particulate which preferably does not exceed an amount which degrades the plastic matrix so as to eliminate the beneficial flexibility thereof, assists the tensile strength, flowability for molding and other physical properties of the intrauterine device composite. In addition, the presence of the metal salt particulate, which is preferably a salt which is capable of relatively rapid ionization after insertion of the intrauterine device composite within the uterine cavity, is believed to ionize much more rapidly than the free metal particulate and causes rapid release of metal ions. When only a metal salt particulate is utilized, the ionization of the salt provides early protection, whereas protection at a later time is provided by the chemotactic effect of the plastic matrix. Preferably, the biologically active particulate is capable of enhancing the chemotactic effect of the otherwise relatively inert plastic material. By virtue of the "controlled release" of the biologically active particulate, relatively low concentrations thereof are capable of exerting a gameto toxic effect.

Whether the presence of the metal salt and/or metal exerts a spermicidal and/or ovacidal action or causes the tissue to react in such a manner so as to produce a material which itself is spermicidal and/or ovacidal, the presence of the metal in the ion state accelerates this action, and the rapid ionization of the metal salt enhances this result.

By utilizing an intrauterine device composite in accordance with the preferred embodiment of the present invention, the properties and capabilities of an intrauterine device are markedly enhanced.

What is claimed is:

1. An intrauterine device having a body structure encompassing an area which can be contained within a normal uterus, made from a composition enabling flexing to conform to the uterine cavity comprising: a plas-

tic matrix, and a particulate material comprising at least one non-magnetic metal selected from a group consisting of copper, zinc, silver, platinum and cadmium, and at least one salt of a metal selected from said group; said particulate material being dispersed within said plastic matrix; and said particulate material comprising between 0.1% to 10% by weight of the composition of said device.

2. An intrauterine device having a composition in accordance with claim 1, wherein said particulate material comprises a metal and a salt of said metal.

3. An intrauterine device having a composition in accordance with claim 1, wherein the material comprising said plastic matrix has a water permeability of at least 0.3 grams/100 square inches/24 hours/mil at a temperature of 25° Centigrade.

4. An intrauterine device having a composition in accordance with claim 1, wherein the material comprising said plastic matrix has a water permeability of at least 10 grams/100 square inches/24 hours/mil at a temperature of 25° Centigrade.

5. An intrauterine device having a composition in accordance with claim 1, wherein said material comprising the plastic matrix is a copolymer of ethylene and a vinyl monomer material.

6. An intrauterine contraceptive device made from a composition material as defined in claim 1 enabling flexing to conform to the uterine cavity, further comprising: a central body having a perimeter portion with nose, tail and side portions and encompassing an area which can be contained within a normal uterus, and at least three spaced apart short spurs on each of said side portions extending outwardly from said perimeter portion.

7. An intrauterine device having a composition in accordance with claim 6, wherein said material comprising the plastic matrix is a copolymer of ethylene and a vinyl monomer material.

8. An intrauterine contraceptive device made from a composition material as defined in claim 1 enabling flexing to conform to the uterine cavity, further comprising: a ring-like perimeter portion having a nose portion and opposite therefrom a tail portion with side portions joining said nose and tail portions; and a plurality of spur-like retaining means extending outwardly from each said side portion.

9. An intrauterine device having a composition in accordance with claim 8, wherein said particulate material comprises a metal and a salt of said metal.

10. An intrauterine device having a composition in accordance with claim 9, wherein said material comprising the plastic matrix is a copolymer of ethylene and a vinyl monomer material.

11. An intrauterine device having a body structure encompassing an area which can be contained within a normal uterus, made from a composition enabling flexing to conform to the uterine cavity comprising: a plastic matrix, and a particulate material comprising at least copper and a salt of copper; said particulate material being dispersed within said plastic matrix; and said particulate material comprising between 0.1% to 10% by weight of the composition of said device.

12. An intrauterine device having a composition in accordance with claim 11; wherein said particulate material comprises copper and cupric sulfate.

13. An intrauterine device having a composition in accordance with claim 12, wherein the material com-

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prising said plastic matrix has a water permeability of at least 0.3 grams/100 square inches/24 hours/mil at a temperature of 25° Centigrade.

14. An intrauterine device having a composition in accordance with claim 12, wherein the material comprising said plastic matrix has a water permeability of at least 10 grams/100 square inches/24 hours/mil at a temperature of 25° Centigrade.

15. An intrauterine contraceptive device made from a composition material as defined in claim 12, enabling flexing to conform to the uterine cavity, further comprising: a central body having a perimeter portion with nose, tail and side portions and encompassing an area which can be contained within a normal uterus, and at least three spaced apart short spurs on each of said side portions extending outwardly from said perimeter portion.

16. An intrauterine contraceptive device made from a composition material as defined in claim 12, enabling

flexing to conform to the uterine cavity, further comprising; a ring-like perimeter portion having a nose portion and opposite therefrom a tail portion with side portions joining said nose and tail portions; and a plurality of spur-like retaining means extending outwardly from each said side portion.

17. An intrauterine device having a body structure encompassing an area which can be contained within a normal uterus, made from a composition enabling flexing to conform to the uterine cavity comprising: a plastic matrix; and a particulate material comprising at least copper and at least one salt of a metal selected from a group consisting of copper, zinc, silver, platinum and cadmium; said particulate material being dispersed within said plastic matrix; and said particulate material comprising between 0.1% to 10% by weight of the composition of said device.

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[54] NOVEL DRUG PERMEABLE WALL

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

[22] Filed: Oct. 19, 1973

[21] Appl. No.: 408,233

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 209,782, Dec. 20, 1971, abandoned.

[52] U.S. Cl. 128/260; 128/270

[51] Int. Cl.² A61F 5/46; A61F 13/20; A61M 31/00

[58] Field of Search 128/130, 260, 270; 424/19, 424/22; 260/873

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Primary Examiner—Aldrich F. Medbery

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[57] ABSTRACT

A polymeric wall adapted to release drug at a controlled rate for a prolonged period of time from a reservoir comprising a drug and a carrier which is permeable to the drug and saturated therewith during said prolonged period of time, to a body environment or a drug receptor site, the wall comprising a mixture of a polymer which is biologically compatible with said environment or site and maintains its integrity while in contact therewith, has a glass transition temperature between ambient temperature and 150°C, a crystallinity of 5% to 95%, or is rubbery, and is permeable to the drug but at a rate less than that of the carrier and as a minor constituent a polymeric additive such as a polyester prepared from a glycol and a dibasic acid, polyethylene glycol, chlorinated polyethylene or copolymers of ethylene and vinyl esters or vinyl esters or vinyl halides, the amount of additive being sufficient to make the permeability of the wall to the drug substantially different than the permeability of the polymer to the drug but still less than the permeability of the carrier to the drug.

7 Claims, 4 Drawing Figures

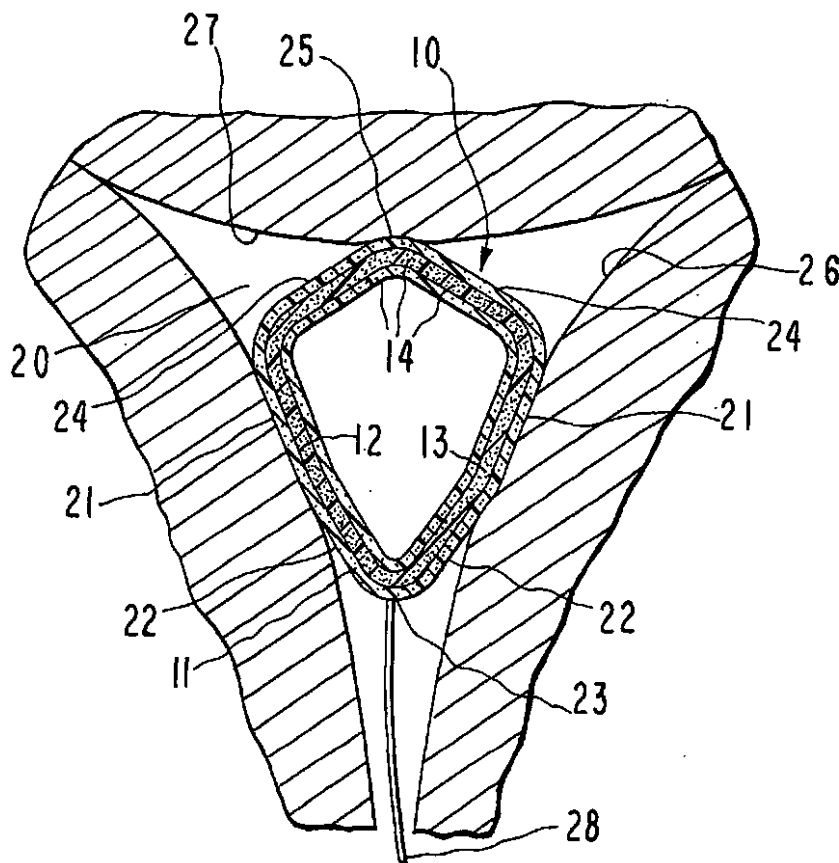


FIG. 1

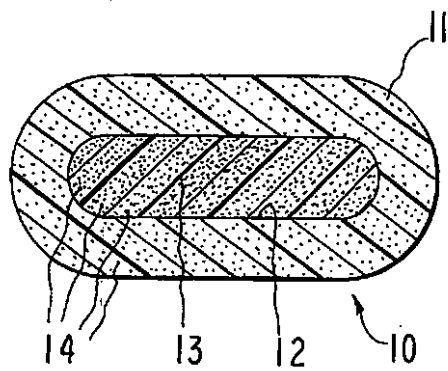


FIG. 2

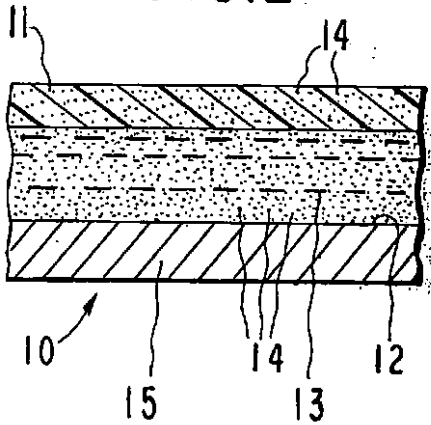


FIG. 3

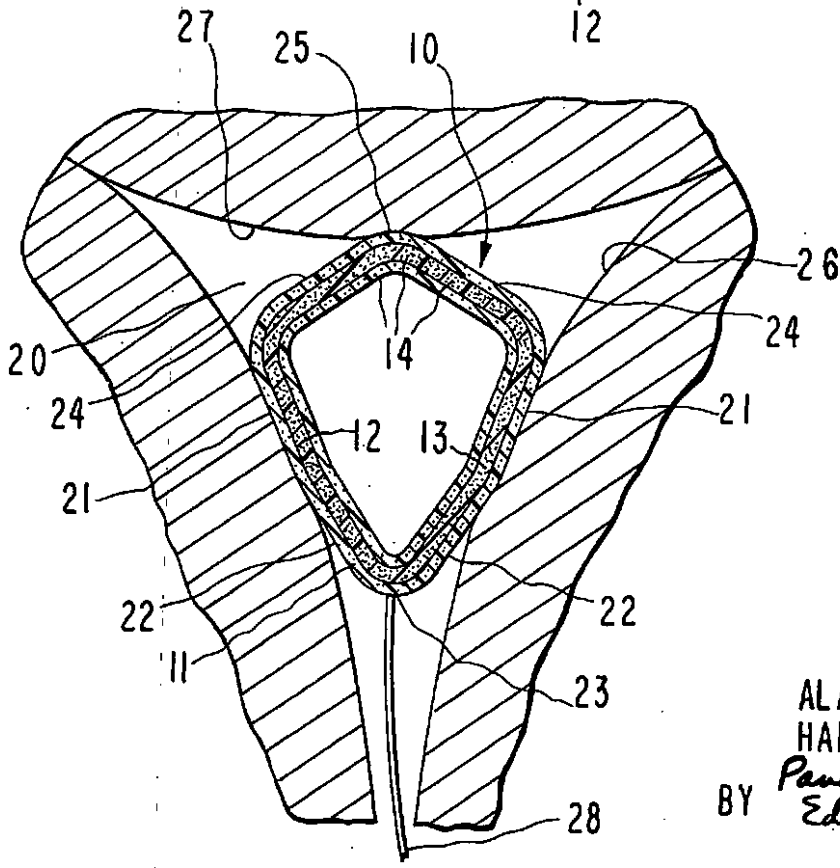
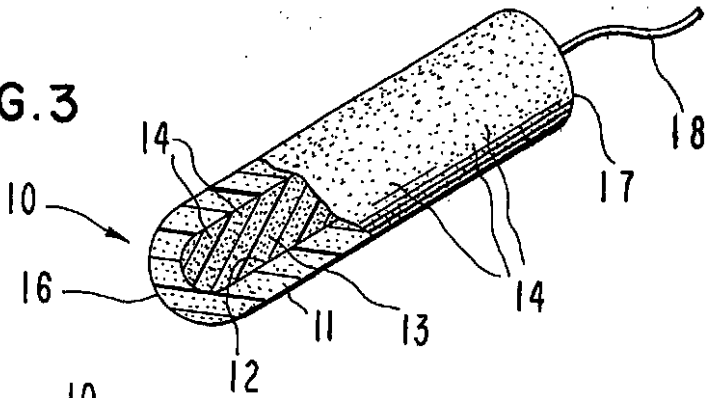


FIG. 4

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NOVEL DRUG PERMEABLE WALL
CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending application Ser. No. 209,782, filed Dec. 20, 1971 and now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a novel drug-permeable polymeric wall adapted to release a drug at a controlled rate from a drug-containing reservoir to a body environment and to novel drug delivery devices including such a wall. It also relates to methods for increasing the permeability of polymers used to make such walls and methods for modifying the rate of drug release through such walls.

2. Description of Prior Art

Prior art drug delivery devices comprised of a drug dispersed in a solid matrix permeable to passage of the drug and surrounded by a polymer membrane, also permeable to passage of the drug but at a lower rate than through the matrix, have proven themselves capable of zero order drug release and represent a substantial improvement over previously proposed drug delivery devices. The drug release rate in these devices is controlled by using certain wall forming materials for releasing the drug, and the release rate for the drug is proportional to its diffusion coefficient in the wall and to the solubility of the drug in the wall. In making these drug delivery devices available to the art, these parameters are developed for each drug, and it has now been found that this can require a large number of wall forming materials for different drugs. This often adds considerable complexity to the design of drug delivery devices.

It is also known to the art to incorporate drug into certain types of liquid carriers, usually in microcapsule formulations, for example, as in U.S. Pat. No. 3,464,413. However, these microcapsules are not designed for the controlled release of drug for a prolonged period of time by using drug release rate controlling wall materials. The microcapsules are frequently crushable, and they merely function as drug carriers supplying their drug in bulk, and not in controlled amounts by rupture of the microcapsules. These types of capsules are not suitable for releasing drug at a controlled rate for a prolonged period of time.

The prior art also discloses incorporating conventional plasticizers in polymer walls of drug delivery devices (U.S. Pat. Nos. 3,630,200 and 3,538,214) to increase the flexibility of such walls.

SUMMARY OF THE INVENTION

A primary object of this invention is to provide means and methods for modifying the permeability of a drugpermeable polymeric wall adapted to release a drug at a controlled rate from a drug-containing reservoir to a body environment or a drug receptor site.

Another object of this invention is to provide drug permeable walls of unique polymeric composition which are adapted for use in drug delivery devices in which drug is released at a controlled rate from a drug-containing reservoir to a body environment by permeation through a polymeric wall. Correlatively yet an-

other object is to provide improved drug delivery devices which include at least one of such walls.

The drug-permeable walls of this invention are adapted for use in the prior art devices which release a drug at a controlled, preferably substantially constant, rate from a reservoir comprising a carrier which is permeable to the drug and drug in an amount sufficient to maintain the concentration of drug in the carrier at saturation concentration during the life of the device to a body environment or drug receptor site by passing the drug through a drug release rate controlling polymer wall which is permeable to the drug but at a rate less than that of the carrier to the drug. They comprise a homogeneous mixture of (1) a polymer which is biologically compatible with said environment or site and maintains its integrity while in association therewith, has a glass transition temperature between about ambient (normal room) temperature and 150°C, a crystallinity in the range of about 5% and about 95% or is rubbery and is permeable to the drug at a rate less than the carrier of the device and (2) a polymeric additive selected from the group consisting of certain polyesters prepared from a glycol and a dibasic acid, polyethylene glycol, chlorinated polyethylene and copolymers of ethylene and vinyl esters or vinyl halides, the amount of said additive in the mixture being sufficient to make the permeability of the mixture to the drug substantially different than the permeability of the polymer to the drug but still less than the permeability of the carrier to the drug.

The methods of this invention involve mixing the above defined polymeric additive into the above defined polymers in various amounts which provide mixtures thereof having a predetermined range of permeabilities to the drug.

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.

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:

FIG. 1 is a perspective, cross-sectional view of a drug delivery device of the invention depicting a wall surrounding a reservoir;

FIG. 2 is an enlarged fragmentary cross-sectional view of a drug delivery device of the invention illustrating two different walls surrounding a reservoir containing a drug;

FIG. 3 is a side, fragmentary view depicting a vaginal drug delivery device of the invention for releasing drug in a body orifice; and

FIG. 4 is a frontal, fragmentary view of a uterine cavity showing a drug releasing intrauterine device positioned in the cavity;

In the drawings and specification, 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 described elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, which are examples of various drug delivery devices of the invention, and which examples are not to be construed as

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limiting, one embodiment of a novel drug delivery device is indicated in FIGS. 1 and 2 by the number 10. In FIG. 1 drug delivery device 10 is comprised of a wall 11 surrounding a reservoir 12. Reservoir 12 is comprised of a drug carrier 13 as shown in FIG. 1 and it contains a drug 14, or a mixture of drugs. Drug carrier 13 is a solid and it is permeable to the passage of drug 14, as by diffusion and/or connection. Wall 11 is formed of a mixture of polymer, defined briefly supra and in detail infra permeable to the passage of drug 14, as by diffusion, and a permeability modifying additive also defined briefly supra and in detail infra that causes the permeability of the wall to be materially different than the permeability of said polymer by itself and likewise causes the rate of passage of drug 14 through wall 11 to be materially different than if wall 11 was formed only of said polymer. The rate of passage of drug 14 through wall 11 is lower than the rate of passage of drug 14 through solid drug carrier 13. Drug 14 consists of a portion which is dissolved in carrier 13 and an undissolved portion and is present within reservoir 12 in an amount sufficient to maintain a saturation concentration of drug in the carrier throughout the use period of the device.

In operation, solid drug carrier 13 serves as a reservoir 12 by supplying dissolved drug 14 to wall 11 as drug molecules move through the carrier to bathe the inner surface of wall 11. Drug 14 present at the drug carrier/wall interface dissolves in and migrates through the wall ultimately reaching the outer surface of wall 11. As drug 14 leaves drug carrier 13, undissolved drug present in reservoir 12 dissolves in solid carrier 13 to maintain a saturation concentration of drug in the carrier for continuously supplying drug at substantially the same rate to wall 11. Thus, a substantially zero order drug release rate of specifically defined magnitude is obtained.

In FIG. 2, wall 15 comprising the remainder of device 10 is formed of a material impermeable to the passage of drug 14. Reservoir 12 of FIG. 2 is comprised of a drug carrier 13 containing a drug 14 or a mixture of drugs. Carrier 13 of FIG. 2 is a liquid carrier and it is permeable to the passage of drug 14 as by diffusion, or by convection, or by an occurrence of both. As in the embodiment of FIG. 1 drug 14 is present in the reservoir as a dissolved portion and an undissolved portion in an amount sufficient to maintain saturation concentration in the carrier during the use period of the device.

In operation, carrier 13 serves as a reservoir by supplying dissolved drug 14 to wall 11 as molecules move through the carrier to bathe the inner surface of wall 11. Drug 14 present at the carrier/wall interface dissolves in and migrates through wall 11, the composition of which is the same as the composition of the wall of FIG. 1, ultimately reaching the outer surface of wall 11 for release to a drug receptor site. Wall 11 is substantially impermeable to carrier 13, and it remains in the reservoir. Additionally, the permeability of wall 11 per se to the diffusion of drug 14 is lower than the permeability of liquid drug carrier 13 to the diffusion of drug 14 and passage through wall 11 thus acts as the rate limiting step for drug release from device 10.

FIG. 3 illustrates another drug delivery device of the invention. In FIG. 3 there is illustrated a drug delivery device 10 designed for administering drug within a body opening, the vaginal canal, not shown. Drug delivery device 10 of FIG. 3 is comprised of a cylindrical

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body having a wall 11 surrounding a reservoir 12. The cylindrical body is provided with a rounded entrant end 16 and at the opposite end 17 with a pull string 18 for easy removal from the vaginal canal. Reservoir 12 is comprised of a drug carrier 13 containing drug 14. Drug carrier 13 is solid or liquid in nature. Drug carrier 13 is permeable, as by diffusion, to the passage of drug 14, which has limited solubility therein. As in the devices of FIGS. 1 and 2, drug 14 consists of a dissolved portion and an undissolved portion and is present in an amount sufficient to maintain saturation concentration in the carrier 13 for the useful life of the device. Wall 11 is made of a mixture of polymer and polymeric additive that is insoluble in body fluids, indigestible and non-erodible and it is permeable to the passage of drug 14, as by diffusion. In this device, as with the devices discussed above, wall 11 contains an effective amount of a permeability modifying additive that affects the rate of drug passage through wall 11, and the permeability of wall 11 to drug is lower than the permeability of carrier 13 to drug. Thus, passage of the drug through wall 11 is the rate controlling step for releasing drug from the drug delivery device.

In FIG. 4 there is graphically depicted an intrauterine contraceptive drug delivery device 10 prepared according to the spirit of the invention. Device 10, it will be seen, consists of a closed perimeter and an open central area and having geometric dimensions generally conforming to the internal shape of a uterus 20. The device generally has a pair of median sides 21 extending downwards into a second pair of sides 22 joined at an apex 23. The upper portion of device 10 has a pair of corresponding sides 24 joined at an apex 25. Device 10 is adapted to be located within the uterine cavity 20 and when positioned therein, it contacts the sides 26 as well as the fundus uteri 27. Device 10 is capable of being substantially straightened by passing through a hollow instrument for positioning it in uterus 20. The device is also equipped with a pair of nylon or surgical threads 28, attached to its trailing end for manually removing the device from the uterus.

Device 10 of FIG. 4 is comprised of a wall 11 housing a reservoir 12. Reservoir 12 is comprised of a drug carrier medium 13 containing a drug 14 in the portion's and amount hereinbefore described. The carrier confined in the reservoir serves several purposes for effectively releasing drug from the device. First, it contains a drug or a mixture of drug and it is permeable to the passage of drug so that drug in the carrier can migrate to wall 11. Secondly, the carrier contacts and bathes the inner surface of wall 11 for facilitating drug transfer from the carrier to the wall so that drug molecules can dissolve in and diffuse through the wall and migrate through it to the outer surface thereof. Thirdly, the carrier serves as a constant source of drug as it has a limited or varying degrees of solubility for drug or a mixture of drugs. Thus, the carrier is a constant source of drug because, as drug dissolves in the carrier and transfers from the carrier to the wall, undissolved drug dissolves in the carrier to insure a constant and uniform supply of drug until essentially all of the drug has been released by the device. This mechanism of continually replenishing the drug contributes to the device's ability to achieve a uniform substantially time independent release rate for the device throughout its use.

As in the above described embodiments wall 11 of the intrauterine contraceptive drug delivery device 10, is formed of a homogeneous mixture of release rate

controlling polymer to continuously meter the flow of a contraceptively effective amount of a drug from reservoir 12 for release within uterus 20 and a release rate (permeability) additive whose presence in wall 11 materially affects the rate of drug release through the wall. That is, by controlling the amount of modifying agent in the wall the rate of drug release through the wall can be effectively controlled to predetermined rates, and this rate of drug release is lower than the passage of drug through and/or from the carrier, so that the former is the rate controlling step for drug release from the intrauterine contraceptive device. The depicted intrauterine drug delivery device is manufactured in a non-traumatizing design for easy insertion into the uterine cavity. The device can be fabricated into assorted sizes, shapes, and thicknesses for adaptation to a wide variety of uteri.

While the above FIGS. 1 through 4 inclusive are illustrative of various drug delivery devices that can be made according to the invention, it is to be understood that these drug delivery devices are not to be construed as limiting, as the drug delivery devices of the invention can take a wide variety of shapes, sizes and forms for administering the drug at controlled rates to different areas of the body or to different drug receptor sites. For example, the invention includes external and internal drug delivery devices such as skin patches, sublingual or buccal drug delivery devices, peroral devices, arterial devices, nasal and ear drug delivery devices, suture materials, plastic heart valves, Starr-Edwards heart valves, hip joints, non-thrombogenic hydrocephalus shunt, bone pins, pessaries, prostheses, artificial glands, cervical rings, troches, intrauterine drug delivery devices of cylindrical, bullet, elliptical, circular, bulbous, loops, bows, or any other geometrical shape that readily lends itself to intrauterine placement such as Birnberg's Bow in U.S. Pat. No. 3,319,625; Comet in U.S. Pat. No. 3,256,878; Majzlin Spring in U.S. Pat. No. 3,397,691; Inhiband in U.S. Pat. No. 3,323,520; Bakunin in U.S. Pat. No. 3,405,711; Shamrock in U.S. Pat. No. 3,077,879; the ring with tail; Ota ring, and the like. In each instance, all of the drug delivery devices made according to the invention have a reservoir comprised of a drug and a drug carrier permeable to the passage of drug, as by diffusion and/or convection. The reservoir is surrounded by a wall, at least a portion of which is formed from a mixture of a polymer permeable to the passage of drug, as by diffusion, and a polymeric release rate modifying additive which significantly affects the rate of drug passage through the wall. The drug rate of release through the wall is lower than the rate of passage through the carrier, so that the drug release rate through the wall is the drug release rate controlling step. Also, all of the drug delivery devices are of appropriate known shapes and sizes for implantation, insertion or positioning in the desired body cavities or on tissues for administering of drug to the body or to a drug receptor site.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the practice of the present invention, it has now been found that the drug delivery devices which include the wall of the invention provide many important advantages over previously known drug delivery devices. One advantage of the device is the ease of construction of the drug delivery device by standard manufacturing techniques into devices of various sizes, shapes and forms for delivering drugs to a

recipient. A more important advantage is that the invention wall may be used to provide a broad range of drug release rates by providing one or more devices having a reservoir, or more than one reservoir in a large multi-purpose device, wherein the reservoir contains a carrier or a mixture of carriers having varying degrees of solubility for a drug or a mixture of drugs and where the carrier simultaneously releases drug to the wall and dissolves replacement drug to maintain a constant supply of drug for release by the device.

Another important advantage of the invention resides in the drug delivery devices' ability to effectively control the rate of release of the drug from the device by providing a zero order ($dM/dt = \text{constant}$) rate of drug release throughout the major portion of the drug release history. The drug time release pattern for the device of the invention is obtained by a selection of the drug release parameters, such as, the nature of the basic polymer component of the wall, the nature and amount of additive per area of wall, the nature of the drug carrier in the reservoir, and the kind of drug contained therein.

The above advantages and objects are achieved by the unique construction and operation of the device and its ability to transfer drug to a recipient or to a drug receptor site. In construction, the device can be viewed as a single unit constructed device comprising two structures acting in concert for effective drug administration to a host. One structure pertains to a wall formed of a drug release rate controlling polymer containing a drug release rate (permeability) modifying additive therein, and the other structure relates to a reservoir comprising a drug and a carrier of a material permeable to the passage of drug. The materials forming the wall and the drug carrier are chemically and structurally different within a single device and the rate of release of drug through the wall is lower than the rate of passage of drug in the drug carriers.

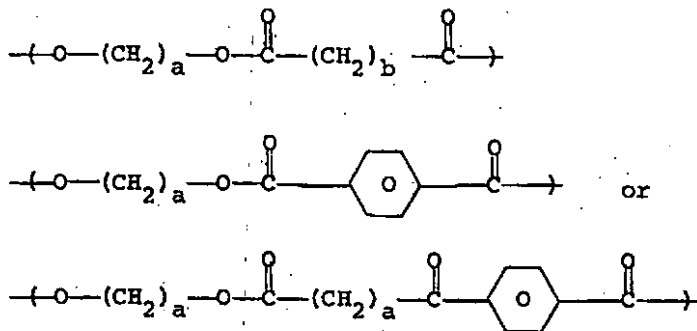
These two structures, comprising the unit drug delivery device, operate to effectively transfer drug from the device by first transferring drug from the carrier to the wall containing the release rate modifying additive, and secondly, by transferring drug through the wall to a drug recipient. The transfer of drug through the wall occurs by diffusion. In the diffusion process, the drug dissolves in the wall and then diffuses in the direction of lower chemical potential. At the second boundary, the outside of the wall, equilibrium is again established. When the boundary conditions on both sides of the wall are maintained constant, a steady state flux of the drug will be established which can be described by Fick's Law of Diffusion. The rate of passage of drug through the wall is generally dependent, in the case of diffusion, on the solubility of the drug in the wall, as well as on the diffusion coefficient. This means that selection of appropriate materials for fabricating the wall will be dependent on the particular wall, the media and the drug to be used.

The polymers which form the basic component of the wall are those which have physical and chemical properties suitable for the fabrication process and suitable for the use environment and through which the drug can pass at a controlled rate of release by the process of diffusion. In this regard they are biologically compatible with body fluids, tissues or organs, and essentially insoluble in body fluids, and non-erodible, with which they will come in contact. Generally, the use of rapidly dissolving materials or materials which are highly solu-

ble, or which swell to lose or distort their predetermined shape, in body fluids is to be avoided since dissolution or loss of properties 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.

These polymers are approximately classified into three categories: (1) polymers whose glass transition temperatures are above room temperature (20°-150°C) and have low permeability to drugs because of low molecular mobility; (2) polymers which are partially crystalline (5-95%) and hence have low permeability to drugs; and (3) polymers which are rubbery, and whose glass transition temperatures are below room temperature, i.e. about 20°C. In the latter category these rubbery polymers may be thermoplastic or thermosetting in nature. Such polymers are commercially available and include polyvinyl chloride, polyvinylidene chloride, polyvinyl fluoride, polyvinylidene fluoride, polyvinyl acetate, polyvinyl butyral, polystyrene, cellulose acetate, cellulose nitrate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, polyurethane, butadiene/acrylonitrile copolymer, chlorinated natural rubber, styrene/butadiene copolymer, ethylene/propylene copolymer, ethylene/vinyl acetate copolymer, ethylene/vinyl chloride copolymer, polyethylene, polypropylene and polyalkyl acrylates in which the alkyl group is of 2 to 4 carbon atoms.

The polymeric release rate modifying additives that are homogeneously mixed with the above described polymers to form the walls of this invention are essentially insoluble in body, that is, animal fluids, nonvolatile and nonleachable and nonextractable from the polymer once they are blended therewith. These additives are commercially available and include: (1) essentially linear olefinically saturated polyesters having a number average molecular weight of less than about 20,000, preferably about 500 to about 8,000, of a diol of 2 to about 7 carbon atoms or polyethylene glycol and a dibasic carboxylic acid of about 6 to about 15 carbon atoms in which the terminating group is a carboxyacyl group of about 2 to about 18 carbon atoms or an alkoxy group of about 3 to about 15 carbon atoms. Such polyesters include those of the recurring general formula:



wherein *a* is an integer from 2 to 4, inclusive, and *b* is an integer from 4 to 13, inclusive. Typical diols which are used in such polyesters are alkylene glycols, e.g. ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, and alkane diols, e.g. 1, 3-butane diol, and 2, 2-dimethyl-1,3-propane diol. Representative of such dibasic carboxylic acids are adipic, azelaic, sebacic, phthalic, isophthalic, terephthalic, pimelic, α,ω -dodecanoic and α,ω -tridecanoic. Examples of such

terminating groups are the acyl derivatives of fatty acids such as a lauryl, stearyl capryl and pelargonyl, acyl derivatives of aromatic acids such as benzoyl; and butoxy, octoxy, 2-ethylhexoxy, decoxy, nonoxy, isodecoxy and the like; (2) polyethylene glycols of about 200 to about 1,500 molecular weight; (3) ethylene-vinyl acetate copolymers of about 20 to about 40% by weight vinyl acetate and about 20,000 to about 30,000 number average molecular weight; (4) chlorinated polyethylene of about 25 to 45% by weight chlorine and about 20,000 to about 30,000 number average molecular weight; (5) ethylene-ethylacrylate copolymers of about 20% to about 40% by weight ethylacrylate and about 20,000 to about 30,000 number average molecular weight; and (6) ethylene-vinyl chloride copolymers of about 25% to about 45% by weight chlorine and about 20,000 to about 30,000 number average molecular weight.

The novel wall compositions of the invention are made by mixing one or more of the above described polymers with one or more of the above described additives. Such mixing may be carried out by conventional techniques and procedures well known in the art. The amount of additive in the mixture is sufficient to provide the mixture with a permeability to drug that is materially different, in nearly all instances materially greater, from the permeability of the polymer itself to drug. By varying the specific amount of additive mixtures of varying permeability may be readily made. Accordingly, permeability and drug release rate may be materially changed by a simple blending process rather than a complete change in the selection of polymer.

Generally the amount of polymeric drug release rate additive present in the mixture will be about 0.2 mg to 5.0 mg per cm², preferably 1 to 2 mg per cm², for a 1 to 5 mil thick wall, or about 0.016 g to 2.0 g per unit volume, that is, for each cc of wall. A typical additive concentration at these ranges, for example 0.1 g to 0.5 g for each cc of wall, will allow a corresponding drug release of 1 microgram to 100 micrograms per hour.

The term "reservoir" as used in the specification and the accompanying claims generally refers to a "drug", a "drug carrier" or to a "medium-containing drug", that constantly bathes the inner surface of the drug release rate controlling wall and supplies drug thereto. That is, the reservoir is comprised of a drug carrier

material saturated with dissolved drug, and undissolved drug in a form and amount sufficient to maintain a saturation concentration of drug throughout the carrier during the useful life of the device. The carrier is permeable to the passage of the drug as by diffusion and/or convection. The drug carrier medium used for the purpose of the invention is a solid, or a liquid, and it can be inorganic or organic, and of naturally occurring or synthetic origin. Examples of solid carriers comprised

within the term solid are, for example, gelatin; starches; carbohydrates; solid extracts of Irish moss; ethylcellulose; cured polymers; silicone carbonate copolymers; hydrophilic polymers such as hydrophilic hydrogels of esters of acrylic acids; modified collagen; surface treated silicone rubbers; plasticized poly(vinylchloride); and the like. Representative of liquid carriers include ethylene glycol, liquid polyethylene glycols having a molecular weight of 200, 300, 400 and 600, fats and oils of plant, animal and marine origin such as almond oil, babassu oil, cocoa butter, corn oil, soybean oil, emulsions of gum arabic, water and ethyl cellulose, liquid glyceryl triesters of a lower molecular weight fatty acid, aqueous suspensions of poly(vinyl pyrrolidone), and the like. Further, for the purpose of this invention, the terms solid carrier and liquid carrier and the examples thereof are deemed as functional equivalents and they can also be generically termed "core" or "carrier". Remington's Pharmaceutical Sciences, pages 1627 to 1679, 1970, published by Mack Publishing Company, Easton, Pa.

The drug carrier medium comprising the reservoir, also has in addition to the properties described supra, limited solubility for contained drug or for a mixture of drugs. By limited solubility is meant that drug is soluble in given amounts in the carrier; that is, it comprises varying concentrations of drug 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, very slightly soluble, and almost practically insoluble. Generally, on a weight basis at 25°C, the amount of drug dissolved in a carrier comprises a range of solubility of drug in the carrier of 1 part of drug to about 10 parts to 15,000 parts of carrier. Presently, when desired to obtain a zero order rate of drug release, the drug incorporated in the carrier is preferably sparingly soluble so as to maintain substantially the same thermodynamic activity of the drug throughout the release period.

The composition wall 11 is chemically and/or structurally different than the composition of the carrier. Both the wall and the carrier are permeable to the passage of drug but the rate of flow through wall 11 is lower than the rate through the carrier. Thus, the rate of passage of drug through the wall is the rate release controlling step for the device. Generally, for the practice of this invention, the ratio of the drug release rate through the drug carrier of the reservoir to the drug release rate through the wall containing the modifier should be from 1000:1 to 2:1 and preferably from 10:1 to 200:1. Of course, the invention is not limited to these release rates, or compositional ranges, as the invention comprises lower or higher release rates from the drug carrier and lower and higher rates through the wall with the release rate through the wall lower than the release rate of the drug carrier. Thus, the invention provides that devices comprised of a carrier with various amounts of additive in the wall and activated by diffusion, can give different dosages of a drug by varying the characteristics of the respective materials to give controlled administration of a drug.

For the above discussed devices, because the reservoir serves to transfer drug molecules to all areas of the wall, the wall of the drug delivery system housing the reservoir remains substantially at the thermodynamic activity corresponding to that of the drug until substantially all of the drug has been released from the reser-

voir. Ordinarily, one would expect drug migration from the reservoir to cease when sufficient drug has entered the wall to establish an equilibrium; however, when the drug delivery system is in contact with body tissues or fluids, drug molecules are continuously removed from the outer surface of the wall. For optimum results, the rate of release of the drug through the wall should be less than the rate of clearance of migrated drug from the external surface of the device. This ensures that the drug administration rate is dependent on the rate of release of drug through the wall which can be controlled, rather than upon clearance of drug from the device in vivo, which can vary.

The rate of release of a drug through various materials, for example the release rate controlling wall, or a carrier, can easily be determined by those skilled in the art by standard procedures. In this manner, particular materials used as the device's wall for use as the drug release rate controlling barrier for release of drug from the reservoirs, as the carrier, can be scientifically 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 accepted is to cast or hot press a film of the wall forming material to a thickness in the range of 1 to 60 mils. The film is used as a barrier between a rapidly stirred, for example, about 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,

$$\text{i.e. } \frac{Q_1 - Q_2}{t_1 - t_2}$$

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. Procedures for determining the rate of drug release through the carrier can be easily used by following standard techniques known to the art as recorded in J. Pharm. Sci., Vol. 52, pages 1145 to 1149, 1963; *ibid.*, Vol. 53, pages 793 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 solubility of a drug in a liquid carrier can be determined by various art known techniques. One method consists in preparing a composition of the given drug and ascertaining by analysis the amount of drug present in a definite quantity of the liquid 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. The liquid carrier and drug 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 liquid 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 results are taken as the degree of solubility of the drug in the liquid carrier. Numerous other methods are available for the determination of the degree of solubility of a drug 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.

The solubility of the drug in a solid carrier used for making a device broadly is determined by preparing a saturated solution of a given drug and ascertaining, by analysis, the amount present in a definite area of the carrier. For example, the solubility of the drug in the carrier is determined by first equilibrating the carrier material with a saturated solution of the drug at a known temperature, for example 37°C, or with a pure liquid drug if the drug is a liquid at 37°C. Next, drug is desorbed from the saturated carrier material with a suitable solvent for the drug. The resultant solution for the drug 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 drug in the solid carrier.

The diffusion coefficient of a drug in a polymer is determined by techniques known to the art such as the transient state sorption-desorption method. The method is carried out by first soaking the membrane in a concentrated solution of a drug for sufficient time to reach equilibrium. Next, the membrane is removed from the solution and its surface wiped or rinsed to remove adhering drug solution. The membrane is then placed into a flask containing drug-free water and the amount of drug subsequently present in the water is measured at regular intervals as it comes out of the membrane until no more drug leaves the membrane. This procedure and the method for calculating the diffusion coefficient using this procedure is described in Diffusion in Polymers, Edited by Crank, J. and Park, G. S., Chapter 1, pages 1 to 37, 1960, published by Academic Press, Inc., London; and in Diffusion In Solids, Liquids, Gasses, by Jost, W., Chapter 1, pages 35 to 39, 1960, published by Academic Press, Inc., New York; and the references cited therein. The diffusion coefficient of a drug in a membrane can also be experimentally determined by using similar procedures as described in Proc. Roy. Sci. London, Ser. A, Vol.

148, page 1935; and J. Pharm. Sci., Vol. 55, pages 1224 to 1229, 1966.

The solubility of a drug in the wall of a device broadly is determined by preparing a saturated solution of a given drug and ascertaining, by analysis, the amount present in a definite area of the wall. For example, the solubility of the drug 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.

Using the procedures and formulas above described, one skilled in the art can design a drug dispensing device according to the invention by ascertaining the properties of the wall and carrier and then fabricating the device by selecting a carrier in which the drug has ascertained solubility and which is permeable to the drug but at a higher rate than the permeability of the wall to the drug. 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 drug in the wall and a distribution coefficient, K , which is a ratio of the solubility of the drug in the wall to the solubility of the drug in the saturated solution, the selection of materials for forming the wall and the carrier can be made for making a device according to the invention. For purposes of comparing the permeability of the wall to that of the liquid carrier, it is convenient to define the permeability as follows: $P_w = PC = D_w S_w$ wherein P , C and D_w have the meaning as above described and S_w is the solubility of the drug in the wall. The permeability of the carrier to the drug can similarly be defined as $P_c = D_c S_c$ wherein D_c and S_c are the diffusion coefficient and the solubility of the drug in the carrier. The solubility, S_c , can be determined by cited methods. The diffusion coefficients of the drug in carriers will be in the range of 10^{-8} to 10^{-5} cm²/sec. The diffusion coefficient of the drug in the wall will be in the range of 10^{-10} to 10^{-8} cm²/sec. Thus, a selection of carrier materials such that $P_c > P_w$, preferably $P_c \geq 5 P_w$, is ascertained for preparing a delivery device. The symbols used herein have the conventional meaning, for example, the symbol ">" means greater than and the symbol " $\geq$ " means greater than or equal to.

In the specification and the accompanying claims, the term "drug", broadly includes physiologically or pharmacologically active substances for producing a localized or systemic effect or effects in mammals including humans and primates, avians such as chicken and turkeys; valuable domestic household, sport or farm animals such as horses, dogs, cats, cattle, sheep and the like; or for administering to laboratory animals such as mice, monkeys, rats, guinea pigs; and the like. That is, the novel drug delivery device can be used for administering drugs that are physiologically or pharmacologically active at a point in near relation to the drug delivery device, or, for administering a systemically active drug which will produce a physiological or pharmacological response at a site remote from the point of application of the drug delivery device. The active

drugs that can be administered by the drug delivery device of the invention include, without limitation: for example, drugs acting on the central nervous system, such as sedatives, hypnotics, psychic energizers, tranquilizers, and the like, drugs such as analgesics, antipyretics, antispasmodics, antimicrobials, hormonal agents, steroids, cardiovascular drugs, diuretics, neoplastic agents, hypoglycemic agents, and the like. Typical drugs are described in *The Pharmacological Basis of Therapeutics*, by Goodman and Gilman, 1970, Macmillan. Also, the drugs can be present as the pharmacologically acceptable derivatives, such as ethers, esters, amides, acetals, etc. that lend themselves to passage into the circulatory system. For highly water soluble drugs, it is preferable that the wall or the reservoir, or both be formed from a material that is substantially impermeable to water to essentially prevent dilution of the drug by absorption of body fluids into the device with an accompanying decrease in drug release rate. These derivatives can be prepared by art known techniques and then used in the practice of the invention. Of course, the drug derivative should be such as to convert to the active drug within the body through the action of body enzymes assisted transformations, pH, specific organ activities, and the like.

The amount of drug 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 a drug that on its release from the device is effective for bringing about the drug's physiological or pharmacological local or systemic effects. For example, the amount of drug present in the reservoir of a drug delivery device when the device is used for a period of time to achieve local or systemic effect is for various drugs, such as 11-desmethoxyreserpine about 5 to 140 mg in the reservoir; for aceptophenazine an amount in the reservoir of 100 to 400 mg; for methoxypropazine about 600 to 750 mg in the reservoir; for emcylamate a reservoir amount of 1.5 to 2.0 gm; for phenylglycodol a reservoir amount of 1.5 to 1.9 gm; about 160 to 250 mg of butabarbital in the reservoir; about 150 to 170 mg of chloradiazepoxide; from 0.5 to 1.2 gm of methsuximide; from 0.7 to 1.9 gm of ethosuximide; from 20 to 40 mg of hydrolazine; about 50 to 100 mg of totazoline; and the like. Generally, the drug delivery devices made according to the invention can contain from about 250 nanograms to 50 grams of drug for releasing it at a controlled rate of from about 25 nanograms to about 25 grams of drug or larger amounts per day. Of course, other devices containing different amounts of drug for use for different time periods such as a week, month and year are also readily made by the invention.

It will be appreciated by those versed in the art that the unique drug delivery device of this invention can provide for the programmed delivery of drug at a rate of delivery characterized by a zero order time dependence for prolonged period of time; and, that the device therefore lends itself to administering an effective amount of drug needed for a therapeutic effect while essentially avoiding the presence of excessive amount of drug at the needed biological site. By a prolonged period of time is meant, as used herein, periods that embrace the time needed for a fast acting drug to effect its end up to periods that embrace the continual, uninterrupted, repetitious time of a long term drug delivery device. For example, the prolonged time can be one hour or more for drugs, like local anesthetics, analge-

sics, prostaglandins or the like, that are effective in nanogram and milligram amounts, or the like, to 3 years or longer for steroids released within the uterine cavity. Other examples include wherein the amount of drug in the reservoir can be 100 to 300 mg of thiopropazate for releasing 15 to 30 mg over a 24 hour period; 200 to 400 mg in the reservoir of phenyltoloxamine for a release of 150 to 200 mg of papaverine in the reservoir for a topical release 30 to 75 mg over a 24 hour period; 2.5 g to 4.0 g of mephenoxalone for a release of 1.0 to 1.5 g per day; 15 to 25 mg of tranlycypromane for a release of 10 to 15 mg as the standard dose; 1 to 2 gm of trimethadione present in the reservoir for a release administration of 0.5 to 1.0 g per day; prostaglandins for example PGE₁, PGE₂, PGA₁, PGF_{2α} in amounts of 0.5 mg to 10 mg for release of 1 ng to 100 ng and the like; for progesterone or progesterone the administration in the uterus of 10 to 200 μg per day for release for 1 year to 3 years as an antifertility agent in a mature, child-bearing woman; an oral device administering 300 mg to 600 mg per day of analgesic acetaminophen to a 60 to 70 kg adult male; and the like.

The drug delivery devices of the invention are easily fabricated by using standard techniques. For example, in one embodiment, the reservoir comprising the carrier and the drug is fabricated by standard techniques. For example, in one embodiment a precured liquid polymer can be mixed with the drug 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, followed by curing to yield a solid carrier. Next, the solid carrier is coated by spraying, dipping, and the like with a material that contains a known concentration of drug release rate additive and can form the wall of the device. In another embodiment a pre-polymer and the drug are mixed and then charged into a drug release rate controlling wall that also contains known amounts of a drug release rate additive or a mixture of additives and then cured into a solid, and sealed therein. In another embodiment solid drug particles and solid carrier particles are compressed into a carrier and then charged into a wall to form a novel drug delivery device.

In another embodiment a liquid, pre-cured material and the drug are mixed charged into and cured in a highly permeable tube that is positioned within a release rate controlling wall. Alternatively, the tube can be coated with the wall material, or a prepolymer can be cast around the tube and finally cured to form the wall. The device can also be manufactured by first forming a mixture comprised of an additive, a resin and a solvent, casting the mixture as a film, and then evaporating the solvent and drying the film to produce a drug release rate membrane that can be laminated with drug confined between the laminae.

The wall material forming the device and having the reservoir contained therein can be formed to a given drug 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 tubes, rods, discs, films, rings and other highly reproducible shapes of controllable composition, readily results in fabrication of drug delivery devices with controlled characteristics and thus overcomes a significant disad-

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vantage of previously described devices. Other standard procedures, as described in Modern Plastics Encyclopedia, Vol. 46, pages 62 to 70, 1969; Plastic Technology, by Swanson, R. S., pages 59 to 229, 1965, published by McKnight and McKnight Publishing Co., Bloomington, Ill.; 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

A drug delivery implant device shaped like a rectangle and comprised of a reservoir containing a drug in a carrier surrounded by a drug release rate wall containing a drug release rate modifying additive is manufactured as follows: first, 100 parts by weight of suspension grade poly(vinyl chloride) resin is mixed with 60 parts by weight of a polyester modifier of butylene glycol and adipic acid terminated with stearic acid of 2000 m.w. and the two mixed ingredients dissolved in 700 parts by weight of tetrahydrofuran to form a solution with a viscosity of about 5000 centipoises. Next, a film is formed by a doctor blade coating the solution onto a glass plate and allowing the solvent to air evaporate. The film is completely dried in an air oven at 50°C for several hours. A drug delivery device is formed by charging steroid dispersed in an aqueous methyl cellulose carrier between two layers of the film and heat sealing the contacting edges to form a drug implant device.

EXAMPLE 2

A drug delivery device for administering drug comprised of a wall surrounding a reservoir containing a drug is formed as follows: first, 100 parts of plastisol grade poly(vinyl chloride) is mixed with 100 parts of a liquid polyester modifier and 2 parts of di-octyl tin maleate and the ingredients mixed on a three-roll mill. The polyester modifier is a condensation polymer of 850 m.w. and is made from triethylene glycol and azelaic acid terminated with 2-ethylhexanol. The result is a thick cream which is cast by standard means, knife coating, on a siliconized paper substrate. The cast film is hot set by heating at 350°F for five minutes to produce a transparent, glass clear film. The film is then cut into predetermined shape and used to surround a reservoir comprised of pilocarpine in an alginic acid gel carrier.

EXAMPLE 3

A drug delivery device comprised of a drug release rate wall surrounding and housing a reservoir containing a drug is manufactured as follows: to 100 phr (parts per hundred) of polyvinyl acetate is added 25 phr of a liquid polyester modifier (a condensation polymer of a propylene glycol and terephthalic acid terminated by dodecyl alcohol, the polyester having a m.w. of 8,000) and 600 parts of methyl ethyl ketone and the ingredients are mixed until a clear homogeneous solution is attained. The resulting solution is then spread on a glass plate with a coating knife and the ketone is allowed to evaporate at room temperature. Final traces of solvent

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ketone are removed by heating to 40°C for 4 hours in a vacuum oven. The resulting flexible film is stripped from the plate and used as a barrier membrane in the construction of drug delivery systems.

EXAMPLE 4

Following the procedure set forth in Example 1 a drug delivery device is prepared by repeating the described procedure except that 100 parts of polyvinylidene chloride and 35 parts of a polyester modifier, comprised of a condensation polymer of polyethylene glycol and phthalic anhydride terminated by stearic acid and m.w. 2,500 are dissolved in tetrahydrofuran, the membrane being made as described in Example 1.

EXAMPLE 5

Four hundred grams of low density (1.18) polyethylene is added to a laboratory size rubber and plastics mill (rolls 6 inches diameter, 13 inches wide) and milled for 3 minutes at 165°C. At this point is added 60 grams of a copolymer of ethylene and vinyl acetate of number average molecular weight 28,500 and a weight ratio of ethylene/vinyl acetate in the copolymer of 74/26. Milling is continued for 15 minutes to blend the modifier into the polyethylene. The resulting modified polyethylene is then extruded through a blow-film die to film thickness of 2.5 mils. This film is then used as a barrier membrane in a drug delivery system.

EXAMPLE 6

Ten grams of cellulose acetate of 38.6% acetyl content and 1.5 grams of polyethylene glycol of m.w. 800 are dissolved in dimethyl formamide and the resulting modified cellulose acetate is cast as a film from this solution onto a teflon belt and is stripped off, when dry, as a 2 mil thick film, which is then used as a barrier membrane for controlled drug delivery.

EXAMPLE 7

Five hundred grams of isotactic polypropylene are milled for 3 minutes at 175°C on a standard 6 inches × 13 inches laboratory mill and to this mass of polypropylene is added 48 grams of chlorinated polyethylene of molecular weight 22,000 and chlorine content of 34.6%. Milling is continued for 15 minutes at 175°C to effect homogenization. The modified polypropylene is then removed from the mill and is extruded through a flat die into a film 4 mils in thickness. This film is then used as a barrier membrane for controlled delivery of drug.

EXAMPLE 8

Six hundred grams of a copolymer of butadiene and acrylonitrile of 32% acrylonitrile content is mixed for 6 minutes at 65°C on a standard 6 inches × 13 inches laboratory rubber mill. At this point, at which time the rubber is smoothly banded on the mill rolls, 120 grams of a liquid polyester is added over a period of 6 minutes. The rubbery copolymer is cut and folded over intermittently to assure good blending of the polyester, which is made from a condensation reaction of 1,3-butanediol with sebacic acid and terminated with n-octanol to give a molecular weight of 3,400. The resulting modified rubbery polymer is compression molded at 120°C into a 4 mil film. This film is then used as a membrane barrier for controlled release of drug.

EXAMPLE 9

Four hundred grams of a copolymer of 95% ethylene and 5% propylene, by weight, is added to a standard 6 inches x 13 inches rubber roll mill and is milled for 3 minutes at 160°C. To the copolymer is then added 40 grams of a copolymer of ethylene and ethyl acrylate of 18% ethyl acrylate content and number average molecular weight 30,000. Milling is continued for 15 minutes and the resulting modified copolymer is removed from the mill and pressed between heated (160°C) platens into a film 4 mils thick. The platens are cooled while the film is under pressure, the pressure is released, and the film is stripped off. The film is then ready for use as a barrier membrane for controlled delivery of drugs.

EXAMPLE 10

Five hundred grams of low density (1.18) polyethylene is added to a laboratory size rubber and plastics mill (rolls 6 inches x 13 inches) and milled for 3 minutes at 165°C. At this point is added 60 grams of a copolymer of ethylene and vinyl chloride of number average molecular weight 26,000 and a chlorine content of 36%. Milling is continued for 15 minutes to blend the modifier into the polyethylene. The resulting modified polyethylene is then extruded through a blow-film die to a film thickness of 2.0 mils. This film is then used as a barrier membrane in a drug delivery system.

In Table 1 there is set forth the drug release rate results obtained by varying the amount of additive present in a wall of a delivery device.

Table 1

Wall	Modifier	Amount	Drug Release Rate Micrograms per hr.
PVC [Ⓢ]	Polyester	100	9
"	"	50	1
PVC [Ⓢ]	Condensation polymer of adipic acid, a glycol, terminated by a monocarboxylic acid	100	19
"	"	75	8
PVC [Ⓢ]	"	100	16
"	"	75	6
"	"	50	2

In Table 1, PVC[Ⓢ] is commercially available poly(vinyl chloride) sold as PVC-450 by Diamond-Shamrock Co., PVC[Ⓢ] is poly(vinyl chloride) Geon 103-EP as sold by the B. F. Goodrich Chemical Company.

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 drug delivery device for administering a drug to produce a local or systemic physiologic or pharmacologic effect; as, the rate of release of drug administered from the device can be controlled to produce these effects, while simultaneously lessening or overcoming the undesirable effects frequently associated with the administration of drugs by prior art methods. It will be further understood to those versed in the art that many 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 therein.

We claim:

1. In a drug delivery device for continuously administering a drug at a controlled rate for a prolonged period of time to a body site, said device comprising a reservoir containing said drug and a carrier permeable to said drug, the amount of said drug being sufficient to maintain saturation within said carrier during said prolonged period, and a wall surrounding said reservoir which is permeable to the drug but at a rate less than that of the carrier, whereby the drug is released from the reservoir by diffusion through the wall in which the drug dissolves in the material forming the wall and moves therethrough in the direction of lower chemical potential, the improvement comprising forming the wall from a composition comprising a mixture of:

- A. a polymer which is rubbery with a glass transition temperature below about 20°C, or is glassy having a glass transition temperature between about 20°C and about 150°C, or has a crystallinity between about 5% and about 95%; and
 - B. a polymeric additive which is essentially insoluble in body fluids, is nonvolatile and nonleachable and nonextractable from the polymer under the use conditions of the composition and is selected from the group consisting of:
 - a. essentially linear olefinically saturated polyesters having a number average molecular weight of about 500 to about 8,000 of a diol of 2 to about 7 carbon atoms or polyethylene glycol and a dibasic carboxylic acid of about 6 to about 15 carbon atoms in which the terminating group is a carboxyacyl group of about 2 to about 18 carbon atoms or an alkoxy group of about 3 to about 15 carbon atoms;
 - b. polyethylene glycols of about 200 to about 1,500 molecular weight;
 - c. ethylene-vinyl acetate copolymers of about 20% to about 40% by weight vinyl acetate and about 20,000 to about 30,000 number average molecular weight;
 - d. chlorinated polyethylene of about 25% to 45% by weight chlorine and about 20,000 to about 30,000 number average molecular weight;
 - e. ethylene-ethylacrylate copolymers of about 20% to about 40% by weight ethylacrylate and about 20,000 to about 30,000 number average molecular weight; and
 - f. ethylene-vinyl chloride copolymers of about 25% to about 45% by weight chlorine and about 20,000 to about 30,000 number average molecular weight, the amount of additive in the mixture being sufficient to make the permeability of the composition of the drug substantially different than the permeability of the polymer to drug but less than the permeability of the carrier to drug, said composition being biologically compatible with the site, essentially non-erodible, essentially insoluble in body fluids, and, if the drug is highly water soluble, substantially impermeable to water to essentially prevent dilution of the drug by absorption of body fluids into the reservoir.
2. The improvement of claim 1 wherein said polymer is selected from the group consisting of polyvinyl chloride, polyvinylidene chloride, polyvinyl fluoride, polyvinylidene fluoride, polyvinyl acetate, polyvinyl butyral, polystyrene, cellulose acetate, cellulose nitrate, ethyl cellulose, cellulose acetate butyrate, cellulose acetate propionate, polyurethane, butadiene/acrylonitrile copolymer, chlorinated natural rubber, styrene/

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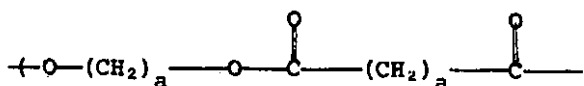
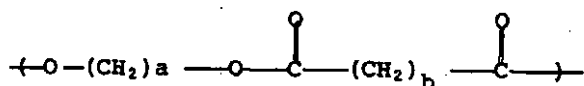
19

butadiene copolymer, ethylene/propylene copolymer, ethylene/vinyl acetate copolymer, ethylene/vinyl chloride copolymer, polyethylene, polypropylene and polyalkyl acrylates in which the alkyl group is of 2 to 4 carbon atoms.

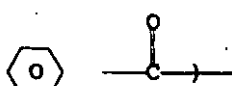
3. The improvement of claim 1 wherein said amount of additive is 1 to 2 mg per cm² of wall.

4. The improvement of claim 2 wherein the amount of additive is 1 to 2 mg per cm² of wall.

5. The improvement of claim 1 wherein said polyester is of the recurring formula:



or

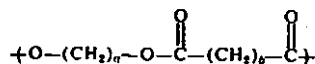


wherein *a* is an integer from 2 to 4, inclusive, and *b* is an integer from 4 to 13, inclusive.

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6. The improvement of claim 1 wherein said amount of additive is about 0.2 mg to 5 mg per cm² of wall.

7. The improvement of claim 1 wherein the polymer is ethylene/vinyl acetate copolymer and the polymeric additive is an essentially linear olefinically saturated polyester having a recurring general formula



wherein *a* is an integer from 2 to 4, inclusive, and *b* is an integer from 4 to 13, inclusive.

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Octrooiraad



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- ③2 --
- ③3 --
- ③1 --
- ③2 --

- ④3 Ter inzage gelegd 18 januari 1988.

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Intra-uterine anticonceptieinrichting.

De uitvinding heeft betrekking op een intra-uterine anticonceptieinrichting, die is voorzien van een lang-gerekte steel.

Een dergelijke inrichting is bekend uit het Ne-
5 derlandse octrooischrift 173707.

De langgerekte steel van de bekende anticoncep-
tieinrichting draagt aan het ene uiteinde twee veerkrachtige,
vrijdragende armen, welke armen aan weerszijden van de steel
naar opzij uitsteken. Na in de baarmoederholte te zijn inge-
10 bracht wordt de bekende anticonceptieinrichting daarin vast-
gehouden met behulp van kleine uitsteeksels, die op de bui-
tenzijde van de armen zijn aangebracht.

Deze bekende anticonceptieinrichting heeft voor
de gebruiker een aantal ernstige nadelen.

15 Voor het verwijderen van de anticonceptieinrich-
ting uit de baarmoeder is het uiteinde van de steel voorzien
van een trekdraad, die buiten de baarmoeder uitsteekt. De
trekdraad kan aanleiding zijn voor infectie, hetgeen onge-
wenst is. Bovendien bestaat het risico, dat de trekdraad bij
20 het bevestigingspunt aan de steel tijdens het uittrekken af-
breekt, hetgeen eveneens ongewenst is.

Voorts heeft de bovengenoemde bekende anticon-
ceptieinrichting het nadeel, dat de lange steel beschadiging
van de baarmoederwand kan veroorzaken, tengevolge van de
25 voortdurende beweging van de baarmoeder, welke beschadiging
aanleiding kan geven tot bloedingen. Ook de uitsteeksels kun-
nen bloedingen veroorzaken, doordat zij de baarmoederwand
kunnen irriteren dan wel beschadigen.

De uitvinding beoogt thans een intra-uterine
30 anticonceptieinrichting te verschaffen, waarbij de nadelen
van de bekende inrichting op doeltreffende wijze zijn opgehe-
ven.

De uitvinding verschaft hiertoe een intra-
uterine anticonceptieinrichting, die is voorzien van een
35 langgerekte steel, met het kenmerk, dat de langgerekte steel
aan een uiteinde vastzit aan een ring van een veerkrachtig

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materiaal, waarbij de lengte van de langgerekte steel gelijk of kleiner is dan de diameter van de ring.

Onder de term "ring" dient volgens de uitvinding te worden verstaan een gesloten vorm, gewoonlijk een cirkel, 5 maar bijvoorbeeld ook een ovale vorm.

Aangezien de ring glad is en geen uitsteeksels bezit doet zich het gevaar van irritatie van de baarmoederwand niet voor.

Doordat bovendien de lengte van de langgerekte 10 steel gelijk of kleiner is dan de diameter van de ring en het vrije uiteinde van de steel afgerond is, is de kans, dat de steel de baarmoederwand beschadigt tot een minimum beperkt. De uit een veerkrachtig materiaal vervaardigde ring heeft bovendien het voordeel, dat de anticonceptieinrichting volgens 15 de uitvinding de bewegingen van de baarmoederwand zonder deze te beschadigen volgt en daarbij kan worden verplaatst naar de meest gunstige positie in de baarmoeder.

De kans op bloeding in de baarmoeder wordt volgens de anticonceptieinrichting volgens de uitvinding tot een 20 minimum beperkt.

De anticonceptieinrichting volgens de uitvinding kan in de baarmoederholte worden ingebracht, bijvoorbeeld met behulp van een huls, waarin de langgerekte steel van de inrichting volgens de uitvinding is opgenomen, door deze huls 25 in de baarmoedermond te steken. Vervolgens blijft de inrichting volgens de uitvinding na terugtrekken van de huls in de baarmoederholte achter.

De anticonceptieinrichting kan voorts ook nog in de baarmoederholte worden gebracht met behulp van een geschikte tang. 30

De verwijdering van de intra-uterine anticonceptieinrichting volgens de uitvinding kan bijvoorbeeld geschieden door gebruik te maken van een kunststof staaf, waarvan het uiteinde haakvormig is uitgevoerd, dan wel met behulp 35 van dezelfde tang waarmee de inrichting is ingebracht.

Aangezien bij de verwijdering van de anticonceptieinrichting volgens de uitvinding geen trekdraad wordt gebruikt, dit in tegenstelling tot de stand der techniek, is de kans op infecties tot een minimum beperkt.

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39
Bij voorkeur is de langgerekte steel vervaardigd uit hetzelfde veerkrachtige materiaal als de ring zelf.

Het veerkrachtige materiaal dient fysiologisch inert te zijn en is bij voorkeur van kunststof. Met voordeel
5 gebruikt men hiervoor polyethyleen, ofschoon ook andere geschikte materialen kunnen worden toegepast.

Teneinde een betere anticonceptieinrichting te krijgen, kan de langgerekte steel voorzien zijn van een bekleding uit een conceptie- en/of zwangerschap verhinderend
10 materiaal.

Hiertoe kan men met voordeel een metaal gebruiken, in het bijzonder koper.

Gebleken is, dat koper in de vorm van een spiraal om de langgerekte steel dan wel in de vorm van ringen
15 bijzonder goed voldoet.

Bovendien kan de steel zijn voorzien van een geneesmiddel, in het bijzonder een zaaddodend of een zaad inactiverend middel.

De intra-uterine anticonceptieinrichting volgens de uitvinding wordt thans aan de hand van de volgende tekeningen nader toegelicht.
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Fig. 1 stelt een uitvoeringsvorm van de intra-uterine anticonceptieinrichting volgens de uitvinding voor, zonder bekleding van de steel.

25 Fig. 2 is een voorkeursuitvoeringsvorm, waarbij de langgerekte steel is voorzien van een koperen bekleding.

Fig. 3 is een uitvoeringsvorm van een samenstel van de intra-uterine anticonceptieinrichting volgens fig. 2 en de bijbehorende buisvormige inbrenghuls.

30 In fig. 1 stelt 1 de intra-uterine anticonceptieinrichting volgens de uitvinding voor. De langgerekte steel 3, die in deze uitvoeringsvorm niet is bekleed, zit aan een uiteinde vast aan de ring 2, waarbij ter plaatse van het aanhechtingspunt van de langgerekte steel aan de ring zich een
35 bolvormige verdikking 4 bevindt.

Het materiaal waaruit de ring 2 is vervaardigd is een flexibel materiaal, bij voorkeur kunststof, zoals een inert polyethyleen. Bij voorkeur bestaat het materiaal, waar-

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uit de langgerekte steel 3 is vervaardigd, uit hetzelfde materiaal als de ring 2 zelf.

In fig. 2 is de langgerekte steel 3 voorzien van een bekleding 5, welke bekleding in deze uitvoeringsvorm een koperen spiraal is. Met voordeel kan de bekleding uit op elkaar gestapelde koperen ringen bestaan. De bekleding kan echter ook uit een voor de onderhavige doeleinden geschikt ander metaal bestaan. Voorts kan de bekleding bestaan uit een geneesmiddel met een anticonceptieve werking, bijvoorbeeld een geschikt hormoon.

Fig. 3 toont een samenstel 6 van de intra-uterine anticonceptieinrichting volgens fig. 2 en de bijbehorende buisvormige inbrenghuls 7. Voorafgaande aan het inbrengen van de intra-uterine anticonceptieinrichting in de baarmoeder wordt de langgerekte steel van de inrichting opgenomen in de buisvormige inbrenghuls 7, die is vervaardigd uit een geschikte kunststof, zodanig, dat de langgerekte steel van de inrichting zich nagenoeg volledig in de huls bevindt. De verdikking 4, die bolvormig is, bevordert de inbrengbaarheid van de inrichting in de baarmoeder, met het gevolg, dat eventuele verwondingen, die bloedingen kunnen veroorzaken, tijdens het inbrengen tot een minimum worden beperkt.

De inrichting volgens de uitvinding kan met behulp van de inbrenghuls 7 in de baarmoeder worden ingebracht, waarna na terugtrekken van de huls de inrichting in de baarmoeder achterblijft.

Het zal duidelijk zijn, dat de uitvinding geenszins is beperkt tot deze uitvoeringsvormen. In plaats van één ring, kunnen meerdere ringen worden toegepast. In dit geval heeft de inrichting de vorm van een korf.

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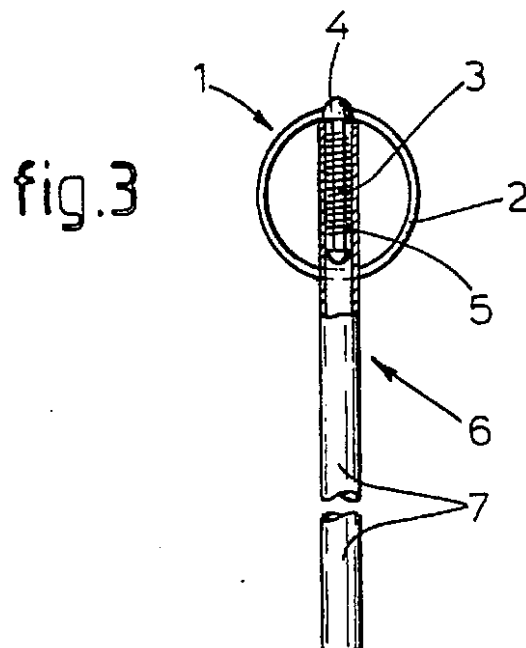
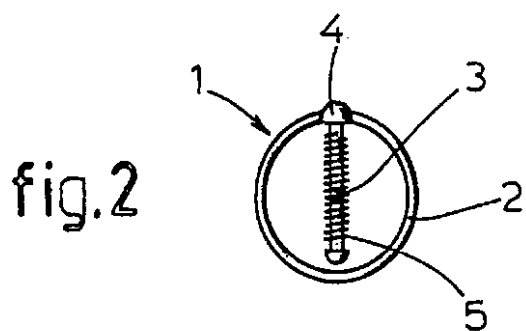
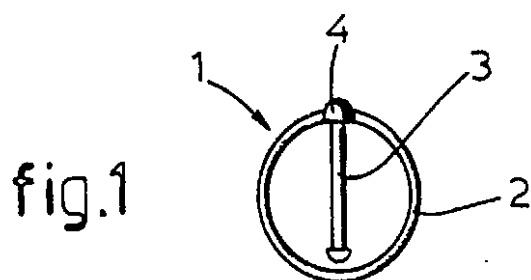
C o n c l u s i e s:

1. Intra-uterine anticonceptieinrichting, die is voorzien van een langgerekte steel, m e t h e t k e n m e r k, dat de langgerekte steel aan een uiteinde vastzit aan een ring van een veerkrachtig materiaal, waarbij de
5 lengte van de langgerekte steel gelijk of kleiner is dan de diameter van de ring.
2. Anticonceptieinrichting volgens conclusie 1, m e t h e t k e n m e r k, dat de langgerekte steel van hetzelfde materiaal is als de ring.
- 10 3. Anticonceptieinrichting volgens conclusie 1 of 2, m e t h e t k e n m e r k, dat het veerkrachtige materiaal een fysiologisch inert kunststofmateriaal is.
4. Anticonceptieinrichting volgens conclusie 3, m e t h e t k e n m e r k, dat het fysiologische inerte
15 kunststofmateriaal polyethyleen is.
5. Anticonceptieinrichting volgens conclusies 1 - 4, m e t h e t k e n m e r k, dat de langgerekte steel voorzien is van een bekleding.
6. Anticonceptieinrichting volgens conclusie 5,
20 m e t h e t k e n m e r k, dat de bekleding uit een de conceptie- en/of zwangerschap verhinderend materiaal bestaat.
7. Anticonceptieinrichting volgens conclusie 6, m e t h e t k e n m e r k, dat de bekleding een metaal is.
- 25 8. Anticonceptieinrichting volgens conclusie 7, m e t h e t k e n m e r k, dat het metaal koper is.
9. Anticonceptieinrichting volgens conclusie 8, m e t h e t k e n m e r k, dat koper in de vorm van een spiraal of ringen om de langgerekte steel is aangebracht.
- 30 10. Anticonceptieinrichting volgens conclusie 5, m e t h e t k e n m e r k, dat de bekleding een geneesmiddel is.
11. Anticonceptieinrichting volgens conclusie 10, m e t h e t k e n m e r k, dat het geneesmiddel een
35 zaaddodend of zaad inactiverend middel is.

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12. Samenstel van de intra-uterine anticonceptieinrichting volgens conclusies 1 - 11 en de bijbehorende buisvormige inbrenghuls, m e t h e t k e n m e r k, dat de langgerekte steel van de inrichting is opgenomen in de buis-
5 vormige inbrenghuls, met behulp waarvan de inrichting volgens de uitvinding in de baarmoederholte kan worden ingebracht, waarna de inrichting door terugtrekking van de huls in de baarmoeder achterblijft.

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РСТ

ВСЕМИРНАЯ ОРГАНИЗАЦИЯ
ИНТЕЛЛЕКТУАЛЬНОЙ СОБСТВЕННОСТИ
Международное бюро



МЕЖДУНАРОДНАЯ ЗАЯВКА, ОПУБЛИКОВАННАЯ В СООТВЕТСТВИИ
С ДОГОВОРом О ПАТЕНТНОЙ КООПЕРАЦИИ (РСТ)

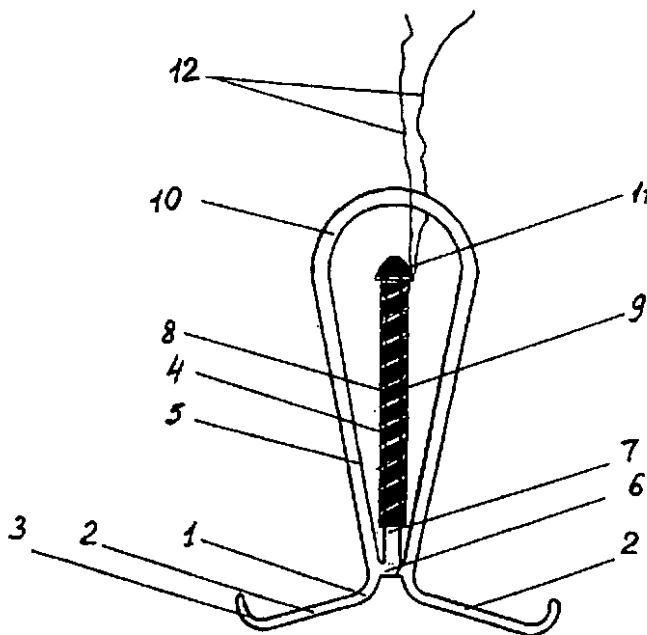
(51) Международная классификация изобретения ⁶ : A61F	A2	(11) Номер международной публикации: WO 96/29026 (43) Дата международной публикации: 26 сентября 1996 (26.09.96)
(21) Номер международной заявки: РСТ/UA96/00004 (22) Дата международной подачи: 17 марта 1996 (07.03.96) (30) Данные о приоритете: 95031079 9 марта 1995 (09.03.95) UA (71)(72) Заявитель и изобретатель: БОРОДИН Юрий Васильевич [UA/UA]; 244002 Сумы, ул. Дзержинская, 21/68 (UA) [BORODIN, Jury Vasilievich, Sumy (UA)].		(74) Агент: ЧЕРЕПОВ Леонид Владимирович; 254119 Киев, а/я 3 (UA) [CHEREP OV, Leonid Vladimirovich, Kiev (UA)]. (81) Указанные государства: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, патент АРИРО (KE, LS, MW, SD, SZ, UG), евразийский патент (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), европейский патент (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), патент ОАПИ (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Опубликована Без отчёта о международном поиске и с повторной публикацией по получении отчёта.

(54) Title: INTRAUTERINE CONTRACEPTIVE DEVICE

(54) Название изобретения: ВНУТРИМАТОЧНОЕ ПРОТИВОЗАЧАТОЧНОЕ СРЕДСТВО

(57) Abstract

The proposed intrauterine contraceptive device comprises a horizontal strip (1) with two legs (2) at least one of which has a curved end (3); a coil (4); and a loop (5) joined to the horizontal strip (1) and provided with a thickened base (6). The legs (2) of the straight section of the horizontal strip (1) are configured at an acute angle to the horizontal plane and symmetrically in relation to the vertical axis; both are provided with curved ends (3), the curve being in the form of a circular section, the coil (4) takes the form of a polyethylene strip and is situated inside the loop (5) on an anchoring element (7) connected to the base (6) of the horizontal strip (1) and coaxial with the vertical axis of symmetry of the intrauterine contraceptive device. The legs (2) of the horizontal strip (1) are at an angle of between 5 and 30° to the horizontal. The coil (4) is provided with a coating (8) of refined copper which is applied to the outer surface of the polyethylene strip by plasma deposition. The lower part of the loop (5) is springy and is at least twice the length of the anchoring element (7). The free end of the anchoring element (7) is provided with a spherically curved section (11) and serves as the base for securing locating threads (12).



(57) Реферат

Внутриматочное противозачаточное средство содержит горизонтальную планку /I/ с двумя ветвями /2/, по меньшей мере одна из которых выполнена с закругленным концом /3/, спираль /4/ и петлю /5/, связанную с горизонтальной планкой /I/ и имеющую утолщенное основание /6/, причем ветви /2/ прямолинейного участка горизонтальной планки /I/ расположены под острым углом к горизонтальной плоскости и симметрично относительно вертикальной оси, обе выполнены с закругленными концами /3/, закругление выполнено в виде части окружности, а спираль /4/ выполнена в виде полиэтиленовой ленты и размещена внутри петли /5/ на якоре /7/, связанном с основанием /6/ горизонтальной планки /I/ и расположенном соосно с вертикальной осью симметрии внутриматочного противозачаточного средства. Величина угла установки ветвей /2/ с горизонтальной планкой /I/ составляет 5 - 30°. Спираль /4/ снабжена покрытием /8/ в виде слоя рафинированной меди, нанесенного на наружную поверхность полиэтиленовой ленты способом плазменного напыления. Нижняя часть петли /5/ выполнена упругой и по размеру составляет не менее двух длин якоря /7/. Свободный конец якоря /7/ снабжен закруглением /II/ в виде части сферы и служит основанием для закрепления опознавательных нитей /I2/.

ИСКЛЮЧИТЕЛЬНО ДЛЯ ЦЕЛЕЙ ИНФОРМАЦИИ

Коды, используемые для обозначения стран-членов РСТ на титульных листах брошюр, в которых публикуются международные заявки в соответствии с РСТ.

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ВНУТРИМАТОЧНОЕ ПРОТИВОЗАЧАТОЧНОЕ СРЕДСТВО

ОБЛАСТЬ ТЕХНИКИ

5 Настоящее изобретение относится к области медицинской техники, в частности, к устройствам, предохраняющим от беременности.

ПРЕДШЕСТВУЮЩИЙ УРОВЕНЬ ТЕХНИКИ

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Известные конструкции внутриматочных противозачаточных устройств /SU, А, 535883/ содержат петлю с отогнутыми по радиусу ветвями Т-образной формы, которая имеет суженную часть, а угол между суженной частью и любой из отходящих ветвей составляет менее 90° , причем вершина петли выполнена по радиусу, а на концах ветвей выполнены утолщения.

15 Однако такая конструкция внутриматочного противозачаточного средства обладает некоторыми недостатками. Конструкция утяжелена и недостаточно эластична, что способствует экспульсии, при этом угол отходящих ветвей не позволяет им мешать прохождению сперматозоидов в фаллопиевы трубы к яичникам и мешать плодному яйцу закрепиться на верхней части полости матки. Кроме того, это внутриматочное противозачаточное средство не имеет медной проволоки или медной спирали, что снижает противозачаточный эффект вдвое.

Наиболее близкой к заявляемому изобретению по технической сущности и достигаемому положительному эффекту является конструкция внутриматочного противозачаточного средства /SU, А, 1520685/, содержащая горизонтальную планку с двумя ветвями, по меньшей мере одна из которых выполнена с закругленным концом в виде гладкой головки, спираль в виде медной оплетки и связанную с горизонтальной планкой упругую петлю с утолщенным основанием.

35 Однако такая конструкция внутриматочного противозачаточного средства имеет некоторые недостатки. Сложность и относительно большие габаритные размеры конструкции не по-

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- звolyют без травм или резких болевых ощущений ввести внутриматочное противозачаточное средство в матку. Расположенная горизонтально медная оплетка прижимается к верхней части матки, что может привести к ее перфорации и воспалительным процессам в результате воздействия солей меди, образующихся на поверхности медной оплетки.

РАСКРЫТИЕ ИЗОБРЕТЕНИЯ

- 10 В основу настоящего изобретения поставлена задача повышения надежности контрацептивного эффекта путем нахождения анатомически правильной формы контрацептива, позволяющей применять один типоразмер в различных по форме и размерам полостях маток у женщин, рожавших полновесных детей, и отказа от медной проволоки и ее замены полимерной спиралью, омедненной химически чистой медью, а также удержания средства в полости матки путем предотвращения его выброса /экспульсии/.

- Внутриматочное противозачаточное средство, согласно изобретению, содержит горизонтальную планку с двумя ветвями, по меньшей мере одна из которых выполнена с закругленным концом, спираль и связанную с горизонтальной планкой петлю с утолщенным основанием, причем ветви прямолинейного участка горизонтальной планки расположены под острым углом к горизонтальной плоскости и симметрично относительно вертикальной оси, обе выполнены с закругленными концами, при этом закругление выполнено в виде части окружности, а спираль выполнена в виде полиэтиленовой ленты и размещена внутри петли на якоре, связанном с основанием горизонтальной планки и расположенном соосно с вертикальной осью симметрии внутриматочного противозачаточного средства. Величина угла установки ветвей с горизонтальной планкой составляет 5 - 30°. Спираль снабжена покрытием в виде слоя рафинированной меди, нанесенного на наружную поверхность полиэтиленовой ленты способом плазменного напыления. Нижняя часть петли выполнена упругой и по размеру составляет не менее двух длин якоря. Свободный конец якоря снабжен

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закруглением в виде части сферы, который служит фиксатором для закрепления спирали и основанием для закрепления опознавательных нитей.

5 Таким образом, предлагаемая конструкция внутриматочного противозачаточного средства обладает следующими существенными отличительными признаками:

10 - ветви прямолинейного участка горизонтальной планки расположены под острым углом к горизонтальной плоскости и симметрично относительно вертикальной оси, что позволяет за счет маточных сокращений не пропускать сперматозоиды к фаллопиевым трубам и к яичникам;

15 - ветви выполнены с закругленными концами, причем закругление выполнено в виде части окружности, что позволяет исключить травмирование и болевые ощущения при смещении внутриматочного противозачаточного средства, вызываемом физическими перегрузками женщины;

20 - спираль размещена внутри петли, что позволяет исключить контакт петли со слизистой оболочкой матки и предотвратить перфорацию ее стенок;

25 - спираль выполнена в виде полиэтиленовой ленты и размещена на якоре, связанном с основанием горизонтальной планки и расположенном соосно с вертикальной осью симметрии внутриматочного противозачаточного средства, что позволяет исключить воспалительные процессы от солей, увеличить площадь медного покрытия и снизить травматизм во время нахождения внутриматочного противозачаточного средства внутри матки и при удалении его из полости матки;

30 - величина угла установки ветвей по отношению к горизонтальной планке составляет $5 - 30^\circ$, что позволяет им прижиматься к слизистой оболочке дна матки и, таким образом, оказывать механическое противозачаточное действие;

35 - спираль снабжена покрытием в виде слоя рафинированной меди, нанесенного на наружную поверхность полиэтиленовой ленты способом плазменного напыления, что позволяет гарантировать не менее чем трехлетний контрацептивный эффект и исключить травмирование при нахождении средства внутри матки и при его выводе из потребления;

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- петля имеет упругую нижнюю часть по размеру не менее двух длин якоря, что позволяет исключить экспульсию;

- 5 - свободный конец якоря снабжен закруглением в виде части сферы и служит основанием для закрепления опознавательных нитей, что позволяет закрепить собственно спираль на стержне, а также закрепить опознавательные нити.

Таким образом, все существенные признаки настоящего изобретения направлены на решение поставленной задачи, а именно, на повышение надежности удержания средства в по-

10 лости матки путем предотвращения выброса /экспульсии/.

КРАТКОЕ ОПИСАНИЕ ФИГУР ЧЕРТЕЖЕЙ

Сущность настоящего изобретения поясняется чертежами,

15 на которых представлены:

фиг. 1 - внутриматочное противозачаточное средство согласно изобретению, общий вид;

фиг. 2 - то же, вид сверху;

фиг. 3 - внутриматочное противозачаточное средство

20 согласно изобретению, размещенное в полости матки.

ВАРИАНТ ОСУЩЕСТВЛЕНИЯ ИЗОБРЕТЕНИЯ

Внутриматочное противозачаточное средство, согласно

25 изобретению, содержит горизонтальную планку I с двумя ветвями 2, по меньшей мере одна из которых выполнена с закруглением 3, спираль 4 и связанную с горизонтальной планкой I петлю 5 с утолщенным основанием 6. Ветви 2 прямолинейного участка горизонтальной планки I расположены под

30 острым углом к горизонтальной плоскости и симметрично относительно вертикальной оси, обе выполнены с закругленными концами 3, причем закругление выполнено в виде части окружности. Спираль 4 выполнена в виде полиэтиленовой ленты и размещена внутри петли 5 на якоре 7, который связан с ос-

35 нованием 6 горизонтальной планки I и расположен соосно с вертикальной осью симметрии внутриматочного противозачаточного средства. Величина угла установки ветвей 2 по от-

- ношению к горизонтальной планке I составляет $5 - 30^\circ$. Спираль снабжена покрытием 8 в виде слоя рафинированной меди, нанесенного на наружную поверхность 9 полиэтиленовой ленты способом плазменного напыления. Нижняя часть 10 петли 5
- 5 выполнена упругой и по размеру составляет не менее двух длин якоря 7. Свободный конец якоря 7 снабжен закруглением II в виде части сферы, которое служит фиксатором для закрепления спирали и основанием для закрепления опознавательных нитей 12.
- 10 Внутриматочное противозачаточное средство, согласно изобретению, применяют следующим образом.
- После извлечения внутриматочного противозачаточного средства /контрацептива/ из фабричной упаковки его отсоединяют от вводной трубки. Последнюю берут в левую руку и
- 15 фиксируют положение ограничителя, что является ориентиром правильного введения контрацептива. Затем большим и указательным пальцами правой руки захватывают контрацептив, крепко прижав обе нисходящие ветви 2 петли 5 к стержню и друг к другу, причем опознавательные нити 12 должны быть
- 20 вставлены в трубку и охватывать петлю 5, и в таком виде вставляют нижнюю часть контрацептива в дистальный конец вводной трубки. При этом ограничитель на вводной трубке удлиненной плоскостью должен соответствовать центру фронтальной плоскости контрацептива, чтобы задать направление
- 25 раскрытия горизонтальных ветвей 2 после того, как они будут выпущены из трубки, облегчая врачу правильную ориентацию установки внутриматочного противозачаточного средства в полости матки. После того, как вертикальный стержень контрацептива полностью войдет в вводную трубку, указате-
- 30 льным и большим пальцами правой руки горизонтальные ветви 2 приподнимают, складывают вместе и продвигают внутрь вводной трубки. Затем сложенный таким образом контрацептив при помощи нитей 12 втягивают внутрь вводной трубки, направляя силу натяжения строго вдоль трубки, на глубину не
- 35 менее 10 мм от ее дистального конца, через проксимальный конец вводной трубки вводят поршень до его касания с нижним краем контрацептива и после дезинфекции влагалища и

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шейки матки накладывают пулевые щипцы, после чего зондированием устанавливают направление цервикального канала, положение матки и длину ее полости и устанавливают ограничитель на расстояние, соответствующее длине последней. При-

5 держащая шейку матки щипцами, осторожно, без усилия вводят вводную трубку с контрацептивом через цервикальный канал в полость матки до дна /до упора/. Если введение трубки затруднено, расширяют шейный канал бужами или вводят в цер-

10 викальный канал в сомкнутом состоянии изогнутый кровоостанавливающий зажим и немного расширяют бранши. Коснувшись дна, при фиксированном левой рукой толкателе вводную трубку низводят, т.е. как бы натягивают трубку на поршень, правой рукой. При этом контрацептив остается в полости

15 матки, а вводная трубка с поршнем осторожно, с небольшими поворотами вправо и влево извлекается наружу. Операционные нити I2 отрезают на длину, достаточную для контроля и изъятия.

Для извлечения контрацептива во влагалище вводят зеркало Куско, влагалище и шейку матки дезинфицируют. Кори-

20 цангом, кровоостанавливающим зажимом или щипцами для удаления плодного яйца захватывают обе нити I2, свисающие из цервикального канала, и подтягиванием их на себя извлекают контрацептив. Если нити I2 оборвались или оказались втяну-

25 тыми в полость матки, в последнюю вводят за внутренний зев специальный крючок-экстрактор внутриматочного противозачаточного средства, цепляют им петлю 5 контрацептива и извлекают его. При осечке можно воспользоваться прямым или изогнутым детским корицангом.

Благодаря предложенной конструкции якоря 7, внутриматочное противозачаточное средство согласно изобретению обладает двойным противозачаточным эффектом: механическим и химическим. Маточные сокращения стимулируют пружинящее свойство упругого элемента - петли 5, реакция которого передается на поперечные ветви 2, прижимая их к слизистой

30 дна матки, т.е. месту первичной миграции плодного яйца, и оказывая, таким образом, механическое противозачаточное действие. Второй противозачаточный эффект создается хими-

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чески чистой атомарной медью, полученной путем плазменного напыления на полиэтиленовую спираль. Медь, постепенно растворяясь, вступает в реакцию с ферментами желез эндометрия, не давая, таким образом, возможности nidации оплодотворенной яйцеклетки. В предлагаемом контрацептиве удачно использованы геометрия якоря 7 и физико-механические свойства конструкции в целом, что делает его анатомически правильным, идеально подходящим практически всем гинекологически здоровым женщинам независимо от размеров и формы матки. В отличие от других известных конструкций его можно применять даже при загибах матки. Петля 5, мягко реагируя на мышечные сокращения матки, не вызывает растяжения стенок и болезненных синдромов, не приводит к самопроизвольному изгнанию /экспульсии/ контрацептива, защищает стенки от перфорации. Предложенное внутриматочное противозачаточное средство предполагает расширенные показания к применению, в частности, возможность его введения женщинам в послеродовой период, когда матка не имеет необходимых физиологических размеров, которые являются обязательным условием введения внутриматочных противозачаточных средств других типов.

Благодаря чистоте меди, не имеющей примеси других металлов, на ее поверхности не образуются соли, которые могли бы вызвать воспалительные процессы. Более того, чистая атомарная медь, нанесенная на полиэтиленовую спираль 4, помимо противозачаточного действия оказывает также и бактерицидное действие. Открытая площадь поверхности медной спирали составляет примерно 390 мм^2 .

Благодаря применению омедненной полимерной спирали 4, предложенное внутриматочное противозачаточное средство безопасно, с точки зрения травматизма а процессе эксплуатации и во время выведения из употребления.

Испытания показали высокую эффективность предложенного внутриматочного противозачаточного средства: число забеременевших на тысячу исследованных женщин составило 5 человек; противозачаточный эффект составил 99,6 %.

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ФОРМУЛА ИЗОБРЕТЕНИЯ

1. Внутриматочное противозачаточное средство, содержащее горизонтальную планку /I/ с двумя ветвями /2/, по меньшей мере одна из которых выполнена с закругленным концом /3/, спираль /4/ и петлю /5/, связанную с горизонтальной планкой /I/ и имеющую утолщенное основание /6/, отличающееся тем, что ветви /2/ прямолинейного участка горизонтальной планки /I/ расположены под острым углом к горизонтальной плоскости и симметрично относительно вертикальной оси, обе ветви /2/ выполнены с закругленными концами /3/, причем закругление выполнено в виде части окружности, а спираль /4/ выполнена в виде полиэтиленовой ленты и размещена внутри петли /5/ на якоре /7/, связанном с утолщенным основанием /6/ горизонтальной планки /I/ и расположенном соосно с вертикальной осью симметрии внутриматочного противозачаточного средства.

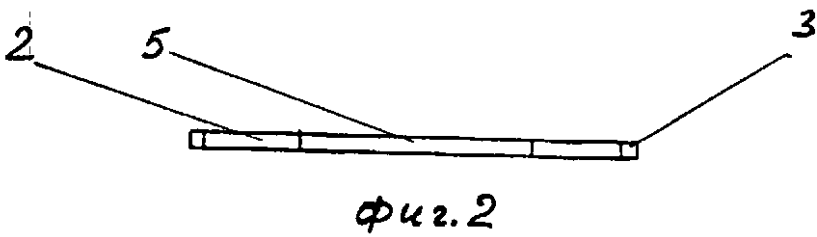
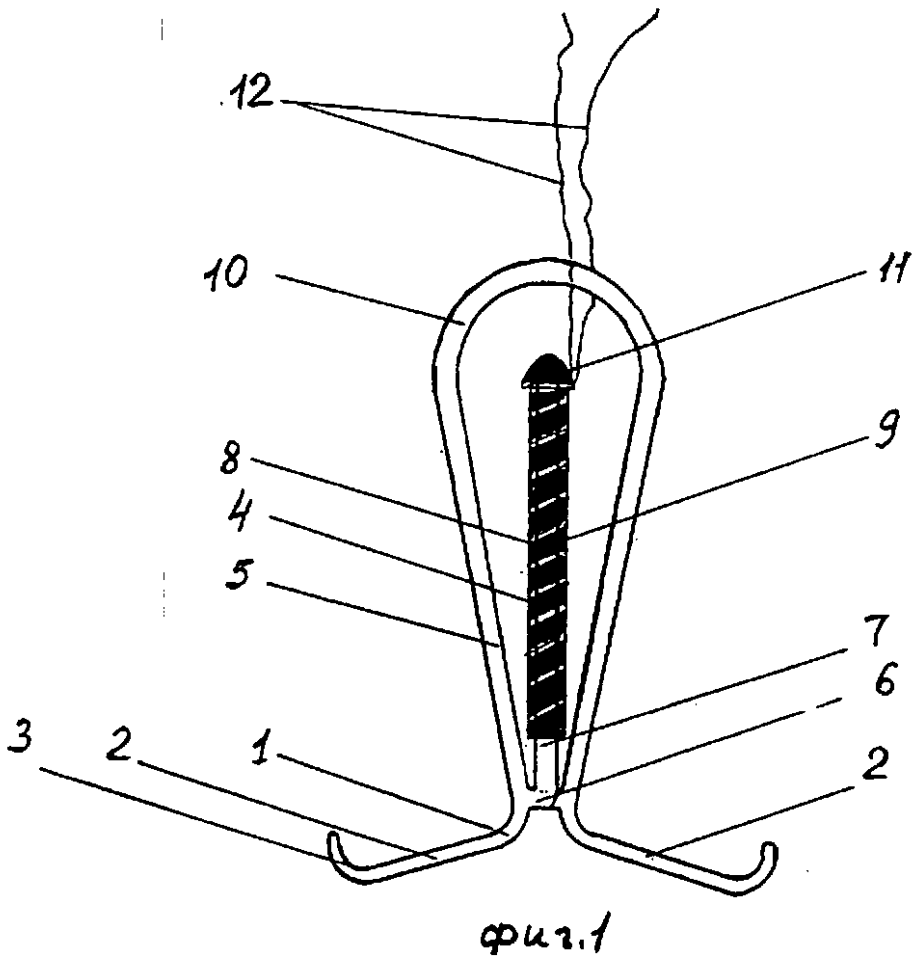
2. Внутриматочное противозачаточное средство по п. 1, отличающееся тем, что величина угла установки ветвей /2/ с горизонтальной планкой /I/ составляет 5 - 30°.

3. Внутриматочное противозачаточное средство по п. 1 или 2, отличающееся тем, что спираль /4/ снабжена покрытием /8/ в виде слоя рафинированной меди, нанесенного на наружную поверхность полиэтиленовой ленты способом плазменного напыления.

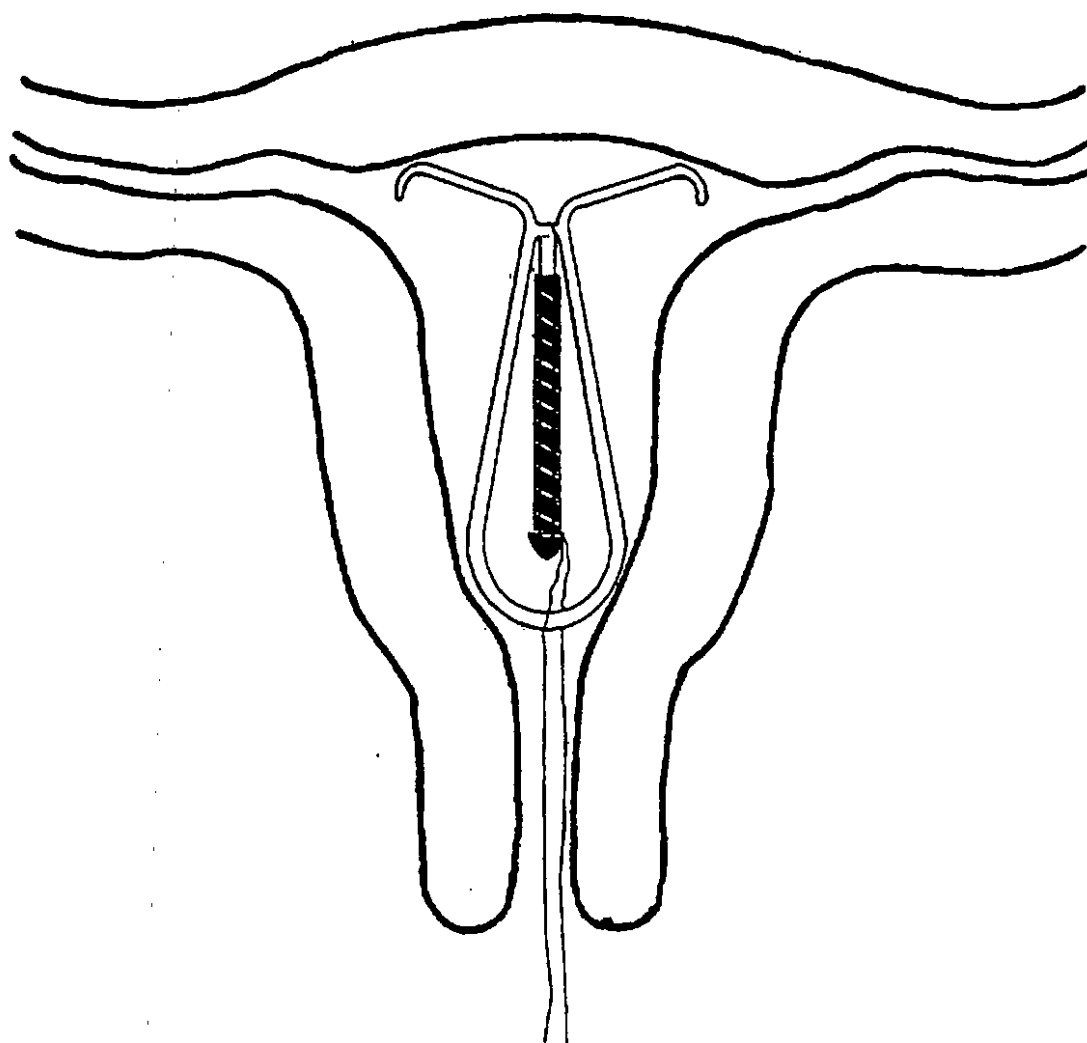
4. Внутриматочное противозачаточное средство по п. 1, 2 или 3, отличающееся тем, что нижняя часть петли /5/ выполнена упругой и по размеру составляет не менее двух длин якоря /7/.

5. Внутриматочное противозачаточное средство по п. 1, 2, 3 или 4, отличающееся тем, что свободный конец якоря /7/ снабжен закруглением /II/ в виде части сферы, который служит фиксатором для закрепления спирали /4/ и основанием для закрепления опознавательных нитей /I2/.

1/2



2/2



φκ2.3



(12)

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(54) Pharmaceutical product for application to uterus mucosa

(57) A drug comprising either a peptide having the LH-RH action or an LH-RH antagonist is carried on an intrauterine contraceptive device (IUD) so as to be able to provide controlled release. Once the IUD is put in the uterus, the carried drug is gradually released over such a prolonged period of treatment time as, for example,

several months to be continuously absorbed through the uterus mucosa or the vagina mucosa. This construction makes it possible to reduce the patient's pain and such a troublesomeness as frequent drug administration and continuously administer a necessary drug over a prolonged period of time while taking a contraceptive measures.

Description

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a pharmaceutical product for application to the uterus mucosa, which carries a drug comprising a peptide having the luteinizing hormone releasing hormone (hereafter referred to only as 'LH-RH') action, an LH-RH antagonist or the like on an intrauterine contraceptive device (hereafter referred to as 'IUD') and is adjusted to be able to administer the drug over a prolonged period of time while taking a contraceptive measures by being fitted in the uterus or the like.

2. Description of the Prior Art

In order to treat breast cancer, uterus cancer, endometriosis or central precocious puberty, an LH-RH agonist, i.e. a peptide having the LH-RH action, and an LH-RH antagonist or the like are administered. However, these drugs can be hardly absorbed through the alimentary canal, so that there exist as conventional drugs for administration an injection drug to be administered by injection and a vaginally administered drug to be absorbed through the vagina mucosa rapidly, for example, as disclosed in Japanese Patent Publication No. Hei 5-24129.

3. Problems Presented by the Prior Art

The injection drug causes pain to a patient when administered and besides has to be administered for a long time so as to cure the above-mentioned diseases. Therefore, either of the above drugs required so frequent administration that it was troublesome.

In order to solve this problem, a drug having the property of providing controlled release is prepared as an injection drug by forming it into microcapsules and the like so as to lengthen its administration interval to, for example, four weeks or the like. However, this way entails a problem that the patient cannot be relieved from the pain the patient experiences when the drug is administered and besides the drug cannot be interrupted nor changed once it is administered.

Additionally, the patient should not become pregnant because the therapy for the above-mentioned diseases is likely to exert a bad influence on an embryo. Consequently, there was caused a problem that the patient must undergo a non-hormone contraceptive treatment such as fitting an IUD separately from the administration of the above drug.

SUMMARY OF THE INVENTION

The present invention has an object to solve the

foregoing problems and provide a pharmaceutical product for application to the uterus mucosa, capable of softening the patient's pain as well as reducing the number of administration so as to decrease such a troublesome-ness as frequent administration and continuously administering a necessary drug over a prolonged period of time while taking a contraceptive measures.

In order to accomplish the object, the present invention has constructed a pharmaceutical product for application to the uterus mucosa as follows.

A first invention is characterized in that a drug comprising either a peptide having the LH-RH action or an LH-RH antagonist is carried on an intrauterine contraceptive device so as to be able to provide controlled release.

Here the construction of carrying so as to be able to provide controlled release means a construction able to gradually release a carried drug. Concrete examples of such construction can be listed as follows:

A capsule type means for controlled release which comprises covering pharmaceutical particles with a high polymer film and diffusing the pharmaceutical particles gradually through the high polymer film;

A matrix type means for controlled release which comprises dispersing pharmaceutical particles in a high polymer material of a spherical shape or the like and gradually diffusing them from a surface of the high polymer material;

A means for controlled release with the use of an osmotic pressure pump, which comprises a container formed from a semi-permeable membrane and provided with a delivering outlet at one portion thereof and delivers through the outlet a drug accommodated in the container by an osmotic pressure of the moisture invading from around the container;

A means for controlled release which employs a container provided with pores in its peripheral wall instead of the foregoing semi-permeable membrane;

A closure-type means for controlled release which comprises a container accommodating a drug and covered with a closure formed from a biodegradable or soluble high polymer; and

A pulse-type means for controlled release which comprises a plurality of small chambers arranged in series and accommodating a drug, a partition wall of each chamber being made of a biodegradable or soluble high polymer.

However, the construction of carrying so as to be able to provide controlled release according to the present invention is not limited to those means.

When carrying the above drug on the intrauterine contraceptive device (IUD), an excipient or the like additives are mixed if needed. Examples of them are listed below:

Water and polyatomic alcohols as a solvent for dissolving the drug;

Sugar-alcohols, sugars, polysaccharides, gelatinizer and grease as an excipient for dispersing the drug and keeping it dispersed;

Sorbitan fatty acid esters and polyoxyethylene sorbitan fatty acid esters as a surfactant; and

Inorganic salts, organic acid salts, inorganic bases and inorganic acids as a pH regulator or an osmotic pressure regulator.

The above-mentioned IUD may take such a shape as having been widely used up to now. Further, it may be opened instead of being closed in the shape of a ring. Generally, it means an IUD to be fitted in the uterus but may be fitted in the vagina.

A second invention is characterized in that an intra-uterine contraceptive device is formed from a biodegradable high polymer and carries a drug so as to be able to provide controlled release of the drug.

Here the biodegradable high polymer means a high polymer material gradually decomposing in vivo. Copolymers of lactic and glycolic acids (PLGA), polymers of lactic acid (PLA), copolymers of butyric and glycolic acids (PBGA), esters of these polymers, a complex consisting of at least two of these polymers or esters and collagen can be listed as its examples but it is not limited to these ones.

Further, besides leuporelin acetate, an LH-RH agonist and the LH-RH antagonist, for example, the following ones can be used as the above drug:

Follicle Estrogen or Progestogen;

allylestrenol, estradiol benzoate, estriol benzoate, estradiol, estriol, ethinylestradiol, gestnorone caproate, hydroxyprogesterone caproate, estradiol valerate, estrogens conjugated, chlormadinone acetate, medroxyprogesterone acetate, dydrogesterone, estradiol dipropionate, estriol tripropionate, norethisterone, pregnanediol, progesterone, fosfestrol, and mestranol.

Antipyretic, analgesic and anti-inflammatory agents;

actarit, aspirin, aspirin*ascorbic acid, aspirin*dialuminate, acetaminophen, acemetacin, alclofenac, alminoprofen, ampiroxicam, amfenac sodium, isopropylantipyrine, ibuprofen, indometacin, indometacin farnesil, ethenzamide, etodolac, epirozole, emorfazone, tiaramide hydrochloride, tinoridine hydrochloride, tramadol hydrochloride, buprenorphine hydrochloride, oxaprozin, obelon, camphor*sodium salicylate, cleamine A, cleamine S, ketophenylbutazone, ketoprofen, chondroitin sulfate sodium*sodium salicylate, sasapyrine, salicylamide, sodium salicylate, saridon, salsocain, zaltoprofen, simetride*anhydrous caffeine, eplazocinehydrobromide, ergotamine tartrate*anhydrous caffeine, butorphanol tartrate, diclofenac so-

dium, diflunisal, sulindac, sulpyrine, tiaprofenic acid, tenoxicam, tolfenamic acid, tolmetin sodium, nabumetone, naproxen, neo vitacain, piroxicam, phenacetin, fenoprofen calcium, fenbufen, flufenamic acid, flufenamic acid aluminium, flurbiprofen, flurbiprofen axetil, floctafenine, bucolome, pranoprofen, pentazocine, proglumetacin maleate, migrenin, dimetotiazine mesilate, metiazinic acid, mefenamic acid, mofezolac, loxoprofen sodium, lobenzarit disodium, and an extract from inflammatory rabbit skin inoculated by vaccinia virus.

Metabolic inhibitors;

6-mercaptapurine riboside, enocitabine, carmofur, cytarabine, cytarabine ocphosphate, tegafur, tegafur*uracil, doxifluridine, hydroxycarbamide, fluorouracil, methotrexate, and mercaptopurine.

Alkylating agents;

ifosfamide, nitrogen mustard-N-oxide hydrochloride, nimustine hydrochloride, carboquone, cyclophosphamide, dacarbazine, thiotepa, improsulfan tosilate, busulfan, mitobronitol, melphalan, ranimustine, and estramustine phosphate sodium.

Anti-tumor and antibiotic agents;

actinomycin D, aclarubicin hydrochloride, idarubicin hydrochloride, epirubicin hydrochloride, daunorubicin hydrochloride, doxorubicin hydrochloride, pirarubicin hydrochloride, bleomycin hydrochloride, zinzostatin stimalamer, neocarzinostatin, mitomycin C, bleomycin sulfate and peplomycin sulfate.

Anti-tumor plant agents;

etoposide, irinotecan hydrochloride, vincristine sulfate, vindesine sulfate, and vinblastine sulfate.

Other anti-tumor agents;

aceglatone, ubenimex, L-asparaginase, fadrozole hydrochloride hydrate, procarbazine hydrochloride, mitoxantrone hydrochloride, carboplatin, tamoxifen citrate, toremifene citrate, krestin, medroxyprogesterone acetate, cisplatin, schizophyllan, sobuzoxane, tretinoin, nedaplatin, picibanil, flutamide, pentostatin, porfimer sodium, and lentinan.

Anti-endometriosis agents or anti-uterine fibroids agents;

nafarelin acetate, buserelin acetate, dydrogesterone, danazol and ethinylestradiol*norgestrel.

However, the above drug is not limited to these ones but at least two of them may be compounded when needed.

A third invention comprises defining the drug set forth in the second invention to either a peptide having the LH-RH action or an LH-RH antagonist.

A drug carried on an IUD is gradually released to be continuously absorbed through the uterus mucosa or the vagina mucosa for such a long period of treatment time as, for example, several months once the IUD is

put in the uterus. Besides, during this treatment term, the fitted IUD prevents pregnancy.

If the IUD is formed from a biodegradable high polymer, it gradually decomposes by itself while providing controlled release of the drug and will completely decompose after the elapse of an administration term. Therefore, it need not be removed from the living body.

The present 1st to 3rd invention produces the following advantages because it is constructed and functions as mentioned above.

(1) The present invention can administer a necessary drug without giving such a pain as caused by injection and besides can do it continuously over such a prolonged period of time as at least several months if only once fitted. Additionally, since the fitting itself is a contraceptive measures, no other contraceptive measures is needed to result in the possibility of reducing the patient's pain and the troublesomeness such as frequent administration.

(2) The drug administration can be interrupted or changed at an optional time by removing the fitted IUD. Therefore, it is possible to make a proper drug administration depending on the condition of the patient, differently from the conventional technique which employs an injection drug having the property of providing controlled release.

Moreover, the pharmaceutical product for application to the uterus mucosa according to the second or the third invention has the following characteristic:

(3) An IUD being made of a biodegradable high polymer, it is not necessary to remove the IUD from the living body because it is completely decomposed after the elapse of an administration term. Only the fitting of this IUD is sufficient when administering the drug. This can further lessen the troublesomeness experienced when administering the drug.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a sectional view of a pharmaceutical product for application to the uterus mucosa, showing a first embodiment;
 Fig. 2 is a view corresponding to Fig. 1 and showing a second embodiment; and
 Fig. 3 is a view corresponding to Fig. 1 and showing a modification of the second embodiment.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENT

First Embodiment

A pharmaceutical product 1 for application to the uterus mucosa according to a first embodiment of the present invention as shown in Fig. 1 was formed by dispersing a drug 2 such as a peptide having the LH-RH

action in a biodegradable high polymer 3 and molding it to a predetermined shape of IUD 4 by a casting mold.

When such IUD 4 is fitted in the uterus, the biodegradable high polymer 3 gradually decomposes and at the same time the drug 2 provides controlled release to be efficiently absorbed through the uterus mucosa over a prolonged period of time.

And after the elapse of a predetermined period of time, for example, three months, while the drug 2 carried on the IUD 4 is completely released, the IUD 4 itself disappears from the uterus with the whole biodegradable high polymer 3 decomposed.

Then another new IUD 4 carrying the drug 2 is fitted in the uterus to continue the treatment.

Notably, it is possible to interrupt the treatment at an optional time by taking the IUD 4 away from the uterus. When changing the amount and term for controlled release as well as the kind of the drug, a new IUD 4 carrying a desired drug so as to be able to provide controlled release of the drug for a desired period of time is fitted in the uterus after the old IUD 4 has been removed from the uterus.

Example 1

596 mg of leuporelin acetate, an LH-RH agonist and 94 mg of gelatine were dissolved in 0.5 g of water to prepare an aqueous solution. Meanwhile, 4.78 g of 75/25 (w/w) copolymer of lactic and glycolic acids having a molecular weight of about 14,000 (PLGA) was dissolved in 8.0 g of dichloromethane. Then this solution was added to the above aqueous solution to prepare a W/O emulsion and cool it to 19°C.

Next, this emulsion was dispersed into 1 liter of 0.1% PVA solution preliminarily cooled to 19°C to thereby make a (W/O)/W emulsion. This (W/O)/W emulsion was dried in water for three hours to volatilize the dichloromethane. Thereafter, the resulting microcapsules were scavenged through centrifugation and freeze dried.

Thus dried microcapsules were heat molded by a casting mold to obtain a pharmaceutical product for application to the uterus mucosa in a desired shape of IUD.

This pharmaceutical product continued to release leuporelin acetate in the uterus over a period of at least one month.

Example 2

433 mg of leuporelin acetate was dissolved in 0.5 g of water to prepare an aqueous solution. Meanwhile, 3.83 g of poly-lactic acid (PLA) having a molecular weight of 17,000 was dissolved in 6.4 g of dichloromethane. This solution was added to the above aqueous solution to prepare a W/O emulsion and cool it to 15°C.

Next, this emulsion was dispersed into 1 liter of 0.1% PVA solution preliminarily cooled to 15°C to make a (W/O)/W emulsion. Then this (W/O)/W emulsion was

dried in water for three hours. The resulting microcapsules were scavenged through centrifugation and freeze dried. Thereafter, they were compression molded to a desired shape of IUD by a casting mold.

The obtained pharmaceutical product for application to the uterus mucosa continued to release leuporelin acetate in the uterus over a period of at least three months.

Example 3

500 mg of leuporelin acetate was dissolved in 50 g of water to prepare an aqueous solution. Meanwhile, 4.5 g of copolymer of butyric and glycolic acids having a molecular weight of about 18,500 (PBGA) was dissolved in 10 g of dichloromethane. This solution was added to the above aqueous solution to prepare a W/O emulsion.

Next, this emulsion was vacuum dried in a casting mold and compression molded to a desired shape of IUD. The obtained pharmaceutical product for application to the uterus mucosa continued to release leuporelin acetate in the uterus over a period of at least one month.

Example 4

5 g of leuporelin acetate was dissolved in 50 g of water to prepare an aqueous solution. Meanwhile, 45 g of PLGA having the same grade as that used in Example 1 was dissolved in 100 g of dichloromethane. This solution was added to the above aqueous solution to prepare a W/O emulsion.

Next, this emulsion was dried at a temperature of 40°C under a condition of 100 to 300 Torr by a vacuum drier. The resulting dried product was ground by a turbo-counter jet mill. The thus ground substance was accommodated in a casting mold and heat molded to obtain a pharmaceutical product for application to the uterus mucosa in a desired shape of IUD.

The obtained product continued to release leuporelin acetate in the uterus over a period of at least one month.

Example 5

4.5 g of 55/45 (w/w) copolymer of lactic and glycolic acids, PLGA having a molecular weight of about 20,000 was dissolved in 10 g of dichloromethane. 0.5 g of cisplatin, an antineoplastic (anticancer) agent was added to this solution so as to suspend it therein homogeneously with ultrasonic.

This suspension was accommodated in a casting mold and vacuum dried at room temperature to obtain a pharmaceutical product for application to the uterus mucosa in a desired shape of IUD.

The obtained pharmaceutical product continued to release cisplatin in the uterus over a period of at least

one month.

Second Embodiment

A pharmaceutical product 1 for application to the uterus mucosa according to a second embodiment of the present invention as shown in Fig. 2 comprises a drug 2 enclosed in a diffusion controlled film 5 made of a high polymer material such as, for example, a copolymer of ethylene and vinyl acetate and then supported by silicon elastomer 6 or the like to be formed into an IUD 4.

The drug 2 carried on the IUD 4 gradually passes through the diffusion controlled film 5 and diffuses to be absorbed through the uterus mucosa. Since the transmission and diffusion of the drug decrease after a predetermined period of time has elapsed, this IUD 4 is removed from the uterus and a new IUD 4 is fitted if the administration is continued.

Example 6

500 mg of leuporelin acetate and 4.5 g of PLA having a molecular weight of about 25,000 were dissolved in 10 g of dichloromethane. This solution was dispersed into 1 liter of 0.1% PVA solution to prepare an O/W emulsion.

This O/W emulsion was dried in water for three hours. The resulting microcapsules were scavenged through centrifugation and freeze dried. The dried substance was suspended in silicon oil. This suspension was enclosed in a film made of a copolymer of ethylene and vinyl acetate and supported by silicon elastomer to obtain a pharmaceutical product for application to the uterus mucosa formed in a desired shape of IUD.

This pharmaceutical product continued to release leuporelin acetate in the uterus over a period of at least three months.

The IUD 4 may take the shape of the modification shown in, for example, Fig. 3 or other shapes as far as they don't cause any abnormality to the living body when fitted.

Needless to say, the drug to be used is not limited to those shown in Examples 1 to 6. The term within which the drug can be administered for controlled release in the uterus can be suitably fixed to, for example, at least six months by controlling the amount and delivery speed of the drug to be carried as far as it does not cause any abnormality to the living body.

Claims

1. A controlled release drug delivery device for administering a pharmaceutical to the uterine mucosa which comprises:

an intrauterine contraceptive device; and

- a pharmaceutical carried on the intrauterine contraceptive device,
- wherein the pharmaceutical comprises a peptide having luteinising hormone-releasing hormone activity or luteinising hormone-releasing hormone antagonist activity.
2. A delivery device according to claim 1 in which the pharmaceutical comprises leuporelin acetate.
3. A delivery device according to claim 1 or 2 in which the pharmaceutical is accommodated in the intrauterine contraceptive device and in which the pharmaceutical can diffuse out of the intrauterine contraceptive device.
4. A delivery device according to any preceding claim in which the pharmaceutical is in a pharmaceutically acceptable excipient, carrier or diluent.
5. A delivery device according to claim 4 in which the carrier comprises a capsule which accommodates the pharmaceutical and which is permeable to it.
6. A delivery device according to claim 4 in which the carrier comprises a matrix in which the pharmaceutical is dispersed, the pharmaceutical being able to diffuse from the matrix.
7. A delivery device according to claim 4 in which the carrier comprises an osmotic pressure pump, the osmotic pressure pump comprising:
 - a container which accommodates the pharmaceutical and which is formed from a semi-permeable membrane;
 - a delivery outlet which can release the pharmaceutical from the container as water enters the container through the semi-permeable membrane.
8. A delivery device according to claim 4 in which the carrier comprises a container which accommodates the pharmaceutical and in which a wall of the container is biodegradable or soluble.
9. A delivery device according to claim 4 in which the carrier comprises a plurality of chambers arranged in series, each chamber accommodating the pharmaceutical, the partition walls of each chamber being biodegradable or soluble.
10. A delivery device according to any of claims 4 to 9 in which the excipient or diluent comprises at least one of water, alcohols, sugar-alcohols, sugars, polysaccharides, gelatinizer, grease, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters, inorganic salts, organic acid salts, inorganic bases or inorganic acids.
11. A delivery device according to any preceding claim in which the intrauterine contraceptive device is biodegradable.
12. A controlled release drug delivery device for administering a pharmaceutical to the uterine mucosa which comprises:
 - a biodegradable intrauterine contraceptive device; and
 - a pharmaceutical carried on the intrauterine contraceptive device.
13. A delivery device according to claim 12 in which the pharmaceutical comprises a peptide having luteinising hormone-releasing hormone activity or luteinising hormone-releasing hormone antagonist activity.
14. A delivery device according to claim 12 or 13 in which the intrauterine contraceptive device is of a biodegradable high polymer.
15. A delivery device according to claim 14 in which the biodegradable high polymer comprises at least one of a copolymer of lactic acid and glycolic acid, a polymer of lactic acid, a copolymer of butyric acid and glycolic acid, esters of those said polymers or a complex comprising at least two of said polymers or esters and collagen.
16. A delivery device according to any of claims 12 to 15 in which the pharmaceutical comprises leuporelin acetate.
17. A pharmaceutical product for application to the uterus mucosa characterised in that a drug (2) comprising either a peptide having the LH-RH action or an antagonist is carried on an intrauterine contraceptive device (4) so as to be able to provide controlled release.
18. A pharmaceutical product for application to the uterus mucosa characterised in that an intrauterine contraceptive device (4) is formed from a biodegradable high polymer (3), a drug (2) being carried on the intrauterine contraceptive device (4) so as to be able to provide controlled release.
19. A pharmaceutical product for application to the uterus mucosa as set forth in claim 18, wherein the drug (2) is either a peptide having the LH-RH action or an LH-RH antagonist.

FIG. 1

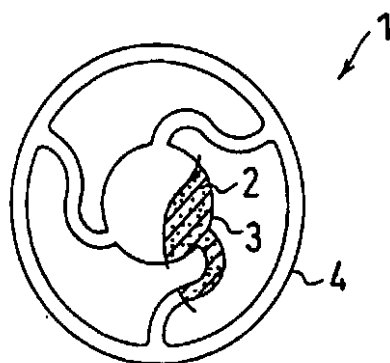


FIG. 2

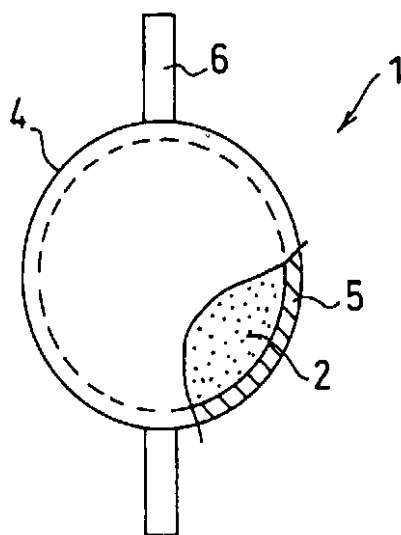
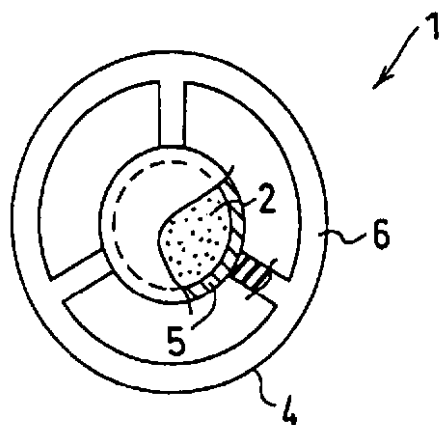
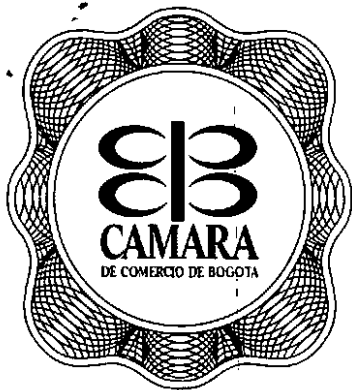


FIG. 3





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* 1 1 2 4 7 2 6 8 7 *

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

HORA: 09:06:21

OPERACION: 09ERP1117026

PAGINA: 1

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

SIGLA : LAFRANCOL S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : CRA. 1 NRO. 46 84

DIRECCION NOTIFICACION JUDICIAL: CRA. 1 NRO. 46 84

CIUDAD: CALI

MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958

DIRECCION ELECTRONICA : lafrancolsa@lafrancol.co

DIRECCION WEB : www.lafrancol.com

AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

QUE POR ESCRITURA NRO. 3672 DEL 24 DE AGOSTO DE 2009 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 27 DE AGOSTO DE 2009 BAJO EL NRO. 9876 DEL LIBRO IX , CAMBIO SU NOMBRE DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. . POR EL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. SIGLA: LAFRANCOL S. A. .

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
19467				
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
20089				
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
24528				
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	

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PAGINA: 2

26360

E.P. 2422 25/10/1963 NOTARIA CUARTA DE CALI 28/10/1963

26717

E.P. 1720 16/09/1964 NOTARIA CUARTA DE CALI 22/09/1964

28406

E.P. 101 31/01/1966 NOTARIA CUARTA DE CALI 01/02/1966

31039

E.P. 552 21/03/1968 NOTARIA CUARTA DE CALI 01/04/1968

35711

E.P. 4964 12/12/1972 NOTARIA CUARTA DE CALI 16/01/1973

2975 IX

E.P. 1956 30/05/1973 NOTARIA CUARTA DE CALI 13/06/1973

4337 IX

E.P. 4964 12/12/1972 NOTARIA CUARTA DE CALI 28/11/1973

5994 IX

E.P. 5579 12/11/1973 NOTARIA CUARTA DE CALI 28/11/1973

5995 IX

E.P. 4406 30/09/1974 NOTARIA CUARTA DE CALI 28/11/1974

10887 IX

E.P. 192 03/02/1978 NOTARIA CUARTA DE CALI 14/02/1978

25355 IX

E.P. 3479 07/09/1979 NOTARIA CUARTA DE CALI 19/09/1979

34204 IX

E.P. 4274 12/12/1984 NOTARIA NOVENA DE CALI 19/12/1984

73088 IX

E.P. 1155 21/05/1985 NOTARIA SEPTIMA DE CALI 03/06/1985

76917 IX

E.P. 1553 20/06/1986 NOTARIA SEPTIMA DE CALI 08/07/1986

85997 IX

E.P. 1458 09/06/1987 NOTARIA SEPTIMA DE CALI 24/12/1987

3508 IX

E.P. 7222 14/12/1988 NOTARIA TERCERA DE CALI 19/12/1988

13847 IX

E.P. 4530 04/09/1989 NOTARIA TERCERA DE CALI 07/09/1989

21508 IX

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PAGINA: 3

E.P. 3865	02/08/1990	NOTARIA	TERCERA	DE	CALI	13/08/1990
31708 IX						
E.P. 8305	13/12/1995	NOTARIA	TERCERA	DE	CALI	23/01/1996
557 IX						
E.P. 4559	16/11/1999	NOTARIA	TERCERA	DE	CALI	26/11/1999
7911 IX						
E.P. 6.004	02/12/2004	NOTARIA	TERCERA	DE	CALI	14/12/2004
13371 IX						
E.P. 6241	27/12/2006	NOTARIA	TERCERA	DE	CALI	19/01/2007
625 IX						
E.P. 389	07/02/2008	NOTARIA	TERCERA	DE	CALI	19/02/2008
1880 IX						
E.P. 1907	11/05/2009	NOTARIA	TERCERA	DE	CALI	26/05/2009
5950 IX						
E.P. 3672	24/08/2009	NOTARIA	TERCERA	DE	CALI	27/08/2009
9876 IX						
ACT 116	04/03/2010	ASAMBLEA	GRAL	ORDINARIA		11/05/2010
5470 IX						
E.P. 4421	21/10/2010	NOTARIA	TERCERA	DE	CALI	26/10/2010
12622 IX						
E.P. 1786	16/05/2011	NOTARIA	TERCERA	DE	CALI	24/05/2011
6318 IX						

CERTIFICA:

QUE POR ACTA NRO. 116 DEL 04 DE MARZO DE 2010 ASAMBLEA GRAL ORDINARIA, INSCRITA EN LA CAMARA DE COMERCIO EL 11 DE MAYO DE 2010 BAJO EL NRO. 5470 DE LIBRO IX, SE TRANSFORMO DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. SIGLA: LAFRANCOL S.A. POR EL DE LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.S. SIGLA: LAFRANCOL S.A.S.

CERTIFICA

QUE POR ESCRITURA, NRO. 2339 DEL 10 DE JUNIO DE 2010 NOTAIRA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 15 DE JUNIO DE 2010 BAJO EL NRO. 7070 DEL LIBRO IX, SE INSCRIBIO LA RESOLUCION DE LA TRANSFORMACION DE SOCIEDAD POR ACCIONES SIMPLIFICADA A SOCIEDAD ANONIMA.

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

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CAMARA DE COMERCIO DE CALI

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PAGINA: 4

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ REALIZAR, ENTRE OTROS, LAS SIGUIENTES ACTIVIDADES COMERCIALES Y EMPRESARIALES: 1) FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES. 2) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. 3) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPO DE PRODUCTOS VETERINARIOS. 4) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. 5) IMPORTAR CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTICIOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES, DE PERFUMERÍA, DISPOSITIVOS MÉDICOS Y AFINES Y/O PRODUCTOS INTERMEDIOS O A GRANEL. 6) EN DESARROLLO DE SU OBJETO SOCIAL PODRÁ LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN O NO LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS. 7) ADEMÁS DE LAS ACTIVIDADES REFERIDAS, PODRÁ REALIZAR CUALQUIER ACTIVIDAD, DE GESTIÓN DE LICENCIAS, REGISTROS DE EXPORTACIÓN O IMPORTACIÓN, CONVENIOS RELATIVOS A ESAS ACTIVIDADES Y LOS ACTOS RELACIONADOS CON EL MISMO.

PARÁGRAFO: LA SOCIEDAD NO PODRÁ CONSTITUIRSE GARANTE, NI FIADORA DE OBLIGACIONES DISTINTAS DE LAS PROPIAS, NI GARANTIZAR CON SUS BIENES OBLIGACIONES DE TERCEROS, A MENOS QUE LO AUTORICE EN CADA CASO LA JUNTA DIRECTIVA CON EL VOTO DE LA TOTALIDAD DE LOS MIEMBROS PRESENTES EN LA REUNIÓN CORRESPONDIENTE.

CERTIFICA:

ÓRGANOS DE ADMINISTRACIÓN DE LA SOCIEDAD.

LA DIRECCIÓN Y ADMINISTRACIÓN DE LA SOCIEDAD ESTARÁN A CARGO DE: 1. LA ASAMBLEA GENERAL DE ACCIONISTAS; 2. LA JUNTA DIRECTIVA; 3. LOS REPRESENTANTES LEGALES.

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FUNCIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS, ADEMÁS DE LAS ESTABLECIDAS EN LA LEY, ESTE ÓRGANO TENDRÁ LAS SIGUIENTES FUNCIONES, ENTRE OTRAS: 5) DELEGAR EN LA JUNTA DIRECTIVA, CUANDO LO ESTIME OPORTUNO, ALGUNA O ALGUNAS DE SUS FUNCIONES CUYA DELEGACIÓN NO ESTÉ PROHIBIDA POR LA LEY O POR LOS ESTATUTOS; 9) NOMBRAR Y REMOVER EL LIQUIDADOR DE LA SOCIEDAD Y SU SUPLENTE, FIJAR SU REMUNERACIÓN Y CONSIDERAR, APROBAR O IMPROBAR SUS CUENTAS; 10) DECLARAR ORDINARIA O EXTRAORDINARIAMENTE DISUELTA Y EN ESTADO DE LIQUIDACIÓN A LA SOCIEDAD; 11) AUTORIZAR LA VENTA, TRANSFERENCIA, ACTOS DISPOSITIVOS, DE ADMINISTRACIÓN, O ARRIENDO, HIPOTECAR, GRAVAR, TOTAL O PARCIALMENTE LOS BIENES QUE COMPONEN SU PATRIMONIO; 12) DECRETAR EL AUMENTO DE CAPITAL AUTORIZADO; 13) DECRETAR LA PRÓRROGA DEL TÉRMINO DE DURACIÓN DE LA SOCIEDAD; 14) REMOVER EN CUALQUIER MOMENTO AL PRESIDENTE EJECUTIVO, A LOS MIEMBROS DE LA JUNTA DIRECTIVA O AL REVISOR FISCAL Y SUS RESPECTIVOS SUPLENTE; 15) REALIZAR CUALQUIER MODIFICACIÓN ESTATUTARIA; 16) DISPONER LA ESCISIÓN, FUSIÓN O TRANSFORMACIÓN DE LA SOCIEDAD; 17) NOMBRAR A LOS MIEMBROS DE LA JUNTA DIRECTIVA Y EL REVISOR FISCAL DE LA SOCIEDAD Y SUS RESPECTIVOS SUPLENTE; 19) ADOPTAR TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS Y EL INTERÉS DE LOS ACCIONISTAS Y DE LA SOCIEDAD. 20) LAS QUE POR LEY Y POR SU CONDICIÓN DE SUPREMO ÓRGANO SOCIAL NATURALMENTE LE CORRESPONDAN Y NO ESTÉN ASIGNADAS A OTRO ÓRGANO SOCIETARIO.

LA JUNTA DIRECTIVA. SE COMPONE DE TRES (3) MIEMBROS QUE SERÁN ELEGIDOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS... LAS SUPLENCIAS SERÁN NUMÉRICAS...

FUNCIONES DE LA JUNTA DIRECTIVA, ADEMÁS DE LAS FUNCIONES DE LEY, ENTRE OTRAS: 2) CREAR LOS CARGOS QUE JUZGUE NECESARIOS PARA LA BUENA MARCHA DE LA EMPRESA, NOMBRAR A QUIEN DEBA EJERCERLOS, SEÑALAR SUS FUNCIONES, FIJAR SUS ASIGNACIONES O LA FORMA DE RETRIBUCIÓN, NOMBRAR Y REMOVER LIBREMENTE A LOS EMPLEADOS DE LA SOCIEDAD, EXCEPTO AQUELLOS CUYO NOMBRAMIENTO O REMOCIÓN CORRESPONDA A LA ASAMBLEA GENERAL DE ACCIONISTAS. 3) NOMBRAR, REMOVER Y FIJAR ASIGNACIONES AL PRESIDENTE EJECUTIVO, VICEPRESIDENTES Y ADMINISTRADORES QUE REPORTEN DIRECTAMENTE A LA PRESIDENCIA EJECUTIVA. 9) AUTORIZAR AL PRESIDENTE EJECUTIVO, PARA QUE SOLICITE, DE ACUERDO CON LA LEY VIGENTE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPAÑÍA EN LA CELEBRACIÓN DE PROCESO CONCURSAL CON SUS ACREEDORES, O REESTRUCTURACIÓN EMPRESARIAL. 17) AUTORIZAR AL TERCER REPRESENTANTE LEGAL QUE ES EL PRESIDENTE EJECUTIVO, AL CUARTO Y QUINTO REPRESENTANTES LEGALES PARA COMPROMETER A LA SOCIEDAD O A LOS NEGOCIOS

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SOCIALES EN CUANTÍA SUPERIOR A SEIS MIL SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES (6.000 SMLV) PARA CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA CON LA NACIÓN (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PÚBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMÍA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, NACIONALES O EXTRANJERAS, CUALQUIERA QUE SEA SU NATURALEZA, GOBIERNOS O ENTIDADES EXTRANJEROS, CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTÍAS NECESARIOS HASTA LA CUANTÍA ANTES MENCIONADA Y REPRESENTAR A LA COMPAÑÍA EN CUALQUIER TRÁMITE O PROCESO JUDICIAL QUE SE ADELANTE ANTE LAS JURISDICCIONES CIVIL, LABORAL, COMERCIAL, PENAL Y CONTENCIOSO ADMINISTRATIVA EN CALIDAD DE DEMANDANTES O DEMANDADOS Y CUALQUIER OTRO TRÁMITE EN EL QUE SE REQUIERA REPRESENTAR A LA COMPAÑÍA ANTE ENTIDADES Y ORGANISMOS DEL ESTADO DE CUALQUIER ORDEN O ENTIDADES DE NATURALEZA PRIVADA.

18) AUTORIZAR AL TERCER Y CUARTO REPRESENTANTE LEGAL PARA ADQUIRIR ACTIVOS FIJOS SUPERIOR A DOSCIENTOS UN SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES (201 SMLV), CRÉDITOS CON ENTIDADES FINANCIERAS SUPERIORES A UN MILLÓN QUINIENTOS MIL DÓLARES AMERICANOS (USD\$1.500.0000) Y DEFINIR LAS ATRIBUCIONES AL TERCER Y CUARTO REPRESENTANTE LEGAL CORRESPONDIENTE A OTRAS COMPRAS POR CONCEPTO DE ASESORÍAS Y GASTOS DIFERENTES A LOS ANTERIORES. 19) AUTORIZAR AL TERCER Y CUARTO REPRESENTANTE LEGAL DE LA COMPAÑÍA PARA QUE CELEBREN CONTRATOS DE SOCIEDAD O PARTICIPEN EN OTRAS COMPAÑÍAS COMERCIALES, NACIONALES O EXTRANJERAS. 20) AUTORIZAR AL TERCER Y CUARTO REPRESENTANTE LEGAL PARA QUE SUSCRIBAN TODA CLASE DE DOCUMENTOS PÚBLICOS O PRIVADOS Y CON EL PROPÓSITO DE INSTRUMENTAR CUALQUIER TIPO DE ACTOS, NEGOCIOS JURÍDICOS, OPERACIONES DE CUALQUIER ÍNDOLE, Y SIEMPRE Y CUANDO SUPERE LA CUANTÍA PREVISTA PARA LA REALIZACIÓN DE ACTOS POR PARTE DEL REPRESENTANTE LEGAL DE LA COMPAÑÍA. 22) AUTORIZAR LA CONSTITUCIÓN O SUPRESIÓN DE SUCURSALES O AGENCIAS. 26) AUTORIZAR LA NOVACIÓN O CUALQUIER FORMA EXTINTIVA DE OBLIGACIONES. 27) AUTORIZAR LA ENAJENACIÓN A CUALQUIER TÍTULO, RELACIONADA CON MAQUINARIA INDUSTRIAL, TERRENOS, EDIFICIOS E INTANGIBLES Y APROBAR DONACIONES. IGUALMENTE AUTORIZARÁ LA CONSTITUCIÓN DE GARANTÍAS HIPOTECARIAS, PRENDARIAS O DE CUALQUIER OTRA ÍNDOLE SOBRE DICHOS ACTIVOS. 29) LAS DEMÁS QUE LE ASIGNEN LOS ESTATUTOS Y LAS LEYES SOBRE LA MATERIA.

REPRESENTACIÓN LEGAL. ADMINISTRACIÓN.

LA ADMINISTRACIÓN DE LA SOCIEDAD CORRESPONDE AL PRESIDENTE EJECUTIVO, TERCER

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REPRESENTANTE LEGAL DE LA COMPAÑÍA, ASÍ COMO LA GESTIÓN Y EJECUCIÓN DE LOS NEGOCIOS Y ASUNTOS SOCIALES. EL PRESIDENTE EJECUTIVO DE LA SOCIEDAD, SERÁ DESIGNADO POR LA JUNTA DIRECTIVA PARA PERÍODOS DE UN (1) AÑO, SIN PERJUICIO DE SU LIBRE REMOCIÓN Y REELECCIÓN INDEFINIDA.

EL PRESIDENTE Y VICEPRESIDENTE DE LA JUNTA DIRECTIVA, SERÁ TAMBIÉN REPRESENTANTE LEGAL PRIMERO Y SEGUNDO DE LA SOCIEDAD.

LAS ATRIBUCIONES INHERENTES A LA CALIDAD DE REPRESENTANTES LEGALES, DE ESTOS CARGOS Y EN ESPECIAL LAS DISPOSITIVAS, SERÁN EJERCIDAS SIN LAS LIMITACIONES ESTABLECIDAS EN ÉSTOS ESTATUTOS PARA OTROS REPRESENTANTES LEGALES.

EL CUARTO Y QUINTO REPRESENTANTE LEGAL, SERÁN REPRESENTANTES LEGALES DE LA SOCIEDAD QUIENES SON ELEGIDOS POR LA JUNTA DIRECTIVA CON SUS LIMITACIONES EN SUS FUNCIONES.

LAS ATRIBUCIONES INHERENTES A LA CALIDAD DEL CUARTO REPRESENTANTE LEGAL, Y EN ESPECIAL LAS DISPOSITIVAS, SERÁN EJERCIDAS CON SUJECCIÓN A LAS LIMITACIONES ESTABLECIDAS EN ÉSTOS ESTATUTOS PARA EL PRESIDENTE EJECUTIVO QUIEN ES EL TERCER REPRESENTANTE LEGAL.

EXISTIRÁ UN QUINTO REPRESENTANTE LEGAL DE LA SOCIEDAD QUE TENDRÁ LIMITACIÓN EN SUS FUNCIONES CUANDO SE TRATE DE COMPROMETER A LA SOCIEDAD O A LOS NEGOCIOS SOCIALES EN CUANTÍA NO SUPERIOR A SEIS MIL SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES (6.000 SMLV) PARA CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA CON LA NACIÓN (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PÚBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMÍA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, NACIONALES O EXTRANJERAS, CUALQUIERA QUE SEA SU NATURALEZA, GOBIERNOS Y ENTIDADES DEL EXTERIOR, CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTÍAS NECESARIOS HASTA LA CUANTÍA ANTES MENCIONADA Y REPRESENTAR A LA COMPAÑÍA EN CUALQUIER TRÁMITE O PROCESO JUDICIAL QUE SE ADELANTE ANTE LAS JURISDICCIONES CIVIL, LABORAL, COMERCIAL, PENAL Y CONTENCIOSO ADMINISTRATIVA EN CALIDAD DE DEMANDANTES O DEMANDADOS Y CUALQUIER OTRO TRÁMITE EN EL QUE SE REQUIERA REPRESENTAR A LA COMPAÑÍA ANTE ENTIDADES Y ORGANISMOS DEL ESTADO DE CUALQUIER ORDEN O ENTIDADES DE NATURALEZA PRIVADA.

FUNCIONES DEL PRESIDENTE EJECUTIVO. EL PRESIDENTE EJECUTIVO DE LA SOCIEDAD ES UN MANDATARIO CON REPRESENTACIÓN, INVESTIDO DE FACULTADES EJECUTIVAS Y ADMINISTRATIVAS, Y COMO TAL, TIENE A SU CARGO LA TERCERA REPRESENTACIÓN LEGAL, LA GESTIÓN COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCIÓN

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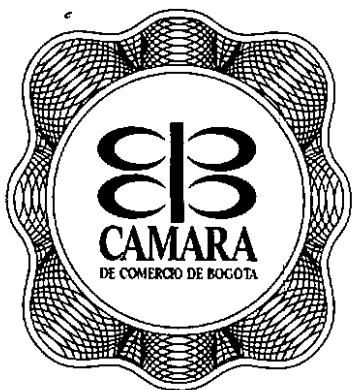
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ADMINISTRATIVA, LA COORDINACIÓN Y SUPERVISIÓN GENERAL DE LA EMPRESA, LAS CUALES CUMPLIRÁ CON ARREGLO A LAS NORMAS DE ESTOS ESTATUTOS Y LAS DISPOSICIONES LEGALES, Y CON SUJECCIÓN A LAS ÓRDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA. ADEMÁS DE LAS FUNCIONES ANTES INDICADAS, CORRESPONDE AL PRESIDENTE EJECUTIVO DE LA SOCIEDAD: 1) COMPROMETER A LA SOCIEDAD O A LOS NEGOCIOS SOCIALES EN CUANTÍA NO SUPERIOR A SEIS MIL SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES (6.000 SMLV) PARA CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA CON LA NACIÓN (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PÚBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMÍA MIXTA), EMPRESAS SOCIALES CIVILES Y COMERCIALES, NACIONALES O EXTRANJERAS, CUALQUIERA QUE SEA SU NATURALEZA, CON GOBIERNOS O ENTIDADES EXTRANJERAS, CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTÍAS NECESARIOS HASTA LA CUANTÍA ANTES MENCIONADA Y REPRESENTAR A LA COMPAÑÍA EN CUALQUIER TRÁMITE O PROCESO JUDICIAL QUE SE ADELANTE ANTE LAS JURISDICCIONES CIVIL, LABORAL, COMERCIAL, PENAL Y CONTENCIOSO ADMINISTRATIVA EN CALIDAD DE DEMANDANTES O DEMANDADOS Y CUALQUIER OTRO TRÁMITE EN EL QUE SE REQUIERA REPRESENTAR A LA COMPAÑÍA ANTE ENTIDADES Y ORGANISMOS DEL ESTADO DE CUALQUIER ORDEN O ENTIDADES DE NATURALEZA PRIVADA; ADQUISICIÓN DE ACTIVOS FIJOS NO SUPERIOR A DOSCIENTOS UNO SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES (201 SMLV); OBTENER CRÉDITOS CON ENTIDADES FINANCIERAS NO SUPERIORES A UN MILLÓN QUINIENTOS MIL DÓLARES AMERICANOS (US\$1.500.0000) Y CONTRATAR OTRAS COMPRAS POR CONCEPTO DE ASESORÍAS Y GASTOS DIFERENTES A LOS ANTERIORES PREVIA APROBACIÓN DE LA JUNTA DIRECTIVA. 2) CUMPLIR Y HACER CUMPLIR LAS DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZÓN SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICÍAS ADUANALES, POSTALES, ETC. 3) ORGANIZAR LOS SERVICIOS Y LAS OFICINAS DE LA SOCIEDAD, LA CONTABILIDAD Y APLICAR LOS ESTATUTOS Y REGLAMENTOS. 4) LLEVAR A CABO LA GESTIÓN COMERCIAL Y FINANCIERA. 5) TENDRÁ LA PLENA RESPONSABILIDAD DE LA ACCIÓN ADMINISTRATIVA, LA COORDINACIÓN Y LA SUPERVISIÓN GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRÁ CON ARREGLO A LAS NORMAS DE ESTOS ESTATUTOS. 6) COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALESQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GÉNERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 7) HACER DEPÓSITOS EN BANCOS Y

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AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARÉS, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASÍ COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS Y PAGARLOS, DESCARGARLOS, ETC. 8) NOMBRAR Y REMOVER LIBREMENTE A LOS EMPLEADOS DISTINTOS DE LOS QUE LA JUNTA DIRECTIVA TENGA ATRIBUCIONES. 9) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, EN SUS REUNIONES ORDINARIAS, EL INFORME SOBRE LA FORMA COMO HAYA LLEVADO A CABO SU GESTIÓN E INNOVACIONES QUE CONVENGA INTRODUCIR PARA EL MEJOR SERVICIO DE SUS INTERESES. 10) SUSCRIBIR TODA CLASE DE DOCUMENTOS PÚBLICOS O PRIVADOS, CUANDO LA JUNTA DIRECTIVA LO AUTORICE Y CON EL PROPÓSITO DE INSTRUMENTAR CUALQUIER TIPO DE ACTOS, NEGOCIOS JURÍDICOS, OPERACIONES DE CUALQUIER ÍNDOLE, Y SIEMPRE Y CUANDO NO SUPERE LA CUANTÍA PREVISTA EN ESTOS ESTATUTOS COMO LÍMITE DEL EJERCICIO DE SUS FUNCIONES, Y POR ENCIMA DE LA CUAL REQUIERE AUTORIZACIÓN DE LA JUNTA DIRECTIVA. 11) PODRÁ EJERCER LA REPRESENTACIÓN LEGAL, SIN PERJUICIO DE LA MISMA FUNCIÓN ASIGNADA A LOS OTROS REPRESENTANTES LEGALES PARA OTORGAR PODERES A TERCEROS, NOMBRAR ABOGADOS Y PROCURADORES, INTERPONER RECLAMACIONES EN LA VÍA GUBERNATIVA, ANTE TRIBUNALES, JURISDICCIONES ORDINARIAS, LABORALES Y ESPECIALES, REPRESENTAR A LA SOCIEDAD ANTE ADMINISTRACIONES O HACIENDAS PÚBLICAS, PRIVADAS, NACIONALES, INTERNACIONALES Y AUTONÓMICAS, CONCURRIR A TODA CLASE DE SUBASTAS, CONCURSOS O SUMINISTROS OFICIALES O PARTICULARES, PUDIENDO POR TANTO REDACTAR, SUSCRIBIR, PRESENTAR Y, EN SU CASO, MEJORAR EN LICITACIÓN VERBAL O ESCRITA LAS OFERTAS O PROPOSICIONES PERTINENTES, ACEPTAR DONACIONES PARA LA SOCIEDAD Y ACEPTAR CON BENEFICIO DE INVENTARIO, LEGADOS, EJERCITAR ACCIONES O PONER EXCEPCIONES, PARA ACTUAR EN CALIDAD DE DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. 12) ORDENAR LOS PAGOS A REALIZAR POR LA SOCIEDAD PARA QUE EL TESORERO O QUIEN HAGA SUS VECES, EXPIDA LAS ÓRDENES DE PAGO USANDO EL MEDIO MÁS EXPEDITO PARA CONTAR CON LA CELERIDAD QUE LOS NEGOCIOS SOCIALES EXIGEN; TODO ELLO DENTRO DE LAS LIMITACIONES ESTABLECIDAS EN ESTOS ESTATUTOS.

REVISOR FISCAL. LA DESIGNACIÓN DEL REVISOR FISCAL Y SUS RESPECTIVOS SUPLENTE CORRESPONDE A LA ASAMBLEA GENERAL DE ACCIONISTAS Y SERÁ ELEGIDO POR LA MAYORÍA ABSOLUTA DE LOS ACCIONISTAS PRESENTES.

CERTIFICA:

DOCUMENTO: ACTA No. 116 DEL 04 DE MARZO DE 2010

ORIGEN: ASAMBLEA GRAL ORDINARIA

INSCRIPCION: 11 DE MAYO DE 2010 No. 5472 DEL LIBRO IX

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FUE(RON) NOMBRADO(S):

PRESIDENTE DE LA JUNTA DIRECTIVA Y REPRESENTANTE LEGAL

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

VICEPRESIDENTE DE LA JUNTA DIRECTIVA Y SEGUNDO REPRESENTANTE LEGAL

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

PRESIDENTE EJECUTIVO - TERCER REPRESENTANTE LEGAL

JUAN CAMILO PALACIO RAMIREZ

C.C.19455622

CUARTO REPRESENTANTE LEGAL

ROBERTO MAURICE VENTURA CRISPINO

C.C.9086003

QUINTO REPRESENTANTE LEGAL

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

CERTIFICA:

DOCUMENTO: ACTA No. 116 DEL 04 DE MARZO DE 2010

ORIGEN: ASAMBLEA GRAL ORDINARIA

INSCRIPCION: 11 DE MAYO DE 2010 No. 5471 DEL LIBRO IX

FUE(RON) NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO RENGLON

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

TERCER RENGLON

LUIS ALFONSO MORA TEJADA

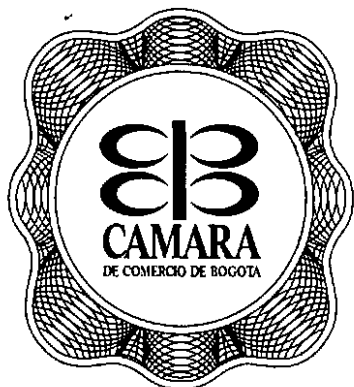
C.C.4610260

SUPLENTES

PRIMER RENGLON

JUAN MANUEL RENDON VENTURA

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C.C.79939921

SEGUNDO RENGLON

ADRIANA RENDON DE ANTORCHA

C.C.66901857

TERCER RENGLON

CARLOS ANTONIO ESPINOSA PEREZ

C.C.16684716

CERTIFICA:

DOCUMENTO: ACTA No. 118 DEL 29 DE JUNIO DE 2010

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 12 DE AGOSTO DE 2010 No. 9529 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL FIRMA

DELOITTE & TOUCHE LTDA D & T LTDA

NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 02 DE AGOSTO DE 2010

ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA

INSCRIPCION: 12 DE AGOSTO DE 2010 No. 9530 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL PRINCIPAL

LEANDRO FELIPE PAZ AGELVIS

C.C.14700811

REVISOR FISCAL SUPLENTE

HEYMAN ANTONIO GIL BALCAZAR

C.C.16796791

CERTIFICA:

CAPITAL AUTORIZADO: \$40,000,000,000

NUMERO DE ACCIONES: 4,000,000,000

VALOR NOMINAL: \$10

CAPITAL SUSCRITO: \$20,150,975,220

NUMERO DE ACCIONES: 2,015,097,522

VALOR NOMINAL: \$10

CAPITAL PAGADO: \$20,150,975,220

NUMERO DE ACCIONES: 2,015,097,522

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VALOR NOMINAL: \$10

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 03 DE DICIEMBRE DE 2009
INSCRIPCIÓN: 28 DE DICIEMBRE DE 2009 BAJO EL NRO. 14869 DEL LIBRO IX
CONSTA LA SITUACIÓN DE CONTROL:
CONTROLANTE: DORAL INVESTMENTS INTERNATIONAL INC
DOMICILIO: ISLAS VIRGENES BRITÁNICAS
ACTIVIDAD: OTRAS ACTIVIDADES EMPRESARIALES
CONTROLADA: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
NIT: 890301463-8
DOMICILIO: CALI VALLE
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA
REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS,
PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTOS FUNCIONALES, COSMÉTICOS Y
FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS
DIETÉTICOS, COLORANTES DE PERFUMERÍA Y AFINES.
PRESUPUESTO DE CONTROL: POSEE PARTICIPACIÓN ACCIONARIA MAYOR AL 50% A PARTIR
DEL 10 DE NOVIEMBRE DE 2009.

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 30 DE ABRIL DE 2004
INSCRIPCIÓN: 03 DE MAYO DE 2004 No. 4859 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 29 DE ABRIL DE 2005
INSCRIPCIÓN: 06 DE MAYO DE 2005 No. 4983 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 15 DE JUNIO DE 2006
INSCRIPCIÓN: 21 DE JUNIO DE 2006 No. 7526 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 01 DE NOVIEMBRE DE 2006
INSCRIPCIÓN: 28 DE NOVIEMBRE DE 2006 No. 13380 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2006
INSCRIPCIÓN: 21 DE DICIEMBRE DE 2006 No. 14301 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE DICIEMBRE DE 2007
INSCRIPCIÓN: 21 DE DICIEMBRE DE 2007 No. 13604 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 19 DE OCTUBRE DE 2009
INSCRIPCIÓN: 22 DE OCTUBRE DE 2009 No. 12216 DEL LIBRO IX
DOCUMENTO: DOCUMENTO PRIVADO DEL 23 DE FEBRERO DE 2010

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INSCRIPCIÓN: 25 DE FEBRERO DE 2010 No. 2203 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 27 DE ABRIL DE 2010

INSCRIPCIÓN: 28 DE ABRIL DE 2010 NRO. 4911 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 10 DE JUNIO DE 2010

INSCRIPCION: 17 DE JUNIO DE 2010 NRO. 7195 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 25 DE AGOSTO DE 2010

INSCRIPCION: 07 DE SEPTIEMBRE DE 2010 BAJO EL NRO. 10541 DEL LIBRO IX

DOCUMENTO: DOCUMENTO PRIVADO DEL 14 DE JUNIO DEL 2011

INSCRIPCION: 22 DE JUNIO DE 2011 BAJO EL NRO. 7772 LIBRO IX

CONSTA EL SIGUIENTE GRUPO EMPRESARIAL:

CONTROLANTE

LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

NIT. 890301463-8

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

ACTIVIDAD: A) LA FABRICACIÓN, DISTRIBUCIÓN Y VENTA EN EL TERRITORIO DE LA REPÚBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUÍMICOS, FARMACÉUTICOS, ALIMENTOS FUNCIONALES, COSMÉTICOS Y FISIOLÓGICOS, REACTIVOS, ANTIBIÓTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETÉTICOS, COLORANTES DE PERFUMERÍA Y AFINES. B) LA REPRESENTACIÓN DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACIÓN, IMPORTACIÓN, DISTRIBUCIÓN Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACIÓN DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PUEDE LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAÍCES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAÍCES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD, DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

SUBORDINADA

AMERICAN GENERICS S A S

NIT. 800223214-9

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

HORA: 09:06:21

OPERACION: 09ERP1117026

PAGINA: 14

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL INTERNACIONAL S.A.S.

NIT. 815003912-2

DOMICILIO: PALMIRA VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 3, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: REALIZACIÓN DE ACTIVIDADES DESDE LA ZONA FRANCA, LAS CUALES CONSISTEN EN LA PRESTACIÓN DE TODO TIPO DE SERVICIOS ASÍ COMO DISTRIBUIR, VENDER, COMPRAR, IMPORTAR, EXPORTAR Y ALMACENAR TODO TIPO DE MATERIAS PRIMAS, PRODUCTOS TERMINADOS Y SEMITERMINADOS RELACIONADOS CON LA INDUSTRIA DE ALIMENTOS, COSMÉTICA Y FARMACÉUTICA.

SUBORDINADA

LAFRANCOL PERÚ S.A

DOMICILIO: LIMA

NACIONALIDAD: PERU

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LABORATORIOS PAULY PHARMACEUTICAL S.A.S.

NIT. 800097402-6

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTÍCULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO HUMANO.

SUBORDINADA

LAFRANCOL (USA) CORP

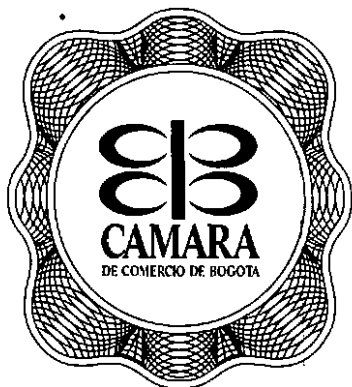
DOMICILIO: ESTADOS UNIDOS

NACIONALIDAD: ESTADOS UNIDOS

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

HORA: 09:06:21

OPERACION: 09ERP1117026

PAGINA: 15

HUMANO.

SUBORDINADA

GAMAR SOCIEDAD S A S EN LIQUIDACION

NIT. 890312050-7

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: TODAS LAS ACTIVIDADES RELACIONADAS CON LAS ARTES GRÁFICAS.

SUBORDINADA

LAFRANCOL GUATEMALA S.A.

NIT. 4088707

DOMICILIO: GUATEMALA

NACIONALIDAD: GUATEMALA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: PRODUCCIÓN, FABRICACIÓN, EXPORTACIÓN Y DISTRIBUCIÓN DE PRODUCTOS

FARMACÉUTICOS Y/O ALIMENTICIOS Y NATURALES DE CONSUMO HUMANO Y LA

COMERCIALIZACIÓN DE TODA CLASE DE MERCANCÍAS POR CUENTA PROPIA O EN NOMBRE DE

TERCEROS.

SUBORDINADA

DISTRIBUCIONES UQUIFA S A S

NIT. 800182021-7

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS Y

ALIMENTOS FUNCIONALES DE CONSUMO HUMANO.

SUBORDINADA

LABORATORIOS NATURMEDIK S A S

NIT. 800226363-1

DOMICILIO: CALI VALLE

NACIONALIDAD: COLOMBIA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995.

ACTIVIDAD: DISTRIBUCIÓN Y COMERCIALIZACIÓN DE PRODUCTOS FARMACÉUTICOS DE USO

HUMANO.

SUBORDINADA

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

HORA: 09:06:21

OPERACION: 09ERP1117026

PAGINA: 16

LAFRANCOL DOMINICANA S.A.

DOMICILIO:SANTO DOMINGO REPÚBLICA DOMINICANA

NACIONALIDAD:REPÚBLICA DOMINICANA

PRESUPUESTO DE CONTROL:NUMERAL 1, ARTÍCULO 27 DE LA LEY 222.

ACTIVIDAD:FABRICACIÓN DE PRODUCTOS FARMACÉUTICOS.

SUBORDINADA

LABORATORIO FRANCO-COLOMBIANO DEL ECUADOR S.A.

DOMICILIO: GUAYAQUIL, REPÚBLICA DEL ECUADOR

NACIONALIDAD: ECUATORIANA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995. LA FECHA DE LA PRIMERA TRANSACCION COMERCIAL FUE EN JUNIO DE 2009 Y LA CAPITALIZACION SE HIZO EN OCTUBRE DE 2009.

ACTIVIDAD: DEDICARSE A LA FABRICACIÓN, PRODUCCIÓN, EMPAQUE, COMERCIALIZACIÓN, DISTRIBUCIÓN, COMPRAVENTA, IMPORTACIÓN, EXPORTACIÓN Y/O REPRESENTACIÓN DE TODO TIPO DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, COSMÉTICOS, ALIMENTICIOS, DIETÉTICOS Y BAJOS EN CALORÍAS, VETERINARIOS, APARATOS E INSTRUMENTOS QUIRÚRGICOS, MÉDICOS, DENTALES Y VETERINARIOS. PODRÁ ADQUIRIR ACCIONES, PARTICIPACIONES O CUOTAS SOCIALES DE CUALQUIER CLASE DE COMPAÑÍA, SEA NACIONAL O EXTRANJERA, PUDIENDO INTERVENIR EN LA FUNDACIÓN O AUMENTO DE CAPITAL DE OTRAS SOCIEDADES QUE TENGAN OBJETIVOS SOCIALES RELACIONADOS CON EL SUYO. PODRÁ CONSTRUIR, ADQUIRIR EN PROPIEDAD, ARRENDAMIENTO O EN ASOCIACIÓN TODA CLASE DE PLANTAS INDUSTRIALES PARA PRODUCCIÓN, EMPAQUE, PROCESAMIENTO O CUALQUIER OTRA FORMA PARA LA COMERCIALIZACIÓN EN EL MERCADO INTERNO Y EXTERNO DE PRODUCTOS FARMACÉUTICOS YA SEA PARA EL CONSUMO HUMANO, VEGETAL O ANIMAL.

SUBORDINADA

FOCUS PHARMACEUTICAL S.A.S.

NIT: 900.104.555-8

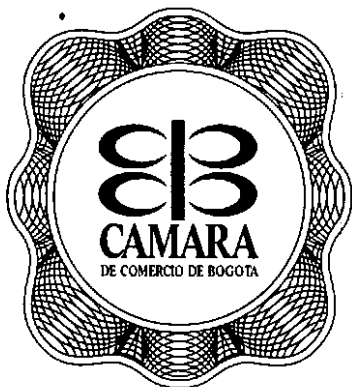
DOMICILIO: BOGOTÁ D.C.

NACIONALIDAD: COLOMBIANA

PRESUPUESTO DE CONTROL: NUMERAL 1, ARTICULO 27 DE LA LEY 222 DE 1995. LA FECHA DE LA PRIMERA TRANSACCION COMERCIAL FUE EN ENERO DE 2010 Y LA CAPITALIZACION SE HIZO EN ENERO DE 2010.

ACTIVIDAD: EL OBJETO PRINCIPAL DE LA SOCIEDAD ES EL DESARROLLO, FABRICACIÓN O PRODUCCIÓN, DIRECTAMENTE O A TRAVÉS DE TERCEROS EN CUALQUIER MODALIDAD NEGOCIAL, LA COMERCIALIZACIÓN Y DISTRIBUCIÓN, NACIONAL O INTERNACIONAL, DE

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

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OPERACION: 09ERP1117026

PAGINA: 17

TODA CLASE DE ARTÍCULOS DE GÉNERO FARMACÉUTICO, ESPECÍFICAMENTE DE MEDICAMENTOS ESA ACTIVIDAD PRINCIPAL CONLLEVA LA HABILITACIÓN PARA DESARROLLAR TODA OTRA CONEXA O NECESARIA, INCLUYENDO DE MANERA ESPECIAL PERO NO LIMITATIVA, LA INVESTIGACIÓN FARMACÉUTICA, EL DESARROLLO DE PRODUCTOS MÉDICOS Y FARMACÉUTICOS, EQUIPOS MÉDICOS, TRATAMIENTOS ALTERNATIVOS Y EN GENERAL, TODO AQUELLO VINCULADO A LA PROTECCIÓN DE LA SALUD HUMANA.

PODRÁ EFECTUAR LA INVERSIÓN EN BIENES INMUEBLES, URBANOS O RURALES Y LA ADQUISICIÓN, ADMINISTRACIÓN, ARRENDAMIENTO, GRAVAMEN Y ENAJENACIÓN DE LOS MISMOS.

LA INVERSIÓN DE FONDOS PROPIOS, EN BIENES INMUEBLES, BONOS, VALORES BURSÁTILES Y PARTES DE INTERÉS EN SOCIEDADES COMERCIALES, ASÍ COMO LA NEGOCIACIÓN DE TODA CLASE DE DERECHOS DE CRÉDITO.

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.5234- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: ---K 1 46 84 DE CALI

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369809- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: --K 1 46A 70 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: ---K 1A 46 A 32 DE CALI

FECHA MATRICULA : 29 DE ABRIL DE 1994

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734908- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

HORA: 09:06:21

OPERACION: 09ERP1117026

PAGINA: 18

LAFRANCOL

UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI

FECHA MATRICULA : 28 DE MARZO DE 2008

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734911- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI

FECHA MATRICULA : 28 DE MARZO DE 2008

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.734913- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO LAFRANCOL

UBICADO EN: CRA. 3 NRO. 47 25 DE CALI

FECHA MATRICULA : 28 DE MARZO DE 2008

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 30 DE MARZO DE 2011 .

CERTIFICA:

QUE HACIENDA CALI FUE INFORMADO(A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 734908-2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL

QUE LA SECRETARIA DE SALUD FUE INFORMADO (A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 734908- 2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL

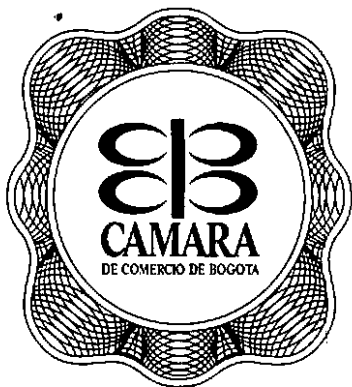
QUE PLANEACION FUE INFORMADO (A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 734908-2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL

QUE HACIENDA CALI FUE INFORMADO(A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 734913-2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL

QUE LA SECRETARIA DE SALUD FUE INFORMADO (A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 734913- 2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL

QUE PLANEACION FUE INFORMADO (A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/11/17

HORA: 09:06:21

OPERACION: 09ERP1117026

PAGINA: 19

ESTABLECIMIENTO DE COMERCIO. 734913-2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL
QUE HACIENDA CALI FUE INFORMADO(A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL
ESTABLECIMIENTO DE COMERCIO. 734911-2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL
QUE LA SECRETARIA DE SALUD FUE INFORMADO (A) EL 03 DE ABRIL DE 2008 DE LA
APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 734911- 2 LABORATORIO FRANCO
COLOMBIANO LAFRANCOL
QUE PLANEACION FUE INFORMADO (A) EL 03 DE ABRIL DE 2008 DE LA APERTURA DEL
ESTABLECIMIENTO DE COMERCIO. 734911-2 LABORATORIO FRANCO COLOMBIANO LAFRANCOL

CERTIFICA:

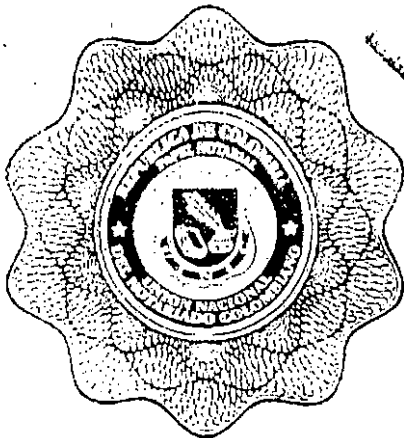
QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL
PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES
DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO
TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR
LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A
CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 17 DIAS DEL MES DE NOVIEMBRE DEL AÑO 2011 HORA: 09:15:06
AM

[Firma manuscrita]



1658 B

AA 8567146

REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

JULIO - - - - -

DEL AÑO DOS MIL DOS (2002). -----

ACTO: -----

1.- PODER ESPECIAL.-----

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-E - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá.-----

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,

DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,

ANTE MI, DIANA BEATRIZ LOPEZ, - - - - -

NOTARIA TREINTA Y TRES (33) - - - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE

SE CONSIGNA EN LOS SIGUIENTES TERMINOS:-----

COMPARECIO: JUAN MARIA RENDON, mayor de edad,

vecino de Bogotá, D.C, identificado con la cédula de
ciudadanía número 17.125.100.000 de Bogotá D.C. después de la confrontación

Expedida en Bogotá - correspondiente al documento que se ha

Y manifestó:-----

PRIMERO: Que obra en su carácter de Representante

Legal de en nombre y representación de LAFRANCOL

S.A, sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio y

sede principal en Cali - Valle, constituida mediante

escritura pública número

De la Notaría

De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR**, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo y judicial, como NOVENO DE BOGOTÁ D.C. después de la debida confrontación a la copia auténtica del documento, ha tomado y

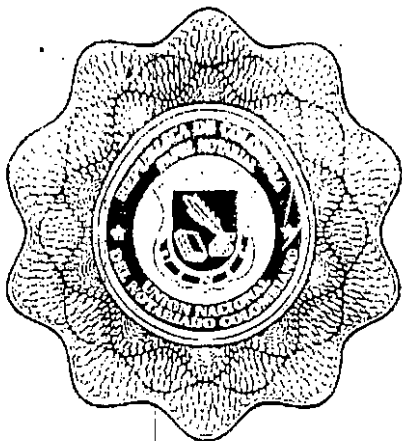
concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de oberservaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que

NOTARIO NOVENO DE BOGOTÁ D.C. después de la debida confrontación a la copia auténtica del documento, ha tomado y

16 ABR 2008



16583

AA 8567152

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promueva Lafrancol S.A., o se
promuevan contra esta y.-----

c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del
artículo 70 del C.P.C. pueda sustituir este
mandato, transigir, conciliar, admitir los hechos del
proceso, desistir, cancelar, recibir, renunciar y
ratificar los actos de agentes oficiosos y ceder a
título gratuito y/o oneroso, licenciar, inscribir
contratos de cesión y de licencia, inscripción de
prendas, levantamiento de prendas, inscribir
derechos de retención y en general todos los asuntos
que se deban tramitar ante la Superintendencia de
Industria y Comercio.-----

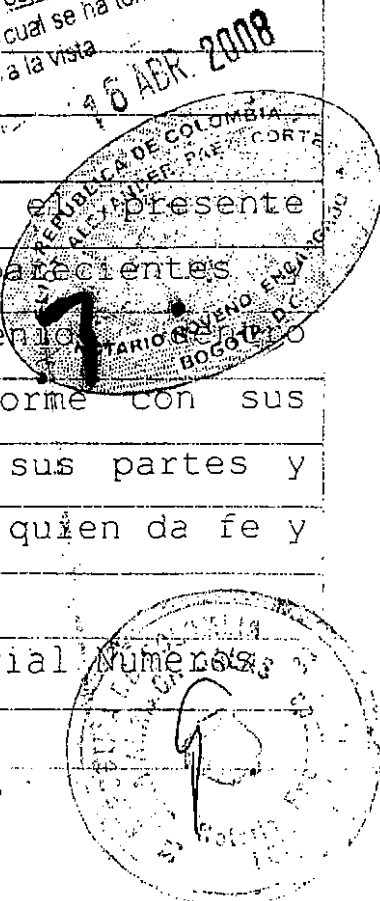
Manifestamos que de la veracidad de las
declaraciones del contenido y autenticidad de los
documentos anexos en éste instrumento público sólo
respondemos los comparecientes como NOTARIO NOVENO DE

HASTA AQUI LA MINUTA PRESENTADA

OTORGAMIENTO Y AUTORIZACION: Leído y presente
instrumento Público por los comparecientes
advertidos de la formalidad de su contenido
del término legal, lo hallaron conforme con sus
intenciones y lo aprobaron en todas sus partes y
firmaron junto con la Suscrita Notaria quien da fe y
lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números

AA 8567146, 8567152.



DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

[Signature]
JUAN MARIA RENDON

C.C. No. 17.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

[Signature]
JOSE LUIS REYES VILLAMIZAR

C.C. No. 79.152.473

TEL: 621-2631

[Signature]
DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

n.c.a.

~~La Segunda~~ COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

hojas útiles con destino a Jose Luis Reyes

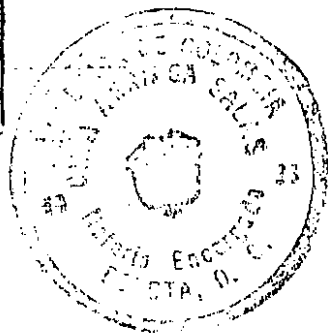
Villamizar

Santafé de

1772/79

05 JUL 2002

[Signature]



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 112141

Bogotá D.C., Noviembre 17 de 2011 - 13:02:56

RECIBIDO DE : REYES Y REYES ABOGADOS

NI 900.048.328

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	382917953	17/11/2011	304.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. LINDITARIO	Vr. CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	304.000.00	304.000.00
				\$304.000.00
=====				

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-135578- -00003-0000

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