

REYES & REYES

A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-094203- -00006-0000

Fecha: 2008-06-17 16:36:05 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 329 CTOINFORMACION Folios: 42

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SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 06-094-203

**TÍTULO SOLICITADO: DISPOSITIVO DE SUMINISTRO DE DROGA VISIBLE
CON RAYOS X.**

PUBLICACIÓN: Gaceta 583 N° de publicación 1064

PRIORIDAD: EP 04101151.1 de 19/03/2004

SOLICITANTE: N.V. ORGANON

APODERADO: EMILIO FERRERO

TRÁMITE: SUSTENTACION 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 **TECNOQUIMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN.

La solicitud colombiana 06-094-203 en trámite, que se refiere a un dispositivo liberación de fármaco visible con rayos X para la administración sub-dérmica de

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radio-opaco (sulfato de bario o alambre de titanio) y un polímero termoplástico no medicada (polietileno vinil acetato) que cubre el núcleo, carece de los requerimientos fundamentales para otorgársele el beneficio de patente de invención, tal y como se puede evidenciar a través de los siguientes argumentos:

- La patente americana US 2003/153983 publicada el 14 de agosto de 2003 y titulada "IMPLANTABLE OR INSERTABLE MEDICAL DEVICE RESISTANT TO MICROBIAL GROWTH AND BIOFILM FORMATION" revela:

[0022] The term "matrix polymer" as used herein refers to a polymeric material that forms at least a portion or region of the implantable or insertable medical device of the present invention. The matrix polymer is selected to be biocompatible and provide mechanical properties consistent with the intended function and operation of the implantable or insertable medical device. The matrix polymer also serves as a repository in which at least one and, in some preferred embodiments, both the antimicrobial agent and microbial attachment/biofilm synthesis inhibitor are dispersed and/or dissolved. The matrix polymer may also contain, as optional components, a radio-opacifying agent and/or one or more therapeutic agents.

1. An implantable medical device comprising (a) at least one biocompatible matrix polymer region and (b) bioactive agents comprising an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor. (...)

7. The medical device of claim 1, wherein said matrix polymer comprises a biocompatible non-biodegradable polymer.

8. The medical device of claim 7, wherein said non-biodegradable polymer is selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, elastomeric polyurethanes and polyurethane copolymers, metallocene catalyzed polyethylene, ionomers and vinyl aromatic copolymers. (...)

10. The medical device of claim 8, wherein said non-biodegradable polymer is an ethylene vinyl acetate copoly-

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20. The medical device of claim 1, wherein said matrix polymer further comprises a radio-opacifying agent.

21. The medical device of claim 20, wherein said radio-opacifying agent comprises bismuth subcarbonate.

22. The medical device of claim 20 wherein the amount of said radio-opacifying agent present in said matrix polymer is from about 0.5% to about 45% by weight of the matrix polymer.

(...)

25. The medical device of claim 23, wherein the therapeutic agent is selected from the group consisting of cisplatin, methotrexate, doxorubicin, paclitaxel, docetaxel, dexamethasone, hydrocortisone and prednisone.

(...)

27. The medical device of claim 26, comprising a first matrix polymer region; a first polymeric barrier layer at least partially covering an interior surface of said first matrix polymer region; and a second polymeric barrier layer at least partially covering an exterior surface of said first matrix polymer region.

28. The medical device of claim 27, wherein each of said first matrix polymer region, and said first and second polymeric barrier layers is in the form of an annulus.

29. The medical device of claim 28, wherein the first and second polymeric barrier layers comprise the same polymeric materials.

(...)

32. The medical device of claim 27, wherein the first matrix polymer region comprises an ethylene vinyl acetate copolymer.

(...)

35. The medical device of claim 1, wherein the medical device is selected from the group consisting of a stent cover, a biliary stent, a ureteral stent, a pancreatic stent, a urinary catheter, a venous access device, a peritoneal access device, a device connecting or providing drainage between two sterile body environments, and a device connecting or providing drainage between a non-sterile and a sterile body environment.

(...)

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72. An implantable or insertable medical device comprising at least one biocompatible matrix polymer region comprising a material selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, metallocene catalyzed polyethylenes and polyethylene copolymers, ionomers, vinyl aromatic copolymers, elastomeric polyurethanes and polyurethane copolymers, silicones and mixtures thereof; bioactive agents comprising an antimicrobial agent selected from the group consisting of triclosan, chlorhexidine and mixtures thereof; a microbial attachment/biofilm synthesis inhibitor selected from the group consisting of salicylic acid and salts and derivatives thereof, and, a radio-opacifying agent selected from the group consisting of bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, barium sulfate, tungsten and mixtures thereof.

(...)

De la lectura de lo consignado anteriormente, podemos observar que este documento se refiere a un dispositivo implantable con las mismas características fundamentales que el que describe en su capítulo reivindicatorio la solicitud colombiana en trámite; específicamente se refiere a un dispositivo médico implantable que utiliza en su formulación copolímeros de etileno vinil acetato y agentes activos que hacen parte del núcleo, así mismo contiene un material radio-opaco, entre los que se menciona al Sulfato de bario y que puede estar entre 0,5 y 45% y además, dicha matriz está al menos parcialmente cubierta por una o más capas o barreras de copolímeros de etileno vinil acetato.

Si bien es cierto que en el dispositivo de la anterioridad no se incluyen los mismos activos de la solicitud colombiana en trámite y en consecuencia no sería útil en la aplicación de un tratamiento contraceptivo o de reemplazo hormonal, es claro que este tipo de herramientas farmacológicas han sido usadas en otras terapias y con otros fármacos tal es el caso de agente antimicrobianos, anticancerígenos y esteroidales (ver Rv 25 de la US 2003/0153983 en mención), por tanto, es claro que se dejan abiertas las opciones para la inserción de otro tipo de agentes activos, por tanto, cualquier persona medianamente versada en la materia y específicamente personas

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ejemplo desogestrel, 3-cetodesogestrel, a una formulación farmacéutica de este tipo.

Entonces, estando incluidas en esta anterioridad todas las características fundamentales que describen la invención del dispositivo reivindicado en la solicitud colombiana en trámite, queda desvirtuado así el nivel inventivo de dicha invención.

- La publicación internacional WO 2004/011055 publicada el 05 de febrero de 2004 y titulada "IMPLANTABLE OR INSERTABLE MEDICAL DEVICES FOR CONTROLLED DRUG DELIVERY" revela:

[0007] According to one aspect of the present invention, implantable or insertable medical devices are provided, which comprise: (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, an anesthetic agent, and an antispasmodic agent. The medical devices are adapted for implantation or insertion at sites associated with pain or discomfort upon implantation or insertion.

(...)

[0031] Another aspect of the invention is directed to the use of such an implantable or insertable medical device to bring about a reduction in discomfort or pain subsequent to implantation or insertion (in addition to other therapeutic benefits that the device is implanted/inserted to provide, for example, to facilitate drainage, etc.). In some embodiments, the medical device will also be used to resist microbial growth and/or biofilm formation.

(...)

[0039] Where only a single distinct polymeric matrix region is provided in the medical device, the polymeric matrix region will preferably contain the therapeutic agent as well as any optional additives, such as radio-opacifying agents, pigments, antimicrobial agents, plasticizers, lubricants, and so forth. In other embodiments, the medical device comprises two or more distinct polymeric matrix regions. Where two or more distinct polymeric matrix regions are present in the medical device, it is not necessary that the therapeutic agent and any optional additive(s) be present in a single polymeric matrix region. For example, a therapeutic agent may be present in a first polymeric matrix region, and one or more optional additives may be present in a second polymeric matrix region.

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(...)

[0060] The polymeric regions used in the implantable or insertable medical device of the present invention may comprise any biocompatible polymer suitable for use in implantable or insertable medical devices. The biocompatible polymer may be substantially non-biodegradable or biodegradable.

(...)

[0067] As another example, a medical device in accordance with the present invention may comprise a three-layer structure comprising a first layer comprising biocompatible polymer, radio-opacifying agent and therapeutic agent, a second layer on an external surface of the first layer that acts as a barrier layer, and a third layer on an external surface of the second layer that provides lubricity. A simplified schematic

(...)

1. An implantable or insertable medical device comprising: (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, an anesthetic agent, and an antispasmodic agent, wherein said medical device is adapted for implantation or insertion at a site associated with pain or discomfort upon implantation or insertion.

(...)

3. The implantable or insertable medical device of claim 1, further comprising a radio-opacifying agent.

(...)

15. The implantable or insertable medical device of claim 9, wherein said biocompatible polymer is an ethylene-vinyl acetate (EVA) copolymer.

(...)

20. The implantable or insertable medical device of claim 18, wherein said medical device comprises (a) a first polymeric matrix region comprising a first biocompatible polymer and said therapeutic agent, and (b) a second polymer matrix region comprising a second biocompatible polymer and said radio-opacifying agent, wherein said first and second biocompatible polymers may be the same or different.

Luego de la lectura de lo consignado anteriormente, podemos observar que

en su formulación polímeros de polietileno vinil acetato así como un material radio-opaco y un agente activo. Aunque a dicho dispositivo no se le mencione explícitamente como útil en la aplicación de un tratamiento contraceptivo o de reemplazo hormonal, es empleado en otras terapias mediante la inclusión de fármacos antiinflamatorios, analgésicos, anestésicos, etc, en consecuencia, cualquier persona medianamente versada en la materia y específicamente personas dedicadas a la formulación y desarrollo de productos y luego de los respectivos ensayos de preformulación podría llegar a incluir un principio activo distinto, por ejemplo desogestrel, 3-cetodesogestrel, a una formulación farmacéutica de este tipo.

Adicionalmente, vemos que en esta anterioridad (WO 04/011055) se describe lo siguiente:

[0053] The radio-opacifying agent facilitates viewing of the medical device during insertion of the device and at any point while the device is implanted. A radio-opacifying agent typically functions by scattering x-rays. The areas of the medical device that scatter the x-rays are detectable on a radiograph. Among radio-opacifying agents useful in the medical device of the present invention are included a bismuth salt such as bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, barium sulfate, tungsten, and mixtures thereof, with bismuth salts typically being preferred. Where present, the radio-

Esto permite ver claramente que la inclusión de un agente radio-opaco dentro de uno de estos tipos de implantes médicos permite su detección a través de rayos X, motivo por el cual, no resultaría de ninguna manera novedoso o que demuestre nivel inventivo el empleo de este tipo de agentes en formulaciones implantables tal como se pretende hacer creer en la presente solicitud colombiana en trámite.

- Ahora bien, y en continuidad con lo aportado hasta el momento, me permito mencionar la existencia de algunas patentes en las que se describen implantes contraceptivos subdérmicos que comprenden un núcleo formado por un copolímero de etileno/vinil acetato que funciona como una matriz para el agente contraceptivo seleccionado del grupo que

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septiembre de 1990 y la US 5,150,718 publicada el 29 de septiembre de 1992; lo que permite inequívocamente demostrar que la solicitud colombiana en trámite carece de novedad o al menos de nivel inventivo (teniendo en cuenta las distintas anterioridades mencionadas en el presente escrito); ahora bien, si la supuesta novedad está dada por la detección de dicho implante a través de rayos X, es del caso resaltar lo revelado en el siguiente artículo científico:

Nonpalpable ultrasonographically not detectable Implanon rods can be localized by magnetic resonance imaging Contraception, Volume 63, Issue 6, June 2001, Pages 325-328

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Gabriele S. Merki-Feld, Caspar Brekenfeld, Björn Migge, and Paul J. Keller.

Abstract:

Recently, the contraceptive implant Implanon has been introduced in several European countries. In comparison to the six-capsule preparation Norplant, the removal of this single-rod system should be associated with less complications. However, the removal of nonpalpable Implanon rods can be difficult because the implant is not always visible with ultrasound. The aim of this study was to find a radiologic method for the localization of Implanon implants that are nonpalpable and can not be detected by ultrasound. X-ray, ultrasound, computed tomography, and magnetic resonance imaging (MRI) were investigated as methods to localize Implanon in a pig chest preparation and in a woman with a nonpalpable implant. The implant in the woman could be localized unequivocally only by MRI. We conclude that MRI is the best method for the unequivocal localization of nonpalpable, ultrasonographically not detectable Implanon rods. To avoid unnecessary scar tissue formation, it may be appropriate to defer surgery for the removal until definitive localization.

Este documento sin más, señala que el implante contraceptivo Implanon®¹ cuando no puede ser detectado a través de Ultrasonido, puede ser localizado por otras técnicas entre las que se menciona Rayos X, y siendo preferida la MRI (Imágenes por Resonancia Magnética), lo que demuestra que al menos desde 2001 y tras una investigación científica, este tipo de implantes contraceptivos son susceptibles de ser detectadas o de ser visibles a los rayos X.

Así mismo, y para terminar el artículo "**Localization of non-palpable single-rod contraceptive implants using ultrasound sonography**" (presented at the 7th Congreso of the European Society of Contraception, Genova, Italy, 2002) señala que, la correcta inserción de un implante como el Implanon® puede ser localizado por ultrasonido, pero, si el implante no es radio-opaco,

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además, sugerir y promover en una persona medianamente versada en la materia la inclusión de un agente radio-opaco en implantes contraceptivos para que puedan ser visibles a los Rayos X.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

III. ANEXOS

- La patente americana US 2003/153983 publicada el 14 de agosto de 2003 y titulada "IMPLANTABLE OR INSERTABLE MEDICAL DEVICE RESISTANT TO MICROBIAL GROWTH AND BIOFILM FORMATION" pagina 2 y capitulo reivindicatorio.
- La publicación internacional WO 2004/011055 publicada el 05 de febrero de 2004 y titulada "IMPLANTABLE OR INSERTABLE MEDICAL DEVICES FOR CONTROLLED DRUG DELIVERY" paginas 2, 5, 7, 14, 17 y capitulo reivindicatorio.
- La patente americana US 4,957,119 publicada el 18 de septiembre de 1990.
- La patente americana US 5,150,718 publicada el 29 de septiembre de 1992.
- Abstract del Artículo Nonpalpable ultrasonographically not detectable Implanon rods can be localized by magnetic resonance imaging Contraception, Volume 63, Issue 6, June 2001. Gabriele S. Merki-Feld, Caspar Brekenfeld, Björn Migge, and Paul J. Keller.
- **"Localization of non-palpable single-rod contraceptive implants using untrasound sonography"** M.C.J.Kaptein and R. Ganpat (presented at the 7th Congreso of the European Society of Contraception, Genova, Italy, 2002).

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR



US 20030153983A1

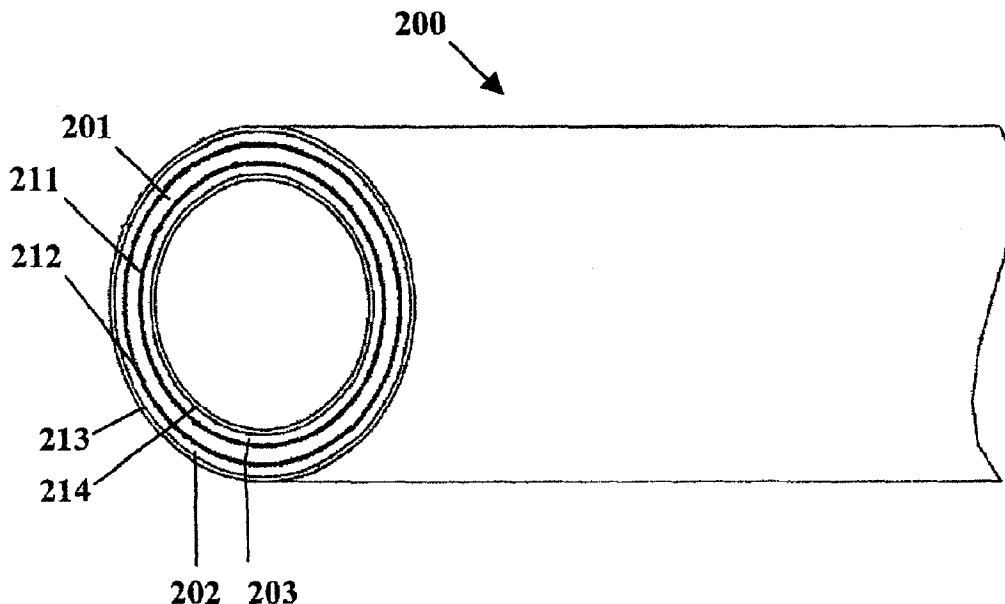
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131(19) **United States**(12) **Patent Application Publication**(10) Pub. No.: **US 2003/0153983 A1****Miller et al.**

(43) Pub. Date:

Aug. 14, 2003(54) **IMPLANTABLE OR INSERTABLE MEDICAL
DEVICE RESISTANT TO MICROBIAL
GROWTH AND BIOFILM FORMATION****Publication Classification**(51) Int. Cl.⁷ **A61F 2/04**(52) U.S. Cl. **623/23.7; 623/23.71; 424/426**(75) Inventors: **Kathleen M. Miller**, Shrewsbury, MA
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(US); **Kurt Geitz**, Sudbury, MA (US);
Peter L. Dayton, Brookline, MA (US);
Ronald A. Sahatjian, Lexington, MA
(US)(57) **ABSTRACT**

Disclosed are implantable or insertable medical devices that provide resistance to microbial growth on and in the environment of the device and resistance to microbial adhesion and biofilm formation on the device. In particular, the invention discloses implantable or insertable medical devices that comprise at least one biocompatible matrix polymer region, an antimicrobial agent for providing resistance to microbial growth and a microbial adhesion/biofilm synthesis inhibitor for inhibiting the attachment of microbes and the synthesis and accumulation of biofilm on the surface of the medical device. Also disclosed are methods of manufacturing such devices under conditions that substantially prevent preferential partitioning of any of said bioactive agents to a surface of the biocompatible matrix polymer and substantially prevent chemical modification of said bioactive agents

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WESTFIELD, NJ 07090 (US)(73) Assignee: **Scimed Life Systems, Inc.**(21) Appl. No.: **10/071,840**(22) Filed: **Feb. 8, 2002**

release of SA from the extruded tube. After incubation in PBS, the tubes are exposed a solution containing approximately 10^{-4} to 10^{-5} cfu/ml *e. coli* for about 4 hr at 37° C. with rotation at about 100 rpm. Subsequent to this exposure, the samples are rinsed in saline and "rolled" following an established pattern onto a standard Mueller-Hinton agar plate. The plates are incubated for about 18 to 24 hr to allow colonies to form. The colonies are counted and expressed as cfu per inch of tube.

[0101] FIG. 3 shows the normalized inhibitory response of the tubes. The amounts of TCN, SA and BsC in the tubes are represented as % TCN/% SA/% BsC (wt % based on weight of vinyl acetate EVA copolymer). Therefore, a tube having 10% TCN, 0% SA and 30% BsC is designated in FIG. 3 as "10/0/30". FIG. 3 shows the inhibitory response of five tubes having varying weight percentages of TCN and SA and 30% BsC, normalized to a 10/0/30 tube, given an inhibitory response value of 1. FIG. 3 shows that tubes containing 10% TCN and varying amounts (1%, 3% and 10% SA) inhibited bacterial attachment more effectively than tubes containing only TCN ("10/0/30") and inhibited bacterial attachment more effectively than tubes containing neither TCN nor SA ("0/0/30"). FIG. 3 also shows that, as the amount of SA increased from 0% to 10%, with TCN constant at 10%, the tubes were generally more effective at inhibiting bacterial attachment, suggesting that SA provides a synergistic effect. FIG. 3 further shows that incubation of the tubes in PBS prior to exposure to *e. coli* did not significantly affect bacterial inhibition, suggesting that effective amounts of TCN and SA remained in the extruded tubes after extended incubation in PBS, i.e., that the bioactive agents were not excessively or prematurely leached out of the extruded tubes. FIG. 4 shows results (not normalized) for similar tubes incubated for 3 and 8 days in PBS prior to exposure to *e. coli*.

EXAMPLE 4

[0102] Approximately 2 cm lengths of extruded 19% vinyl acetate EVA copolymer tubing containing varying amounts of triclosan (TCN), salicylic acid (SA) and bismuth subcarbonate (BsC) are inserted into an agar lawn of either *e. coli* (FIG. 5) or staph (FIG. 6). The tubes are positioned so as to extend vertically upwardly from the surface of the agar lawn (similar to birthday candles). After 24 hours in the agar lawn, the zone (diameter) of bacterial growth inhibition around the tubes is measured. The tubes are repositioned in fresh agar plates every 24 hours, and the zone of bacterial growth inhibition is again measured. FIG. 5 shows the measurement results for the tubes positioned in the agar lawn of *e. coli* and FIG. 6 shows the results for the tubes positioned in the agar lawn of staph. FIGS. 5 and 6 show that the zone of bacterial growth inhibition was larger as the percentage of TCN increased from 0% to a maximum of 10%. A tube containing no TCN, but varying amounts of SA did not effectively inhibit bacterial growth, suggesting that bacterial growth inhibition (as opposed to inhibition of bacterial attachment) is predominantly provided by TCN. FIGS. 5 and 6 also show that, for a given percentage of TCN, the measured zone of bacterial growth inhibition is similar over a period extending to about 40 days or longer, suggesting that the TCN component in the extruded tubes effectively maintains its activity for extended periods of time.

[0103] The invention may be embodied in other specific forms without departing from its proper scope. The

described embodiments and Examples are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes that come within the meaning and range of equivalency of the claims are to be embraced within their scope.

What is claimed is:

1. An implantable medical device comprising (a) at least one biocompatible matrix polymer region and (b) bioactive agents comprising an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor.
2. The medical device of claim 1, wherein both the antimicrobial agent and microbial attachment/biofilm synthesis inhibitor are present in a single distinct matrix polymer region.
3. The medical device of claim 1, wherein the antimicrobial agent and the microbial attachment/biofilm synthesis inhibitor are present in distinct matrix polymer regions.
4. The medical device of claim 1, wherein said antimicrobial agent is present in an amount effective to inhibit the growth of microbes on and around the device and the microbial attachment/biofilm synthesis inhibitor is present in an amount effective to inhibit the attachment of microbes onto and the synthesis and accumulation of biofilm from attached microbes on the surface of the device.
5. The medical device of claim 1, wherein said device is adapted to remain implanted for a period of greater than about 30 days.
6. The medical device of claim 1, wherein said matrix polymer comprises a biocompatible biodegradable polymer.
7. The medical device of claim 1, wherein said matrix polymer comprises a biocompatible non-biodegradable polymer.
8. The medical device of claim 7, wherein said non-biodegradable polymer is selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, elastomeric polyurethanes and polyurethane copolymers, metallocene catalyzed polyethylene, ionomers and vinyl aromatic copolymers.
9. The medical device of claim 6, wherein said biodegradable polymer is selected from the group consisting of polylactic acid, polyglycolic acid, copolymers and mixtures thereof.
10. The medical device of claim 8, wherein said non-biodegradable polymer is an ethylene vinyl acetate copolymer.
11. The medical device of claim 10, wherein said ethylene vinyl acetate copolymer has a vinyl acetate content of from about 19% to about 28%.
12. The medical device of claim 10, wherein said ethylene vinyl acetate copolymer has a vinyl acetate content of from about 3% to about 15%.
13. The medical device of claim 1, wherein said antimicrobial agent is selected from the group consisting of triclosan and chlorhexidine and mixtures thereof.
14. The medical device of claim 13, wherein said antimicrobial agent is triclosan.
15. The medical device of claim 14, wherein said microbial attachment/biofilm synthesis inhibitor is selected from the group consisting of NSAIDs, EDTA and EGTA.

16. The medical device of claim 15, wherein said microbial attachment/biofilm synthesis inhibitor is salicylic acid or a salt or derivative thereof.

17. The medical device of claim 16, wherein said microbial attachment/biofilm synthesis inhibitor is salicylic acid.

18. The medical device of claim 4, wherein the amount of said antimicrobial agent present in said matrix polymer is from about 0.5% to about 25% by weight of the matrix polymer.

19. The medical device of claim 4, wherein the amount of said microbial attachment/biofilm synthesis inhibitor present in said matrix polymer is from about 0.5% to about 25% by weight of the matrix polymer.

20. The medical device of claim 1, wherein said matrix polymer further comprises a radio-opacifying agent.

21. The medical device of claim 20, wherein said radio-opacifying agent comprises bismuth subcarbonate.

22. The medical device of claim 20 wherein the amount of said radio-opacifying agent present in said matrix polymer is from about 0.5% to about 45% by weight of the matrix polymer.

23. The medical device of claim 1, wherein the matrix polymer further comprises at least one therapeutic agent.

24. The medical device of claim 23, wherein the therapeutic agent is selected from the group consisting of chemotherapeutic agents, NSAIDs, steroidal anti-inflammatory agents, and mixtures thereof.

25. The medical device of claim 23, wherein the therapeutic agent is selected from the group consisting of cisplatin, methotrexate, doxorubicin, paclitaxel, docetaxel, dexamethasone, hydrocortisone and prednisone.

26. The medical device of claim 1, further comprising one or more barrier layers at least partially covering said at least one matrix polymer region.

27. The medical device of claim 26, comprising a first matrix polymer region; a first polymeric barrier layer at least partially covering an interior surface of said first matrix polymer region; and a second polymeric barrier layer at least partially covering an exterior surface of said first matrix polymer region.

28. The medical device of claim 27, wherein each of said first matrix polymer region, and said first and second polymeric barrier layers is in the form of an annulus.

29. The medical device of claim 28, wherein the first and second polymeric barrier layers comprise the same polymeric materials.

30. The medical device of claim 28, wherein the first and second polymeric barrier layers comprise different polymeric materials.

31. The medical device of claim 27, further comprising a second and, optionally, a third matrix polymer region and a third and, optionally, a fourth polymeric barrier layer; wherein the second matrix polymer region is disposed on an outside surface of the second polymeric barrier layer and the third polymeric barrier layer at least partially covers an exterior surface of said second matrix polymer region; and, wherein the third matrix polymer region, when present, is disposed on an interior surface of said first polymeric barrier layer and the fourth polymeric barrier layer at least partially covers an interior surface of said third matrix polymer region.

32. The medical device of claim 27, wherein the first matrix polymer region comprises an ethylene vinyl acetate copolymer.

33. The medical device of claim 32, wherein each of the first and second polymeric barrier layers comprises a material selected from the group consisting of metallocene catalyzed polyethylenes and polyethylene copolymers, ionomers, elastomeric polyurethanes and polyurethane copolymers, ethylene vinyl acetate copolymers and copolymers of ethylene with acrylic acid or methacrylic acid.

34. The medical device of claim 33, wherein the antimicrobial agent is selected from the group consisting of triclosan, chlorhexidine and combinations thereof, and the microbial attachment/biofilm synthesis inhibitor is salicylic acid or a salt thereof.

35. The medical device of claim 1, wherein the medical device is selected from the group consisting of a stent cover, a biliary stent, a ureteral stent, a pancreatic stent, a urinary catheter, a venous access device, a peritoneal access device, a device connecting or providing drainage between two sterile body environments, and a device connecting or providing drainage between a non-sterile and a sterile body environment.

36. The medical device of claim 35, wherein the device comprises a device connecting or providing drainage between a non-sterile and a sterile body environment.

37. The medical device of claim 36, wherein the device comprises a hollow tubular structure.

38. The medical device of claim 35, wherein the device comprises a stent cover.

39. The medical device of claim 38, wherein said biocompatible polymeric matrix comprises polyurethane, said antimicrobial agent comprises triclosan, said microbial attachment/biofilm synthesis inhibitor comprises salicylic acid or a salicylic acid derivative and further comprising a bismuth subcarbonate radio-opacifying agent.

40. The medical device of claim 38, wherein the stent cover comprises a hollow tubular structure adapted to be placed over a stent that comprises a woven, knitted or braided open mesh design comprising a biocompatible material.

41. The medical device of claim 40, wherein the stent cover is placed over a biliary stent.

42. The medical device of claim 40, wherein the biocompatible material is selected from the group consisting of stainless steel or a shape memory material.

43. The medical device of claim 35, wherein the medical device comprises a pancreatic stent that provides drainage from the pancreas to the duodenum.

44. The medical device of claim 43, wherein the pancreatic stent comprises a buffering agent.

45. The medical device of claim 44, wherein said buffering agent, upon exposure to physiological fluids, creates a pancreas-compatible pH level in an environment in which the pancreatic stent is implanted.

46. The medical device of claim 45, wherein said buffering agent is a bicarbonate salt.

47. The medical device of claim 46, wherein said bicarbonate salt is selected from the group consisting of sodium and potassium bicarbonate.

48. A method of manufacturing an implantable or insertable medical device comprising: providing a combination of (a) one or more biocompatible matrix polymers and (b) bioactive agents comprising an antimicrobial agent and a microbial attachment/biofilm synthesis inhibitor; processing said combination under conditions that substantially prevent preferential partitioning of any of said bioactive agents to a

surface of any of said biocompatible matrix polymers and that substantially prevent chemical modification of said bioactive agents.

49. The method of claim 48, further comprising controlling either or both of the temperature and moisture content during said processing.

50. The method of claim 48, wherein said processing comprises mixing said one or more biocompatible matrix polymers with one or more of said bioactive agents to form a homogeneous mixture of said one or more matrix polymers and said one or more bioactive agents.

51. The method of claim 50, wherein said homogeneous mixture comprises both bioactive agents.

52. The method of claim 50, wherein said mixing comprises applying mechanical shear to said one or more biocompatible matrix polymers and said one or more bioactive agents with a device selected from the group consisting of a single screw extruder, a twin screw extruder, a banbury mixer, a high-speed mixer and a ross kettle.

53. The method of claim 50, where said mixing comprises forming a solvent solution or a liquid dispersion of said one or more bioactive agents and said one or more biocompatible matrix polymers.

54. The method of claim 50, further comprising shaping said homogenous mixture into a matrix polymer region of an implantable or insertable medical device.

55. The method of claim 54, wherein said shaping comprises a process selected from molding, calendaring, casting and solvent coating.

56. The method of claim 54, wherein said shaping comprises extrusion.

57. The method of claim 56, wherein said extrusion comprises forming at least one annular matrix polymer region.

58. The method of claim 57, further comprising forming at least one polymeric barrier layer at least partially covering a surface of said annular matrix polymer region.

59. The method of claim 58, wherein said method comprises a process selected from extrusion coating said polymeric barrier layer onto said annular matrix polymer region and solvent coating said polymeric barrier layer onto said annular matrix polymer region.

60. The method of claim 58, wherein said covering comprises coextruding said polymeric barrier layer and said annular matrix polymer region.

61. The method of claim 58, forming a first polymeric barrier layer at least partially covering an interior surface of said annular matrix polymer region and forming a second polymeric barrier layer at least partially covering an exterior surface of said annular matrix polymer region.

62. The method of claim 61, wherein said covering comprises coextruding said first and second polymer barrier layers with said annular matrix polymer region.

63. The method of claim 50, wherein said processing comprises forming homogeneous first and second mixtures of first and second biocompatible matrix polymers and one or more of said bioactive agents and, optionally, forming a homogenous third mixture of a third biocompatible matrix polymer and one or more of said bioactive agents.

64. The method of claim 63, comprising coextruding said homogenous first and second mixtures to form first and second annular matrix polymer regions and, optionally, coextruding therewith said homogenous third mixture to form a third annular matrix polymer region.

65. The method of claim 64, further comprising forming at least first and second polymeric barrier layers at least partially covering interior and exterior surfaces of said first annular matrix polymer region; forming a third polymer barrier layer at least partially covering an exterior surface of said second annular matrix polymer region and, optionally, forming a fourth polymeric barrier layer at least partially covering an interior surface of third annular matrix polymer region.

66. The method of claim 65, wherein said covering comprises coextruding said first, second and third polymeric barrier layers with said first and second annular matrix polymer regions and, optionally, coextruding therewith said fourth polymeric barrier layer and said third annular matrix polymer region.

67. The method of claim 62, wherein said first annular matrix polymer region and said first and second barrier layers comprise a material selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, elastomeric polyurethanes and polyurethane copolymers, metallocene catalyzed polyethylene and polyethylene copolymers, ionomers, vinyl aromatic copolymers, silicones and mixtures thereof.

68. The method of claim 67, wherein said first annular matrix polymer region comprises an ethylene vinyl acetate copolymer having a vinyl acetate content of from about 19% to about 28% and said first and second polymeric barrier layers comprise a metallocene catalyzed polyethylene or polyethylene copolymer, or an ionomer.

69. The method of claim 68, wherein said first annular matrix polymer region comprises salicylic acid or a salt thereof as said microbial attachment/biofilm synthesis inhibitor, triclosan as said antimicrobial agent and bismuth subcarbonate as a radio-opacifying agent; and, said coextrusion is performed under conditions such that said salicylic acid or salt thereof does not preferentially partition to a surface of said first annular matrix polymer region or to a surface of said first or second polymeric barrier layers.

70. The medical device of claim 26, wherein at least one of said one or more barrier layers comprises a biodegradable polymer.

71. The medical device of claim 70, where said biodegradable polymer is selected from the group consisting of polylactic acid, polyglycolic acid and copolymers and mixtures thereof.

72. An implantable or insertable medical device comprising at least one biocompatible matrix polymer region comprising a material selected from the group consisting of ethylene vinyl acetate copolymers, copolymers of ethylene with acrylic acid or methacrylic acid, metallocene catalyzed polyethylenes and polyethylene copolymers, ionomers, vinyl aromatic copolymers, elastomeric polyurethanes and polyurethane copolymers, silicones and mixtures thereof; bioactive agents comprising an antimicrobial agent selected from the group consisting of triclosan, chlorhexidine and mixtures thereof; a microbial attachment/biofilm synthesis inhibitor selected from the group consisting of salicylic acid and salts and derivatives thereof, and, a radio-opacifying agent selected from the group consisting of bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, barium sulfate, tungsten and mixtures thereof.

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(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
5 February 2004 (05.02.2004)

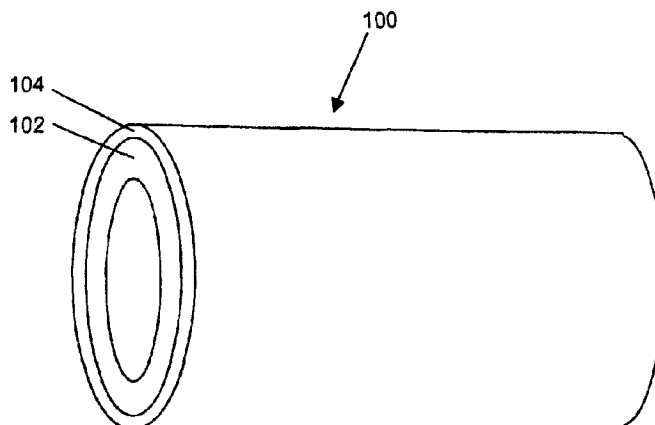
PCT

(10) International Publication Number
WO 2004/011055 A2

- (51) International Patent Classification⁷: A61L 31/00 (74) Agents: BONHAM, David, B. et al.; Mayer Fortkort & Williams, PC, 251 North Avenue West, 2nd Floor, Westfield, NJ 07090 (US).
- (21) International Application Number: PCT/US2003/024131
- (22) International Filing Date: 31 July 2003 (31.07.2003) (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
10/209,476 31 July 2002 (31.07.2002) US
10/377,131 28 February 2003 (28.02.2003) US
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- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:
— without international search report and to be republished upon receipt of that report

[Continued on next page]

(54) Title: IMPLANTABLE OR INSERTABLE MEDICAL DEVICES FOR CONTROLLED DRUG DELIVERY



(57) Abstract: Implantable or insertable medical devices are provided, which comprises: (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, an anesthetic agent, and an antispasmodic agent. The medical devices are adapted for implantation or insertion at a site associated with pain or discomfort upon implantation or insertion. In many embodiments, the therapeutic will be selected from at least one of (i) ketorolac and pharmaceutically acceptable salts thereof (e.g., ketorolac tromethamine) and (ii) 4-diethylamino-2-butanylphenylcyclohexyl glycolate and pharmaceutically acceptable salts thereof (e.g., oxybutynin chloride). Also provided are uses for the implantable or insertable medical devices, which uses comprise reducing pain or discomfort accompanying the implantation or insertion of such devices. Further uses may comprise reducing microbial buildup along the device. Methods for manufacturing implantable or insertable medical devices are also provided.

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example, EVA based ureteral stents are widely used to facilitate drainage in the upper urinary tract (e.g., from the kidney to the bladder), for example, following ureteroscopy, endourerotomies, and endopyelotomy for ureteral strictures, as well as in other instances where ureteral obstruction may occur. However, such stents are typically associated with pain and discomfort in the bladder and flank area after insertion. At present, one way by which pain and discomfort are minimized is to orally administer drugs to the patient. To date the most commonly prescribed oral drugs are opioid analgesia, which are controlled substances and have the potential for abuse by patients.

SUMMARY OF THE INVENTION

[0007] According to one aspect of the present invention, implantable or insertable medical devices are provided, which comprise: (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, an anesthetic agent, and an antispasmodic agent. The medical devices are adapted for implantation or insertion at sites associated with pain or discomfort upon implantation or insertion.

[0008] In many embodiments, the therapeutic agent will be selected from at least one of (i) ketorolac and pharmaceutically acceptable salts thereof (e.g., ketorolac tromethamine) and (ii) 4-diethylamino-2-butynylphenylcyclohexylglycolate and pharmaceutically acceptable salts thereof (e.g., oxybutynin chloride).

[0009] The medical device may also contain one or more optional agents, including one or more radio-opacifying agents such as bismuth subcarbonate (e.g., to enhance visibility), and one or more antimicrobial agents such as triclosan (e.g., to reduce microbial buildup along the device).

[0010] The implantable or insertable medical devices of the present invention can be provided with a variety of release profiles. For instance, a cumulative therapeutic agent release selected from 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, and 99%, relative to the total therapeutic agent in the device, can be obtained after implantation or insertion for a period selected from 1 day, 2 days, 4 days, 1 week, 2 weeks, 1 month, 2 months, 4 months, 1 year and 2 years.

[0011] A variety of biocompatible polymers can be used in the medical devices of

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[0028] Fig. 6 is a plot of estimated *in vitro* cumulative ketorolac release based on release as a function of time at 37°C in artificial urine, in accordance with an embodiment of the present invention.

[0029] Fig. 7 is a plot of ketorolac concentration as a function of time at 37°C in artificial urine, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0030] In one aspect, the present invention is directed to an implantable or insertable medical device that comprises (a) a biocompatible polymer and (b) a therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, a local anesthetic agent, and an antispasmodic agent. The medical device is of a type such that symptoms of pain or discomfort are typically experienced by the patient (e.g., a mammalian subject such as a human subject) after implantation or insertion.

[0031] Another aspect of the invention is directed to the use of such an implantable or insertable medical device to bring about a reduction in discomfort or pain subsequent to implantation or insertion (in addition to other therapeutic benefits that the device is implanted/inserted to provide, for example, to facilitate drainage, etc.). In some embodiments, the medical device will also be used to resist microbial growth and/or biofilm formation.

[0032] As a specific example, ureteral stents, for instance, ethylene-vinyl acetate (EVA) based ureteral stents, are widely used in urology to facilitate drainage in the upper urinary tract (e.g., from the kidney to the bladder) following various procedures (e.g., ureteroscopy, endourerotomies, endopyelotomy for ureteral strictures, as well as in other instances where ureteral obstruction is encountered). However, as noted above, such stents are typically associated with pain and discomfort after insertion. One way by which pain and discomfort are minimized is to orally administer drugs to the patient, which drugs are typically opioid analgesia having the potential for abuse by patients. In addition, drugs administered locally with the intention of providing a site-specific effect require significantly lower doses than oral administration of the same drug for the same therapeutic purpose. The advantage of the lower doses in site-specific delivery is that often unwanted or even toxic side affects of systemic concentrations of the same drug can be avoided.

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to, shape memory alloys such as nickel-titanium alloys and other metallic materials including, but not limited to, stainless steel, tantalum, nickel-chrome, or cobalt-chromium, for example, Nitinol® and Elgiloy®.

[0038] In many embodiments of the invention, a therapeutic agent of interest is released from a polymeric matrix. The term "polymeric matrix" refers to a region that comprises a biocompatible polymer and at least one additive, for example, one or more therapeutic agents, one or more radio-opacifying agents, one or more pigments, and/or one or more antimicrobial agents, among other materials. The polymeric matrix can constitute the entirety of an implantable or insertable medical device, or it can correspond to only a portion or region of the medical device.

[0039] Where only a single distinct polymeric matrix region is provided in the medical device, the polymeric matrix region will preferably contain the therapeutic agent as well as any optional additives, such as radio-opacifying agents, pigments, antimicrobial agents, plasticizers, lubricants, and so forth. In other embodiments, the medical device comprises two or more distinct polymeric matrix regions. Where two or more distinct polymeric matrix regions are present in the medical device, it is not necessary that the therapeutic agent and any optional additive(s) be present in a single polymeric matrix region. For example, a therapeutic agent may be present in a first polymeric matrix region, and one or more optional additives may be present in a second polymeric matrix region distinct from the first polymeric matrix region.

[0040] Without wishing to be bound by theory, it is believed that therapeutic agent is released from a non-biodegradable polymeric matrix region, at least in part, by a mechanism wherein the polymeric matrix imbibes or contacts physiological fluid. In such a polymeric matrix, the therapeutic agent may diffuse to some extent through the polymer matrix toward an external surface and/or the physiological fluid diffuses into the polymeric matrix. The therapeutic agent then dissolves in the physiological fluid. A concentration gradient is believed to be set up at or near the matrix region, and the therapeutic agent in solution is then released via diffusion into the surrounding physiological fluid and local tissues. Where the polymeric matrix is biodegradable, similar diffusion-dissolution-diffusion processes may also occur. In a biodegradable polymeric matrix, however, therapeutic agent may also be released as the biodegradable polymeric matrix containing the therapeutic agent biodegrades upon contact with the

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well as the rate of release into the environment of the implanted medical device. Thus, a device that is intended to remain implanted for a longer period will generally require a higher percentage of the antimicrobial agent. Similarly, a faster release of the antimicrobial agent may require a higher amount of the bioactive agent. One skilled in the art can readily determine an appropriate antimicrobial agent content to achieve the desired outcome.

[0058] In this connection, it is noted that certain of the therapeutic agents listed above are useful in providing microbial resistance. For example, non-steroidal anti-inflammatory drugs (NSAIDs), for example, salicylic acid, its salts and its derivatives, have been described as microbial attachment/biofilm synthesis inhibitors. A "microbial attachment/biofilm synthesis inhibitor" is a substance that inhibits the attachment of microbes onto a surface and/or the ability of such microbes to synthesize or accumulate biofilm on a surface. Further information can be found in the above-incorporated U.S. Serial No. 10/071,840.

[0059] In some embodiments, the medical device further comprises a pigment, while in others it does not. Pigments include any biocompatible and pharmaceutically acceptable colorant, regardless of type or color, including titanium dioxide, phthalocyanine organic pigments, quinaridone organic pigments, carbon black, iron oxides, and ultramarines. Where present, pigment is typically included in an amount ranging from 0.001 to 5%, more typically from 0.01 to 1%.

[0060] The polymeric regions used in the implantable or insertable medical device of the present invention may comprise any biocompatible polymer suitable for use in implantable or insertable medical devices. The biocompatible polymer may be substantially non-biodegradable or biodegradable.

[0061] The term "biocompatible" as used herein describes a material that is not substantially toxic to the human body, and that does not significantly induce inflammation or other adverse response in body tissues. Biocompatible polymers include essentially any polymer that is approved or capable of being approved by the United States Food and Drug Administration or Department of Agriculture for use in humans or animals when incorporated in or on an implantable or insertable medical device. Substantially non-biodegradable biocompatible polymers include thermoplastic and elastomeric polymeric materials. Polyolefins such as polyethylenes (e.g., metallocene

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layer. For example, a medical device in accordance with the present invention may comprise a two-layer structure comprising a first polymeric matrix layer containing biocompatible polymer, therapeutic agent and radio-opacifying agent, and a second layer on an external surface of the first polymeric matrix layer that provides lubricity. Such a lubricious layer may be desirable, for example, to facilitate insertion, implantation and/or removal of the medical device. A simplified schematic representation of a device of this type is depicted in Fig. 1, in accordance with an embodiment of the present invention. Implantable or insertable medical device 100 comprises an annular polymeric matrix region 102, which further comprises a biocompatible polymer (e.g., EVA), a therapeutic agent (e.g., ketorolac tromethamine or oxybutynin chloride) and a radio-opacifying agent (e.g., bismuth subcarbonate). The device 100 also comprises a lubricious layer 104 (e.g., a hydrogel layer) at least partially covering an exterior surface of the annular polymeric matrix region 102.

[0067] As another example, a medical device in accordance with the present invention may comprise a three-layer structure comprising a first layer comprising biocompatible polymer, radio-opacifying agent and therapeutic agent, a second layer on an external surface of the first layer that acts as a barrier layer, and a third layer on an external surface of the second layer that provides lubricity. A simplified schematic representation of a device of this type is depicted in Fig. 2, in accordance with an embodiment of the present invention. Referring now to Fig. 2, implantable or insertable medical device 100 comprises an annular polymeric matrix region 102, which further comprises a biocompatible polymer (e.g., EVA), a therapeutic agent (e.g., ketorolac tromethamine or oxybutynin chloride) and a radio-opacifying agent (e.g., bismuth subcarbonate). The device 100 also comprises a polymeric barrier layer 106 (e.g., an EVA barrier layer) at least partially covering an exterior surface of the annular polymeric matrix region 102. The device 100 further comprises a lubricious layer 104 (e.g., a hydrogel layer) at least partially covering an exterior surface of the polymeric barrier layer 106.

[0068] As another example, a medical device in accordance with the present invention may comprise a three-layer structure comprising a first layer comprising biocompatible polymer and radio-opacifying agent, a second layer on an external surface of the first layer comprising biocompatible polymer and the therapeutic agent, and a third

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What is claimed is:

1. An implantable or insertable medical device comprising: (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, an anesthetic agent, and an antispasmodic agent, wherein said medical device is adapted for implantation or insertion at a site associated with pain or discomfort upon implantation or insertion.
2. The implantable or insertable medical device of claim 1, wherein said medical device does not contain an antimicrobial agent.
3. The implantable or insertable medical device of claim 1, further comprising a radio-opacifying agent.
4. The implantable or insertable medical device of claim 1, wherein said medical device is a ureteral stent.
5. Use of an implantable or insertable medical device, said use comprising reducing pain or discomfort accompanying implantation or insertion of said implantable or insertable medical device, and said implantable or insertable medical device comprising (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from an anti-inflammatory agent, an analgesic agent, an anesthetic agent, and an antispasmodic agent, and a radio-opacifying agent.
6. The use of claim 5, wherein the implantable or insertable medical device further comprises a radio-opacifying agent.
7. The use of claim 5, wherein said medical device is a ureteral stent.
8. The use of claim 5, said use further comprising reducing microbial buildup along the device, wherein the device further comprises an antimicrobial agent.

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9. An implantable or insertable medical device comprising: (a) a biocompatible polymer; and (b) at least one therapeutic agent selected from (i) ketorolac and pharmaceutically acceptable salts thereof and (ii) 4-diethylamino-2-butynylphenylcyclohexylglycolate and pharmaceutically acceptable salts thereof, wherein said medical device is adapted for implantation or insertion at a site that is associated with pain or discomfort upon implantation or insertion.

10. The implantable or insertable medical device of claim 9, wherein said therapeutic agent is ketorolac tromethamine.

11. The implantable or insertable medical device of claim 9, wherein said therapeutic agent is oxybutynin chloride.

12. The implantable or insertable medical device of claim 9, wherein the cumulative release of therapeutic agent is in an amount selected from 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, and 99%, relative to the total therapeutic agent in the device, after implantation or insertion at said site for a period selected from 1 day, 2 days, 4 days, 1 week, 2 weeks, 1 month 2 months, 4 months, 1 year and 2 years.

13. The implantable or insertable medical device of claim 9, wherein said medical device is a ureteral stent.

14. The implantable or insertable medical device of claim 9, wherein said biocompatible polymer is selected from or more of polyether block amides (PEBA), thermoplastic polyurethanes (TPU), and polyoctenamers.

15. The implantable or insertable medical device of claim 9, wherein said biocompatible polymer is an ethylene-vinyl acetate (EVA) copolymer.

16. The implantable or insertable medical device of claim 9, wherein said medical device comprises a polymeric matrix region comprising said biocompatible polymer and said therapeutic agent.

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17. The implantable or insertable medical device of claim 9, further comprising a radio-opacifying agent.

18. The implantable or insertable medical device of claim 17, wherein said medical device comprises a polymeric matrix region comprising said biocompatible polymer, said therapeutic agent and said radio-opacifying agent.

19. The implantable or insertable medical device of claim 17, wherein said radio-opacifying agent is bismuth subcarbonate.

20. The implantable or insertable medical device of claim 18, wherein said medical device comprises (a) a first polymeric matrix region comprising a first biocompatible polymer and said therapeutic agent, and (b) a second polymer matrix region comprising a second biocompatible polymer and said radio-opacifying agent, wherein said first and second biocompatible polymers may be the same or different.

21. The implantable or insertable medical device of claim 18, wherein said matrix region comprises 5-20% therapeutic agent.

22. The implantable or insertable medical device of claim 18, wherein said therapeutic agent is ketorolac tromethamine.

23. The implantable or insertable medical device of claim 18, wherein said therapeutic agent is oxybutynin chloride.

24. The implantable or insertable medical device of claim 18, wherein said matrix region comprises 15-30% radio-opacifying agent.

25. The implantable or insertable medical device of claim 16, wherein said biocompatible polymer is a thermoplastic polymer.

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26. The implantable or insertable medical device of claim 25, wherein said thermoplastic polymer is an ethylene-vinyl acetate (EVA) copolymer.
27. The implantable or insertable medical device of claim 16, wherein said biocompatible polymer is an elastomeric polymer.
28. The implantable or insertable medical device of claim 16, further comprising a barrier layer.
29. The implantable or insertable medical device of claim 9, further comprising an antimicrobial agent.
30. The implantable or insertable medical device of claim 18, further comprising an antimicrobial agent.
31. The implantable or insertable medical device of claim 18, further comprising a hydrogel.
32. The implantable or insertable medical device of claim 18, wherein said matrix is an extruded matrix.
33. The implantable or insertable medical device of claim 32, wherein the extruded matrix comprises ethylene-vinyl acetate (EVA) copolymer, ketorolac tromethamine and bismuth subcarbonate.
34. The implantable or insertable medical device of claim 33, wherein the degradation level of the ketorolac tromethamine is less than 2%.
35. A method of manufacturing the implantable or insertable medical device of claim 16, comprising:
- providing a combination comprising said biocompatible polymer and said therapeutic agent; and

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forming said polymeric matrix from said combination.

36. The method of claim 35, wherein forming said polymeric matrix comprises a thermoplastic process.

37. The method of claim 36, wherein said thermoplastic process is an extrusion process.

38. The method of claim 36, wherein said thermoplastic process is conducted at a temperature that is (a) above the softening temperature of the biocompatible polymer, (b) below the melting point of the therapeutic agent, and (c) sufficiently low to avoid substantial degradation of said therapeutic agent.

39. The method of claim 38, wherein mechanical shear is further controlled to avoid said substantial degradation.

40. The method of claim 35, wherein forming said polymeric matrix comprises a solution forming process.

41. The method of claim 40, wherein said solution forming process is a solution coating process.

42. The method of claim 35, wherein said combination further comprises a radio-opacifying agent.

43. The method of claim 42, wherein forming said polymeric matrix comprises (a) forming an initial blend comprising said biocompatible polymer and said radio-opacifying agent; (b) combining said initial blend and said therapeutic agent; and (c) forming said polymeric matrix.

44. The method of claim 43, wherein said initial blend is formed using a thermoplastic process.

45. The method of claim 43, wherein said initial blend is formed using an extrusion process.
46. The method of claim 44, wherein said polymeric matrix is formed using a further thermoplastic process.
47. The method of claim 46, wherein said further thermoplastic process is conducted under conditions such that substantial degradation of said therapeutic agent is avoided.
48. The method of claim 46, wherein said further thermoplastic process is conducted under conditions such that degradation of said therapeutic agent is less than 2%.
49. The method of claim 43, wherein said initial blend is formed using a solution process and wherein said polymeric matrix is formed using a thermoplastic process.

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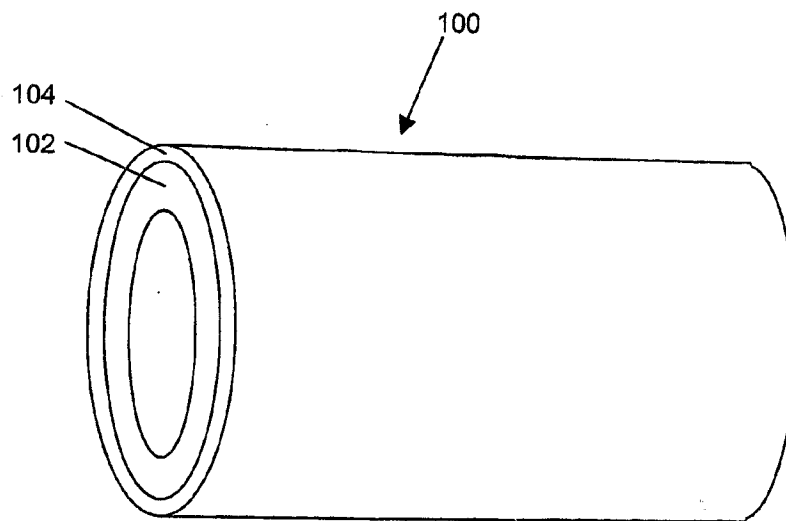


Fig. 1

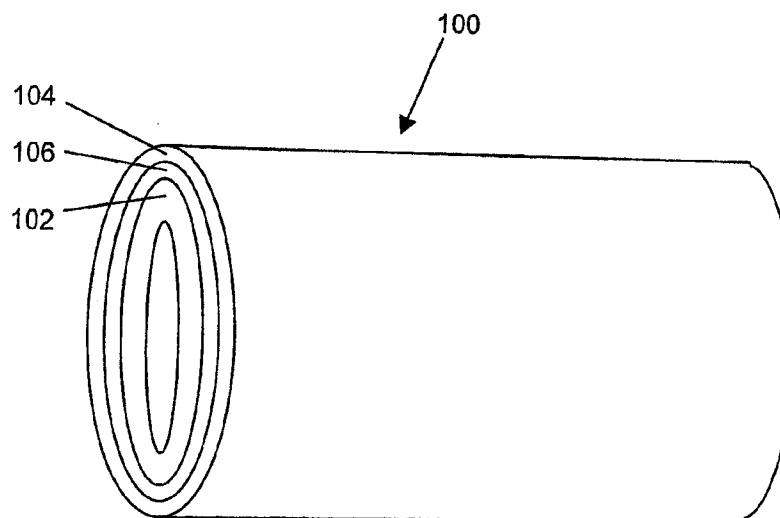


Fig. 2

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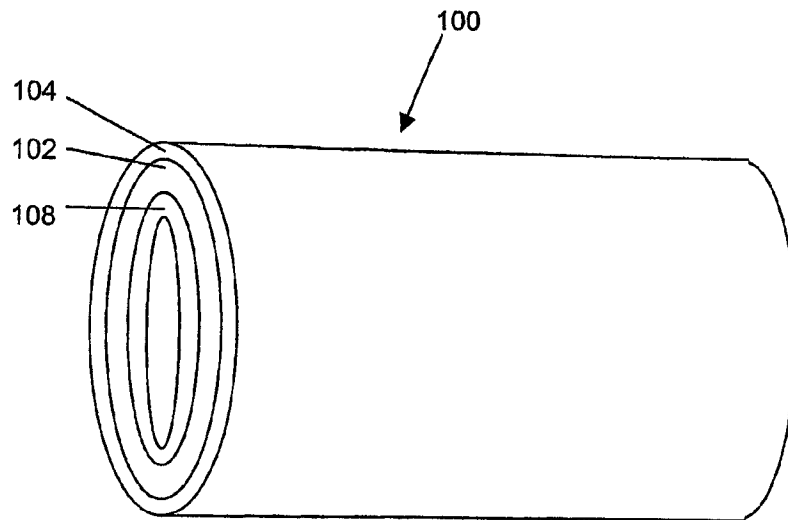


Fig. 3

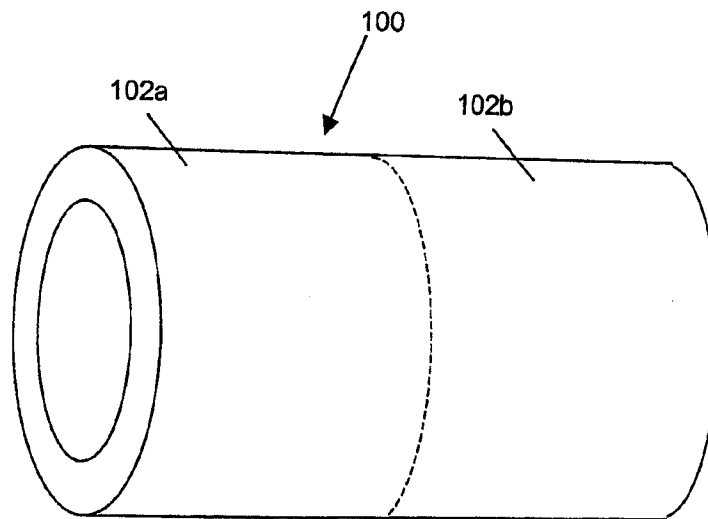


Fig. 4

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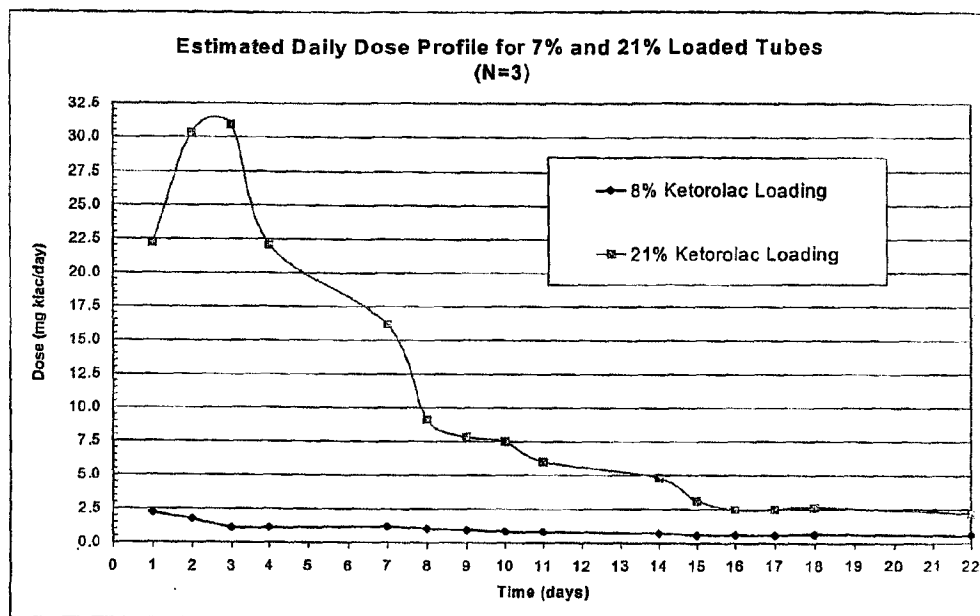


Fig. 5

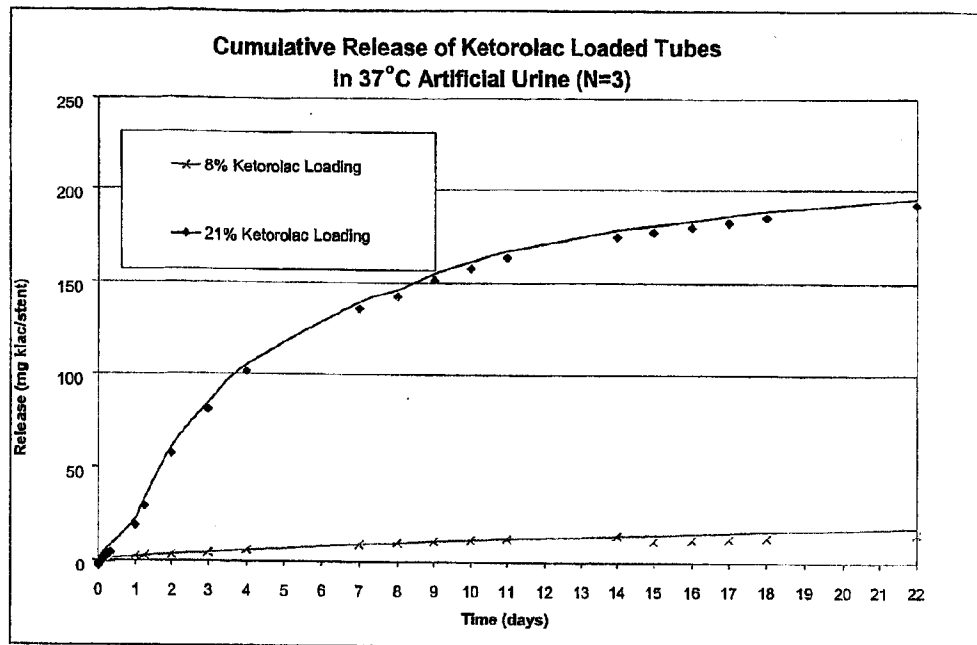
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Fig. 6

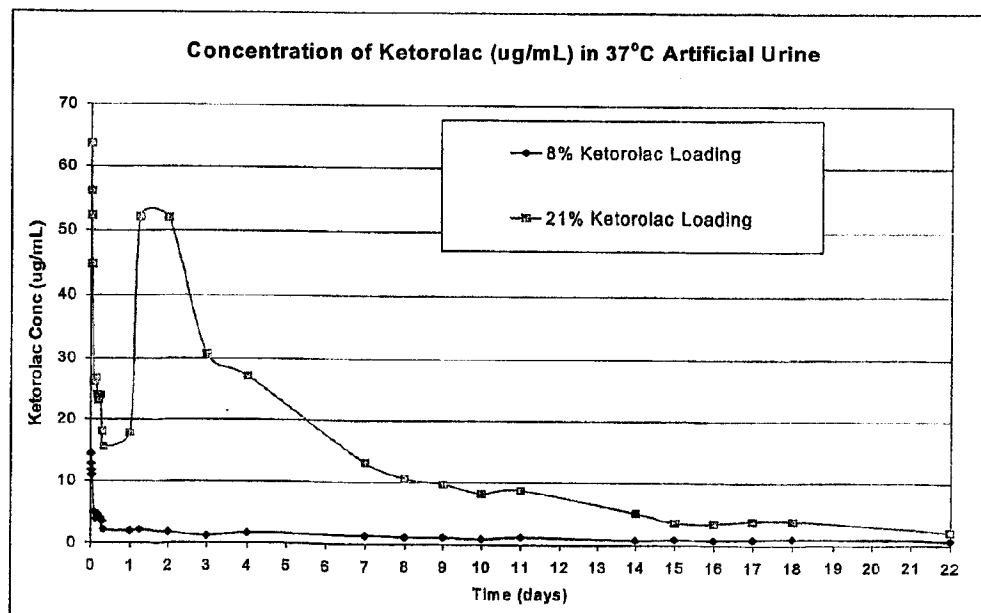


Fig. 7

United States Patent [19]
de Nijs

[11] **Patent Number:** 4,957,119
[45] **Date of Patent:** Sep. 18, 1990

[54] **CONTRACEPTIVE IMPLANT**

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[21] **Appl. No.:** 229,066

[22] **Filed:** Aug. 5, 1988

[30] **Foreign Application Priority Data**

Aug. 8, 1987 [NL] Netherlands 8701868

[51] **Int. Cl.⁵** A61K 9/22

[52] **U.S. Cl.** 128/832; 128/833;
604/890.1

[58] **Field of Search** 604/19, 48, 890.1, 891.1;
514/171, 841-843; 424/81, 424; 128/832, 833,
839

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,903,880 9/1975 Higuchi et al. 128/833
4,582,052 4/1986 Dunn et al. 128/839
4,596,576 6/1986 de Nijs 128/832
4,673,565 6/1987 Di Luccio et al. 424/443
4,720,384 1/1988 Di Luccio et al. 424/78

FOREIGN PATENT DOCUMENTS

2120937 5/1982 United Kingdom 604/890

OTHER PUBLICATIONS

D. N. Robertson et al., "Release Rates of Levonorgestrel from Silastic Capsules, Homogeneous Rods and Covered Rods in Humans," Chemical Abstracts, 99(8), pp. 308-309, 1983.

D. N. Robertson et al., "Release Rates of Levonorges-

trel from Silastic Capsule Homogeneous Rods and Covered Rods in Humans," Contraception, 27(5), 483-495, 1983.

W. Losert et al., "Progestogens with Antimineralocorticoid Activity," Arzneim.-Forsch/Drug. Res., 35(I), No. 2 (1985).

M. J. D. Eenink et al., "Biodegradable Hollow Fibres for the Controlled Release of Hormones," J. of Controlled Release, 6, pp. 225-247 (1987).

Long Acting Contraceptive Delivery Systems, Zatzuchni et al., "Implantable Levonorgestrel Rod Systems . . .", Harper & Row, Phila., 1983, pp. 133-139.

Chemical Contraception, Bennett, John P., Columbia University Press, N.Y., 1974, pp. 56-58.

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[57] **ABSTRACT**

The invention relates to an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally. The implant comprises a core material of ethylene/vinyl acetate copolymer which functions as a matrix for a contraceptive substance, an ethylene/vinyl acetate membrane encasing the core material, and a contact layer at the interface of the core material and membrane which prevents the separation of the core material from the membrane. The implant of the invention is made by a co-extrusion process.

15 Claims, No Drawings

CONTRACEPTIVE IMPLANT

The invention relates to an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally. More specifically, the invention relates to an implant of such small dimensions that it can be fitted subcutaneously with an ordinary hypodermic needle.

There is a large demand for the development of new, long-acting contraceptives which require a minimum of medical guidance. This is valid in particular for those areas of the world where the medical infrastructure is poor, and where family planning can be organized only to an insufficient extent.

An implant of this type, which can release a contraceptive agent in virtually constant quantities over a period of at least 2 years, but preferably for about 4 to 5 years, is a new development which can certainly supply what is needed. The great problem, however, is that the often large amount of the contraceptive agent with which the polymeric material of the implant has to be charged to guarantee release for about 4 years leads to very large implants which can only be fitted surgically, or to several smaller implants which have to be fitted simultaneously.

The need for subcutaneous fitting of a plurality of (smaller) implants also offers little attraction at the present time.

In theory any polymeric material is suitable for the development of an implant provided only that it is biologically compatible, and also any material with a progestational action. In this context reference may be made, for example, to U.S. Pat. No. 3,279,996 (Long et al.) in which an implant is described which contains an active substance encased by a polysiloxane membrane, and to Dutch Patent No. 167,850 (Zaffaroni) in which an implant is described in which the active substance is contained in a polymer, and this polymer loaded with active substance is encased by a polymer membrane which completely controls the rate of release. However, if a limit is set to the dimensions of the implant, if a certain amount of implant rigidity is required to facilitate introduction, and, furthermore, if the achievement of a release duration of the contraceptive substance of a minimum of 2 years, and preferably of up to 4 to 5 years, is desired, then all available theoretical solutions seem to fail.

The implant of the invention can be considered one of the release systems known per se which consist of a core of active material encased by a release rate-regulating membrane. The choice of polymers to be used, the choice of the contraceptive substances, and the dimensions of the implant are, however, matched in such a way that a unique release system is obtained which complies completely with the requirements stipulated above.

The implant of the invention is cylindrical or virtually cylindrical with a maximum section of about 2 mm, but preferably between 1.5 and 2.0 mm, and possesses a variable length. The length of the implant will, however, not exceed about 5 cm for practical reasons. The length is preferably between 1 and 4 cm. These dimensions of the implant of the invention are so small that subcutaneous fitting can be carried out with an ordinary hypodermic needle.

The implant of the invention is characterized by:

(a) core material of ethylene/vinyl acetate copolymer (hereafter called EVA) having such a molecular weight that the melt index is greater than 10 gram per 10 minutes, and a vinyl acetate content of 20% by weight or more; which core material functions as a matrix for 3-keto-desogestrel, levonorgestrel or gestodene as active contraceptive substances, in a quantity which is sufficient for a long-lasting constant release of at least 15-30 µg of active substance per day, and

(b) a membrane having a layer thickness of 50-250 µm which encases the core material and also consists of EVA material, but with such a molecular weight that the melt index is less than 10 gram per 10 minutes, and an acetate content of less than 20% by weight,

this implant being completely or virtually completely cylindrical with a maximum external diameter of about 2 mm and a length which is smaller than about 5 cm.

The contraceptively active substance, which can be employed in the context of the present invention, is a highly active progestogen, particularly 3-ketodesogestrel, levonorgestrel or gestodene. These contraceptive substances are highly active substances which show an effective progestational action with a daily dosage of 15-30 µg.

This core material can be charged to about 75 percent by weight with the active substance without seriously affecting the utility of the EVA core material. However, a degree of charging of 50-60% by weight is preferred.

The core material used in the present invention is an EVA polymer with a melt index greater than 10 gram/10 min. and preferably between 25 and 30 g/10 min. The vinyl acetate content of the core material is greater than 20% by weight and preferably greater than 25% by weight.

Very suitable EVA polymers which can be used as core material are, for example, Evatane® with the designations 28-150, 28-399, and 28-400, supplied by ICI and 28.420 and in particular 28.25 and 33.25 supplied by Atochem, and Elvax® with the designations 310, 250, 230, 220, and 210, supplied by Du Pont de Nemours.

The membrane polymer is also an EVA polymer which, however, has a higher molecular weight than that of the core material. The melt index of this membrane material is less than 10 g/10 min., and preferably less than or equal to 8 g/10 min. The vinyl acetate content is less than 20% by weight.

Suitable EVA polymers which can be used as a membrane are, for example, Evatane® with the designations 501/502 (melt index 2, vinyl acetate content 7.5%), 554/555 (4, 12.5%), 540 (10, 18%) and particularly 571 (8, 15%), Elvax® with the designations 450, 460, 470, 550, 560, 650, 660, 670, 750, 760 and 770, and Evatane® 1080 VN 5 and in particular 1040 VN 4 supplied by Atochem.

The release characteristic of the contraceptive substance (through the membrane) is determined to a large extent by the vinyl acetate content of the EVA membrane.

The implant of the invention is obtained by means of a so-called co-axial extrusion process, a method in which the two EVA polymers are extruded co-axially in preset layer thicknesses with the aid of a co-axial extrusion head.

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This co-axial extrusion process means that both polymers are transported in the molten state through the co-axial extrusion head, the molten core material at the same time containing the active substance.

Due to this co-axial extrusion process, a contact layer is produced on the interface of the two polymers, which layer is probably fully or partially responsible for the outstanding drug-release properties of the coextrudate, but in any event prevents the two polymer layers working loose from each other after a period of time, due to disappearance of the active substance from the core polymer, which loosening would fundamentally disturb the release pattern.

The co-axial extrusion process is art known per se so that it will not be gone into further within the scope of this description.

A thick, co-axial filament with a maximal external diameter of about 2 mm, and preferably between about 1.5 and 2.0 mm, is obtained by means of the co-axial extrusion process. The filament is then cut into pieces up to a maximum of about 5 cm long, using conventional techniques.

Although certainly not necessary the circular ends of the implant may—if desired—be additionally protected by an inert polymer, for example polyethylene, polypropylene or the EVA polymer which is used for the membrane, or also, for example, by a (medical grade) silicone adhesive. This protective layer is obtained, for example, by dipping the surface into a smelt or solution of the particular polymer. If necessary, the end can also be singed or pinched closed.

Another embodiment of the implant of the invention possesses a thin layer of polysiloxane around the whole external surface of the implant described above, in addition to the assembly as described above. This polysiloxane is chosen so that the release pattern is not influenced to any appreciable extent; the formation of a second release-rate-regulating layer is thus not intended by this. The layer in question can therefore be extremely thin, even of the order of 20–50 μm ; a somewhat thicker layer, however, is just as permissible.

This protective layer can be obtained by dipping or immersing the implant in a thin tubing of polysiloxane.

The implant of the invention should in each case contain a sufficient quantity of active substance when used for application in humans which is such that it can bring about virtually constant release of the active substance for a minimum of 1 year, which roughly means that the core material must be charged with 5 to 15 mg of 3-keto-desogestrel, levonorgestrel or gestodene. An additional quantity of active substance of about 5 to 15 mg is necessary for each additional year in which the implant must release, so that a quantity of 25–75 mg of active material can be needed for a release duration of 5 years.

The implant of the invention is preferably used as a subcutaneous implant, but may also be applied locally, e.g. in the uterine or cervical region.

EXAMPLE 1

The active substance 3-keto-desogestrel and EVA core material (melt index 400 g/10 min., vinyl acetate content 28% by weight)—Evatane® 28–400—were mixed in a ratio of 1:1 (on a weight basis) on a heatable mill at a temperature of 80° C. The polymer sheets charged with 3-keto-desogestrel were reduced in size and then processed into pellets by means of an extruder and a so-called chopper.

The pellets charged with 3-keto-desogestrel intended for the core, and EVA pellets intended for the membrane (melt index 8 g/10 minutes; vinyl acetate content 15% by weight, Evatane® 571), were transferred to two separate hoppers of the co-axial extrusion apparatus. The co-axial filament was extruded at a temperature of about 100° C. A co-axial filament with an external diameter of 1.9 mm and a skin thickness of 150 μm was obtained with a correct choice and a correct adjustment of the spinneret geometry, the feed rates of the core and skin material to the spinneret, and the winding rate of the fibre. The extruded co-axial filament was cooled in a water bath, and then wound onto bobbins with a draw rate of 0.25N. The extrusion rate of the filament was 2.3 meters per sec. Typical preparation conditions:

	Temperature (°C.)	Pressure (bar)
Extruder (barrel)	100	60 → 173
Extruder (core)	80	5 → 46
Spinneret	100	

The extruded co-axial filament was then cut into the required length. The filament pieces were wrapped in polysiloxane if desired using polysiloxane tubing (dimensions 1.57/2.41 mm internal/external diameter) to be swelled in cyclohexane and thereafter to be filled with the co-axial filament of the required length, and finally dried under vacuum. The two ends of the implant obtained were sealed with silicone adhesive (medical grade). The external diameter of the implant provided with a polysiloxane layer was 2.5 mm, the external diameter of the implant not provided with a polysiloxane layer was 1.9 mm.

The in vitro release of 3-keto-desogestrel from this implant was tested in 250 ml demineralized water at 37° C. This medium was contained in a 300 ml conical flask which was shaken at 150 cycles/minute with an amplitude of 2.5 cm.

RESULTS

TABLE 1

In vitro release of 3-keto-desogestrel from a 3 cm implant with and without a polysiloxane external layer.		
Day	Release ($\mu\text{g/day.cm}$)	
	without polysiloxane layer	with polysiloxane layer
1	10.0	6.7
2	10.7	9.7
3	11.3	10.0
4	10.3	9.7
7	10.3	9.3
9	10.0	9.7
10	10.0	9.7
14	10.3	9.7

The polysiloxane external layer here has practically no influence on the release pattern.

TABLE 2

In vitro release of 3-keto-desogestrel from an implant (3 cm) prepared in this way and provided with a polysiloxane layer. The implant was sterilized by heat treatment (20 min. 120° C).	
Day	Release ($\mu\text{g/day.cm}$)
2	57.0*
5	14.7
10	10.3
20	11.3

TABLE 2-continued

In vitro release of 3-keto-desogestrel from an implant (3 cm) prepared in this way and provided with a polysiloxane layer. The implant was sterilized by heat treatment (20 min, 120° C).	
Day	Release (μg/day.cm)
30	10.3
40	10.0
50	10.0
90	9.0
100	9.3
200	8.7
300	8.3
376	8.3
400	7.7
471	7.7
500	8.0
550	7.7
600	8.0
650	7.0
700	6.3
750	6.0
800	6.3

*boost of 3-keto-desogestrel because of heat sterilization.

TABLE 3

In vivo release: Average plasma concentrations (3 dogs) of 3-keto-desogestrel after subcutaneous introduction of an implant prepared in this way (see implant of Table 2).	
Day	Plasma concentration (pmol/ml)
1	2.11*
2	0.81
3	0.62
7	0.66
14	0.46
21	0.53
28	0.49
35	0.56
42	0.56
51	0.56
56	0.54
63	0.59
70	0.60
77	0.59
84	0.59
91	0.63

*boost of 3-keto-desogestrel because of heat sterilization.

EXAMPLE 2

The active substance 3-keto-desogestrel and Evatane® 28-400 were blended in 1:1 weight ratio in a 10 mm extruder at a temperature of 100° C.

The extrudate obtained was granulated with the acid of a pelletizer, after which the pellets were heated in vacuo at 135° C. for one hour.

In the same manner as described in Example 1 a co-axial filament was extruded using the above 3-keto-desogestrel charged pellets as core material and uncharged Evatane® 571 pellets as membrane material. The membrane thickness of the co-axial fibre was 135 μm, and the external diameter of the implant was 1.65 mm. The dimensions of the polysiloxane tubing were: 1.47 (internal)×1.95 mm (external diameter). The ends of the 4-cm long implant were sealed with medical grade silicone adhesive. The external diameter of an implant provided with a polysiloxane layer was 2.05 mm.

Typical preparation conditions of the relevant co-axial filament:

	Temperature (°C.)	Pressure (bar)
Extruder (barrel)	80 → 100	50 → 160
Extruder (core)	70 → 85	60 → 70
Spinneret	100	

TABLE 4

In vitro release of 3-keto-desogestrel from this 4 cm long implant. The implant was gamma-sterilized (25 kGy).	
Day	Release (μg/day.cm)
1	10.0*
2	7.8
3	7.8
4	7.5
10	8.0
20	7.8
30	7.3
40	7.3
50	7.3
100	6.0
150	6.5
200	6.0
250	5.5
300	5.8
350	5.3
400	5.0
450	4.6
500	4.3
550	4.0

*boost of 3-keto-desogestrel is minimal as gamma sterilization was used instead of heat sterilization.

EXAMPLE 3

Analogous to Example 2, a co-axial filament was spun, but in this case with a membrane thickness of 90 μm. The external diameter of the implant was also about 1.65 mm in this case. Polysiloxane tubing (1.47×1.95 mm) was again used for the polysiloxane jacket and the ends were sealed with medical-grade silicone adhesive. The external diameter of the implant provided with a polysiloxane layer was 2.05 mm.

Typical preparation condition of the co-axial filament.

	Temperature (°C.)	Pressure (bar)
Extruder (barrel)	75 → 100	160 → 150
Extruder (core)	60 → 100	150 → 110
Spinneret	125	

The length of the implant was 3 cm.

TABLE 5

In vitro release of 3-keto-desogestrel from this non-sterilized implant:	
Day	Release (μg/day.cm)
1	13.7
6	9.7
9	9.7
10	10.7
20	10.7
30	9.3
40	9.0
50	8.7
60	9.7
70	9.3
80	9.0
90	9.3
100	8.3

TABLE 5-continued

In vitro release of 3-keto-desogestrel from this non-sterilized implant:	
Day	Release ($\mu\text{g/day.cm}$)
110	9.0

EXAMPLE 4

Co-axial filament was obtained according to the method described in Example 2.

The filament consists of Evatane® 28.25 as core material and Evatane® 1040 VN 4 as the membrane material.

Further data: membrane thickness: 75 μm ; core material charged with 60% (wt) 3-keto-desogestrel; external diameter of the implant: 1.7 mm; length implant: 3.0 cm; polysiloxane jacket up to external diameter: 2.05 mm; sealing of the implant ends with silicone adhesive.

TABLE 6

In vitro release from the non sterilized implant:	
Day	Release ($\mu\text{g/day.cm}$)
1	24.7
5	22.0
10	13.7
20	12.8
30	12.3
40	11.0
50	11.3
60	11.3
70	11.0
80	11.0
90	10.7
100	10.3
110	10.3
120	8.3
130	10.0
140	8.7
150	8.3
160	9.3

EXAMPLE 5

Same procedure and material as described in Example 4.

Specifications: core material: Evatane® 28.25; membrane: Evatane® 1040 VN 4 membrane thickness: 60 μm core charged with 60% (wt) 3-keto-desogestrel; external diameter: 2.0 mm; length: 4.0 cm; no polysiloxane jacket; no sealing of implant ends.

TABLE 7

In vitro release:	
Day	Release ($\mu\text{g/day.cm}$)
1	43.9
5	27.8
10	24.9
20	21.3
30	21.1
40	18.9
50	19.1
60	17.4
70	15.4
80	16.1
90	18.5
100	16.8
110	16.5
120	16.3

I claim:

1. An implant intended for subcutaneous or local administration, comprising:

core material of ethylene/vinyl acetate copolymer having such a molecular weight that the melt index is greater than 10 grams/10 minutes, and a vinyl acetate content of at least 20% by weight, which core material functions as a matrix for at least one contraceptive substance selected from the group consisting of 3-keto-desogestrel, levonorgestrel and gestodene in a quantity which is sufficient for a constant release of at least 15–30 μg contraceptive substance per day over a predetermined term, and a membrane having a layer thickness of 50–250 μm which encases the core material and also consists of ethylene/vinyl acetate copolymer, but with such a molecular weight that the melt index is less than 10 grams/10 minutes and a vinyl acetate content of less than 20% by weight, which membrane, with the core material, forms a contact layer at the interface of the core material and membrane, said contact layer preventing the core material and membrane from separating from one another.

2. The implant of claim 1, wherein the core material comprises an ethylene/vinyl acetate copolymer with a melt index between 25 and 30 grams/10 minutes and a vinyl acetate content of greater than 25% by weight.

3. The implant of claim 1 wherein the membrane comprises ethylene/vinyl acetate copolymer with a melt index of 8 grams/10 minutes or less, and a vinyl acetate content of less than 20% by weight.

4. Implant according to claim 1, wherein the contraceptive substance comprises 3-keto-desogestrel.

5. Implant according to claim 1, which is of essentially cylindrical shape with a maximum external diameter of about 2 mm and a length of less than about 5 cm.

6. The implant of claim 1 wherein said core consists of from 50 to 75% contraceptive substance and from 50 to 25% ethylene/vinyl acetate copolymer.

7. The implant of claim 6 wherein the ends of the implant are covered by an inert polymer.

8. The implant of claim 7 further comprising a layer of polysiloxane coating the entire implant.

9. An implant comprising:

a core including a contraceptive substance selected from the group consisting of 3-keto-desogestrel, levonorgestrel, gestodene, and mixtures thereof, in a matrix consisting of ethylene/vinyl acetate copolymer having a melt index greater than 10 grams/10 minutes, and further having a vinyl acetate content of at least 20% by weight, the contraceptive substance present in the matrix in a sufficient amount to release at least 15–30 μg of contraceptive substance per day from the implant over a predetermined term;

a membrane for controlling the rate of contraceptive substance release from the implant, said membrane having a layer thickness of 50–250 μm encasing said core, said membrane consisting of ethylene/vinyl acetate copolymer having a molecular weight such that the membrane's melt index is less than 10 grams/10 minutes and further having a vinyl acetate content of less than 20% by weight; and a contact layer, at the interface of said core and said membrane, said contact layer preventing the separation of said membrane from said matrix.

10. The implant of claim 9 wherein said core consists of from 50 to 75% contraceptive substance and from 50 to 25% ethylene/vinyl acetate copolymer by weight.

11. The implant of claim 10 wherein the ends of the implant are covered by an inert polymer.

12. The implant of claim 10 further comprising a layer of polysiloxane coating the entire implant.

13. The implant of claim 11 further comprising a layer of polysiloxane coating the entire implant.

14. The implant of claim 13 wherein the ethylene/vinyl acetate copolymer of the core has a melt index

between 25 and 30 grams/10 minutes and a vinyl acetate content of greater than 25% by weight.

15. The implant of claim 13 wherein the ethylene/vinyl acetate copolymer of the membrane has a melt index less than 8 grams/10 minutes and a vinyl acetate content of less than 20% by weight.

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US005150718A

United States Patent [19]

De Nijs

[11] **Patent Number:** **5,150,718**[45] **Date of Patent:** **Sep. 29, 1992**[54] **METHOD OF CONTRACEPTION**[75] **Inventor:** **Hendrik De Nijs, Oss, Netherlands**[73] **Assignee:** **Akzo N.V., Arnhem, Netherlands**[21] **Appl. No.:** **836,632**[22] **Filed:** **Feb. 14, 1992****Related U.S. Application Data**

[60] Continuation of Ser. No. 541,559, Jun. 21, 1990, Pat. No. 5,088,505, Division of Ser. No. 229,066, Aug. 5, 1988, Pat. No. 4,957,119.

[51] **Int. Cl.⁵** **A61K 9/22**[52] **U.S. Cl.** **128/832; 128/833; 128/898; 604/49; 604/890.1**[58] **Field of Search** **604/49, 890.1, 891.1, 604/892.1; 128/830, 832, 833, 839, 898; 424/457, 465, 486**[56] **References Cited****U.S. PATENT DOCUMENTS**

3,903,880	9/1975	Higuchi et al.	128/833
4,582,052	4/1986	Dunn et al.	128/839
4,596,576	6/1986	De Nijs	128/832
4,673,565	6/1987	Di Luccio et al.	424/443
4,720,384	1/1988	Di Luccio et al.	424/78

OTHER PUBLICATIONSD. N. Robertson et al., "Release Rates of Levonorgestrel from Silastic Capsules, Homogeneous Rods and Covered Rods in Humans," *Chemical Abstracts*, 99(8), pp. 308-309, 1983.D. N. Robertson et al., "Release Rates of Levonorgestrel from Silastic Capsule Homogeneous Rods and Covered Rods in Humans," *Contraception*, 27(5), 483-495, 1983.W. Losert et al., "Progestogens with Antimineralocorticoid Activity," *Arzneim.-Forsch/Drug. Res.* 35(I), No. 2 (1985).M. J. D. Eenink et al., "Biodegradable Hollow Fibres for the controlled Release of Hormones," *J. of Controlled Release* 6, pp. 225-247 (1987).*Primary Examiner*—Stephen C. Pellegrino*Assistant Examiner*—Michael Rafa*Attorney, Agent, or Firm*—Donna Bobrowicz; William M. Blackstone

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ABSTRACT

The invention relates to an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally.

8 Claims, No Drawings

METHOD OF CONTRACEPTION

This is a continuation of U.S. Ser. No. 07/541,559, filed Jun. 21, 1990, now U.S. Pat. No. 5,088,505 which was a divisional of U.S. Ser. No. 07/229,066, now U.S. Pat. No. 4,957,119, filed Aug. 5, 1988.

The invention relates to an implant of polymeric material which can release a contraceptive agent for a relatively long time when fitted subcutaneously or locally. More specifically, the invention relates to an implant of such small dimensions that it can be fitted subcutaneously with an ordinary hypodermic needle.

There is a large demand for the development of new, long-acting contraceptives which require a minimum of medical guidance. This is valid in particular for those areas of the world where the medical infrastructure is poor, and where family planning can be organized only to an insufficient extent.

An implant of this type, which can release a contraceptive agent in virtually constant quantities over a period of at least 2 years, but preferably for about 4 to 5 years, is a new development which can certainly supply what is needed. The great problem, however, is that the often large amount of the contraceptive agent with which the polymeric material of the implant has to be charged to guarantee release for about 4 years leads to very large implants which can only be fitted surgically, or to several smaller implants which have to be fitted simultaneously.

The need for subcutaneous fitting of a plurality of (smaller) implants also offers little attraction at the present time.

In theory any polymeric material is suitable for the development of an implant provided only that it is biologically compatible, and also any material with a progestational action. In this context reference may be made, for example, to U.S. Pat. No. 3,279,996 (Long et al.) in which an implant is described which contains an active substance encased by a polysiloxane membrane, and to Dutch Patent 167,850 (Zaffaroni) in which an implant is described in which the active substance is contained in a polymer, and this polymer loaded with active substance is encased by a polymer membrane which completely controls the rate of release. However, if a limit is set to the dimensions of the implant, if a certain amount of implant rigidity is required to facilitate introduction, and, furthermore, if the achievement of a release duration of the contraceptive substance of a minimum of 2 years, and preferably of up to 4 to 5 years, is desired, then all available theoretical solutions seem to fail.

The implant of the invention can be considered one of the release systems known per se which consist of a core of active material encased by a release rate-regulating membrane. The choice of polymers to be used, the choice of the contraceptive substances, and the dimensions of the implant are, however, matched in such a way that a unique release system is obtained which complies completely with the requirements stipulated above.

The implant of the invention is cylindrical or virtually cylindrical with a maximum section of about 2 mm, but preferably between 1.5 and 2.0 mm, and possesses a variable length. The length of the implant will, however, not exceed about 5 cm for practical reasons. The length is preferably between 1 and 4 cm. These dimensions of the implant of the invention are so small that

subcutaneous fitting can be carried out with an ordinary hypodermic needle.

The implant of the invention is characterized by:

- a) core material of ethylene/vinyl acetate copolymer (hereafter called EVA) having such a molecular weight that the melt index is higher than 10 gram per 10 minutes, and a vinyl acetate content of 20% by weight or more; which core material functions as a matrix for 3-keto-desogestrel, levonorgestrel or gestodene as active contraceptive substances, in a quantity which is sufficient for a long-lasting constant release of at least 15-30 µg of active substance per day, and
- b) a membrane having a layer thickness of 50-250 µm which encases the core material and also consists of EVA material, but with such a molecular weight that the melt index is less than 10 gram per 10 minutes, and an acetate content of less than 20% by weight, this implant being completely or virtually completely cylindrical with a maximum external diameter of about 2 mm and a length which is smaller than about 5 cm.

The contraceptively active substance, which can be employed in the context of the present invention, is a highly active progestagen, particularly 3-ketodesogestrel, levonorgestrel or gestodene. These contraceptive substances are highly active substances which show already an effective progestational action with a daily dosage of about 15-30 µg.

This core material can be charged to about 75 percent by weight with the active substance without seriously affecting the utility of the EVA core material. However, a degree of charging of about 50-60% by weight is preferred.

The core material used in the present invention is an EVA polymer with a melt index higher than 10 gram/10 min. and preferably between 25 and 30 g/10 min. The vinyl acetate content of the core material is higher than 20% by weight and preferably higher than 25% by weight.

Very suitable EVA polymers which can be used as core material are, for example, Evatane® with the designations 28-150, 28-399, and 28-400, supplied by ICI and 28.420 and in particular 28.25 and 33.25 supplied by Atochem, and Elvax® with the designations 310, 250, 230, 220, and 210, supplied by Du Pont de Nemours.

The membrane polymer is also an EVA polymer which, however, has a higher molecular weight than that of the core material. The melt index of this membrane material is less than 10 g/10 min., and preferably less than or equal to 8 g/10 min.; the vinyl acetate content is less than 20% by weight.

Suitable EVA polymers which can be used as a membrane are, for example, Evatane® with the designations 501/502 (melt index 2, vinyl acetate content 7.5%), 554/555 (4, 12.5%), 540 (10, 18%) and particularly 571 (8, 15%), Elvax® with the designations 450, 460, 470, 550, 560, 650, 660, 670, 750, 760 and 770, and Evatane® 1080 VN 5 and in particular 1040 VN 4 supplied by Atochem.

The release characteristic of the contraceptive substance (through the membrane) is determined to a large extent by the vinyl acetate content of the EVA membrane.

The implant of the invention is obtained by means of a so-called co-axial extrusion process, a method in which the two EVA polymers are extruded co-axially

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in preset layer thicknesses with the aid of a co-axial extrusion head.

This co-axial extrusion process means that both polymers are transported in the molten state through the co-axial extrusion head, the molten core material at the same time containing the active substance.

Due to this co-axial extrusion process a contact layer is produced on the interface of the two polymers, which layer is probably fully or partially responsible for the outstanding drug-release properties of the co-extrudate, but in any event prevents the two polymer layers working loose from each other after a period of time, due to disappearance of the active substance from the core polymer, which loosening would fundamentally disturb the release pattern.

The co-axial extrusion process is art known per se so that it will not be gone into further within the scope of this description.

A thick, co-axial filament with a maximum external diameter of about 2 mm, and preferably between about 1.5 and 2.0 mm, is obtained by means of the co-axial extrusion process. The filament is then cut into pieces up to a maximum of about 5 cm long, using conventional techniques.

Although certainly not necessary the circular ends of the implant may—if desired—be additionally protected by an inert polymer, for example polyethylene, polypropylene or the EVA polymer which is used for the membrane, or also, for example, by a (medical grade) silicone adhesive. This protective layer is obtained, for example, by dipping the surface into a smelt or solution of the particular polymer. If necessary, the end can also be singed or pinched closed.

An other embodiment of the implant of the invention possesses a thin layer of polysiloxane around the whole external surface of the implant described above, in addition to the assembly as described above. This polysiloxane is chosen so that the release pattern is not influenced to any appreciable extent; the formation of a second release-rate-regulating layer is thus not intended by this. The layer in question can therefore be extremely thin, even of the order of about 20–50 μm ; a somewhat thicker layer, however, is just as permissible.

This protective layer can be obtained by dipping or immersing the implant in a thin tubing of polysiloxane.

The implant of the invention should in each case contain a sufficient quantity of active substance when used for application in humans which is such that it can bring about virtually constant release of the active substance for a minimum of 1 year, which roughly means that the core material must be charged with 5 to 15 mg of 3-keto-desogestrel, levonorgestrel or gestodene. An additional quantity of active substance of about 5 to 15 mg is necessary for each additional year in which the implant must release, so that a quantity of 25–75 mg of active material can be needed for a release duration of 5 years.

The implant of the invention is preferably be used as a subcutaneous implant, but may also be applied locally, e.g. in the uterine or cervical region.

EXAMPLE 1

The active substance 3-keto-desogestrel and EVA core material (melt index 400 g/10 min., vinyl acetate content 28% by weight)-Evatane® 28-400—were mixed in a ratio of 1:1 (on a weight basis) on a heatable mill at a temperature of 80° C. The polymer sheets charged with 3-keto-desogestrel were reduced in size

and then processed into pellets by means of an extruder and a so-called chopper.

The pellets charged with 3-keto-desogestrel intended for the core, and EVA pellets intended for the membrane (melt index 8 g/10 minutes; vinyl acetate content 15% by weight, Evatane® 571), were transferred to two separate hoppers of the co-axial extrusion apparatus. The co-axial filament as extruded at a temperature of about 100° C. A co-axial filament with an external diameter of 1.9 mm and a skin thickness of 150 μm was obtained with a correct choice and a correct adjustment of the spinneret geometry, the feed rates of the core and skin material to the spinneret, and the winding rate of the fibre. The extruded co-axial filament was cooled in a water bath, and then wound onto bobbins with a draw rate of 0.25 N. The extrusion rate of the filament was 2.3 metres per sec. Typical preparation conditions:

	Temperature (°C.)	Pressure (bar)
Extruder (barrel)	100	60 → 173
Extruder (core)	80	5 → 46
Spinneret	100	

The extruded co-axial filament was then cut into the required length. The filament pieces were wrapped in polysiloxane if desired using polysiloxane tubing (dimensions 1.57/2.41 mm internal/external diameter) to be swelled in cyclohexane and thereafter to be filled with the co-axial filament of the required length, and finally dried under vacuum. The two ends of the implant obtained were sealed with silicone adhesive (medical grade). The external diameter of the implant provided with a polysiloxane layer was 2.5 mm, the external diameter of the implant not provided with a polysiloxane layer was 1.9 mm.

The in vitro release of 3-keto-desogestrel from this implant was tested in 250 ml demineralized water at 37° C. This medium was contained in a 300 ml conical flask which was shaken at 150 cycles/minute with an amplitude of 2.5 cm.

TABLE 1

Results		
In vitro release of 3-keto-desogestrel from a 3 cm implant with and without a polysiloxane external layer.		
Release ($\mu\text{g/day} \cdot \text{cm}$)		
Day	without polysiloxane layer	with polysiloxane layer
1	10.0	6.7
2	10.7	9.7
3	11.3	10.0
4	10.3	9.7
7	10.3	9.3
9	10.0	9.7
10	10.0	9.7
14	10.3	9.7

The polysiloxane external layer here has practically no influence on the released pattern.

TABLE 2

In vitro release of 3-keto-desogestrel from an implant (3 cm) prepared in this way and provided with a polysiloxane layer. The implant was sterilized by heat treatment 20 min. 120° C.)	
Day	Release ($\mu\text{g/day} \cdot \text{cm}$)
2	57.0*
5	14.7
10	10.3

TABLE 2-continued

In vitro release of 3-keto-desogestrel from an implant (3 cm) prepared in this way and provided with a polysiloxane layer. The implant was sterilized by heat treatment 20 min. 120° C.).	
Day	Release (μg/day · cm)
20	11.3
30	10.3
40	10.0
50	10.0
90	9.0
100	9.3
200	8.7
300	8.3
376	8.3
400	7.7
471	7.7
500	8.0
550	7.7
600	8.0
650	7.0
700	6.3
750	6.0
800	6.3

*boost of 3-keto-desogestrel because of heat sterilization.

TABLE 3

In vivo release: Average plasma concentrations (3 dogs) of 3-keto-desogestrel after subcutaneous introduction of an implant prepared in this way (see implant of table 2)	
Day	Plasma concentration (pmol/ml)
1	2.11*
2	0.81
3	0.62
7	0.66
14	0.46
21	0.53
28	0.49
35	0.56
42	0.56
51	0.56
56	0.54
63	0.59
70	0.60
77	0.59
84	0.59
91	0.63

*boost of 3-keto-desogestrel because of heat sterilization.

EXAMPLE 2

The active substance 3-keto-desogestrel and Evatane® 28-400 were blended in 1:1 weight ratio in a 10 mm extruder at a temperature of 100° C.

The extrudate obtained was granulated with the acid of a pelletizer, after which the pellets were heated in vacuo at 135° C. for one hour.

In the same manner as described in Example 1 a co-axial filament was extruded using the above 3-keto-desogestrel charged pellets as core material and uncharged Evatane® 571 pellets as membrane material. The membrane thickness of the co-axial fibre was 135 μm, and the external diameter of the implant was 1.65 mm. The dimensions of the polysiloxane tubing were: 1.47 (internal) × 1.95 mm (external diameter). The ends of the 4-cm long implant were sealed with medical grade silicone adhesive. The external diameter of an implant provided with a polysiloxane layer was 2.05 mm.

Typical preparation conditions of the relevant co-axial filament:

	Temperature (°C.)	Pressure (bar)
Extruder (barrel)	80 → 100	50 → 160
Extruder (core)	70 → 85	60 → 70
Spinneret	100	

TABLE 4

In vitro release of 3-keto-desogestrel from this 4 cm long implant. The implant was gamma-sterilized (25 kGy).	
Day	Release (μg/day · cm)
1	10.0*
2	7.8
3	7.8
4	7.5
10	8.0
20	7.8
30	7.3
40	7.3
50	7.3
100	6.0
150	6.5
200	6.0
250	5.5
300	5.8
350	5.3
400	5.0
450	4.6
500	4.3
550	4.0

*boost of 3-keto-desogestrel is minimal as gamma sterilization was used instead of heat sterilization.

EXAMPLE 3

Analogous to Example 2, a co-axial filament was spun, but in this case with a membrane thickness of 90 μm. The external diameter of the implant was also about 1.65 mm in this case. Polysiloxane tubing (1.47 × 1.95 mm) was again used for the polysiloxane jacket and the ends were sealed with medical-grade silicone adhesive. The external diameter of the implant provided with a polysiloxane layer was 2.05 mm.

Typical preparation condition of the co-axial filament.

	Temperature (°C.)	Pressure (bar)
Extruder (barrel)	75 → 100	160 → 130
Extruder (core)	60 → 100	150 → 110
Spinneret	125	

The length of the implant was 3 cm.

TABLE 5

In vitro release of 3-keto-desogestrel from this non-sterilized implant:	
Day	Release (μg/day · cm)
1	13.7
6	9.7
9	9.7
10	10.7
20	10.7
30	9.3
40	9.0
50	8.7
60	9.7
70	9.3
80	9.0
90	9.3
100	8.3

TABLE 5-continued

In vitro release of 3-keto-desogestrel from this non-sterilized implant:	
Day	Release ($\mu\text{g/day} \cdot \text{cm}$)
110	9.0

EXAMPLE 4

Co-axial filament was obtained according to the method described in Example 2.

The filament consists of Evatane® 28.25 as core material and Evatane® 1040 VN 4 as the membrane material.

Further data:

- membrane thickness: 75 μm ;
- core material charged with 60% (wt) 3-keto-desogestrel;
- external diameter of the implant: 1.7 mm;
- length implant: 3.0 cm;
- polysiloxane jacket up to external diameter: 2.05 mm;
- sealing of the implant ends with silicone adhesive.

TABLE 6

In vitro release from the non sterilised implant:	
Day	Release ($\mu\text{g/day} \cdot \text{cm}$)
1	24.7
5	22.0
10	13.7
20	12.8
30	12.3
40	11.0
50	11.3
60	11.3
70	11.0
80	11.0
90	10.7
100	10.3
110	10.3
120	8.3
130	10.0
140	8.7
150	8.3
160	9.3

EXAMPLE 5

Same procedure and material as described in Example 4.

Specifications:

- core material: Evatane® 28.25;
- membrane: Evatane® 1040 VN 4
- membrane thickness: 60 μm
- core charged with 60% (wt) 3-keto desogestrel;
- external diameter: 2.0 mm;
- length: 4.0 cm;
- no polysiloxane jacket;
- no sealing of implant ends.

TABLE 7

In vitro release:	
Day	Release ($\mu\text{g/day} \cdot \text{cm}$)
1	43.9

TABLE 7-continued

In vitro release:	
Day	Release ($\mu\text{g/day} \cdot \text{cm}$)
5	27.8
10	24.9
20	21.3
30	21.1
40	18.9
50	19.1
60	17.4
70	15.4
80	16.1
90	18.5
100	16.8
110	16.5
120	16.3

I claim:

1. A method of contraception comprising: subcutaneously or locally administering an implant said implant comprising:

core material of ethylene/vinyl acetate copolymer having such a molecular weight that the melt index is equal to or greater than 10 grams/10 minutes, and a vinyl acetate content of at least 20% by weight, which core material functions as a matrix for at least one highly active progestogen present in a quantity sufficient for a release rate of greater than 30 μg of said progestogen per day over a term of at least one year, and

a membrane having a layer thickness of 50-250 μm which encases the core material and also consists of ethylene/vinyl acetate copolymer, but with such a molecular weight that the melt index is less than or equal to 10 grams/10 minutes, and a vinyl acetate content of less than 20% by weight, which membrane, with the core material, forms a contact layer at the interface of the core material and membrane thus preventing the core material and membrane, from separating from one another.

2. The method of claim 1, wherein the core material of said implant comprises an ethylene/vinyl acetate copolymer with a melt index between 25 and 30 grams/10 minutes and a vinyl acetate content of greater than 25% by weight.

3. The method of claim 1, wherein the membrane of said implant comprises an ethylene/vinyl acetate copolymer with a melt index less than or equal to 8 grams/10 minutes and a vinyl acetate content of less than 20% by weight.

4. The method of claim 1, wherein the highly active progestogen comprises 3-ketodesogestrel.

5. The method according to claim 1, wherein said implant is of essentially cylindrical shape with a maximum external diameter of about 2 mm and a length of less than about 5 cm.

6. The method of claim 1, wherein said core of the implant comprises about 50 to 75% contraceptive substance and from about 50 to 25% ethylene vinyl acetate copolymer.

7. The method of claim 6, wherein the ends of the implant are covered by an inert polymer.

8. The method of claim 3, wherein the implant further comprises a layer of polysiloxane coating the entire implant.

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Localization of non-palpable single-rod contraceptive implants using ultrasound sonography

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INTRODUCTION

Since its introduction, Implanon® (N.V. Organon, Oss, The Netherlands), the single rod contraceptive implant containing etonogestrel, has been received positively by both physicians¹ and users.² More than 300,000 women worldwide are currently using this method of contraception.

A small number of cases have been reported in which the implant has not been inserted in accordance with the correct insertion procedure as described in the package insert. This can result in non-palpable implants and will therefore necessitate the use of other localization techniques such as ultrasound sonography (USS).

Two main reasons why the implant may not be palpable are either a failed or non insertion procedure or an implant inserted too deeply.

OBJECTIVE

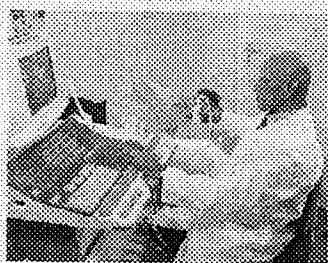
This study was conducted to confirm that single-rod contraceptive implants that have been inserted too deeply can be visualized by USS and to find the most effective USS transducer for locating these non-palpable implants.

DESIGN AND METHODS

Four women were included in this study, conducted in the Netherlands. All had undergone insertion with the single-rod contraceptive implant, but in contrast to the normal situation, the implant was not (clearly) palpable.

From an earlier study it is known that a correctly inserted single-rod implant can be located by ultrasound³, but since the implant is not radio-opaque it cannot be located by X-ray or CT-scan. For this study a Philips Ultrasound HDI 5000 system was used (Fig. 1). Five different USS transducers were used on each of the four women to quantitatively and qualitatively locate the rod. The USS transducers tested consisted of a vaginal probe (8–4 MHz), a low frequency transducer (5–2 MHz), an intermediate frequency transducer (7–4 MHz), a high frequency linear array transducer (12–5 MHz), and a very high frequency linear array transducer (15–7 MHz).

Figure 1. Locating an Implanon rod with Philips HDI 5000 ultrasound equipment.



In contrast to the surrounding tissues, Implanon can be identified and located by its acoustic shadow. The SonoCT Compound technique in the Philips Ultrasound equipment is helpful in the exact positioning of the implant since it produces a distinct acoustic shadow (Fig. 2). The implant itself is visible as a small but clear echogenic spot.

We started each examination at a 90° angle to the presumed longitudinal direction of the implant. Normally the implant is positioned 6–8 cm from the elbow crease on the inner side of the upper arm in the

Figure 2. Distinct (SonoCT) acoustic shadow from a correctly inserted contraceptive implant. The arrow marks the echogenic spot produced by the rod. The circle marks the distinct SonoCT-produced acoustic shadow. B: Schematic representation of Figure 2A indicating the position of the acoustic shadow (b) opposite the echogenic spot (a).

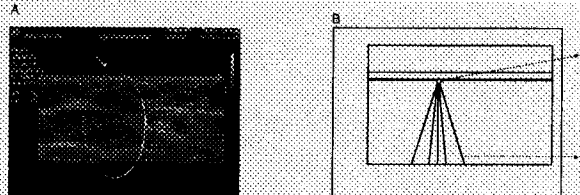


Figure 3. Transverse view of an intramuscularly inserted contraceptive implant using five (A/E) different USS transducers. The circle marks the echogenic spot produced by the rod itself and its acoustic shadow in the surrounding tissue.

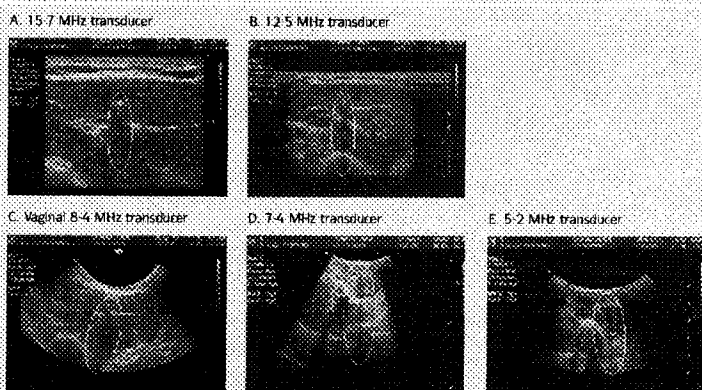
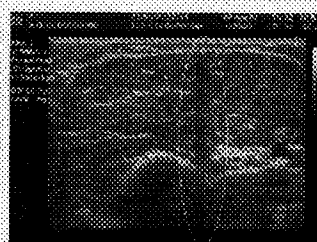


Figure 4. Transverse view of a too deeply subdermally inserted contraceptive implant using a high frequency (12–5 MHz) linear array transducer. The circle marks the echogenic spot produced by the rod itself and its clear acoustic shadow in the surrounding tissue.



sulcus bicipitalis medialis. We started focusing superficially since it was unlikely that the implant was inserted deeper than 3 cm after an incorrect procedure. After identifying the acoustic shadow of the implant we looked for the echogenic spot indicating the actual implant itself. Once the actual implant had been identified the transducer was turned 90° to obtain a longitudinal view. Finally, the exact position of both tips of the implant were indicated on the skin.

RESULTS

In three of the women, the rod was clearly visualized and located with all available transducers, including the vaginal probe. Best results were obtained with the high and very high frequency linear array transducers (12–5 and 15–7 MHz) (Fig. 3). When using a low or intermediate frequency transducer (5–2 and 8–4 MHz), application of a silicone patch or a large amount of gel was found to enhance visibility.

In two women, the rods were located intra-muscularly in the m. biceps and just beneath the fascia of the m. biceps, respectively. In one woman the distal tip of the implant was located just underneath the skin while the proximal tip was inserted too deeply indicating an incorrect 'injection' technique (Fig. 4). For the woman in whom the implant could not be visualized, a negative serum etonogestrel level (i.e. active component of Implanon) supported the USS finding that the implant had not been inserted.

REFERENCES

1. Moscaenhas L. Insertion and removal of Implanon practical considerations. *Eur J Contracept Reprod Health Care* 2000; 5 (Suppl 2): 29–34.
2. Urbanosok J. An integrated analysis of non-contraceptive adverse events with Implanon. *Contraception* 1998; 58 (Suppl): 109S–115S.
3. Lantz A, Noshier JL, Pasquale S, Siegel RL. Ultrasound characteristics of subdermally implanted Implanon contraceptive rods. *Contraception* 1997; 56: 525–7.

CONCLUSIONS

- In three of the women, the rod was clearly visualized and located with all available transducers, including the vaginal probe. Best results were obtained with the high and very high frequency linear array transducers (12–5 and 15–7 MHz).
- When using a low or intermediate frequency transducer (5–2 and 8–4 MHz), application of a silicone patch or a large amount of gel was found to enhance visibility.
- In two women, the rods were located intra-muscularly in the m. biceps and just beneath the fascia of the m. biceps, respectively.
- In one woman the distal tip of the implant was located just underneath the skin while the proximal tip was inserted too deeply indicating an incorrect 'injection' technique.
- For the woman in whom the implant could not be visualized, a negative serum etonogestrel level (i.e. active component of Implanon) supported the USS finding that the implant had not been inserted.

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1: Contraception. 2001 Jun;63(6):325-8.

Links

Nonpalpable ultrasonographically not detectable Implanon rods can be localized by magnetic resonance imaging.**Merki-Feld GS, Brekenfeld C, Migge B, Keller PJ.**

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Recently, the contraceptive implant Implanon has been introduced in several European countries. In comparison to the six-capsule preparation Norplant, the removal of this single-rod system should be associated with less complications. However, the removal of nonpalpable Implanon rods can be difficult because the implant is not always visible with ultrasound. The aim of this study was to find a radiologic method for the localization of Implanon implants that are nonpalpable and can not be detected by ultrasound. X-ray, ultrasound, computed tomography, and magnetic resonance imaging (MRI) were investigated as methods to localize Implanon in a pig chest preparation and in a woman with a nonpalpable implant. The implant in the woman could be localized unequivocally only by MRI. We conclude that MRI is the best method for the unequivocal localization of nonpalpable, ultrasonographically not detectable Implanon rods. To avoid unnecessary scar tissue formation, it may be appropriate to defer surgery for the removal until definitive localization.

PMID: 11672555 [PubMed - indexed for MEDLINE]

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