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(54) Title: DRUG DELIVERY DEVICE, ESPECIALLY FOR THE DELIVERY OF ANDROGENS

(57) **Abrégé/Abstract:**

The invention relates to a delivery device for the controlled release of a therapeutically active agent, especially an androgen, over a prolonged period of time, said device comprising a core comprising said therapeutically active agent, and a membrane encasing said core wherein said membrane is made of an elastomer. According to the invention, the elastomer is a siloxane-based elastomer comprising 3,3,3-trifluoropropyl groups attached to the Si-atoms of the siloxane units.



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(21) International Application Number: PCT/FI99/00886 (22) International Filing Date: 26 October 1999 (26.10.99) (30) Priority Data: 09/190,607 12 November 1998 (12.11.98) US (71) Applicant (for all designated States except US): LEIRAS OY [FI/FI]; P.O. Box 415, FIN-20101 Turku (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): MARKKULA, Tommi [FI/GB]; 154 Marsland Road, Sale, Cheshire M33 3NF (GB). ALA-SORVARI, Juha [FI/FI]; Ruonankatu 12 as 3, FIN-20900 Turku (FI). JUKARAINEN, Harri [FI/FI]; Tavastilankatu 6 A 5, FIN-20610 Turku (FI). LEHTINEN, Matti [FI/FI]; Kirjosieponkatu 2, FIN-20760 Piispanristi (FI). RUOHONEN, Jarkko [FI/FI]; Vanha Härkätie 10, FIN-21410 Vanhalinna (FI). (74) Agent: TURUN PATENTTITOIMISTO OY; P.O. Box 99, FIN-20521 Turku (FI).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
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DRUG DELIVERY DEVICE, ESPECIALLY FOR THE DELIVERY OF ANDROGENS

FIELD OF THE INVENTION

This invention relates to a drug delivery device, particularly to an implantable device intended for subcutaneous administration of a drug at a substantially constant rate for a prolonged period of time.

5 BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated by reference.

- 10 There is a great need for long-acting drug delivery devices, especially for contraceptives, which require a minimum of medical guidance. This concerns particularly the underdeveloped and developing countries where the medical infrastructure is weak and where family planning can be
15 organized only to an insufficient level.

A great number of subcutaneous implants for female contraception are known in the art. As example can be mentioned the commercially available product Norplant^R, which is an implant having a core containing levonorgestrel
20 as the active substance, and where the core is surrounded by a membrane of a silicone elastomer of poly(dimethylsiloxane) (PDMS). A special preparation of this kind is Jadelle^R in which the core is a poly(dimethylsiloxane) based matrix with levonorgestrel
25 dispersed therein. The membrane is an elastomer made from PDMS and silica filler, which, besides giving necessary strength properties to the membrane, also retards the permeation of the active agent through the membrane.

US 3,854,480 describes a drug delivery device, e.g. an implant, for releasing a drug at a controlled rate for a prolonged period of time. The device has a core of a matrix in which the drug is dispersed. The core is surrounded by a membrane that is insoluble in body fluids. The core matrix as well as the membrane are permeable to the drug by diffusion. The materials of the core and the membrane are chosen so that the drug diffuses through the membrane at a lesser rate than through the core matrix. Thus, the membrane controls the release rate of the drug. As a suitable polymer for the core matrix is mentioned poly(dimethylsiloxane) (PDMS), and as suitable polymers for the membrane are mentioned polyethylene and a copolymer of ethylene and vinyl acetate (EVA).

EP-B1-300306 describes an implant for subcutaneous or local use and for the release of a contraceptive agent for a relatively long time. The contraceptively active substance is dispersed in a core matrix and the core is surrounded by a membrane. As active substances are mentioned highly active progestins such as 3-keto-desogestrel, levonorgestrel and gestodene. The materials of the core matrix and the membrane are both based on copolymers of ethylene and vinyl acetate. The vinyl acetate concentration of the matrix polymer is higher than that of the membrane polymer. Therefore, the drug permeation of the membrane is slower than its permeation of the core matrix.

Androgen based implants for male contraception as well as treatment of benign prostate hypertrophy and other conditions due to hormonal disturbance such as hypogonadism have been described in the art.

US 5,733,565 discloses a male contraceptive implant which comprises 7- α -methyl-19-nortestosterone (MENT) or 7- α -methyl-19-Nortestosterone acetate (MENT Ac) as the active agent. The materials of the core matrix and the membrane are both based on copolymers of ethylene and vinyl acetate

(EVA). The vinyl acetate concentration of the matrix polymer is higher than that of the membrane polymer. The test results show that an implant releasing MENT AC over a prolonged period of time (about 180 days) is achieved with
5 the EVA copolymer. These results demonstrate an improvement over PDMS based implants containing androgens such as MENT Ac. The latter are useless in practice because of the very rapid release of the androgen.

10 Devices manufactured from EVA suffer, however, from certain drawbacks. The materials are rather stiff and non-flexible and are therefore rather inconvenient to wear as implants beneath the skin. Moreover, the tests carried out in US
5,733,565 mentioned above, showed that the EVA based system
15 released MENT Ac but did not release MENT in a sufficient amount.

Polysiloxanes, such as PDMS, are preferred polymers in drug delivery devices for a great variety of different drugs.
20 These polymers are particularly useful in subcutaneous implants.

In EP-B1-300306, Example 1, it is mentioned that a polysiloxane layer around the implant did not retard the release rate of the drug. The retarding effect on the drug
25 permeation that can be achieved by mixing silica into the PDMS is, however, rather limited. If silica is mixed into the PDMS polymer to about 40 weight-% of the final elastomer composition, typically a decrease in drug penetration of approximately 20 % is achieved. In general,
30 silica loading will have only a minimal influence on the drug permeation. The only way to achieve an essentially stronger retardation would be to use a thicker membrane. This would, however, result in devices of greater cross section and this would in turn lead to devices, such as
35 implants and the like, which are difficult to inject and inconvenient to wear.

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The cross section of a cylindrical implant should not exceed 3 mm. Preferably, it should be in the range of 1.5 to 2.7 mm. This feature makes demands upon the maximal membrane thickness: the thickness should not be greater than 0.4 mm. The suitable length of the implant should not exceed 50 mm.

OBJECTS AND SUMMARY OF THE INVENTION

The object of this invention is to provide a drug delivery device, particularly an implantable device intended for subcutaneous administration of a drug at a substantially constant rate for a prolonged period of time.

The object is particularly to provide a device with which the drug release rate easily can be adjusted to a desirable level.

The object is particularly to provide a flexible and smooth device, which has a small cross section and which is easy to insert or inject and convenient to wear.

Thus, the invention concerns a delivery device for the controlled release of a therapeutically active agent, especially an androgen, over a prolonged period of time, said device comprising a core comprising said therapeutically active agent, and a membrane encasing said core wherein said membrane is made of an elastomer. According to the invention, the elastomer is a siloxane-based elastomer comprising 3,3,3-trifluoropropyl groups attached to the Si-atoms of the siloxane units.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the daily *in vitro* release rate of MENT from a series of implants in which the membrane contains variable amounts of 3,3,3-trifluoropropyl substituents.

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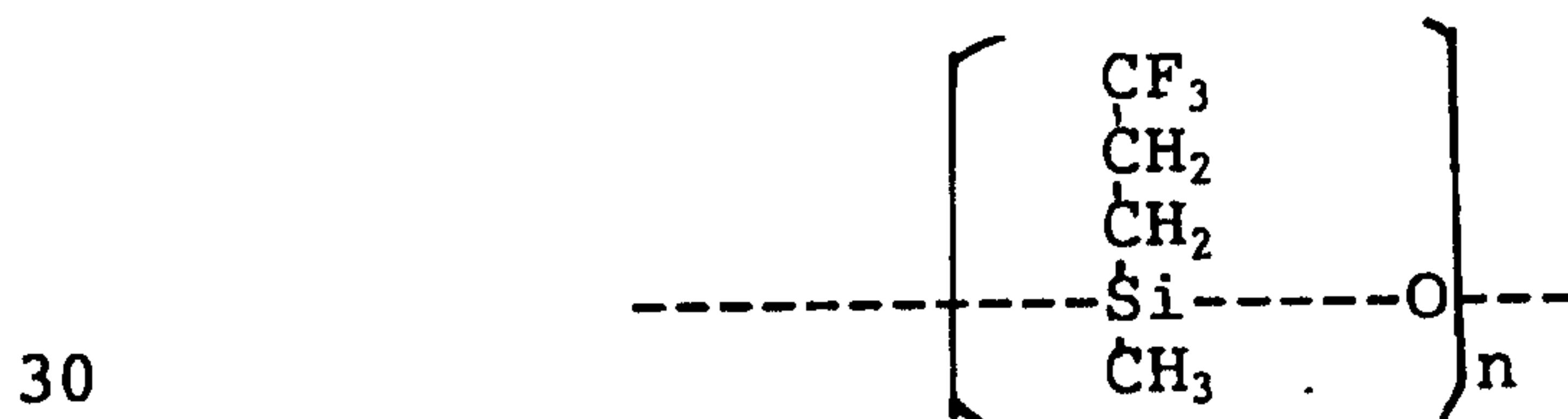
DETAILED DESCRIPTION OF THE INVENTION

Description of the elastomer

The elastomer suitable for use in the device according to this invention, particularly for use in the membrane of the device, is a siloxane-based elastomer comprising 3,3,3-trifluoropropyl groups attached to the Si-atoms of the siloxane units.

The term "siloxane-based elastomer" shall be understood to cover elastomers made of poly(disubstituted siloxanes) where the substituents mainly are lower alkyl, preferably alkyl groups of 1 to 6 carbon atoms, or phenyl groups, wherein said alkyl or phenyl can be substituted or unsubstituted. A widely used and preferred polymer of this kind is poly(dimethylsiloxane) (PDMS).

A certain amount of the substituents attached to the Si-atoms of the siloxane units in the elastomer shall be 3,3,3,-trifluoropropyl groups. Such an elastomer can be achieved in different ways. According to one embodiment, the elastomer can be based on one single crosslinked siloxane-based polymer, such as a poly(dialkyl siloxane) where a certain amount of the alkyl groups at the Si-atoms are replaced by 3,3,3-trifluoropropyl groups. A preferred example of such polymers is poly(3,3,3-trifluoropropyl methyl siloxane) the structure of which is shown as compound I.



Compound I

A polymer of this kind, in which approximately 50 % of the methyl substituents at the Si-atoms replaced by 3,3,3-

trifluoropropyl groups, is commercially available. The term "approximately 50 %" means that the degree of 3,3,3-trifluoropropyl substitution is in fact somewhat below 50 %, because the polymer must contain a certain amount (about 5 0.15 % of the substituents) of crosslinkable groups such as vinyl or vinyl-terminated groups. Similar polymers having lower substitution degree of 3,3,3-trifluoropropyl groups can easily be synthesized.

The retarding effect of the 3,3,3-trifluoropropyl groups on 10 the permeation of drugs across a membrane of the elastomer is dependent on the amount of these groups. Furthermore, the effect is highly dependent on the drug used. If the elastomer is made of one single polymer only, it would be necessary to prepare and use polymers with different 15 amounts of 3,3,3,-trifluoropropyl groups for different drugs.

According to another embodiment, which is particularly preferred if suitable elastomers for several different drugs are needed, is to crosslink a mixture comprising a) a 20 non-fluorosubstituted siloxane-based polymer and b) a fluorosubstituted siloxane-based polymer, where said polymer comprises 3,3,3,-trifluoropropyl groups attached to the Si-atoms of the siloxane units. The first ingredient of the mixture, the non-fluorosubstituted polymer, can be any 25 poly(disubstituted siloxane) where the substituents mainly are lower alkyl, preferably alkyl groups of 1 to 6 carbon atoms, or phenyl groups, wherein said alkyl or phenyl can be substituted or unsubstituted. A preferred non-fluorosubstituted polymer is PDMS. The second ingredient of 30 the mixture, the fluoro-substituted polymer, can for example be a poly(dialkyl siloxane) where a certain amount of the alkyl groups at the Si-atoms are replaced by 3,3,3-trifluoropropyl groups. A preferred example of such polymers is poly(3,3,3-trifluoropropyl methyl siloxane) as 35 mentioned above. A particularly preferable polymer of this kind is a polymer having as high amount of 3,3,3,-

trifluoropropyl substituents as possible, such as the commercially available polymer, in which approximately 50 % of the methyl substituents at the Si-atoms are replaced by 3,3,3-trifluoropropyl groups. An elastomer with great permeation retarding effect can be achieved by using exclusively or mainly the aforementioned polymer. Elastomers with less retarding influence on the permeation of the drug can be obtained by using mixtures with increasing amounts of the non-fluorosubstituted siloxane-based polymer.

The elastomer should preferably comprise a filler, such as amorphous silica, in order to give a sufficient strength for the membrane made from said elastomer.

Methods for the preparation of the elastomer

According to one embodiment, the elastomer is prepared by crosslinking, in the presence of a catalyst, a vinyl-functional polysiloxane component and a silicon hydride-functional crosslinking agent.

By crosslinking is meant the addition reaction of the silicon hydride-functional crosslinking agent with the carbon-carbon double bond of the vinyl-functional polysiloxane component.

According to another embodiment, the elastomer is prepared by crosslinking the polymer in the presence of a peroxide catalyst.

The term "vinyl-functional" polysiloxane shall be understood to cover polysiloxanes substituted with vinyl groups or with vinyl-terminated groups. The "vinyl-functional polysiloxane component" and the "polysiloxane component" to be crosslinked shall also be understood to cover copolymers with polysiloxanes having vinyl substituents or vinylterminated substituents.

For crosslinking, the amounts of the components are preferably selected so that the ratio of the molar amounts of the silicon hydrides to the double bonds is at least 1.

As stated above, the elastomer can be made by crosslinking one single fluorosubstituted siloxane-based polymer, or by crosslinking a mixture of a non-fluorosubstituted siloxane-based polymer and a fluorosubstituted siloxane-based polymer. The term "vinyl-functional polysiloxane component" can thus be a mixture comprising a non-fluorosubstituted siloxane-based polymer and a fluorosubstituted siloxane-based polymer, where said polymer comprises 3,3,3,-trifluoropropyl groups attached to the Si-atoms of the siloxane units. Alternatively, the "vinyl-functional polysiloxane component" can be a single fluorosubstituted siloxane-based polymer, where said polymer comprises 3,3,3,-trifluoropropyl groups attached to the Si-atoms of the siloxane units.

Additionally, a so called compatibilizer can be mixed with the above mentioned components. The compatibilizer is typically a block copolymer of a non-fluorosubstituted polymer and a fluorosubstituted polymer.

The silicon hydride-functional crosslinking agent is preferably a hydride-functional polysiloxane which may be straight-chain, branched or cyclic. The hydride-functional siloxane crosslinking agent may also contain trifluoropropyl groups.

The fluorosubstituted siloxane-based polymer is preferably a PDMS polymer where approximately 50 % of the methyl groups in said PDMS have been replaced by 3,3,3,-trifluoropropyl groups.

A filler, such as amorphous silica, is preferably added to the vinyl-functional component before the crosslinking.

In case the elastomer is made by crosslinking a polymer component in the presence of a peroxide catalyst, such a polymer component can be a mixture comprising a non-fluorosubstituted siloxane-based polymer and a
5 fluorosubstituted siloxane-based polymer comprising 3,3,3,-trifluoropropyl groups attached to the Si-atoms of the siloxane units. Alternatively, this polymer component can be a single fluorosubstituted siloxane-based polymer, where said polymer comprises 3,3,3,-trifluoropropyl groups
10 attached to the Si-atoms of the siloxane units.

The catalyst to be used in the crosslinking is preferably a noble metal catalyst, most commonly a platinum complex in alcohol, xylene, divinyl siloxane or cyclic vinyl siloxane. An especially suitable catalyst is a Pt(0)-divinyl-
15 tetramethyl disiloxane complex.

Different types of devices

The device can be any device suitable for delivery of an active agent at a controlled rate over a prolonged period of time. The device can take a wide variety of shapes and
20 forms for administering the active agent at controlled rates to different areas of the body. Thus, the invention includes external and internal drug delivery devices such as transdermal patches and implants for releasing a therapeutically active agent in the body tissues.

25 According to a preferred embodiment, the device is an implant for subcutaneous use.

Construction of the core

The core of the device can consist of the active agent as such, e.g. in liquid or crystallized form, or in a mixture
30 with pharmaceutically acceptable excipients.

Preferably, the core is an elastomer matrix, such as a PDMS

elastomer matrix in which the drug is dispersed.

According to an other alternative, the core matrix can be made of the novel elastomer, which is a siloxane-based elastomer comprising 3,3,3-trifluoropropyl groups attached
5 to the Si-atoms of the siloxane units.

Therapeutically active agents

The therapeutically active agent is preferably a hormone, but is not restricted hereto. Especially preferable hormones are androgens, such as 7- α -methyl-19-
10 nortestosterone (MENT), 7- α -methyl-19-nortestosterone acetate (MENT Ac), testosterone, methandroil, oxymetholone, methanedione, oxymesterone, nardrolone phenylpropionate, norethandrolone and their pharmaceutically acceptable esters. Particularly preferable are 7- α -methyl-19-
15 nortestosterone (MENT) and 7- α -methyl-19-nortestosterone acetate (MENT Ac).

Most preferably, the device is an implant for subcutaneous use and administration of a MENT or MENT Ac at a controlled rate over a prolonged period of time. Such an implant can
20 be used for male contraception as well as treatment of benign prostate hypertrophy and other conditions due to hormonal disturbance such as hypogonadism and male menopause. In male contraception, a progestin is preferably combined with the androgen (MENT or MENT Ac). Thus, the
25 implant can contain a mixture of the androgen and the progestin.

Manufacture of implants

The implants according to this invention can be manufactured in accordance with standard techniques. The
30 therapeutically active agent is mixed with the core matrix polymer such as PDMS, processed to the desired shape by molding, casting, extrusion, or other appropriate methods.

The membrane layer can be applied onto the core according to known methods such as by mechanical stretching, swelling or dipping. Reference is made to the US-patents US 3,832,252, US 3,854,480 and 4,957,119. An especially
5 suitable method for preparation of the implants is disclosed in the Finnish patent FI 97947. This patent discloses an extrusion technology where prefabricated rods containing the active ingredient are coated by an outer
10 membrane. Each such rod is, for example, followed by another rod without any active ingredient. The formed string is cut at the rods that contain no active agent. In this way, no special sealing of the ends of the implant is necessary.

The invention is described in more detail by the following
15 non-limiting examples.

EXPERIMENTAL SECTION

The invention is described below in greater detail in the following examples.

Elastomer membranes of different types (A - E) were
20 prepared. Type A represents an elastomer made from a mixture comprising fluorosubstituted (3,3,3-trifluoropropyl substitution degree 49.5 %) and non-fluorosubstituted siloxane-based polymers wherein the crosslinking was performed by peroxide catalyst. Three different mixtures
25 with varying amounts of fluorosubstituted polymer were prepared (Example 1). The B type (Examples 2 and 3) represents an elastomer made from a single fluorosubstituted siloxane-based polymer wherein the crosslinking was performed by peroxide catalyst. Type C
30 (Example 4) represents an elastomer made from a mixture comprising fluorosubstituted (3,3,3-trifluoropropyl substitution degree 30 %) and non-fluorosubstituted siloxane-based polymers wherein the crosslinking was performed by peroxide catalyst. The D type (Example 5)

represents and elastomer made from a single fluorosubstituted siloxane-based polymer wherein the crosslinking was performed by hydrosilylation. Type E (Example 6) represents an elastomer made from a mixture comprising fluorosubstituted (3,3,3-trifluoropropyl substitution degree 49.5 %) and non-fluorosubstituted siloxane-based polymers wherein the crosslinking was performed by hydrosilylation.

EXAMPLE 1

10 Type A elastomers with varying amounts fluorosubstituted polymers

A series of 50 [and further 25 and 75] parts by weight of silica-filled poly(trifluoropropylmethylsiloxane-co-vinylmethylsiloxane), 50 [and 75 and 25 respectively] parts by weight of silica-filled poly(dimethylsiloxane-co-vinylmethylsiloxane) and 1.2 parts by weight of dibentsoylperoxide-polydimethylsiloxane paste were mixed with a 2-roll mill. The mixture was cured at +115 °C for 5 minutes with a thermal press to give 0.4 mm thick membranes, which were post-cured at +150 °C for 2 hours.

EXAMPLE 2

Elastomer type B

100 parts by weight of silica-filled poly(trifluoropropylmethylsiloxane-co-dimethylsiloxane-co-vinylmethylsiloxane) (content of trifluoropropylmethylsiloxane units 60 mol-%; i.e. degree of trifluoropropyl substitution groups is 30 %) and 1.2 parts by weight of dibentsoylperoxide-polydimethylsiloxane paste were mixed with a 2-roll mill. The mixture was cured at +115 °C for 5 minutes with a thermal press to give 0.4 mm thick membranes, which were post-cured at +150 °C for 2 hours.

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EXAMPLE 3

Elastomer type B

100 parts by weight of silica-filled
poly(trifluoropropylmethylsiloxane-co-dimethylsiloxane-co-
5 vinylmethylsiloxane) (content of trifluoropropylmethyl-
siloxane units 99 mol-%; i.e. degree of trifluoropropyl
substitution 49.5 %) and 1.2 parts by weight of
dibentsoylperoxide-polydimethylsiloxane paste were mixed
with a 2-roll mill. The mixture was cured at +115 °C for 5
10 minutes with a thermal press to give 0.4 mm thick
membranes, which were post-cured at +150 °C for 2 hours.

EXAMPLE 4

Elastomer type C

50 parts by weight of the silica-filled fluoro-substituted
15 polysiloxane in Example 2, 50 parts by weight of silica-
filled poly(dimethylsiloxane-co-vinylmethylsiloxane) and
1.2 parts by weight of dibentsoylperoxide-
polydimethylsiloxane paste were mixed with a 2-roll mill.
The mixture was cured at +115 °C for 5 minutes with a
20 thermal press to give 0.4 mm thick membranes, which were
post-cured at +150 °C for 2 hours.

EXAMPLE 5

Elastomer type D

100 parts by weight of silica-filled
25 poly(trifluoropropylmethylsiloxane-co-vinylmethylsiloxane)
(substitution degree of 3,3,3-trifluoropropyl groups = 49.5
%), 0.04 parts by weight of Pt(0)-divinyldimethyl-
siloxane complex, 0.05 parts by weight of 1-ethynyl-1-
cyclohexanol and 1.0 parts by weight of silicon hydride
30 crosslinking agent were mixed with a two-chamber mixer. The

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mixture was cured at +115 °C for 5 minutes with a thermal press to give 0.4 mm thick membranes.

EXAMPLE 6

Elastomer type E

- 5 50 parts by weight of the silica-filled fluoro-substituted polysiloxane in Example 5, 50 parts by weight of silica-filled poly(dimethylsiloxane-co-vinylmethylsiloxane), 0.04 parts by weight of Pt(0)-divinyltetramethylsiloxane complex, 0.05 parts by weight of 1-ethynyl-1-cyclohexanol
10 and 1.0 parts by weight of silicon hydride crosslinking agent were mixed with a two-chamber mixer. The mixture was cured at +115 °C for 5 minutes with a thermal press to give 0.4 mm thick membranes.

Membrane permeation studies

- 15 The permeation of different drugs through elastomers of types A, B and C described above were tested.

The test apparatus described in the publication Yie W. Chien, Transdermal Controlled Systemic Medications, Marcel Dekker inc. New York and Basel 1987, page 173, was used in
20 the permeation tests.

The drug fluxes (permeations) through membranes were measured with a two-compartment diffusion cell at 37 °C (side-by-side diffusion cell, Crown Glass Company). The apparatus consisted of two concentric cells (donor and
25 receptor compartments) that were separated by the elastomer membrane to be investigated. The donor and receptor compartments were both jacketed and thermostated by an external circulating bath and each compartment had a magnetic stirrer. A drug solution and solvent (without
30 drug) was added into the donor and the receptor compartments. At each predetermined time interval, samples

were withdrawn from the receptor compartment and replaced with the same volume of solvent. The amount of the drug that permeated through the membrane was measured by HPLC. In all measurements, the thickness (0.4 mm) of the membrane and the surface area of the membranes were constant.

In the following tables, the relative permeation through different elastomer membranes were studied for different drugs. The reference membrane is made of an elastomer based on dimethylsiloxane-vinylmethylsiloxane copolymer, which contains silica filler. In the tables below, the term "trifluoropropyl substitution degree, %" has the same meaning as mentioned before and this percentage means the substituents at the Si-atoms of the siloxane units in the elastomer, i.e. the 3,3,3-trifluoropropyl substituents.

15 Drug 1: Gestodene

	Elastomer type	trifluoropropyl substitution degree, %	Relative permeation
	reference	0	1
	A	7	0.63
20	A	16	0.37
	A	29.5	0.18
	B	30	0.45
	B	49.5	0.06

25 Drug 2: NestoroneTM (16-methylene-17- α -acetoxy-19-norprogesterone)

	Elastomer type	trifluoropropyl substitution degree, %	Relative permeation
	reference	0	1
	B	49.5	0.29

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Drug 3: MENT (7- α -methyl-19-nortestosterone)

	Elastomer type	trifluoropropyl substitution degree, %	Relative permeation
	reference	0	1
5	B	49.5	0.09

Drug 4: MENT Ac (7- α -methyl-19-nortestosterone acetate)

	Elastomer type	trifluoropropyl substitution degree, %	Relative permeation
	reference	0	1
10	A	7	0.59
	A	16	0.49
	A	29.5	0.28
	B	49.5	0.20

Drug 5: Levonorgestrel

	Elastomer type	trifluoropropyl substitution degree, %	Relative permeation
	reference	0	1
	B	20	0.77
	B	30	0.41
20	B	49.5	0.05
	C	11	0.73

The elastomer described above is used preferably either as a membrane or as a matrix for controlling drug permeation.

The permeation tests show that the elastomer is highly
25 suited for controlling the permeation of drugs having
hormonal action.

The elastomer is particularly suitable for the release of
hormonally active drugs such as androgens, antiprogestins

and progestins.

Preparation of implants containing MENT as the active agent

The implants manufactured consisted of three parts: a core containing MENT in a polymer matrix, a membrane covering
5 the core and silicone adhesive end-caps.

Membrane preparation

The poly(trifluoropropylmethylsiloxane-co-vinylmethylsiloxane) used in the implant tests described in the following is a copolymer, where the content of
10 trifluoropropylmethyl siloxane units is nearly 100 mol-%, i.e. corresponding to a substitution degree of silicon of nearly 50 %.

[100] 50 parts (by weight) of silica-filled poly(trifluoropropylmethylsiloxane-co-vinylmethylsiloxane),
15 [0] 50 parts of silica-filled poly(dimethylsiloxane-co-vinylmethylsiloxane) and 1.2 parts of dibenzoylperoxide-poly(dimethylsiloxane) paste were mixed with a 2-roll mill. The mixture was extruded to a tube-like form with a wall thickness of 0.2 mm and cured by heat. The membrane was
20 post-cured at +150 °C for 2 hours and cut to 50 mm pieces.

As reference was used an implant with a membrane of commercially available PDMS. The polymer of the core matrix was also PDMS.

Core preparation

25 100 parts (by weight) of poly(dimethylsiloxane-co-vinylmethylsiloxane), 1 part of poly(hydrogenmethylsiloxane-co-dimethylsiloxane) crosslinker, 0.05 parts of 1-ethynyl-1-cyclohexanol inhibitor, 0.1 parts of Pt(0)-divinyltetramethyl disiloxane complex (platinum content 1 %
30 weight-%) and 100 parts (by weight) of MENT were mixed in a

two-chamber mixer. The mixture was casted to a PTFE-coated stainless steel mold, which was heated at +115 °C for 30 minutes. The cores were removed, cooled and cut to 40 mm pieces.

5 Implant preparation

50 mm membrane pieces were swelled with cyclohexane and the MENT containing cores were inserted. Cyclohexane was allowed to evaporate and the ends of the implants were closed with a silicone adhesive. After 24 hours the ends
10 were cut to give 2 mm end-caps.

Drug release tests

The release rate of the drug from the implant was measured *in vitro* as follows:

The implants were attached into a stainless steel holder in
15 vertical position and the holders with the implants were placed into glass bottles containing 75 ml of a dissolution medium. The glass bottles were shaken in shaking waterbath 100 rpm at 37 °C. The dissolution medium was withdrawn and replaced by a fresh dissolution medium at predetermined
20 time intervals, and the released drug was analysed by HPLC. The concentration of the dissolution medium and the moment of change (withdrawal and replacement) of medium were selected so that sink-conditions were maintained during the test.

25 Results

Figure 1 shows the daily *in vitro* release rate of MENT from a series of implants in which the membrane contains variable amounts of 3,3,3-trifluoropropyl substituents. The diamond marked curve refers to a membrane of a polymer
30 containing no 3,3,3-trifluoropropyl substituents (i.e. normal PDMS). The square marked curve refers to a membrane

with a substitution degree of 16 % (i.e. 16 % of the substituents at the Si-atoms in the siloxane units in the membrane elastomer are 3,3,3-trifluoropropyl groups); and the X-marked curve refers to a membrane with a substitution
5 degree of 49.5 % (defined as above). Thus, the experiments demonstrate clearly the strong retarding effect caused by the 3,3,3-trifluoropropyl substitution of the membrane polymer. Moreover, the figure shows that the release rate of MENT from the implants having a membrane of the novel
10 elastomer is essentially constant over a prolonged period of time, while the release rate of MENT from the implants having a membrane of normal PDMS declines clearly as function of time.

15 According to this technique, implants containing androgens, particularly MENT or MENT Ac, for use over long periods can be prepared.

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of
20 embodiments, only a few of which are disclosed herein. It will be apparent for the specialist in the field that other embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

CLAIMS

1. A delivery device for the controlled release of a therapeutically active agent, especially an androgen, over a prolonged period of time, said device comprising
- a core comprising said therapeutically active agent, and
 - 5 - a membrane encasing said core wherein said membrane is made of an elastomer, characterized in that the elastomer is a siloxane-based elastomer comprising 3,3,3-trifluoropropyl groups attached to the Si-atoms of the siloxane units.
- 10 2. The device according to claim 1, characterized in that it is an implantable device intended for subcutaneous administration of the active agent.
3. The device according to claim 1, characterized in that in the elastomer 1 to approximately 50 % of the
- 15 substituents attached to the Si-atoms in the siloxane units are 3,3,3,-trifluoropropyl groups.
4. The device according to claim 3, characterized in that the elastomer is made of either
- i) a mixture comprising a) a non-fluorosubstituted
 - 20 siloxane-based polymer and b) a fluorosubstituted siloxane-based polymer, said polymer comprising 3,3,3,-trifluoropropyl groups attached to the Si-atoms of the siloxane units, or
 - ii) a single siloxane-based polymer comprising 3,3,3,-
 - 25 trifluoropropyl groups attached to the Si-atoms of the siloxane units,
- wherein said polymer or mixture of polymers are crosslinked to form the elastomer.
5. The device according to claim 4, characterized in that
- 30 the mixture of polymers is a mixture of a) poly(dimethylsiloxane) and b) poly(dimethylsiloxane) in

which the methyl groups attached to the Si-atoms of the siloxane units to some extent have been replaced by 3,3,3,-trifluoropropyl groups.

6. The device according to claim 5, characterized in that
5 approximately 50 % of the methyl groups in the polymer b) have been replaced by 3,3,3,-trifluoropropyl groups.

7. The device according to claim 1, characterized in that the the core is an elastomer matrix in which the drug is dispersed.

10 8. The device according to claim 7, characterized in that the core elastomer is PDMS.

9. The device according to claim 7, characterized in that also the core elastomer is a siloxane-based elastomer comprising 3,3,3-trifluoropropyl groups attached to the Si-
15 atoms of the siloxane units.

10. The device according to claim 1, characterized in that the therapeutically active agent is an androgen.

11. The device according to claim 10, characterized in that the androgen is MENT or MENT Ac, and that the device is an
20 implant for subcutaneous use.

12. The device according to any of the foregoing claims, characterized in that the elastomer comprises a filler.

IN VITRO RELEASE RATE OF MENT

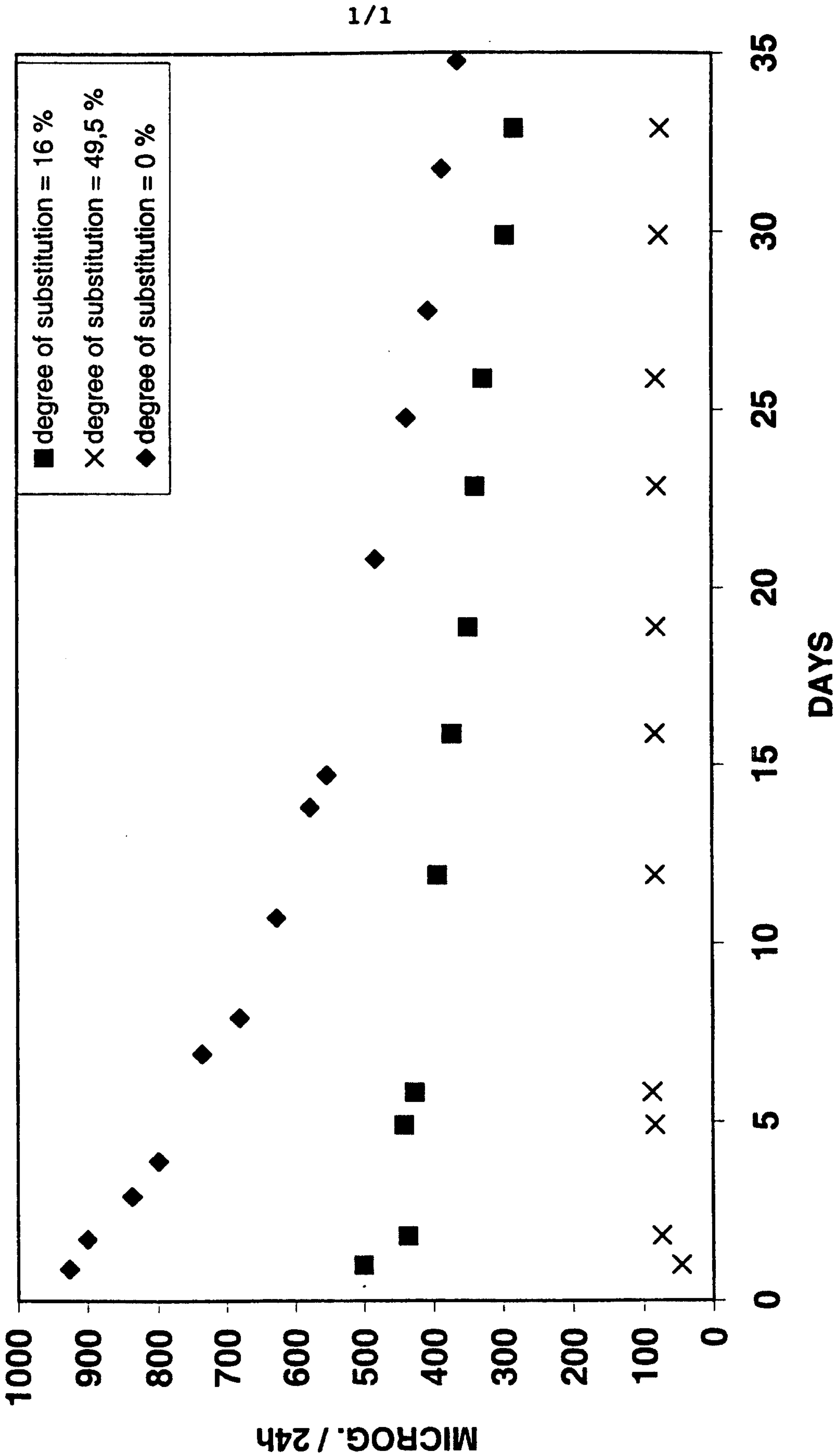


FIG. 1