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(54) Title: X-RAY VISIBLE DRUG DELIVERY DEVICE

(57) Abstract: The subject invention provides an X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone remplacement therapy.

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X-ray visible drug delivery device

FIELD OF THE INVENTION

The present invention relates to the field of contraception and hormone replacement therapy.

The present invention relates to an X-ray visible drug delivery device for subdermal (subcutaneous) administration of a contraceptive or hormone replacement therapy.

The device according to the invention is particularly in the form of an implant, and will hereinafter be referred to as an implant.

BACKGROUND OF THE INVENTION

Implanon® is a contraceptive implant that is inserted in the human body for periods up to 3 years. Cases have been reported in which the implants could not easily be removed due to either incorrect insertions by physicians or due to non-insertion of the implant by physicians. Implanon can be visualized in the body using ultrasonography and MRI techniques. Visualization by MRI is not always readily available, relatively complicated and expensive. Visualization by ultrasonography is also not always readily available and may be difficult in the hands of inexperienced physicians especially in the event the implant was inserted incorrectly.

The implant should be removed (and replaced) after three years. Furthermore, women may want to remove the implant if they wish to become pregnant. Another reason for removal can be disease, such as cancer, especially breast cancer, ovary cancer or cancer of the uterus.

It would therefore be convenient to have an Implanon-like implant which will be X-ray visible. This in order to have additional methods to locate and identify the implant, either

to facilitate removal of the implant or to be able to reassure the patient that the implant has been inserted.

Such a contemplated X-ray visible implant must be such that the radio-opaque component does not (i) influence the hormone release profile of the implant and (ii) does not migrate into the body through the open-ended implant.

X-ray visible medical devices, such as stents, catheters, intra-uterine devices such as MultiLoad®, biodegradable implants and dental devices are known. An X-ray visible drug delivery device known in the field of contraception is described in GB 2168257 which shows an X-ray visible vaginal ring comprising the progestogen levonorgestrel. GB2168257 does not relate to the influence of the radio-opaque component on the release rate of levonorgestrel from the ring, nor does such a ring have open-ends.

It is however crucial to ascertain that the hormone release rate is not significantly affected by a radio-opaque component present in the contraceptive device because that could possibly result in pregnancy, the unwanted effect for a woman using contraception.

Moreover, it is also crucial that a radio-opaque component present in the contraceptive/HRT device does not migrate outside the (open-ended) implant into the body in undesired amounts causing potential radio-opaque component related adverse effects.

Thus, the subject invention provides for a contraceptive and/or HRT X-ray visible implant wherein the radio-opaque component does not negatively influence the release rate of hormones from the device and does not migrate into the body.

SUMMARY OF THE INVENTION

The subject invention provides an X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone replacement therapy comprising one

compartment consisting of (i) a thermoplastic polymer core loaded with (a) a contraceptively effective or therapeutically effective amount of desogestrel or 3-ketodesogestrel and (b) about 4-30% by weight radio-opaque material and (ii) a non-medicated thermoplastic polymer skin covering the core.

The subject invention further provides an X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone replacement therapy comprising one compartment consisting of (i) a thermoplastic polymer core loaded with a contraceptively effective or therapeutically effective amount of desogestrel or 3-ketodesogestrel and containing an inert metal wire and (ii) a non-medicated thermoplastic polymer skin covering the core.

FIGURES

Figure 1: X-ray photographs of implants a) without barium sulphate ($BaSO_4$)(i.e. identical to Implanon); b) with 20 wt% $BaSO_4$ in skin; and c) with 11.5 wt% $BaSO_4$ in core.

Figure 2: X-ray photographs of implants without barium sulphate (sample 8) and with 11.5 wt% $BaSO_4$ in core (sample 7) inserted in pig tissue.

Figure 3: Accelerated release profiles of implants with 0, 8, 11.5 and 15 wt% barium sulphate in the core. (The implant with 0 wt% is identical to Implanon.)

Figure 4: Real time release profiles up to 190 days of implants with 0, 8, 11.5 and 15 wt% barium sulphate in the core. (The implant with 0 wt% is identical to Implanon).

Figure 5: X-ray photographs of implants a) without $BaSO_4$ or titanium wire (i.e. identical to Implanon); and b) with 0.5 mm titanium wire.

Figure 6: X-ray photographs of implants without titanium wire (sample 3) and with a 0.5 mm titanium wire in the core (sample 4) inserted in pig tissue.

Figure 7: Accelerated release profiles of implants with a 0.25 mm titanium wire in the core, a 0.50 mm titanium wire in the core and a reference implant (identical to Implanon) with no titanium wire.

Figure 8: Real time release profiles of implants with a 0.25 mm titanium wire in the core, a 0.50 mm titanium wire in the core and a reference implant (identical to Implanon) with no titanium wire.

Figure 9: Back Scatter Electron (BSE) detector photograph (magnification 350x) of implant with 11.5 wt% barium sulphate in the core

Figure 10: BSE detector photograph (magnification 3500x) of leached implant with 11.5 wt% barium sulphate in the core. The dark section on the left is the skin.

Figure 11: X-ray photographs of implants a) without $BaSO_4$ (i.e. identical to Implanon, sample 1); b) with 11.5 wt% $BaSO_4$ in core (samples 2 and 3); c) with 4 wt% $BaSO_4$ in core; d) with 20wt% $BaSO_4$ in core; and e) with 30 wt% $BaSO_4$ in core.

Figure 12: X-ray transmission of implants as function of content $BaSO_4$(wt(%)).

Figure 13: Accelerated release profiles of implants with 0, 4, 20 and 30 wt% barium sulphate in the core. (The implant with 0 wt% is identical to Implanon.)

Figure 14: Real time release profiles up to 76 days of implants with 0, 4, 20 and 30 wt% barium sulphate in the core. (The implant with 0 wt% is identical to Implanon).

Figure 15: Back Scatter Electron (BSE) detector photograph (magnification 350x) of implant with a) 4 wt% barium sulphate in the core; b) 20 wt% barium sulphate in the core; and c) 30 wt% barium sulphate in the core.

Figure 16: BSE detector photograph (magnification 3500x) of leached implant with a) 4 wt% barium sulphate in the core; b) 20 wt% barium sulphate in the core; and c) 30 wt% barium sulphate in the core. The dark section on the left is the skin.

DETAILED DESCRIPTION OF THE INVENTION

Implanon® is a subdermal contraceptive implant consisting of a coaxial rod. The core of this rod contains a mixture of etonogestrel (3-keto desogestrel) and ethylene vinylacetate (EVA) copolymer, i.e. EVA 28 which has a vinylacetate content of about 28% (m/m). The skin layer also consists of EVA polymer, i.e. EVA 14, which has a vinyl acetate content of about 14% (m/m). Each rod has a mass of 129 mg and contains 68 mg etonogestrel. Implanon has a length of 40 mm and a diameter of 2 mm and has open ends.

The implant may be placed within an applicator consisting of a stainless steel needle, which is fitted to an acrylonitrile-butadiene-styrene polymer (ABS) applicator. The applicator is a syringe-like apparatus consisting of a body, plunger, needle and polypropylene shield. The loaded applicator may be placed in a polyethylene terephthalate glycol (PETG) tray, which may be subsequently sealed with lidding paper.

The object of the invention is to add a radio-opaque element to a contraceptive/HRT implant such as Implanon® providing the possibility to identify and locate it in the body by X-ray techniques while maintaining the hormone release profile thereof and while ensuring that the radio-opaque component does not migrate outside of the implant in undesired amounts into the body.

One skilled in the art will appreciate that a hormone release profile of a batch of a drug delivery device is never exactly identical to another batch of the same drug delivery device. Therefore, according to the subject invention, when the hormone release profile of an X-ray visible implant of the invention deviates less than about 15% from the hormone release profile of Implanon®, these hormone release profiles are considered identical or equivalent. The deviation can be calculated using a difference factor (F_1) to

compare dissolution profiles. The difference factor (F_1) calculates the percentage difference between two curves at each time point

$$F_1 = \{[\sum_{t=1}^{n} |R_t - T_t|]/[\sum_{t=1}^{n} R_t]\} * 100$$

Where R_t is the reference assay at time point t, T_t is the test assay at time point t and n is the number of pull points. F1 values up to 15 (0-15) provide assurance of the sameness or equivalence of the two curves. The reference curve is chosen such that other release controlling parameters, than the one that is tested, are kept as constant as possible.

When incorporating a radio-opaque element in the skin layer of the implant, X-ray visibility was hardly accomplished. However, X-ray visibility was accomplished when incorporating the radio-opaque element in the core of the implant. Despite the incorporation of the radio-opaque element in the core of the implant which also contains the active hormone material, the hormone release profile was not affected.

When evaluating where the radio-opaque component was located in the implant after production thereof, it was surprisingly found that almost all of the radio-opaque component was encapsulated within the polymer component and hardly any radio-opaque component was encapsulated in the hormone crystals. This was unexpected in view of the fact that the polymer component represents only about 36 wt% of the implant whereas the hormone component comprises about 52.5 wt% of the implant. As a result of the encapsulation within the polymer component, the radio-opaque component crystals could not migrate out of the implant through the open ends of the implant in undesired amounts. Had the radio-opaque component been present in the hormone crystals, it may have been able to migrate outside of the implant in case where the hormone crystals are inter-connected.

Thus, the subject invention provides an X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone replacement therapy comprising one compartment consisting of (i) a thermoplastic polymer core loaded with (a) a contraceptively effective or therapeutically effective amount of desogestrel or 3-

ketodesogestrel and (b) about 4-30% by weight radio-opaque material and (ii) a non-medicated thermoplastic polymer skin covering the core.

In one specific embodiment, the X-ray visible drug delivery device is an implant.

The radio-opaque element can be any such element known in the art, such as barium sulphate, titanium oxide, bismuth oxide, tantalum, tungsten, or platinum. In a specific embodiment, the radio-opaque material is barium sulphate.

In one embodiment, the radio-opaque material is about 4-25% by weight. In another embodiment, the radio-opaque material is about 6-20% by weight. In yet another embodiment, the radio-opaque material is about 4-15% by weight. In a specific embodiment, the radio-opaque material is about 8-15% by weight.

The thermoplastic polymer that can be used in practising the invention, may in principle be any thermoplastic polymer or elastomer material suitable for pharmaceutical use, such as low density polyethylene, ethylene-vinylacetate copolymers and styrene-butadiene-styrene copolymers. In a specific embodiment, ethylene-vinylacetate copolymer (poly-EVA) is used due to its excellent mechanical and physical properties (e.g. solubility of the steroids in the material). The poly-EVA material may be used for the core as well as the skin and can be any commercially available ethylene-vinylacetate copolymer, such as the products available under the trade names: Elvax, Evatane, Lupolen, Movriton, Ultrathene, Ateva and Vestypar.

The radio-opaque material in the core does not affect the release of the desogestrel or 3-ketodesogestrel from the device and does not migrate out of the implant.

The subject invention further provides an X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone replacement therapy comprising one compartment consisting of (i) a thermoplastic polymer core loaded with a contraceptively effective or therapeutically effective amount of desogestrel or 3-

ketodesogestrel and containing an inert metal wire and (ii) a non-medicated thermoplastic polymer skin covering the core.

The radio-opaque element may be an inert titanium wire or other inert material such as certain grades of stainless steel or gold alloys. In a specific embodiment, the inert metal wire is a titanium wire.

The metal wire in the core does not affect the release of the desogestrel or 3-ketodesogestrel from the device.

The present invention is further described in the following examples which are not in any way intended to limit the scope of the invention as claimed.

EXAMPLES

EXAMPLE 1 – Preparation of two-layered implant containing barium sulphate in the core

Preparation of two layered implant containing barium sulphate in the core consisted of two steps, i.e. manufacturing of core granulate (pre-mixing and blend extrusion) containing a mixture of etonogestrel (3-keto desogestrel), barium sulphate and EVA-28 copolymer and manufacturing of a co-axial fiber consisting of the core and a skin layer of EVA-14 copolymer.

The core material was prepared by adding the desired amount (e.g. 52.5 wt% etonogestrel, 36 wt% EVA, 11.5 wt% Barium sulphate) of ingredients to a stainless steel drum after which the powder mixture was pre-mixed by rotating the drum on a rhönrad, or equivalent, at 47 rpm. The powder mixture was subsequently fed to a Berstorff ZE25 co-rotating twin screw extruder (or equivalent) and blend extruded at an extrusion temperature of 125°C. Blend extrusion resulted in strands in which etonogestrel (3-keto desogestrel) and barium sulphate were homogeneously dispersed in the EVA-28 matrix. The strands were subsequently granulated to core granulate.

The co-extrusion set-up consisted of a skin extruder that processed the skin material and a core extruder that processed the core material as delivered by the blend extruder. The melt flows were combined in a spinneret resulting in a skin-core fibre. The volume flow rate of both melt flows was controlled by a set of separate spinning pumps. An extrusion temperature of 145°C and an extrusion rate of 1 m/min was used. Extrusion lead to a co-axial fiber with a diameter of 2 mm and a skin thickness of 60 μm. The fiber was cooled down to room temperature in a water bath, dried on air and wound on a reel. The coaxial fiber was cut into 4.0 cm rods using a semi-automatic cutter (Diosynth or equivalent).

EXAMPLE 2 – Preparation of two layered implant containing barium sulphate in the skin

Preparation of two layered implant containing barium sulphate in the skin consisted of three steps, i.e. manufacturing of core granulate (pre-mixing and blend extrusion) containing a mixture of etonogestrel (3-keto desogestrel) and EVA-28 copolymer, manufacturing of skin granulate (pre-mixing and blend extrusion) containing a mixture of Barium sulphate and EVA-14 copolymer, and manufacturing of a co-axial fiber consisting of the core and a skin layer.

The core material (e.g 60 wt% etonogestrel and 40 wt % EVA-28) and skin material (e.g. 20 wt% barium sulphate and 80 wt % EVA-14) were prepared by adding the desired ingredients to a stainless steel drum after which the powder mixtures were pre-mixed by rotating the drum on a rhönrad, or equivalent, at 47 rpm.
The core powder mixture was subsequently fed to a Berstorff ZE25 co-rotating twin screw extruder (or equivalent) and blend extruded at an extrusion temperature of 125°C. Blend extrusion resulted in strands in which etonogestrel (3-keto desogestrel) was homogeneously dispersed in the EVA-28 matrix. The strands were subsequently granulated to core granulate. Essentially the same process, except for a higher extrusion temperature of 150°C, was executed for the skin powder mixture resulting in strands in

which barium sulphate was homogeneously dispersed in the EVA-14 matrix. The strands were subsequently granulated to skin granulate.

The co-extrusion set-up consisted of a skin extruder that processed the skin granulate as delivered by the blend extruder and a core extruder that processed the core granulate as delivered by the blend extruder. The melt flows were combined in a spinneret resulting in a skin-core fibre. The volume flow rate of both melt flows was controlled by a set of separate spinning pumps. An extrusion temperature of 120°C and an extrusion rate of 1 m/min was used. Extrusion lead to a co-axial fiber with a diameter of 2 mm and a skin thickness of 60 μm. The fiber was cooled down to room temperature in a water bath, dried on air and wound on a reel. The coaxial fiber was cut into 4.0 cm rods.

EXAMPLE 3 – comparison of X-ray visibility between implant containing barium sulphate in the core, implant containing barium sulphate in the skin and implant without barium sulphate (Implanon)

X-ray photographs were taken from implants and subsequently the X-ray visibility between implants having barium sulphate in either core or skin versus x-ray visibility of implants without barium sulphate (Implanon) were compared. Figure 1 demonstrates that incorporation of barium sulphate in the skin layer hardly improved the x-ray visibility when compared to implants without barium sulphate. However, incorporation of barium sulphate into the core greatly improved the X-ray visibility of the implant.

The x-ray visibility of the implant with barium sulphate in the core was also tested in vivo in pig tissue. For this purpose implants having barium sulphate in the core and implants without barium sulphate (Implanon) were inserted in hind legs of pigs and subsequently X-ray photographs were taken. Figure 2 demonstrates that the barium sulphate containing implant (sample 7) is clearly visible while the Implanon implant is not (sample 8).

EXAMPLE 4 – Hormone release profile of implant containing barium sulphate in the core in comparison to hormone release profile of commercially available Implanon

In-vitro release rate profiles of the implants were tested by two methods. An accelerated release rate method was performed by testing the implant in an ethanol/water (90/10) solution. For the real time release rate method the in-vitro release profile was tested in water. For both tests the release profile of an implant containing barium sulphate in the core was compared to the profile of Implanon without barium sulphate.

Implants were manufactured loaded with 8, 11.5 and 15 wt% barium sulphate in the core. The resulting accelerated release profiles are shown in Figure 3 which demonstrates that all release profiles are similar and that within the tested range of barium sulphate content of the core (0-15 wt%) the radio-opaque component does not influence the release of hormones from the device. The same conclusion can be drawn from the real time release profiles up to 190 days (Figure 4), i.e. within the tested range of barium sulphate content of the core (0-15 wt%) the radio-opaque component does not influence the release of hormones from the device.

These conclusions were substantiated by calculating F1 values. The F1 values were calculated for both accelerated release rate profiles (up to and including 18 days) as real time release rate profiles (up to and including 190 days) taking the Implanon release profiles as reference. The results are given in Table 1. F1 values up to 15 (0-15) provide assurance of the sameness or equivalence of the two curves.

Table 1: F1 values for Implants loaded with 8, 11.5 and 15 wt% barium sulphate in the core

barium sulphate (wt%)	Accelerated release	Real time release
8	3.3	9.8
11.5	2.4	9.7
15	2.1	8.7

EXAMPLE 5 – Preparation of an implant containing a titanium wire in the core

To prepare implants in which the core contains an inert titanium wire, Implanon rods with a diameter of 2 mm were adapted such that a titanium wire could be inserted. This was done by carefully drilling a canal in the implants in longitudinal direction. Spiral drills (Guhring Spiralbohre, Germany) with a diameter of either 0.40 or 0.60 mm were applied. A 0.40 mm spiral drill was applied for the implants in which a 0.25 mm titanium wire was inserted, whereas a 0.60 mm drill was used for the implant in which a 0.50 mm titanium wire was inserted. After the canal was prepared, the titanium wire was carefully inserted taking in consideration that the wire did not penetrate the skin layer. After insertion, the wire was cut at the rod end using a sharp cutter.

EXAMPLE 6: comparison of X-ray visibility between implant containing a titanium wire in the core and implant without a titanium wire (Implanon)

X-ray photographs were taken from implants and subsequently the X-ray visibility between implants having a titanium wire in the core was compared to implants without a titanium wire (Implanon) . As demonstrated in Figure 5, insertion of a titanium wire into the core greatly improved the X-ray visibility of the implant.

The x-ray visibility of the titanium wire implant was also tested in vivo in pig tissue. For this purpose implants having a titanium wire in the core and implants without a wire (Implanon) were inserted in hind legs of pigs and subsequently X-ray photographs were taken. Figure 6 demonstrates that the titanium wire containing implant (sample 4) is clearly visible while the Implanon implant is not (sample 3).

EXAMPLE 7 - Hormone release profile of implant containing titanium wire in core in comparison to hormone release profile of commercially available Implanon

In-vitro release rate profiles of Implanon were determined by two methods. An accelerated release rate method was performed by testing the implant in an ethanol/water

(90/10) solution. For the real time release rate method the in-vitro release profile was tested in water. For both tests the release profile of implants containing titanium wire in the core was compared to the profiles of Implanon without titanium wire. The resulting accelerated release profiles are shown in Figure 7 which demonstrates that all release profiles are comparable to the Implanon reference implant and that within the tested range of titanium wire diameters (0.25-0.50 mm) the influence on the release of hormones from the device by the radio-opaque component is acceptable.

The same conclusions can be drawn form the real time release profiles up to 118 days (Figure 8), i.e. that all release profiles are comparable to the Implanon reference implant and that within the tested range of titanium wire diameters (0.25-0.50 mm) the influence on the release of hormones from the device by the radio-opaque component is acceptable.

These conclusions were substantiated by calculating F1 values. The F1 values were calculated for both accelerated release rate profiles (up to and including 18 days) as real time release rate profiles (up to and including 118 days) taking the Implanon release profiles as reference. The results are given in Table 2. F1 values up to 15 (0-15) provided assurance of the sameness or equivalence of the two curves.

Table 2: F1 values for Implants loaded with 0.25 and 0.50 mm titanium wires

Titanium wire (mm)	Accelerated release	Real time release
0.25	2.6	8.1
0.50	7.7	10.8

EXAMPLE 8: Migration of barium sulphate particles out of implant with open ends

To reveal the distribution of barium sulphate in the implant and to obtain an impression of the loss of barium sulphate particles upon leaching, cryogenic sections were made of implants using a ultramicrotome. Subsequently the sections of the implants were analyzed using Scanning Electron Microscopy / Energy Dispersed Xspectroscopy

(SEM/EDX) before and after leaching. Leaching the implants leads to removal of the etonogestrel crystals from the implant. By examining before and after leaching information is obtained on the morphology of the barium sulphate/etonogestrel/EVA-28 mixture. A back scatter electron (BSE) detector was used for imaging. In the BSE image the presence of barium sulphate particles is easily recognized by the high brightness of the barium sulphate particles.

Figure 9 reveals the morphology of an implant in which the core is loaded with about 11.5 wt% barium sulphate. It can be seen that the bright spots, representing barium sulphate, are mainly located in the EVA-28 material, i.e. the irregular shaped grey/black spots, representing etonogestrel crystals, contain no bright spots. Figure 10 reveals the same sample that was leached . The left part is the skin material while the right part shows the leached core. Dark holes are clearly visible. The holes, representing the location at which etonogestrel crystals were present before leaching, hardly contain any bright spots.

The content barium sulphate in several batches was also tested using incineration before and after leaching (18 days in ethanol/water (90/10)). This gives information on possible migration of barium sulphate crystals out of the implant after the etonogestrel crystals were leached out of the implant. The results (table 3) show that there is no major change in content of barium sulphate upon leaching. It can therefore be concluded that no or hardly any barium sulphate crystals migrated out of the implant through the open ends.

Combining Figures 9 and 10 with the results in table 3 it can be concluded that hardly any radio-opaque component (shown by the bright spots) was encapsulated by the hormone crystals and that most of the radio- opaque component was encapsulated by the polymer EVA-28.

Table 3: Remnant content $BaSO_4$ of implants (average is given and range of 6 samples is given in brackets)

Batch	untreated [mg $BaSO_4$/implant]	Leached (18 days EtOH/H_2O) [mg $BaSO_4$/implant]
Core with 11.5 wt% $BaSO_4$	14.7 (14.5 – 14.8)	14.9 (14.7 – 15.1)
Core with 8 wt% $BaSO_4$	10.3 (10.2 – 10.4)	9.5 (9.4 – 9.6)
Core with 15 wt% $BaSO_4$	19.7 (19.4 – 20.1)	19.5 (19.4 – 19.6)

EXAMPLE 9 – comparison of X-ray visibility between implant containing barium sulphate in the core, and implant without barium sulphate (Implanon)

X-ray photographs (at 26 KW and 0.6 mAs) were taken from implants and subsequently the X-ray visibility between implants having barium sulphate in the core versus x-ray visibility of implants without barium sulphate (Implanon) were compared. Figure 11 demonstrates that incorporation of barium sulphate into the core greatly improved the X-ray visibility of the implant. The implant with only 4 wt% barium sulphate content in the core (sample 4) is clearly visible while the Implanon (sample 1) implant without the barium sulphate is not.

The measured transmission of X-ray is a quantitative value for the X-ray visibility of the implants. The number represents the X-ray exposure (pixels per area) of a X-ray camera (transmission X-rays). Table 4 and Figure 12 show that the amount of X-ray transmission of the implant with a low barium sulphate content in the core of 4 wt% (sample 4) is significantly different from the implant without $BaSO_4$ (sample 1).

Table 4: X-ray visibility of implant with and without $BaSO_4$

Sample no.	**BaS04 content**	**Transmission of X-ray [pixels/area]**	
	[wt.%]	**Mean [n=4]**	**SD**
1	0	1588	21
2	11.5	736	28
3	11.5	729	29
4	4	1140	29
5	20	486	24
6	30	292	17

EXAMPLE 10 – Hormone release profile of implant containing barium sulphate in the core in comparison to hormone release profile of commercially available Implanon (no barium sulfate)

In-vitro release rate profiles of the implants were tested by two methods. An accelerated release rate method was performed by testing the implant in an ethanol/water (90/10) solution. For the real time release rate method the in-vitro release profile was tested in water. For both tests the release profile of an implant containing barium sulphate in the core was compared to the profile of Implanon without barium sulphate.

Implants were manufactured loaded with 4, 20 and 30 wt% barium sulphate in the core. The resulting accelerated release profiles are shown in Figure 13 which demonstrates that all release profiles are similar and that within the tested range of barium sulphate content of the core (0-30 wt%) the radio-opaque component does not influence the release of hormones from the device. The same conclusion can be drawn from the real time release profiles up to 76 days (Figure 14), i.e. within the tested range of barium sulphate content of the core (0-30 wt%) the radio-opaque component does not influence the release of hormones from the device.

These conclusions were substantiated by calculating F1 values. The F1 values were calculated for both accelerated release rate profiles (up to and including 18 days) as real time release rate profiles (up to and including 76 days) taking the 0 wt% implant release profiles as reference. The results are given in Table 5. F1 values up to 15 (0-15) provide assurance of the sameness or equivalence of the two curves.

Table 5: F1 values for Implants loaded with 4, 20 and 30 wt% barium sulphate in the core

Barium sulphate [wt%]	**Accelerated release**	**Real time release**
4	4.2	2.9
20	5.8	6.9

Barium sulphate [wt%]	Accelerated release	Real time release
30	6.8	7.5

EXAMPLE 11: Migration of barium sulphate particles out of implant with open ends

To reveal the distribution of barium sulphate in the implant and to obtain an impression of the loss of barium sulphate particles upon leaching, cryogenic sections were made of implants using a ultramicrotome. Subsequently the sections of the implants were analyzed using Scanning Electron Microscopy / Energy Dispersed Xspectroscopy (SEM/EDX) before and after leaching. Leaching the implants leads to removal of the etonogestrel crystals from the implant. By examining before and after leaching information is obtained on the morphology of the barium sulphate/etonogestrel/EVA-28 blend. A back scatter electron (BSE) detector was used for imaging. In the BSE image the presence of barium sulphate particles is easily recognized by the high brightness of the barium sulphate particles.

Figure 15 reveals the morphology of implants in which the core is loaded with about 4, 20 and 30 wt% barium sulphate. It can be seen that the bright spots, representing barium sulphate, are mainly located in the EVA-28 material, i.e. the irregular shaped grey/black spots, representing etonogestrel crystals, contain no bright spots. Figure 16 reveals the same samples that were leached . The blank part is the skin material while the part containing the bright spots shows the leached core. Dark holes are clearly visible. The holes, representing the location at which etonogestrel crystals were present before leaching, hardly contain any bright spots.

The content barium sulphate in several batches was also tested using incineration before and after leaching (18 days in ethanol/water (90/10)). This gives information on possible migration of barium sulphate crystals out of the implant after the etonogestrel crystals were leached out of the implant. The results (table 6) show that there is no major change

in content of barium sulphate upon leaching. It can therefore be concluded that no or hardly any barium sulphate crystals migrated out of the implant through the open ends.

By combining Figures 15 and 16 with the results in Table 6 it can be concluded that hardly any radio-opaque component (shown by the bright spots) was encapsulated by the hormone crystals and that most of the radio- opaque component was encapsulated by the polymer EVA-28.

Table 6: Remnant content $BaSO_4$ of implants (average is given and range of 6 samples is given in brackets)

Batch	**Untreated [mg $BaSO_4$/implant]**	**Leached (18 days EtOH/H_2O) [mg $BaSO_4$/implant]**
Core with 4 wt% $BaSO_4$	5.0 (4.9 – 5.1)	5.6 (5.5 – 5.6)
Core with 20 wt% $BaSO_4$	26.2 (26.0 – 26.3)	26.8 (26.6 – 26.9)
Core with 30 wt% $BaSO_4$	45.6 (45.4 – 45.8)	45.2 (45.1 – 45.4)

CLAIMS

1. An X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone replacement therapy comprising one compartment consisting of (i) a thermoplastic polymer core loaded with (a) a contraceptively effective or therapeutically effective amount of desogestrel or 3-ketodesogestrel and (b) about 4-30% by weight radio-opaque material and (ii) a non-medicated thermoplastic polymer skin covering the core.

2. An X-ray visible drug delivery device according to claim 1 wherein the radio-opaque material is about 6-20% by weight

3. An X-ray visible drug delivery device according to claim 1 wherein the radio-opaque material is about 8-15% by weight.

4. An X-ray visible drug delivery device according to any one of the preceding claims wherein the radio-opaque material in the core does not affect the release of the desogestrel or 3-ketodesogestrel from the device.

5. An X-ray visible drug delivery device according to any one of the preceding claims wherein the radio-opaque particles do not migrate out of the implant.

6. An X-ray visible drug delivery device according to any one of the preceding claims wherein the radio-opaque material is barium sulphate.

7. An X-ray visible drug delivery device according to any one of the preceding claims wherein the device is an implant.

8. An X-ray visible drug delivery device according to any one of the preceding claims wherein the thermoplastic polymer is polyethylene vinyl acetate.

9. An X-ray visible drug delivery device for subdermal administration of a contraceptive or hormone replacement therapy comprising one compartment consisting of (i) a thermoplastic polymer core loaded with a contraceptively effective or therapeutically effective amount of desogestrel or 3-ketodesogestrel and containing an inert metal wire and (ii) a non-medicated thermoplastic polymer skin covering the core.

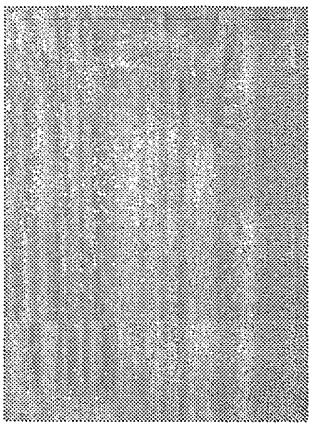
10. An X-ray visible drug delivery device according to claim 9 wherein the metal wire in the core does not affect the release of the desogestrel or 3-ketodesogestrel from the device.

11. An X-ray visible drug delivery device according to claims 9 or 10 wherein the inert metal wire is a titanium wire.

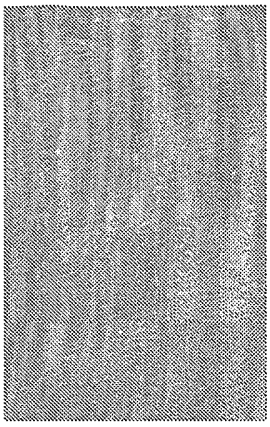
12. An X-ray visible drug delivery device according to any one of claims 9-11 wherein the device is an implant.

13. An X-ray visible drug delivery device according to any one of claims 9-12 wherein the thermoplastic polymer is polyethylene vinyl acetate.

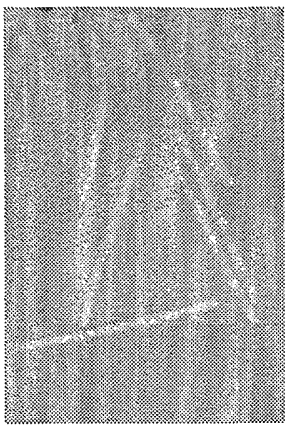
Figure 1



a) No $BaSO_4$ (Implanon)

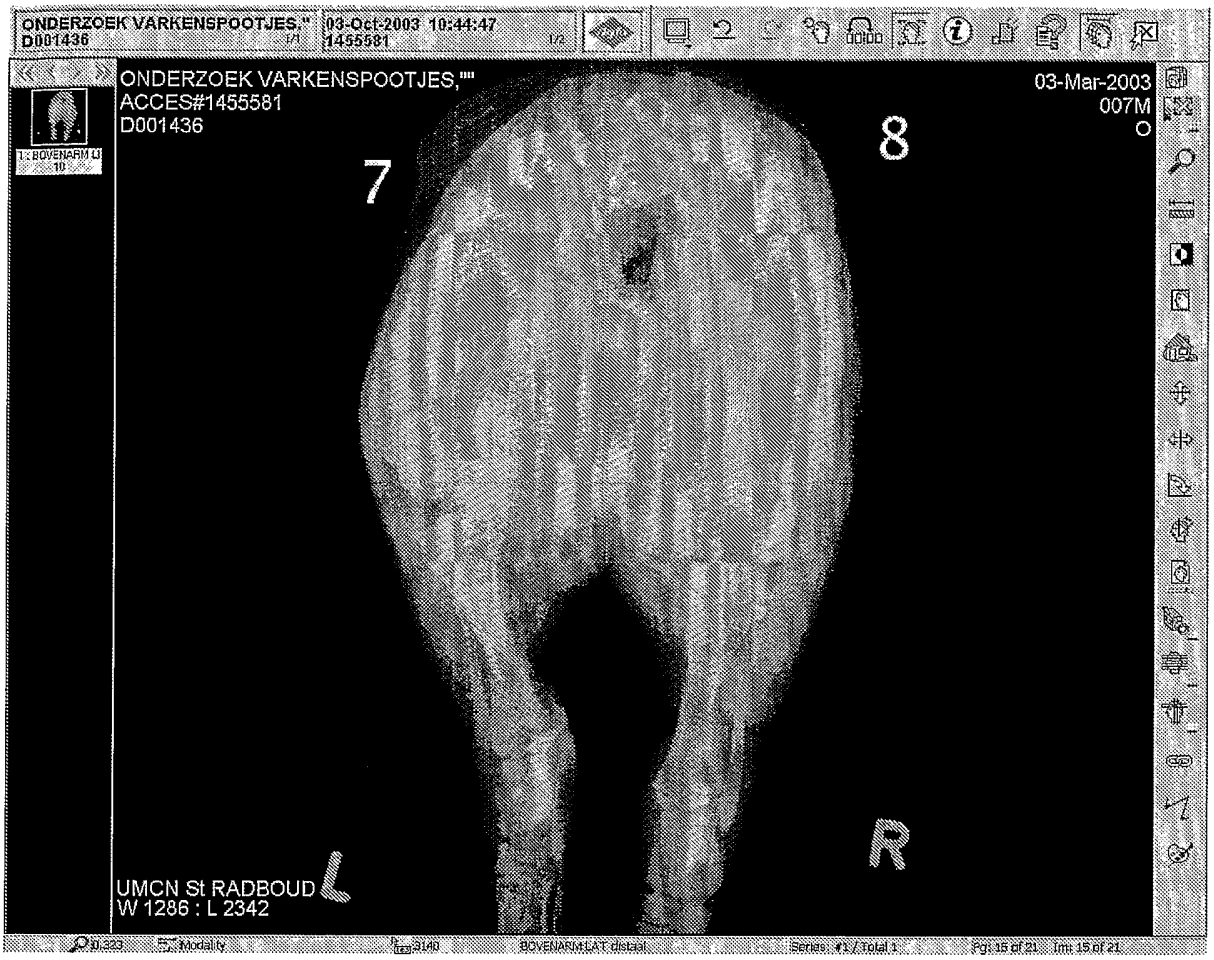


b) 20wt% $BaSO_4$ in skin



c) 11.5 wt% $BaSO_4$ in core

Figure 2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ACCES#1455581
D001436
03-Mar-2003
007M
O
7
8
L
R
UMCN St RADBOUD
W 1286 : L 2342

Figure 3

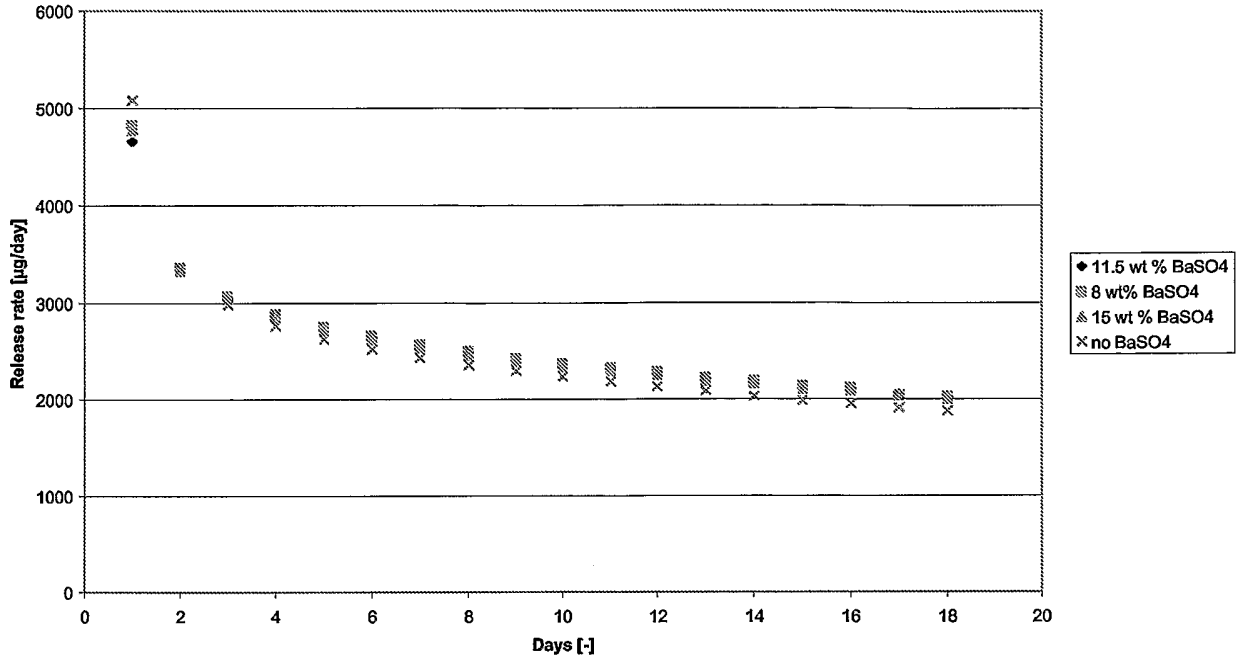

6000
5000
4000
3000
2000
1000
0
Release rate [µg/day]
0
2
4
6
8
10
12
14
16
18
20
Days [-]
11.5 wt % BaSO4
8 wt% BaSO4
15 wt % BaSO4
no BaSO4

Figure4

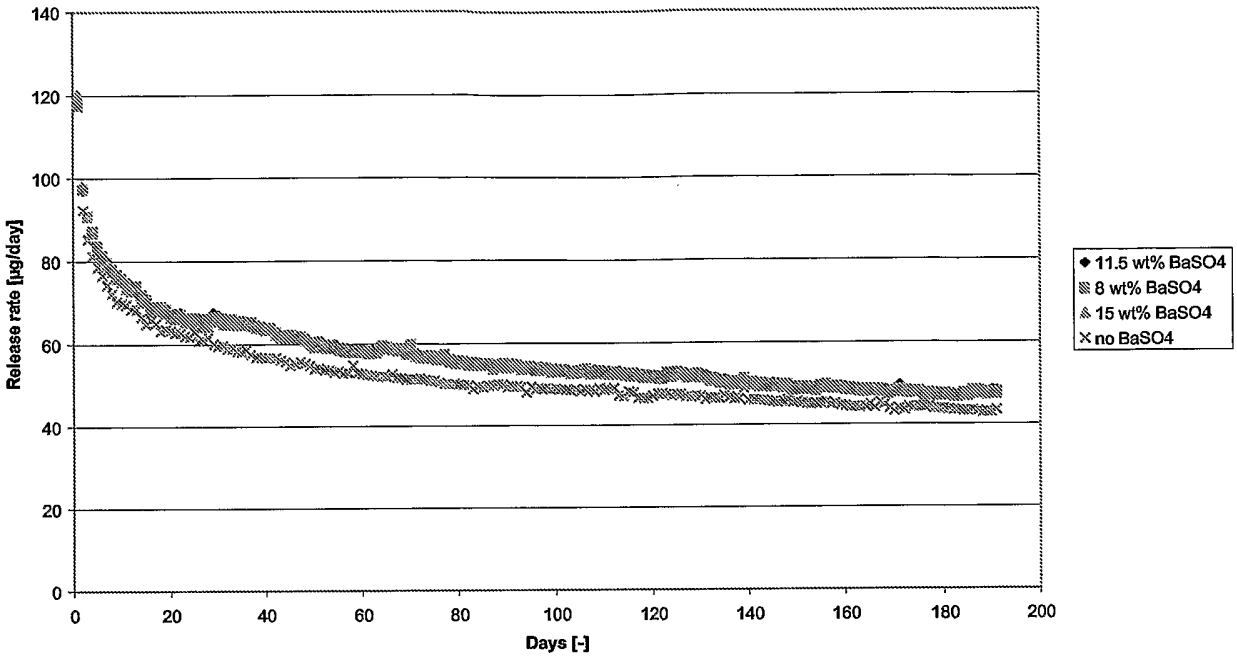
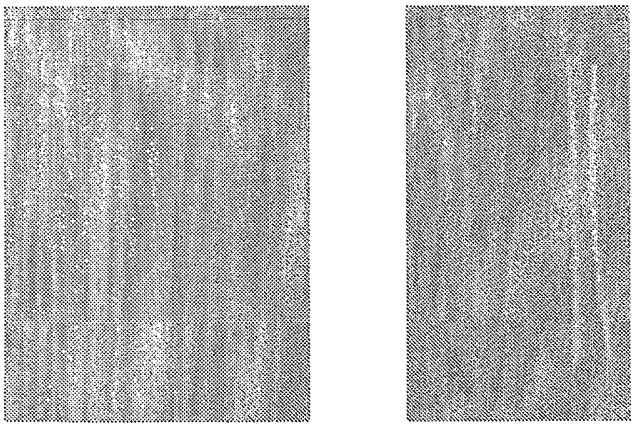

140
120
100
80
60
40
20
0
Release rate [µg/day]
0
20
40
60
80
100
120
140
160
180
200
Days [-]
11.5 wt% BaSO4
8 wt% BaSO4
15 wt% BaSO4
no BaSO4

Figure 5



a) No wire (Implanon) b) 0.5 mm wire

Figure 6:

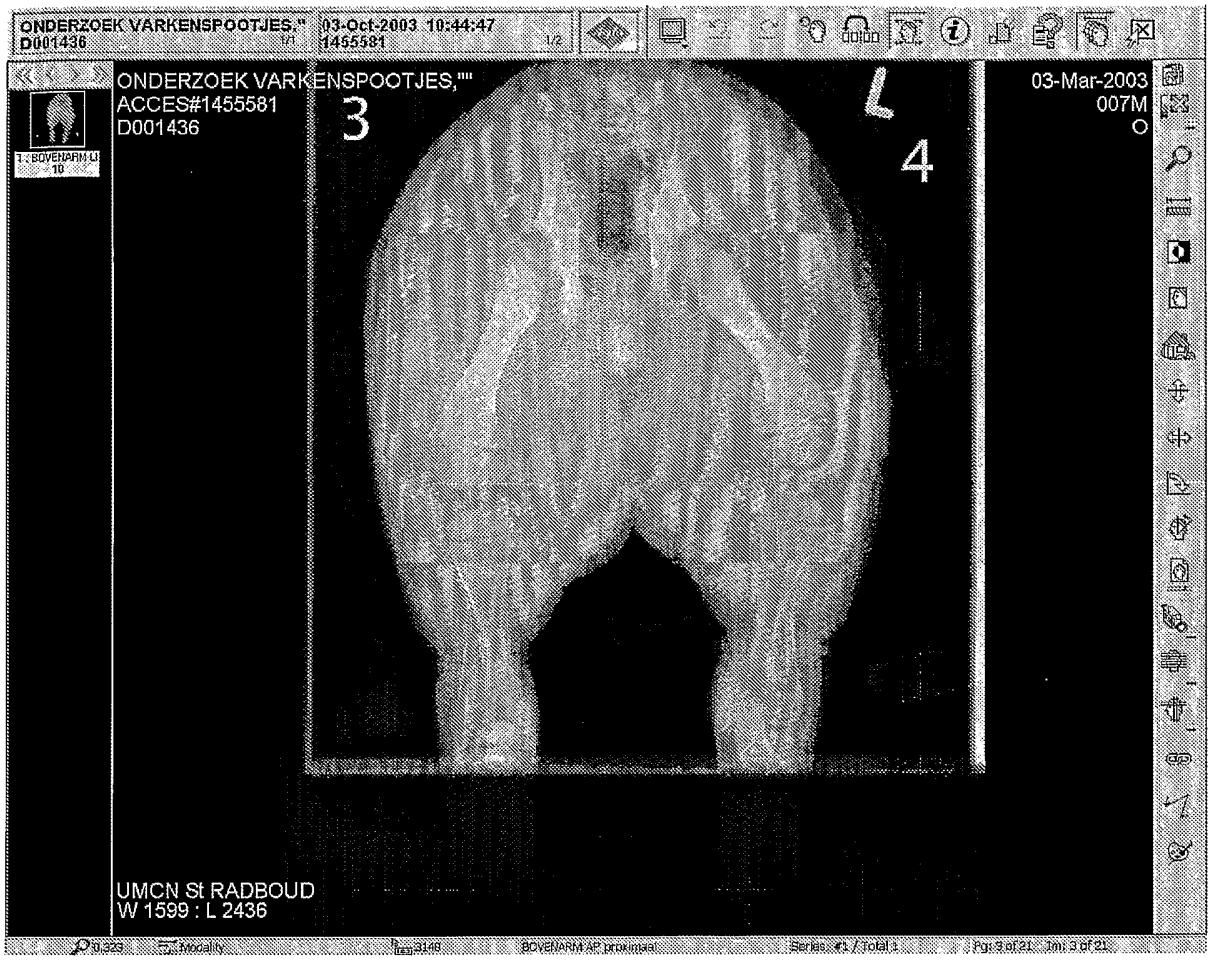

ONDERZOEK VARKENSPOOTJES,""
ACCES#1455581
D001436
03-Mar-2003
007M
3
L
4
UMCN St RADBOUD
W 1599 : L 2436

Figure 7

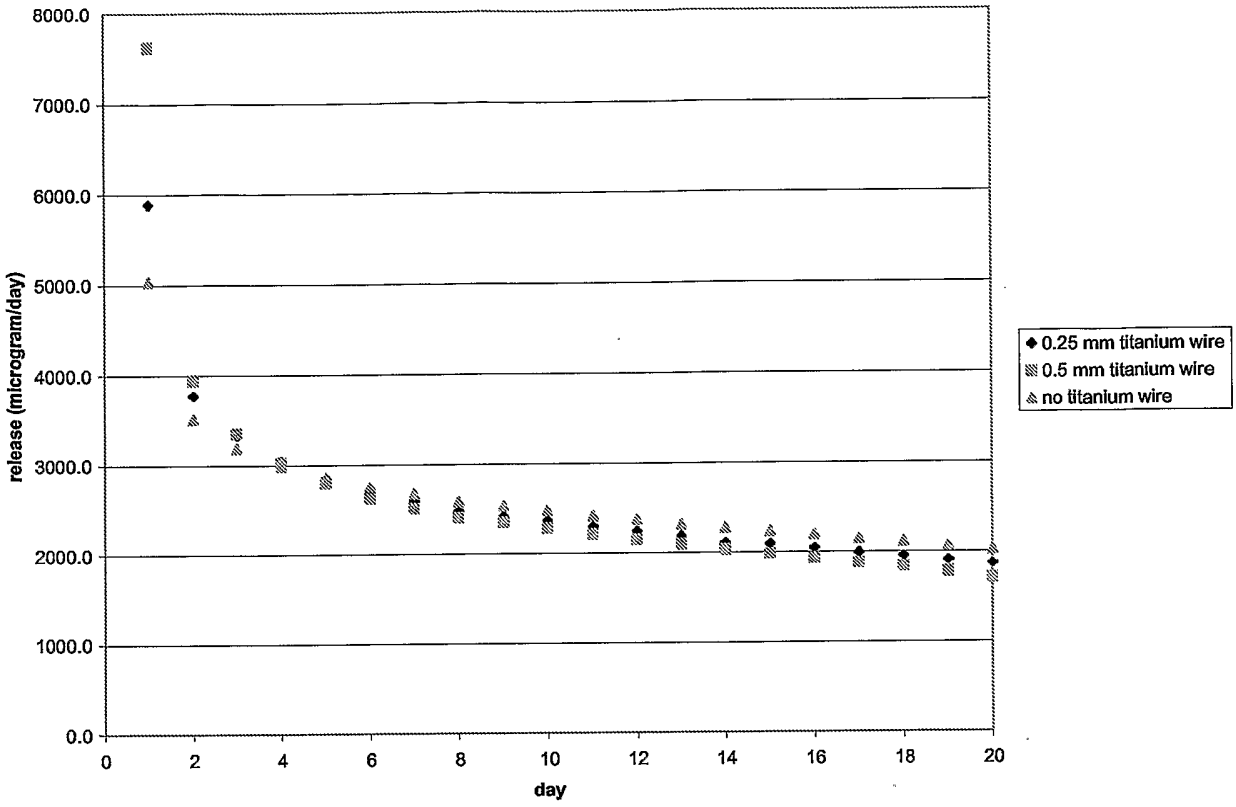

8000.0
7000.0
6000.0
5000.0
4000.0
3000.0
2000.0
1000.0
0.0
release (microgram/day)
0
2
4
6
8
10
12
14
16
18
20
day
0.25 mm titanium wire
0.5 mm titanium wire
no titanium wire

Figure 8

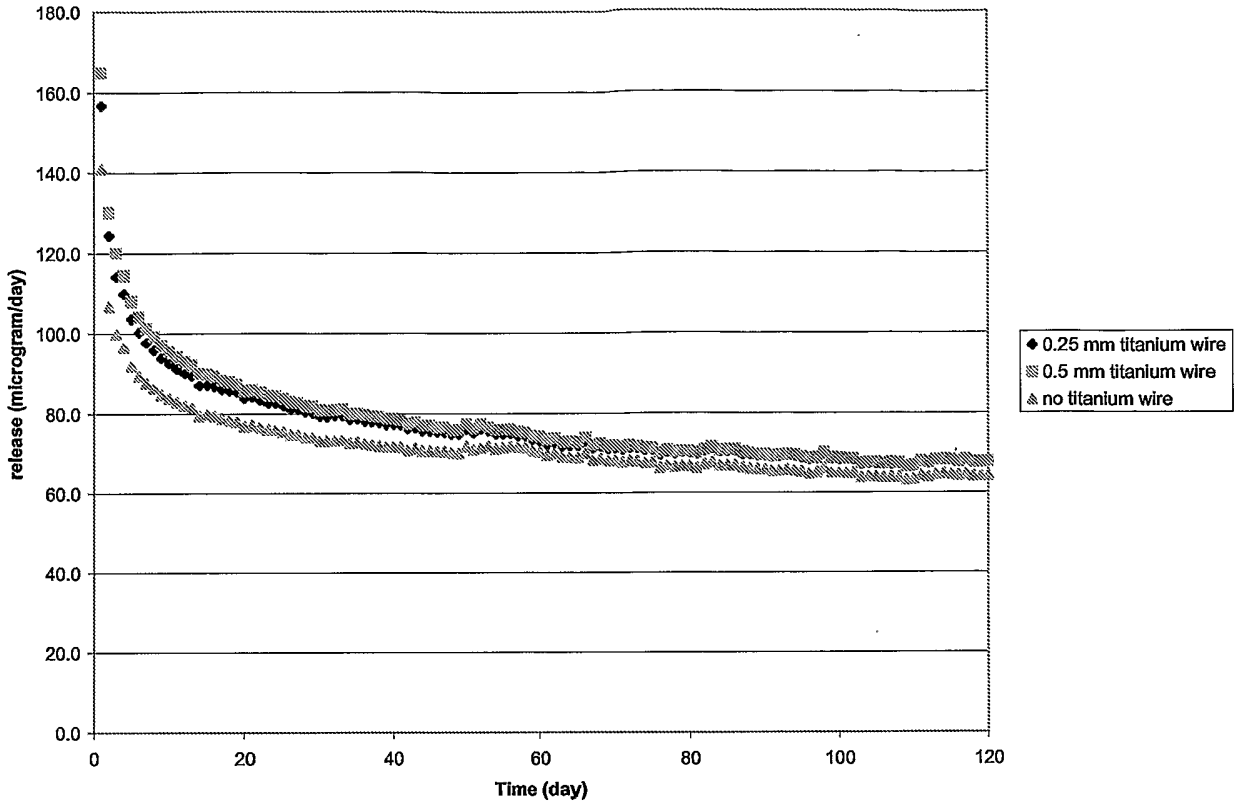

180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
release (microgram/day)
0
20
40
60
80
100
120
Time (day)
0.25 mm titanium wire
0.5 mm titanium wire
no titanium wire

Figure 9:

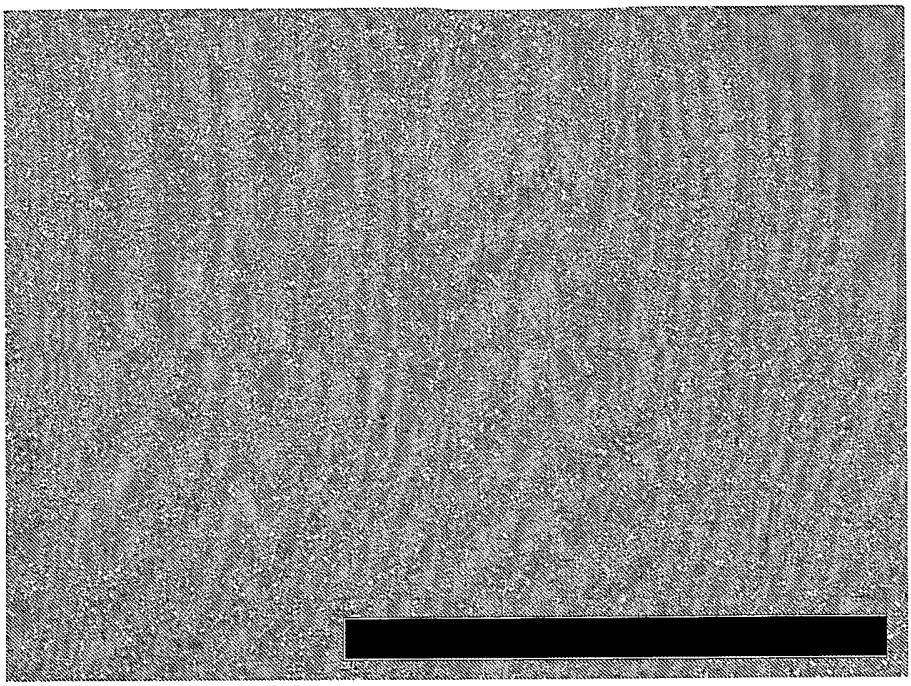


Figure 10:

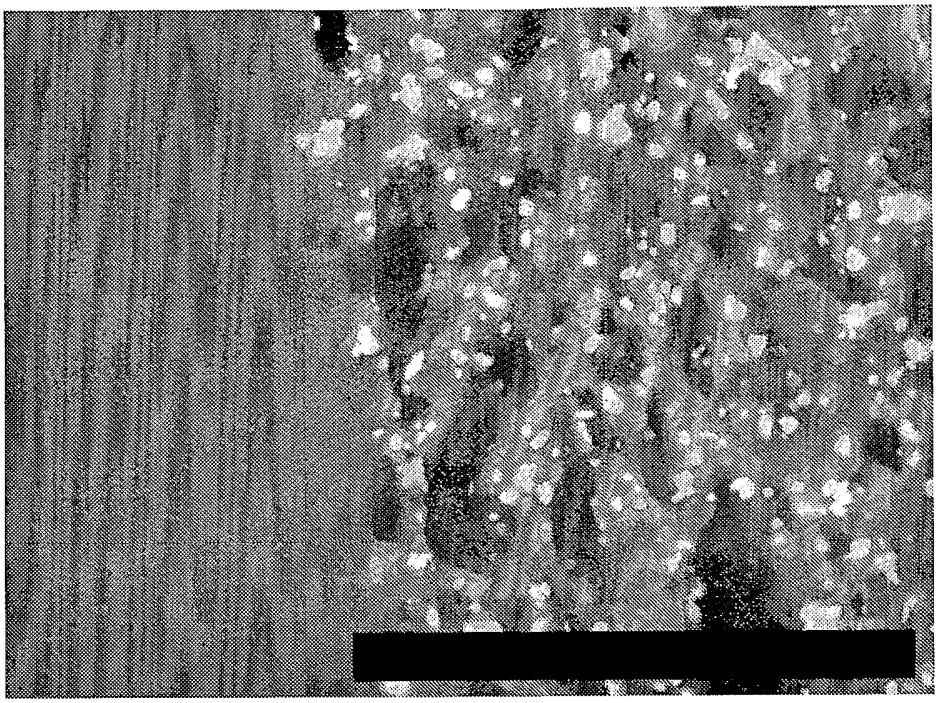
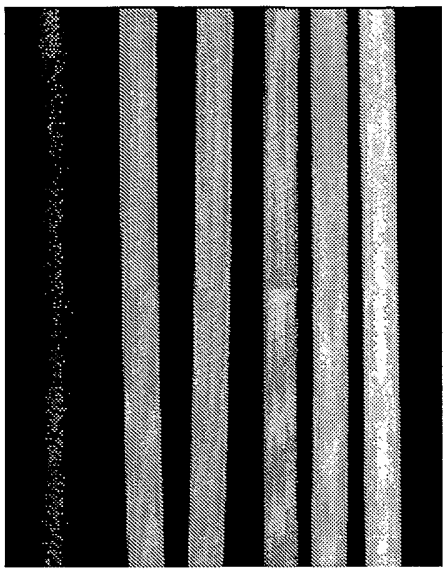


Figure 11



Sample no.: 1 2 3 4 5 6

Figure 12

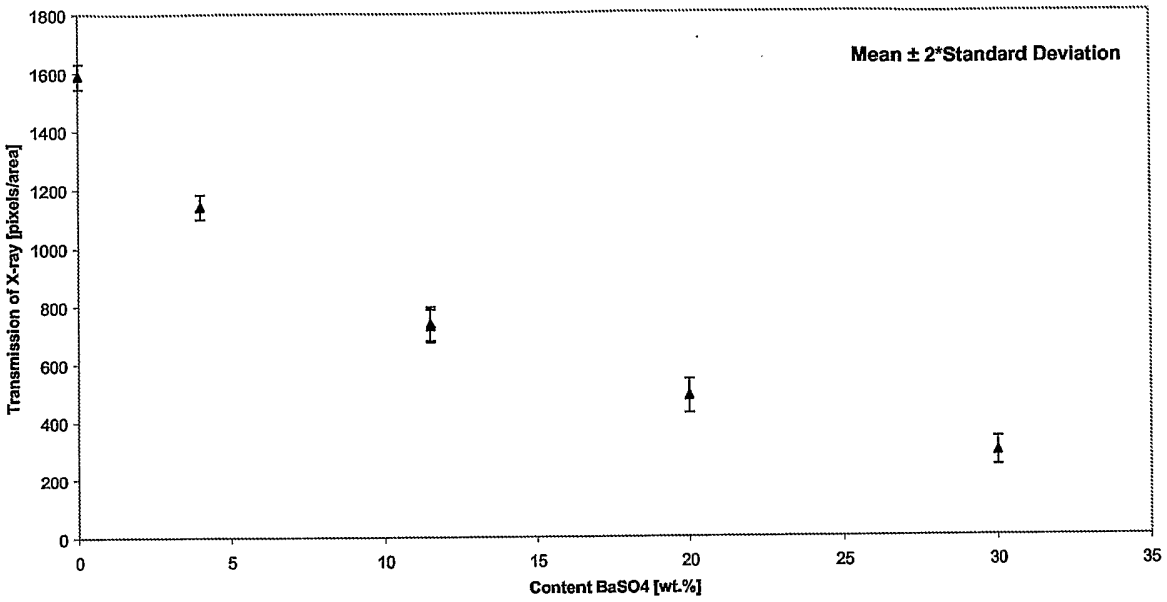

Mean ± 2*Standard Deviation
Transmission of X-ray [pixels/area]
Content BaSO4 [wt.%]
1800
1600
1400
1200
1000
800
600
400
200
0
0
5
10
15
20
25
30
35

Figure 13

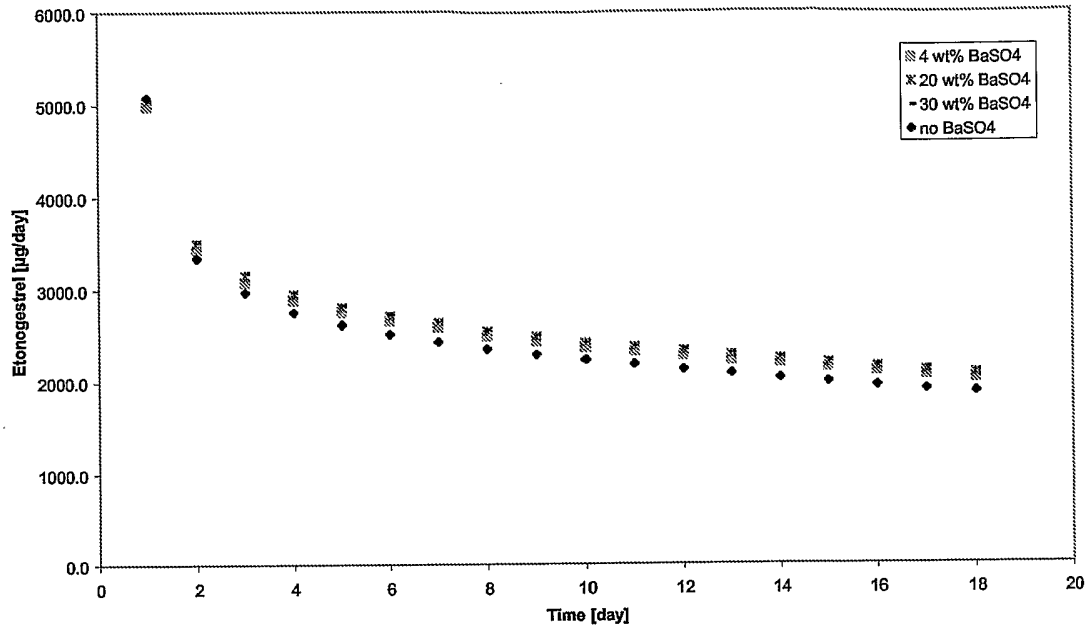

6000.0
5000.0
4000.0
3000.0
2000.0
1000.0
0.0
Etonogestrel [µg/day]
0
2
4
6
8
10
12
14
16
18
20
Time [day]
4 wt% BaSO4
20 wt% BaSO4
30 wt% BaSO4
no BaSO4

Figure 14

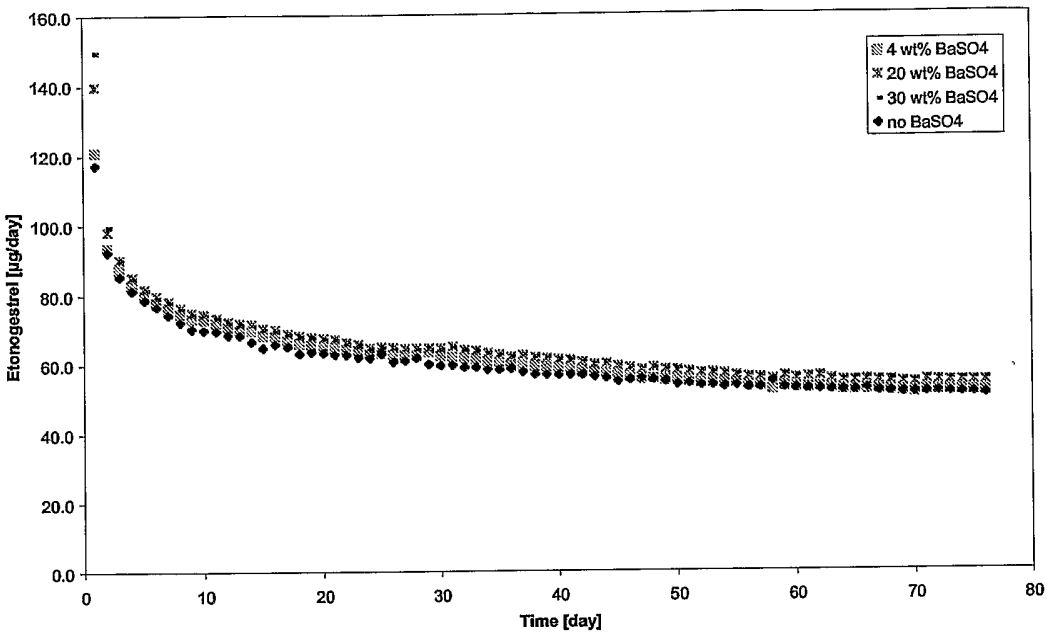
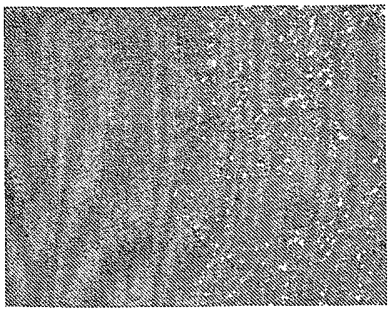
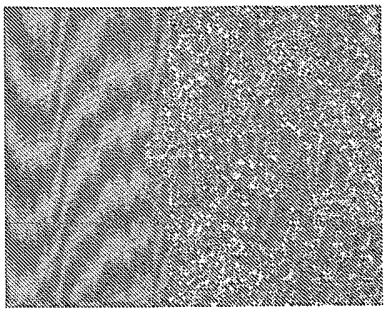

160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Etonogestrel [µg/day]
0
10
20
30
40
50
60
70
80
Time [day]
4 wt% BaSO4
20 wt% BaSO4
30 wt% BaSO4
no BaSO4

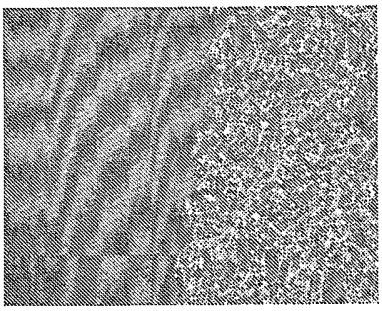
Figure 15



a) 4 wt% $BaSO_4$

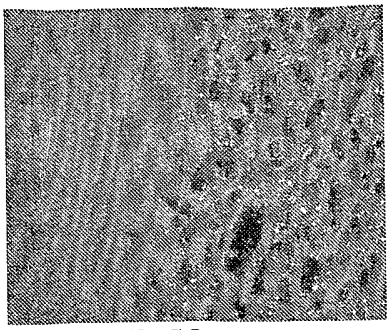


b) 20 wt% $BaSO_4$

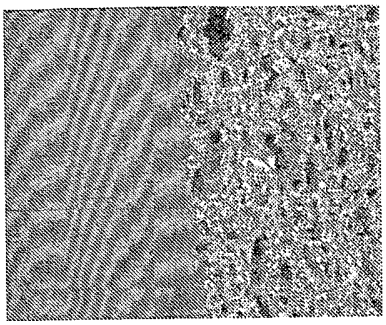


c) 30 wt% $BaSO_4$

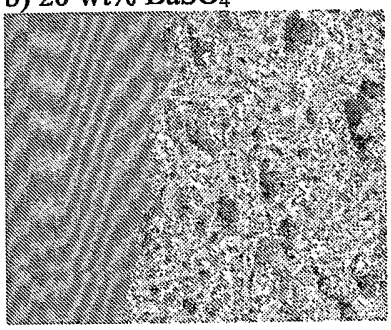
Figure 16



a) 4 wt% $BaSO_4$



b) 20 wt% $BaSO_4$



c) 30 wt% $BaSO_4$

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/051150

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K49/04 A61K9/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/153983 A1 (MILLER KATHLEEN M ET AL) 14 August 2003 (2003-08-14) claims 1-35 paragraph [0022] - paragraph [0063]	1-13
Y	examples 1-3	1-13
X	WO 2004/011055 A (SCIMED LIFE SYSTEMS INC) 5 February 2004 (2004-02-05) claims 1-42 paragraphs [0031] - [0039], [0042] - [0055], [0060] - [0067], [0075] - [0083], [0090] - [0101], [0107]	1-13
Y	EP 0 303 306 A (AKZO NV) 15 February 1989 (1989-02-15) claims 1-5 example 1	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2005	02. 08. 2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schifferer, H

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/051150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 168 257 A (LRC PRODUCTS) 18 June 1986 (1986-06-18) cited in the application page 2, left-hand column, line 21 - page 2, left-hand column, line 25 claims 1-3	1-13
A	US 2003/059371 A1 (MATSON LOUIS R ET AL) 27 March 2003 (2003-03-27) paragraph [0015] - paragraph [0022] claims 1-14	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/051150

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1476205 A1	17-11-2004
		WO 03066119 A1	14-08-2003
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