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PRECURSEURS D'ESTRADIOL-17 β
(54) Title: INTRAVAGINAL DRUG DELIVERY DEVICES FOR THE ADMINISTRATION OF 17 β -OESTRADIOL
PRECURSORS

(57) **Abrégé/Abstract:**

The invention relates to an intravaginal drug delivery device for administration to a female mammal of certain 17 β -oestradiol precursors at a substantially constant rate for a period of at least three weeks. The 17 β -oestradiol precursor is a 17 β -oestradiol moiety in which the, or each, hydroxyl group of the 17 β -oestradiol moiety is blocked by a blocking group, which blocking group is readily removed from the 17 β -oestradiol moiety in vivo. The 17 β -oestradiol precursor must either have a solubility in liquid silicone of not less than 0.1 mg/100 ml or have a standard k value of not less than 0.1 μ g/day/mm. The 17 β -oestradiol precursor must also have a solubility in distilled water of not less than 1 μ g/100 ml.



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(21) International Application Number: PCT/IE95/00063 (22) International Filing Date: 19 December 1995 (19.12.95) (30) Priority Data: <table border="0"> <tr> <td>S940976</td> <td>19 December 1994 (19.12.94)</td> <td>IE</td> </tr> <tr> <td>S950247</td> <td>5 April 1995 (05.04.95)</td> <td>IE</td> </tr> </table> (71) Applicant (for all designated States except US): GALEN (CHEMICALS) LIMITED [IE/IE]; Burton Hall Park, Sandyford Industrial Estate, Foxrock, Dublin 18 (IE). (72) Inventor; and (75) Inventor/Applicant (for US only): McCLAY, Allen [GB/GB]; 56 Tullagh Road, Cookstown, Co. Tyrone BT80 9RJ (GB). (74) Agent: O'CONNELL, Maura; F.R. Kelly & Co., 27 Clyde Road, Ballsbridge, Dublin 4 (IE).		S940976	19 December 1994 (19.12.94)	IE	S950247	5 April 1995 (05.04.95)	IE	(81) Designated States: AL, AM, AT, AT (Utility model), AU, BB, BG, BR, BY, CA, CH, CN, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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(54) Title: INTRAVAGINAL DRUG DELIVERY DEVICES FOR THE ADMINISTRATION OF 17β-OESTRADIOL PRECURSORS (57) Abstract The invention relates to an intravaginal drug delivery device for administration to a female mammal of certain 17β-oestradiol precursors at a substantially constant rate for a period of at least three weeks. The 17β-oestradiol precursor is a 17β-oestradiol moiety in which the, or each, hydroxyl group of the 17β-oestradiol moiety is blocked by a blocking group, which blocking group is readily removed from the 17β-oestradiol moiety <i>in vivo</i>. The 17β-oestradiol precursor must either have a solubility in liquid silicone of not less than 0.1 mg/100 ml or have a standard k value of not less than 0.1 μg/day/mm. The 17β-oestradiol precursor must also have a solubility in distilled water of not less than 1μg/100 ml.								

INTRAVAGINAL DRUG DELIVERY DEVICES FOR THE
ADMINISTRATION OF 17 β -OESTRADIOL PRECURSORS

This invention relates to intravaginal drug delivery devices for the administration of 17 β -oestradiol precursors. The term "17 β -oestradiol precursor" is intended to embrace certain compounds which can be converted into 17 β -oestradiol, which compounds possess physicochemical and clinical properties as defined hereinbelow. In particular, the present invention relates to intravaginal drug delivery devices for the administration of a 17 β -oestradiol precursor at a substantially constant rate over a prolonged period for oestrogen-requiring conditions such that either the symptoms associated with hypo-oestrogenism may be alleviated or prevented or, alternatively, fertility is controlled. More particularly, the invention relates to, but is not limited to, an intravaginal drug delivery device for the administration of a 17 β -oestradiol precursor for hormone replacement therapy in the human female.

Hypo-oestrogenism in the premenopausal human female may occur due to disease, oophorectomy or traumatic injury [2]. In the postmenopausal human female, hypo-oestrogenism occurs as a natural consequence of the ageing process. Fertility control involves the administration of sufficient oestrogen to prevent ovulation, in effect, an induced hyper-oestrogenism. The description hereinafter primarily concerns the utility of intravaginal drug

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delivery devices of the invention for the alleviation or prevention of symptoms associated with hypo-oestrogenism, specifically, hormone replacement therapy, but it will be appreciated that the
5 intravaginal drug delivery devices of the invention may also be used to induce hyper-oestrogenism, specifically, to prevent ovulation and, therefore, to act as a contraceptive.

10 In the normal, healthy human female, 17 β -oestradiol is the principal oestrogen produced by the functioning premenopausal ovary, primarily in the ovulating follicle, during each menstrual cycle [1]. Circulating 17 β -oestradiol levels vary during the
15 monthly cycle in the premenopausal human female, being at their highest during the peri-ovulatory phase (about 1000 pmol per litre). As ageing progresses in the human female, ovulation becomes less frequent and less predictable, resulting in diminished production of
20 17 β -oestradiol. At the menopause, when irreversible failure of ovarian follicular activity occurs, 17 β -oestradiol production decreases dramatically to less than 20 μ g per day, giving circulating levels of 17 β -oestradiol in serum of less than 30 pg/ml [2]
25 (1 pg/ml is equivalent to 3.676 pmol/l, assuming a molecular weight of 272 for oestradiol).

Non-oral 17 β -oestradiol preparations intended for use in hormone replacement therapy typically deliver
30 plasma levels of 17 β -oestradiol corresponding to mean levels of the hormone in the premenopausal subject at days 6 to 8 (about 200 pmol per litre) and days 8 to 10 (about 360 pmol per litre) of the cycle. For the transdermal route, which is one non-oral route, these

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plasma concentrations correspond to a dose of 50 μ g per day (low dose) to 100 μ g per day (high dose). This is generally accepted as the desirable non-oral dosage range in order to provide efficacious relief of postmenopausal symptoms whilst minimising potential toxicity [1].

Hypo-oestrogenic (including postmenopausal) symptoms may be classified [3] as:-

(a) Neuroendocrine symptoms, characterised by one or more of the following: hot flushes, night sweats, insomnia, mood changes, anxiety, irritability, loss of memory and loss of concentration.

(b) Lower urinogenital tract symptoms, characterised by one or more of the following: genital tract atrophy, dyspareunia, loss of libido, urethral syndrome.

(c) Miscellaneous symptoms, characterised by one or more of the following: joint aches, paraesthesia, dry skin, dry or brittle hair, brittle nails.

In those cases where the combination of symptoms is sufficiently severe, it is well recognised that oestrogen hormone replacement therapy is indicated. In the postmenopausal human female requiring such therapy, the aim is to restore premenopausal oestrogen balance by delivering the natural oestrogenic hormone, 17 β -oestradiol, to the systemic circulation in a pattern that mimics its physiological secretion, that is, continuously and at a low but effectively constant rate [4]. It is well recognised by practitioners that

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hormone replacement therapy, once initiated in the human female, may be necessary for many years extending from the onset of the menopause. A physiologically effective dose of 17β -oestradiol, sufficient to provide effective control of all postmenopausal symptoms, is considered to be at least $50 \mu\text{g}$ per day [1], although transdermal patches delivering as low as $25\mu\text{g}$ per day will elevate plasma oestradiol levels and are used in oestrogen replacement therapy.

Oral administration of oestrogen, including 17β -oestradiol, for hormone replacement therapy has a number of disadvantages [1,5]:-

(a) Oral administration of a drug is followed, primarily, by absorption through the gastrointestinal tract, from where the blood flow is to the liver. Some 60-90% of orally administered drug will be metabolised during this first pass through the liver. As a result, oral oestrogen therapy results in oestrone, a less potent oestrogen, as the predominant circulating oestrogen.

(b) Oral therapy involves bolus doses resulting in high initial oestrogen levels which are non-physiological, a non-steady state of circulating serum oestrogen and a non-physiological 17β -oestradiol:oestrone ratio.

Given the long-term nature of hormone replacement therapy, a drug delivery system that promotes improved patient compliance and convenience by reducing the dosing frequency or by requiring less frequent dosing is desirable. Various routes of oestrogen administration have been suggested, including

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transdermal, subcutaneous and intravaginal administration:-

5 Oestrogens are efficiently absorbed by the
transdermal route. First pass effects are avoided and
a physiological 17β -oestradiol:oestrone ratio is
maintained. Transdermal administration of
17 β -oestradiol is, therefore, preferable to the oral
route [4]. Patient compliance and convenience are also
10 enhanced. However, the physical size of the
transdermal drug delivery system is such that a new
device must be used every few days. This can lead to
fluctuations in circulating serum oestrogen levels,
which is inconvenient and has possible compliance
15 problems for the patient.

Subcutaneous implantation of
17 β -oestradiol-loaded pellets provides therapy
extending to several months and is therefore
20 advantageous in respect of both patient compliance and
convenience. However, subcutaneous implants have a
number of disadvantages [2]:-

(a) A surgical procedure is required for
25 insertion of the pellets.

(b) Infection can arise at the insertion site.

(c) The pellets are difficult to remove in the
30 event of a problem developing and any attempted removal
requires a further surgical exploration of the site.

Many of the problems associated with oestrogen
delivery for hormone replacement therapy and other

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long-term oestrogen-requiring conditions can be overcome by intravaginal administration of oestrogen. It is well-known that steroids in general, including oestrogens, are efficiently and rapidly absorbed through vaginal mucosal epithelium [6,7]. The vaginal route avoids undesirable first-pass hepatic metabolism. Delivery of oestrogen by the vaginal route is analogous to secretion of oestrogen into the systemic circulation by the ovary. Oestrogens may be administered intravaginally by the use of creams, solutions or vaginal tablets [2]. However, to achieve controlled-release of the oestrogenic agent, sustained over at least one month in order to enhance both patient compliance and convenience, an intravaginal device, optionally in the shape of a ring, is the most suitable drug delivery device. The intravaginal ring can be self-inserted high into the vagina where it is held in place.

U.S. Patent No. 3,545,439 discloses an intravaginal ring fabricated from a biocompatible organopolysiloxane elastomer and containing the steroidal compound medroxyprogesterone acetate for the purpose of providing contraception in the human female. There is no teaching that such a device can be used for the administration of 17 β -oestradiol precursors at a substantially constant (or zero order pattern) rate for a period of at least three weeks, for the treatment of long-term oestrogen-requiring conditions in general or, more specifically, for hormone replacement therapy.

An article by Jackanicz [8] teaches that three basic designs of intravaginal ring are possible, though additional design variations do exist:-

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(a) The homogeneous ring, in which the steroid is homogeneously distributed in a hydrophobic elastomeric system, typically a grade of Silastic (Trade Mark), which is commercially available from Dow Corning. In this design, a high drug loading is possible and, consequently, comparatively large daily release rates are achievable over prolonged periods. However, this design is associated with an initial high release of drug, producing a non-physiological level of the circulating steroid in the plasma, followed by a decline in the drug release rate as the outer portions of the ring are depleted of drug. Consequently, this design of ring cannot achieve the desired pattern of a controlled, substantially constant drug release rate, which will be recognised by those skilled in the art as zero order pattern release, over a sustained period of at least three weeks, preferably several months.

(b) The shell design, in which the steroid is contained in a narrow band or hollow annulus between a non-medicated central hydrophobic elastomeric core or central member and a narrow, outer non-medicated hydrophobic elastomeric sheath. The outer sheath acts as a metering, or rate-controlling, membrane. With this design, burst effects are reduced compared to the homogeneous ring. However, this design has the disadvantage that the drug reservoir is physically limited in size and the relative diameters of core, steroid band and rate-controlling sheath are such that, where comparatively high daily drug release rates are required, as in hormone replacement therapy, this design cannot achieve the desired pattern of a controlled, substantially constant comparatively high daily drug release rate for the desired period of at least three weeks, preferably several months. The shell design is, therefore, most suitable for contraception.

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(c) The core design, in which the steroid is homogeneously mixed with a hydrophobic elastomeric polymer to form a homogeneous core, the core being surrounded by a rate-controlling, non-medicated hydrophobic elastomeric sheath. In this design high drug loadings are possible and the relative diameters of core and rate-controlling sheath are such that a higher drug release rate can be achieved compared to the shell design. Burst release of drug is reduced, but not necessarily eliminated, as compared to the homogeneous ring design. Substantially zero order release can be achieved due to the presence of a rate-controlling sheath and such release can be sustained for several months due to the higher drug loading possible with this design.

Intravaginal elastomeric rings designed to deliver 17 β -oestradiol for use in hormone replacement therapy are known.

20

For example, a report by Englund and co-workers [9] discloses an intravaginal elastomeric ring of shell design releasing *in vitro* 17 β -oestradiol at a rate of 200 μ g per day, which corresponds to plasma 17 β -oestradiol levels in human female patients of from 50 to 200 pg per ml. In this report, it is further disclosed that all of the human female subjects participating in the study had non-physiologically high 17 β -oestradiol plasma levels in the first 24 hours of the study period and that there was a gradual decline in the plasma oestradiol levels over the study period of 21 days. There is no teaching in this study that substantially constant plasma levels of 17 β -oestradiol can be maintained even within the comparatively short-term study period of 21 days, nor is there any teaching to suggest that the device could be used for

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the delivery of a suitable 17β -oestradiol precursor compound. This study, however, does state that a 17β -oestradiol release rate of $200\text{ }\mu\text{g}$ per day is too high for hormone replacement therapy in post-menopausal women as the resulting plasma levels of 17β -oestradiol are non-physiological, that is, they exceed the oestrogen levels seen in the follicular phase of fertile women. The authors conclude, in agreement with the teaching of Lievertz [1], that a device with a release rate of $50\text{-}100\text{ }\mu\text{g}$ per day of 17β -oestradiol would provide an appropriate dosage for hormone replacement therapy.

A study by Roy and Mishell [10] discloses an elastomeric intravaginal ring comprising a polymer matrix containing a combination of levonorgestrel and 17β -oestradiol in dimethylpolysiloxane. This study teaches that 17β -oestradiol has a lower solubility in, and diffusion from, the dimethylpolysiloxane elastomer than levonorgestrel. The ring design in this example was of the shell type, which had an outer diameter of 58 mm and a thickness of 9.5 mm, and released $290\text{ }\mu\text{g}$ per day of levonorgestrel and $180\text{ }\mu\text{g}$ per day of 17β -oestradiol, respectively. The rings were studied over six or seven consecutive 21-day cycles. In each case, 17β -oestradiol absorption produced an initial peak for the first few days of each cycle, after which plasma levels declined rapidly. The initial 17β -oestradiol serum peak was due to burst release from the outer sheath, rather than from the polymer matrix, the burst effect then building up again during each week of storage between cycles.

Thus, the ring design disclosed in this study is unsuitable for sustained delivery of 17β -oestradiol for

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oestrogen-requiring conditions, including hormone replacement therapy.

A study by Stumpf et al [11] on hypo-oestrogenic women discloses an intravaginal ring of shell design intended specifically for use in hormone replacement therapy. The ring was 9.5 mm in cross-section and 54 mm in diameter. The steroid band or hollow annulus contained either 100, 200 or 400 mg of 17 β -oestradiol. One hour after insertion, mean serum 17 β -oestradiol was raised to 300 pg/ml, characteristic of a burst release of steroid, but approached the baseline level of 24 pg/ml within 24 hours. Over 1 month, the mean 17 β -oestradiol level increased minimally to about 50 pg/ml, falling back to the baseline at 2 and 3 months. The authors concluded that this design fails to provide effective therapeutic delivery of 17 β -oestradiol over a sufficiently long period as desired for hormone replacement therapy.

Stumpf et al [11] also discloses an alternative intravaginal ring of homogeneous design, comprising a polymer matrix containing 400 mg of 17 β -oestradiol in polydimethylsiloxane. This ring had a surface area of 22 cm² and a cross-sectional area of 48 mm². With this ring design, the initial serum 17 β -oestradiol level was raised to about 700 pg/ml within one hour, with the level maintained above 300 pg/ml for at least the first week of administration. Despite the authors' conclusion that this ring design maintains physiological oestradiol levels, it will be recognised by those skilled in the art that such levels of 17 β -oestradiol are non-physiological and, therefore, unacceptable for use in the human female requiring hormone replacement therapy.

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European Patent Publication No. 0 253 109
discloses an intravaginal ring of core design capable
of delivering 17 β -oestradiol at rates per 24 hours
varying from 0.5 to 25 μ g per day, preferably from 4 to
5 8 μ g per 24 hours, as selected. According to the
teaching therein, symptoms in the human female arising
from a hypo-oestrogenic condition can be alleviated by
17 β -oestradiol delivered at these rates. These rates
of 17 β -oestradiol delivery are substantially lower than
10 those generally recognised as being required to
alleviate all of the possible symptoms associated with
a hypo-oestrogenic condition - a daily delivery rate,
as determined *in vitro*, of between 50 and 100 μ g of
17 β -oestradiol is generally accepted by those skilled
15 in the art as necessary for effective hormone
replacement therapy [1] [9] [11] [12]. The symptoms
referred to in EP-A-0 253 109 relate exclusively to
symptoms associated with the lower urinogenital tract.
There is no teaching that such a low daily delivery
20 rate of 17 β -oestradiol can relieve neuroendocrine and
other miscellaneous symptoms associated with
hypo-oestrogenism in the human female.

Smith et al [13] teaches that daily delivery of
25 17 β -oestradiol at a rate of between 5 and 10 μ g per
day, as determined *in vitro*, is effective at
alleviating those symptoms associated with
hypo-oestrogenism that relate specifically to atrophy
of vaginal and urethral epithelium. There is no
30 teaching that other symptoms associated with
hypo-oestrogenism are relieved by such low daily doses
of 17 β -oestradiol.

A number of difficulties arise in incorporating
17 β -oestradiol into intravaginal drug delivery devices.

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Specifically, the drug is too polar in its chemical character to be practically delivered in sufficient daily quantities to alleviate all of the clinical symptoms typically associated with hypo-oestrogenism in the human female and, most particularly, in postmenopausal females requiring hormone replacement therapy with oestrogen. These difficulties mean that a daily drug release in excess of 50 μ g of 17 β -oestradiol, as determined *in vitro*, an amount clinically acknowledged as necessary for effective hormone replacement therapy, cannot be practically achieved since:

- A narrow sheath surrounding a large diameter polymer matrix is difficult to mass produce reliably to acceptable limits by methods presently known in the art.
- A high drug concentration is required in the polymer matrix of the device, which consequently must be of large diameter. Thus, such devices are uneconomic to produce.
- The high drug residue left after use raises environmental concerns.
- It is not possible to include an additional active ingredient in known intravaginal drug delivery devices, typically a progestogen.

According to a first aspect of the invention there is provided an intravaginal shell or core drug delivery device suitable for administration to a female mammal, the device comprising a 17 β -oestradiol precursor as defined hereinbelow in a polymer matrix and having a sheath surrounding the polymer matrix, said device being adapted to release the 17 β -oestradiol precursor in a substantially zero order pattern for at least three weeks, preferably for at least three months and to release up to 1 mg/day 17 β -oestradiol.

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The 17 β -oestradiol precursor must:

- be a 17 β -oestradiol moiety in which the, or each, hydroxyl group of the 17 β -oestradiol moiety is blocked by a blocking group; the, or each, blocking group being so linked to the 17 β -oestradiol moiety as to be readily removed from the 17 β -oestradiol moiety *in vivo* and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the female mammal, when removed from the 17 β -oestradiol moiety *in vivo*.
- have sufficient lipophilicity as defined hereinbelow.
- have sufficient hydrophilicity as defined hereinbelow.

Specifically, the 17 β -oestradiol precursors must have sufficient lipophilicity as determined directly by measurement of their solubilities in liquid silicone (Dow Corning Grade 360 Medical Fluid) at 37°C such that their solubilities must be not less than 0.1 mg per 100 ml or, alternatively, as determined indirectly by measurement of standard k (to be defined hereinafter) such that standard k must be not less than 0.1 μ g/day/mm. Such lipophilicity is required to ensure adequate diffusion of the precursor through the device.

Specifically, the 17 β -oestradiol precursors must have sufficient hydrophilicity such that their solubilities in distilled water at 20°C are not less than 1 μ g per 100 ml. Such hydrophilicity is required to ensure that an adequate concentration of the precursor is achieved in the aqueous diffusion layer between the device and the vaginal epithelium.

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Precursor release from a cylindrical device of core design, which comprises a polymer matrix in the form of a core incorporating 17 β -oestradiol precursor and a sheath surrounding the core, can be described by
 5 Crank's equation:-

$$R = \frac{2 \cdot \pi \cdot C_s \cdot l \cdot D}{\ln(b/a)}$$

10 in which

R = precursor release rate ($\mu\text{g/day}$)

C_s = saturation solubility of precursor in polymer matrix ($\mu\text{g/ml}$)

15 D = diffusion coefficient of precursor in polymer matrix (cm^2/day)

π = partition coefficient of precursor between polymer matrix and the dissolution medium

l = core length (mm)

20 b = sheath cross-sectional diameter (mm)

a = core cross-sectional diameter (mm)

Crank's equation relates the precursor release rate (R), in sink conditions, to the solubility (C_s) and diffusibility (D) of the precursor in the polymer matrix, its partition characteristics (π) between the polymer matrix and the dissolution medium; and the ring dimensions (l, b, a). For any given precursor in any given polymer matrix, C_s , D and π will be constant and
 25 can be grouped together to form the composite constant, k:-
 30

$$k = 2C_s \cdot D \cdot \pi$$

35 The k value can be empirically derived using Crank's equation in the following manner:-

- 15 -

$$k = \frac{R \cdot \ln(b/a)}{l}$$

The k value is dependent on core length for certain of the 17 β -oestradiol precursors (see Example 6 hereinafter). Accordingly, the k value at a core length of 35 mm has been denoted "standard k" value hereinafter.

The use of 17 β -oestradiol precursors with enhanced lipophilicity, relative to 17 β -oestradiol itself, is one parameter involved in overcoming the difficulties which arise in incorporating 17 β -oestradiol itself into intravaginal drug delivery devices. However, only 17 β -oestradiol precursors possessing the above-recited additional physicochemical property of sufficient hydrophilicity and clinical characteristics of ready *in vivo* conversion to 17 β -oestradiol without yielding toxic substances as a result of that conversion, are suitable for use in intravaginal devices for the delivery of therapeutic quantities of oestrogen to the human female for long-term oestrogen-requiring conditions, including hormone replacement therapy. In addition, such 17 β -oestradiol precursors are also suitable for fertility control. Thus, for example, 17 β -oestradiol-17-valerate, a highly hydrophobic precursor, will not give detectable blood levels of 17 β -oestradiol in the human female when delivered intravaginally from an intravaginal drug delivery device, since its hydrophilicity or aqueous solubility is too low. The invention therefore defines the characteristics of 17 β -oestradiol precursors, and identifies those suitable precursors, such that an intravaginal drug delivery device containing said precursors will deliver therapeutic quantities of

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17 β -oestradiol to the female mammal without any of the disadvantages previously associated with such systems.

5 Whilst it will be apparent that said intravaginal drug delivery device can have any shape and be of any dimensions compatible both with intravaginal administration to the female mammal, including the human female and with the requirements imposed by drug delivery kinetics, a particularly preferred device
10 according to the present invention is an intravaginal ring.

Said ring includes the outer, rate-controlling sheath surrounding the polymer matrix in the form of a
15 core, which sheath may be fabricated from the same polymer as that of the polymer matrix or from any other suitable, compatible polymer known in the art. Alternatively, said ring includes the sheath surrounding the polymer matrix in the form of a hollow
20 annulus and the device is provided with a central member within the annulus, which sheath and central member may each be fabricated from the same polymer as that of the polymer matrix or from any other suitable, compatible polymer known in the art.

25 More preferably, daily release rates of the 17 β -oestradiol precursor equivalent to up to 1 mg per day of 17 β -oestradiol itself can be sustained for up to at least 12 months in a substantially zero order
30 pattern.

Preferably, said intravaginal drug delivery device additionally includes a progestogen in the polymer matrix, the progestogen being selected from the group

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comprising norethisterone-17-acetate and
levonorgestrel. Said 17β -oestradiol precursor can be
delivered in a substantially zero order pattern for
durations of at least three weeks and, preferably, up
5 to 12 months at rates of delivery equivalent to up to 1
mg per day of 17β -oestradiol itself and said
progestogen can be delivered for a similar duration at
rates of delivery of up to 1 mg per day.

10 According to a second aspect of the invention there
is provided use of a suitable 17β -oestradiol precursor
as defined hereinbefore for the manufacture of an
intravaginal shell or core drug delivery device for
daily release of up to 1 mg 17β -oestradiol in a
15 substantially zero order pattern for at least three
weeks and, preferably, for up to 12 months for treating
hypo-oestrogenic symptoms. The diameter of a
rate-controlling sheath is such that it can be
manufactured within acceptable tolerances by methods
20 presently known in the art.

According to a third aspect of the invention there
is provided a process for the preparation of an
intravaginal shell or core drug delivery device
25 suitable for administration to a female mammal. Said
process comprises the steps of combining a suitable
 17β -oestradiol precursor as defined hereinabove, a
polymer, a suitable cross-linking agent and a curing
catalyst to form a mix; curing the mix to form the
30 polymer matrix; and providing a sheath surrounding the
polymer matrix.

Alternatively, the polymer matrix forms a hollow annulus and the process comprises the steps of forming a central member; combining the 17β -oestradiol precursor with the polymer, the suitable cross-linking agent and the curing catalyst to form the mix and curing the mix to form the polymer matrix in the form of the hollow annulus surrounding the central member; and providing the sheath surrounding the polymer matrix. The relative amounts of the respective polymer matrix and sheath components are chosen, and the geometry of the ring components selected, in order to provide a daily release of 17β -oestradiol precursor equivalent to between 50 and 250, and most preferably between 50 and 100, μg per day of 17β -oestradiol.

15

According to a fourth aspect of the invention there is provided use of a suitable 17β -oestradiol precursor as defined hereinabove in an intravaginal shell or core drug delivery device for release of up to 1 mg/day 17β -oestradiol in a substantially zero order pattern for at least three weeks and, preferably, for up to 12 months.

According to an aspect of the present invention, there is provided an intravaginal shell or core drug delivery device suitable for administration to a female mammal, the device comprising a 17β -oestradiol precursor in a biocompatible hydrophobic elastomeric polymer matrix and having a sheath surrounding the polymer matrix, the device being adapted to release the 17β -oestradiol precursor in a substantially zero order pattern for at least three weeks and to release up to 1mg/day 17β -oestradiol; the precursor being a 17β -oestradiol moiety in which the, or each, hydroxyl group of the 17β -

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oestradiol moiety is blocked by a blocking group; the precursor having sufficient lipophilicity as determined by one of a solubility in liquid silicone of at least 0.1 mg/100 ml and a standard k value, wherein $k=2C_sD\pi$ wherein
5 Cs corresponds to the saturation solubility of the precursor in the polymer matrix and D corresponds to the diffusion coefficient of the precursor in polymer matrix, of at least 0.1 $\mu\text{g/day/mm}$; the precursor having sufficient hydrophilicity as determined by a solubility
10 in distilled water of at least 1 $\mu\text{g}/100\text{ ml}$; the, or each, blocking group being so linked to the 17 β -oestradiol moiety as to be readily removed from the 17 β -oestradiol moiety *in vivo*, and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the
15 female mammal, when removed from the 17 β -oestradiol moiety *in vivo*.

According to another aspect of the present invention, there is provided a process for the preparation of an intravaginal shell or core drug delivery device suitable for administration to a female mammal, the process comprising the steps of combining a 17 β -oestradiol precursor, the precursor being a 17 β -oestradiol moiety in which the, or each, hydroxyl group of the 17 β -oestradiol moiety is blocked by a blocking group; the precursor having sufficient lipophilicity as determined by one of a solubility in liquid silicone of at least 0.1 mg/100 ml and a standard k value, as defined hereinabove, of at least 0.1 $\mu\text{g/day/mm}$; the precursor having sufficient hydrophilicity as determined by a solubility in distilled water of at least 1 $\mu\text{g}/100\text{ ml}$; the, or each, blocking group being so linked to the 17 β -oestradiol moiety as to be readily removed from the 17 β -oestradiol moiety *in*

18b

vivo; and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the female mammal, when removed from the 17β -oestradiol moiety *in vivo*, with a biocompatible hydrophobic elastomeric polymer, a suitable cross-linking agent and a curing catalyst to form a mix; curing the mix to form a polymer matrix; and providing a sheath surrounding the polymer matrix.

According to a further aspect of the present invention, there is provided use of a 17β -oestradiol precursor in an intravaginal shell or core drug delivery device for release of up to 1mg/day 17β -oestradiol from a biocompatible hydrophobic elastomeric polymer matrix in a substantially zero order pattern for at least three weeks, the 17β -oestradiol precursor being a 17β -oestradiol moiety in which the, or each, hydroxyl group of the 17β -oestradiol moiety is blocked by a blocking group; the precursor having sufficient lipophilicity as determined by one of a solubility in liquid silicone of at least 0.1 mg/100 ml and a standard k value, as defined hereinabove, of at least 0.1 μ g/day/mm; the precursor having sufficient hydrophilicity as determined by a solubility in distilled water of at least 1 μ g/100 ml; the, or each, blocking group being so linked to the 17β -oestradiol moiety as to be readily removed from the 17β -oestradiol moiety *in vivo*; and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the female mammal, when removed from the 17β -oestradiol moiety *in vivo*.

According to another aspect of the present invention, there is provided use of a 17β -oestradiol

18c

precursor for the manufacture of an intravaginal shell or core drug delivery device for daily release of up to 1mg 17 β -oestradiol from a biocompatible hydrophobic elastomeric polymer matrix in a substantially zero order pattern for at least three weeks for treating hypo-oestrogenic symptoms, the 17 β -oestradiol precursor being a 17 β -oestradiol moiety in which the, or each, hydroxyl group of the 17 β -oestradiol moiety is blocked by a blocking group; the precursor having sufficient lipophilicity as determined by one of a solubility in liquid silicone of at least 0.1 mg/100 ml and a standard k value, wherein $k=2C_sD\pi$ wherein C_s corresponds to the saturation solubility of the precursor in the polymer matrix and D corresponds to the diffusion coefficient of the precursor in polymer matrix, of at least 0.1 μ g/day/mm; the precursor having sufficient hydrophilicity as determined by a solubility in distilled water of at least 1 μ g/100 ml; the, or each, blocking group being so linked to the 17 β -oestradiol moiety as to be readily removed from the 17 β -oestradiol moiety *in vivo*; and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the female mammal, when removed from the 17 β -oestradiol moiety *in vivo*.

According to the present invention, a particularly preferred group of 17 β -oestradiol precursors are those possessing one or more acyl groups esterically linked as blocking groups to the hydroxyl group(s) of the 17 β -oestradiol moiety. Preferably, the, or each, blocking group is an aliphatic short-chain acyl group with the proviso that, when the acyl group is acetyl, each hydroxyl group cannot be blocked with acetyl. More preferably, the acyl group is the acyl moiety of a

18d

saturated or unsaturated monocarboxylic or dicarboxylic acid. The one or more acyl groups may block the 3-position and/or the 17-position of the 17 β -oestradiol moiety. It will be known to those

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skilled in the art that therapeutically active esters are rapidly hydrolysed in human plasma by non-specific esterases to the corresponding parent acid and alcohol. In the case of 17 β -oestradiol precursors, it will be
5 apparent to those skilled in the art that hydrolysis of said precursors in human plasma will yield 17 β -oestradiol itself, together with one or more acidic components, the number of such acidic components depending on the number of acyl groups present per
10 molecule of said precursor. Said acyl groups include saturated aliphatic short-chain (C1-5) straight or branched mono- and dicarboxylic acids such as formyl, acetyl, propionyl, butyryl, isobutyryl, oxalyl, malonyl, glutaryl and succinyl; unsaturated aliphatic
15 short-chain (C2-5) straight or branched mono- and dicarboxylic acids such as acryloyl, propioloyl, methacryloyl, crotonoyl, isocrotonoyl, maleoyl, fumaroyl, citraconoyl and mesaconoyl; carbocyclic carboxylic acids or other such groups known to those
20 skilled in the art. Such acyl groups are disclosed by way of example only and it will be understood that the scope of the invention is not limited in any way by such disclosure.

25 The preferred 17 β -oestradiol precursors must have sufficient lipophilic character such that their solubilities in liquid silicone (Dow Corning Grade 360 Medical Fluid) at 37°C are not less than 0.1 mg per 100 ml. Alternatively, the preferred 17 β -oestradiol ester
30 precursors must have sufficient lipophilic character such that their standard k values (as defined hereinabove) are not less than 0.1 μ g/day/mm.

35 Further, said precursors must have a hydrophilic character such that their solubilities in distilled water at 20°C are not less than 1 μ g per 100 ml.

- 20 -

17 β -oestradiol-3-benzoate and
17 β -oestradiol-17-valerate are examples of
17 β -oestradiol precursors not possessing the requisite
aqueous solubility.

5

Although not essential for the purposes of the
invention, said precursors should, preferably, be
micronised.

10

According to the present invention, a preferred
acyl group is acetyl or propionyl and particularly
preferred 17 β -oestradiol precursors are

17 β -oestradiol-17-acetate, 17 β -oestradiol-3-acetate,
17 β -oestradiol-17-propionate and

15

17 β -oestradiol-3-propionate.

20

According to the present invention, the acyl
group preferably blocks the 3-position, so that
particularly preferred 17 β -oestradiol precursors are
17 β -oestradiol-3-acetate and
17 β -oestradiol-3-propionate. 17 β -oestradiol-3-acetate
is most particularly preferred.

25

Suitable progestogens for use in the intravaginal
drug delivery devices of the present invention include,
but are not limited to, levonorgestrel and
norethisterone-17-acetate. Further suitable
progestogens would be expected to include
chlormadinone, desorgestrel, gestodene,
medroxyprogesterone, megestrol, norgestimate and
progesterone.

30

The intravaginal ring may be constructed from one
or more biocompatible polymers, for example,
elastomers, compatible with said 17 β -oestradiol
precursors, such as organopolysiloxanes or

35

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polyurethanes. Where the elastomer is chosen from the room-temperature vulcanising type of hydroxyl-terminated organopolysiloxanes, suitable cross-linking agents and curing catalysts known in the art may be required. Dimethylpolysiloxane compositions may also be used as the elastomeric component of the intravaginal drug delivery device of the invention.

The geometry of the intravaginal drug delivery device of the invention may be chosen such that the daily release of the 17β -oestradiol precursor can be varied up to 1 mg per day, expressed as 17β -oestradiol itself, and preferably from between 50 to 100 μ g per day, again expressed as 17β -oestradiol itself. Said ring geometries can also be varied to permit the simultaneous delivery, at therapeutically desirable rates, from an individual intravaginal drug delivery device, of a suitable 17β -oestradiol precursor and a progestogenic substance. The term "geometry" encompasses the overall diameter of the ring; the cross-sectional diameter of the ring; the ratio of the core diameter to the diameter of the whole device in cross-section; and the length of the core.

The percentage loading of 17β -oestradiol precursor contained in the core can vary from 1% (w/w) to in excess of 50% (w/w) and is only limited by the physical characteristics of the final mix. It will be apparent to those skilled in the art that the only importance of said drug loading in a device of core or shell design with an outer, rate-controlling sheath is to ensure that there is sufficient drug present at all times to allow a substantially zero order pattern of drug release to be maintained throughout the required period of sustained drug release. Thus, to ensure maintenance of the substantially zero order drug

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release pattern throughout the lifetime of the device, the necessary drug loading will be sufficiently in excess of the total drug required to be delivered over the defined sustained-release period.

5

Several embodiments of the invention will now be demonstrated by reference to the following General Method of Manufacture of an intravaginal drug delivery device in the form of a ring for the delivery of a
10 suitable 17 β -oestradiol precursor as defined hereinabove, either alone or in combination with a progestogenic substance. This General Method of Manufacture is exemplified by reference to Examples 1 to 10. It should be understood that these examples are
15 disclosed solely by way of further illustrating the invention and should not be taken in any way to limit the scope of said invention. Thus, for instance, it will be obvious to those skilled in the art that the technique of injection moulding referred to in the
20 General Method of Manufacture may be replaced in whole or in part by other manufacturing techniques, for example, extrusion, that will produce a similar end product.

25

General Method of Manufacture: Core Design

An elastomer mix is prepared by blending 97 parts by weight of a hydrophobic elastomeric polymer containing about 25% (w/w) diatomaceous earth as the
30 filler with 2.5 parts by weight of a cross-linking agent, n-propylorthosilicate. A suitable hydrophobic elastomeric polymer is stannous octoate-cured polydimethylsiloxane polymer, two suitable examples of which are those known as Dow Corning* QCF7 3099 and Nasil* Med 7.6382.

*=Trade-mark

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The elastomer mix thus formed is further blended in the ratio of 85 parts by weight of the elastomer mix, 5 parts by weight of barium sulphate and 10 parts by weight of a 17β -oestradiol precursor, preferably a 17β -oestradiol ester, more preferably, 17β -oestradiol-3-acetate, 17β -oestradiol-17-acetate, 17β -oestradiol-3-propionate or 17β -oestradiol-17-propionate. Thereby, an active mix is formed.

10

The core of the intravaginal drug delivery device of the invention is produced by mixing 200 parts by weight of the active mix with 1 part by weight of an activating catalyst, for example, stannous octoate. The resultant core mix is injected into a core mould and cured at 80°C for 2 minutes. The mould is then opened, following which the core is removed and trimmed.

15

An intravaginal drug delivery device in the form of a half ring is produced by mixing 200 parts by weight of elastomer mix with 1 part by weight of an activating catalyst, for example, stannous octoate. The resultant half ring mix is injected into a half ring mould containing a core previously prepared as described in the immediately preceding paragraph and cured at 80°C for 2 minutes. The mould is then opened, following which the half ring is removed and trimmed.

20

25

An intravaginal drug delivery device in the form of a complete ring is produced by mixing 200 parts by weight of elastomer mix with 1 part by weight of an activating catalyst, for example, stannous octoate. The resultant full ring mix is injected into a full ring mould containing a half ring previously prepared as

30

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described in the immediately preceding paragraph and cured at 80°C for 2 minutes. The mould is then opened, following which the full ring is removed and trimmed.

5 The geometric characteristics of the ring can be varied as required by the use of appropriately sized moulds, as exemplified by the following examples, or by the use of appropriately sized extrusion nozzles, as will be obvious to those skilled in the art.

10 **Example 1**

 An intravaginal drug delivery device in the form of a ring having a nominal *in vitro* daily release rate
15 of 10 µg per day of 17β-oestradiol-17-acetate was prepared with a ring geometry as described in Table 1, by following the General Method of Manufacture set out hereinabove.

20 **Example 2**

 An intravaginal drug delivery device in the form of a ring having a nominal *in vitro* daily release rate
25 of 50 µg per day of 17β-oestradiol-17-acetate was prepared with a ring geometry as described in Table 1, by following the General Method of Manufacture set out hereinabove.

30 **Example 3**

 An intravaginal drug delivery device in the form of a ring having a nominal *in vitro* daily release rate
35 of 50 µg per day of 17β-oestradiol-3-acetate was prepared with a ring geometry as described in Table 1, by following the General Method of Manufacture set out hereinabove.

- 25 -

Example 4

An intravaginal drug delivery device in the form of a ring having a nominal *in vitro* daily release rate of 100 µg per day of 17β-oestradiol-3-acetate was prepared with a ring geometry as described in Table 1, by following the General Method of Manufacture set out hereinabove.

Example 5

10

An intravaginal drug delivery device in the form of a ring having a nominal daily *in vitro* release rate of, simultaneously, 50 µg per day of 17β-oestradiol-3-acetate and 20 µg per day of the progestogenic substance, levonorgestrel, was prepared with a ring geometry as described in Table 1, by following the General Method of Manufacture set out hereinabove.

20

The nominal *in vitro* release rates set out in Table 1 for the rings of Examples 1-5 were determined under sink conditions of 1% (w/v) benzalkonium chloride. These release rates were determined in the following manner.

25

Each ring (n=4) was suspended in the dissolution medium in an individual flask which is then capped, placed in a suitable oven at 37°C and shaken. The dissolution medium was changed every 24 hours (± 30 minutes). An aliquot of the used dissolution medium was analysed by high performance liquid chromatography (HPLC) using reverse phase packing and UV detection (at 235 nm for 17β-oestradiol-3-acetate and for

30

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Table 1 Drug-loaded core dimensions for intravaginal rings, 9 x 54 mm, having a nominal in vitro daily release, in sink conditions, of a 17 β -oestradiol precursor, either alone or in combination with a progestogen.

Active ingredient	Example	Nominal daily release (μ g) (in vitro)	Core dimensions (mm) as cross-sectional diameter x length
17 β -oestradiol-17-acetate	1	10	2 x 15
17 β -oestradiol-17-acetate	2	50	2 x 75
17 β -oestradiol-3-acetate	3	50	2 x 8
17 β -oestradiol-3-acetate	4	100	2 x 16
17 β -oestradiol-3-acetate (E3A) in combination with levonorgestrel (LN)	5	50 E3A and 20 LN	2 x 8 (E3A) 3 x 105 (LN)

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17 β -oestradiol-3-propionate; at 281 nm for
17 β -oestradiol-17-acetate, for
17 β -oestradiol-17-propionate and for 17 β -oestradiol),
with reference to the appropriate standard solutions.

5 Due to hydrolysis to 17 β -oestradiol during storage,
17 β -oestradiol-3-acetate levels were determined by
analysis for both 17 β -oestradiol and

17 β -oestradiol-3-acetate. An improved analytical
method was subsequently developed for

10 17 β -oestradiol-3-acetate - this involves hydrolysing an
aliquot of used dissolution medium with 0.5N NaOH to
yield 17 β -oestradiol with subsequent buffering prior to
injection into the HPLC system for detection at 281 nm
of the hydrolysis product, 17 β -oestradiol, with
15 reference to the appropriate standard solutions.

The original analytical method has a precision of
less than 2% RSD (relative standard deviation) for
17 β -oestradiol and for the 17 β -oestradiol precursors,
20 with the exception of 17 β -oestradiol-3-acetate for
which the original and improved analytical methods had
precisions of less than 4% RSD and less than 2% RSD,
respectively. The sensitivity of the original and
improved analytical methods is 5 μ g/100 ml.

25 Re-analysis of the daily *in vitro* release rate
data for 17 β -oestradiol-3-acetate given in Table 1 from
the original method, yields altered daily release rates
which, in turn, result in corrected
30 precursor-containing core dimensions of 2 x 10 mm, 2 x
20 mm and 2 x 10 mm respectively, for the rings of
Examples 3-5, in order to nominally release 50 μ g, 100
 μ g and 50 μ g/day, respectively, of the active
ingredient, 17 β -oestradiol-3-acetate.

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Example 6: Mean Daily *In Vitro* Release Rates over 90 days (maximum)

5 The *in vitro* dissolution characteristics of the
intravaginal rings of the invention, which contain
various 17 β -oestradiol precursors, and of an
intravaginal ring containing 17 β -oestradiol itself are
illustrated by reference to Table 2. Four identical
10 rings were prepared for each compound according to the
General Method of Manufacture, the elastomer mix having
a stannous octoate-cured polydimethylsiloxane polymer
as the hydrophobic elastomeric polymer. In all cases
the ring geometries comprise a ring of dimensions 9 mm
15 (cross-sectional diameter) x 54 mm (outer diameter) and
containing a full length core (141 mm) of
cross-sectional diameter 2 mm. The rings were tested
in vitro at a constant temperature of 37°C for their
release characteristics in a sufficient volume of each
20 of the following media: 0.9% (w/v) saline, 0.133% (w/v)
aqueous benzalkonium chloride and 1.0% (w/v) aqueous
benzalkonium chloride. The saline medium was chosen
because the ability of a particular 17 β -oestradiol
precursor to achieve substantial release from an
25 intravaginal ring into saline may be regarded as a
significant indicator of its likely *in vivo* absorption
characteristics. The saline and benzalkonium
chloride-containing media were chosen to ensure 'sink
conditions' in at least one medium for each
30 intravaginal ring. It will be recognised by those
skilled in the art that the term 'sink conditions'
refers to that set of experimental conditions *in vitro*
which effectively simulates the active haemoperfusion
that occurs *in vivo*, and which results in a maximum
35 drug concentration gradient and maximum drug diffusion

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Table 2 Mean daily release rates of 17 β -oestradiol and 17 β -oestradiol precursors from intravaginal rings into various media. Rings were 9 x 54 mm containing a drug-loaded core of full length (141 mm) having a cross-sectional diameter of 2 mm.

Active ingredient	Mean Daily Release μ g per day (N=4)			
	Release Medium			
	0.9% (w/v) saline	0.133% (w/v) BKC*	1.0% (w/v) BKC*	
17 β -oestradiol	8	-	-	
17 β -oestradiol-17-valerate	**	365	550	
17 β -oestradiol-17-propionate	26	112	218	
17 β -oestradiol-17-acetate	24	56	96	
17 β -oestradiol-3-benzoate	<5	42	66	
17 β -oestradiol-3-acetate	350	700	850	
17 β -oestradiol-3-propionate	-	-	1200	

*BKC = benzalkonium chloride in aqueous solution

**Not detected

-Not determined

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rate, at any given time, across the aqueous boundary layer. Thus, an *in vitro* dissolution experiment can be designed such that the solution solubility of the released drug in the dissolution medium is much greater than its bulk concentration in this medium at any given time, for example, by micellar drug solubilisation due to incorporation of a surfactant such as benzalkonium chloride (BKC), at a concentration above its critical micelle concentration.

Thus, each ring was suspended by a thread in an individual closed flask containing the dissolution medium, maintained at a constant temperature of 37°C. The contents of the flask were gently agitated in order to prevent the occurrence of a hydrostatic layer on the surface of the ring. After 24 hours, the ring was removed and suspended in a flask of fresh dissolution medium of identical volume by a method identical to that previously described. This process was repeated at each successive 24 hour interval until a total maximum time of 90 days had elapsed. At the end of each 24 hour period, a sample of the dissolution medium was immediately analysed, as desired, for its precursor content by a suitable analytical method, typically by high performance liquid chromatography (see Example 5).

The data in Table 2 refer to mean daily *in vitro* release rates of 17 β -oestradiol and various 17 β -oestradiol precursors as determined by the method described, in each of the three specified release media, over a continuous period of up to 90 days. Sink conditions were evident for the 17 β -oestradiol precursors in 1.0% BKC. The low release rates into saline of the more lipophilic 17 β -oestradiol precursors, the valerate and benzoate esters, were due

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to their intrinsically low aqueous solubilities. The best release rates under sink conditions, in combination with substantial aqueous solubilities as indicated by the release rates into saline, were observed for the acetate and propionate esters. Thus, in particular, 17 β -oestradiol-3-acetate exhibited substantial release, in both BKC and in saline, from intravaginal rings of ring geometry as described in Table 2.

Figure 1 of the accompanying drawings shows the *in vitro* daily release of 17 β -oestradiol-17-acetate (as 17 β -oestradiol) from a 9 x 54 mm intravaginal ring (core length of 141 mm and core cross-sectional diameter of 2mm) over 90 days into a 1.0% (w/v) aqueous solution of benzalkonium chloride. The ring was prepared by following the General Method of Manufacture set out hereinabove.

Figure 2 of the accompanying drawings shows the *in vitro* daily release from a 7.6 x 56 mm ring of 17 β -oestradiol-3-acetate (as 17 β -oestradiol (core length 35mm; core cross-sectional diameter 2mm)) and norethisterone-17-acetate (core length 90mm; core cross-sectional diameter 2mm) over 12 days into a 1.0% (w/v) aqueous solution (250 ml) of benzalkonium chloride. The ring was prepared by following the General Method of Manufacture set out hereinabove.

The data presented in the figures confirm the efficacy of intravaginal drug delivery devices according to the present invention in releasing 17 β oestradiol *in vitro* in a substantially zero order pattern over the up to 90 day period of study.

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Table 3 Mean daily release rates of 17 β -oestradiol precursors into 250 ml of 1% (w/v) benzalkonium chloride. Rings were 9 x 54 mm containing a drug-loaded core of varying length having a cross-sectional diameter of 2 mm.

Active ingredient	Core length (mm)	Mean Daily Release (μ g/day) (n=5) (as precursor) *	k
17 β -oestradiol-3-acetate	6	49.25	12.347
	12	91.88	11.517
	25	177.15	10.658
	35	236.66	10.017
17 β -oestradiol-3-propionate	35	300.00	12.89
	70	600.00	12.89
	140	1200.00	12.89
17 β -oestradiol-17-acetate	35	19.50	0.8380
	70	40.94	0.8797
	140	87.45	0.9395
17 β -oestradiol-17-propionate	17	24.08	2.130
	35	42.86	1.842
	70	83.54	1.795
	140	155.20	1.667

*The release rate data for 17 β -oestradiol-3-acetate are based on the amount of anhydrous 17 β -oestradiol detected by the improved analytical method. These data have been converted to 17 β -oestradiol as 17 β -oestradiol-3-acetate by multiplication by the correction factor 1.154.

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Intravaginal drug delivery devices in the form of rings were prepared, each with a ring geometry as described in Table 3, by following the General Method of Manufacture set out hereinabove. Table 3 also shows
5 in vitro release rates into 1% (w/v) benzalkonium chloride for these rings and the apparent k values observed when the core length is varied.

The dissolution medium was changed daily,
10 following the protocol set out hereinabove. Mean daily release rates from the second week of dissolution experiments were used to determine the apparent k values presented in Table 3.

15 It will be observed that the apparent k value varies with core length for 17 β -oestradiol-3-acetate, 17 β -oestradiol-17-acetate and 17 β -oestradiol-17-propionate. It was, therefore, decided to determine k values at a core length of 35 mm
20 and such k values are hereinafter referred to as "standard k" values.

**Example 7: Solubility Parameters for 17 β -Oestradiol
and Certain 17 β -Oestradiol Precursors.**

25 The standard k value was determined from the mean daily release rates observed in Example 6. The dissolution medium of 1.0% (w/v) of an aqueous solution of benzalkonium chloride was used in respect of the
30 various 17 β -oestradiol precursors, so as to ensure sink conditions. The relevant data are presented in Table 4.

Aqueous solubility was determined at 20°C in distilled water. The relevant data are presented in
35 Table 5.

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Silicone solubility was determined at 37°C in Dow Corning (Trade Mark) 360 medical fluid. The relevant data are presented in Table 5.

5 **Example 8: In Vitro Plasma Hydrolysis**

The stability of 17 β -oestradiol-3-acetate and 17 β -oestradiol-17-acetate were determined in human blood by incubation at 37°C at concentrations of 100
10 pg/ml and 500 pg/ml - these concentrations were chosen to be of the same order or slightly higher than circulating 17 β -oestradiol levels expected from use of an intravaginal drug delivery device according to the invention. In addition, a supranormal concentration of
15 10 ng/ml was also investigated.

Samples were collected at 1, 5, 10, 15, 30 and 60 minutes and at 2, 4, 6 and 24 hours after commencement of incubation. On collection of each sample, the
20 reaction was stopped by the addition of sodium fluoride (0.05 - 0.1M final concentration), the plasma separated by centrifugation and analysed for 17 β -oestradiol using ELISA on a Behring OPUS Plus instrument, by reference to the appropriate standard solutions.

25 The hydrolysis half-lives for 17 β -oestradiol-3-acetate and 17 β -oestradiol-17-acetate were <1 minute and 4 hours, respectively.

30 **Example 9: In vivo Characteristics**

The in vivo dissolution characteristics of intravaginal drug delivery devices according to the invention were assessed in the following manner.

35

Table 4 Mean daily release rates of 17 β -oestradiol precursors from intravaginal rings into various media. Rings were 9 x 54 mm containing a drug-loaded core of 35 mm length having a cross-sectional diameter of 2 mm.

Active ingredient	Mean Daily Release (μ g/day) (n = 5)		Standard k
	Release medium		
	0.9% (w/v) saline	1.0% (w/v) BKC	
17 β -oestradiol-3-acetate	-	236.66	10.017
17 β -oestradiol-3-propionate	250-350	300.00	12.89
17 β -oestradiol-17-acetate	-	19.50	0.838
17 β -oestradiol-17-propionate	-	42.86	1.842

- not determined

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Table 5

Active Ingredient	Aqueous solubility (μ g/100 ml)	Silicone solubility (mg/100 ml)	k (μ g/day/mm)
17 β -Oestradiol	190	1.63 ¹	0.09***
17 β -Oestradiol-17-valerate	*	15.02 ¹	5.86***
17 β -Oestradiol-17-propionate	5	-	1.842**
17 β -Oestradiol-17-acetate	12	1.7	0.838**
17 β -Oestradiol-3-benzoate	*	3.68 ¹	0.70***
17 β -Oestradiol-3-acetate	380	18.6	10.017**
17 β -Oestradiol-3-propionate	230	30.0	12.89**

* not detected

- not determined

** standard k

*** k using core of 141 mm length

1 compiled from Novel Drug Delivery Systems; Yie W. Chien;
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Intravaginal rings containing the 17 β -oestradiol precursors, 17 β -oestradiol-3-acetate or 17 β -oestradiol-17-acetate, were prepared according to the General Method of Manufacture, having a stannous octoate-cured polydimethylsiloxane polymer as the hydrophobic elastomeric polymer. The 9 x 54 mm rings have nominal *in vitro* daily release rates of 115-125 or 230-250 μ g (each calculated as anhydrous 17 β -oestradiol) or 100 μ g (hereinafter referred to as "120 μ g" or "240 μ g" or "100 μ g" rings, respectively), by virtue of respective core dimensions of 2 x 24 mm and 2 x 47 mm and 2 x 141 mm (cross-sectional diameter x length).

Several female post-menopausal subjects, who gave informed consent before participation, entered a randomised cross-over study of 18 weeks duration in which, following a run in period of 2 weeks (for baseline plasma oestradiol determinations), each subject successively received each of a 100 μ g, 120 μ g and 240 μ g ring, with a washout period of 2 weeks between successive rings. The rings were inserted on Day 0 and removed on Day 28. Plasma 17 β -oestradiol levels were regularly measured during the run in period before the start of the study, immediately preceding insertion on Day 0 and for the following four week period ending on Day 28, when the ring was removed. The observed mean plasma 17 β -oestradiol levels are set out in Tables 6, 7 and 8.

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Table 6: 120 µg ring (n=5): 17β-Oestradiol-3-Acetate

Day	Mean Plasma 17β-Oestradiol level (pmol/l)
5	
-14	46.0
-10	49.6
-5	43.0
0	48.6
10	2
	431.0
	4
	394.4
	7
	364.0
	9
	359.8
	11
	350.0
15	14
	371.8
	18
	321.4
	21
	338.8
	28
	284.0

20 It will be observed that the mean baseline
17β-oestradiol level was 46.8 pmol/l and that the mean
17β-oestradiol level, post-ring insertion, was 357.24
pmol/l. Thus, the 120 µg ring according to the
invention delivered a mean increase in plasma
25 17β-oestradiol of 310.4 pmol/l over the 28 day study
period.

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Table 7: 240 μ g ring (n=5): 17 β -Oestradiol-3-Acetate
Mean Plasma 17 β -Oestradiol level

Day	(pmol/l)
5	-14
	46.0
	-10
	49.6
	-5
	43.0
	0
	35.9
	2
	817.4
10	4
	697.2
	7
	676.6
	9
	667.8
	11
	645.0
	14
	671.2
15	18
	667.2
	21
	642.8
	28
	665.2

It will be observed that the mean baseline
20 17 β -oestradiol level was 43.6 pmol/l and that the mean
17 β -oestradiol level, post-ring insertion, was 683.37
pmol/l. Thus, the 240 μ g ring according to the
invention, delivered a mean increase in plasma
17 β -oestradiol of 639.7 pmol/l over the 28 day study
25 period.

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Table 8: 100 μ g ring (n=4): 17 β -Oestradiol-17-Acetate

Day		Mean Plasma 17 β -oestradiol level (pmol/l)
5	-14	46.00
	-10	49.60
	-5	43.00
	0	55.75
	2	193.00
10	4	110.25
	7	103.25
	9	91.25
	11	89.50
	14	95.75
15	18	87.25
	21	104.00
	28	102.50

It will be observed that the mean baseline 17 β -oestradiol level was 48.59 pmol/l and that the mean 17 β -oestradiol level, post-ring insertion, was 108.53 pmol/l. Thus, the 100 μ g ring according to the invention, delivered a mean increase in plasma 17 β -oestradiol of 59.94 pmol/l over the 28 day study period.

It will be appreciated that the 120 μ g and 240 μ g rings of the present invention will be suitable for the alleviation or prevention of symptoms associated with hypo-oestrogenism, specifically hormone replacement therapy and for inducing hyper-oestrogenism, specifically to prevent ovulation. It will also be appreciated that the 100 μ g ring of the present invention will be suitable for hypo-oestrogenism responding to low dose hormone replacement therapy and

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that a ring having a larger core diameter would, of course, release more oestradiol precursor and, therefore, deliver more 17β -oestradiol into the blood stream.

5

The data presented in Tables 6-8 confirm the efficacy of intravaginal drug delivery devices according to the present invention in releasing 17β -oestradiol into the blood stream in a substantially zero order pattern over the 28 day period of study.

10

Example 10: *In vivo* characteristics

15

Intravaginal rings containing the 17β -oestradiol precursor, 17β -oestradiol-3-acetate, were prepared according to the General Method of Manufacture, having a stannous octoate-cured polydimethylsiloxane polymer as the hydrophobic elastomeric polymer. The 9 x 54 mm rings have a nominal *in vitro* daily release rate of 57.5 - 62.5 μ g calculated as anhydrous 17β -oestradiol (hereinafter referred to as a "60 μ g" ring) by virtue of dimensions of 2 x 12 mm (cross-sectional diameter x length).

20

25

Six female post-menopausal subjects, who gave informed consent before participation, received the 60 μ g intravaginal ring. These rings were inserted on Day 0 and removed on Day 14. Plasma 17β -oestradiol levels were measured on Day 0 and regularly during the two week period and the results are set out in Table 9.

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Table 9: 60 μ g ring (n=6): 17 β -Oestradiol-3-Acetate

Day	Mean Plasma 17 β -oestradiol level (pmol/l)
5	
0	31.5
2	229.3
4	146.8
7	131.5
10	9
11	139.8
14	114.8
	134.7

It will be observed that the mean baseline 17 β -oestradiol level was 31.5 pmol/l and that the mean 17 β -oestradiol level, post-ring insertion, was 149.48 pmol/l. Thus, the 60 μ g ring according to the present invention, delivered a mean increase in plasma 17 β -oestradiol of 117.98 pmol/l over the 14 day study period.

It will be appreciated that the 60 μ g ring of the present invention will be suitable for the alleviation or prevention of symptoms associated with hypo-oestrogenism, specifically, hormone replacement therapy.

It will also be appreciated that the 60 μ g ring of the present Example and the 120 and 240 μ g rings of Example 9 demonstrate a core length-dependent delivery of 17 β -oestradiol into the blood stream in a substantially zero order pattern. The core length can, therefore, be adjusted to yield the desired incremental plasma 17 β -oestradiol level to treat symptoms associated with hypo-oestrogenism or to induce hyper-oestrogenism.

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CLAIMS

1. An intravaginal shell or core drug delivery device suitable for administration to a female mammal, the device comprising a 17β -oestradiol precursor in a biocompatible hydrophobic elastomeric polymer matrix and having a sheath surrounding the polymer matrix, the device being adapted to release the 17β -oestradiol precursor in a substantially zero order pattern for at least three weeks and to release up to 1mg/day 17β -oestradiol; the precursor being a 17β -oestradiol moiety in which the, or each, hydroxyl group of the 17β -oestradiol moiety is blocked by a blocking group; the precursor having sufficient lipophilicity as determined by one of a solubility in liquid silicone of at least 0.1 mg/100 ml and a standard k value, wherein $k=2C_sD\pi$ wherein C_s corresponds to the saturation solubility of the precursor in the polymer matrix and D corresponds to the diffusion coefficient of the precursor in polymer matrix, of at least $0.1 \mu\text{g/day/mm}$; the precursor having sufficient hydrophilicity as determined by a solubility in distilled water of at least $1\mu\text{g/100 ml}$; the, or each, blocking group being so linked to the 17β -oestradiol moiety as to be readily removed from the 17β -oestradiol moiety *in vivo*, and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the female mammal, when removed from the 17β -oestradiol moiety *in vivo*.
2. An intravaginal drug delivery device according to Claim 1, in which the, or each, blocking group is an

aliphatic short-chain acyl group, with the proviso that, when the acyl group is acetyl, each hydroxyl group cannot be blocked with acetyl.

- 5 3. An intravaginal drug delivery device according to
 Claim 2, in which the acyl group is the acyl moiety
 selected from the group comprising a saturated
 monocarboxylic acid and a saturated dicarboxylic
 acid.
- 10
4. An intravaginal drug delivery device according to
 Claim 3, in which the acyl group is selected from
 the group comprising formyl, acetyl, propionyl,
 butyryl, isobutyryl, oxalyl, malonyl, succinyl and
15 glutaryl.
5. An intravaginal drug delivery device according to
 Claim 2, in which the acyl group is the acyl moiety
 selected from the group comprising an unsaturated
20 monocarboxylic acid and an unsaturated dicarboxylic
 acid.
6. An intravaginal drug delivery device according to
 Claim 5, in which the acyl group is selected from
25 acryloyl, propioloyl, methacryloyl, crotonoyl,
 isocrotonoyl, maleoyl, fumaroyl, citraconoyl and
 mesaconoyl.
7. An intravaginal drug delivery device according to
30 Claim 1 or 2, in which the blocking group blocks the
 3-hydroxyl group of the 17β -oestradiol moiety.
8. An intravaginal drug delivery device according to

Claim 1 or 2, in which the blocking group blocks the 17-hydroxyl group of the 17 β -oestradiol moiety.

- 5 9. An intravaginal drug delivery device according to Claim 7 or 8, in which the blocking group is selected from the group comprising acetyl and propionyl.
- 10 10. An intravaginal drug delivery device according to Claim 7, in which the precursor is selected from the group comprising 17 β -oestradiol-3-acetate and 17 β -oestradiol-3-propionate.
- 15 11. An intravaginal drug delivery device according to Claim 10, in which the precursor is 17 β -oestradiol-3-acetate.
- 20 12. An intravaginal drug delivery device according to Claim 8, in which the precursor is selected from the group comprising 17 β -oestradiol-17-acetate and 17 β -oestradiol-17-propionate.
- 25 13. An intravaginal drug delivery device according to Claim 12, in which the precursor is 17 β -oestradiol-17-acetate.
- 30 14. An intravaginal drug delivery device according to any one of Claims 1 to 13, in which the device additionally includes a progestogen in the polymer matrix.
15. An intravaginal drug delivery device according to Claim 14 in which the progestogen is selected from

the group comprising norethisterone-17-acetate and levonorgestrel.

16. An intravaginal drug delivery device according to
5 any one of Claims 1 to 15 suitable for alleviating or preventing symptoms associated with hypo-oestrogenism including hormone replacement therapy, in which the polymer matrix forms a core and the sheath surrounds the core.
- 10 17. An intravaginal drug delivery device according to any one of Claims 1 to 15 suitable for inducing hyper-oestrogenism including fertility control, in which the polymer matrix forms a hollow annulus and
15 the device is provided with a central member within the annulus, the sheath surrounding the polymer matrix.
18. A process for the preparation of an intravaginal
20 shell or core drug delivery device suitable for administration to a female mammal, the process comprising the steps of combining a 17β -oestradiol precursor, the precursor being a 17β -oestradiol moiety in which the, or each, hydroxyl group of the
25 17β -oestradiol moiety is blocked by a blocking group; the precursor having sufficient lipophilicity as determined by one of a solubility in liquid silicone of at least 0.1 mg/100 ml and a standard k value, wherein $k=2C_sD\pi$ wherein C_s corresponds to the
30 saturation solubility of the precursor in the polymer matrix and D corresponds to the diffusion coefficient of the precursor in polymer matrix, of at least 0.1 $\mu\text{g/day/mm}$; the precursor having

- sufficient hydrophilicity as determined by a solubility in distilled water of at least $1\mu\text{g}/100\text{ ml}$; the, or each, blocking group being so linked to the 17β -oestradiol moiety as to be readily removed from the 17β -oestradiol moiety *in vivo*; and the, or each, blocking group being so chosen as to yield a substance which is non-toxic to the female mammal, when removed from the 17β -oestradiol moiety *in vivo*, with a biocompatible hydrophobic elastomeric polymer, a suitable cross-linking agent and a curing catalyst to form a mix; curing the mix to form a polymer matrix; and providing a sheath surrounding the polymer matrix.
- 15 19. A process according to Claim 18, in which the polymer matrix forms a hollow annulus and the process comprises the steps of forming a central member; combining the 17β -oestradiol precursor with the polymer, the suitable cross-linking agent and the curing catalyst to form the mix and curing the mix to form the polymer matrix in the form of the hollow annulus surrounding the central member; and providing the sheath surrounding the polymer matrix.
- 25 20. An intravaginal drug delivery device suitable for administration to a female mammal, whenever prepared by a process claimed in Claim 18 or 19.
- 30 21. Use of a 17β -oestradiol precursor in an intravaginal shell or core drug delivery device for release of up to $1\text{mg}/\text{day}$ 17β -oestradiol from a biocompatible hydrophobic elastomeric polymer matrix in a substantially zero order pattern for at least three

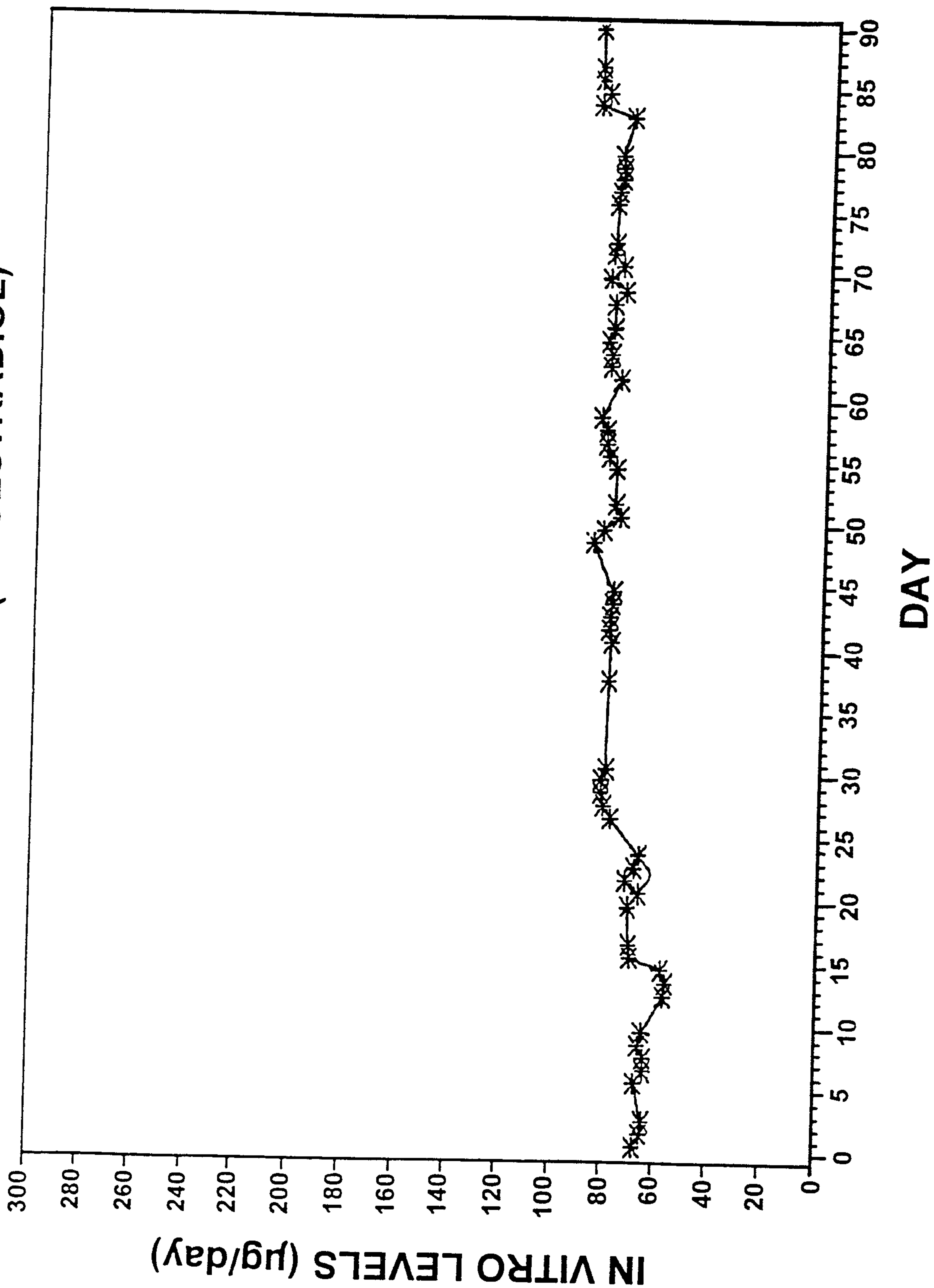
5 weeks, the 17β -oestradiol precursor being a 17β -
oestradiol moiety in which the, or each, hydroxyl
group of the 17β -oestradiol moiety is blocked by a
blocking group; the precursor having sufficient
10 lipophilicity as determined by one of a solubility
in liquid silicone of at least 0.1 mg/100 ml and a
standard k value, wherein $k=2C_sD\pi$ wherein C_s
corresponds to the saturation solubility of the
precursor in the polymer matrix and D corresponds to
15 the diffusion coefficient of the precursor in
polymer matrix, of at least 0.1 $\mu\text{g/day/mm}$; the
precursor having sufficient hydrophilicity as
determined by a solubility in distilled water of at
least 1 $\mu\text{g/100 ml}$; the, or each, blocking group
20 being so linked to the 17β -oestradiol moiety as to
be readily removed from the 17β -oestradiol moiety *in vivo*;
and the, or each, blocking group being so
chosen as to yield a substance which is non-toxic to
the female mammal, when removed from the 17β -
oestradiol moiety *in vivo*.

22. Use of a 17β -oestradiol precursor for the
manufacture of an intravaginal shell or core drug
delivery device for daily release of up to 1mg 17β -
25 oestradiol from a biocompatible hydrophobic
elastomeric polymer matrix in a substantially zero
order pattern for at least three weeks for treating
hypo-oestrogenic symptoms, the 17β -oestradiol
precursor being a 17β -oestradiol moiety in which
30 the, or each, hydroxyl group of the 17β -oestradiol
moiety is blocked by a blocking group; the precursor
having sufficient lipophilicity as determined by one
of a solubility in liquid silicone of at least 0.1

mg/100 ml and a standard k value, wherein $k=2C_sD\pi$
wherein C_s corresponds to the saturation solubility
of the precursor in the polymer matrix and D
corresponds to the diffusion coefficient of the
5 precursor in polymer matrix, of at least 0.1
 $\mu\text{g/day/mm}$; the precursor having sufficient
hydrophilicity as determined by a solubility in
distilled water of at least 1 $\mu\text{g/100 ml}$; the, or
each, blocking group being so linked to the 17β -
10 oestradiol moiety as to be readily removed from the
 17β -oestradiol moiety *in vivo*; and the, or each,
blocking group being so chosen as to yield a
substance which is non-toxic to the female mammal,
when removed from the 17β -oestradiol moiety *in vivo*.

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FIG. 1 OESTRADIOL-17-ACETATE IVR (100µg/day)
IN VITRO RELEASE (AS OESTRADIOL)



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FIG. 2

Daily release rates.

