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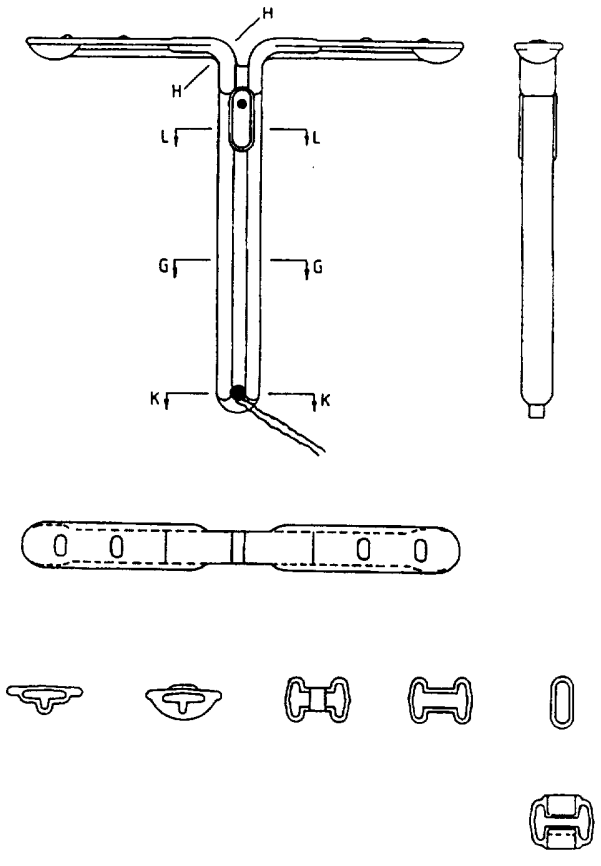
(54) Title: SYNCHRONISING OF ANIMAL OESTRUS AND INTRA VAGINAL DEVICES USEFUL THEREIN

(57) Abstract

An intra vaginal device which is of a variable geometry kind and which includes a silicone matrix impregnated with progesterone, the confirmation and content of the progesterone impregnated matrix being such as to optimise effectiveness with a lower initial loading of progesterone.



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SYNCHRONISING OF ANIMAL OESTRUS AND INTRA VAGINAL DEVICES USEFUL THEREIN

TECHNICAL FIELD

The present invention relates to improvements in and/or relating to the synchronising of animal oestrus and intra vaginal devices useful therein together with related means and methods.

BACKGROUND ART

It is useful for farmers to synchronise the oestrus of animals whether they be cattle beasts (whether for dairy or beef purposes) sheep, goats, horses, or the like where artificial insemination is practised. By way of example, in relation to cattle beasts, in a normal 365 day year 282 days on average is taken up of the year with the gestation period itself. With approximately 30 days to recover after delivery of its progeny each cow therefore has an average of only two and a half cycles if there is to be a timely management of the herd. Thus it is important over that remaining period of less than 53 days to ensure each cow in a herd becomes pregnant.

The traditional method of mating dairy cows with bulls is now largely superseded by the use of artificial insemination procedures which offer the prospect of rapid herd improvements although bulls are still presented to the herd frequently to catch those animals that have not conceived by the artificial insemination procedure.

There is therefore a great advantage attached to bringing such herd animals into oestrus simultaneously so as to make it easier to ensure effective usage of the artificial insemination procedure and subsequently to enable still within the "window" a further prospect of artificial insemination of those animals synchronistically brought to oestrus that have not already conceived.

Various means of achieving such a management of the synchronisation of the coming into oestrus of cows (whether heifers or lactating cows) and even sheep and goats has been disclosed in the art which includes the "EAZI-BREED CIDR Controlled Breeding and Reproductive Management" booklet made available to interested parties by InterAg a division of the applicant company in respect of its intra vaginal Eazi-Breed ™ CIDR ® product line.

The disclosures in the aforementioned publication, the full contents of which are here included by way of reference, comprehensively describe treatment protocols applicable at least to New Zealand herds of cattle beasts for synchronising oestrus and treatment of anoestrus.

These treatment protocols often utilise Eazi-Breed™ CIDR® devices in combination with drugs such as prostaglandin and/or oestradiol benzoate, and extend in general for periods of 7, 10 or 12 days.

If both control of the oestrus cycle and high fertility are to be optimised in cattle, studies have shown that an intra vaginal device must deliver sufficient progesterone (when used with combination drugs i.e. oestradiol or GnRH) to produce a minimum plasma progesterone concentration of 2 ng/mL over the terminal period of treatment (1,2).

1. Kesner, J.S., Padmanabhan, V. and Convey, E.M. Biol. Reprod. 26 (1982) 571-578.

2. Kinder, J.E., Kojima, F.N., Bergfeld, E.G.M., Wehrman, M.E. and Fike, K.E. J.Anim. Sci 74 (1996) 1424-1440.

A cost factor arises in the adoption of such protocols as a farmer is faced with the costs of the intra vaginal progesterone containing device as well as the use of the combination drugs. This ignores also the economic cost of the artificial breeding materials themselves.

The intra vaginal progesterone containing devices hitherto used in New Zealand and to a large extent elsewhere are typified by the CIDR® product of the applicant company depicted hereinafter in Figure 1 being a variable geometry device for vaginal insertion and retention which comprises a structural frame of a metal or appropriate plastics material encased in a progesterone impregnated plastics material from which the material can leach in the vaginal environment and from which it can be timely withdrawn by appropriate means (e.g: a string, tail or a tool) to allow the animal to progress into oestrus shortly after the removal. Hereinafter the aforementioned device will be referred to by its registered trademark CIDR®.

Another product available in the market place of this kind is another variable geometry device and such a device is depicted hereinafter in Figure 2. Such a device is a helical coil capable of being helically tightened and which is retainable in its helical form in the animals vagina. The device includes a withdrawal cord and carries a gelatine capsule which includes oestradiol benzoate so that there can be co-administration of the progesterone to be released over a protracted period and the oestradiol benzoate which is to be released at a different rate. Such a device includes a progesterone impregnated plastics matrix about a helical spine. Such a device is available from Sanofi Animal Health Limited, PO Box 209, Rhodes Way, Watford, Herts, WD24QE, England under its registered trademark PRID®.

The aforementioned CIDR® and PRID® devices are manufactured in large volumes

with the most expensive material being the progesterone active ingredient and thus small reductions in the progesterone inclusion in such devices will provide an economic advantage to a producer and to a farmer. Also any such reduction provides a reduced risk to the environment owing to a likely reduced residual amount of the progesterone in the matrix after the device has been withdrawn from an animal. This reduced residual amount not only provides safety but also dis-encourages the unrecommended reuse of a device in another animal where the unknown condition of such a device will give unpredictable results.

The CIDR® prior art device of the applicant company has been marketed with a silicone plastics matrix about its spine which contains about 1.9 grams of progesterone (USP) which drops to 1.33 grams still retained in the silicone matrix if the device is withdrawn after seven days. The same device drops to 1.05 grams of progesterone if it is not withdrawn until after 12 days.

The PRID® coil intra vaginal device contains at the outset 1.55 grams of progesterone which reduces down to 1.18 grams after 7 days and down to 0.94 grams after 10 days. The leach rate from the PRID® product may be affected in part by the inclusion of inorganic materials in the silicone plastics material such as calcium carbonate. The CIDR® silicone matrix is largely free of any such inclusions.

Hoechst US Patent 5,398,698 discloses the use of milled sheets of silicone rubber in intra-vaginal devices which carry progesterone. The milled sheets (2 to 10 mm thick) are vulcanised for from 4 to 8 minutes at from 70°C to 120°C.

The accepted test for the delivery of progesterone or its metabolites to the appropriate site of action in order to postpone oestrus is by reference to the progesterone level in the blood plasma of the animal. The design of such devices has to date usually been on the basis of an acceptance of the Higuchi equation based on a square root of time model (see hereinafter) which suggests that progesterone inclusions in such a plastics matrix would achieve plasma levels which decline with time.

Our investigations have found surprisingly that it is inappropriate in the design of such intra vaginal devices to rely upon the Higuchi equation or the square root of time model. In our device release is constant with time up to 7 days resulting in constant steady state plasma levels over that time period.

We have determined that by modifying the levels of progesterone initially in a silicone matrix, by controlling the thickness of the silicone matrix over the spine and by giving attention to the surface area of the device savings to a manufacturer arising from reduced quantities of progesterone being needed while at the same time achieving the same blood levels can be achieved. Savings are also achieved over the prior art devices

in terms of the amount of silicone used, since silicone is the second-most costly material used in the devices, with corresponding benefits being able to be passed on to the user.

The present invention relates to intra vaginal devices, methods of producing intra vaginal devices, and the use of such intra vaginal devices for managing oestrus and for the treatment of anoestrus in cattle, sheep, deer and goats.

DISCLOSURE OF INVENTION

In one aspect the invention is **an intra vaginal device** of a variable geometry kind capable of being applied into the vaginal cavity of an animal selected from the group consisting of cattle, sheep, deer and goats, retainable therein over a period of time within the range of from 7 to 12 days and then to be withdrawable therefrom to allow the onset of oestrus, said device being characterised in that:

a matrix of a cured silicone rubber material that includes greater than 5% by weight progesterone to the weight of the matrix defines an exterior surface (which may be all or part only of the device) of at least 75 cm^2 contactable once inserted in the vagina of such an animal by the vaginal membrane and/or vaginal fluid(s) of the animal,

the matrix of progesterone containing silicone rubber material has been formed by injection of the uncured progesterone containing matrix as a liquid into a mould for a sufficient time to achieve at a mould temperature or temperatures within the range of from 100°C to 210°C and a shape retaining at least partial cure thereof,

the total progesterone load (irrespective of whether alpha or beta progesterone or mixtures thereof) being from 1 to 1.5 grams within said matrix,

said surface area is available to at least substantially all of the matrix for progesterone release over a thickness of no greater than about 1 millimetre, and

said device upon vaginal insertion into such an animal is able to achieve and then maintain in the animal for a least seven days a minimum progesterone blood plasma level of 2 nanograms per millilitre of plasma of the animal and which after seven days of insertion will have a residual load in the silicone rubber matrix of less than 65% by weight of its progesterone load at insertion.

Preferably said exterior surface is from 100 to 150 cm^2, more preferably 120 to 125 cm^2.

Preferably said matrix has about 10% by weight progesterone by weight of progesterone to the weight of matrix.

Preferably said matrix at least in part encases a deformable frame.

Preferably said frame is resilient.

Preferably said frame is substantially in the form of a "T" with the arms of the "T"

being deformable to allow introduction into the vagina of an animal, the "T" form being defined by a resilient spine about which (at least in part) there is moulded said matrix.

Preferably said frame is of nylon.

Preferably after seven days from insertion the matrix will have a residual load of less than 60% by weight of its progesterone load at insertion.

In a further aspect the invention is **an intra vaginal device** of a variable geometry kind capable of being applied into the vaginal cavity of an animal selected from the group consisting of cattle, sheep, deer and goats, retainable therein over a period of time within the range of from 7 to 12 days and then to be withdrawable therefrom to allow the onset of oestrus, said device being characterised in that

on a frame or spine (hereafter "frame") of variable geometry there is a matrix of a cured silicone rubber material that includes greater than 5% and less than 20% by weight progesterone to the weight of the matrix defines and exterior surface (which may be all or part only of the device) of at least 100 cm^2 contactable once inserted in the vagina of such an animal by the vaginal membrane and/or vaginal fluid(s) of the animal,

the matrix of progesterone containing silicone rubber material has been formed by injection of the uncured progesterone containing matrix as a liquid into a mould for a sufficient time to achieve at a mould temperature of temperatures within the range of from 190°C to 195° C and a shape retaining at least partial cure thereof,

the total progesterone load (irrespective of whether alpha or beta progesterone or mixtures thereof) being from 1 to 1.5 grams (preferably about 1.35 grams) within said matrix,

said surface area is available to at least substantially all of the matrix for progesterone release over a thickness of no greater than about 1 millimetre, and

said device upon vaginal insertion into such an animal is able to achieve and then maintain in the animal for at least seven days a minimum progesterone blood plasma level of 2 nanograms per millilitre of plasma of the animal and which after seven days from insertion will have a residual load in the silicone rubber matrix of less than 65% by weight of its progesterone load at insertion.

Preferably said device is substantially as herein defined with reference to any one or more of the accompanying drawings.

In still a further aspect the invention **a method of postponing oestrus or treatment of anoestrus in an animal** which includes the steps of

administering into said animal by means of an intra vaginal device sufficient progesterone from a progesterone impregnated silicone rubber matrix where the progesterone content in the matrix is 5% or greater by weight via a surface area greater

than 75 cm^2 so as to achieve on the last few days of insertion a progesterone blood plasma level of greater than 2 nanograms per millilitre, and

removing the device after an insertion period of from 7 to 12 days.

Preferably said device is as previously defined.

Preferably said method includes the administration of oestradiol at or near the time of insertion of said device.

Preferably said method includes the administration of a prostaglandin at about day 6 of about a 7 to 10 day device insertion period.

In still a further aspect the invention is, **in a method of attempting to synchronise the onset of oestrus of a herd of cattle beasts, the procedure of**

administering intra vaginally to each animal of the herd progesterone from an intra vaginal device of the present invention and

after an appropriate period of time removing such devices to allow the onset of oestrus (the procedure optionally including the steps of administration of oestradiol benzoate and/or prostaglandin etc. as known in the art or otherwise), **said method being further characterised in that** levels of progesterone in the blood plasma of each animal is greater than 2 nanograms per millilitre until such time as the devices are withdrawn.

In still a further aspect the invention consists in **a method of synchronising the onset of oestrus in a herd of cattle beasts** which comprises

administering by means of an intra vaginal device to each animal from a progesterone impregnated matrix of the device an effective amount of progesterone for the period the device is retained intra vaginally, the device having being administered with a progesterone quantity of about 1.35 grams and being removed with a progesterone quantity of the order of about 0.85 grams.

As used here in "surface area" of the progesterone impregnated matrix is that area directly contactable by vaginal fluid(s) and/or membrane.

As used herein "surface area" is independent of any surface area of the spine (if any) which may or may not be of a plastics material. However, thicknesses of the progesterone impregnated medium or matrix are to the surface of the spine.

While reference has been made to cattle beasts the device and method is believed to be equally applicable to other mammals, e.g. sheep, goat, horse, etc.

BRIEF DESCRIPTION OF DRAWINGS

The present invention will now be described with reference to the accompanying drawings in which:

Figure 1 shows a series of drawings (a) through (e) of a prior art EaziBreed™

CIDR™ product of this company having a progesterone impregnated silicone matrix of an average depth of about 1.5 mm but having the depth thereof varying greatly,

Figure 1A is an elevation of the "T" shaped device capable of having the top arms thereof resiliently bent to alongside the upstanding body during insertion with an appropriate applicator pull and capable of assuming some return to the "T" form so as to be retained within the vagina of an appropriate animal such as a cattle beast,

Figure 1B is a section at "FF" of the top arms of the "T" form,

Figure 1C is a section at "DD" of the body,

Figure 1D is a view "CC" of the end of the body showing a slot formed therein from a hole through the body so as to allow the lying therein of a retained withdrawal string or other device,

Figure 1E is a section of the body at "EE".

Figure 1' shows the preferred spine of the prior art device, a spine which with no or little modification is useful in a device in accordance with the present invention,

Figure 1'A shows an elevation of the spine,

Figure 1'B showing a side elevation of the spine,

Figure 1'C showing the plan view of the top arms of the device,

Figure 1'D shows the section at "AA",

Figure 1'E shows the section at "BB",

Figure 2 shows the PRID™ device previously referred to,

Figure 3 shows a preferred device in accordance with the present invention having an average progesterone impregnated matrix of about or less than 1 mm thick over a spine of a kind shown in Figure 1',

Figure 3A shows an elevation of the (CIDR-B™) device in accordance with the present invention,

Figure 3B shows the side elevation of the device of Figure 3A,

Figure 3C shows a plan view of the top of the device as shown in Figures 3A and 3B,

Figure 3D shows a section at "DD" of Figure 3A,

Figure 3E shows a section at "CC"" of Figure 3A,

Figure 3F shows a section at "BB" of Figure 3A,

Figure 3G shows a section at "AA' of Figure 3A,

Figure 3H shows a section at "PP" of Figure 3A, being the hinging region of the arms from the body, and

Figure 3I is the section "HH" of Figure 3A, and

Figures 4 through 15 show results, plots, models and concepts hereinafter

described in greater detail.

DETAILED DESCRIPTION

The device of the present invention will now be described with reference to both *in vitro* and *in vivo* studies. In the following description the reference to the CIDR™ device is by reference to the device of the form depicted in Figures 1A to 1E. The reference hereafter to the device of the present invention (to be known as the CIDR-B ™ device) is preferably that substantially as depicted in Figures 3A through 3I and described hereinafter in more detail.

In vitro studies

The *in vitro* release assessment method for the existing CIDR™ device was based on the equipment and general procedures documented in the US Pharmacopoeia, XXIII pp 1791-1975 (1995). *In vitro* release of progesterone from the device followed a declining profile with time (Figure 4).

- **Mechanism of Release**

Release data was plotted as cumulative amount of progesterone released per unit area versus square-root-of-time. the release profile over greater than 75% of total release from the existing CIDR™ device followed a **square-root-of-time** model (Figure 5; linear dependence of progesterone release as a function of the square root of time).

- **Effect of drug load**

Release rate was observed to be affected by initial drug load as expected from the **square-root-of-time** model (Figure 6:- linear dependence of progesterone release rate as a function of the square root of twice the amount of initial drug load).

- **Determination of the depletion zone within silicone**

Depletion zone determinations clearly showed the formation of a depletion zone in the silicone skin (Figure 7) which is consistent with the square-root-of-time theory (Figure 8).

the results of all *in vitro* experiments conducted on the CIDR™ device suggested that progesterone was being released from the silicone matrix according to the square-root-of-time model of release.

In vivo studies

The following *in vivo* studies which led to our discoveries were conducted on the existing CIDR™ device and on devices of the present invention (i.e., devices referred to as the CIDR-B™ devices).

- **Blood level parameter (steady-state blood level)**

Following insertion of the existing CIDR™ device into ovariectomized cattle a characteristic plasma profile was observed (Figure 9). There was a rapid absorption phase. blood levels peaked within a few hours. The peak level was sustained for 48 hours before it fell over the following 24 to 48 hours to levels which were constant or diminished only very slightly over the remaining 4 days of the 7 day insertion period (apparent steady-state levels). Following removal of the device, plasma levels fell rapidly to basal levels. Based on Figure 9 we selected average progesterone steady-state plasma levels over the last four days of a 7 day insertion period as the performance indicator of the device.

- **Effect of initial progesterone concentration**

The effect of initial progesterone concentration in the device on the average progesterone steady-state plasma levels over the last four days of a 7 day insertion period is shown in Figure 10. Figure 10 shows that the devices containing above a 5% w/w initial progesterone concentration produce average progesterone steady-state plasma levels over the last four days of a 7 day insertion period above 2 ng/mL.

- **Effect of surface area**

The effect of surface area upon the average progesterone steady-state plasma levels over the last four days of a 7 day insertion period is shown in Figure 11. An increase in surface area produced an increase in average progesterone steady-state plasma levels over the last four days of a 7 day insertion period (Figure 11). A surface area of greater than 75 cm^2 is required to ensure that average progesterone steady-state plasma levels over the last four days of a 7 day insertion period are above 2ng/mL.

- **Determination of the depletion zone within silicone of used devices**

Progesterone concentration at various depths of a spent existing device that had been inserted for 7 days in cattle is shown in Figure 12. Figure 12 shows clearly that no distinct depletion zone was apparent following removal of the device after a 7 day insertion period in the vagina of cattle (cf. the clear depletion zone which was observed

in the *in vitro* experiments; Figure 7). Indeed following *in vivo* insertion the 0-0.5 mm outermost layer of silicone rubber skin still contained drug but at a concentration less than that originally incorporated into the device, the 0.5-1.0 mm layer also still contained drug but at a concentration less than that originally incorporated into the device. Beyond 1 mm the original amount of progesterone incorporated into the device was detected (Figure 12). These results (Figure 12) clearly demonstrate that progesterone was only eluted out of the first 1 mm of silicone rubber skin. The results also suggest that no distinct depletion zone forms as the drug is being released while the device is inside the animal but instead as release occurs a gradation of solid particles forms within the first 1 mm of skin. Possible reasons why such observations were detected are shown in Figure 13. These observations are not consistent with the square-root-of-time model. Indeed, the *in vivo* release of progesterone from the device was observed to be constant with time (figure 14) and follow a zero-order release mechanism (cf. the declining profile when the amount of progesterone released from the CIDR-B *in vitro* was plotted against time; Figure 4).

- **Investigations on a device of the present invention**

From these studies a device was manufactured which had a uniform silicone rubber skin thickness of <1 mm, surface area of 120 cm^2 and initially contained 1.25 g (10% w/w) of progesterone. Figure 15 shows the average progesterone steady-state plasma levels over the last four days of a 7 day insertion period determined for the existing CIDR device and a device in accordance with the present invention (CIDR-B device). Figure 15 clearly shows that the CIDR-B device is able to effectively sustain progesterone steady-state plasma levels over the last four days of a 7 day insertion period above 2 ng/mL. In addition, the final:initial content ratio for the CIDR-B device is less than 60% following a 7 day insertion period (Table 1).

Table 1: Comparison of the initial amount of progesterone, residual progesterone in spent devices and amount of progesterone released from existing CIDR™ device and device (CIDR-B™ device) which has characteristics described in this patent application following removal after 7 days.

Intra vaginal progesterone release device	Initial progesterone concentration in device (%w/w)	Initial amount of progesterone in device (g)	Residual amount of progesterone remaining in device (g)	Amount of progesterone released over 7 days (g)	Final:Initial ratio
Existing CIDR™ device	10	1.92	1.36	0.56	0.71
Device of the present invention (CIDR-B™)	10	1.25	1.36	™0.56	0.59

The following table of *in vivo* comparative data compares a device in accordance with the present invention (CIDR-B™) with a CIDR™ device and a PRID™device.

***In vivo* Comparisons**

Parameter	Existing CIDR™ device	New CIDR-B™ device (Present invention)	PRID™ DEVICE
At least 10% Progesterone in skin	Yes (10%)	Yes (10%)	No (Approx. 7.5%)
Progesterone bloods>2 ng/mL for at least 7 days	Yes	Yes	Yes
Initial Progesterone (g)	1.9	1.35	1.55
Final Progesterone (7 days)	1.3	0.8	1.18
Final Progesterone (10 days)	1.18	0.63	0.94
Final/Initial (7 days)	0.68	0.59	0.76
Final/Initial (10 days)	0.62	0.47	0.61
Skin thickness (mm)	Variable (0.9-5)	1.0	1.0
Surface area (cm^2)	120	120	220

- **The device of the present invention (CIDR-B™)**

The device (CIDR-B™) consists of a progesterone impregnated silicone elastomer skin moulded over an inert nylon spine. The active ingredient of the device is micronised USP natural progesterone. Device potency is determined by the percentage of active ingredient present in the inactive silicone elastomer.

The progesterone is mixed into each of two liquid silicone parts prior to the silicone being introduced to the machine for moulding. The progesterone is preferably mixed in

at 10% by total weight.

At the moulding stage the two parts of the liquid silicone are pumped under pressure of approximately 100 bar from pails into the injection chambers of an injection moulding machine. Upon injection, the two parts of silicone are simultaneously forced through a static mixer before flowing into an electrically heated mould.

The nylon spine is inserted into the mould prior to the silicone being injected. The mould has a die surface temperature of typically 190° - 195° C, but preferably never exceeding 200° C. The mould is kept clamped shut under approximately 30 tonnes of static pressure while the silicone cures. At the indicated temperature and pressure, the liquid silicone takes approximately 50 seconds to cure into a rubber.

Following curing, the finished product is removed from the mould and cooled before packaging.

The surface area of the silicone skin is approximately 120 - 125 cm^2 with the typical formulation for the device being:

Outer Skin (Impregnated Matrix)	Nominal Weight (gm)	Percentage of Skin	Percentage of Device
Active progesterone USP	1.35	10%	5.1%
Inactive silicone elastomer	12.15	90%	45.9%

WHAT WE CLAIM IS:

1. An intra vaginal device of a variable geometry kind capable of being applied into the vaginal cavity of an animal selected from the group consisting of cattle, sheep, deer and goats, retainable therein over a period of time within the range of from 7 to 12 days and then to be withdrawable therefrom to allow the onset of oestrus, said device being characterised in that

a matrix of a cured silicone rubber material that includes greater than 5% by weight progesterone to the weight of the matrix defines an exterior surface (which may be all or part only of the device) of at least 75 cm^2 contactable once inserted in the vagina of such an animal by the vaginal membrane and/or vaginal fluid(s) of the animal,

the matrix of progesterone containing silicone rubber material has been formed by injection of the uncured progesterone containing matrix as a liquid into a mould for a sufficient time to achieve at a mould temperature or temperatures within the range of from 100° C to 210° C and a shape retaining at least partial cure thereof,

the total progesterone load (irrespective of whether alpha or beta progesterone or mixtures thereof) being from 1 to 1.5 grams within said matrix,

said surface area is available to at least substantially all of the matrix for progesterone release over a thickness of no greater than about 1 millimetre, and

said device upon vaginal insertion into such an animal is able to achieve and then maintain in the animal for at least seven days a minimum progesterone blood plasma level of 2 nanograms per millilitre of plasma of the animal and which after seven days from insertion will have a residual load in the silicone rubber matrix of less than 65% by weight of its progesterone load at insertion.

2. A device of claim 1 wherein said exterior surface is from 100 to 1500 cm^2.

3. A device of claim 1 or 2 wherein said matrix has about 10% by weight progesterone to the weight of matrix.

4. A device of any one of the preceding claims wherein said matrix at least in part encases a deformable frame.

5. A device of claim 4 wherein said frame is resilient.

6. A device of claim 5 wherein said frame is substantially in the form of a "T" with the arms of the "T" being deformable to allow introduction into the vagina of an animal, the "T" form being defined by a resilient spine about which (at least in part) there is moulded said matrix.

7. A device of any one of claims 4 to 6 wherein said frame is of nylon.

8. An intra vaginal device of a variable geometry kind capable of being applied into the vaginal cavity of an animal selected from the group consisting of cattle, sheep, deer

and goats, retainable therein over a period of time within the range of from 7 to 12 days and then to be withdrawable therefrom to allow the onset of oestrus, said device being characterised in that

on a frame or spine (hereafter "frame") of variable geometry there is a matrix of a cured silicone rubber material that includes greater than 5% and less than 20% by weight progesterone to the weight of the matrix defines and exterior surface (which may be all or part only of the device) of at least 100 cm^2 contactable once inserted in the vagina of such an animal by the vaginal membrane and/or vaginal fluid(s) of the animal,

the matrix of progesterone containing silicone rubber material has been formed by injection of the uncured progesterone containing matrix as a liquid into a mould for a sufficient time to achieve at a mould temperature or temperatures within the range of from 190°C to 195°C and a shape retaining at least partial cure thereof,

the total progesterone load (irrespective of whether alpha or beta progesterone or mixtures thereof) being from 1 to 1.5 grams within said matrix,

said surface area is available to at least substantially all of the matrix for progesterone release over a thickness of no greater than about 1 millimetre, and

said device upon vaginal insertion into such an animal is able to achieve and then maintain in the animal for at least seven days a minimum progesterone blood plasma level of 2 nanograms per millilitre of plasma of the animal and which after seven days from insertion will have a residual load in the silicone rubber matrix of less than 60% by weight of its progesterone load at insertion.

9. A device of any one of the preceding claims substantially as hereinbefore defined with reference to any one or more of the accompanying drawings.

10. **A method of postponing oestrus or treating anoestrus in an animal** which includes the steps of **administering** into said animal by means of an intra vaginal device sufficient progesterone from a progesterone impregnated silicone rubber matrix where the progesterone content in the matrix is 5% or greater by weight via a surface area greater than 75 cm^2 so as to achieve on the last few days of insertion a progesterone blood plasma level of from 2 to about 4 nanograms per millilitre, and **removing** the device after an insertion period of from 5 to 12 days.

11. A method of claim 10 wherein said device is as claimed in any one of claims 1 to 9.

12. A method of claim 10 or 11 which includes the administration of oestradiol at or near the time of insertion of said device.

13. A method of any one of claim 10 to 12 which includes the administration of a prostaglandin at about day 6 of about a 7 day or 10 day device insertion period.

14. **In a method of attempting to synchronise the onset of oestrus of a herd of cattle beasts, the procedure of**

administering intra vaginally to each animal of the herd progesterone from an intra vaginal device as claimed in any one of claims 1 to 9 and

after and appropriate period of time removing such devices to allow the onset of oestrus (the procedure optionally including the steps of administration of oestradiol and/or prostaglandin etc. as known in the art or otherwise), **said method being further characterised in that** level of progesterone in the blood plasma of each animal is at least 2 nanograms per millilitre until such time as the devices are withdrawn.

15. A method of claim 14 wherein the devices are withdrawn at about day 7 or day 10 after insertion.

16. **A method of synchronising the onset of oestrus in a herd of cattle beasts** which comprises

administering by means of an intra vaginal device to each animal from a progesterone impregnated matrix of the device an effective amount of progesterone for the period the device is retained intra vaginally, the device having being administered with a progesterone quantity of about 1.35 grams and being removed with a progesterone quantity of the order of about 0.85 grams.

FIG 1

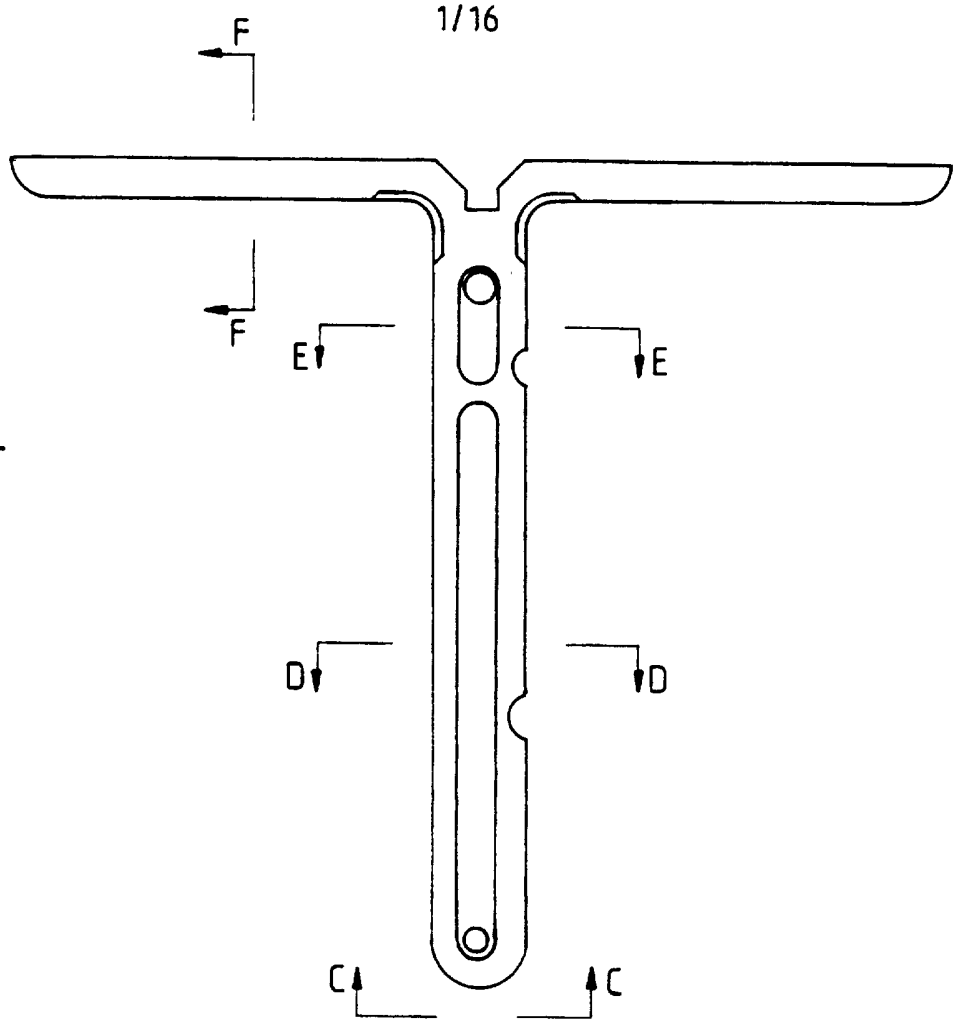


FIG. 1A

FIG. 1B

FIG. 1C

FIG. 1E

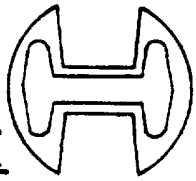


FIG. 1D

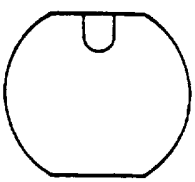


FIG 1'

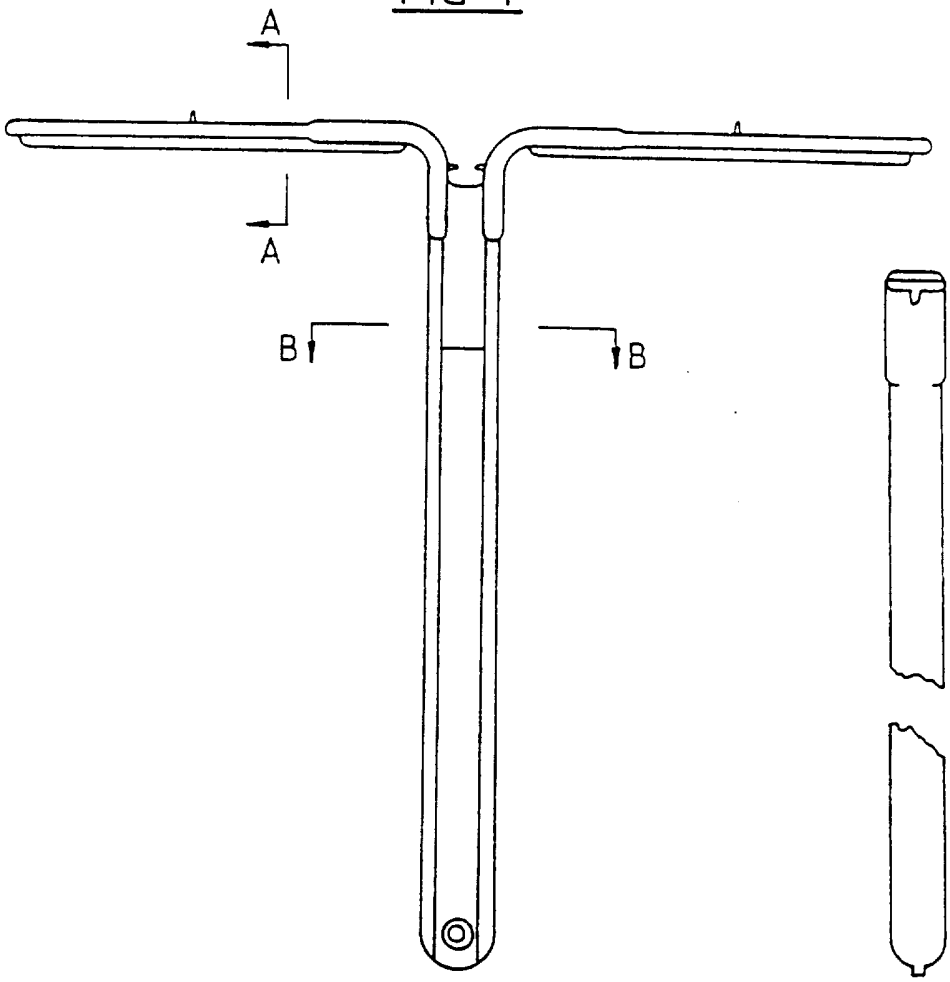


FIG 1'A

FIG 1'B

FIG 1'C

FIG 1'D

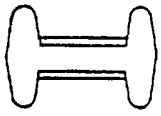


FIG 1'E

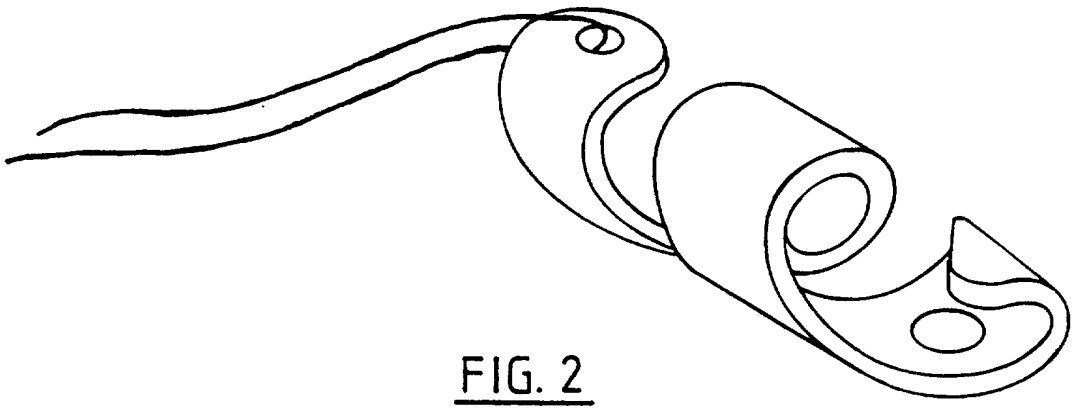


FIG. 2

FIG 3

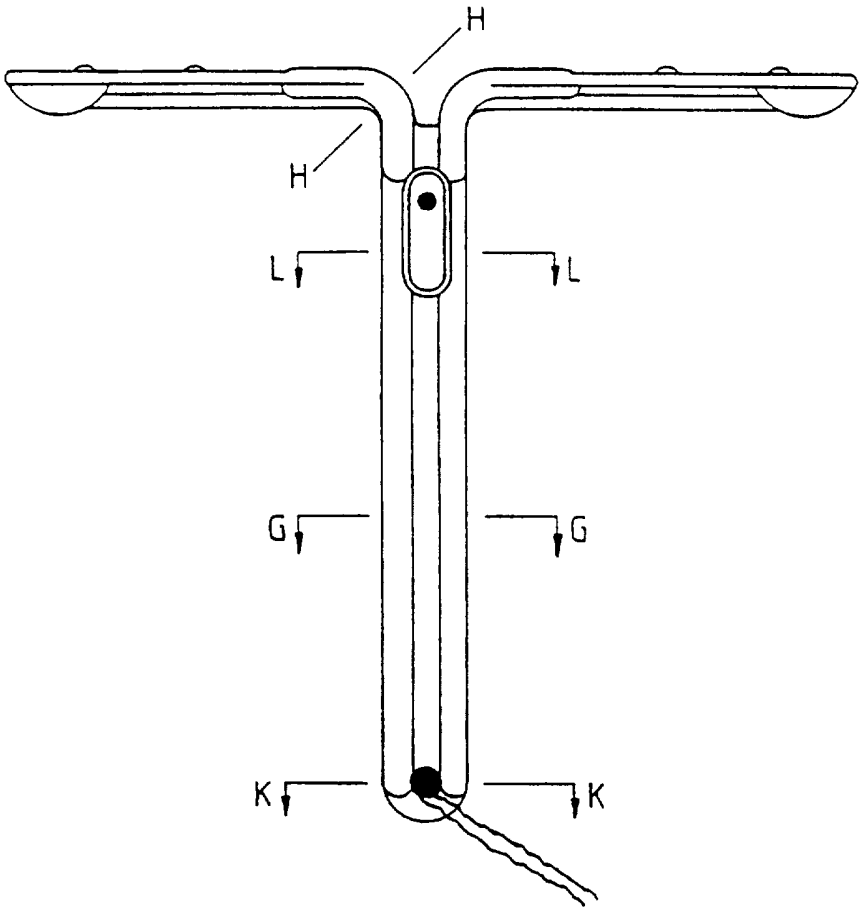


FIG 3A

FIG 3B

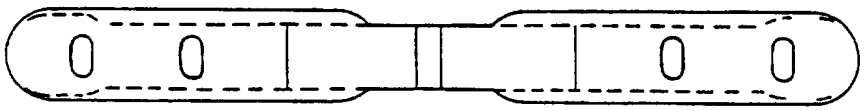


FIG 3C

FIG 3E

FIG 3D

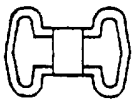


FIG 3F

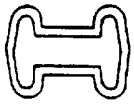
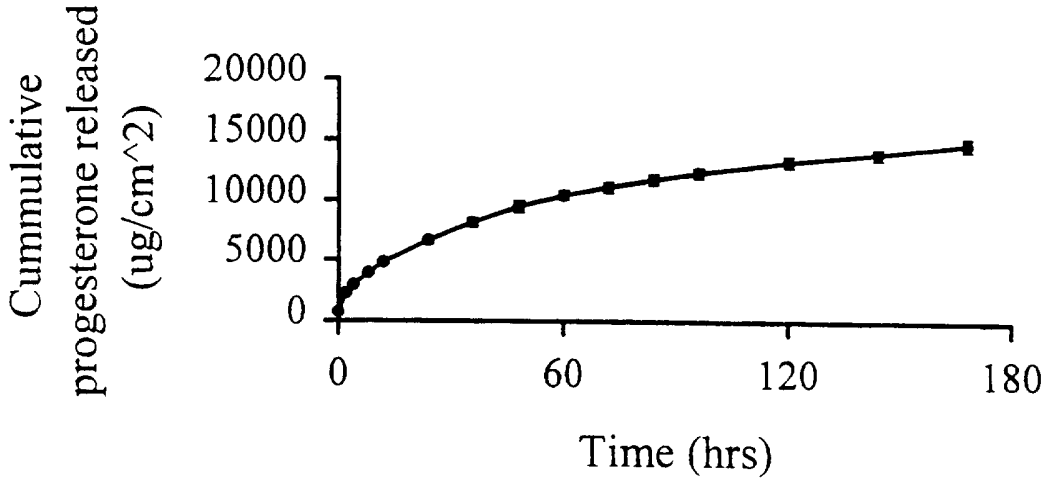


FIG 3G

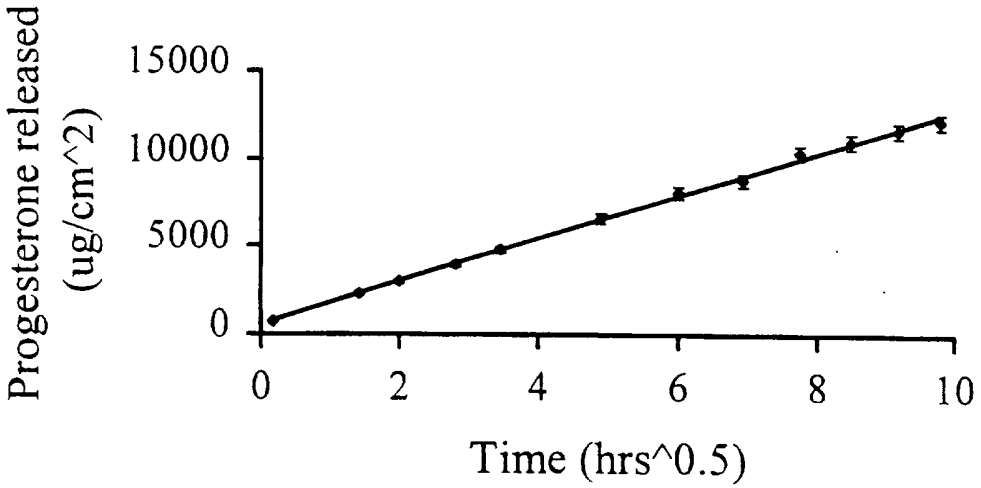
FIG 3H

FIG 3I



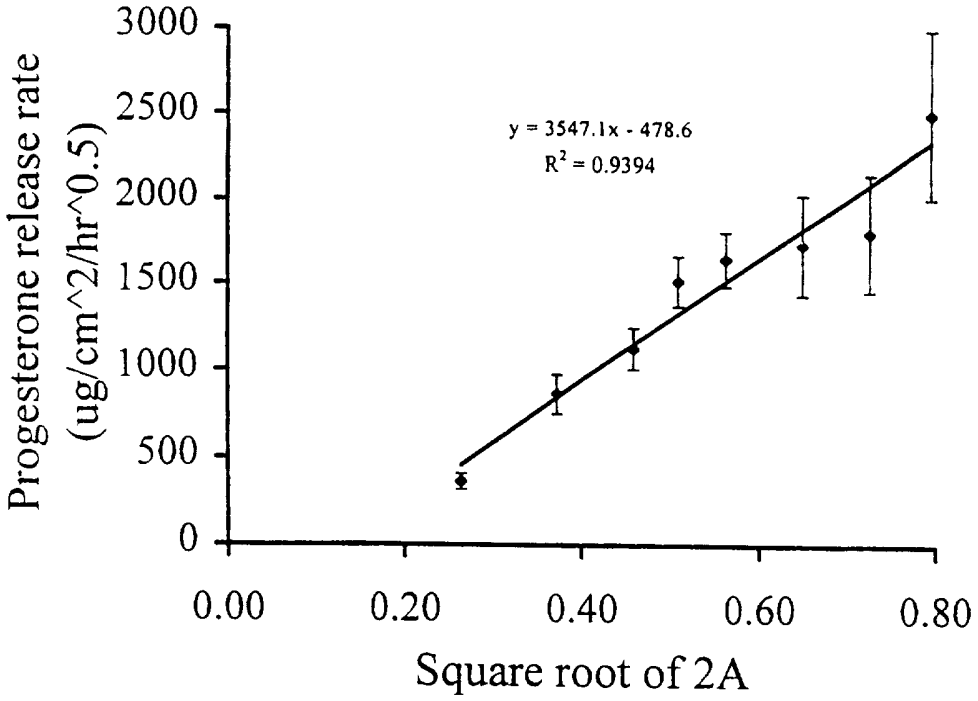
Cumulative amount of progesterone released per unit area of the existing CIDR™ as a function of time. Error bars are standard errors of means (n=7).

FIG. 4



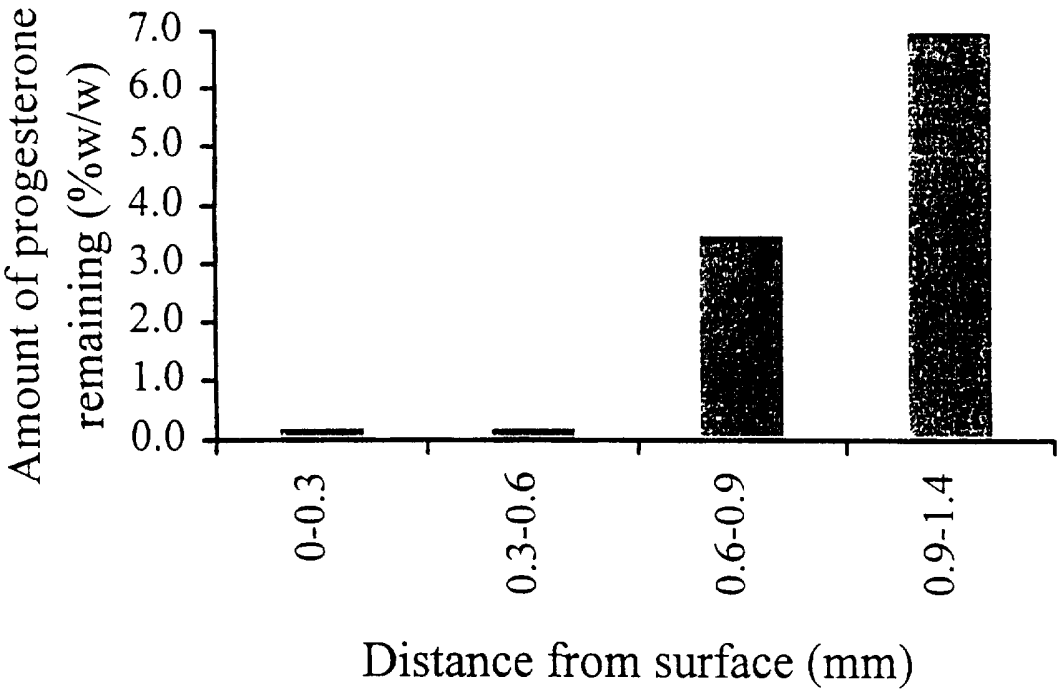
In vitro cumulative amount of progesterone release per unit area of existing CIDR™ up to 96 hours verses the square-root-of-time. Error bars are standard errors of means (n=7).

FIG. 5



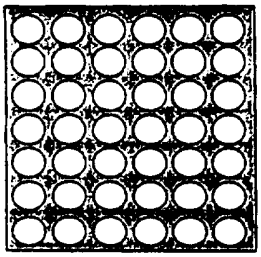
Effect of *in vitro* release rate of progesterone from existing CIDR™ upon the square root of twice the progesterone load. Error bars are standard errors of means (n=3).

FIG. 6



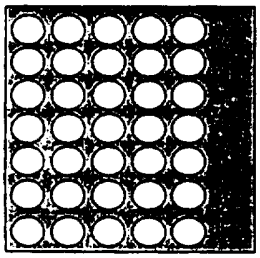
Progesterone content of *in vitro* drug depletion zone for the existing CIDR™ retained in 60%v/v alcohol:water for 4 days determined by chemical analysis.

FIG. 7



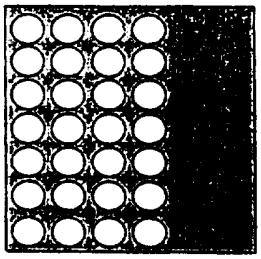
The drug is assumed (i) to be homogeneously dispersed thoughout the polymer, (ii) be present in excess of its solubility and (iii) exist in the form of layers of drug within the polymer

Incorporated drug can be visualised as existing in layers.

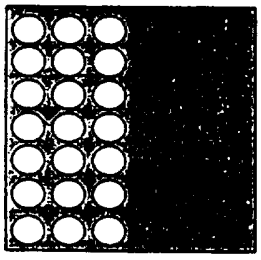


As time goes by each consecutive layer becomes eluted from the polymer.

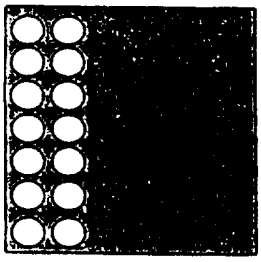
The outermost layer that is closest to the release medium is released (eluted) first.



When the first layer has been eluted from the polymer the second layer begins to elute out of the polymer.



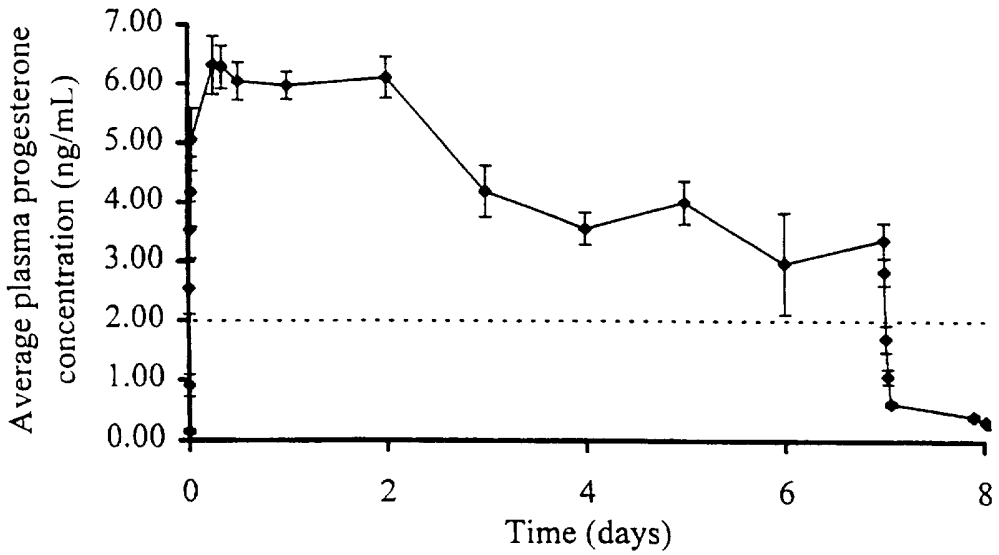
As time goes by each successive layer of drug is released.



Only when the surface layers have been eluted can the deeper layers of drug be released.

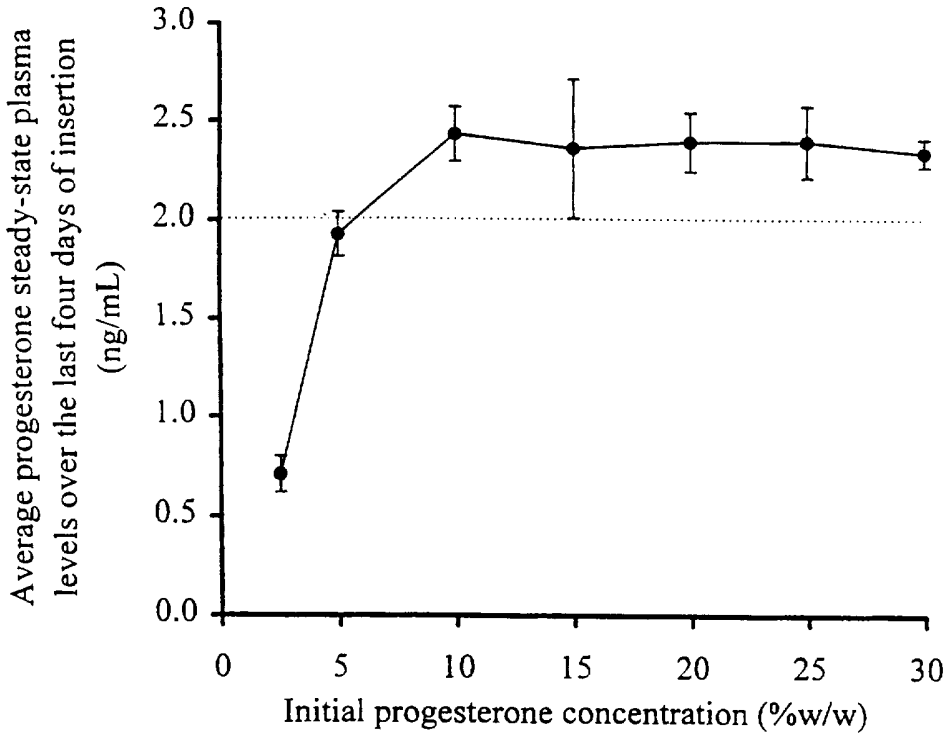
Idealised pictorial model of progesterone release from the existing CIDR™ according to the square-root-of-time model.

FIG. 8



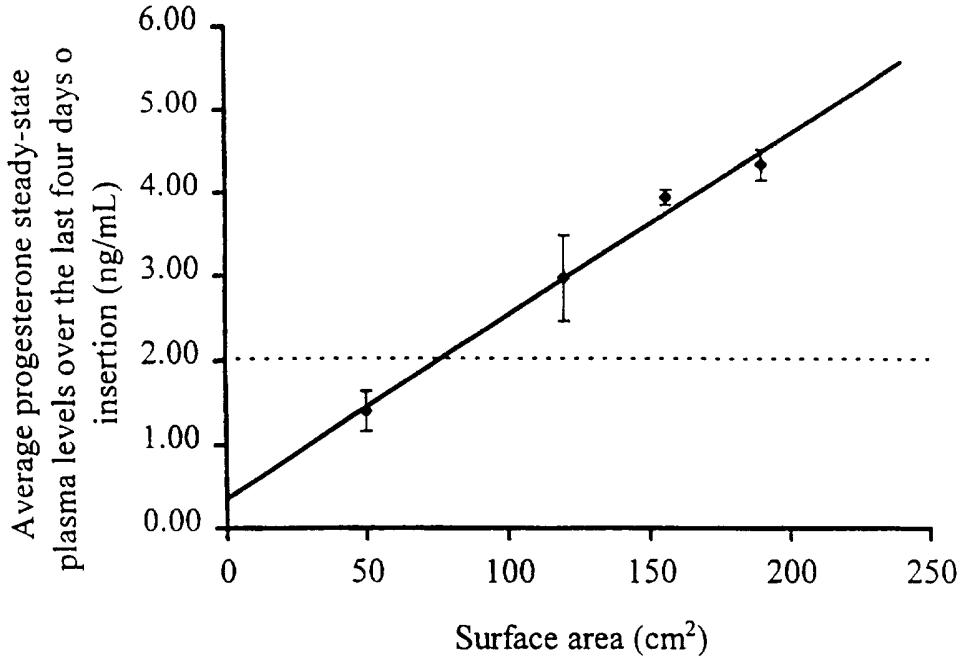
Plasma progesterone levels during a 7 day insertion of the existing CIDR™ device. Error bars are standard errors of means (n=4 cattle).

FIG. 9



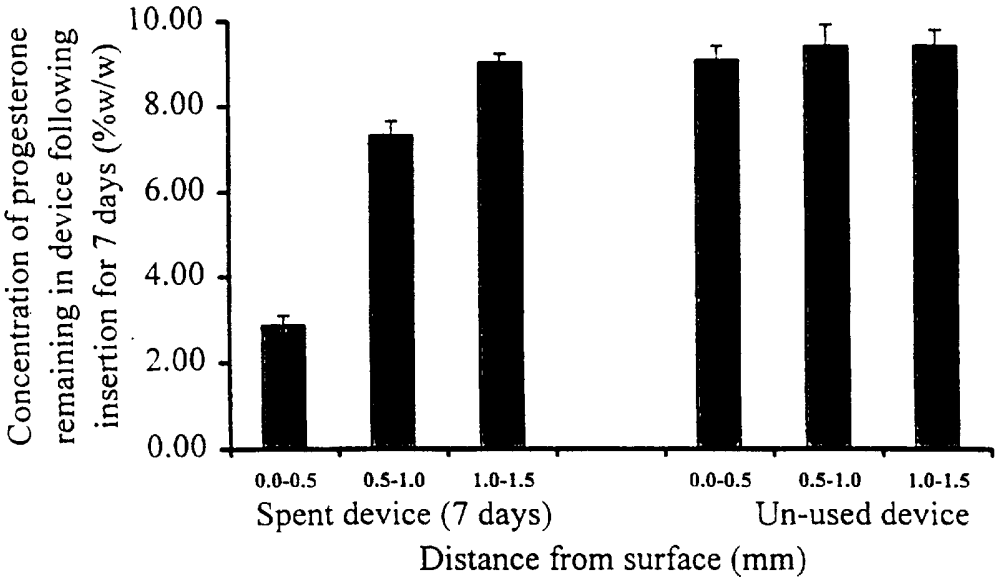
Effect of initial progesterone concentration (%w/w) in the existing CIDR™ on average steady-state progesterone levels over the last four days of a 7 day insertion period.

FIG. 10



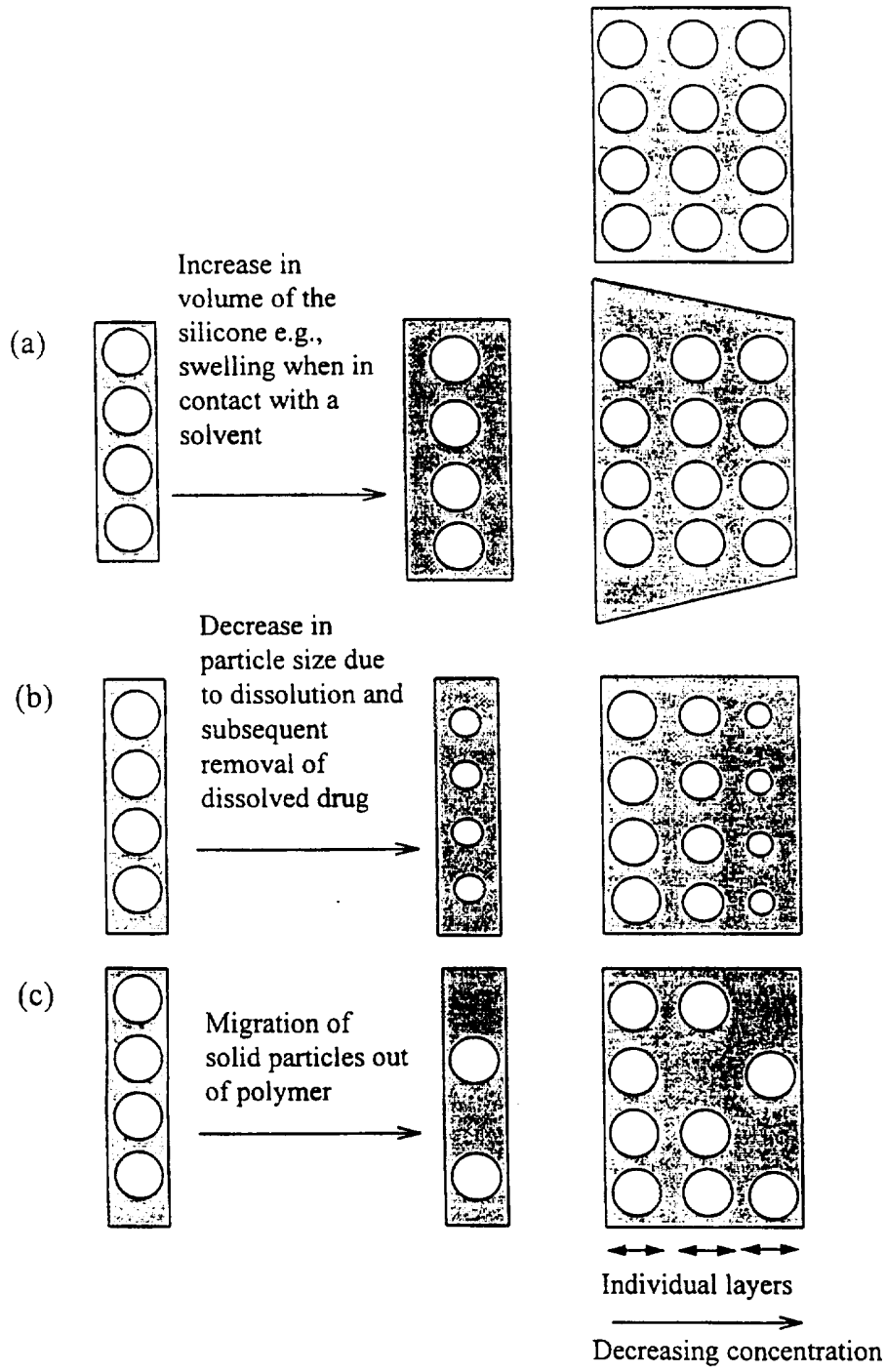
Effect of surface area of existing CIDR™ on average progesterone steady-state plasma levels over the last four days of a 7 day insertion period. Error bars are standard errors of means (n=4 cattle).

FIG. 11



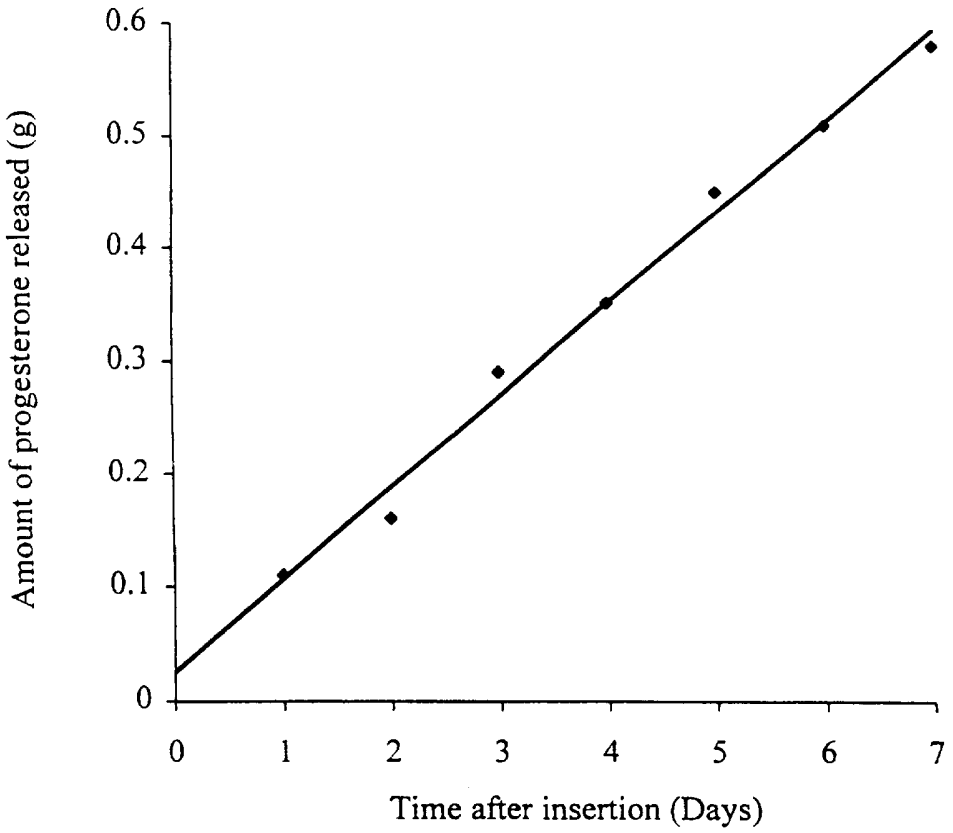
Average concentration (%w/w) of progesterone at various depths in spent existing CIDR™ devices which had been inserted for 7 days. Error bars are standard errors of means (n=3).

FIG. 12



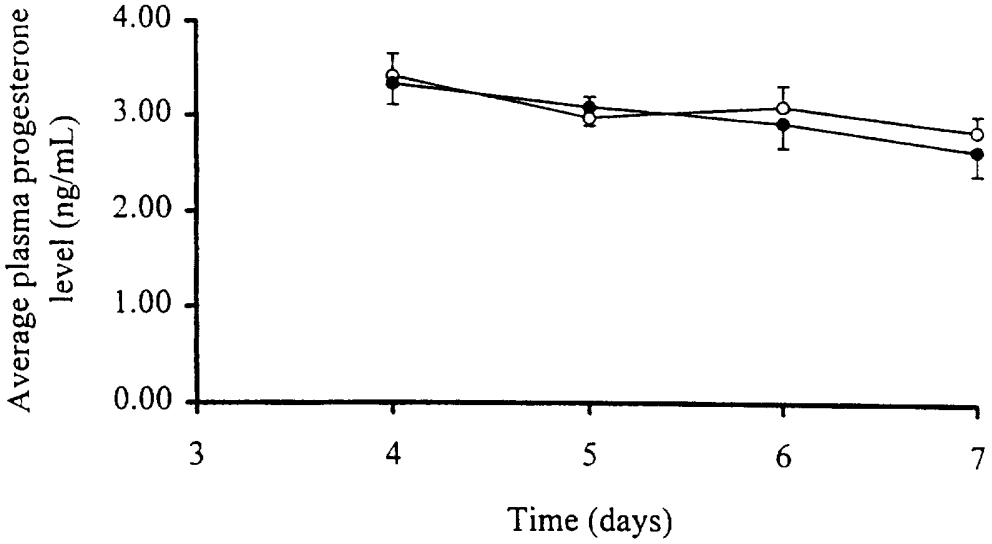
Possible reasons why progesterone particles in a layer of silicone could decrease in concentration; (a) increase in volume of silicone, (b) decrease in particle size due to dissolution and (c) delocalisation of particles out of the layer of silicone.

FIG. 13



In vivo release profile of progesterone over a 7 day insertion period (n=3 cattle) from an existing CIDR™ device containing a 10%w/w initial progesterone concentration.

FIG. 14



Average plasma progesterone levels over the last four days of a 7 day insertion period for the CIDR-B™ (●) and existing CIDR™ device (O) both containing a 10%w/w initial progesterone concentration. Error bars are standard errors of means (n=14 cattle).

FIG. 15

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/NZ 97/00052

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61D 19/00 A61K 47/34 A61K 31/57 A61K 9/00

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

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT: (INTRA(W) VAGINAL OR INTRAVAGINAL: OR VAGINAL:) AND (OESTRUS OR ANOESTRUS OR PROGEST:) PROGESTERONE AND SILICON:
Medline: (PROGEST? AND (SILICON? OR SILASTIC)) AND (CATTLE OR COW? OR HEIFER?)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4012496 (SCHÖPFLIN) 15 March 1977 whole document	1-15
X		16
X	JOURNAL OF REPRODUCTION & FERTILITY, volume 46, ISSUED JANUARY 1976 (ENGLAND) J.F. Roche "Retention rate in cows and heifers of intravaginal silastic coils impregnated with progesterone" pages 253-5 whole document	10-13
Y		8, 16

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

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 1997	22 AUG 1997

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INTERNATIONAL SEARCH REPORT

.ternational Application No.
PCT/NZ 97/00052

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 4402695 (WONG) 6 September 1983	
Y	whole document	10-13
X		10
	US 4961931 (WONG) 9 October 1990	
Y	whole document	10-13
X		16
	US 5398698 (HILLER) 21 March 1995	
Y	whole document	10-13
X		16
	US 4016251 (HIGUCHI) 5 April 1977	
X	whole document	16
X	US 4014987 (HELLER) 29 March 1977 whole document	16
	US 3545439 (DUNCAN) 8 December 1970	
X	whole document	16
	US 3920805 (ROSEMAN) 18 November 1975	
X	whole document	16
	AU 70919/81 (MILLAR et al)	
Y	whole document	16

INTERNATIONAL SEARCH REPORT

.ternational Application No.
PCT/NZ 97/00052

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See supplementary page

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

. ..ernational Application No.
PCT/NZ 97/00052

Box II continued

The international application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept. In coming to this conclusion the International Searching authority considers that:

Claims 10-13 are directed to an intravaginal device which delivers progesterone from an impregnated matrix into an animal to manipulate the onset of oestrus. It is considered that progesterone blood plasma levels of from 2-4 ng/ml comprises a first "special technical feature".

Claim 16 is directed to an intravaginal device which delivers progesterone from an impregnated matrix into an animal to manipulate the onset of oestrus. It is considered that the initial mass of progesterone in the device of 1.35 g comprises a second "special technical feature".

Claims 1 to 9 are directed to an intravaginal device which delivers progesterone from an impregnated matrix into an animal to manipulate the onset of oestrus which comprise both the aforementioned "special technical features".

The above-mentioned groups of claims 10-13 and 16 do not share either of the technical features identified. A "technical relationship" between the inventions as defined in PCT Rule 13.2 does not exist.

Accordingly the international application does not relate to one invention or to a single inventive concept.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No.
PCT/NZ 97/00052

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	4012496	AU	85835/75	BE	843624	CA	1084791
		DE	2450107	DK	4635/75	EG	11804
		ES	441814	FI	752848	FR	2287917
		GB	1528602	IL	48277	IN	141998
		IT	1048462	JP	51064793	NL	7512254
		NO	753500	SE	7511619	US	4155991
		ZA	7506580				
US	4402695	US	4250611	US	4215691	US	4286587
US	4961931	US	4629449				
US	5398698	DE	3838815	DK	5746/89	EP	369400
		PT	92331	ZA	8908748		
US	4016251	US	4351978				
US	4014987	AR	206692	AT	10749/73	AU	63804/73
		BE	809161	CA	1046408	CH	603165
		DE	2363963	ES	421677	FR	2247259
		GB	1417527	IL	43915	IT	1055547
		JP	49094818	NL	7317731	ZA	7309568
		US	4180064	US	4249531		
US	3545439	BE	726454	CA	985173	CH	554172
		DE	1900196	ES	360946	FR	1604934
		GB	1252021	MY	59/75	NL	6818655
US	3920805	AU	49088/72	BE	792502	CA	985624
		CH	586043	DE	2259070	FR	2162628
		GB	1366796	JP	48062916	NL	7215327
		ZA	7208177				
AU	70919/81	CA	1182695	DE	3122506	FR	2483771
		GB	2079158	GR	72701	JP	57022750
		NL	8102782	NZ	193976	US	4449980

END OF ANNEX