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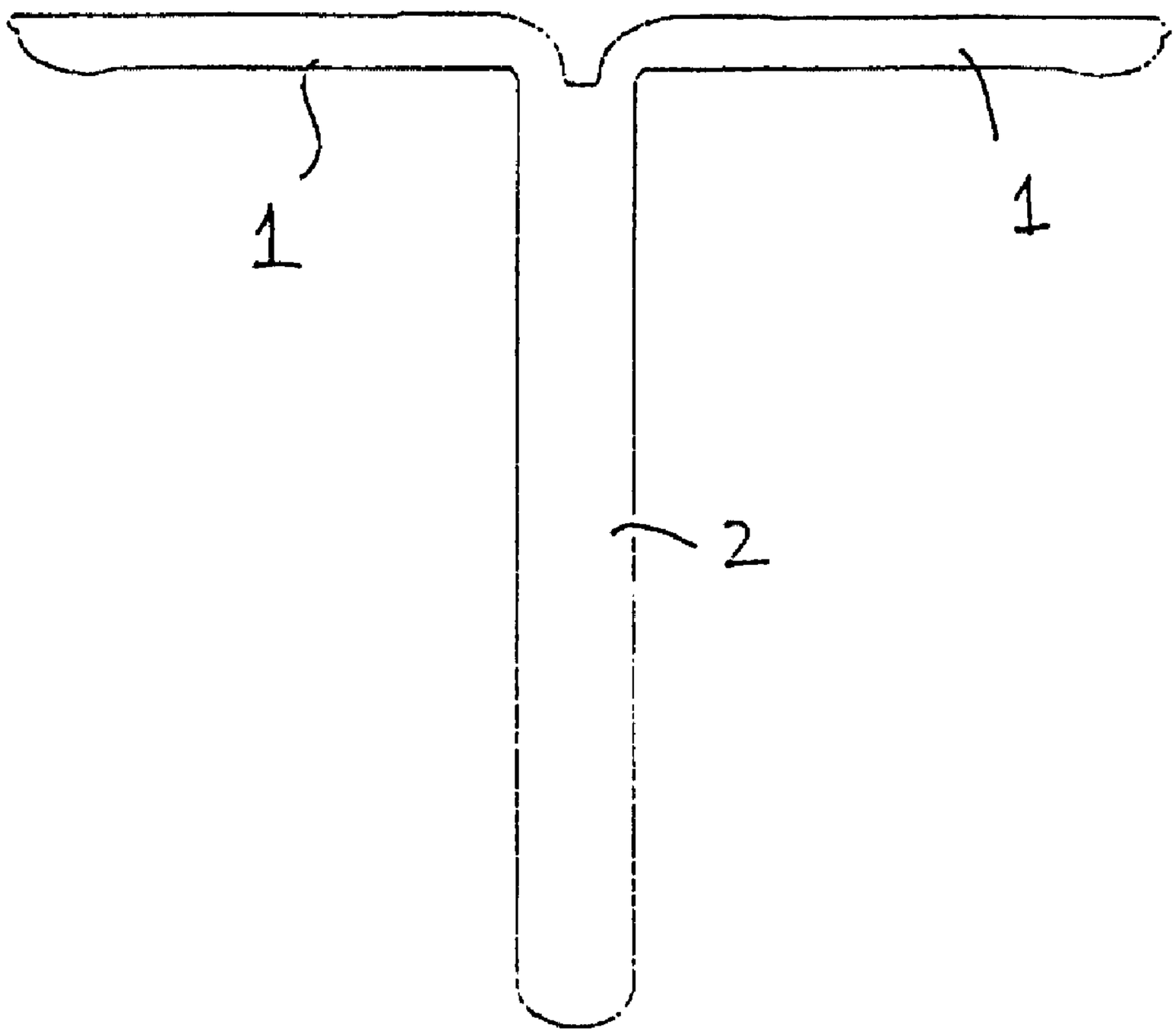

(57) Abrégé/Abstract:
An intra vaginal device for delivering a pharmaceutical agent (e.g. progesterone) into a recipient mammal. The active agent is carried in a matrix of a biodegradable polymer (such as poly ε-caprolactone or a starch-like polysaccharide) having an ability to provide (without reliance on a supporting spine) desired retention characteristics of a variable geometry retention device, an appropriate release profile during a finite insertion period and biodegradability upon removal from the mammal.

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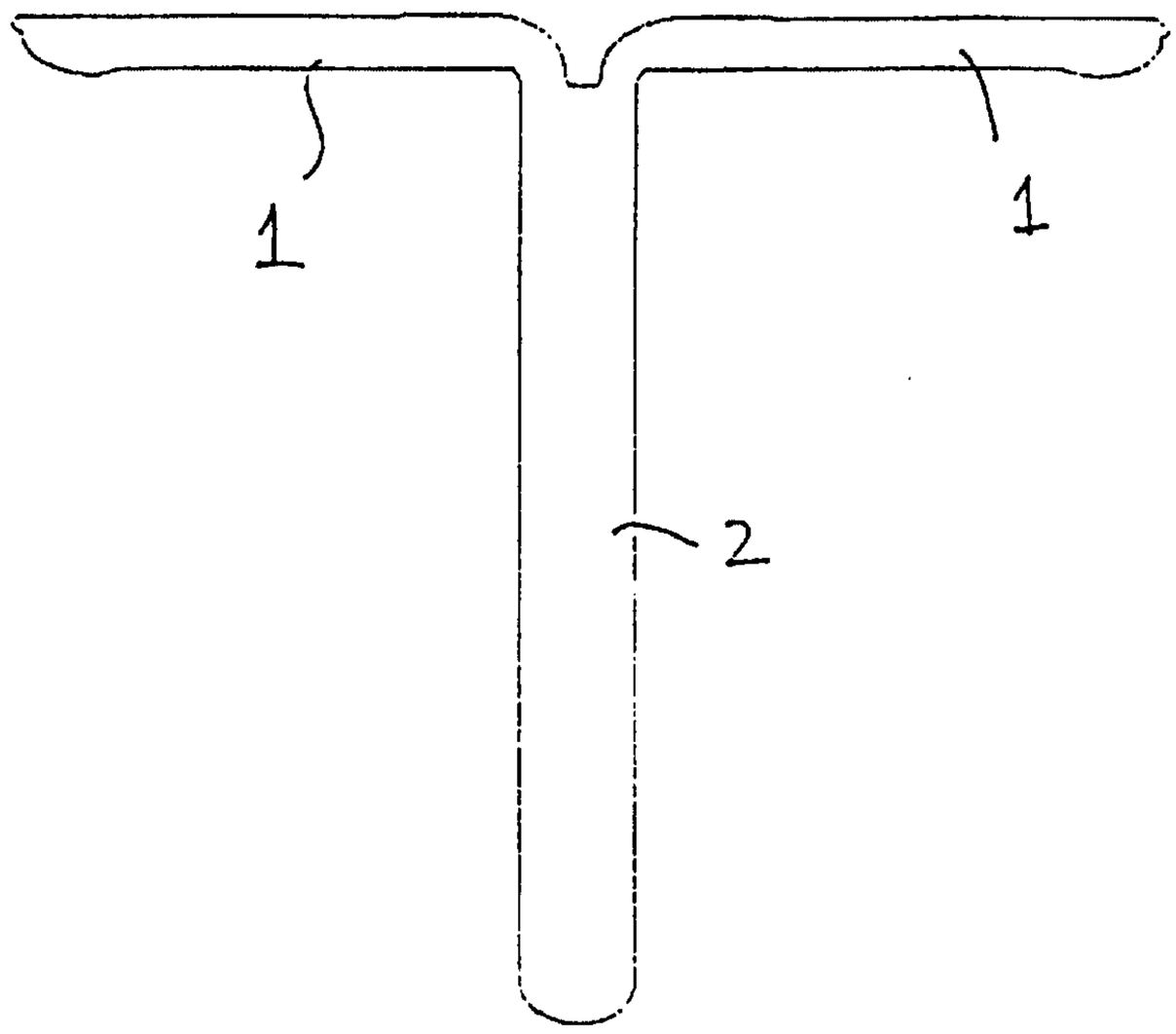


(57) Abstract

An intra vaginal device for delivering a pharmaceutical agent (e.g. progesterone) into a recipient mammal. The active agent is carried in a matrix of a biodegradable polymer (such as poly ϵ–caprolactone or a starch–like polysaccharide) having an ability to provide (without reliance on a supporting spine) desired retention characteristics of a variable geometry retention device, an appropriate release profile during a finite insertion period and biodegradability upon removal from the mammal.

BIODEGRADABLE INTRA VAGINAL DEVICES

The present invention relates to improvements in and/or relating to intra vaginal devices or inserts.

Our PCT/NZ97/00052 (published as WO 97/40776) discloses a variety of different forms of intra vaginal device of a variable geometry type for retention within the intra vaginal cavity of an animal. Such devices hitherto have primarily involved the use of a silicone rubber composition which as a matrix has been impregnated with the active pharmaceutical agent (eg; progesterone). In the variable geometry type devices typified by the CIDR™ devices of this company the impregnated matrix has primarily been supported on a spine of a resilient material such as nylon, the resilience of which is utilised for the variable geometry retention characteristics notwithstanding that such spine is usually fully overlaid with the impregnated matrix.

Various polymers possessing the ability to undergo biodegradation have been used to deliver pharmaceutical agents. A class of polymers possessing this characteristic and extensively utilized for the delivery of pharmaceutical agents are the polyesters. Examples of these polymers include poly lactic acid, poly glycolic acid, poly (ε-caprolactone) and various co-polymers of lactide, glycolide and ε-caprolactone.

Pharmaceutical products utilizing these polymers are typically formulated as microspheres, microcapsules, films, rods or blocks. Retention within a body cavity has been achieved by a number of methods; the addition of dense fillers, injections or surgical implantation into muscle or subcutaneous area.

The present invention relates to a device or insert designed to deliver progesterone over an extended period of time (2 to 20 days) upon insertion into the vagina of animals such as cattle, sheep, horses, pigs, goats, buffalo or deer. The device or insert is retained within the vagina by means of a flexible geometric arrangement (eg; of the arms and body).

Upon completion of treatment the device is removed and disposed of in a manner that preferably capitalizes upon the biodegradable properties of the polymer.

We have determined that biodegradable polymers typified by poly(ε-caprolactone)

or a starch like saccharide can be appropriately impregnated with an intra vaginally effective active agent [such as progesterone (e.g. in concentration of from 5% to 70% w/w)] so as to provide appropriate *in vivo* release characteristics for the active agent over a period of intra vaginal retention required by the particular procedure whereupon, after extraction, the material is readily biodegradable following removal from the animal.

Surprisingly it has also been found that a polymer such as a poly (ε-caprolactone) can be moulded notwithstanding its being impregnated with the active agent to provide not only the impregnated matrix but also to provide the variable geometry device without an obligatory presence of a spine or the like such as in the prior art devices. Similarly, starch like saccharides have been found to be capable of being shaped to the same effect.

Accordingly in a first aspect the present invention consists in **an intra vaginal device or insert** for a target species mammal and of a kind capable of intra vaginal insertion, intra vaginal retention for a period of time and removal from the vaginally a simple pulled withdrawal **characterised in that**

(i) said device or insert has or is a moulded mass of at least primarily one or both of poly (ε-caprolactone) and a mouldable biodegradable starch-like polysaccharide,

(ii) said mass includes a pharmaceutical agent to be administered into the target species mammal by the intra vaginal route,

(iii) said mass delivers said pharmaceutical agent intra vaginally during said retention period of time without substantial degradation of the integrity of the mass yet said mass, upon withdrawal and, over time, will degrade if left in the open, and

(iv) said despite the mass, the device or insert as a whole is intra vaginally retainable by being resiliently conformable to allow insertion and thereafter to recover to a geometry to minimise spontaneous rejection from the vagina.

Preferably the device or insert is vaginally retainable for at least 2 days in a target

species mammal.

Preferably the agent is progesterone.

Preferably the progesterone comprises from 5 to 70% w/w.

Preferably the polymer is or includes poly (ε-caprolactone), or

Alternatively the polymer is or includes a starch-like polysaccharide.

Preferably said mass includes therein cyclodextrin

Preferably the agent does not appear as a fine powder or crystals upon the surface of said mass.

Preferably said device or insert comprises of includes the said mass which defines at least substantially all of said device or insert.

In another aspect the present invention is **an intra vaginal device or insert** for a target species mammal comprising or including an intra vaginally insertable, retainable and removable mass of at least primarily one or both of poly (ε-caprolactone) and a mouldable biodegradable starch-like polysaccharide, the mass by virtue of its resilience being of variable geometry which allows the intra vaginal insertion, retention and removal,

wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than $2^{ng}/_{ml}$ for a period of at least 5 days can follow intra vaginal insertion thereof and wherein after removal the mass is biodegradable after removal from the animal.

Preferably said target species is selected from cattle, sheep, horses, pigs, goats, buffalo and deer.

Preferably said device or insert includes no supporting spine (eg; nylon or polyester).

Preferably the progesterone inclusion is sufficient to deliver progesterone for a period from 2 to 20 days.

Optionally said mass may include cyclodextrin.

In a further aspect the present invention consists in **the use** or **methods of use** of such a device or any device of the present invention.

The present invention also consists in **a method of manufacture of an intra**

vaginal device which results in any device in accordance with the present invention.

In another aspect the invention consists in a **method of manufacture of an intra vaginal device** which comprises the step of including in a mouldable biodegradable polymer matrix both a cyclodextrin and an intra vaginally effective agent.

In still another aspect the invention consists in **the use** inter alia **for animal group oestrus synchrony purposes** of devices or inserts of the present invention.

Preferably said use is intra vaginal use for a period of from 2 to 20 days and said device has a capability in the target species mammal of providing for at least 5 days (if intra vaginally inserted for at least about 5 days) a blood serum level of progesterone of greater than $2\,^{ng}/_{ml}$.

Preferably all polymer(s) of the said mass (if all, as is preferred, is to moulded) can be moulded without use of conditions prejudicial to the pharmaceutical agent and any cyclodextrin (or for that matter, any other absorption enhancing agent) present.

In still a further aspect the invention consists in **a method of achieving with an animal (or group of animals) a blood serum level of progesterone of greater than $2\,^{ng}/_{ml}$ for a period of at least 5 days**, said method comprising inserting and retaining in the or each animal for at least the at least 5 day period a device or insert of the present invention.

We have found that the biodegradable polymers of choice are capable of being effectively impregnated with the pharmaceutical agent and optionally an absorption enhancement agent, being effectively moulded into the form of an intra vaginal device or insert of a kind reliant on variable geometry for retention, providing over the finite insertion period an appropriate tract to provide a desired pharmacological effect without detriment from any propensity of the polymer(s) to *in vivo* biodegrade, and, upon removal much lower in pharmaceutical agent content (see WO 97/40776), of providing no long term disposal problem owing to the propensity of the polymer(s) to biodegrade after removal from the animal.

In another aspect, the present invention provides an intra vaginal device or insert for a target species mammal, said intra vaginal device or insert being capable of intra vaginal insertion, intra vaginal retention for a period of time and removal from a vagina by a simple pulled withdrawal characterised in that (i) said device or insert has

or is a moulded mass formed primarily by poly (ϵ-caprolactone) or a mouldable biodegradable starch-like polysaccharide, or formed primarily by a combination of poly (ϵ-caprolactone) and a mouldable biodegradable starch-like polysaccharide, (ii) said mass includes a pharmaceutical agent to be administered into the target species mammal intra-vaginally, (iii) said mass delivers said pharmaceutical agent intra vaginally during said retention period of time without substantial degradation of the integrity of the mass yet said mass, upon withdrawal will degrade unless placed in conditions similar to that of the vagina, and (iv) despite said mass, the device or insert as a whole is intra vaginally retainable by being resiliently conformable to allow insertion and thereafter to recover to a geometry to minimise spontaneous rejection from the vagina.

In another aspect, the present invention provides an intra vaginal device or insert for a target species mammal comprising or including an intra vaginally insertable, retainable and removable mass formed primarily by poly (ϵ-caprolactone) or a mouldable biodegradable starch-like polysaccharide, or formed primarily by a combination of poly (ϵ-caprolactone) and a mouldable biodegradable starch-like polysaccharide, the mass by virtue of its resilience being of variable geometry which allows the intra vaginal insertion, retention and removal, wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than 2 $^{ng}/_{ml}$ for a period of at least 5 days can follow intra vaginal insertion thereof and wherein after removal the mass is *in vitro* biodegradable.

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which:

Figure 1 shows a device of variable geometry (the geometry being variable much

in the way as discussed in WO 97/40776) but without a need for a spine of a dissimilar material (although if desired that can optionally be present),

Figure 2 shows an *in vitro* cumulative progesterone release against the square-root-of-time (inserts manufactured from poly (ε-caprolactone) (thin line) or silicone (thick line)).

Figure 3 shows an average plasma progesterone concentration against time following two rounds of vaginal treatment with a silicone insert of 134 cm^2 surface area (▫) or a poly (ε-caprolactone) insert of 105 cm^2 surface area (▪), both of which contain 10% $^{w}/_{w}$ progesterone (error bars are standard error means (n-12 for silicone inserts, n=9 for poly (ε-caprolactone) inserts)),

Figure 4 shows a percentage of initial mass lost for drug-loaded (▪) and blank (▫) poly (ε-caprolactone) inserts stored in compost over time (the solid line is the suggested mass loss as per promotional literature supplied by the poly (ε-caprolactone) manufacturer (error bars are ranges (n=2)),

Figure 5 shows a percentage of tensile performance lost for drug-loaded (▪) and blank(▫) poly (ε-caprolactone) inserts buried in compost over time (the solid line is the suggested tensile performance loss as per promotional literature supplied by the manufacturer. (Error bars are ranges (n=2)),

Figure 6 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a silicone insert of 134 cm^2 surface area (▪), poly (ε-caprolactone) insert of 115 cm^2 surface area (▫) or poly (ε-caprolactone) with lactose insert of 115 cm^2 surface area (○) (A final plasma sample was collected 6 hours after removal on day 7. (Error bars are standard error means (n=3)),

Figure 7 shows the percentage of initial mass lost for various poly (ε-caprolactone) formulations stored in compost over time [Poly (ε-caprolactone) (♦), poly (ε-caprolactone) with 10% $^{w}/_{w}$ progesterone (▪), poly (ε-caprolactone) with 12.1% $^{w}/_{w}$ lactose and 10.47% $^{w}/_{w}$ progesterone (▲), poly (ε-caprolactone) with 37.2% $_{w}$/ β-cyclodextrin and 10.3% $^{w}/_{w}$ progesterone (x), poly (ε-caprolactone) with 43.8% $^{w}/_{w}$ hydroxypropyl β-cyclodextrin and 10% $^{w}/_{w}$ progesterone (*) or poly (ε-caprolactone) with 39.9% $^{w}/_{w}$ γ-cyclodextrin and 9.7% $^{w}/_{w}$ progesterone (●). (Error bars are ranges

(n=2))], and

Figure 8 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a Mater-Bi insert of 58 cm^2 surface area with (■) or without (●) the addition of 20% w/w NaCl. (Error bars are ranges (n=2)).

The choice of a resilient mouldable or shapable "polymer" which is biodegradable is such that degradation of the impregnated matrix (but with a low residual active ingredient loading) will occur over time after removal from the animal after having served its purpose during an intra vaginal insertion of preferably from 2 to 20 days (eg; about 7 days). Minimal degradation (if any) occurs during the period of insertion.

In the device of Figure 1 the device is wholly of the impregnated matrix which is poly (ε-caprolactone) impregnated with progesterone in the concentration of 5 to 70% w/w without any solid active pharmaceutical agent appearing as a fine powder or crystals on the surface of the device.

In Figure 1 the wings 1 are resilient with respect to the body 2 and in an intra vaginal injection mode can be reduced to a form or assume a position in an applicator in a known manner which facilitates insertion after which the resilience deploys the wings 1 to such condition as is required for retention. The resilience can be subsequently utilised to withdraw the device from within the vagina.

A suitable source of poly (ε-caprolactone) is that product TONE 767™ from Union Carbide Specialty Polymers and Products, Danbury, Ct, USA.

Starch-like polysaccharides that can likewise be impregnated and can be used for some or all of the device include MATER-Bi™ available from Novamont, Italy.

A preferred method of manufacturing of the device is as follows: Polymer poly ε-caprolactone, starch-like polysaccharide or a blend of the two are mixed with active into a mixing vat using a suitable compound, eg; surfactant to adhere the active to the surface of the polymer granules or the use of compound extruded material.. The polymer/active mixture is then loaded into the hopper of an injection moulding machine, and processed as a conventional thermoplastic, with machine set point parameters as per the technical recommendations of the polymer suppliers literature, and as per injection moulding standard practice.

Key processing set points for poly ε-caprolactone are: barrel temperatures ranging from 80 - 120°C with an injection pressure of 1600 bar. Total cycle time due to long cooling phase of approximately 55 seconds. Product is removed from the die and allowed to cool to equilibrium prior to packaging.

Preferably the performance of the device while inserted and its effect upon withdrawal is substantially as discussed in WO 97/40776 but with the advantages of (I) biodegradability after removal from the animal and (ii) the preferred omission of a spine of resilient material.

The preferred biodegradable polymers (typified by poly (ε-caprolactone) or a starch like saccharide) can be appropriately impregnated with an intra vaginally effective active agent such as progesterone (eg: in concentration of from 5% to 70% w/w) and an absorption enhancing agent such as hydroxypropyl β-cyclodextrin (eg: in concentrations of from 5% to 70% w/w) so as to provide appropriate release characteristics for the active agent over the period of intra vaginal retention.

The preferred device is wholly of the impregnated matrix which is poly (ε-caprolactone) impregnated with hydroxypropyl β-cyclodextrin in the concentration of 5 to 70% w/w.

A suitable source of hydroxypropyl β-cyclodextrin is that product BETA W7 HP available from Wacker Chemicals Australia, Victoria, Australia.

A preferred method of manufacture of the device is as follows: Polymer (poly (ε-caprolactone), starch-like polysaccharide or a blend of the two) are mixed with active and absorption agent into a mixing vat. The polymer/active/absorption agent mixture is then loaded into the hopper of an injection moulding machine; and processed as a conventional thermoplastic, with machine set point parameters as per technical recommendations of the polymers suppliers literature, and as per injection moulding standard practice. Key processing points are: barrel temperatures ranging from 60 - 250^{0}C with an injection pressure of 1600 bar. Total cycle time due and allowed to cool to equilibrium prior to packaging.

Figure 1 shows a device of variable geometry (the geometry being variable much in the way as discussed in WO 97/40776) but without a need for a spine of a dissimilar

material (although if desired that can optionally be present),

When inserts of the type shown in Figure 1 manufactured from poly (ε-caprolactone) are subjected to an *in vitro* dissolution procedure to assess the release of progesterone they display release characteristics similar to the silicone CIDR-B™ insert, Figure 2.

Figure 2 shows an in vitro cumulative progesterone release against the square-root-of-time. Inserts manufactured from poly (ε-caprolactone) (thin line) or silicone (thick line).

When inserts of the type shown in Figure 1 manufactured from poly (ε-caprolactone) of surface area less than the silicone CIDR-B™ inserts are administered to cattle and plasma samples collected for plasma progesterone concentration analysis slightly lower levels are observed, Figure 3.

Figure 3 shows an average plasma progesterone concentration against time following two rounds of vaginal treatment with a silicone insert of 134 cm^2 surface area (▫) or a poly (ε-caprolactone) insert of 105 cm^2 surface area (■), both of which contain 10% $^{w}/_{w}$ progesterone. Error bars are standard error means (n-12 for silicone inserts, n=9 for poly (ε-caprolactone) inserts).

When inserts of the type depicted in Figure 1 manufactured from poly (ε-caprolactone) which container progesterone at 10 % $^{w}/_{w}$ or no progesterone are stored in compost for a period of 6 months the following mass losses are observed, Figure 4.

Figure 4 shows a percentage of initial mass lost for drug-loaded (■) and blank (▫) poly (ε-caprolactone) inserts stored in compost over time. The solid line is the suggested mass loss as per promotional literature supplied by the poly (ε-caprolactone) manufacturer. Error bars are ranges (n=2).

When inserts of the type depicted in Figure 1 manufactured from poly (ε-caprolactone) which contain progesterone at 10 % $^{w}/_{w}$ or no progesterone are stored in compost for a period of 6 months the following tensile performance losses are observed, Figure 5.

Figure 5 shows a percentage of tensile performance lost for drug-loaded (■) and blank(▫) poly (ε-caprolactone) inserts buried in compost over time. The solid line is the

suggested tensile performance loss as per promotional literature supplied by the manufacturer. Error bars are ranges (n=2).

When inserts of the type shown in Figure 1 manufactured from poly (ε-caprolactone) of surface area similar to our silicone CIDR-B™ insert (disclosed in aforementioned WO 97/40776) are administered to cattle and plasma samples collected from plasma progesterone concentration analysis similar levels are observed. See Figure 6.

Figure 6 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a silicone insert of 134 cm^2 surface area (■), poly (ε-caprolactone) insert of 115 cm^2 surface area (▫) or poly (ε-caprolactone) with lactose insert of 115 cm^2 surface area (○). A final plasma sample was collected 6 hours after removal on day 7. Error bars are standard error means (n=3).

When inserts of the type depicted in Figure 1 manufactured from poly (ε-caprolactone) which contain various excipients are stored in compost for a period of 6 months the mass losses shown in Figure 7 are observed.

Figure 7 shows the percentage of initial mass lost for various poly (ε-caprolactone) formulations stored in compost over time. Poly (ε-caprolactone) (♦), poly (ε-caprolactone) with 10% $^{w}/_{w}$ progesterone (■), poly (ε-caprolactone) with 12.1% $^{w}/_{w}$ lactose and 10.47% $^{w}/_{w}$ progesterone (▲), poly (ε-caprolactone) with 37.2% $_{w}$ / β-cyclodextrin and 10.3% $^{w}/_{w}$ progesterone (x), poly (ε-caprolactone) with 43.8% $^{w}/_{w}$ hydroxypropyl β-cyclodextrin and 10% $^{w}/_{w}$ progesterone (*) or poly (ε-caprolactone) with 39.9% $^{w}/_{w}$ γ-cyclodextrin and 9.7% $^{w}/_{w}$ progesterone (●). Error bars are ranges (n=2).

When inserts are the type shown in Figure 1 manufactured using polysaccharide are administered to cattle and plasma samples collected for plasma progesterone concentration analysis the levels of Figure 8 are observed.

Figure 8 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a Mater-Bi insert of 58 cm^2 surface area with (■) or without (●) the addition of 20% w/w NaCl. Error bars are ranges (n=2).

CLAIMS:

1. An intra vaginal device or insert for a target species mammal, said intra vaginal device or insert being capable of intra vaginal insertion, intra vaginal retention for a period of time and removal from a vagina by a simple pulled withdrawal characterised in that

(i) said device or insert has or is a moulded mass formed primarily by poly (ϵ-caprolactone) or a mouldable biodegradable starch-like polysaccharide, or formed primarily by a combination of poly (ϵ-caprolactone) and a mouldable biodegradable starch-like polysaccharide,

(ii) said mass includes a pharmaceutical agent to be administered into the target species mammal intra-vaginally,

(iii) said mass delivers said pharmaceutical agent intra vaginally during said retention period of time without substantial degradation of the integrity of the mass yet said mass, upon withdrawal will degrade unless placed in conditions similar to that of the vagina, and

(iv) despite said mass, the device or insert as a whole is intra vaginally retainable by being resiliently conformable to allow insertion and thereafter to recover to a geometry to minimise spontaneous rejection from the vagina.

2. A device or insert of claim 1 which is vaginally retainable for at least 2 days in a target species mammal.

3. A device or insert of claim 1 or 2 wherein the agent is progesterone.

4. A device or insert of claim 3 wherein the progesterone comprises from 5 to 70% by weight of said device or insert.

5. A device or insert of claim 1 wherein the mass is or includes poly (ϵ-caprolactone).

6. A device or insert of claim 1 wherein the mass is or includes a starch-like polysaccharide.

7. A device or insert of any one of claims 1 to 6 wherein said mass includes therein cyclodextrin.

8. A device or insert of any one of claims 1 to 3, 5 and 6, wherein said mass includes therein cyclodextrin, and wherein the cyclodextrin comprises 5 to 70% by weight of said mass.

9. A device or insert of any one of claims 1 to 8 wherein said mass is formed as a solid mixture with the agent such that the agent is dispersed within the matrix of said mass.

10. A device or insert of any one of claims 1 to 9 wherein said mass defines at least substantially all of said device or insert.

11. An infra vaginal device or insert for a target species mammal comprising or including an infra vaginally insertable, retainable and removable mass formed primarily by poly (ε-caprolactone) or a mouldable biodegradable starch-like polysaccharide, or formed primarily by a combination of poly (ε-caprolactone) and a mouldable biodegradable starch-like polysaccharide, the mass by virtue of its resilience being of variable geometry which allows the intra vaginal insertion, retention and removal,

wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than 2 $^{ng}/_{ml}$ for a period of at least 5 days can follow infra vaginal insertion thereof and wherein after removal the mass is *in vitro* biodegradable.

12. A device or insert of claim 11 wherein said target species is selected from cattle, sheep, horses, pigs, goats, buffalo and deer.

13. A device or insert of claim 11 or 12, wherein said intra vaginal device is formed entirely by said mass and the structure of said intra vaginal device formed entirely by said mass is self supporting.

14. A device or insert of any one of claims 11 to 13 wherein the progesterone inclusion is sufficient to deliver progesterone for a period from 2 to 20 days.

15. A device or insert of any one of claims 11 to 14 wherein said mass includes cyclodextrin.

16. The use or methods of use of a device or insert as defined in any one of claims 1 to 15 for delivering a substance to an animal.

17. A method of manufacture of an intra vaginal device which results in a device or insert in accordance with any one of claims 1 to 15 comprising mixing (A) any one of the following:

(i) poly ϵ-caprolactone,

(ii) starch-like polysaccharide, or

(iii) a blend of poly ϵ-caprolactone and starch-like polysaccharide

with (B) an active agent, and

forming the device or insert therefrom.

18. A method of claim 17 wherein said active agent is selected from one of the following:

(i) progesterone,

(ii) cyclodextrin, or

(iii) a blend of progesterone and cyclodextrin.

19. A method of manufacture of an intra vaginal device or insert which comprises the step of providing in a mouldable biodegradable polymer matrix both a cyclodextrin and an intra vaginally effective agent and thereafter moulding to form the device or insert therefrom.

20. The use inter alia for animal group oestrus synchrony purposes of devices or inserts of any one of claims 1 to 15.

21. A use of claim 20 wherein said use is intra vaginal use for a period of from 2 to 20 days and said device has a capability in the target species mammal of providing for at least 5 days (if intra vaginally inserted for at least about 5 days) a blood serum level of progesterone of greater than 2 $^{ng}/_{ml}$.

22. A method of achieving with an animal (or group of animals) a blood serum level of progesterone of greater than 2 $^{ng}/_{ml}$ for a period of at least 5 days, said method comprising inserting and retaining in each animal for at least a 5 day period a device or insert of any one of claims 1 to 15

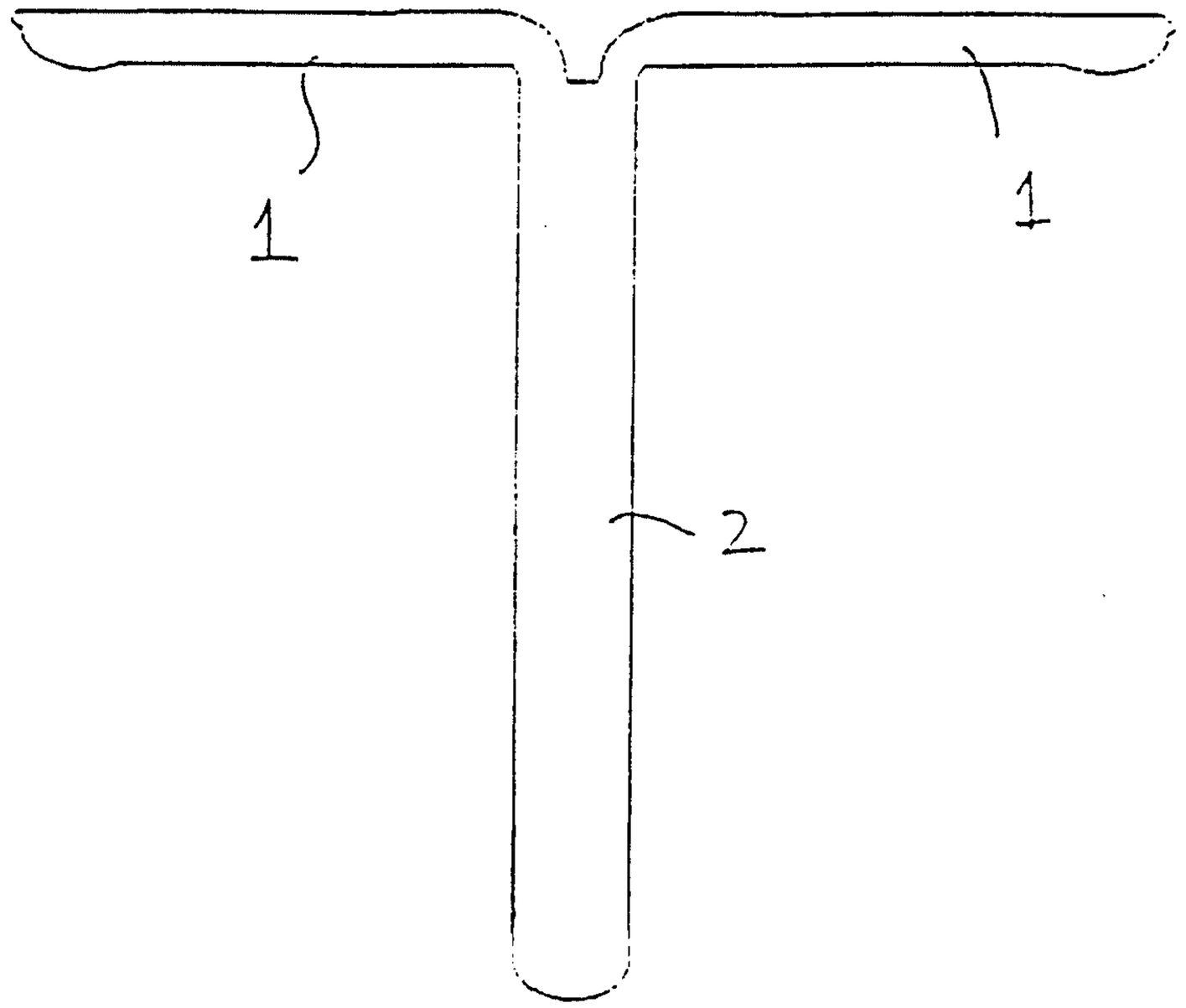


FIGURE 1

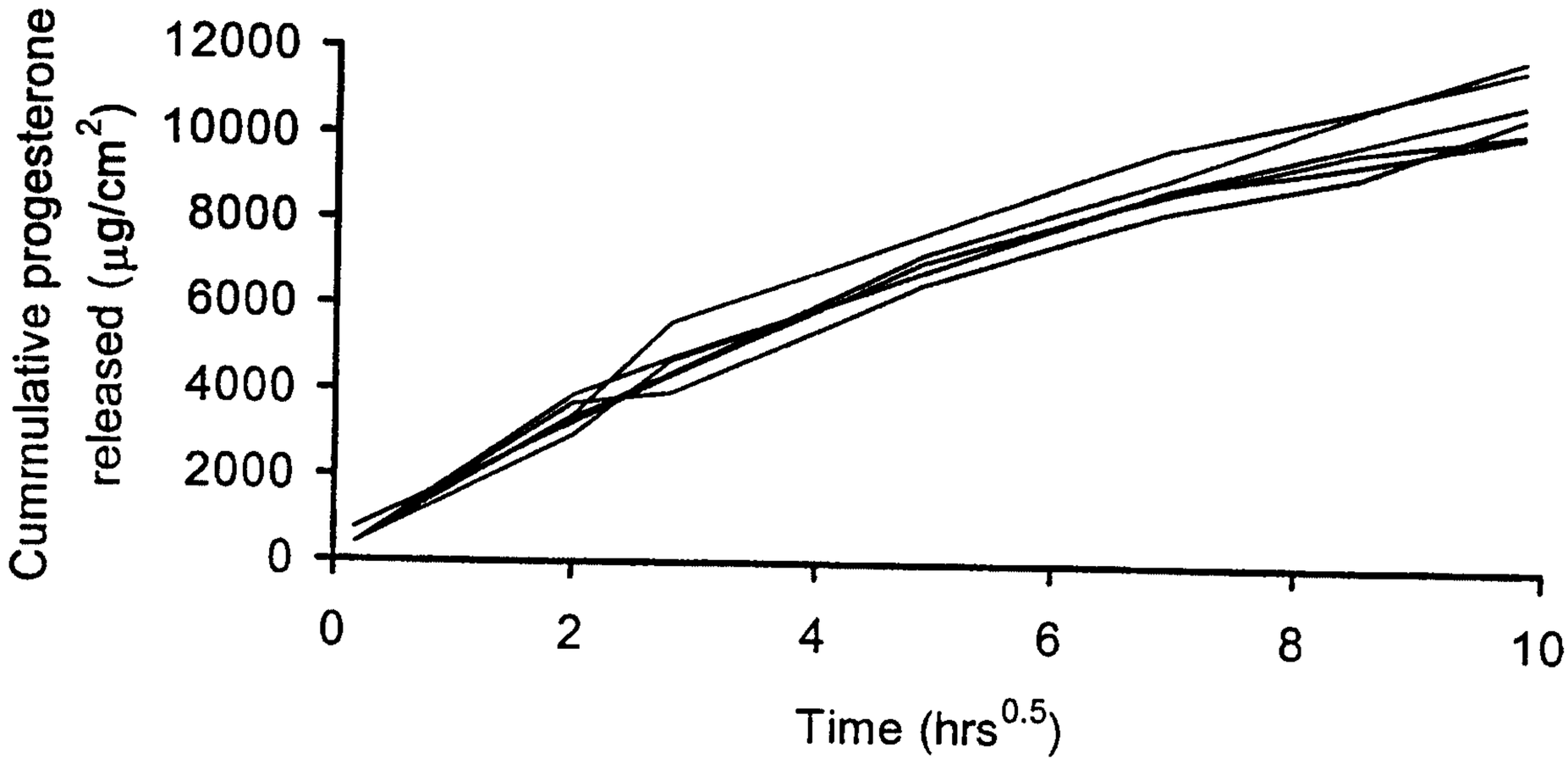


FIGURE 2

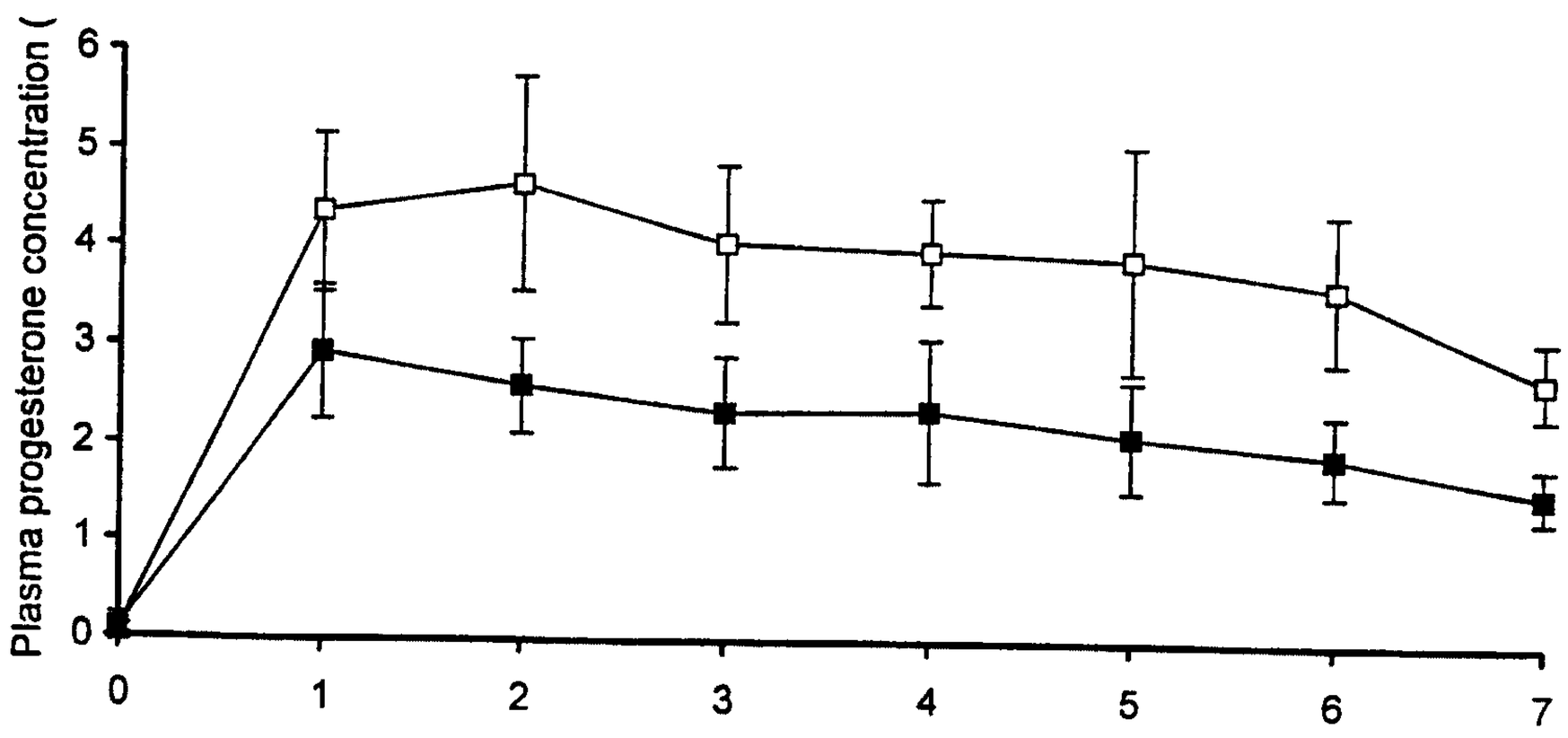


FIGURE 3

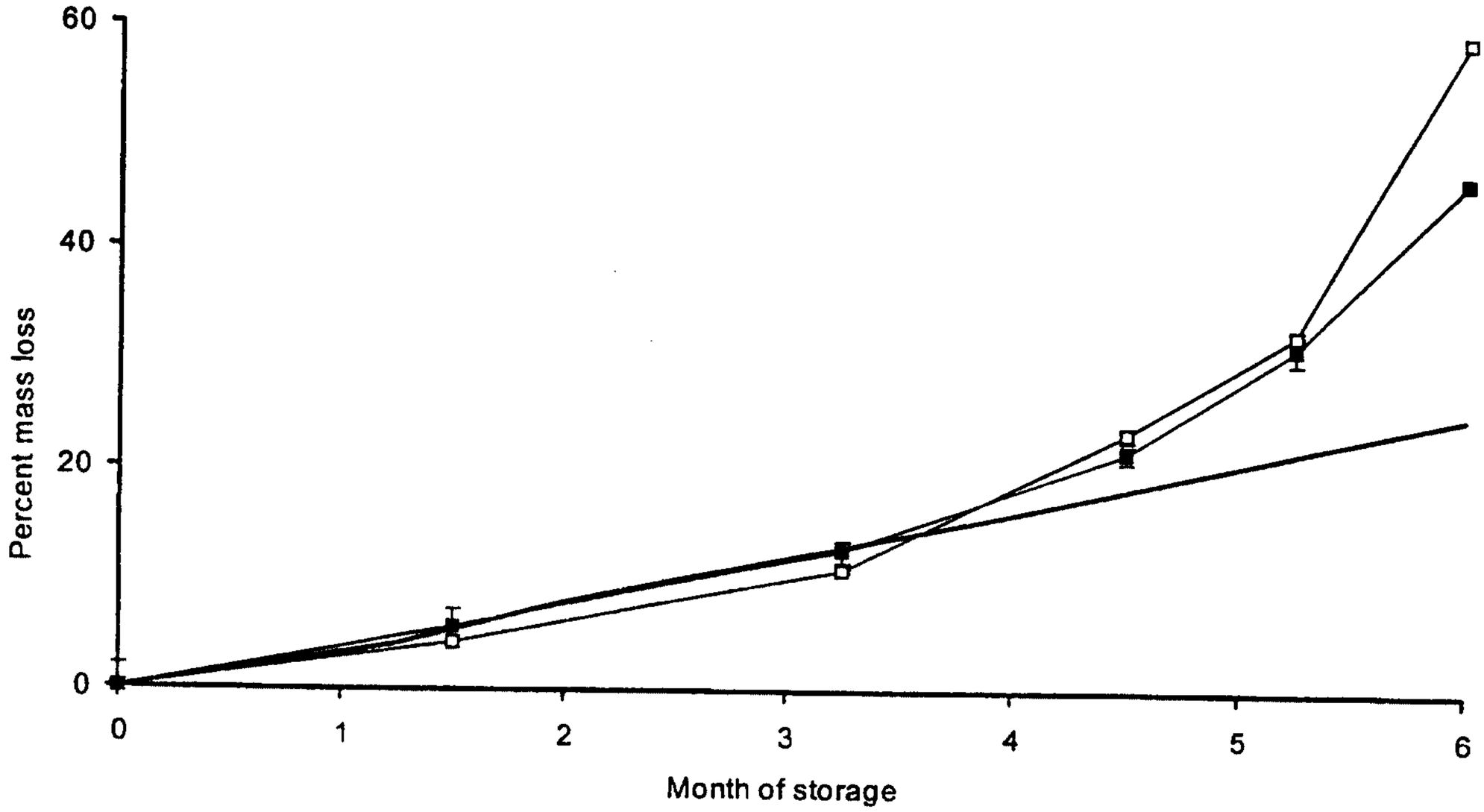


FIGURE 4

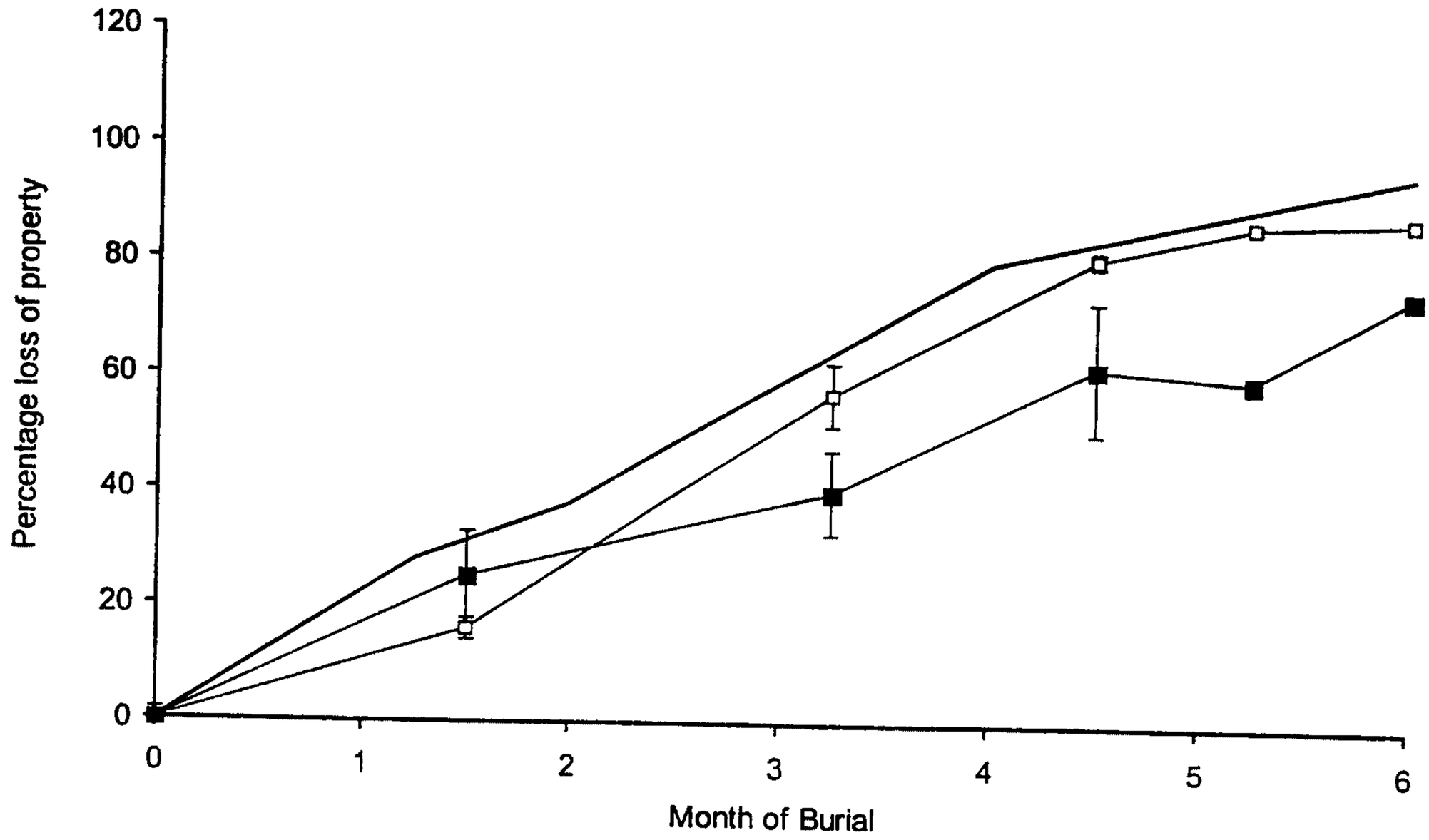


FIGURE 5

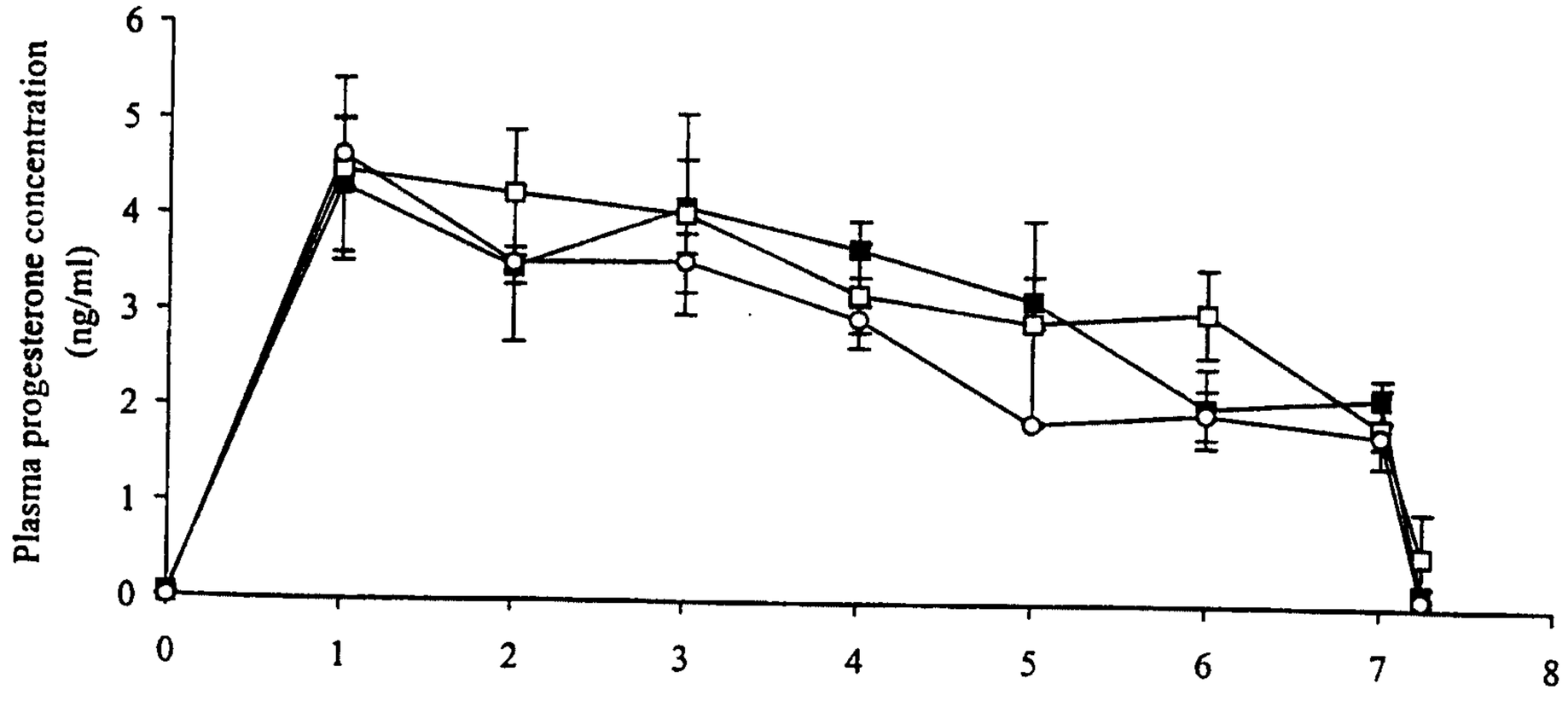


FIGURE 6

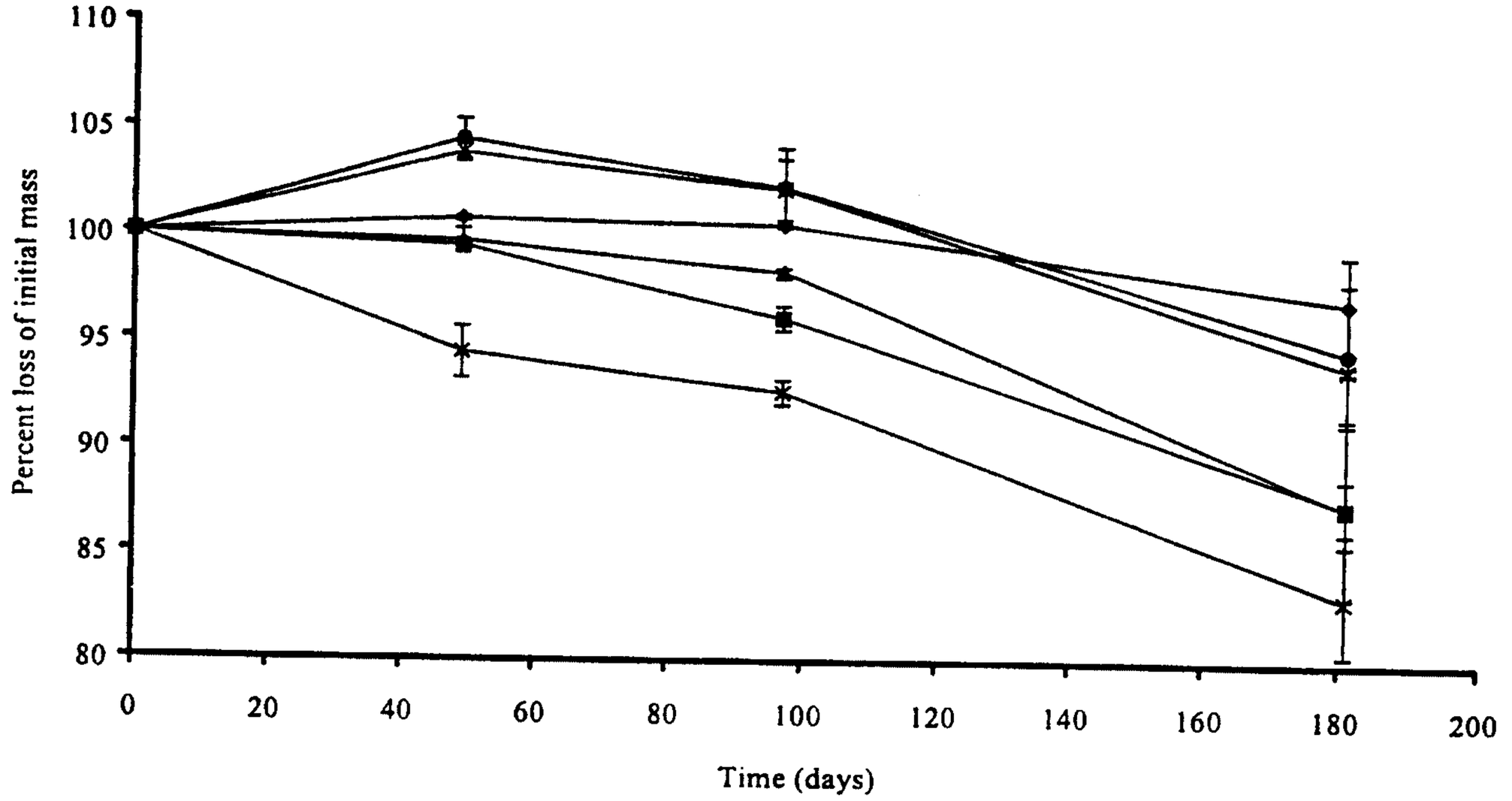

Percent loss of initial mass
110
105
100
95
90
85
80
0
20
40
60
80
100
120
140
160
180
200
Time (days)

FIGURE 7

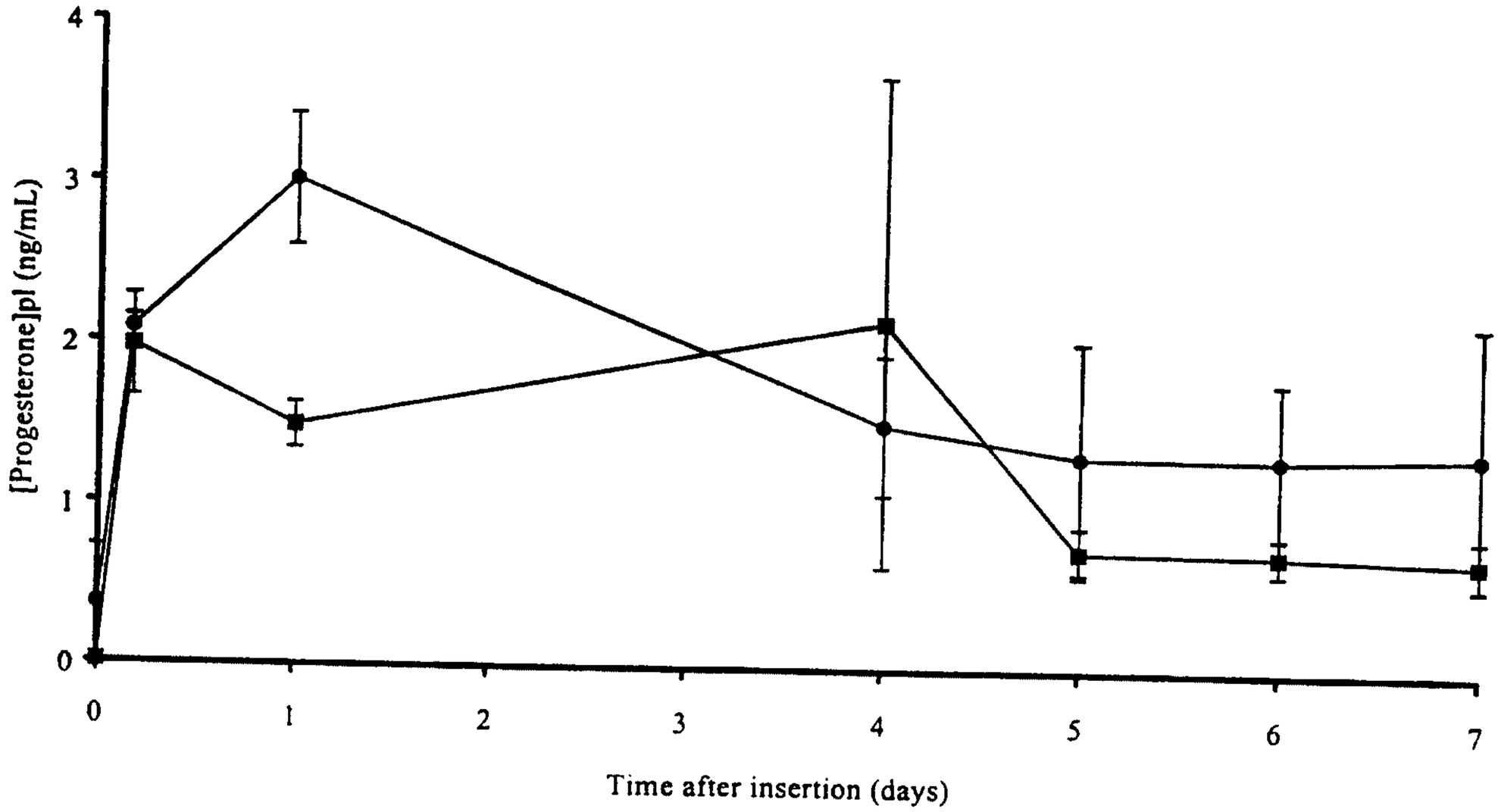
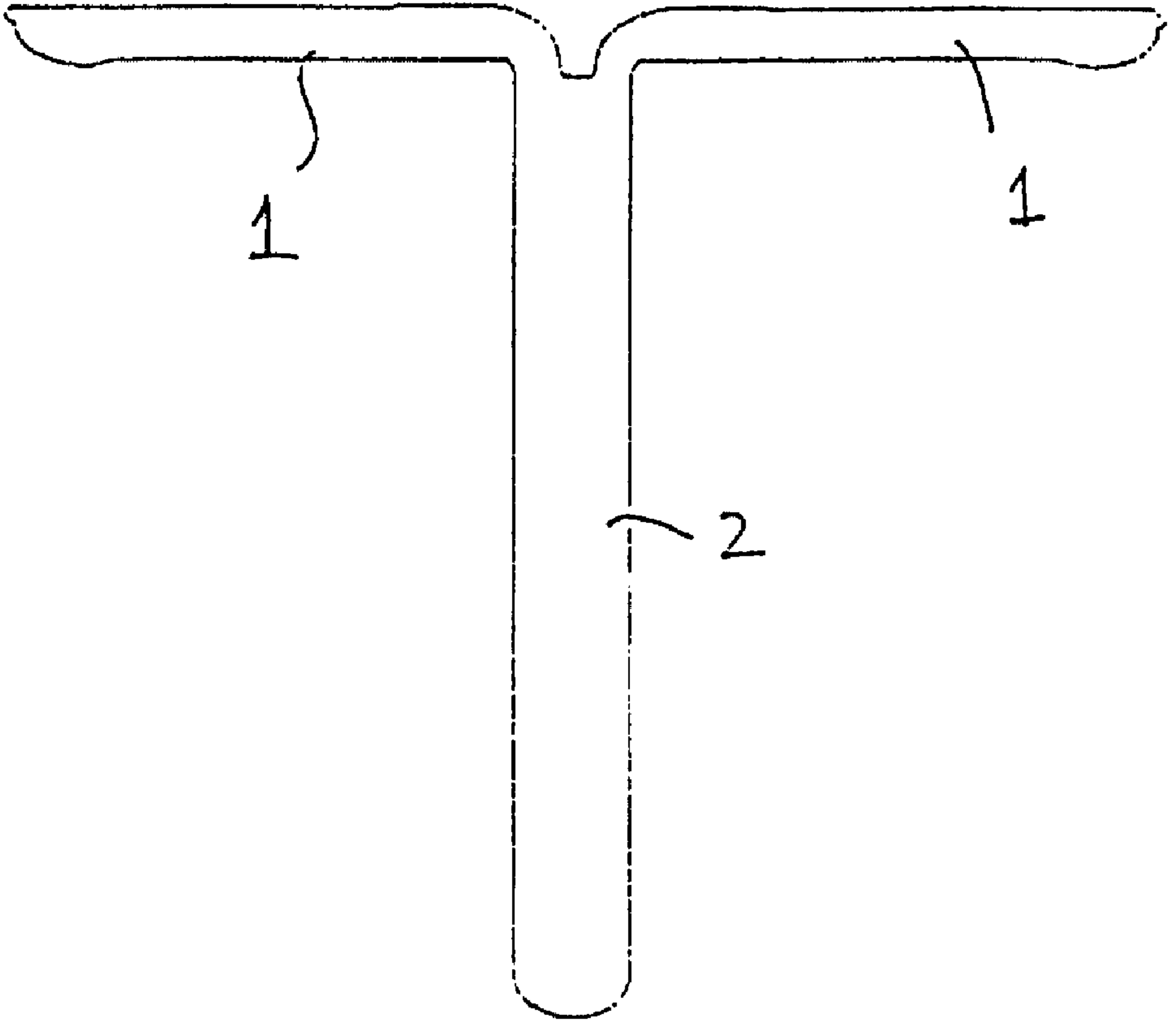

[Progesterone]pl (ng/mL)
0
1
2
3
4
0
1
2
3
4
5
6
7
Time after insertion (days)

FIGURE 8


1
1
2