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FORM 1

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

LODGED AT SUB-OFFICE
10 AUG 1987

Sydney

American Cyanamid Company, of One Cyanamid Plaza, Wayne, New Jersey, UNITED STATES OF AMERICA, hereby apply for the grant of a standard patent for an invention entitled:

Improved Estradiol Implant Composition And Method For Preparation

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No: Country:

Application Date:

895415

UNITED STATES OF AMERICA

11 August 1986

The address for service is:-

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DATED this TENTH day of AUGUST 1987

American Cyanamid Company

By:

M. J. Anderson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 34119
S&F CODE: 50380

5845/2

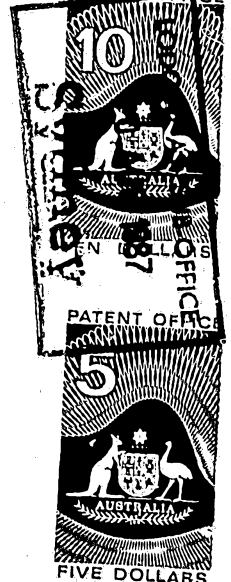
APPLICATION ACCEPTED AND AMENDMENTS

ALLOWED 11.5.90

PATENT OFFICE



PATENT OFFICE



FREE STAMP TO VALUE OF
\$1.75 ATTACHED

MAIL OFFICER

30,369

DECLARATION IN SUPPORT OF A
CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a
patent for an invention entitled: IMPROVED ESTRADIOL IMPLANT COMPOSITION
AND METHOD FOR PREPARATION

Title of Invention

Full name(s) and
address(es) of
Declarant(s)

I/We JOHN J. HAGAN,

of 86 Ocean Drive East, Stamford, State of Connecticut,
United States of America,

do solemnly and sincerely declare as follows:-

Full name(s) of
Applicant(s)

~~I am/We are the applicant(s) for the patent~~

(or, in the case of an application by a body corporate)

1. I am/We are authorised by

AMERICAN CYANAMID COMPANY
the applicant(s) for the patent to make this declaration on
its/their behalf.

2. The basic application(s) as defined by Section 141 of the
Act was/were made

Basic Country(ies)

in United States of America

Priority Date(s)

on August 11, 1986

Basic Applicant(s)

by MIMI YIH-PEI CHOU SCHAAF

Full name(s) and
address(es) of
inventor(s)

~~3. I am/We are the actual inventor(s) of the invention referred
to in the basic application(s)~~

(or where a person other than the inventor is the applicant)

3. MIMI YIH-PEI CHOU SCHAAF, a citizen of the United States of
America

of 13 Tall Timber Drive, Princeton, State of New Jersey 08540,
United States of America

(respectively)

is/are the actual inventor(s) of the invention and the facts upon
which the applicant(s) is/are entitled to make the application are
as follows: 1 Assignment dated August 6, 1986
assigning said invention from said inventor
to the said company

Set out how Applicant(s)
derive title from actual
inventor(s) e.g. The
Applicant(s) is/are the
assignee(s) of the
invention from the
inventor(s)

4. The basic application(s) referred to in paragraph 2 of this
Declaration was/were the first application(s) made in a Convention
country in respect of the invention(s) the subject of the application.

Declared at Stamford this 3rd day of Sept. 19 87
Connecticut, U.S.A.

AMERICAN CYANAMID COMPANY
BY:

To: The Commissioner of Patents

John J. Hagan, Manager
Patent Law Department

11/81

(12) PATENT ABRIDGMENT (11) Document No. AU-B-73724/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 599406

(54) Title
IMPLANT COMPRISING ESTRADIOL IN POLY(LACTIDE-CO-GLYCOLIDE) POLYMER

International Patent Classification(s)
(51)⁴ **A61K 031/565 A61K 047/00**

(21) Application No. : **76724/87** (22) Application Date : **10.08.87**

(30) Priority Data

(31) Number (32) Date (33) Country
895415 11.08.86 US UNITED STATES OF AMERICA

(43) Publication Date : **18.02.88**

(44) Publication Date of Accepted Application : **19.07.90**

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(56) Prior Art Documents
**EP 25698
EP 122709
US 4096239**

(57) Claim

1. A biodegradable implant composition comprising an implant containing on a weight basis 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 which has been washed with an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

7. A method for administering estradiol in a continuous and uniform manner for extended periods of time comprising, implanting a biodegradable composition about 2.4 mm in diameter and about 4 mm to about 6 mm in length comprising on a weight basis 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 which has been washed with an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

30. A method for the preparation of a biodegradable estradiol implant composition, with a porous coating, of about 2.4 mm in

(11) AU-B-76724/87
(10) 599406

-2-

diameter and from about 4 mm to about 6 mm in length containing on a weight basis from 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 comprising dissolving a required quantity of a biodegradable l-lactide/glycolide polymer having a desired l-lactide to glycolide ratio in a solvent while stirring to form a stirred mixture; adding a desired proportion of powdered estradiol to the stirred polymer mixture; then adding to the stirred mixture a miscible cosolvent in which the polymer is insoluble to precipitate the polymer, filtering off and drying resulting solids to form a dry mixture; then grinding the dry mixture and passing it through a 20 mesh screen to form a powder, pressing the powder to a preform tablet, tableting the powder at ambient temperatures or molding the preform tablet at elevated temperatures and washing the so-formed implant in an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

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S & F Ref: 34119

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

This document contains the amendments made under Section 49 and is correct for printing.

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name and Address
of Applicant:

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Complete Specification for the invention entitled:

Improved Estradiol Implant Composition And Method For
Preparation

The following statement is a full description of this invention, including the best method of performing it known to me/us

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IMPROVED ESTRADIOL IMPLANT COMPOSITION
AND METHOD FOR PREPARATION

ABSTRACT OF THE INVENTION

The invention relates to biodegradable compositions which continuously release estradiol in a uniform manner over extended periods of time and do not exhibit initial release of undesirably high levels of active ingredient.

10 The invention also relates to a method for preparation of the compositions, and a method for administering estradiol parenterally to feedlot animals in a continuous and uniform fashion over extended periods of time.

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IMPROVED ESTRADIOL IMPLANT COMPOSITION
AND METHOD FOR PREPARATION

BACKGROUND OF THE INVENTION

Estradiol (17-beta-estradiol) is a naturally occurring estrogen which is frequently administered to ruminant animals to increase weight gains of the animals. To be effective for increasing weight gains in animals estradiol should be administered at a rate to provide about 50 to 70 micrograms/day/animal.

Feedlot animals are normally maintained at this treatment level for from about 120 days to about 210 days, thus an implant suitable for administration of estradiol should deliver about 50 to 70 micrograms/day/animal with a minimum of variation for up to 200 days without releasing excessive dosages or bursts which can lead to undesirable side effects.

Spherical implant pellets of estradiol having an inert core with the drug in a uniform biocompatible and biosoluble coating of cholesterol, solid polyethylene glycols, high molecular weight fatty acids and alcohols, biosoluble waxes, cellulose derivatives and solid polyvinyl pyrrolidone are described in United States Patent 4,096,239.

Cylindrical implants which are not biodegradable, having an inert core which is 2 mm to 10 mm in diameter and 5 mm to 60 mm in length coated with a dimethylpolysiloxane coating, 0.2 mm to 1 mm thick containing 5% to 40% by weight of estradiol in the

coating are disclosed in Lilly's United States Patent 4,191,741 and their Australian Patent Application 476,747 describes improvements of this type of implant obtained by washing the implants and coating them with antibiotics or germicides.

5 Bioabsorbable compositions in particle or pellet form of polylactide-drug mixtures are disclosed in United States Patent 3,773,919. The patent describes broadly pharmaceutical depot compositions designed to release effective amounts of drugs over a controlled period of time utilizing a biodegradable polylactide carrier or matrix of polyglycolide or
10 a copolymer of lactide or glycolide containing up to 50% by weight of a comonomer in conjunction with a drug in drug to polymer ratios of from 1%/99% to 99%/1%. The patent also discloses ratios of estradiol to polymer as one part of drug to from 4 to 20 parts of polylactide i.e., from 5% to 25% by weight of estradiol.

15 It is an object of the invention to provide improved biodegradable compositions which release estradiol in a continuous fashion over extended periods of time and are suitable for parenteral administration to feedlot animals for increasing weight gains of animals. It is another object of this invention to provide improved compositions for administering estradiol
20 parenterally to animals which do not initially or periodically release excessive, undesirable levels of the drug as well as a method for their preparation.

SUMMARY OF THE INVENTION

25 According to a first embodiment of this invention there is provided a biodegradable implant composition comprising an implant containing on a weight basis 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 which has been washed with an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size
30 of less than twenty micrometers.

35 According to a second embodiment of this invention there is provided a method for administering estradiol in a continuous and uniform manner for extended periods of time comprising, implanting a biodegradable composition about 2.4 mm in diameter and about 4 mm to about 6 mm in length comprising on a weight basis 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a



range of from 75/25 to 95/5 which has been washed with an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

According to a third embodiment of this invention there is provided a
5 method for the preparation of a biodegradable estradiol implant
composition, with a porous coating, of about 2.4 mm in diameter and from
about 4 mm to about 6 mm in length containing on a weight basis from 65% to
80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having
10 an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 comprising
dissolving a required quantity of a biodegradable l-lactide/glycolide
polymer having a desired l-lactide to glycolide ratio in a solvent while
stirring to form a stirred mixture; adding a desired proportion of powdered
estradiol to the stirred mixture; then adding to the stirred mixture a
miscible cosolvent in which the polymer is insoluble to precipitate the
15 polymer, filtering off and drying resulting solids to form a dry mixture;
then grinding the dry mixture and passing it through a 20 mesh screen to
form a powder, pressing the powder to a preform tablet, tableting the
powder at ambient temperatures or molding the preform tablet at elevated
temperatures and washing the so-formed implant in an alcohol, a ketone or
20 an ether to provide a porous estradiol free coating having a pore size of
less than twenty micrometers.

The invention is improved biodegradable implant compositions for
parenteral administration which continuously release estradiol in animals
in uniform fashion over extended periods of time



comprising on a weight to weight basis 65% to 80% of estradiol and 20% to 35% of a biodegradable polymer of poly(lactide-co-glycolide) in ratios in a range of from 75/25 to 95/5. Preferred implant compositions of the invention are comprised on a weight basis of 70% to 80% of estradiol and 20% to 30% of a biodegradable poly(lactide-co-glycolide) polymer having a 1-lactide/glycolide ratio of from 80/20 to 95/5. Compositions comprised on a weight basis of 70% to 75% estradiol and 25% to 30% poly(lactide-co-glycolide) polymer having a 1-lactide/glycolide ratio of 90/10 are most preferred.

Implants about 2.4 mm in diameter and from 4 mm to 6 mm in length are the desired size to provide the required dosage for the entire treatment period.

The invention includes a method for preparing an implant with a porous, estradiol-free coating comprising washing the implant in a solvent in which estradiol is freely soluble for example, an alcohol, an ^{ether} ~~ester~~ or a ketone.

It has been found that while prior implant compositions for parenteral administration of estradiol contain on a weight basis a maximum of 50% by weight of the drug, highly effective implant compositions containing 65% to 80% by weight of estradiol may be prepared which do not exhibit erratic release or initial bursts of undesirably high levels of estradiol. Due to the high estradiol content of the compositions of this invention, a single implant of about 2.4 mm in diameter and 4 mm to 6 mm in length can deliver 25 to 35 micrograms/day/animal in a continuous and uniform fashion for extended periods of time. The small size and potency of the estradiol implant compositions of the invention provide several advantages over currently available estradiol implant compositions which are



either considerably larger and/or require multiple or repeated implantation in order to provide the required level of drug for extended periods of time. Initial administration to cattle of two of the implants of this invention are sufficient to provide the required 50 to 70 micrograms/animal/day for the entire treatment period.

The preferred levels of estradiol and lactide/glycolide ratios employed for the preparation of the compositions of this invention which contain these high levels of drug have demonstrated average release rates in animals in the 25 to 35 microgram/day range for from 110 to 200 days, while implants prepared with 50% estradiol and 50% polymer having a lactide/glycolide ratio of 70/30 showed a release rate in animals of 40 micrograms/day for only 63 days with a large increase in release rate thereafter.

Additionally, it has been found that the release rate of estradiol from implant compositions of this invention containing high levels of drug and a biodegradable l-lactide/glycolide polymer ratio as defined above may be controlled by washing the implant with a solvent in which estradiol is soluble such as methanol. Washed implants do not exhibit undesirable high levels of drug and additionally show a gradual increase to the required release rate over time as illustrated in Table I below. This table summarizes the differences in initial blood levels of estradiol in picograms/mL which are obtained by implanting an unwashed implant and a methanol washed implant containing estradiol in a weight range of 70-75% and l-lactide/glycolide polymer in a weight range of 25-30%, having a l-lactide/glycolide ratio of 90/10.

TABLE I
Serum estradiol concentrations
washed (A) vs unwashed (B) picogram/mL¹

5	Day	Washed implant	Unwashed implant
		A	B
10	0	6.6	10.2
	2	15.8	56.6
	5	21.1	59.9
	8	37.3	110.8
	12	22.0	108.3
	14	36.1	63.4

15 ¹Average level of 5 animals

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While washing of the implant compositions would be expected to remove estradiol from the surface, examination of the surface of implants of the invention containing high levels of drug with a biodegradable 1-lactide/glycolide polymer by Scanning Electron Microscopy, reveals that unwashed implants and polymer implants containing no drug have similar featureless surfaces. Examination of the surface of washed implant composition of the invention containing high levels of drug shows that it has developed fine pores, all of which are less than 20 micrometers in diameter and most of which are one micrometer or less, providing a porous membrane like surface to the implant. This resulting porous skin acts like a porous coating on the implant providing additional control in the release rate of the drug.

Solvents suitable for washing the implant compositions of this invention which are capable of providing this porous membrane-like layer on the surface include those solvents in which estradiol is freely soluble such as alcohols, ketones, ethers and the like, with methanol and ethanol being preferred.

The estradiol implant compositions may then be sterilized by optionally coating with an antibiotic such as oxytetracycline hydrochloride or by irradiation for example by exposure to gamma rays to aid in the prevention of infection at the site of administration.

Implant compositions of the invention may be prepared by dissolving the required quantity of a biodegradable 1-lactide/glycolide polymer having the desired 1-lactide to glycolide ratio in methylene chloride while stirring; adding the desired proportion of powdered estradiol to the stirred polymer solution; and then adding to the stirred mixture a miscible cosolvent in which the polymer is insoluble such as

heptane to precipitate the polymer. The resulting solids are filtered off, and dried under reduced pressure. The resulting dry mixture is then ground and passed through a 20 mesh screen and the powder pressed to a preform tablet of approximate weight. Implants may then be prepared by tableting the powder at ambient temperatures or by molding the preform at elevated temperatures. The implants are then washed in a solvent in which estradiol is freely soluble for ten seconds followed by a second wash. The washed implants are then dried and if desired, may then be sterilized by irradiation for example with a cobalt-60 source or if desired be coated with an antibiotic such as oxytetracycline hydrochloride or equivalent.

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1-8

1. Polymer Synthesis

A mixture of L-lactide and glycolide in the desired ratio is heated to a melt under nitrogen. Stannous chloride dihydrate (catalyst) and diethylene glycol (initiator) are added and the mixture is stirred at high temperature (195-208°). Upon completion of the reaction (about 90 minutes), the polymer is discharged, ground and vacuum dried to remove monomers.

2. Polymer Purification (optional)

The polymer is dissolved in methylene chloride and added slowly into methanol with good agitation. The precipitated polymer is then dried under vacuum at 40°C to constant weight.

3. Mixing of Estradiol and Polymer

a. Coacervation

The polymer is dissolved in methylene chloride and estradiol powder is added in the

desired ratio to the polymer. Heptane is slowly added to the stirred mixture and after vigorous stirring, the solid mix is isolated by decantation or filtration and drying; or

b. Wet Granulation

The polymer is dissolved in methylene chloride and added to the stirred estradiol powder in a blade mixer. The solvent is removed after blending and the mixture is discharged.

4. Preform Tableting

The estradiol and polymer mixture is ground and put through a 20-mesh sieve. The powder is fed to a Stokes rotary press to make 7/16 inch tablets of appropriate weight.

5. Implant Molding

A multi-station mold and 12.5 ton hydraulic press are used to fabricate the implants. The mold is heated by a circulating liquid system. The preforms are placed in the stations. The mold is then closed and a line pressure of 300-2000 psig applied, depending on the number of stations used and the polymer characteristics. The implants are released after opening the mold. They are removed.

6. Implant Washing

Implants are placed in a screen-bottomed basket and dipped into a methanol bath for ten seconds followed by a second methanol wash for five seconds. The washed implants are dried at ambient temperature.

7. Oxytetracycline Hydrochloride Dusting

Implants are placed in a container containing oxytetracycline hydrochloride, and are shaken for two minutes. The contents are poured over a sieve

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to remove the excess oxytetracycline hydrochloride and may then be stored or packaged.

8. Sterilization

5 The implants are packed in cartridges, wrapped and boxed and are irradiated using a cobalt-60 source at a nominal dosage of 2.5 megarads.

Utilizing the above procedure yields the implant compositions listed in Table II below.

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TABLE II
Estradiol implant compositions % by weight¹

Composition	1	2	3	4	5	6	7	8
Polymer								
l-lactide-glycolide	28	28	28	28	28	30	20	35
(lactide/glycolide)	(95/5)	(90/10)	(85/15)	(80/20)	(70/30)	90/10	90/10	90/10
Estradiol	72	72	72	72	72	70	80	65

¹Rounded to the nearest whole number

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EXAMPLE 9

Effect of washing implant compositions of the invention
on initial release rate

Estradiol implant compositions comprising approximately 70% estradiol and 30% of a polymer having a l-lactide/glycolide ratio of 90/10 are prepared by the general procedure of Examples 1-8. Ten of the implants are subjected to the washing procedure described in the above examples prior to coating with oxytetracycline hydrochloride (Group A), and ten are not washed but coated with oxytetracycline hydrochloride (Group B).

10 The implants are administered to the groups of five beef type steers (500-600 lbs. each) of approximately equal weight, each animal receiving two implants washed (Group A) or unwashed (Group B) subcutaneously in the back of the ear. Animals are then maintained on a daily ration of hay and grain expected to produce a one pound per day weight gain per animal. Blood samples are obtained from each steer on day 0 (prior to administration) and on days 2, 5, 8, 12 and 14 thereafter. Each plasma sample is assayed by radio immune assay for estradiol 17 beta concentration and the results recorded.

20 The results of these experiments which are summarized in Table I below demonstrate improvement in the control of the initial release of estradiol 17 beta from the implant compositions of the invention.

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TABLE I
Serum estradiol concentrations
washed (A) vs unwashed (B) picogram/mL¹

Day	Washed implant	Unwashed implant
	A	B
0	6.6	10.2
2	15.8	56.6
5	21.1	59.9
8	37.3	110.8
12	22.0	108.3
14	36.1	63.4

¹Average level of 5 animals

EXAMPLE 10

EFFICACY OF IMPLANT COMPOSITIONS OF THE INVENTION

Two estradiol implants weighing 27 mg each prepared as described in Examples 1-8 containing 70-75% estradiol and 25-30% of a polymer having an L-lactide/glycolide ratio of 90/10 which have been washed with methanol and coated with oxytetracycline hydrochloride are administered as described in Example 8 to each of three Hereford steers weighing approximately 500-600 pounds. The animals are maintained on a cattle growing ration which is introduced over a two week period to a rate of 5.0 kg/head/day along with 2.0 kg of mixed grass hay. Water is provided ad libitum.

Experimental Procedures

The test animals are weighed and acclimatized to their individual pens for ten days prior to the day of implantation.

Blood samples are taken from each steer on days -10, -4 and day 9 (just before implantation) to provide baseline information regarding serum estradiol 17 beta and blood urea nitrogen concentrations. On day 0, three animals received two estradiol implant each subcutaneously behind the right ear while the single steer receives no implant and is maintained as an untreated control.

Additional blood samples are taken following implantation on days 7, 10, 14, 21, 28 and then every other week. Each of these samples is analyzed for estradiol 17 beta. Each animal is also weighed and has the implant site examined on these designated days for bleeding. Feed intake of the test animals is monitored throughout the duration of the trial.

The blood samples have the serum separated from the clot by centrifugation and samples are subjected to an RIA assay for estradiol 17 beta determination.

The results of these experiments are summarized in Table III below, which demonstrate the efficacy of the implant compositions of the invention in delivering uniform levels of estradiol in a continuous fashion for extended periods of time.

TABLE III
Estradiol picograms/mL in

	Day	Untreated control	Estradiol implant composition
5	-10	< 8.5	< 8.5
	- 4	< 8.5	< 8.5
	0	< 8.5	< 8.5
	7	< 8.5	46.5
10	10	< 8.5	30.4
	14	< 8.5	18.4
	21	< 8.5	43.3
	28	< 8.5	32.8
	42	15.7	17.7
15	56	12.1	23.2
	70	<11.3	27.4
	84	< 8.6	42.4
	98	<10.3	25.8
	112	<11.9	37.2
20	126	<10.1	16.9
	140	< 7.9	22.8
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35			

The claims defining the invention are as follows:

1. A biodegradable implant composition comprising an implant containing on a weight basis 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 which has been washed with an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

2. The composition according to claim 1 comprising 70% to 80% estradiol and 20% to 30% of a biodegradable poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 80/20 to 95/5.

3. The composition according to claim 2 comprising 70% to 75% estradiol and 25% to 30% poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio of 90/10.

4. An implant comprised of the composition according to claim 2 or 3 which is about 2.4 mm in diameter and from about 4 mm to 6 mm in length.

5. The implant according to claim 4 which has been methanol washed to provide a porous estradiol free coating.

6. The implant according to claim 5 which is coated with oxytetracycline hydrochloride.

7. A method for administering estradiol in a continuous and uniform manner for extended periods of time comprising, implanting a biodegradable composition about 2.4 mm in diameter and about 4 mm to about 6 mm in length comprising on a weight basis 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 which has been washed with an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

8. The method according to claim 7 wherein the composition comprises on a weight basis 70% to 80% estradiol and 20% to 30% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio of from 80/20 to 95/5; which is coated with oxytetracycline hydrochloride.

9. The method according to claim 8 in which the composition has been methanol washed.

10. A method for the preparation of a biodegradable estradiol implant composition, with a porous coating, of about 2.4 mm in



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diameter and from about 4 mm to about 6 mm in length containing on a weight basis from 65% to 80% estradiol and 20% to 35% of a poly(lactide-co-glycolide) polymer having an l-lactide/glycolide ratio in a range of from 75/25 to 95/5 comprising dissolving a required quantity of a biodegradable l-lactide/glycolide polymer having a desired l-lactide to glycolide ratio in a solvent while stirring to form a stirred mixture; adding a desired proportion of powdered estradiol to the stirred polymer mixture; then adding to the stirred mixture a miscible cosolvent in which the polymer is insoluble to precipitate the polymer, filtering off and drying resulting solids to form a dry mixture; then grinding the dry mixture and passing it through a 20 mesh screen to form a powder, pressing the powder to a preform tablet, tableting the powder at ambient temperatures or molding the preform tablet at elevated temperatures and washing the so-formed implant in an alcohol, a ketone or an ether to provide a porous estradiol free coating having a pore size of less than twenty micrometers.

11. The method according to claim 10 wherein the implant is washed in methanol.

12. A biodegradable implant composition as defined in claim 1 and substantially as hereinbefore described with reference to any one of the Examples.

13. A method of increasing weight gains in feedlot animals, comprising parenterally administering to said feedlot animals an effective amount of a biodegradable implant composition as defined in any one of claims 1 to 3 or 12 or an implant as defined in any one of claims 4 to 6.

14. A method for the preparation of a biodegradable estradiol implant composition, substantially as hereinbefore described with reference to any one of Examples 1 to 8.

DATED this FOURTH day of APRIL 1990
American Cyanamid Company

Patent Attorneys for the Applicant
SPRUSON & FERGUSON



Q/EH/0065f