Industria y Comercio
SUPERINTENDENCIA

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES 2000-10

1 SOLICITUD DE:

☐ Corrección de Error Material ☒ Modificación a una solicitud

2 SOLICITANTE

Nombre: **N.V. ORGANON** sociedad constituida y existente bajo las leyes de los Países Bajos
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Teléfono: 546 09 70
E-mail: clientes@camyp.com
Fax: 249 40 70
Domicilio: Oss, Países Bajos

IDENTIFICACION
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Número: _____

3 REPRESENTANTE O APODERADO

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Domicilio: Bogotá, Colombia

IDENTIFICACION
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Número: 438.019 TP 31.929

4 **Número de expediente: 04.128.951** **Clase: A61P 15/00**

Título del Invento: USO DE NUEVOS ÉSTERES DE ETONOGESTREL

5 Descripción de la corrección o modificación solicitada:

Informo a ese Despacho que la sociedad **AKZO NOBEL N.V.** domiciliada en Velperweg 76, Arnhem 6824, Holanda, traspasó el derecho a la patente de invención que se tramita en el presente expediente, a la sociedad **N.V. ORGANON** domiciliada en Kloosterstraat 6, NL-5349 Oss, Países Bajos.

Por lo tanto, solicito otorgar el privilegio de patente de invención a favor de la sociedad **N.V. ORGANON.**

6 **Comprobante de pago No. 06 – 99,047** **Fecha: 27 de diciembre de 2006**

7 Anexos:

☒ Comprobante de pago de la tasa por concepto de modificaciones en solicitud pendiente.
☒ Poderes, si fuere el caso
☒ Certificado de existencia y representación legal, cuando el solicitante sea persona jurídica
☒ Documento que acredita el traspaso.

8 **NOMBRE: EMILIO FERRERO** **FIRMA:**
C.C. 438.019 de Usaquén T.P. 31.929

JGG / ID.603

150

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a. No. 72-35
BOGOTA 8, COLOMBIA

For patents, designs, trademarks, service marks, commercial names, ensigns.

Para patentes, modelos, dibujos, marcas de fábrica y de servicio, nombres comerciales y enseñas.

PODER

Yo (nosotros), abajo firmado (s)
N.V. Organon

domiciliado (s) en Kloosterstraat 6, 5349 AB OSS, Países Bajos

por el presente conferimos poder a GERMAN CAVELIER, GONZALO PERDOMO y ERNESTO CAVELIER, domiciliados en Carrera 4a. No. 72-35, Bogotá, Colombia, para

y para obtener la protección de mi (nuestra) propiedad industrial, y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me(nos) represente(n) ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos y dibujos industriales; el registro de marcas de fábrica, colectivas, defensivas y de servicio; el depósito de nombres comerciales y enseñas; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria, y el registro de licencias de uso de esos derechos; b) las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan; y c) para que en todos los asuntos arriba determinados, puedan sustituir este poder, transigir, desistir, cancelar, recibir, renunciar, aceptar notificaciones nombrar apoderados judiciales y extrajudiciales, y ratificar los actos de agentes oficiosos.

Dado y firmado hoy 5 de noviembre de 1986

en Arnhem

POWER OF ATTORNEY

I (we), the undersigned
N.V. Organon

of Kloosterstraat 6, 5349 AB OSS, the Netherlands

hereby grant to GERMAN CAVELIER, GONZALO PERDOMO and ERNESTO CAVELIER, domiciled at Carrera 4a. No. 72-35, Bogotá, Colombia, Power of Attorney to

and to obtain the protection of my (our) industrial property and against unfair competition, for which purpose I (we) authorize the said attorneys to represent us before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, in all matters concerning the following: a) Obtainment of patents, models and designs; the registration of trademarks, collective, defensive and service marks; the deposit of commercial names and ensigns; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b) actions of opposition, cancellation, nullity, infringement, granting of licenses, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us); and that in all the above matters they may substitute this Power of Attorney, compromise, desist, cancel, receive, renounce, accept notifications appoint attorneys-in-fact in or out of Court, and ratify the acts made by agents without power of attorney.

Given and signed this 5th day of November 1986

in Arnhem

N.V. Organon

J. Werkman
firma
proxyholders

J.H.H. de Carpentier Wolf
signature

TRADUCCION OFICIAL No. 281/86 de un documento escrito en Inglés, el cual para su identificación se sella con el sello del traductor lo mismo que la presente. ----------

Autenticaciones que se hallan a continuación de un Poder, escrito en Inglés y en Español, otorgado por la sociedad N. V. ORGANON, a los doctores GERMAN CAVELIER, GONZALO PERDOMO y ERNESTO CAVELIER.

Dado y firmado el día 5 de noviembre de 1986, en Arnhem.

N. V. Organon

(firmado) (firma ilegible) (firmado) (firma ilegible)

J. Werkman J.H.H. de Carpentier Wolf

Apoderados

Al dorso, dice:

LEGALIZACION

Noviembre 6 de 1986

REINO DE LOS PAISES BAJOS

Legalización entre otros ex Sección 69 Código de Comercio.

Yo, Pierre Henri Marie KEESOM, "Makelaar" (comerciante) en Marcas de la Corte de Apelaciones de Amsterdam, por el presente certifico que las firmas anteriores son las del señor Jan WERKMAN y del señor Jan Hilbrand Herderik de CARPENTIER WOLF, procuradores de N.V. Organon.

(firmado) Keesom

COMO NOTARIO SEXTO ... FOTOCOPIA COINCIDE CON EL ORIGINAL ... 26 DIC 2006 ... JUAN ... NOTARIO

En español, legalizaciones de la firma de Pierre Henri Marie Keesom, así como de la existencia legal de la sociedad N.V. Organon, y de las firmas de J. Werkman y J.H.H. de Carpentier Wolf, como sus representantes oficiales, hasta por el Ministerio de Relaciones Exteriores de la República de Colombia, bajo el Número 184600, de fecha 2 de diciembre de 1986.

TRADUCCION OFICIAL No. 281/86
JUNTA CENTRAL
INTERPRETE OFICIAL
RESOLUCION No. 2155, ABRIL 17, 1969
DEL MINISTERIO DE JUSTICIA.

REPUBLICA DE COLOMBIA ... IMPUESTOS NACIONALES ... AUTORIZACION ... MES-DIA ... TIMBRE NACIONAL

CAVELIER - ABOGADOS

1 2 1 3 7 3

Adherida y debidamente anulada, estampilla del Servicio Exterior de Colombia, por un valor de Cinco pesos ($5.oo). Pagado el Impuesto de Timbre, por máquina registradora, por un valor de Veinte pesos ($20.oo).

ES TRADUCCION FIEL Y COMPLETA del documento en referencia.

Bogotá, Diciembre 3 de 1986.

AG/c.

Alicia Groot

TRADUCCION OFICIAL No. 281/86
ALICIA GROOT
INTERPRETE OFICIAL
RESOLUCION No. 2195, ABRIL 17, 1969
DEL MINISTERIO DE JUSTICIA.

REPUBLICA DE COLOMBIA
IMPUESTOS NACIONALES
AUTORIZACION No. F 011 $ 00150 A-3
198 6 XII 4 3
TIMBRE NACIONAL
CAVELIER - ABOGADOS

REPUBLICA DE COLOMBIA
IMPUESTOS NACIONALES
AUTORIZACION No. F 011 $ 00020 A-3
198 6 XII 4 3
TIMBRE NACIONAL
CAVELIER - ABOGADOS

1 2 1 5 8 5

... FIRMA QUE ... Y QUE ... Alicia Groot
ES AUTENTICA
BOGOTA D.E.
05 DIC 1986

REPUBLICA DE COLOMBIA
MIGUEL TORRES ARROYO
NOTARIO SEXTO
BOGOTA

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2006
JUAN MANUEL BOTERO MEDINA
NOTARIO

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.
1998 MAR 18 A 11:49
NO SE ASUME
RESPONSABILIDAD DEL TEXTO

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA FUNCIONES INDICADAS
221119

TRADUCCIÓN OFICIAL 342/2006 DE UN DOCUMENTO ESCRITO EN IDIOMA INGLÉS REALIZADA POR EDUARDO CALADO NOGUERA, TRADUCTOR OFICIAL AUTORIZADO POR RESOLUCIÓN 541 DEL 27 DE FEBRERO DE 1976 Y DEBIDAMENTE INSCRITO ANTE EL MINISTERIO DE RELACIONES EXTERIORES DE COLOMBIA.

CESIÓN

Entre los abajo firmantes, Pieter Cornelis Schalkwijk y Petrus Hubertus van Deursen, quienes actúan en calidad de apoderados de AKZO NOBEL N.V., una empresa debidamente constituida y existente de conformidad con las leyes de los Países Bajos y domiciliada en Velperweg 76, NL-6824 BM Arnhem, Países Bajos, que a continuación se llamará el CEDENTE y Pieter Cornelis Schalkwijk y Petrus Hubertus van Deursen, quienes actúan en su calidad de apoderados de N.V. Organon, una empresa legalmente constituida y existente de conformidad con las leyes de los Países Bajos y domicilada en Kloosterstraat 6, NL-5349 Oss, Países Bajos, a continuación llamada el CESIONARIO y

A. Considerando que el CEDENTE es el copropietario de los derechos relacionados con la siguiente solicitud de patente o patentes o registros en Colombia

PATENTE/SOLICITUD DE PATENTE NÚMERO 99037966

FECHA DE EXPEDICIÓN/RADICACIÓN : 17 de junio de 1999

B. Considerando que el CESIONARIO está interesado en obtener la cesión de los derechos relacionados con las solicitudes de patente o registros arriba mencionados y que el CEDENTE está interesado en cederlas al CESIONARIO

Se ha realizado el siguiente convenio:

Primero: EL CEDENTE cede al CESIONARIO su parte de los derechos pertenecientes al CEDENTE con relación a las solicitudes de patente y/o registros mencionados en la letra A de este convenio.

Segundo: El CESIONARIO acepta la cesión arriba mencionada

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 737 477 A1

(12) EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

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(54) PERCUTANEOUSLY ABSORBABLE PREPARATION

(57) A first percutaneously absorbable preparation comprises a base, at least one drug selected from the group consisting of 3-ketodesogestrel and 17-esters thereof, and/or at least one drug selected from the group consisting of 17-β-estradiol and esters thereof. A second percutaneously absorbable preparation comprises a support layer and, formed on one side thereof, a pressure-sensitive adhesive base layer comprising a pressure-sensitive adhesive, at least one drug selected from the group consisting of 3-ketodesogestrel and 17-esters thereof, and optionally at least one drug selected from the group consisting of 17-β-estradiol and esters thereof. These preparations are easy to produce and use, and can supply 3-ketodesogestrel or 17-esters thereof, and/or 17-β-estradiol or esters thereof through horny skins uniformly for long. Therefore they can be utilized for contraception, alleviation of menopause symptom, asteoporosis, menstruation disorder, and so forth.

EP 0 737 477 A1

Description

TECHNICAL FIELD

The present invention relates to a percutaneous pharmaceutical preparation.

3-Ketodesogestrel and its 17-esters belong to a kind of progestogen, and are known to be effective as a contraceptive and to relieve the symptoms of menopausal disorders. 17-β-estradiol and its esters belong to a kind of estrogen and are known to be effective in relieving the symptoms of menopausal disorders, osteoporosis, emmeniopathy, etc. In addition, it is also known that the combined administration of 17-β-estradiol and progestogen has a contraceptive effect and is effective in relieving the symptoms of menopausal disorders. (For instance, refer to Contraception, Vol. 17; 19-25 (1978).)

However, such progestogen has substantial side effects and, progestogen causes cerebral thrombosis, cerebral infarction, arteriosclerosis, stenocardia, myocardial infarction, uterine cancer, etc when a large amount of it is administered. On the other hand, estrogen also increases the risk of endometriosis, uterine cancer and others when it is continuously administered in large amounts, and also adversely affects the lipometabolic system, the hemocoagulative system, the cardiovascular system and others. In particular, there is a possibility that estrogen causes cholecystitis, cholecystolithiasis and others, when it is administered orally. Furthermore, it is defective in that its peroral administration is much less efficacious than its administration by injection.

In order to overcome these serious drawbacks, various methods for preparing slow-release drugs have been reported. For instance, in Japanese Patent Application Laid-Open No. 64-70410, an implantation device has been proposed for subcutaneous application or local application, which is ethylene-vinyl acetate copolymer film coating core material composed of ethylene-vinyl acetate copolymer and 3-ketodesogestrel.

In Japanese Patent Application Laid-Open No. 61-106508, a vaginal ring release system is described comprising a two-partitioned tubular ring made of a porous film of a polymer such as polysiloxane, polyurethane and each partition of the ring contains progestogen and estrogen separately.

However, the above-mentioned implant shall be either subcutaneously implanted or locally applied into the uterus or into the region of the cervical canal. The subcutaneous implantation was not economically feasible in that it required a doctor to perform the implantation which is costly and time-consuming. The local application was also disadvantageous in that it required much time, and, after the application, the patient felt discomfort.

The latter vaginal ring release system was disadvantageous in that the preparation of the system is difficult and that much time is needed to introduce it into the vagina and, in addition, the patient will experience some degree of discomfort during its use.

The object of the present invention is to provide a percutaneous pharmaceutical preparation which is easy to produce, is easy to use and provide 3-ketodesogestrel and its 17-ester or a combinaiton of 3-ketodesogestrel and its 17-ester and 17-β-estradiol and its ester for a prolonged periods through the skin with the stratum corneum.

DESCRIPTION OF THE INVENTION

The first percutaneous pharmaceutical preparation of the present invention comprises a base material, one or more active ingredients selected from a group consisting of 3-ketodesogestrel and its 17-esters, and/or one or more active ingredients selected from a group consisting of 17-β-estradiol and its esters.

The second percutaneous pharmaceutical preparation of the present invention is composed of a backing layer and an adhesive base layer laminated on one surface of the backing layer, in which the adhesive base layer comprises an adhesive, one or more active ingredients selected from a group consisting of 3-ketodesogestrel and its 17-esters, and optionally one or more active ingredients selected from a group consisting of 17-β-estradiol and its esters.

The first percutaneous pharmaceutical preparation is described below.

The active ingredients used in the present invention are 3-ketodesogestrel and its 17-esters, and/or 17-β-estradiol and its esters. The esters of 17-β-estradiol may be either mono-esters or di-esters. The esters of 3-ketodesogestrel and 17-β-estradiol are obtained by esterifying 3-ketodesogestrel and 17-β-estradiol, respectively, with acids. The acids are organic monocarboxylic acids such as acetic acid, valeric acid, benzoic acid, propionic acid, cipionic acid, undecylenic acid, enanthic acid, etc.

The first percutaneous pharmaceutical preparation of the present invention comprises the above-mentioned base material and one or more active ingredients selected from a group consisting of 3-ketodesogestrel and its 17-esters, and/or one or more active ingredients selected from a group consisting of 17-β-estradiol and its esters. If the amount of the active ingredient(s) in the first preparation is small, the preparation will be inefficacious, but if it is too large, the active ingredient(s) will precipitate out of the base material. Therefore, the optimal preparation amount of the active ingredient(s) is from 0.001 to 20 % by weight, more preferably from 0.05 to 15 % by weight, especially preferably from 0.1 to 10 % by weight, of the percutaneous pharmaceutical preparation in order that the excess amount of active ingredient(s) does not precipitate.

Table 18

Example No.	Wrapping Condition	Fresh Sample	After storage at 25°C	After storage at 40°C	After storage at 60°C
131	1	100	99	98	97.4
	2	100	100	100	100
	3	100	100	100	99
145	1	100	97	94.5	91
	2	100	100	100	100
	3	100	98	96	93
146	1	100	81	67.7	38.2
	2	100	98	94	91
	3	100	85	68	40
147	1	100	94	88.7	78
	2	100	99	98	96
	3	100	96	88.9	79
148	1	100	98	96.5	94
	2	100	100	100	100
	3	100	98	97	94

INDUSTRIAL APPLICABILITY

The percutaneous pharmaceutical preparations of the present invention are easily produced and easily used, and they percutaneously release 3-ketodesogestrel or its 17-ester, and/or 17-β-estradiol or its ester uniformly over a prolonged period of time through the skin with stratum corneum.

Accordingly, the percutaneous pharmaceutical preparations of the present invention can be used efficaciously for contraception and also for relieving the symptoms of menopausal disorders, osteoporosis, emmeniopathy, etc.

Claims

1. A percutaneous pharmaceutical preparation comprising a base material, one or more active ingredients selected from a group consisting of 3-ketodesogestrel and its 17-esters, and/or one or more active ingredients selected from a group consisting of 17-β-estradiol and its esters.

2. The percutaneous pharmaceutical preparation according to claim 1, in which the amount of one or more active ingredients selected from a group consisting of 3-ketodesogestrel and its 17-esters and/or one or more active ingredients selected from a group consisting of 17-β-estradiol and its esters is from 0.001 to 20 % by weight of the preparation.

3. The percutaneous pharmaceutical preparation according to claim 2, in which the amount of the active ingredient(s) is from 0.1 to 10 % by weight of the preparation.

4. The percutaneous pharmaceutical preparation according to any one of claims 1 to 3, in which the base material is composed of one or more selected from a group consisting of sodium alginate, gelatin, corn starch, tragacanth gum, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, dextrin, carboxymethyl starch, polyvinyl alcohol, polyacrylic acid, polyacrylates, methoxyethylene-maleic anhydride copolymer, polyvinyl ether, polyvinyl pyrrolidone, colloidal aluminium silicate hydrate

minerals, colloidal magnesium aluminium silicate hydrate minerals, bees wax, olive oil, cacao oil, sesame oil, soybean oil, camellia oil, peanut oil, beef tallow, lard, lanolin, vaseline, white vaseline, paraffins, liquid paraffin, plastibase, glycerin, ethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol, higher fatty acids, lower alcohols, higher alcohols and water, or a composition containing one or more of these.

5. The percutaneous pharmaceutical preparation according to any one of claims 1 to 4, which further contains one or more percutaneous absorption accelerating agents selected from a group consisting of N-acylsarcosines or their salts; monocarboxylic acids having from 8 to 14 carbon atoms or their salts; dicarboxylic acids having from 2 to 8 carbon atoms or their salts; hydroxydicarboxylic acids having from 3 to 8 carbon atoms; fatty acid amides, or reaction products of aliphatic monocarboxylic acid(s) having from 8 to 16 carbon atoms and mono- or di-ethanolamine(s); and esters of higher fatty acids, or reaction products of higher fatty acid(s) having from 10 to 18 carbon atoms and alcohol(s) having from 1 to 18 carbon atoms.

6. The percutaneous pharmaceutical preparation according to claim 5, in which the amount of the percutaneous absorption accelerating agent(s) is from 0.1 to 20 % by weight of the preparation.

7. The percutaneous pharmaceutical preparation according to claim 6, in which the amount of the percutaneous absorption accelerating agent(s) is from 3 to 10 % by weight of the preparation.

8. The percutaneous pharmaceutical preparation according to any one of claims 1 to 7, which is ointment.

9. The percutaneous pharmaceutical preparation according to claim 8, in which the base material comprises a polyacrylic acid or its salt, polyethylene glycol or propylene glycol, a lower alcohol and water.

10. The percutaneous pharmaceutical preparation according to claim 9, in which the amount of the polyacrylic acid or its salt is from 0.01 to 3 % by weight of the ointment, the amount of the polyethylene glycol or propylene glycol is from 5 to 45 % by weight of the same, the amount of the lower alcohol is from 20 to 65 % by weight of the same, and the amount of water is from 5 to 30 % by weight of the same.

11. The percutaneous pharmaceutical preparation according to claim 10, in which the amount of the polyacrylic acid or its salt is from 0.5 to 2.3 % by weight of the ointment, the amount of the polyethylene glycol or propylene glycol is from 10 to 44 % by weight of the same, the amount of the lower alcohol is from 25 to 64 % by weight of the same, and the amount of water is from 10 to 28 % by weight of the same.

12. The percutaneous pharmaceutical preparation according to claim 8, in which the percutaneous absorption accelerating agent is lauric acid diethanolamide.

13. The percutaneous pharmaceutical preparation according to claim 12, in which the amount of lauric acid diethanolamide is from 0.1 to 20 % by weight of the preparation.

14. The percutaneous pharmaceutical preparation according to claim 13, in which the amount of lauric acid diethanolamide is from 3 to 10 % by weight of the preparation.

15. A percutaneous pharmaceutical preparation comprising polyacrylic acid as base, lauric acid diethanolamide as percutaneous absorption accelerating agent, and an active ingredient.

16. The precutaneous pharmaceutical preparation of claim 15, wherein the active ingredient is a steroid.

17. The percutaneous pharmaceutical preparation of claim 15 or 16 wherein the active ingredient comprises an progestagenic compound.

18. The percutaneous pharmaceutical preparation of any one of claims 15-17, wherein the active ingredient comprises a 19-nor-testosterone derivative.

19. The percutaneous pharmaceutical preparation of claim 18, wherein the 19-nor-testosterone derivative is selected from desogestrel, 3-ketodesogestrel, levonorgestrel, gestodene, norgestrel, norgestrienone, noretistherone, norethindron, and norgestimate, or an ester thereof.

20. The percutaneous pharmaceutical preparation of claim 19, wherein the 19-nor-testosterone derivative is 3-ketodesogestrel or an ester thereof.

21. The percutaneous pharmaceutical preparation of any one of claims 17-20, wherein the active ingredient further comprises an estrogenic compound.

22. The percutaneous pharmaceutical preparation of claim 21, wherein the estrogenic compound is selected from ethynyl estradiol and β-estradiol, or an ester thereof.

23. The percutaneous pharmaceutical preparation of claim 20, wherein the preparation comprises 3-ketodesogestrel and β-estradiol, or an ester thereof.

24. The percutaneous pharmaceutical preparation of any one of claims 15-23, wherein the amount of lauric acid diethanolamide is from 0.1 to 20% by weight of the preparation.

25. The percutaneous pharmaceutical preparation of any one of claims 15-24, wherein the amount of lauric acid diethanolamide is from 3 to 10% by weight of the preparation.

26. The percutaneous pharmaceutical preparation of any one of claims 15-25, further comprising a backing layer and an adhesive base layer laminated on one surface of the backing layer, in which the adhesive base layer comprises an adhesive.

27. The percutaneous pharmaceutical preparation of claim 26, wherein the amount of the active ingredient is from 0.001 to 20% by weight of the adhesive base layer.

28. The percutaneous pharmaceutical preparation of claim 27, wherein the amount of the active ingredient is from 0.5 to 12% by weight of the adhesive base layer.

29. The percutaneous pharmaceutical preparation of any one of claims 26-28, wherein the adhesive is selected from acrylic adhesives, rubber adhesives, silicone adhesives and urethane adhesives.

30. The percutaneous pharmaceuical preparation of claim 29, wherein the adhesive is an acrylic adhesive, comprising a copolymer composed of monomers of alkyl (meth)acrylate(s) and copolymerizable vinyl compound(s).

31. The percutaneous pharmaceutical preparation of claim 30, wherein the acrylic adhesive comprises a copolymer composed of monomers of alkyl (meth)acrylate(s) and N-vinyl-2-pyrrolidone.

32. The percutaneous phamaceutical preparation of claim 31, wherein the acrylic adhesive comprises a copolymer composed of from 55 to 95% by weight of 2-ethylhexyl acrylate, from 5 to 45% by weight of N-vinyl-2-pyrrolidone, and from 0 to 0.5% by weight of polyfunctional monomer(s).

33. The percutaneous pharmaceutical preparation of claim 29, wherein the acrylic adhesive comprises a copolymer composed of plural alkyl (meth)acrylate monomers.

34. The percutaneous pharmaceutical preparation of claim 33, wherein the acrylic adhesive comprises a copolymer composed of from 65 to 90% by weight of 2-ethylhexyl methacrylate, from 5 to 30% by weight of 2-ethylhexyl acrylate, from 5 to 30% by weight of dodecyl methacrylate and from 0 to 0.5% by weight of polyfunctional monomer(s).

35. The percutaneous pharmaceutical preparation of any one of claims 15-34 which is wrapped with a wrapping container having an oxygen permeability of 20 cm^3/m^2.atm.24h (25°C) or less and selected from aluminium sheeting, polyvinylidene chloride film, polyvinylidene chloride-polyethylane laminate film, polyvinylidene chloride-polypropylene laminate film, polyvinylidene chloride-polyvinyl chlorode laminate film, polyvinyl alcohol film and nylon film.

also relates and the preparation of which will be described hereinafter.

13-Ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one itself is known to be a substance having an extraordinarily high gestagenic activity which is used in the form of its pro-drug, 13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-17ß-ol (J. of Steroid Biochem., 14, 1981, 175 ff. and Europ. J. of Clin. Pharmacol., 15, 1979, 349 ff.), in combination with oestrogenically active compounds for the preparation of agents having a contraceptive action that are to be administered orally (Marvelon®).

It has now been found that, surprisingly, the esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally in combination with one or more oestrogens, can often be used better for the preparation of an agent for transdermal administration of the active ingredients than can combination preparations that contain 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one itself.

By esterifying the hydroxyl group in the 17ß-position of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one the physico-chemical properties of that substance are altered specifically and bioreversibly in the sense of a pro-drug formation.

If one compares the skin penetration of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one with that of its esters, the latter are generally distinguished by markedly higher transdermal flows. That is especially true when the esters are processed into matrix transdermal systems, such as, for example, those of the acrylate type (as are described hereinafter in

Example 2).

The extraordinarily high transdermal flows can be explained, in particular, by the surprisingly favourable solubilities that the said esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one have been found to have in the customary skin-adhesives and mixtures thereof with co-solvents and penetration-enhancers. By virtue of that property, it is now possible for the first time to prepare highly charged and stable matrix transdermal systems with molecularly disperse pro-drugs. Even active ingredient charges that, on a molecular basis, are 15 times higher than the comparable charges that can be achieved with 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one itself result in stable systems. This is a crucial advantage over systems containing 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one that are prior-known from WO 94/04157, since the concentration fall between transdermal systems and skin is decisively responsible for the level of the transdermal flows that are achievable.

It is therefore possible by means of the agent according to the invention to achieve high, uniform flows of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one using comparatively small transdermal systems.

It has already been mentioned that, in addition to containing the gestagen, the agent according to the invention may also contain one or more oestrogens. Suitable oestrogens are, for example, oestradiol, oestriol, ethinyloestradiol, mestranol, 14α,17α-ethanoestra-1,3,5(10)-triene-3,17ß-diol (WO 88/01275), 14α,17α-ethanoestra-1,3,5(10)-triene-3,16α,17ß-triol

(WO 91/08219) and esters thereof (EP-A 163 596), such as oestradiol dipropionate, oestradiol dihexanoate and oestradiol didecanoate. These combination preparations according to the invention contain, in addition to 1 or 2 gestodene esters, preferably from 1 to 3, especially 1 or 2, oestrogen(s).

For the manufacture of pharmaceutical preparations the active ingredient or active ingredient mixture may be dissolved or suspended in suitable volatile solvents and/or penetration-enhancing agents. The resulting solutions or suspensions may be combined with customary adjuvants, such as matrix formers and bactericides, and, where appropriate after sterilisation, introduced into customary dosing vessels. On the other hand, it is also possible, however, to process those solutions or suspensions further, with the incorporation of emulsifiers and water, to form lotions or ointments. It is also possible to produce sprays - optionally with the addition of propellant gas - which can be introduced into the customary dosing vessels.

Suitable volatile solvents are, for example, lower alcohols, ketones or lower carboxylic acid esters, such as ethanol, isopropanol, acetone or ethyl acetate, polar ethers, such as tetrahydrofuran, lower hydrocarbons, such as n-hexane, cyclohexane or benzine, or also halogenated hydrocarbons, such as dichloromethane, trichloromethane, trichlorotrifluoroethane and trichlorofluoromethane. It goes without saying that mixtures of those solvents are also suitable.

Suitable penetration-enhancing agents are, for example, monohydric or polyhydric alcohols, such as ethanol, 1,2-propanediol or benzyl alcohol, saturated and unsaturated

~~Patent Claims~~

CLAIMS

1. Agent for transdermal administration, characterised in that it contains from one to three esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one and/or with from one to three oestrogen(s).

2. Agent for transdermal administration according to patent claim 1, characterised in that it contains esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 12 carbon atoms in the ester radical.

3. Agent for transdermal administration according to patent claims 1 and 2, characterised in that it contains an ester of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 8 carbon atoms in the alkanoyl radical.

4. Agent for transdermal administration according to patent claims 1 to 3, characterised in that there are used as oestrogen(s) oestradiol, oestriol, 17α-ethinyl-oestradiol, mestranol, 14α,17α-ethanooestra-1,3,5,(10)-triene-3,17ß-diol, 14α,17α-ethanooestra-1,3,5(10)-triene-3,16α,17ß-triol, or esters of those compounds.

5. Agent for transdermal administration according to patent claims 1 to 4, characterised in that the agent is a transdermal therapeutic system (TTS).

6. Agent for transdermal administration according to patent claim 5, characterised in that the transdermal therapeutic system consists of

a) an impermeable cover layer,
from one to three matrix layer(s) which adhere(s) to the cover layer, which contain(s) the ester(s) of 13-ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and, if desired, penetration-enhancing agents and is(are) permeable to those components, and which is(are) self-adhesive or covered or surrounded by a skin-adhesive that, if desired, contains penetration-enhancing agents,
and a removable protective layer, or

b) a cover provided with an adhesive that, if desired, contains penetration-enhancing agents,
from one to three matrix layer(s) which are each attached by means of an impermable cover to the adhesive, leaving a border of adhesive uncovered, and which contain(s) the ester(s) of 13-ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and penetration-enhancing agents,
and a removable protective layer, or

c) an impermeable cover layer,
from one to three medicament reservoir(s) which is(are) located on or in the cover layer, which contain(s) the ester(s) of 13-ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and, if desired, penetration-enhancing agents,
from one to three polymer layer(s) that is(are) permeable to those components,
a permeable skin-adhesive layer optionally containing penetration-enhancing agents,
and a removable protective layer.

7. Agent for transdermal administration according to patent claim 6, characterised in that it contains one

active-ingredient-containing matrix layer or one medicament reservoir.

8. Agent for transdermal administration according to patent claim 6, characterised in that it contains two or three active-ingredient-containing matrix layers or medicament reservoirs.

9. Agent for transdermal administration according to patent claim 8, characterised in that the active-ingredient-containing matrix layers or the medicament reservoirs contain different active ingredients.

10. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s), for the preparation of an agent for the transdermal administration of the active ingredient or active ingredient mixture.

11. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, in combination with one or more oestrogen(s), for the preparation of an agent according to patent claim 10, characterised in that there are used as oestrogen(s) oestradiol, oestriol, 17α-ethynyloestradiol, mestranol, 14α,17α-ethanooestra-1,3,5(10)-triene-3,17ß-diol, 14α,17α-ethanooestra-1,3,5(10)-triene-3,16α,17ß-triol, or esters of those compounds.

12. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s), for the

preparation of an agent according to patent claims 11 and 12, characterised in that the agent is a transdermal therapeutic system (TTS).

13. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s), for the preparation of an agent according to patent claim 12, characterised in that it is a transdermal therapeutic system according to patent claims 6 to 9.

14. The use of oestrogen-free agents for transdermal administration according to patent claims 1 to 9 for transdermal contraception, for the treatment of endometriosis, for the treatment of gestagen-dependent tumours and for the treatment of premenstrual syndrome.

15. The use of agents for transdermal administration according to patent claims 1 to 9, optionally in combination with oestrogen-containing agents, for the treatment of climacteric complaints, for the prevention of osteoporosis, for regulation of the menstrual cycle, for stabilisation of the menstrual cycle and for transdermal contraception.

16. Esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 8 carbon atoms in the alkanoyl radical.

17. 17ß-Acetoxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

18. 17ß-Butyryloxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

BUCCAL DRUG DELIVERY SYSTEM FOR USE IN MALE CONTRACEPTION

TECHNICAL FIELD

This invention relates generally to pharmaceutical compositions and methods for administering pharmacologically active agents. More particularly, the invention relates to buccal drug delivery, and to a buccal dosage unit and method for administering a contraceptive composition to a mammalian male.

BACKGROUND ART

To date, there are no commercially available oral contraceptive methods for males which are safe, reliable, and effective. Currently available male contraceptive methods suffer from the disadvantages of being unreliable, cumbersome, or, in the case of vasectomy, generally irreversible. In spite of these drawbacks, approximately 35% of contraception worldwide involves male practices. *Popul. Rep.* (1986) 14: J889.

It has been proposed that spermatogenesis is driven by gonadotropins. Gonadotropin releasing hormone (GnRH), a decapeptide released in bi-hourly pulses from the hypothalamus, pituitary secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) regulate the functioning of the gonads to produce testosterone in the testes and the production and maturation of gametes. Within the testis, FSH binds to specific receptors on Sertoli cells, and LH stimulates Leydig cells. In addition, LH stimulates cells to produce testosterone, which interacts with intracellular androgen receptors in testicular Sertoli and peritubular cells. Spermatogenesis is thus thought to be driven by both FSH and testosterone. Accordingly, most hormonal approaches to male contraception have focused on inhibition of GnRH, gonadotropins, or both.

Exogenously administered androgens inhibit gonadotropin secretion, consequently inhibiting spermatogenesis, and have been studied as potential contraceptive agents in men. Cummings et al. (1994) *Clin. Androl.* 23:893-992 . An intramuscular (IM) injection of 200 mg per week of testosterone enanthate results in azoospermia in 50% to 70% of Caucasian men and 95% of Asian men after approximately 4 months. Side effects included oily skin.

acne, irritation of the injection site, an increase in aggressiveness, a decrease of the high-density lipoprotein (HDL)-cholesterol and possible adverse effects on the prostate gland.

The effect of lower doses of testosterone enanthate in combination with prosgestogenic agents has also been studied and has been reported to produce azoospermia comparable to those obtained with high doses of testosterone enanthate alone. An IM injection of 100 mg per week of testosterone enanthate in combination with 500 µg per day of levonorgestrel administered orally resulted in about 67% of the males achieving azoospermia in about 10 weeks. The side effects included a slight gain in weight and a significant decrease in the serum HDL-cholesterol. Bebb et al. (1996) *J. Clin. Endocr. Metab.* 81:757-762.

Co-administration of testosterone enanthate (100 mg/week, IM injection) with the synthetic steroid cyproterone acetate (100 mg/day or 50 mg per day) has been evaluated and was found to result in azoospermia within 7 to 8 weeks. However, the side effects included a slight decrease in body weight and a significant decrease in testis size during treatment. Meriggiola et al. (1996) *J. Clin. Endocr. Metab.* 81:3018-3023; Meriggiola et al. (1997) *J. Androl.* 18:240-244.

In another study, testosterone enanthate (25 mg/week, IM injection) was co-administered with a GnRH antagonist Nal-Glu (10 mg/day, subcutaneous injection). This combination resulted in azoospermia in approximately 75% of the men tested. However, the major side effect was an increase in the concentration of HDL-cholesterol. Pavlou et al. (1991) *J. Clin. Endocr. Metab.* 73:1360-1369; Tom et al. (1992) *J. Clin. Endocr. Metab.* 75:476-483.

The methods of effecting male contraception using testosterone enanthate currently being studied require intramuscular or a subcutaneous injection that can be painful. In addition, self-administration of an injectable composition typically suffers from low user acceptance.

Attempts at alternative routes of administration have not been successful for a number of reasons. Testosterone, for example, is well absorbed after oral administration but is quickly metabolized during passage through the liver and intestine. Therefore, it is not possible to achieve effective blood levels of testosterone via oral administration. 17α-alkylated derivatives of testosterone can be administered orally and are resistant to hepatic metabolism, but are not recommended for clinical use because of their potential hepatoxicity.

Bhasin et al. (1997) *J. Clin.. Endocr. Metab.* 82:3-8. Delivery of testosterone through the skin has been achieved using conventional transdermal patches. However, transdermal administration of steroids requires a permeation enhancer, which can result in skin irritation and sensitization.

Drug therapy involving buccal administration of steroid hormones has been described. For example, U.S. Patent No. 4,755,386 to Hsiao et al. generally describes the buccal administration of various medicaments, including estrogens, progestins and androgens; however, male contraceptive compositions are not contemplated. U.S. Patent No. 4,764,378 to Keith et al. describes rapidly disintegrating dosage forms utilizing a combination of high and low molecular weight polyethylene glycols; the dosage forms, which are preferably 50 mg to 100 mg tablets, may be administered orally or through the buccal mucosa. Similarly, U.S. Patent No. 5,135,752 to Snipes et al. describes buccal delivery systems containing polyethylene glycols of varying molecular weights for the delivery of methyl testosterone or estradiol. U.S. Patent No. 4,877,774 to Pitha et al. describes crystalline complexes of steroid hormones and gamma-cyclodextrin for administration of steroids through mucosal tissue.

The present male contraceptive compositions and methods are, however, new and completely unsuggested by the art. Applicants' contraceptive compositions are in the form of a compact drug dosage unit to be applied to the buccal mucosa, wherein the dosage unit comprises an androgenic agent and a progestin in a bioerodible polymeric carrier that facilitates adhesion to the buccal mucosa. The present buccal dosage units provide for a highly effective method of male contraception, and overcome a number of the disadvantages associated with prior male contraceptive compositions and methods. In particular, the present buccal dosage units, in contrast to the prior art, are simple in design and easily manufactured, are pharmacologically reliable, and do not result in the side effects associated with intramuscular injection, transdermal drug delivery or other modes of administration.

DISCLOSURE OF THE INVENTION

Accordingly, it is a primary object of the invention to address the aforementioned need in the art by providing a drug dosage unit for buccally administering to a male individual a pharmaceutical composition comprising an androgenic agent and a progestin.

It is another object of the invention to provide a method for effecting contraception in a male individual by buccally administering a contraceptive composition using the aforementioned drug dosage unit.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

Accordingly, in a first embodiment, then, a pharmaceutical composition is provided in the form of a simple, compact buccal dosage unit comprising therapeutically effective amounts of an androgenic agent and a progestin in a bioerodible polymeric carrier, wherein the carrier is such that it enables the dosage unit to adhere to the buccal mucosa. Following application to the buccal mucosa, gradual and complete erosion of the unit occurs over a predetermined time period, thus providing drug delivery throughout that time period. In a preferred embodiment, the dosage unit contains only the active agents to be administered and the polymeric carrier. However, other components, particularly a lubricant, may be incorporated to facilitate manufacture of the unit or if otherwise found to be necessary or desirable. The buccal dosage units are typically far smaller than conventional buccal delivery systems--the present tablets are on the order of 5-20 mg, typically 10-15 mg--and do not require a plurality of excipients, disintegrants, adhesives, or the like, nor are fragrances or permeation enhancers necessary. Accordingly, the novel dosage units are more comfortable than conventional systems because of their compact size. The novel units are also highly effective in providing effective contraceptive levels of steroidal agents. While the dosage units are designed to erode and thus deliver the active agents over a predetermined time period that is generally in the range of about 8 hours to about 24 hours, 12-hour dosage units are preferred, such that the individual receiving drug therapy can conveniently use two dosage units in a 12-hour period, enabling two "breaks" for dental hygiene or the like during the day. In this regard, the dosage units can be applied to an area of a subject's buccal mucosa such that the subject can eat and/or drink with the unit in place.

In another embodiment of the invention, a method is provided for effecting contraception in a mammalian male, comprising buccally administering the aforementioned contraceptive composition comprising an androgenic agent and a progestin. The composition

is administered through the buccal mucosa by affixing a dosage unit as provided herein to the buccal mucosa and allowing the dosage unit to remain in place until erosion is complete.

In an additional embodiment of the invention, a kit is provided to assist an individual in buccal drug administration. Generally, the kit includes the following components: a buccal dosage unit comprising a contraceptive composition and a bioerodible polymeric carrier; a container housing the dosage unit prior to use; and written instructions for carrying out administration of the composition. These objects, embodiments and features of the invention will become apparent to those skilled in the art upon reading the following disclosures and description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 schematically illustrates a preferred embodiment of a buccal dosage unit according to the invention.

Figure 2 schematically illustrates an alternative embodiment of a buccal dosage unit according to the invention.

Figure 3 schematically illustrates a second alternative embodiment of a buccal dosage unit according to the invention.

Figure 4 illustrates the placement of the buccal dosage unit in the preferred location in the oral cavity.

MODES FOR CARRYING OUT THE INVENTION

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular drugs or drug delivery systems, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an androgenic agent" includes a mixture of two or more androgenic agents, reference to "a progestin" includes a mixture of two or more progestins,

reference to "a polymeric carrier" includes mixtures of two or more suitable polymeric carriers, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "drug" or "pharmacologically active agent" or "active agent" as used herein refer to a compound or composition of matter which, when administered to an organism (human or animal) induces a desired pharmacologic and/or physiologic effect by local and/or systemic action. The active agents herein are steroid hormones, including androgenic agents, e.g., testosterone and derivatives, analogs, esters and salts thereof, and progestins, e.g. progesterone, cyproterone acetate, norethindrone, norethindrone acetate or levonorgestrel.

By "buccal" drug delivery is meant delivery of a drug by passage of a drug through the buccal mucosa into the bloodstream. Preferably, buccal drug delivery is effected herein by placing the buccal dosage unit on the upper gum or opposing inner lip area of the individual undergoing drug therapy.

"Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of the buccal mucosal tissue to a pharmacologically active agent, i.e., so that the rate at which the drug permeates through the mucosal tissue is increased.

"Excipients" or "vehicles" as used herein refer to any excipients or vehicles suitable for buccal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is nontoxic and which does not interact with other components of the composition in a deleterious manner.

By an "effective" amount of a pharmacologically active agent or pharmaceutical composition is meant a nontoxic but sufficient amount of the agent or composition to provide the desired effect. Thus, in the context of the present invention, an "effective" amount of a pharmacologically active agent or pharmaceutical composition is an amount sufficient to effect contraception.

"Compact" as used herein refers to a buccal dosage unit that is preferably no larger than about 5 mm in diameter and 2 mm in height, so that the unit occupies at most about 40 mm^3, typically weighs less than about 40 mg (preferably 5 to 20 mg, more preferably 10 to 15 mg), and has a contact surface area of no more than approximately 20 mm^3.

The terms "erodible" and "bioerodible" as used herein refer to a compound or composition that hydrolyzes upon contact with the buccal mucosa.

In one embodiment, then, a pharmaceutical composition is provided in the form of a buccal dosage unit for the administration of a combination of steroidal agents, i.e., an androgenic agent and a progestin. The dosage unit comprises (a) effective amount of an androgenic agent and a progestin, and (b) a bioerodible polymeric carrier as will be described in detail below. The dosage unit is fabricated so as to erode gradually over a predetermined time period, wherein drug delivery is provided essentially throughout. The time period is typically in the range of 8 hours to 24 hours; that is, for an 8-hour unit, erosion will occur throughout an 8-hour period and be substantially complete at the 8-hour point, while for a 24-hour unit, erosion will occur throughout a 24-hour period and be substantially complete at the 24-hour point. The buccal dosage unit may further comprise a lubricant to facilitate manufacture, e.g., magnesium stearate or the like. Additional components that may be included in the buccal dosage unit, but are neither required nor preferred, are flavorings, permeation enhancers, diluents, binders, and the like. As a buccal drug delivery system, the novel dosage unit avoids the disadvantages encountered with oral drug administration, e.g., degradation of active agents by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. In addition, because of its compact size, the unit is not associated with the discomfort encountered with larger, conventional buccal drug delivery systems. Also, the units are convenient in that the wearer need change the unit only once or twice daily, i.e., with 24-hour or 12-hour systems, respectively; a 12-hour unit to be applied once in the morning and once in the evening is optimal. Finally, because of the compositional simplicity of the unit--in a preferred embodiment, the unit contains only the active agents and the polymeric carrier--manufacture of the dosage form is straightforward and economical.

Suitable androgenic agents that may be used in the formulations of the present invention include, but are not limited to: the naturally occurring androgens and derivatives thereof, including androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androstenediol, androstenediol-3-acetate, androstenediol-17-acetate, androstenediol-3,17-diacetate, androstenediol-17-benzoate, androstenediol-3-acetate-17-benzoate, androstenedione, dehydroepi-androsterone (DHEA; also termed "prasterone"), sodium dehydroepiandrosterone sulfate, 4-dihydrotestosterone (DHT; also termed

"stanolone"), 5α-dihydro-testosterone, dromostanolone, dromostanolone propionate, ethylestrenol, nandrolone phenpropionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone cyclohexanepropionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, oxandrolone, stanozolol and testosterone; pharmaceutically acceptable esters of testosterone and 4-dihydrotestosterone, typically esters formed from the hydroxyl group present at the C-17 position, including, but not limited to, the enanthate, propionate, cypionate, phenylacetate, acetate, isobutyrate, buciclate, heptanoate, decanoate, undecanoate, caprate and isocaprate esters; and pharmaceutically acceptable derivatives of testosterone such as methyl testosterone, testolactone, oxymetholone and fluoxymesterone. Testosterone and testosterone esters, such as testosterone enanthate, testosterone propionate and testosterone cypionate, are particularly preferred androgenic agents for use in conjunction with the present invention. The aforementioned testosterone esters are commercially available or may be readily prepared using techniques known to those skilled in the art or described in the pertinent literature. (Generally, the 17-hydroxyl group of the testosterone molecule is caused to react with a suitable organic acid under esterifying conditions, such conditions typically involving the use of a strong acid such as sulfuric acid, hydrochloric acid, or the like, and a temperature sufficient to allow the reaction to proceed at reflux.)

Suitable progestins for use in the buccal drug delivery units of the invention include, but are not limited to, acetoxypregnenolone, allylestrenol, anagestone acetate, chlormadinone acetate, cyproterone, cyproterone acetate, desogestrel, dihydrogesterone, dimethisterone, ethisterone (17α-ethynyltestosterone), ethynodiol diacetate, flurogestone acetate, gestadene, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxymethyl-progesterone, hydroxymethylprogesterone acetate, 3-ketodesogestrel, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol acetate, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, normethisterone, and progesterone. Progesterone, cyproterone acetate, norethindrone, norethindrone acetate and levonorgestrel are preferred progestins.

The aforementioned steroidal agents are selected from the group consisting of naturally occurring steroids, synthetic steroids, and derivatives thereof. The active agents may be incorporated into the present dosage units and thus administered in the form of a

pharmaceutically acceptable derivative, analog, ester or salt, or the agents may be modified by appending one or more appropriate functionalities to enhance selected biological properties such as penetration through the mucosal tissue. In general, with regard to androgenic agents, esters are preferred relative to salts or other derivatives. Preparation of esters involves functionalization of hydroxyl and/or carboxyl groups that may be present, as will be appreciated by those skilled in the arts of pharmaceutical chemistry and drug delivery. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures.

To administer any one of the active agents in salt form, suitable pharmaceutically acceptable salts can be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th Ed. (New York: Wiley-Interscience, 1992). Acid addition salts are prepared from an active agent in the free base form (e.g., compounds having a neutral $-NH_2$ group) using conventional means, involving reaction with a suitable acid. Suitable acids for preparing acid addition salts include both organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like, as well as inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. An acid addition salt may be reconverted to the free base by treatment with a suitable base. Preparation of basic salts of acid moieties which may be present (e.g., carboxylic acid groups) are prepared in a similar manner using a pharmaceutically acceptable base such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, magnesium hydroxide, trimethylamine, or the like.

For those active agents that are chiral in nature and can thus be in enantiomerically pure form or in a racemic mixture, the drug may be incorporated into the present dosage units either as the racemate or in enantiomerically pure form.

The quantity of active agents in the buccal dosage unit will depend on the potency of each agent and the intended dosage. Suitable doses of androgenic agents and progestins agents will be known to those skilled in the art, or may be deduced from the literature in

CLAIMS

1. A buccal dosage unit for use in male contraception, comprising a polymeric carrier which adheres to the oral mucosa and erodes upon sustained contact therewith, and, incorporated in the polymeric carrier, a contraceptive composition comprising an androgenic agent and a progestin.

2. The dosage unit of claim 1, wherein the androgenic agent is selected from the group consisting of androsterone, androsterone acetate, androsterone propionate, androsterone benzoate, androstenediol, androstenediol-3-acetate, androstenediol-17-acetate, androstenediol-3,17-diacetate, androstenediol-17-benzoate, androstenediol-3-acetate-17-benzoate, androstenedione, dehydroepi-androsterone, sodium dehydroepiandrosterone sulfate, dromostanolone, dromostanolone propionate, ethylestrenol, fluoxymesterone, methyl testosterone, nandrolone phenpropionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone cyclohexane-propionate, nandrolone benzoate, nandrolone cyclohexanecarboxylate, oxandrolone, oxymetholone, stanozolol, testosterone, 4-dihydrotestosterone, 5α-dihydro-testosterone, testolactone, pharmaceutically acceptable esters and salts thereof, and combinations of any of the foregoing.

3. The dosage unit of claim 2, wherein the androgenic agent is testosterone or a pharmaceutically acceptable ester thereof.

4. The dosage unit of claim 3, wherein the androgenic agent is a testosterone ester.

5. The dosage unit of claim 4, wherein the testosterone ester is selected from the group consisting of testosterone enanthate, propionate, cypionate, phenylacetate, acetate, buciclate, heptanoate, decanoate, undecanoate, caprate and isocaprate.

6. The dosage unit of claim 5, wherein the testosterone ester is selected from the group consisting of testosterone enanthate, propionate and cypionate.

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2. Objeto de la invención.

- Título de la solicitud: Uso de nuevos ésteres de etonogestrel.

El objeto de la presente solicitud de patente de invención consiste en una composición farmacéutica de ésteres de etonogestrel y combinaciones de este con un éster de andrógeno y con un estrógeno.

Reivindicaciones 1- 2 : Una composición farmacéutica que comprende un éster de etonogestrel con una longitud de cadena grasa de C7-C15.

Reivindicaciones 3-5 : Una composición farmacéutica que comprende un èster de etonogestrel con una longitud de cadena grasa de C7-C15 y un éster de andrógeno.

Reivindicación 6 : Una composición farmacéutica que comprende un èster de etonogestrel con una longitud de cadena grasa de C7-C15 y un estrógeno.

El problema planteado en esta solicitud es la necesidad de composiciones farmacéuticas útiles como métodos contraceptivos efectivos y eficientes para hombres y mujeres, terapia de reemplazo hormonal masculino y femenino (TRH) y tratamiento / prevención de desórdenes ginecológicos

Para solucionar este problema técnico la solicitud en estudio proporciona composiciones farmacéuticas que comprenden un èster de etonogestrel con una longitud de cadena grasa de C7-C15 y combinaciones de este con un éster de andrógeno y con un estrógeno.

El objeto de la invención definido anteriormente se clasifico de acuerdo con la Clasificación Internacional de Patentes (IPC) : A61K31/569, A61K31/565, A61P15/00.

3. De la solicitud de Patente

3.1. Descripción *(artículo 28 D. 486)*

Teniendo en cuenta lo reivindicado en el folio (147), lo que se observa a lo largo descriptivo para las composiciones de ésteres de etonogestrel y combinaciones de este con un estrógeno , es que se esta reclamando el uso de dichas composiciones. Adicionalmente la composición que comprende ésteres de etonogestrel combinado con un éster de andrógeno (undecanoato de Ment) no se encuentra sustentada en el aparte descriptivo por lo que no se puede observar la ventaja técnica. Las demás composiciones se encuentran afectadas por el estado de la técnica.

En consecuencia, las reivindicaciones 1-6 no encuentran sustento dentro del aparte descriptivo de la solicitud

Se requiere al solicitante ajustar su capítulo descriptivo y reivindicatorio de acuerdo a aquellas modalidades que son objeto de la invención y a las observaciones realizadas, teniendo cuidado de no ampliar la materia más allá de cómo se estableció originalmente.

3.2. Reivindicaciones *(artículo 30 D 486)*

- La reivindicación 5 no es clara ni concisa y resulta amplia y especulativa, ya que se reclama nuevamente la composición ya reivindicada en 4 , sin aportar ninguna característica técnica adicional.

- La reivindicación 6 habla sobre una composición que comprende esteres de etonogestrel **con un estrógeno** la cual es amplia y especulativa en el sentido que existen múltiples posibilidades de composiciones obtenidas de esteres de etonogestrel con **"un estrógeno** ". Por este motivo la característica esencial de la composición no es representativa. Se le requiere al interesado definir o especificar el **estrógeno** que es relevante para la invención.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es 30 de Mayo de 2002se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud :

N°	Documento	Título	Fecha de Publicación*
D1	EP0737477	PERCUTANEOUSLY ABSORBABLE PREPARATION	16 de Octubre de 1996.
D2	ZA9606083	AGENT FOR TRANSDERMAL ADMINISTRATION CONTAINING ESTERS OF 13-ETHYL-17β-HYDROXY-11-METHYLENE-18,19 DINOR-17α-PREGN-4-EN-20-YN-3-ONE	19 de Junio de 1998.
D3	WO0042942	BUCCAL DRUG DELIVERY SYSTEM FOR USE IN MALE CONTRACEPTION	27 de Julio de 2000.

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Novedad (artículo 16 D486)

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La presente Solicitud de Patente Colombiana No 041128951, se refiere a:

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Para las reivindicaciones 1-2.

Una composición farmacéutica que comprende un éster de etonogestrel con una longitud de cadena grasa de C7-C15.

D1 (folios 166-170) divulga preparaciones farmacéuticas , que contienen **17-esteres de 3-ceto desogestrel (etonogestrel), como por ejemplo los esteres del ácido enántico (C7) y los esteres del ácido undecilénico (C11).** (Ver folio 167, página 2-líneas 33-24 , líneas 49-51 y folio 168 Reivindicación 1),los cuales son útiles como anticonceptivos y adicionalmente sirven para aliviar los síntomas relacionados con la menopausia , osteoporosis y desórdenes menstruales(TRH) (folio 166 , resumen).

Como se observa, el elemento característico de la composición farmacéutica reinvidicada en 1-2 era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

D2 (folios 171-181) divulga preparaciones farmacéuticas que continen **esteres de 3-cetodesogestrel de C1-C20** (Ver folio 173, página 1 y folio177 reivindicaciones 1-2), los cuales son útiles como anticonceptivos y como TRH (osteroporosis, regulación del ciclo mestrual entre otras. Ver folio 180 , reivindicación 15).

Como se observa, el elemento característico de la composición farmacéutica reinvidicada en 1-2 era conocido en D2 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

Para la reivindicación 6

Una composición farmacéutica que comprende un èster de etonogestrel con una longitud de cadena grasa de C7-C15 y un estrógeno.

D1 divulga preparaciones farmacéuticas , que contienen **17-esteres de 3-ceto desogestrel (etonogestrel), como por ejemplo los esteres del ácido enántico C7) y los esteres del ácido undecilénico (C11) los cuales se encuentran combinados con 17β estradiol y sus esteres (estrógenos) ,** (Ver folio167 , página 2, líneas 7-10 y 47-51).

Como se observa, el elemento característico de la composición farmacéutica reinvidicada en 6 era conocido en D1 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

D2 divulga preparaciones farmacéuticas que confinen **esteres de 3-cetodesogestrel de C1-C20 los cuales se encuentran combinados con uno o más estrógenos** (Ver folio, página 1 **) como por ejemplo oestradiol, oestriol, etiniloestradiol, mestranol entre otros , (Ver folios 175 y 176 , páginas 3y 4 y folio 177, reivindicaciones 1,4).**

Como se observa, el elemento característico de la composición farmacéutica reinvidicada en 6 era conocido en D2 y está comprendido en el estado de la técnica, con lo cual se considera que NO cumple con el requisito de Novedad.

5.2. Nivel inventivo *(artículo18 D486)*

Para las reivindicaciones 3-5

El documento del estado de la técnica más cercano es D3 (Folios 182-192) enseña composiciones anticonceptivas para hombre que comprenden un andrógeno y una progestina. El andrógeno incluye derivados de nandrolona . La progestina incluye 3-cetodesogestrel y tanto el andrógeno como la progestina pueden ser usadas en la forma de un derivado farmacéuticamente aceptable , por ejemplo de èster (Ver folio 189 página 7 líneas 25-31, folio 190 página 8 y folio 191 página 9 línea 1).)

La diferencia con D3 es que en esta solicitud el andrógeno es específicamente el undecanoato de MENT y la progestina es específicamente un éster de etonogestrel de C7-C15.

Esta diferencia no parece conceder un efecto técnico inesperado ò una ventaja a la composición reivindicada en comparación con la composición del Estado de la Técnica más cercano; porque esta composición sigue siendo útil para la anticoncepción masculina.

Así que el Problema Técnico planteado en esta solicitud : la necesidad de composiciones farmacéuticas útiles como métodos contraceptivos efectivos y eficientes para hombres y terapia de reemplazo hormonal masculino (HRT), se había solucionado previamente mediante composiciones muy similares de progestinas con andrógenos . De manera que la nueva composición es **una alternativa las composiciones conocidas** porque sigue siendo útil para la anticoncepción masculina.

El experto en la materia, en vista del Estado de la Técnica en su totalidad, es decir en vista de D3 y D2, hubiera sugerido sin mucho esfuerzo de su parte reemplazar la progestina de D3 por los ésteres de 3-cetodesogestrel de C1-C20 de D2 y el derivado de nandrolona (éster) de D3 por otro derivado de andrógeno (undecanoato de MENT, que es un éster de nandrolona) de la presente solicitud y así obtener la composición reivindicada en 3-5.

Por lo cual se considera obvio para el experto en la materia. En consecuencia, carecen de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	EP0737477	1-2,6	Novedad
D2	ZA9606083	1-2,6 3-5	Novedad Nivel inventivo
D3	WO0042942	3-5	Nivel inventivo