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(54) Title: ORODISPERSIBLE DOSAGE UNIT CONTAINING AN ESTETROL COMPONENT

(57) Abstract: The invention provides an orodispersible solid pharmaceutical dosage unit having a weight between 30 and 1,000 mg, said dosage unit consisting of: 0.1-25 wt.% of estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof; and 75-99.9 wt.% of one or more pharmaceutically acceptable ingredients; the solid dosage unit comprising at least 100 μg of the estetrol component; and wherein the solid dosage unit can be obtained by a process that comprises compressing a dry blend of estetrol particles and one or more pharmaceutically acceptable excipients into a solid dosage unit. The solid dosage unit is easy to manufacture and perfectly suited for sublingual, buccal or sublabial administration.

ORODISPERSIBLE DOSAGE UNIT CONTAINING AN ESTETROL COMPONENT

TECHNICAL FIELD OF THE INVENTION

The present invention provides an orodispersible solid pharmaceutical dosage unit having a weight of 30-1,000 mg and containing at least 0.1 mg of an estetrol component selected from estetrol, estetrol esters and combinations thereof. This solid dosage unit consists of:

- 0.1-25 wt.% of estetrol particles containing at least 80 wt.% of the estetrol component; and
- 75-99.9 wt.% of one or more pharmaceutically acceptable ingredients.

The invention also provides a process of preparing the aforementioned solid dosage unit.

Furthermore, the invention relates to the use of the solid dosage unit in medical treatment, female hormone replacement therapy and female contraception, said use comprising sublingual, buccal or sublabial administration of the said dosage unit..

BACKGROUND OF THE INVENTION

Estetrol is a human steroid, produced by the fetal liver during pregnancy only. This natural hormone was discovered in urine of pregnant women by Diczfalusy and coworkers in 1965. Estetrol has the structure of an estrogenic steroid with four hydroxyl groups. Estetrol is synthesized in the fetal liver from estradiol and estriol by the two enzymes 15α- and 16α-hydroxylase. After birth the neonatal liver rapidly loses its capacity to synthesize estetrol because these two enzymes are no longer expressed.

Estetrol reaches the maternal circulation through the placenta and was already detected at nine weeks of pregnancy in maternal urine. During the second trimester of pregnancy high levels were found in maternal plasma, with steadily rising concentrations of unconjugated estetrol to about 1 ng/mL (> 3 nmol/L) towards the end of pregnancy. So far the physiological function of estetrol is unknown. The possible use of estetrol as a marker for fetal well-being has been studied quite extensively. However, due to the large intra- and inter-individual variation of maternal estetrol plasma levels during pregnancy this appeared not to be feasible.

Since 2001 estetrol has been studied extensively. In humans estetrol was shown to have a high and dose-proportional oral bioavailability and a long terminal elimination half-life of about 28 hours. Results from *in vitro* studies showed that estetrol binds highly selective to the estrogen receptors with preference for the ERα form of the receptor, unlike the estrogens ethinyl estradiol and 17β-estradiol. Also in contrast with ethinyl estradiol and especially with 17β-estradiol, estetrol does not bind to sex hormone binding globulin (SHBG) and does not stimulate the production of SHBG *in vitro*.

The properties of estetrol have also been investigated in a series of predictive, well validated pharmacological *in vivo* rat models. In these models, estetrol exhibited estrogenic effects on the vagina, the uterus (both myometrium and endometrium), body weight, bone mass, bone strength, hot flushes and on ovulation (inhibition). All these effects of estetrol were dose-dependent with maximum effects at comparable dose levels. Surprisingly, estetrol prevented tumour development in a DMBA mammary tumour model to an extent and at a dose level similar to the anti-estrogen tamoxifen and to ovariectomy. This anti-estrogenic effect of estetrol in the presence of 17β-estradiol has also been observed in *in vitro* studies using human breast cancer cells.

Buccal, sublingual or sublabial administration of estetrol is mentioned in a number of patent applications, including WO 2002/094275, WO 2002/094276, WO 2002/094278 and WO 2003/018026. Estetrol containing dosage units for buccal, sublingual or sublabial administration are not described in these publications.

WO 2010/033832 describes an oral dosage form comprising an estriol compound and a pharmaceutically acceptable matrix material, wherein the oral dosage form releases at least about 90% of the estriol compound in a time of less than about 300 seconds when contacted with saliva of the buccal and/or sublingual cavity.

US 2007/286829 describes an orally administered solid dosage form capable of delivering ethinyl estradiol with improved bioavailability, said solid dosage form comprising (i) about 0.5 μg to about 50 μg of ethinyl estradiol and (ii) an oral dissolution enhancing carrier that provides

for at least 15% absorption of the ethinyl estradiol through the oral mucosa when said solid dosage form is orally administered to the patient with 2 ounces of water or less.

US 6,117,446 describes a buccal dosage unit for administering a combination of steroidal active agents, comprising a compressed tablet of a bioerodible polymeric carrier and therapeutically effective amounts of an androgenic agent selected from testosterone and pharmacologically acceptable esters thereof, a progestin and an estrogen. The examples describe buccal dosage units that were prepared by thoroughly mixing the following components: estrogen, progestogen, androgen, polyethylene oxide, carbomer and magnesium stearate. Next, the mixture was granulated by means of fluid bed granulation and the granulate so obtained was pressed into tablets.

Oral dosage units containing estetrol have been described in several patent publications.

WO 2002/094276 describes a pharmaceutical composition for use in a method of hormone replacement therapy, which method comprises administering to a person in need of such a therapy an effective amount of estetrol, said composition containing virtually no progestogen or anti-progestin. WO 2002/094276 describes the preparation of estetrol tablets having a weight of 185 mg, containing 1.5 mg estetrol, on the basis of the following formulation:

	mg
Estetrol	1.5
Polyvinylpyrrolidone (Kollidon 25® ex BASF)	12.5
Lactose	135.795
Microcrystalline cellulose (Avicel PH 101 ®)	26.25
Glyceryl palmitostearate (Precirol ®)	2.775
Anhydrous colloidal silica (Aerosil 200 ®)	1.0
Crospovidone (Polyplasdone XL ®)	4.0
Coloring agent	0.18

WO 2002/094275 describes the use of an estetrol in a method of increasing libido in a woman, said method comprising administering to said woman an effective amount of estetrol. Oral

administration is mentioned as a suitable mode of administration. This patent application describes the same estetrol tablet as WO 2002/094276.

WO 2002/094279 describes the use of estetrol in a method of contraception in mammalian females, which method comprises the oral administration of said estrogenic component and a progestogenic component to a female of childbearing capability in an effective amount to inhibit ovulation. The following formulation for a 185 mg estetrol tablet is described in this international patent application.

	mg
Estetrol	1.5
Levonorgestrel	0.15
Polyvinylpyrrolidone (Kollidon 25® ex BASF)	13.5
Lactose	135.645
Microcrystalline cellulose (Avicel PH 101 ®)	26.25
Glyceryl palmitostearate (Precirol ®)	2.775
Anhydrous colloidal silica (Aerosil 200 ®)	1.0
Crospovidone (Polyplasdone XL ®)	4.0
Coloring agent	0.18

WO 2003/041718 describes the use of estetrol in a method of hormone replacement in mammals, which method comprises the oral administration of estetrol and a progestogenic component to a mammal in an effective amount to prevent or treat symptoms of hypoestrogenism. This patent application describes the same estetrol tablet as WO 2002/094279.

WO 2007/081206 describes the use of estetrol in a method of treating an acute vascular disorder in a mammal, said method comprising orally administering to said mammal, upon demand, an effective amount of the estetrol to the mammal. This patent application describes the preparation of hard gelatine capsules, containing 100 mg estetrol and 25 mg sildenafil citrate per capsule.

WO 2008/156365 describes the use of estetrol in the treatment of Meconium Aspiration Syndrome (MAS) in a newborn infant, said treatment comprising administering an effective amount of estrogen to said newborn infant within 7 days after birth. The international patent application describes a suppository for use in newborn infants comprising at least 1 μg of estrogen, said suppository further being characterized by a maximum diameter of less than 10 mm and a weight of less than 0.5 g. The excipient contained in the suppository may be based on lipid material that melts at body temperature or it may be based on a hydrophilic component that dissolves or disintegrates when it comes into contact with water.

SUMMARY OF THE INVENTION

The present invention provides an orodispersible solid pharmaceutical dosage unit containing an estetrol component. The dosage unit rapidly releases the estetrol in aqueous environment. The solid dosage unit is easy to manufacture by direct compression and perfectly suited for sublingual, buccal or sublabial administration. Sublingual, buccal and sublabial administration each offer the advantages that the estetrol component does not have to pass through the digestive system and avoids first-pass liver exposure. Furthermore, these modes of administration provide a rapid onset of action.

The solid dosage unit according to the present invention has a weight between 30 and 1,000 mg and contains at least 100 μg of an estetrol component selected from estetrol, estetrol esters and combinations thereof; and consists of:

- 0.1-25 wt.% of estetrol particles containing at least 80 wt.% of the estetrol component; and
- 75-99.9 wt.% of one or more pharmaceutically acceptable ingredients.

This solid dosage is obtainable by a process comprising:

- providing estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof, said estetrol particles having a volume median diameter in the range of 2 μm to 50 μm;
- preparing a dry blend by mixing the estetrol particles with one or more pharmaceutically acceptable ingredients; and
- compressing the dry blend into a solid dosage unit.

Rapid and complete dissolution of the estetrol component into saliva is essential for efficient delivery of the component via sublingual, buccal or sublabial administration of the solid dosage unit. The inventors have unexpectedly found that the estetrol component is rapidly released and dispersed into saliva and absorbed through the mucosal lining of the oral cavity if it is present in the solid dosage unit in the form of very small particles.

The invention also provides a process of preparing the aforementioned solid dosage unit, said process comprising the steps of:

- providing estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof, said estetrol particles having a volume median diameter in the range of 2 μm to 50 μm;
- preparing a dry blend by mixing 1 part by weight of the estetrol particles with 2-1,000 parts by weight of one or more pharmaceutically acceptable excipients; and
- compressing the dry blend into a solid dosage unit.

BRIEF DESCRIPTION OF THE FIGURE

Figure 1 illustrates the manufacturing process flow chart used in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

A first aspect of the invention relates to an orodispersible solid pharmaceutical dosage unit having a weight between 30 and 1,000 mg, said dosage unit consisting of:

- 0.1-25 wt.% of estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof; and
- 75-99.9 wt.% of one or more pharmaceutically acceptable ingredients;

the solid dosage unit comprising at least 100 μg of the estetrol component;

wherein the solid dosage unit can be obtained by a process comprising:

- providing estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof, said estetrol particles having a volume median diameter in the range of 2 μm to 50 μm;
- preparing a dry blend by mixing the estetrol particles with one or more pharmaceutically acceptable excipients; and

- compressing the dry blend into a solid dosage unit.

The term 'estetrol' as used herein refers to 1,3,5 (10)-estratrien-3,15α,16α,17β-tetrol or 15α-hydroxyestriol as well as hydrates of estetrol, e.g. estetrol monohydrate.

The term 'orodispersible dosage unit' as used herein refers to a dosage unit that is designed to rapidly disintegrate in the oral cavity when it comes into contact with saliva and to disperse the estetrol component into the saliva so it may be absorbed through the mucosal lining of the oral cavity.

The terms 'pharmaceutically acceptable ingredients' as used herein include both pharmaceutically acceptable excipients and pharmaceutically active ingredients other than the estetrol component, as further defined below.

The term 'sublingual' as used herein refers to the pharmacological route of administration by which the estetrol component diffuses into the blood through tissues under the tongue.

The term 'buccal' as used herein refers to the pharmacological route of administration by which the estetrol component diffuses into the blood through tissues of the buccal vestibule, the area inside the mouth between the lining of cheek (the buccal mucosa) and the teeth / gums.

The term 'sublabial' as used herein refers to the pharmacological route of administration by which the estetrol component is placed between the lip and the gingiva.

Unless indicated otherwise, all percentages mentioned herein are percentages by weight.

Examples of solid dosage units encompassed by the present invention include tablets, dragees, lozenges and films. In accordance with a preferred embodiment, the dosage unit is a tablet, most preferably a compressed tablet.

The solid dosage unit typically has a weight between 40 and 500 mg, more preferably between 50 and 300 mg, and most preferably between 70 and 150 mg.

The solid dosage unit preferably comprises 0.5-25 wt.%, more preferably 1-20 wt.% and most preferably 1.2-15 wt.% of the estetrol component.

The amount of the estetrol component contained in the solid dosage unit preferably lies within the range of 0.3-100 mg, more preferably of 0.5-40 mg and most preferably of 1-20 mg.

The estetrol component of the present invention preferably is selected from the group consisting of estetrol, esters of estetrol wherein the hydrogen atom of at least one of the hydroxyl groups has been substituted by an acyl radical of a hydrocarbon carboxylic, sulfonic acid or sulfamic acid of 1-25 carbon atoms; and combinations thereof. Even more preferably, the estetrol component is estetrol (including estetrol hydrates). Most preferably, the estetrol component contained in the dosage unit is estetrol monohydrate.

The particle size of the estetrol particles in the solid dosage unit should be adequate for achieving sufficient absorption of the estetrol component after sublingual, buccal or sublabial administration. The estetrol particles within the solid dosage unit and (independently) the estetrol particles used in the preparation of the solid dosage unit preferably have a volume median diameter in the range of 3 μm to 35 μm, more preferably in the range of 4 μm to 25 μm and most preferably in the range of 5 μm to 15 μm.

The estetrol particles within the solid dosage unit and (independently) the estetrol particles used in the preparation of the solid dosage unit preferably contain not more than a limited amount of particles with a particle size in excess of 60 μm. Preferably, not more than 10 vol.% of more than 60 μm (D_{90}), more preferably not more than 5 vol.% of the estetrol particles have a particle size of more than 60 μm (D_{95}). Even more preferably, not more than 10 vol.% of more than 40 μm (D_{90}), more preferably not more than 5 vol.% of the estetrol particles have a particle size of more than 40 μm (D_{95}).

The particles size distribution of the estetrol particles, and of other particulate materials used in the present process, may suitably be determined by means of laser diffraction. The particle size distribution of the estetrol particles within the solid dosage unit can suitably be determined using spectroscopic techniques, e.g. Raman mapping.

The solid dosage unit of the present invention offers the advantage that the estetrol component is rapidly released when the dosage unit is introduced into the oral cavity and comes into contact with saliva. The rate of release of the estetrol component from the dosage unit can suitably be determined using the dissolution test described in the Examples, or a disintegration test according to Ph. Eur. 2.9.1 ("Disintegration of tablets and capsules") and USP <701> ("Disintegration"), also described in the Examples. The solid dosage unit of the present invention, when subjected to the aforementioned dissolution test, typically releases at least 50%, more preferably at least 70% and most preferably at least 80% of the estetrol component after 5 minutes. The solid dosage unit of the present invention, when subjected to the aforementioned disintegration test, typically disintegrates within less than 5 minutes, more preferably within less than 2 minutes, still more preferably within less than 1,5 minutes, still more preferably within less than 1 minute, still more preferably within less than 45 seconds, and most preferably within less than 30 seconds.

The estetrol particles employed in the solid dosage unit and in the present process preferably contain at least 90 wt.% of the estetrol component, more preferably at least 95 wt.% of the estetrol component and most preferably at least 99 wt.% of the estetrol component. Besides the estetrol component, the estetrol particles can suitably contain pharmaceutically acceptable excipients that aid dispersion of the dosage unit and dissolution and absorption of the estetrol component. Examples of such excipients include microcrystalline cellulose, tensioactive agents, cosolvents, absorption enhancer, superdisintegrants and buffering agents.

The estetrol particles typically represent between 0.5-35 wt.% of the dosage unit. More preferably, the estetrol particles represent 1-22 wt.%, most preferably 1.2-15 wt.% of the dosage unit.

The dosage unit of the present invention preferably contains 50-99.5 wt.%, more preferably 55-90 wt.% and most preferably 60-88 wt.% of filler selected from maltose, fructose, sucrose, lactose, glucose, galactose, trehalose, xylitol, sorbitol, erythritol, maltitol, mannitol, isomalt, microcrystalline cellulose, calcium salts (e.g. calcium phosphates) and combinations thereof.

According to a particularly preferred embodiment, the dosage unit contains 30-99.5 wt.%, more preferably 50-90 wt.% and most preferably 60-80 wt.% of filler selected from lactose, xylitol, sorbitol, erythritol, mannitol, microcrystalline cellulose and combinations thereof.

Advantageously, the dosage unit contains at least 20 wt.% of sugar alcohol selected from mannitol, xylitol and combinations thereof. More preferably, the dosage unit contains 30-90 wt.% of sugar alcohol selected from mannitol, xylitol and combinations therof. Most preferably, the dosage unit contains 40-80 wt.% of sugar alcohol selected from mannitol, xylitol and combinations thereof.

Dosage unit according to any one of the preceding claims, wherein the dosage unit contains 0.1-20 wt.%, more preferably 0.2-10 wt.% and most preferably 1-5 wt.% of a disintegrating agent selected from modified starches (e.g. sodium salt of carboxymethyl starch), crosslinked polyvinyl pyrrolidone, crosslinked carmellose and combinations thereof.

The combination of estetrol particles, filler and disintegrating agent typically constitutes at least 70 wt.% of the solid dosage unit. More preferably, said combination constitutes at least 80 wt.% and most preferably at least 90 wt.% of the dosage unit.

The solid dosage unit of the present invention preferably contains 0-60 wt.%, more preferably 5-40 wt.% and most preferably 10-35 wt.% microcrystalline cellulose.

According to another preferred embodiment, the dosage unit contains 0.1-2 wt.%, more preferably 0.2-1.5 wt.% and most preferably 0.5-1 wt.% of lubricant selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, polyethylene glycol, calcium stearate and mixtures thereof.

Other excipients that may suitably be incorporated in the dosage include mucoadhesive agents, flavouring, colouring, sweeteners (other than sweet tasting fillers), glidents and combinations thereof.

The solid dosage unit may contain one or more other pharmaceutically active ingredients besides the estetrol component. Examples of such other pharmaceutically active ingredients

include steroid hormones. The solid dosage unit of the present invention preferably contains 0.05-10 mg, more preferably 0.1-5 mg of one or more progestogens, preferably one or more progestogens selected from progesterone, levonorgestrel, norgestimate, norethisterone, norethisteron-acetate (NETA), dydrogesterone, drospirenone, 3-beta-hydroxydesogestrel, 3-keto desogestrel (=etonogestrel), 17-deacetyl norgestimate, 19-norprogesterone, acetoxypregnenolone, allylestrenol, anagestone, chlormadinone, cyproterone, demegestone, desogestrel, dienogest, dihydrogesterone, dimethisterone, ethisterone, ethynodiol diacetate, flurogestone acetate, gastrinon, gestodene, gestrinone, hydroxymethylprogesterone, hydroxyprogesterone, lynestrenol (=lynoestrenol), medrogestone, medroxyprogesterone, megestrol, melengestrol, nestorone, nomegestrol, nomegestrol-acetate (NOMAC), norethindrone (=norethisterone), norethynodrel, norgestrel (includes d-norgestrel and dl-norgestrel), norgestrienone, normethisterone, progesterone, quingestanol, (17alpha)-17-hydroxy-11-methylene-19-norpregna-4,15-diene-20-yn-3-one, tibolone, trimegestone, algestone acetophenide, nestorone, promegestone, 17-hydroxyprogesterone esters, 19-nor-17hydroxyprogesterone, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone, d-17beta-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime and prodrugs of these compounds. Preferably the one or more progestogens used in accordance with the present invention is selected from the group consisting of progesterone, desogestrel, etonogestrel, gestodene, dienogest, levonorgestrel, norgestimate, norethisterone, norethisteron-acetate (NETA), nomegestrol, nomegestrol-acetate (NOMAC), drospirenone, trimegestone, nestorone and dydrogesterone.

The solid dosage unit according to the present invention preferably contains 0.05-100 mg, more preferably 0.1-50 mg of one or more androgens, preferably one or more androgens selected from testosterone, dehydroepiandrosterone (DHEA); DHEA-sulphate (DHEAS); testosterone esters (e.g. testosterone undecanoate, testosterone propionate, testosterone phenylpropionate, testosterone isohexanoate, testosterone enantate, testosterone bucanate, testosterone decanoate, testosterone buciclate); methyltestosterone; mesterolon; stanozolol; androstenedione; dihydrotestosterone; androstanediol; metenolon; fluoxymesterone; oxymesterone; methandrostenolol; MENT and prodrugs of these compounds. Most preferably the one or more androgens are selected from the group consisting of testosterone, DHEA and MENT.

Another aspect of the present invention relates to the use of the aforementioned solid dosage unit in medical treatment, in female hormone replacement therapy or in female contraception, said use comprising sublingual, buccal or sublabial administration of the dosage unit. Examples of medical treatment in which the solid dosage unit of the present invention may suitably be used include treatment of osteoporosis and estrogen add-back treatment in endometriosis, breast cancer or prostate cancer. In accordance with a preferred embodiment, the solid dosage unit is used in female hormone replacement therapy or female contraception. Most preferably, the solid dosage is used in female hormone replacement therapy, especially to treat vulvovaginal atrophy and/or vasomotor symptoms.

The use of the solid dosage unit in medical treatment, in female hormone replacement therapy or in female contraception, typically comprises sublingual, buccal or sublabial administration of the dosage unit to provide at least 0.1 mg, more preferably 0.5-100 mg and most preferably 1-40 mg of the estetrol component.

To treat vulvovaginal atrophy the dosage unit is preferably administered in an amount sufficient to provide at least 0.1 mg of the estetrol component. More preferably, the administered dosage unit provides at least 0.5 mg, most preferably at least 1 mg of the estetrol component. In the treatment of vulvovaginal atrophy the dosage unit is preferably administered in an amount that provides no more than 50 mg, more preferably not more than 20 mg and most preferably not more than 10 mg of the estetrol component.

To treat vasomotor symptoms the dosage unit is preferably administered in an amount sufficient to provide at least 0.2 mg of the estetrol component. More preferably, the administered dosage unit provides at least 1 mg, most preferably of at least 2 mg of the estetrol component. In the treatment of vasomotor symptoms the dosage unit is preferably administered in an amount that provides no more than 100 mg, more preferably not more than 40 mg and most preferably not more than 20 mg of the estetrol component.

Typically, these uses of the solid dosage unit comprise once daily administration of the dosage unit during a period of at least 1 week, more preferably of at least 2 weeks. During these periods

the solid dosage unit is preferably administered to provide a daily dose of at least 0.05 mg, more preferably of 0.1-40 mg and most preferably of 0,2-20 mg of the estetrol component.

To treat vulvovaginal atrophy the dosage unit is preferably administered to provide a daily dose of at least 0.1 mg of the estetrol component. More preferably, the dosage unit is administered to provide a daily dose of 0.5-20 mg, most preferably of 1-10 mg of the estetrol component. To treat vasomotor symptoms the dosage unit is preferably administered to provide a daily dose of at least 0.2 mg of the estetrol component. More preferably, the dosage unit is administered to provide a daily dose of 1-40 mg, most preferably 2-20 mg of the estetrol component.

Yet another aspect of the invention relates to a process of preparing a solid dosage unit as described herein before, said process comprising the steps of:

- providing estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof, said estetrol particles having a volume median diameter in the range of 2 μm to 50 μm;
- preparing a dry blend by mixing 1 part by weight of the estetrol particles with 2-1,000 parts by weight of one or more pharmaceutically acceptable excipients; and
- compressing the dry blend into a solid dosage unit.

The process of the present process preferably does not comprise addition of liquid solvent during or after the combining of the estetrol particles and the one or more pharmaceutically acceptable excipients.

In the present process the dry blend that is compressed into a solid dosage unit is preferably produced by combining the estetrol particles with the one or more pharmaceutically acceptable excipients in a weight ratio that is in the range of 1:3 to 1:500, more preferably in the range of 1:4 to 1:100 and most preferably in the range of 1:5 to 1:10.

The dry blend that is compressed into the solid dosage unit preferably contains 50-99.5 wt.%, more preferably 55-90 wt.% and most preferably 60-88 wt.% of filler as defined herein before.

According to a particularly preferred embodiment the dry blend contains 30-99.5 wt.%, more preferably 50-90 wt.% and most preferably 60-80 wt.% of filler selected from lactose, xylitol, sorbitol, erythritol, mannitol, microcrystalline cellulose and combinations thereof.

Sugar alcohol selected from mannitol, xylitol and combinations thereof is advantageously contained in the dry blend in a concentration of at least 20 wt.%. More preferably, said sugar alcohol is contained in the dry blend in a concentration of 30-90 wt.%, most preferably of 40-80 wt.%.

According to another preferred embodiment, the dry blend contains 0.1-20 wt.%, more preferably 0.2-10 wt.% and most preferably 1-5 wt.% of a disintegrating agent selected from modified starches, croslinked polyvinylpyrrolidone, crosslinked carmellose and combinations thereof.

The combination of estetrol particles, filler and disintegrating agent typically constitutes at least 70 wt.% of the dry blend. More preferably, said combination constitutes at least 80 wt.% and most preferably at least 90 wt.% of the dry blend.

The solid dosage unit of the present invention preferably contains 0-60 wt.%, more preferably 5-40 wt.% and most preferably 10-35 wt.% microcrystalline cellulose.

The dry blend employed in the present process preferably contains 0-60 wt.%, more preferably 5-40 wt.% and most preferably 10-35 wt.% microcrystalline cellulose.

The dry blend that is compressed into the solid dosage unit preferably contains 0.1-2 wt.%, more preferably 0.2-1.5 wt.% and most preferably 0.5-1 wt.% of lubricant selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, polyethylene glycol, calcium stearate and mixtures thereof.

The dry blend is preferably compressed into a solid dosage unit by means of direct compression.

The solid dosage units obtained by the present method can be packaged in different ways. Preferably, the dosage units are packaged in a blister pack containing at least 14 dosage units.

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

EXAMPLES

Dissolution test

The dissolution test described below can be used to study the dissolution behaviour of orodispersible dosage units.

Dissolution apparatus

- Paddle and basket dissolution tester VanKel VK 7010 or VK 7025, autosampler VK 8000, 1000 mL dissolution vessels and porous micron filters (35 pin)

Dissolution Medium

- Transfer 9,000 ml of demineralised water into a volumetric flask of 10,000 ml.
- Add 68.05 g of KH_2PO_4 and 8.96 g NaOH and stir the solution until everything is dissolved.
- Mix the solution and adjust the pH to 6.8 with NaOH or phosphoric acid, if necessary and make up to volume with demineralised water.

Dissolution Procedure

- Transfer 900 ml of Dissolution Medium into each vessel of the paddle apparatus.
- Assemble the apparatus, warm the medium to 37 ± 0.5 °C, and remove the thermometer.
- Place in each of the six vessels one tablet at the bottom before starting the rotation of the paddles.
- Start the rotation of the paddles immediately.
- Use a stirring speed of 50 rpm.
- Take samples of 5 ml from the dissolution vessels after 5, 10, 20, 30, 45, 60, 75 and 90 minutes for a complete dissolution profile. Take the sample from a position midway between the surface of the dissolution medium and the top of the paddle blade and not less

than 10 mm from the vessel wall. The removed dissolution volume is not replaced by fresh dissolution medium.

Estetrol concentrations in the samples were determined by means of HPLC using estetrol stock solutions as a reference.

Preparation of mobile phase (MP) phosphate buffer

- Transfer 1.15 g of $NH_4H_2PO_4$ (10 mM) into a 1,000 ml of demineralised water, dissolve it and adjust the pH to 3.0 with phosphoric acid.

HPLC apparatus

- Alliance 2695 Separations module consisting of a quaternary solvent delivery system, a variable volume injector, a temperature controlled autosampler, column thermostat and Photodiode array detector 2996 (all by Waters)
- Analytical colunm: Symmetry C18, 3.9 x 150 mm, dp = 5 µm (ex Waters)
- Guard column: Security guard columg C18, 4x3 mm (Phenomenex)
- Flow: 1.0 mL/min
- Detection: UV @ 280 nm
- Column temperature: 30°C
- Autosampler temperature: 10°C
- Injection volume: 100 µL
- Run time: 12 min

Elution gradient

Time (min)	**Acetonitrile (%)**	**Phosphate buffer (%)**
0	20	80
9	75	25
10	20	80
12	20	80

The dissolution tests are conducted in triplicate.

Particle size measurements

Particle size distribution of estetrol monohydrate is performed using a MALVERN MASTERSIZER MICROPLUS laser particle size analyzer.

Preparation of dispersion medium:

- Weigh 1g of estetrol monohydrate and 1g of sorbitan trioleate into a flask.
- Add 1 litre of n-hexane and mix for at least 1 hour at room temperature
- Filter through a 0.45 µm filter.

Sample preparation:

- Put 100 mg of sample in a 25 mL beaker.
- Add some drops of dispersion medium.
- Mix carefully with a glass rod to suspend well the powder.
- Add 10 mL of dispersion medium.
- Perform the analysis with the sample dispersion unit's speed at 3000-3500 rpm.

Analysis:

Particle size measurements are performed three times using the same dispersion. The final result is obtained by averaging the results of the three determinations.

Example 1

A sublingual tablet is prepared by means of the procedure described below.

A tabletting mixture having the composition shown in Table 1 is prepared by dry blending, using a low shear mixer.

Table 1

Ingredients	**Wt.%**
Milled estetrol [1]	12.5
Mannitol	47.5
Lactose	30
PVP (polyvinylpyrrolidone)	4
Sodium crosscarmellose	4
Flavour	0.5
Aspartame	1
Magnesium stearate	0.5

[1] $D_{(v;0.5)}$ = 15µm

The tabletting mixture is compressed into 80 mg round tablets with a diameter of 6.5 mm. The estetrol content of these tablets is 10 mg.

Example 2

A sublingual tablet is prepared by means of the procedure described below.

A tabletting mixture having the composition shown in Table 2 is prepared by dry blending using a low shear mixer.

Table 2

Ingredients	**Wt.%**
Milled estetrol [1]	12.5
Mannitol	37.5
Xylitol	10
Microcrystalline cellulose	33
Sodium starch glycolate	5
Flavour	0.5
Aspartame	1
Magnesium stearate	0.5

[1] $D_{(v;0.5)}$ = 15µm

The tabletting mixture is compressed into 80 mg round tablets with a diameter of 6.5 mm. The estetrol content of these tablets is 10 mg.

Example 3

Five different sets of sublingual tablets (formulations A to E) were prepared by means of the procedure described below and illustrated in Figure 1.

The target amounts of estetrol per tablet were as follows: 100 µg for formulation A, 1 mg for formulation B, and 10 mg for formulations C, D and E.

The target weights for the tablets were as follows: 30 mg for formulation A, 1000 mg for formulation B, and 80 mg for formulations C, D and E.

The estetrol was mixed with a part of the main diluent and screened over a 800 µm screen. All other excipients were also screened over a 800 µm screen.

The materials were weighed and transferred into the mixing container (except for magnesium stearate) and mixed for 15 minutes. Finally, magnesium stearate was added and mixed for a further 3 minutes.

Compression was executed using a single punch machine equipped with a proper punch (5 mm punch for 30 mg tablets (A), 6 mm for 80 mg tablets (C, D and E) and 15 mm for 1000 mg tablets (B)).

Disintegration time was quantified according to the known protocol described in Ph. Eur. 2.9.1 ("Disintegration of tablets and capsules"), and in USP <701> ("Disintegration") using water as the specified liquid.

Hardness was measured using the known protocol described in Ph. Eur. 2.9.8 ("Resistance to crushing of tablets").

The final formulations and corresponding tablet results can be found in Tables 3 and 4 below.

All formulations were prepared and processed into tablets without encountering any specific difficulties. It should be noted that a good flowing diluent was used in all formulations to

overcome flowability issues and that the concentration of magnesium stearate was at least 1.5% to avoid sticking.

Table 3 – details of the formulations in Wt.%

Formulation #	A	B	C	D	E
Milled Estetrol [1]	0.33	0.1	12.50	12.40	12.35
Mannitol	83.14	83.47	71.00	48.47	38.62
Maize starch	10.01	10.00	10.00		
Crospovidone	5.01	5.01	4.99		
Lactose				29.68	
PVP (polyvinylpyrrolidone)				3.98	
Sodium crosscarmellose				3.98	
Xylitol DC					9.91
Microcrystalline cellulose					32.66
Sodium starch glycolate					4.97
Magnesium stearate	1.51	1.51	1.50	1.49	1.48

[1] $D_{(v;0.5)}$ = 15µm

Table 4 – experimentally determined characteristics of the Tablets

Test (average result of 6 samples)	Disintegration time	Hardness	Weight
Formulation #	**(min:sec)**	**(N)**	**(mg)**
A	0:53	39.57	33.22
B	1:07	86.07	1060.37
C	0:39	57.49	81.16
D	0:39	42.71	78.48
E	0:38	37.29	76.49

It can be seen that all tablets were obtained with a final weight close to their target weight and that the disintegration times, even for the largest 1g tablet, were very short, in accordance with the intended sublingual, buccal or sublabial administration route for these tablets.

Finally, the hardness of all tablets was within a very acceptable range.

Example 4

A randomized, open-label, two-period, cross-over, pharmacokinetic study is conducted to compare sublingual bioavailability of 10 mg estetrol administered in one 100 mg tablet with oral availability of estetrol contained in a 83 mg tablet containing 10 mg estetrol. These tablets are administered sublingually and orally to healthy female volunteers under fasting conditions.

Ten healthy female subjects are selected on the basis of the following criteria: age of 45-65 years (inclusive), nonsmokers or past smokers (at least 6 months before dosing), body-mass index (BMI) = 18.5 to 30 kg/m^2 (inclusive at the time of the screening).

The composition of the 100 mg sublingual tablets is described in Table 5 below.

Table 5

	Quantity (Wt.%)	Function
Milled Estetrol [1]	10	Active ingredient
Ludiflash® [2]	84	Diluent/binder/super disintegrant
Kollidon CL-SF® [3]	3	Super disintegrant
Magnesium stearate	3	Lubricant

[1] $D_{(v;0.5)}$ = 15µm

[2] A mixture of mannitol (90 wt.%), Kollidon CL-SF® [3] (5 wt.%) and Kollicoat® SR30D (a polyvinyl acetate dispersion in povidone) (5 wt.%)

[3] crospovidone superfine grade

These tablets have a very fast disintegration time (of 40 seconds on average).

At the start of the first and the second period of the study, between 07:00 am and 07:28 am, 5 subjects receive a single dose of the sublingual formulation of estetrol by administering one estetrol tablet (tablet weight 100 mg; 10 mg estetrol) and 5 subjects receive a single oral dose of the oral estetrol formulation by administering one estetrol tablet (tablet weight 83 mg; 10 mg estetrol), ingested together with 200 ml water.

Subjects are required to fast for at least 10 hours prior to tablet administration and for at least 4 hours after administration. Drinking of water or beverages is not permitted within 1 hour before the drug administration. Subjects receive 200 ml of water 1 hour prior to and 2 hours

after tablet administration. Subjects are free to drink water and fruit tea from 4 hours following the tablet administration. Standardized meals are provided 10.5 hours before and 4, 6, 9, and 13 hours after tablet administration.

The sequence of events that occurs during the first and second period is shown in Table 6:

Table 6

	Event
First period	
• Day 1	Confinement from 19:00
• Day 2	Dosing, blood and urine sampling, confinement
• Day 3	Exit procedure, confinement till 8 am
• Days 4-8	Return visits
• Days 9-13	Wash out
Second period	
• Day 14	Confinement from 19:00
• Day 15	Dosing, blood and urine sampling, confinement
• Day 16	Exit procedure, confinement till 8 am
• Days 17-21	Return visits
• Days 22-26	Wash out
• Day 27	Administration of a progestin
• Day 28	Phone call, progestin withdrawal test check

The blood and urine sampling schedule used in this study is shown in Table 7.

Table 7

Blood sampling	Blood collection (4 ml) is performed prior to administration of the tablet (0), and subsequently 0:10, 0:15, 0:20, 0:25, 0:30, 0:35, 0:40, 0:45, 0:50, 0:55, 1:00, 1:10, 1:20, 1:30, 2, 3, 4, 6, 10, 16, 24, 48, 72, 96, 120, 144 hours after administration. Total number of blood collections in each period is 27.
Urine sampling	Urine collection is performed prior to administration of the tablet and 2, 4, 8, 12, 24, 48, 72, 96, 120 and 144 hours after administration. Total number of urine collections in each period is 11.

The estetrol concentration in the collected blood samples is determined by means of HPLC/MS/MS. The concentrations of glucuronided estetrol (D-ring) in the urine samples is also determined with the help of HPLC/MS/MS.

Results of these analyses show that the bioavailability of sublingually administered estetrol is comparable or even superior to orally administered estetrol. Furthermore, the data suggest that sublingually administered estetrol has an earlier bioavailability compared to orally administered estetrol. Sublingual estetrol has less impact on a liver function parameter.

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CLAIMS

1. An orodispersible solid pharmaceutical dosage unit having a weight between 30 and 1,000 mg, said dosage unit consisting of:
   - 0.1-25 wt.% of estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof; and
   - 75-99.9 wt.% of one or more pharmaceutically acceptable ingredients;

   the solid dosage unit comprising at least 100 μg of the estetrol component;
   wherein the solid dosage unit can be obtained by a process comprising:
   - providing estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof, said estetrol particles having a volume median diameter in the range of 2 μm to 50 μm;
   - preparing a dry blend by mixing the estetrol particles with one or more pharmaceutically acceptable excipients; and
   - compressing the dry blend into a solid dosage unit.

2. Dosage unit according to claim 1, wherein the dosage unit has a weight between 40 and 500 mg.

3. Dosage unit according to claim 1 or 2, wherein the dosage unit contains 0.5-25 wt.% of the estetrol component.

4. Dosage unit according to any one of the preceding claims, wherein the dosage unit contains 0.3-100 mg of the estetrol component.

5. Dosage unit according to any one of the preceding claims, wherein the estetrol component is estetrol.

6. Dosage unit according to any one of the preceding claims, wherein the estetrol particles have a volume median diameter of 3-35 μm.

7. Dosage unit according to any one of the preceding claims, wherein the dosage unit contains 50-99.5 wt.% of filler selected from maltose, fructose, sucrose, lactose, glucose, galactose, trehalose, xylitol, sorbitol, erythritol, maltitol, mannitol, isomalt, microcrystalline cellulose, calcium salts and combinations thereof.

8. Dosage unit according to claim 7, wherein the dosage unit contains 50-99.5 wt.% of filler selected from lactose, xylitol, sorbitol, erythritol, mannitol, microcrystalline cellulose and combinations thereof.

9. Dosage unit according to claim 7 or 8, wherein the dosage unit contains at least 20 wt.% of sugar alcohol selected from mannitol, xylitol and combinations thereof.

10. Dosage unit according to any one of the preceding claims, wherein the dosage unit contains 0.1-20 wt.% of a disintegrating agent selected from modified starches, crosslinked polyvinyl pyrrolidone, crosslinked carmellose and combinations thereof.

11. Dosage unit according to any one of the preceding claims, wherein the dosage unit contains 0-60 wt.% of microcrystalline cellulose.

12. Dosage unit according to any one of the preceding claims, wherein the dosage unit contains 0.1-2 wt.% of lubricant selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, polyethylene glycol, calcium stearate and mixtures thereof.

13. A solid dosage unit according to any one of the preceding claims for use in medical treatment or for use in female hormone replacement therapy, said use comprising sublingual, buccal or sublabial administration of the dosage unit.

14. Solid dosage unit for the use according to claim 13, said use comprising once daily administration during a period of at least 1 week.

15. A method of female contraception, said method comprising sublingual, buccal or sublabial administration of a dosage unit according to any one of claims 1-12.

16. Method according to claim 15, said method comprising once daily administration during a period of at least 1 week.

17. A process of preparing a solid dosage unit according to any one of claims 1-12, said process comprising the steps of:
    - providing estetrol particles containing at least 80 wt.% of an estetrol component selected from estetrol, estetrol esters and combinations thereof, said estetrol particles having a volume median diameter in the range of 2 μm to 50 μm;
    - preparing a dry blend by mixing 1 part by weight of the estetrol particles with 2-1,000 parts by weight of one or more pharmaceutically acceptable excipients; and
    - compressing the dry blend into a solid dosage unit.

18. Process according to claim 17, wherein the process does not comprise addition of liquid solvent during or after the combining of the estetrol particles and the one or more pharmaceutically acceptable excipients.

19. Process according to claim 17 or 18, wherein the estetrol particles have a volume median diameter of 3-35 μm.

20. Process according to any one of claims 17-19, wherein the dry blend contains 50-99.5 wt.% of a filler selected from maltose, fructose, sucrose, lactose, glucose, galactose, trehalose, xylitol, sorbitol, erythritol, maltitol, mannitol, isomalt, microcrystalline cellulose, calcium salts and combinations thereof.

21. Process according to claim 20, wherein the dosage unit contains 50-99.5 wt.% of filler selected from lactose, xylitol, sorbitol, erythritol, mannitol, microcrystalline cellulose and combinations thereof.

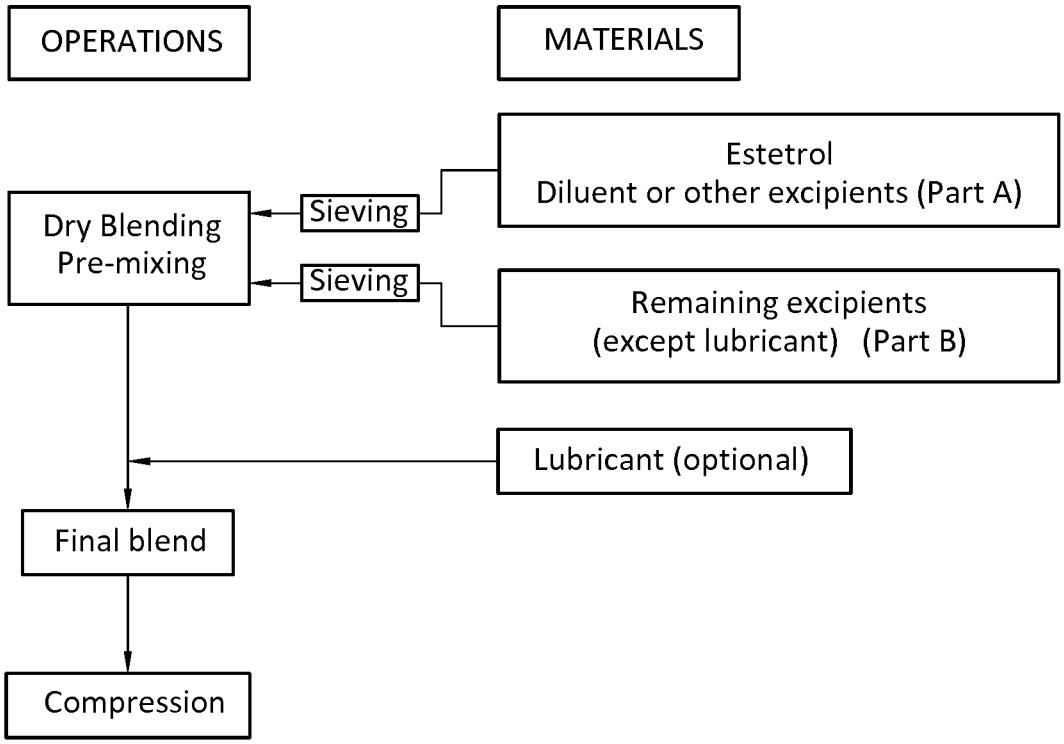
22. Process according to claim 20 or 21, wherein the dry blend contains at least 20 wt.% of sugar alcohol selected from mannitol, xylitol and combinations thereof.

23. Process according to any one of claims 17-22, wherein the dry blend contains 0.1-20 wt.% of a disintegrating agent selected from modified starches, crosslinked polyvinylpyrrolidone, crosslinked carmellose and combinations thereof.

24. Process according to any one of claims 17-23, wherein the dosage unit contains 0-60 wt.% of microcrystalline cellulose.

25. Process according to any one of claims 17-24, wherein the dry blend contains 0.1-2 wt.% of lubricant selected from sodium stearyl fumarate, magnesium stearate, stearic acid, sodium lauryl sulfate, talc, polyethylene glycol, calcium stearate and mixtures thereof.

26. Process according to any one of claims 17-25, wherein the solid dosage unit is formed by direct compression.


OPERATIONS
MATERIALS
Estetrol
Diluent or other excipients (Part A)
Dry Blending
Pre-mixing
Sieving
Sieving
Remaining excipients
(except lubricant) (Part B)
Lubricant (optional)
Final blend
Compression

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/20 A61K31/565
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 2005/070488 A1 (COELINGH BENNIK HERMAN JAN TIJ [NL] ET AL) 31 March 2005 (2005-03-31) paragraph [0035] - paragraph [0037] paragraph [0048] - paragraph [0050] paragraph [0060] paragraph [0098] example 6 -----	1-26
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 00/42955 A1 (PLACE VIRGIL A [US]) 27 July 2000 (2000-07-27) page 2, line 6 - page 3, line 14 page 4, lines 19-25 examples	1-26
X,P	WO 2015/086643 A1 (DONESTA BIOSCIENCE B V [NL]) 18 June 2015 (2015-06-18) page 4, line 24 - page 6, line 27 page 11, line 17 - line 25 page 12, line 17 - line 25 claims	1-26

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/064074

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		WO 2015086643 A1	18-06-2015

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A61P 5/30(2006.01)
A61P 15/18(2006.01)

权利要求书2页 说明书14页 附图1页

(54)发明名称

含雌四醇组分的口腔分散剂量单位

(57)摘要

本发明提供重量为30-1000mg的口腔分散固体药物剂量单位，所述剂量单位由以下组成：0.1-25重量%的含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒；和75-99.9重量%的一种或多种药学上可接受的成分；所述固体剂量单位包含至少100μg的所述雌四醇组分；且其中所述固体剂量单位可以通过包括将雌四醇颗粒与一种或多种药学上可接受的赋形剂的干燥的混合物压制成固体剂量单位的方法获得。所述固体剂量单位易于制造并且非常适合于舌下、口腔或唇下给药。

CN 107771075 A

1.重量为30-1000mg的口腔分散固体药物剂量单位，所述剂量单位由以下组成：

• 0.1-25重量%的含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒；和

• 75-99.9重量%的一种或多种药学上可接受的成分；

所述固体剂量单位包含至少100μg的所述雌四醇组分；

其中所述固体剂量单位可以通过以下方法获得，所述方法包括：

• 提供含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒，所述雌四醇颗粒的体积中值直径为2μm至50μm；

• 通过将所述雌四醇颗粒与一种或多种药学上可接受的赋形剂混合制备干燥的混合物；和

• 将所述干燥的混合物压制成固体剂量单位。

2.如权利要求1所述的剂量单位，其中所述剂量单位的重量为40-500mg。

3.如权利要求1或2所述的剂量单位，其中所述剂量单位含有0.5-25重量%的所述雌四醇组分。

4.如前述权利要求中任一项所述的剂量单位，其中所述剂量单位含有0.3-100mg的所述雌四醇组分。

5.如前述权利要求中任一项所述的剂量单位，其中所述雌四醇组分是雌四醇。

6.如前述权利要求中任一项所述的剂量单位，其中所述雌四醇颗粒的体积中值直径为3-35μm。

7.如前述权利要求中任一项所述的剂量单位，其中所述剂量单位含有50-99.5重量%的填充剂，所述填充剂选自麦芽糖、果糖、蔗糖、乳糖、葡萄糖、半乳糖、海藻糖、木糖醇、山梨糖醇、赤藓糖醇、麦芽糖醇、甘露糖醇、异麦芽酮糖醇、微晶纤维素、钙盐及其组合。

8.如权利要求7所述的剂量单位，其中所述剂量单位含有50-99.5重量%的填充剂，所述填充剂选自乳糖、木糖醇、山梨糖醇、赤藓糖醇、甘露糖醇、微晶纤维素及其组合。

9.如权利要求7或8所述的剂量单位，其中所述剂量单位含有至少20重量%的选自甘露糖醇、木糖醇及其组合的糖醇。

10.如前述权利要求中任一项所述的剂量单位，其中所述剂量单位含有0.1-20重量%的崩解剂，所述崩解剂选自改性淀粉、交联聚乙烯吡咯烷酮、交联羧甲基纤维素及其组合。

11.如前述权利要求中任一项所述的剂量单位，其中所述剂量单位含有0-60重量%的微晶纤维素。

12.如前述权利要求中任一项所述的剂量单位，其中所述剂量单位含有0.1-2重量%的润滑剂，所述润滑剂选自硬脂酰富马酸钠、硬脂酸镁、硬脂酸、十二烷基硫酸钠、滑石、聚乙二醇、硬脂酸钙及其混合物。

13.如前述权利要求中任一项所述的固体剂量单位，其用于医学治疗或用于女性激素替代疗法的用途，所述用途包括所述剂量单位的舌下、口腔或唇下给药。

14.如权利要求13所述的用于所述用途的固体剂量单位，所述用途包括在至少1周的时段期间每日一次给药。

15.女性避孕方法，所述方法包括根据权利要求1-12中任一项所述的剂量单位的舌下、口腔或唇下给药。

16.如权利要求15所述的方法，所述方法包括在至少1周的时段期间每日一次给药。

17.制备如权利要求1-12中任一项所述的固体剂量单位的方法，所述方法包括以下步骤：

• 提供含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒，所述雌四醇颗粒的体积中值直径为2μm至50μm；

• 通过将1重量份的所述雌四醇颗粒与2-1000重量份的一种或多种药学上可接受的赋形剂混合制备干燥的混合物；和

• 将所述干燥的混合物压制成固体剂量单位。

18.如权利要求17所述的方法，其中所述方法不包括在所述雌四醇颗粒和所述一种或多种药学上可接受的赋形剂组合期间或之后加入液体溶剂。

19.如权利要求17或18所述的方法，其中所述雌四醇颗粒的体积中值直径为3-35μm。

20.如权利要求17-19中任一项所述的方法，其中所述干燥的混合物含有50-99.5重量%的填充剂，所述填充剂选自麦芽糖、果糖、蔗糖、乳糖、葡萄糖、半乳糖、海藻糖、木糖醇、山梨糖醇、赤藓糖醇、麦芽糖醇、甘露糖醇、异麦芽酮糖醇、微晶纤维素、钙盐及其组合。

21.如权利要求20所述的方法，其中所述剂量单位含有50-99.5重量%的填充剂，所述填充剂选自乳糖、木糖醇、山梨糖醇、赤藓糖醇、甘露糖醇、微晶纤维素及其组合。

22.如权利要求20或21所述的方法，其中所述干燥的混合物含有至少20重量%的选自甘露糖醇、木糖醇及其组合的糖醇。

23.如权利要求17-22中任一项所述的方法，其中所述干燥的混合物含有0.1-20重量%的崩解剂，所述崩解剂选自改性淀粉、交联聚乙烯吡咯烷酮、交联羧甲基纤维素及其组合。

24.如权利要求17-23中任一项所述的方法，其中所述剂量单位含有0-60重量%的微晶纤维素。

25.如权利要求17-24中任一项所述的方法，其中所述干燥的混合物含有0.1-2重量%的润滑剂，所述润滑剂选自硬脂酰富马酸钠、硬脂酸镁、硬脂酸、十二烷基硫酸钠、滑石、聚乙二醇、硬脂酸钙及其混合物。

26.如权利要求17-25中任一项所述的方法，其中所述固体剂量单位通过直接压制而形成。

含雌四醇组分的口腔分散剂量单位

技术领域

[0001] 本发明提供重量为30-1000mg且含有至少0.1mg的选自雌四醇、雌四醇酯及其组合的雌四醇组分的口腔分散固体药物剂量单位。该固体剂量单位由以下组成：

[0002] • 0.1-25重量%的含有至少80重量%的雌四醇组分的雌四醇颗粒；和

[0003] • 75-99.9重量%的一种或多种药学上可接受的成分。

[0004] 本发明还提供制备上述固体剂量单位的方法。

[0005] 此外，本发明涉及固体剂量单位在医学治疗、女性激素替代疗法和女性避孕中的用途，所述用途包括所述剂量单位的舌下、口腔或唇下给药。

[0006] 发明背景

[0007] 雌四醇是仅在妊娠期间由胎儿肝脏产生的人体类固醇。这种天然激素是在1965年由Diczfalusy及其同事在孕妇的尿液中发现的。雌四醇具有带有四个羟基的雌激素类固醇的结构。雌四醇通过15α-和16α-羟化酶两种酶在胎儿肝脏中从雌二醇和雌三醇合成。出生后新生儿肝脏迅速丧失其合成雌四醇的能力，因为这两种酶不再表达。

[0008] 雌四醇通过胎盘到达母体循环，并且已经在妊娠九周时在母体尿液中检测到。在妊娠中期，在母体血浆中发现高水平，在接近妊娠结束时，未结合雌四醇的浓度稳定地升高到约1ng/mL(>3nmol/L)。到目前为止，雌四醇的生理功能是未知的。雌四醇作为胎儿健康标志物的可能用途已被相当广泛地研究。然而，由于妊娠期间母体雌四醇血浆水平的个体内和个体间的变化较大，这似乎是不可行的。

[0009] 自2001年以来，雌四醇已被广泛研究。在人体中证明雌四醇具有较高且剂量成比例的口服生物利用度和约28小时的长终末消除半衰期。来自体外研究的结果显示，与雌激素乙炔雌二醇和17β-雌二醇不同，雌四醇与雌激素受体高度选择性地结合，对受体的ERα形式有偏好。同样地与乙炔雌二醇和特别是与17β-雌二醇相比，雌四醇不与性激素结合球蛋白(SHBG)结合，并且不会刺激体外SHBG的产生。

[0010] 也已经在一系列预测的、经很好验证的药理学体内大鼠模型中研究了雌四醇的性质。在这些模型中，雌四醇对阴道、子宫(子宫肌膜和子宫内膜)、体重、骨量、骨强度、热潮红和排卵(抑制)表现出雌激素作用。雌四醇的所有这些作用都是剂量依赖性的，在可比较的剂量水平下具有最大作用。令人惊奇的是，在一定程度上并且在类似于抗雌激素他莫昔芬和卵巢切除术的剂量水平，雌四醇在DMBA乳腺肿瘤模型中预防了肿瘤发展。在使用人乳腺癌细胞的体外研究中也观察到雌四醇在17β-雌二醇存在下的抗雌激素作用。

[0011] 包括WO 2002/094275、WO 2002/094276、WO 2002/094278和WO 2003/018026的多个专利申请中提到了雌四醇的口腔、舌下或唇下给药。这些公开中没有记载用于口腔、舌下或唇下给药的含有雌四醇的剂量单位。

[0012] WO 2010/033832记载了包含雌三醇化合物和药学上可接受的基质材料的口服剂型，其中口服剂型在与口腔和/或舌下腔的唾液接触的小于约300秒的时间内释放至少约90%的雌三醇化合物。

[0013] US 2007/286829记载了能够递送具有改善的生物利用度的乙炔雌二醇的口服给

药固体剂型，所述固体剂型包含(i)约0.5μg至约50μg乙炔雌二醇和(ii)口腔溶出增强载体，其在所述固体剂型用2盎司或更少的水口服给药于患者时提供通过口腔粘膜至少15%乙炔雌二醇的吸收。

[0014] US 6,117,446记载了用于给药类固醇活性剂的组合的含服剂量单位，其包含生物可蚀解聚合载体和治疗有效量的雄激素剂(选自睾酮及其药理学可接受的酯)、黄体制剂(progestin)和雌激素的压制片剂。实施例记载了通过彻底混合以下组分制备的含服剂量单位：雌激素、孕激素、雄激素、聚环氧乙烷、卡波姆和硬脂酸镁。接着，通过流化床造粒将混合物造粒，将如此获得的粒子压制成片剂。

[0015] 在几个专利公开中已经记载了含有雌四醇的口服剂量单位。

[0016] WO 2002/094276记载了用于激素替代疗法方法的药物组合物，该方法包括向需要这样的疗法的人给药有效量的雌四醇，所述组合物实际上不含有孕激素或抗黄体制剂。WO 2002/094276记载了基于以下配方制备含有1.5mg雌四醇，重量为185mg的雌四醇片剂：

[0017]

	mg
雌四醇	1.5
聚乙烯吡咯烷酮(Kollidon 25® ex BASF)	12.5
乳糖	135.795
微晶纤维素(Avicel PH 101 ®)	26.25
硬脂酸棕榈酸甘油酯(Precirol ®)	2.775
无水胶态二氧化硅(Aerosil 200 ®)	1.0
交联聚维酮(Polyplasdone XL ®)	4.0
着色剂	0.18

[0018] WO 2002/094275记载了雌四醇在提高女性性欲方法中的用途，所述方法包括向所述女性给药有效量的雌四醇。口服给药被认为是合适的给药方式。该专利申请记载了与WO 2002/094276相同的雌四醇片剂。

[0019] WO 2002/094279记载了雌四醇在雌性哺乳动物避孕方法中的用途，该方法包括将所述雌激素组分和孕激素组分以有效量口服给药于有生育能力的女性以抑制排卵。该国际专利申请中记载了用于185mg雌四醇片剂的以下配方。

[0020]

	mg
雌四醇	1.5
左炔诺孕酮	0.15
聚乙烯吡咯烷酮(Kollidon 25® ex BASF)	13.5
乳糖	135.645
微晶纤维素(Avicel PH 101 ®)	26.25
硬脂酸棕榈酸甘油酯(Precirol ®)	2.775
无水胶态二氧化硅(Aerosil 200 ®)	1.0
交联聚维酮(Polyplasdone XL ®)	4.0
着色剂	0.18

[0021] WO 2003/041718记载了雌四醇在哺乳动物激素替代方法中的用途，该方法包括将雌四醇和孕激素组分以有效量口服给药于哺乳动物以预防或治疗雌激素过少症。该专利申请记载了与WO 2002/094279相同的雌四醇片剂。

[0022] WO 2007/081206记载了雌四醇在治疗哺乳动物急性血管疾病的方法中的用途，所述方法包括根据需要将有效量的哺乳动物用雌四醇口服给药于所述哺乳动物。该专利申请记载了硬明胶胶囊的制备，每个胶囊都含有100mg雌四醇和25mg枸橼酸西地那非。

[0023] WO 2008/156365记载了雌四醇在治疗新生儿胎粪吸入综合征(MAS)中的用途，所述治疗包括在出生后7天内向所述新生儿给药有效量的雌激素。该国际专利申请记载了用于新生儿的包含至少1μg雌激素的栓剂，所述栓剂的特征还在于最大直径小于10mm，且重量小于0.5g。在栓剂中含有的赋形剂可基于在体温下熔化的脂类材料，或者其可基于在与水接触时溶解或崩解的亲水性组分。

发明内容

[0024] 本发明提供含有雌四醇组分的口腔分散固体药物剂量单位。剂量单位在含水环境中迅速释放雌四醇。固体剂量单位易于通过直接压制制造并且非常适合于舌下、口腔或唇下给药。舌下、口腔和唇下给药每个都提供如下优点，即雌四醇组分不必经过消化系统并且避免首过肝脏暴露。此外，这些给药方式提供快速起效。

[0025] 根据本发明的固体剂量单位具有30-1000mg的重量且含有至少100μg的选自雌四醇、雌四醇酯及其组合的雌四醇组分；且由以下组成：

[0026] • 0.1-25重量%的含有至少80重量%的雌四醇组分的雌四醇颗粒；和

[0027] • 75-99.9重量%的一种或多种药学上可接受的成分。

[0028] 该固体剂量单位可通过以下方法获得，所述方法包括：

[0029] • 提供含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒，所述雌四醇颗粒的体积中值直径为2μm至50μm；

[0030] • 通过将所述雌四醇颗粒与一种或多种药学上可接受的成分混合制备干燥的混

合物;和

[0031] • 将所述干燥的混合物压制成固体剂量单位。

[0032] 对于经由固体剂量单位的舌下、口腔或唇下给药而有效地递送组分而言,将雌四醇组分快速且完全地溶解于唾液中是必不可少的。本发明人已经出乎意料地发现,如果以极小颗粒形式存在于固体剂量单位中,则雌四醇组分被快速释放并分散到唾液中,并且通过口腔的粘膜内层吸收。

[0033] 本发明还提供制备上述固体剂量单位的方法,所述方法包括以下步骤:

[0034] • 提供含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒,所述雌四醇颗粒的体积中值直径为2μm至50μm;

[0035] • 通过将1重量份的所述雌四醇颗粒与2-1000重量份的一种或多种药学上可接受的赋形剂混合制备干燥的混合物;和

[0036] • 将所述干燥的混合物压制成固体剂量单位。

附图说明

[0037] 图1图示了实施例3中使用的制造方法流程图。

[0038] 发明详述

[0039] 本发明的第一方面涉及重量为30-1000mg的口腔分散固体药物剂量单位,所述剂量单位由以下组成:

[0040] • 0.1-25重量%的含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒;和

[0041] • 75-99.9重量%的一种或多种药学上可接受的成分;

[0042] 所述固体剂量单位包含至少100μg的所述雌四醇组分;

[0043] 其中所述固体剂量单位可以通过以下方法获得,所述方法包括:

[0044] • 提供含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒,所述雌四醇颗粒的体积中值直径为2μm至50μm;

[0045] • 通过将所述雌四醇颗粒与一种或多种药学上可接受的赋形剂混合制备干燥的混合物;和

[0046] • 将所述干燥的混合物压制成固体剂量单位。

[0047] 本文所用术语‘雌四醇’是指1,3,5(10)-雌甾三烯-3,15α,16α,17β-四醇或15α-羟雌三醇以及雌四醇水合物,例如雌四醇单水合物。

[0048] 本文所用术语‘口腔分散剂量单位’是指如下剂量单位,其被设计为当其与唾液接触时在口腔中快速崩解并将雌四醇组分分散到唾液中,使其可通过口腔的粘膜内层吸收。

[0049] 如下面进一步定义的,本文所用术语‘药学上可接受的成分’包括药学上可接受的赋形剂和除雌四醇组分以外的药学活性成分。

[0050] 本文所用术语‘舌下’是指通过舌下组织将雌四醇组分扩散到血液中的药理学给药途径。

[0051] 本文所用术语‘口腔’是指通过口腔前庭的组织,即脸颊内层(口腔粘膜)与牙齿/齿龈之间的口内区域,将雌四醇组分扩散到血液中的药理学给药途径。

[0052] 本文所用术语‘唇下’是指将雌四醇组分放置在唇和牙龈之间的药理学给药途径。

[0053] 除非另有说明，否则本文提及的所有百分比均为重量百分比。

[0054] 本发明所涵盖的固体剂量单位的实例包括片剂、糖衣丸、锭剂和膜剂。根据优选实施方案，剂量单位是片剂，最优选是压制片剂。

[0055] 固体剂量单位通常具有40-500mg，更优选50-300mg以及最优选70-150mg的重量。

[0056] 固体剂量单位优选地包含0.5-25重量%，更优选1-20重量%以及最优选1.2-15重量%的雌四醇组分。

[0057] 在固体剂量单位中含有的雌四醇组分的量优选地在0.3-100mg，更优选0.5-40mg以及最优选1-20mg的范围内。

[0058] 本发明的雌四醇组分优选选自雌四醇、雌四醇酯(其中至少一个羟基的氢原子已被1-25个碳原子的烃羧酸、磺酸或氨基磺酸的酰基替代)及其组合。甚至更优选地，雌四醇组分是雌四醇(包括雌四醇水合物)。最优选地，在剂量单位中含有的雌四醇组分是雌四醇单水合物。

[0059] 固体剂量单位中的雌四醇颗粒的粒径应足以在舌下、口腔或唇下给药后实现雌四醇组分的充分吸收。固体剂量单位中的雌四醇颗粒和(独立地)用于制备固体剂量单位的雌四醇颗粒优选具有3-35μm的体积中值直径，更优选4-25μm和最优选5-15μm。

[0060] 固体剂量单位中的雌四醇颗粒和(独立地)用于制备固体剂量单位的雌四醇颗粒优选含有不超过有限量的粒径超过60μm的颗粒。优选地不超过10体积%的超过60μm(D_{90})，更优选地不超过5体积%的雌四醇颗粒具有超过60μm的粒径(D_{95})。甚至更优选地，不超过10体积%的超过40μm(D_{90})，更优选地不超过5体积%的雌四醇颗粒具有超过40μm的粒径(D_{95})。

[0061] 本发明方法中使用的雌四醇颗粒和其他颗粒材料的粒度分布可借助于激光衍射适当地测定。固体剂量单位内的雌四醇颗粒的粒度分布可以使用光谱技术(如拉曼映射)适当地测定。

[0062] 本发明的固体剂量单位提供如下优点，即当剂量单位被引入口腔并与唾液接触时，雌四醇组分被迅速释放。雌四醇组分从剂量单位的释放速率可以使用实施例中所述的溶出试验或同样如实施例中所述的根据欧洲药典2.9.1(“片剂和胶囊的崩解”)以及USP<701>(“崩解”)的崩解试验来合适地测定。当进行上述溶出试验时，本发明的固体剂量单位通常在5分钟后释放至少50%，更优选至少70%以及最优选至少80%的雌四醇组分。当进行上述崩解试验时，本发明的固体剂量单位通常在少于5分钟内，更优选在少于2分钟内，还更优选在少于1.5分钟内，还更优选在少于1分钟内，还更优选在少于45秒内以及最优选在少于30秒内崩解。

[0063] 固体剂量单位中和本发明方法中采用的雌四醇颗粒优选含有至少90重量%的雌四醇组分，更优选至少95重量%的雌四醇组分和最优选至少99重量%的雌四醇组分。除雌四醇组分外，雌四醇颗粒还可以合适地含有药学上可接受的赋形剂，其有助于剂量单位的分散以及雌四醇组分的溶出和吸收。这样的赋形剂的实例包括微晶纤维素、表面活性剂、共溶剂、吸收促进剂、超级崩解剂和缓冲剂。

[0064] 雌四醇颗粒通常占剂量单位的0.5-35重量%。更优选地，雌四醇颗粒占剂量单位的1-22重量%，最优选地，占剂量单位的1.2-15重量%。

[0065] 本发明的剂量单位优选地含有50-99.5重量%，更优选55-90重量%和最优选60-

88重量%的填充剂，所述填充剂选自麦芽糖、果糖、蔗糖、乳糖、葡萄糖、半乳糖、海藻糖、木糖醇、山梨糖醇、赤藓糖醇、麦芽糖醇、甘露糖醇、异麦芽酮糖醇、微晶纤维素、钙盐(如磷酸钙)及其组合。

[0066] 根据特别优选的实施方案，剂量单位含有30-99.5重量%，更优选50-90重量%和最优选60-80重量%的填充剂，所述填充剂选自乳糖、木糖醇、山梨糖醇、赤藓糖醇、甘露糖醇、微晶纤维素及其组合。

[0067] 有利地，剂量单位含有至少20重量%的选自甘露糖醇、木糖醇及其组合的糖醇。更优选地，剂量单位含有30-90重量%的选自甘露糖醇、木糖醇及其组合的糖醇。最优选地，剂量单位含有40-80重量%的选自甘露糖醇、木糖醇及其组合的糖醇。

[0068] 根据前述权利要求中任一项的剂量单位，其中所述剂量单位含有0.1-20重量%，更优选0.2-10重量%和最优选1-5重量%的崩解剂，所述崩解剂选自改性淀粉(例如羧甲基淀粉的钠盐)、交联聚乙烯吡咯烷酮、交联羧甲基纤维素及其组合。

[0069] 雌四醇颗粒、填充剂和崩解剂的组合通常构成固体剂量单位的至少70重量%。更优选地，所述组合构成剂量单位的至少80重量%和最优选地至少90重量%。

[0070] 本发明的固体剂量单位优选含有0-60重量%，更优选5-40重量%和最优选10-35重量%的微晶纤维素。

[0071] 根据另一个优选的实施方案，剂量单位含有0.1-2重量%，更优选0.2-1.5重量%和最优选0.5-1重量%的润滑剂，所述润滑剂选自硬脂酰富马酸钠、硬脂酸镁、硬脂酸、十二烷基硫酸钠、滑石、聚乙二醇、硬脂酸钙及其混合物。

[0072] 可合适地掺入剂量单位中的其他赋形剂包括粘膜粘附剂、调味剂、着色剂、甜味剂(除甜味填充剂以外)、助流剂及其组合。

[0073] 除了雌四醇组分之外，固体剂量单位还可含有一种或多种其它药学活性成分。这样的其它药学活性成分的实例包括类固醇激素。本发明的固体剂量单位优选地含有0.05-10mg，更优选0.1-5mg的一种或多种孕激素，优选一种或多种选自以下的孕激素：孕酮、左炔诺孕酮、诺孕酯、炔诺酮、醋酸炔诺酮(NETA)、地屈孕酮、屈螺酮、3-β-羟基去氧孕烯、3-酮基去氧孕烯(=依托孕烯)、17-去乙酰诺孕酯、19-去甲孕酮、乙酰孕烯醇酮、烯丙雌醇、阿那孕酮、氯地孕酮、环丙孕酮、地美孕酮、去氧孕烯、地诺孕素、二氢孕酮(dihydrogesterone)、地美炔酮、炔孕酮、双醋炔诺醇、醋酸氟孕酮、胃泌素、孕二烯酮、孕三烯酮、羟甲基孕酮、羟孕酮、利奈孕酮(=炔雌烯醇)、美罗孕酮、甲羟基孕酮、甲地孕酮、美仑孕酮、醋酸烯诺孕酮、诺美孕酮、醋酸诺美孕酮(NOMAC)、去甲基脱氢羟孕酮(炔诺酮)、异炔诺酮、甲基炔诺酮(包括d-甲基炔诺酮和dl-甲基炔诺酮)、诺孕烯酮、甲诺酮、孕酮、奎孕醇、(17α)-17-羟基-11-亚甲基-19-去甲孕甾-4,15-二烯-20-炔-3-酮、甲基异炔酮、曲美孕酮、双羟孕酮缩苯乙酮、醋酸烯诺孕酮(nestorone)、普美孕酮、17-羟孕酮酯、19-去甲基-17羟孕酮、17α-乙炔基-睾酮、17α-乙炔基-19-去甲基-睾酮、d-17β-乙酰氧基-13β-乙基-17α-乙炔基-甾烷-4-烯-3-酮肟和这些化合物的前药。优选地，根据本发明使用的一种或多种孕激素选自孕酮、去氧孕烯、依托孕烯、孕二烯酮、地诺孕素、左炔诺孕酮、诺孕酯、炔诺酮、醋酸炔诺酮(NETA)、诺美孕酮、醋酸诺美孕酮(NOMAC)、屈螺酮、曲美孕酮、醋酸烯诺孕酮和地屈孕酮。

[0074] 根据本发明的固体剂量单位优选地含有0.05-100mg，更优选0.1-50mg的一种或多种雄激素，优选地一种或多种雄激素选自睾酮、脱氢表雄酮(DHEA)；DHEA-硫酸盐(DHEAS)；

睾酮酯(例如十一烷酸睾酮、丙酸睾酮、苯丙酸睾酮、异己酸睾酮、庚酸睾酮、丁酸睾酮(testosterone bucanate)、癸酸睾酮、环甲酸睾酮);甲基睾酮;甲氢睾酮(mesterolon);司坦唑醇;雄烯二酮;双氢睾酮;雄烷二醇;美替诺龙(metenolon);氟羟甲睾酮;羟甲睾酮;美雄酮;MENT和这些化合物的前药。最优选地,一种或多种雄激素选自睾酮、DHEA和MENT。

[0075] 本发明的另一方面涉及上述固体剂量单位在医学治疗、女性激素替代疗法或女性避孕中的用途,所述用途包括剂量单位的舌下、口腔或唇下给药。其中本发明的固体剂量单位可合适地使用的医学治疗的实例包括骨质疏松症的治疗和子宫内膜异位症、乳腺癌或前列腺癌的雌激素反加治疗。根据优选实施方案,固体剂量单位用于女性激素替代疗法或女性避孕。最优选地,固体剂量用于女性激素替代疗法,特别是用于治疗外阴阴道萎缩和/或血管舒缩症状。

[0076] 固体剂量单位在医学治疗、女性激素替代疗法或女性避孕中的用途通常包括剂量单位的舌下、口腔或唇下给药,以提供至少0.1mg,更优选0.5-100mg以及最优选1-40mg的雌四醇组分。

[0077] 为了治疗外阴阴道萎缩,剂量单位优选地以足以提供至少0.1mg的雌四醇组分的量给药。更优选地,给药的剂量单位提供至少0.5mg、最优选至少1mg的雌四醇组分。在外阴阴道萎缩的治疗中,剂量单位优选地以提供不超过50mg,更优选不超过20mg以及最优选不超过10mg的雌四醇组分的量给药。

[0078] 为了治疗血管舒缩症状,剂量单位优选地以足以提供至少0.2mg的雌四醇组分的量给药。更优选地,给药的剂量单位提供至少1mg、最优选至少2mg的雌四醇组分。在血管舒缩症状的治疗中,剂量单位优选地以提供不超过100mg,更优选不超过40mg以及最优选不超过20mg的雌四醇组分的量给药。

[0079] 通常,固体剂量单位的这些用途包括在至少1周,更优选至少2周的时段内每日一次给药剂量单位。在这些时段期间,固体剂量单位优选地给药,以提供至少0.05mg,更优选地0.1-40mg以及最优选地0.2-20mg的雌四醇组分的日剂量。

[0080] 为了治疗外阴阴道萎缩,剂量单位优选地以提供至少0.1mg的雌四醇组分的日剂量给药。更优选地,剂量单位以提供0.5-20mg,最优选1-10mg的雌四醇组分的日剂量给药。

[0081] 为了治疗血管舒缩症状,剂量单位优选地以提供至少0.2mg的雌四醇组分的日剂量给药。更优选地,剂量单位以提供1-40mg,最优选2-20mg的雌四醇组分的日剂量给药。

[0082] 本发明的又一方面涉及制备如本文之前所述的固体剂量单位的方法,所述方法包括以下步骤:

[0083] • 提供含有至少80重量%的选自雌四醇、雌四醇酯及其组合的雌四醇组分的雌四醇颗粒,所述雌四醇颗粒的体积中值直径为2μm至50μm;

[0084] • 通过将1重量份的所述雌四醇颗粒与2-1000重量份的一种或多种药学上可接受的赋形剂混合制备干燥的混合物;和

[0085] • 将所述干燥的混合物压制成固体剂量单位。

[0086] 本发明的方法优选不包括在所述雌四醇颗粒和所述一种或多种药学上可接受的赋形剂组合期间或之后加入液体溶剂。

[0087] 在本发明方法中,优选通过将雌四醇颗粒与一种或多种药学上可接受的赋形剂以1:3至1:500,更优选1:4至1:100和最优选1:5至1:10的重量比组合来产生压制成固体剂量

单位的干燥的混合物。

[0088] 压制成固体剂量单位的干燥的混合物优选含有50-99.5重量%，更优选55-90重量%和最优选60-88重量%的如本文之前所定义的填充剂。

[0089] 根据特别优选的实施方案，干燥的混合物含有30-99.5重量%，更优选50-90重量%和最优选60-80重量%的填充剂，所述填充剂选自乳糖、木糖醇、山梨糖醇、赤藓糖醇、甘露糖醇、微晶纤维素及其组合。

[0090] 选自甘露糖醇、木糖醇及其组合的糖醇有利地以至少20重量%的浓度包含在干燥的混合物中。更优选地，所述糖醇以30-90重量%，最优选40-80重量%的浓度包含在干燥的混合物中。

[0091] 根据另一个优选的实施方案，干燥的混合物含有0.1-20重量%，更优选0.2-10重量%和最优选1-5重量%的崩解剂，所述崩解剂选自改性淀粉、交联聚乙烯吡咯烷酮、交联羧甲基纤维素及其组合。

[0092] 雌四醇颗粒、填充剂和崩解剂的组合通常构成干燥的混合物的至少70重量%。更优选地，所述组合构成干燥的混合物的至少80重量%和最优选地至少90重量%。

[0093] 本发明的固体剂量单位优选含有0-60重量%，更优选5-40重量%和最优选10-35重量%的微晶纤维素。

[0094] 本发明方法中采用的干燥的混合物优选含有0-60重量%，更优选5-40重量%和最优选10-35重量%的微晶纤维素。

[0095] 压制成固体剂量单位的干燥的混合物优选含有0.1-2重量%，更优选0.2-1.5重量%和最优选0.5-1重量%的润滑剂，所述润滑剂选自硬脂酰富马酸钠、硬脂酸镁、硬脂酸、十二烷基硫酸钠、滑石、聚乙二醇、硬脂酸钙及其混合物。

[0096] 所述干燥的混合物优选通过直接压制而压制成固体剂量单位。

[0097] 通过本方法获得的固体剂量单位可以以不同方式来包装。优选地，剂量单位被包装在含有至少14个剂量单位的泡罩包装中。

[0098] 通过以下非限制性实施例进一步说明本发明。

实施例

[0099] 溶出试验

[0100] 下面描述的溶出试验可以用于研究口腔分散剂量单位的溶出行为。

[0101] 溶出装置

[0102] • 桨式和篮式溶出测试仪VanKel VK 7010或VK 7025，自动采样器VK 8000，1000mL溶出容器和多孔微米过滤器(35pin)

[0103] 溶出介质

[0104] • 将9000ml去矿质水转移到10000ml的容量瓶中。

[0105] • 加入68.05g的KH_2PO_4和8.96g的NaOH，并且搅拌溶液直到所有物料溶解。

[0106] • 混合溶液，并且用NaOH或磷酸将pH值调节至6.8，如有必要，用去矿质水补足体积。

[0107] 溶出操作

[0108] • 将900ml的溶出介质转移到桨式装置的每个容器中。

[0109] • 组装装置，将介质加温至37±0.5℃，然后移去温度计。

[0110] • 在桨开始旋转之前，在六个容器中的每一个底部放置一片片剂。

[0111] • 立即开始旋转桨。

[0112] • 使用50rpm的搅拌速度。

[0113] • 在5、10、20、30、45、60、75和90分钟后从溶出容器取出5ml样品以获得完全溶出曲线。从溶出介质表面和桨式叶片顶部之间的中间且离容器壁不小于10mm的位置取出样品。除去的溶出体积不被新鲜溶出介质所替代。

[0114] 使用雌四醇储备溶液作为参照，通过HPLC测定样品中的雌四醇浓度。流动相(MP)磷酸盐缓冲液的制备

[0115] • 将1.15g的$NH_4H_2PO_4$(10mM)转移到1000ml去矿质水中，溶解并用磷酸将pH调节至3.0。

[0116] HPLC装置

[0117] • Alliance 2695分离模块由四元溶剂输送系统、可变容积注射器、温度控制自动采样器、柱恒温器和光电二极管阵列检测器2996(均由Waters提供)组成。

[0118] • 分析柱：Symmetry C18，3.9×150mm，dp＝5μm(例如Waters)

[0119] • 保护柱：安全保护柱C18，4x3mm(Phenomenex)

[0120] • 流速：1.0mL/min

[0121] • 检测：UV@280nm

[0122] • 柱温：30℃

[0123] • 自动采样器温度：10℃

[0124] • 注射体积：100μL

[0125] • 运行时间：12min

[0126] 洗脱梯度

[0127]

时间(min)	乙腈(%)	磷酸盐缓冲液(%)
0	20	80
9	75	25
10	20	80
12	20	80

[0128] 溶出试验按照一式三份进行。

[0129] 粒度测量

[0130] 使用MALVERN MASTERSIZER MICROPLUS激光粒度分析仪进行雌四醇单水合物的粒度分布。

[0131] 分散介质的制备：

[0132] • 称取1g雌四醇单水合物和1g脱水山梨醇三油酸酯，加入到烧瓶中。

[0133] • 加入1升正己烷并在室温下混合至少1小时。

[0134] • 通过0.45μm过滤器进行过滤。

[0135] 样品制备：

[0136] • 将100mg样品放入25mL烧杯中。

[0137] • 加入几滴分散介质。

[0138] • 用玻璃棒仔细混合以使粉末充分悬浮。

[0139] • 加入10mL分散介质。

[0140] • 在3000-3500rpm的样品分散单位速度下进行分析。

[0141] 分析：

[0142] 使用相同分散进行三次粒度测量。通过对三次测定结果进行平均来获得最终结果。

[0143] 实施例1

[0144] 通过下面描述的操作制备舌下片剂。

[0145] 具有表1中所示组成的压片混合物使用低剪切混合机通过干混来制备。

[0146] 表1

[0147]

成分	重量%
研磨雌四醇[1]	12.5
甘露糖醇	47.5
乳糖	30
PVP(聚乙烯吡咯烷酮)	4
交联羧甲基纤维素钠	4
调味剂	0.5
阿斯巴甜	1
硬脂酸镁	0.5

[0148] [1]$D_{(v;0.5)}$＝15μm

[0149] 将压片混合物压制成直径为6.5mm的80mg圆形片剂。这些片剂的雌四醇含量为10mg。

[0150] 实施例2

[0151] 通过下面描述的操作来制备舌下片剂。

[0152] 具有表2中所示组成的压片混合物使用低剪切混合机通过干混制备。

[0153] 表2

[0154]

成分	重量%
研磨雌四醇[1]	12.5
甘露糖醇	37.5
木糖醇	10
微晶纤维素	33
淀粉羟乙酸钠	5
调味剂	0.5
阿斯巴甜	1
硬脂酸镁	0.5

[0155] [1]$D_{(v;0.5)}$＝15μm

[0156] 将压片混合物压制成直径为6.5mm的80mg圆形片剂。这些片剂的雌四醇含量为10mg。

[0157] 实施例3

[0158] 通过下面描述及图1所示的操作制备5种不同的舌下片剂(制剂A到E)。

[0159] 每种片剂的雌四醇目标量如下:制剂A为100μg,制剂B为1mg,和制剂C、D和E为10mg。

[0160] 片剂的目标重量如下:制剂A为30mg,制剂B为1000mg,和制剂C、D和E为80mg。

[0161] 将雌四醇与主要稀释剂的一部分混合并在800μm筛网上筛分。所有其他赋形剂也在800μm筛网上筛分。

[0162] 将材料称重并转移至混合容器中(硬脂酸镁除外)混合15分钟。最后加入硬脂酸镁并进一步混合3分钟。

[0163] 使用配备有合适的冲头(5mm冲头用于30mg片剂(A),6mm冲头用于80mg片剂(C、D和E),和15mm冲头用于1000mg片剂(B))的单冲头机进行压制。

[0164] 根据欧洲药典2.9.1(“片剂和胶囊的崩解”)以及USP<701>(“崩解”)中的所述已知方案,通过将水用作指定液体,对崩解时间进行定量。

[0165] 使用欧洲药典2.9.8(“片剂的粉碎阻力”)中所述的已知方案来测量硬度。

[0166] 最终配方和相应的片剂结果可以在下面的表3和表4中找到。

[0167] 所有制剂被制备并加工成片剂没有遇到任何具体的困难。应该注意的是,在所有制剂中使用良好的流动性稀释剂以克服流动性问题,并且硬脂酸镁的浓度至少为1.5%以避免粘连。

[0168] 表3-按重量%计的配方细节

[0169]

配方 #	A	B	C	D	E
研磨雌四醇[1]	0.33	0.1	12.50	12.40	12.35
甘露糖醇	83.14	83.47	71.00	48.47	38.62
玉米淀粉	10.01	10.00	10.00		
交联聚维酮	5.01	5.01	4.99		
乳糖				29.68	
PVP (聚乙烯吡咯烷酮)				3.98	
交联羧甲基纤维素钠				3.98	
木糖醇 DC					9.91
微晶纤维素					32.66
淀粉羟乙酸钠					4.97
硬脂酸镁	1.51	1.51	1.50	1.49	1.48

[0171] [1] $D_{(v;0.5)}=15\mu m$

[0172] 表4-实验测定的片剂特征

[0173]

试验(6个样品的平均结果)	崩解时间	硬度	重量
制剂#	(min:sec)	(N)	(mg)
A	0:53	39.57	33.22
B	1:07	86.07	1060.37
C	0:39	57.49	81.16
D	0:39	42.71	78.48
E	0:38	37.29	76.49

[0174] 可以看出,所有片剂获得的最终重量接近其目标重量,并且崩解时间极短(甚至对于最大的1g片剂也是如此),这与预期的这些片剂的舌下、口腔或唇下给药途径相一致。

[0175] 最后,所有片剂的硬度在非常可接受的范围内。

[0176] 实施例4

[0177] 进行随机开放标签的双周期交叉药代动力学研究,来比较在一个100mg片剂中给药的10mg雌四醇的舌下生物利用度与在含有10mg雌四醇的83mg片剂中含有的雌四醇的口服利用度。这些片剂是在禁食条件下舌下和口服给健康女性志愿者。

[0178] 根据以下标准选择10名健康女性个体:年龄45-65岁(包括端值),不吸烟者或过去吸烟者(给药前至少6个月),体重指数(BMI)=18.5-30kg/m^2(筛选时包括端值)。

[0179] 下表5中描述了100mg舌下片剂的组成。

[0180] 表5

[0181]

	量(重量%)	功能
研磨雌四醇[1]	10	活性成分
Ludiflash®[2]	84	稀释剂/粘合剂/超级崩解剂
Kollidon CL-SF®[3]	3	超级崩解剂
硬脂酸镁	3	润滑剂

[0182] [1]$D_{(v;0.5)}$=15μm

[0183] [2]甘露糖醇(90重量%)、Kollidon CL-SF®[3](5重量%)和Kollicoat®SR30D(聚维酮中的聚乙酸乙烯酯分散体)(5重量%)的混合物

[0184] [3]交联聚维酮超细级

[0185] 这些片剂具有非常快的崩解时间(平均40秒)。

[0186] 在研究的第一和第二时段开始时,在上午07:00至上午07:28之间,通过给药一片雌四醇片剂(片剂重量100mg;10mg雌四醇),5名个体接受单剂量的雌四醇舌下制剂,并且通过给药一片雌四醇片剂(片剂重量83mg;10mg雌四醇)并与200ml水一起摄入,5名个体接受单次口服剂量的口服雌四醇制剂。

[0187] 个体需要在片剂给药前禁食至少10小时,并且在给药后禁食至少4小时。在给药前1小时内不允许饮用水或饮料。片剂给药前1小时和给药后2小时,个体接受200ml的水。片剂给药4小时后,个体可自由饮用水和水果茶。片剂给药前10.5小时以及片剂给药后4、6、9和

13小时，提供标准餐。

[0188] 表6示出了第一和第二时段发生的事件顺序：

[0189] 表6

[0190]

	事件
第一时段	
• 第 1 天	限制从 19:00 开始
• 第 2 天	给药，血液和尿液采样，限制
• 第 3 天	离开(Exit)过程，限制直到上午 8 点
• 第 4-8 天	返回就诊
• 第 9-13 天	洗出

[0191]

第二时段	
• 第 14 天	限制从 19:00 开始
• 第 15 天	给药，血液和尿液采样，限制
• 第 16 天	离开过程，限制直到上午 8 点
• 第 17-21 天	返回就诊
• 第 22-26 天	洗出
• 第 27 天	给药黄体制剂
• 第 28 天	电话，黄体制剂撤退测试(progestin withdrawal test)检查

[0192] 表7中示出了本研究中使用的血液和尿液采样时间表。

[0193] 表7

[0194]

血液采样	在给药片剂(0)之前进行血液采集(4 ml)，随后在给药之后的 0:10、0:15、0:20、0:25、0:30、0:35、0:40、0:45、0:50、0:55、1:00、1:10、1:20、1:30、2、3、4、6、10、16、24、48、72、96、120、144 小时进行。 每个时段的血液采集总数是 27。
尿液采样	在给药片剂之前和给药 2、4、8、12、24、48、72、96、120 和 144 小时后进行尿液采集。 每个时段的尿液采集总数是 11。

[0195] 通过HPLC/MS/MS测定所采集血液样品中的雌四醇浓度。借助于HPLC/MS/MS，也可以测定尿液样品中葡萄糖醛酸苷雌四醇(D-环)的浓度。

[0196] 这些分析的结果显示，舌下给药的雌四醇的生物利用度与口服给药的雌四醇相当或甚至比其更好。此外，数据表明，与口服给药雌四醇相比，舌下给药的雌四醇具有较早的生物利用度。舌下雌四醇对肝功能参数影响较小。

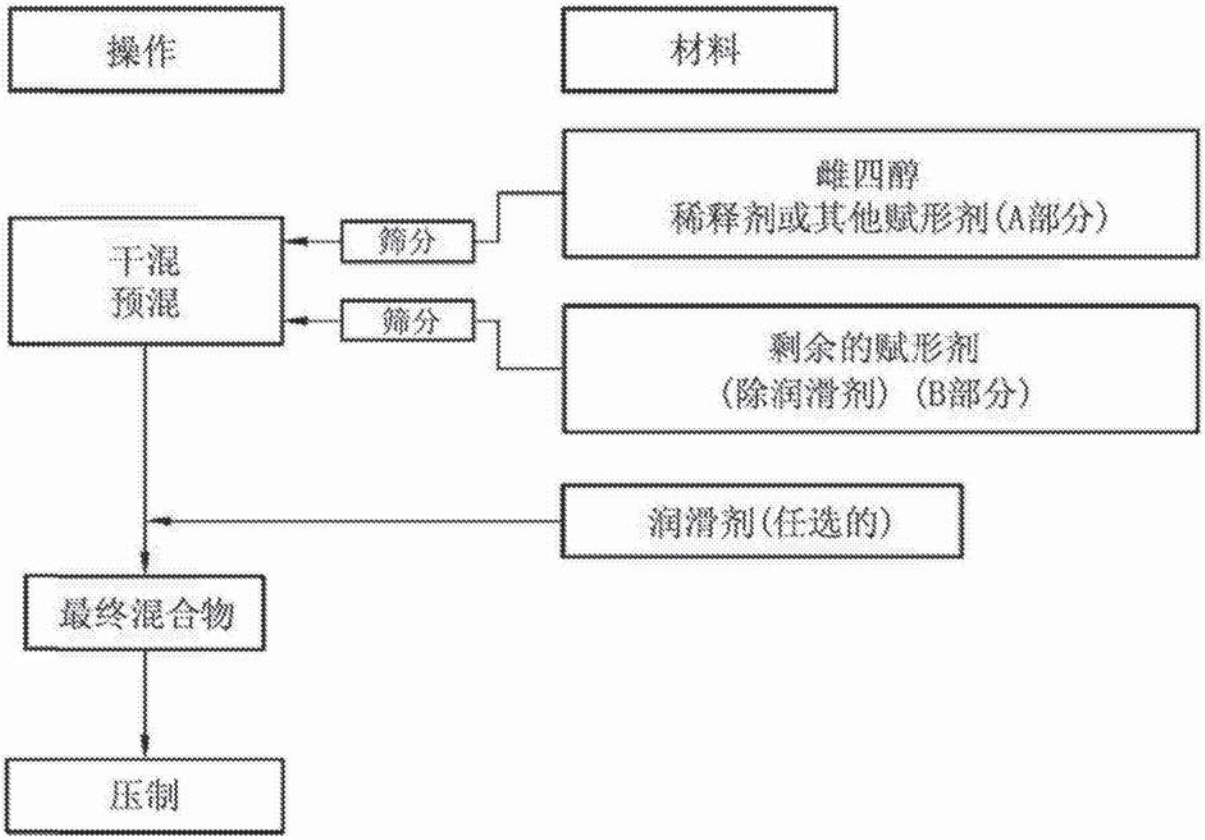
操作
材料
雌四醇
稀释剂或其他赋形剂(A部分)
筛分
干混
预混
筛分
剩余的赋形剂
(除润滑剂)(B部分)
润滑剂(任选的)
最终混合物
压制

图1