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(54) Titre : PRODUITS PHARMACEUTIQUES ORAUX RENFERMANT 17β-ESTRADIOL-3-ALCANOATE INFERIEUR,  
 PROCEDE D'ADMINISTRATION ET DE PREPARATION ASSOCIES  
 (54) Title: ORAL PHARMACEUTICAL PRODUCTS CONTAINING 17β-ESTRADIOL-3-LOWER ALKANOATE, METHOD  
 OF ADMINISTERING THE SAME AND PROCESS OF PREPARATION

(57) **Abrégé/Abstract:**

A pharmaceutical dosage unit for oral administration to a human female comprising a therapeutically effective amount of 17β-estradiol-3-lower Alkanoate, most preferably 17β-estradiol-3-acetate, and pharmaceutically acceptable carrier is disclosed. Also disclosed is a method for treating a human female in need of 17β-estradiol and a contraceptive method by oral administration of the pharmaceutical dosage unit and a method of preparing a pharmaceutical composition that may be used to form the pharmaceutical dosage unit of the invention.

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(54) Title: ORAL PHARMACEUTICAL PRODUCTS CONTAINING 17 $\beta$ -ESTRADIOL-3-LOWER ALKANOATE, METHOD OF ADMINISTERING THE SAME AND PROCESS OF PREPARATION

(57) Abstract: A pharmaceutical dosage unit for oral administration to a human female comprising a therapeutically effective amount of 17 $\beta$ -estradiol-3-lower Alkanoate, most preferably 17 $\beta$ -estradiol-3-acetate, and pharmaceutically acceptable carrier is disclosed. Also disclosed is a method for treating a human female in need of 17 $\beta$ -estradiol and a contraceptive method by oral administration of the pharmaceutical dosage unit and a method of preparing a pharmaceutical composition that may be used to form the pharmaceutical dosage unit of the invention.



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TITLE

5 **ORAL PHARMACEUTICAL PRODUCTS CONTAINING  
17 $\beta$ -ESTRADIOL-3-LOWER ALKANOATE, METHOD OF  
ADMINISTERING THE SAME AND PROCESS OF PREPARATION**

BACKGROUND OF THE INVENTION

Field of the Invention

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This invention relates to a pharmaceutical dosage unit for oral administration containing 17 $\beta$ -estradiol-3-lower alkanoate, most preferably 17 $\beta$ -estradiol-3-acetate, that unexpectedly provides improved bioavailability of estrogen when orally administered to a human female in need of estrogen replacement therapy or receiving estrogen for contraceptive purposes. The invention also relates to a process for producing the pharmaceutical dosage unit.

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Related Background Art

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In the normal, healthy human female, 17 $\beta$ -estradiol is the principal estrogen produced by the functioning premenopausal ovary during each menstrual cycle [Lieveritz, R.W., Amer. J. of Obstetrics and Gynecology, Vol. 156, pp. 1289-1293, 1987]. Estrogen deficiency may occur due to disease, oophorectomy, traumatic

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injury or as a natural consequence of the aging process. As aging progresses, ovulation becomes less frequent and predictable, resulting in diminished production of  $17\beta$ -estradiol. Gradual loss of ovarian function occurs naturally around 45-55 years of age leading to the eventual cessation of the menstrual cycle, that is, the menopause.

During normal ovulatory cycles ovarian production of  $17\beta$ -estradiol ranges from 60-600  $\mu$ g per day, resulting in circulating levels of  $17\beta$ -estradiol in serum ranging from 40-400 pg/ml. Circulating  $17\beta$ -estradiol levels vary during the monthly cycle in the premenopausal woman. At the menopause, when irreversible ovarian failure occurs,  $17\beta$ -estradiol production decreases dramatically to less than 20  $\mu$ g per day, giving circulating levels of the hormone in serum of less than 30 pg/ml. [Stumpf, P.G., Obstetrics and Gynaecology, Vol. 75 (suppl.) pp. 95-135, 1990]. This low level of estrogen production may result in typical postmenopausal symptoms [Marsh, M.S., et al., British Medical Bulletin, Vol. 48, pp. 426-457, 1992]. The physiological consequences of the fall in estradiol levels typically include vasomotor instability (hot flushes), urogenital atrophy and a loss of bone mineral mass leading to osteoporosis.

The most active, naturally occurring human estrogen is unbound  $17\beta$ -estradiol. Hormone replacement therapy (HRT) seeks to counteract the detrimental effects associated with low circulating plasma estrogen levels by restoring these, as far as possible, to a premenopausal physiological status. It follows, therefore, that the preferential estrogen for HRT is  $17\beta$ -estradiol and that the aim of HRT is to deliver this hormone at such a rate as to maintain physiological plasma levels of  $17\beta$ -estradiol.

$17\beta$ -Estradiol is not absorbed efficiently from the gastric mucosa following administration by the oral route and must, therefore, be formulated for administration in micronized form (to provide an increased surface area) or as a conjugate [Lobo, R.A., et al., J. of Reproductive Medicine, Vol. 37, pp. 77-84,

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1992]. The term conjugate encompasses various esters of  $17\beta$ -estradiol and estrogenic compounds, some of which are derived from equine sources. Examples of conjugates known in the art for the oral administration of estrogen for HRT include estradiol-3,17-diacetate, estradiol-17-acetate, estradiol-3,17-valerate, 5 estradiol-3-valerate, estradiol-17-valerate, ethinyl estradiol, and equine estrogens. The latter are mixtures of estrogens purified from the urine of pregnant mares and containing sulphate and glucouronide derivatives, and equine-specific estrogens such as equilin not normally found in humans [Stumpf, 1990]. In addition, less potent metabolites of  $17\beta$ -estradiol have been administered by this route, for 10 example, estrone or its conjugates.

A number of difficulties arise concerning the oral administration of estrogens. Although micronized  $17\beta$ -estradiol is an efficient form of the natural hormone for its oral administration, micronization represents an additional process for 15 pharmaceutical production, with associated increased costs and inconvenience. Micronized  $17\beta$ -estradiol has been shown to be equivalent in pharmacokinetic terms to the oral administration of  $17\beta$ -estradiol valerate, which is metabolised to the parent hormone *in vivo*.  $17\beta$ -estradiol valerate is a highly lipophilic ester with no measurable aqueous solubility, as are other ester derivatives of  $17\beta$ -estradiol 20 administered by the oral route [Woolfson, D., et al., J. of Controlled Release, Vol. 61, pp. 319-328, 1999]. Orally administered  $17\beta$ -estradiol and its various ester and equine conjugates undergo extensive first-pass hepatic metabolism, resulting in poor bioavailability by the oral route. In addition, hepatic metabolism causes undesirable non-physiological circulating levels of the metabolite estrone and 25 elevation of hepatic proteins. Conjugated equine estrogens, in particular, exert a profound hepatic effect [Kuhl, H., Maturitas, Vol. 12, pp. 171-197, 1990] and are thus clinically less desirable than derivatives of the parent hormone. Oral administration of  $17\beta$ -estradiol or its conjugates requires a significantly higher dose for clinical efficacy compared to non-oral routes [Powers, M., et al., Amer. J. 30 of Obstetrics and Gynecology, Vol. 152, pp. 1099-1106, 1985].

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Much of the prior art literature for preparation of oral pharmaceutical formulations of steroids such as estradiol comprises broad disclosures of solution or suspension wet granulation methods (for example, Pasquale, U.S. Pat. No. 4,544,554; Lerner, U.S. Pat. No. 3,568,828; Greaves, U.S. Pat. No. 5,976,570) or dry mixing using specialized excipients (for example, DeHaan, U.S. Pat. No. 5,382,434; Greaves, U.S. Pat. No. 5,928,668).

Dry mixing of low dose drugs is especially prone to significant lack of uniformity in drug distribution, even with the use of specialized excipients. Wet granulation using organic solvents such as chloroform, as described by Lerner, is generally unacceptable from an environmental, cost, and health and safety standpoint. On the other hand, aqueous wet granulation (e.g. Greaves, U.S. Pat. No. 5,976,570) could readily induce hydrolysis of ester derivatives of  $17\beta$ -Estradiol. A method for producing uniform, stable orally administered estrogen products with improved bioavailability is therefore highly desirable.

This invention discloses a method for improving the bioavailability of orally administered estrogen in the form of  $17\beta$ -estradiol-3-lower alkanoate. Parenteral administration of estradiol esters such as estradiol valerate, estradiol cypionate and estradiol benzoate are well known.  $17\beta$ -Estradiol-3-acetate has been shown to be an efficient form of estrogen for intravaginal delivery of HRT ([Woolfson et al, 1999], and McClay U.S. Patent No. 5,855,906), but there has been no disclosure of its surprising advantages when formulated for oral delivery.  $17\beta$ -Estradiol-3-acetate is known to have an aqueous solubility twice that of  $17\beta$ -estradiol and vastly greater than that of conventional  $17\beta$ -estradiol esters such as the valerate, benzoate and 17-acetate esters [Woolfson et al, 1999]. It is well known in the art that esterification of a drug to provide a more lipophilic derivative is a means of improving drug absorption across epithelial membranes, and thus bioavailability. Thus, the highly lipophilic esters of  $17\beta$ -estradiol are all well known to be absorbed via the oral route, suggesting that the more water-soluble  $17\beta$ -estradiol-

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3-acetate would be an unlikely candidate for improving bioavailability of the hormone via the oral route.

#### SUMMARY OF THE INVENTION

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This invention is directed to a pharmaceutical dosage unit for oral administration to a human female comprising a therapeutically effective amount of  $17\beta$ -estradiol-3-lower alkanoate and a pharmaceutically acceptable carrier. As used herein, lower alkanoate includes formate, acetate and propionate.  $17\beta$ -estradiol-3-acetate is most preferable. Surprisingly, it has been found that the oral administration of the dosage unit of this invention unexpectedly results in enhanced bioavailability of  $17\beta$ -estradiol compared to the oral administration of micronized  $17\beta$ -estradiol or  $17\beta$ -estradiol-17-valerate. Since it is well known that the lower alkanoate group and in particular the acetate group is readily hydrolyzed upon ingestion, this discovery of improved bioavailability was completely unexpected.

An important aspect of the dosage unit of this invention is that it must be substantially free of ester hydrolysis of the  $17\beta$ -estradiol-3-lower alkanoate prior to oral administration of the dosage unit. For solid dosage forms, e.g., tablets and capsules, the moisture level in the dosage unit is maintained at a level that substantially inhibits ester hydrolysis of the alkanoate. Generally, the moisture level of the solid dosage unit will be less than 8 %. If necessary, the dosage unit may also include an ester hydrolysis inhibitor.

Another embodiment of this invention is directed to a method of treating a human female in need of  $17\beta$ -estradiol comprising the step of orally administering to the human female a dosage unit comprising a therapeutically effective amount of  $17\beta$ -estradiol-3-lower alkanoate, preferably  $17\beta$ -estradiol-3-acetate, and a pharmaceutically acceptable carrier.

30

A further embodiment of this invention is directed to a method of providing contraception which comprises the step of orally administering to a human female of child bearing age a contraceptive regimen of a daily dosage unit comprising a contraceptively effective amount of  $17\beta$ -estradiol-3-lower alkanoate, most preferably  $17\beta$ -estradiol-3-acetate, and a pharmaceutically acceptable carrier. A typical contraceptive regimen is administration of a daily dosage unit for 21 days, although any regimen that provides contraceptive protection is contemplated. Preferably, the dosage unit will contain a combination of a contraceptively effective amount of  $17\beta$ -estradiol-3-lower alkanoate and at least one progestin.

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Due to the enhanced bioavailability of  $17\beta$ -estradiol obtained when orally administering  $17\beta$ -estradiol-3-lower alkanoate compared to the oral administration of micronized  $17\beta$ -estradiol or  $17\beta$ -estradiol-17-valerate, lesser amounts of the alkanoate need to be administered to achieve the desired therapeutic effect. It is well known that the administration of estrogenic hormones may have significant side effects. Significantly, the methods of this invention allow for  $17\beta$ -estradiol replacement therapy or contraceptive protection with potentially reduced risk of side effects.

Yet another embodiment of this invention is directed to process of making a pharmaceutical composition containing therapeutic quantities of  $17\beta$ -estradiol-3-lower alkanoate using a wet granulation process without substantial ester hydrolysis of the alkanoate. This process employs the use of an ester hydrolysis inhibitor.

In accordance with an aspect of the present invention, there is provided a pharmaceutical solid dosage unit for oral administration to a human female comprising a therapeutically effective amount of  $17\beta$ -estradiol-3-acetate and a pharmaceutically acceptable carrier, wherein the percent moisture of said solid dosage unit is less than or equal to 5%, and the amount of  $17\beta$ -estradiol-3-acetate is from 0.1 to 10 mg as estradiol equivalent.

In accordance with another aspect of the present invention, there is provided the oral use of a solid dosage unit comprising a therapeutically effective amount of  $17\beta$ -estradiol-3-acetate and a pharmaceutically acceptable carrier for treating a human female having a deficiency of  $17\beta$ -estradiol, wherein the percent moisture of said dosage unit is less than or

equal to 5%, and the amount of 17 $\beta$ -estradiol-3-acetate is from 0.1 to 10mg as estradiol equivalent.

#### DETAILED DESCRIPTION OF THE INVENTION

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This invention discloses an oral dosage unit of 17 $\beta$ -estradiol-3-lower alkanoate. The alkanoate maybe selected from 17 $\beta$ -estradiol-3-formate, 17 $\beta$ -estradiol-3- acetate, 17 $\beta$ -estradiol-3-propionate and mixtures thereof. Most preferably, the 17 $\beta$ -estradiol-3-lower alkanoate is 17 $\beta$ -estradiol-3-acetate.

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The oral dosage unit also includes a pharmaceutically acceptable carrier. The term pharmaceutically acceptable in this context refers to a substance having acceptable pharmacological and toxicological properties when administered by the oral route to a person. Such pharmaceutically acceptable carriers are well known.

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The oral dosage unit may be of any form suitable for oral administration to a human. Exemplary oral dosage units include, for example, tablets, capsules, powders, chewable tablets, lozenges, troches, sustained or delayed release products or suspensions. More preferably, the oral dosage unit is in the form of a tablet with  
10 immediate or sustained release properties. Most preferably, the tablet is formulated for immediate release. Generally, the tablet will contain  $17\beta$ -estradiol-3-lower alkanoate in an amount of about 0.1 to about 10 mg (as estradiol equivalent). As used herein, estradiol equivalent means that amount of the lower alkanoate that is the molar equivalent of estradiol.

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The oral dosage unit is formulated in a manner that substantially prevents the ester hydrolysis of the alkanoate group of the  $17\beta$ -estradiol-3-lower alkanoate prior to administration. For solid dosage forms, such as tablets, and capsules, the moisture level of the solid dosage unit is generally less than 8% moisture, and preferably less  
20 than 5% moisture to help prevent ester hydrolysis prior to administration. For liquid dosage forms, such as suspensions, it is important to stabilize the dosage unit by the addition of an inhibitor of ester hydrolysis. Solid dosage forms may also include an inhibitor of ester hydrolysis.

25 Optionally, the oral dosage unit may also comprise, in addition to  $17\beta$ -estradiol-3-alkanoate, other medicament(s) for the treatment or prevention of a human disease. Preferably, the other medicament(s) has a steroidal nucleus (the cyclopentanoperhydrophenanthrene ring system) in its chemical structure, for example, estrogens such as ethinyl estradiol, estrone, mestranol, and esterified  
30 estrogens. More preferably, the other medicament(s) has progestational properties and may be selected from progestins such as 3-ketodesogestrel, desogestrel, levo-

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desogestrel, norgestrel, gestodene, mestranol, norethindrone, norethindrone acetate, medroxyprogesterone acetate or similar progestins known in the art. Typical dosages for various progestins are described in the medical literature such as, for example, in the Physician's Desk Reference.

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The pharmaceutically acceptable carrier includes those carriers well known to those skilled in the art used in the formulation of tablets, capsules, and the like. When formulating the dosage unit of this invention, however, it is important to select adjuvants such as fillers, solvents, binders, disintegrants, lubricants and the  
10 like that will not cause hydrolysis of the alkanoate esters of the  $17\beta$ -estradiol-3-lower alkanoate prior to oral administration. Otherwise, the dosage unit of this invention may be prepared in any manner desired. For example, solid dosage units may be prepared by dry blending the ingredients or using a granulation technique followed by tableting or capsule filling techniques well known to those skilled in  
15 the art.

In a preferred embodiment of this invention, a pharmaceutical composition containing  $17\beta$ -estradiol-3-lower alkanoate, most preferably  $17\beta$ -estradiol-3-acetate and, optionally, other active medicament(s) is prepared using a granulation  
20 technique. An aqueous solvent containing a suspending agent and a predetermined amount of at least one pharmaceutically acceptable inhibitor of ester hydrolysis is used as the suspension medium for the preparation of the granules. The suspending agent is used to effect and maintain uniform distribution of  $17\beta$ -estradiol-3-lower alkanoate and any optional added medicament(s), in the solvent.  
25 Following dispersion of  $17\beta$ -estradiol-3-lower alkanoate and any optional added medicament(s), the suspension is added to suitable pharmaceutical fillers such as lactose and microcrystalline cellulose, then dried to a low moisture content by any suitable method known to those skilled in the art. Optional non-medicated ingredients that may be added to the invention include tablet disintegrants,  
30 lubricants, glidants, and colorants. The resultant blend may be compressed into tablets by any suitable means known to those skilled in the art. The pharmaceutical

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composition prepared according to this invention may also be incorporated into other suitable oral dosage forms, as described hereinbefore.

The term aqueous solvent is used in the context of this invention to denote a water  
5 medium and, optionally, a water-miscible solvent such as ethanol or isopropyl alcohol, to support the suspension of the active medicament(s).

Preferably, the amount of the hydrolysis inhibitor incorporated is calculated based on the saturation solubility of the drug in the aqueous solvent. In practice, a  
10 stoichiometric excess of the inhibitor is added to the medium in order to push the equilibrium of the reversible esterification-hydrolysis reaction in the direction of the ester, thus maintaining stability of  $17\beta$ -estradiol-3-lower alcanoate. The pharmaceutically acceptable inhibitor of ester hydrolysis is preferably an organic acid, such as for example, acetic, formic, propionic, lactic or tartaric acid. More  
15 preferably, the inhibitor is acetic acid, formic or propionic acid. Most preferably, the inhibitor is acetic acid.

The suspending agent is generally a hydrocolloid that includes water dispersible granulating or binding agents such as polyvinylpyrrolidone; cellulose derivatives  
20 such as methylcellulose and hydroxypropylmethylcellulose; polyvinylloxazolidones; gelatin; natural gums such as acacia and tragacanth; starches; sodium alginate; sugars and mixtures thereof.

Suitable pharmaceutical fillers for granulating the prepared drug suspension  
25 include, without limitation, lactose, microcrystalline celluloses, dibasic calcium phosphate, starches and mixtures thereof. Optional components of the granulation include pharmaceutically acceptable colorants or other excipients known in the art.

As noted previously, if the dosage unit of this invention takes the form of a tablet  
30 or capsule, suitable additional ingredients that may be used include disintegrants such as croscarmellose sodium, starch, sodium carboxymethyl starch,

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crospovidone, veegum, and lubricants such as hydrogenated vegetable oils, calcium stearate, magnesium stearate, stearic acid, and talc.

In a preferred embodiment of the invention,  $17\beta$ -estradiol-3-acetate, together with  
5 the optional medicament or medicaments, is suspended in an 8% to 12% dispersion of polyvinyl pyrrolidone in 95:5 mixture of water and ethanol containing 0.01% glacial acetic acid. The resulting aqueous suspension is blended with carriers and granulated in a granulating vessel. The granulation is dried, screened and blended with disintegrants, glidants, and lubricants. The granulation is then compressed  
10 into tablets.

Another embodiment of this invention is directed to a method of treating a human female in need of  $17\beta$ -estradiol comprising the step of orally administering to said human female a dosage unit comprising a therapeutically effective amount of  $17\beta$ -  
15 estradiol-3-lower alkanoate, most preferably  $17\beta$ -estradiol-3-acetate, and a pharmaceutically acceptable carrier. Preferably, the dosage unit is administered to a human female requiring hormone replacement therapy. When used for hormone replacement therapy, the dosage unit of this invention will generally contain  $17\beta$ -estradiol-3-lower alkanoate in an amount from about 0.1 to about 5 mg (as  
20 estradiol equivalent) per dosage unit.

The invention is also directed to a method of providing contraception by orally administering to a human female of child bearing age the dosage unit of this invention containing a contraceptive effective amount of  $17\beta$ -estradiol-3-lower  
25 alkanoate, most preferably  $17\beta$ -estradiol-3-acetate and a pharmaceutically acceptable carrier. For contraceptive purposes the dosage unit will typically be administered for 21 days, although any dosage regimen that provides contraceptive protection is contemplated. Preferably the contraceptive dosage unit will contain a contraceptive effective amount of  $17\beta$ -estradiol-3-lower alkanoate, preferably  $17\beta$ -  
30 estradiol-3-acetate, and at least one progestin. Generally, the contraceptive dosage unit of this invention will contain the  $17\beta$ -estradiol-3-lower alkanoate in an amount

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from about 0.1 to about 10 mg (as estradiol equivalent) per dosage unit. Typically, the total amount of progestin included in the dosage unit for contraceptive use is in amount from about 20  $\mu$ g to about 5 mg per dosage unit.

- 5 In addition, it is contemplated that the invention also provides a means for treating, assisting in the treatment, and/or the prevention of ailments and diseases such as migraine headache associated with menstruation, osteoporosis, alzheimers, vasomotor symptoms, urogenital symptoms such as vulval and vaginal atrophy, hypoestrogenism (low estrogen levels) due to hypogonadism, castration or primary  
10 ovarian failure, breast cancer in women and men, and androgen dependent carcinoma of the prostate. These ailments and diseases have been linked to a deficiency in estrogen levels in the body. For example, menstrual migraines are thought to be triggered by reduced levels of estrogen in the body, which contributes to chemical and electrical imbalances that affect the blood vessels in the brain. The  
15 result is a throbbing pain on one side of the head. Osteoporosis is characterized by a reduction in the amount of bone mass, making the bones more susceptible to fracturing. Deficiencies in estrogen, along with lack of exercise, and dietary calcium are believed to be responsible for the condition. Alzheimers is a neurodegenerative disease that results from the death and loss of function of nerve  
20 cells, which may progressively lead to dementia. Vasomotor symptoms in women, also known as hot flashes, are evidenced by episodes of heat and sweating, changes in mood and behavior, and sleep deprivation. Vulval and vaginal atrophy describes symptoms characterized by itching, burning, dryness in or around the vagina, difficulty or burning during urination, and pain during intercourse. Treatment  
25 and/or preventative measures would employ a method where a  $17\beta$ -estradiol-3-lower alkanoate is administered to a patient in need thereof in a therapeutically effective amount, e.g., about 0.001 to about 100 mg (as estradiol equivalent) per dosage unit. Preferably the  $17\beta$ -estradiol-3-lower alkanoate is administered orally, and preferably the  $17\beta$ -estradiol-3-lower alkanoate is  $17\beta$ -estradiol-3-acetate.  
30 Moreover, the  $17\beta$ -estradiol-3-lower alkanoate can be orally administered for the treatment of wrinkling of the skin, as an anti-wrinkling agent.

Beneficial results may also be obtained by utilizing a 17 $\beta$ -estradiol-3-lower  
alkanoate, such as 17 $\beta$ -estradiol-3-acetate, as part of the treatment and/or  
prevention program for cardiovascular disease in post menopausal women, mood  
disorders related to menopause, and sleeping disorders. Reduced estrogen levels  
5 appear to be a factor in these ailments.

It is also contemplated that the 17 $\beta$ -estradiol-3-lower alkanoate may be used in  
conjunction with other pharmaceutically active compounds, such as, for example,  
anticholinergic agents for treating lower urinary tract symptoms, and antimigraine  
10 medications. Other combinations are possible, particularly where the  
pharmaceutical actives are used to treat ailments involving hormonal imbalances.

Specific embodiments of the invention will now be demonstrated by reference to  
the following examples. It should be understood that these examples are disclosed  
15 solely by way of illustrating the invention and should not be taken in any way to  
limit the scope of said invention. Thus, for example, it will be obvious to those  
skilled in the art that a variety of suitable equipment may be employed to produce  
the dosage unit of this invention.

#### 20 Example 1

##### Tablets Containing 17 $\beta$ -Estradiol-3-Acetate

	<b>Ingredient(s)</b>	<b>% w/w</b>	<b>mg/tablet</b>
25	17 $\beta$ -estradiol-3-acetate	0.500	0.450
	Colorant	0.100	0.090
	Povidone, USP	1.500	1.350
	Lactose Monohydrate, NF	46.949	42.254
	Microcrystalline Cellulose, NF	46.949	42.254
30	Croscarmellose Sodium, NF	3.000	2.700
	Colloidal Silicon Dioxide, NF	0.500	0.450
	Magnesium Stearate, NF	0.500	0.450

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Ingredient(s)	% w/w	mg/tablet
Glacial Acetic Acid, USP	0.002	0.002
Alcohol, USP	-	QS
Purified Water, USP	-	QS

5 Dosage units of the invention in the form of tablets having the above-described constituents are prepared as follows. First, glacial acetic acid, alcohol, and purified water are combined in a suitable vessel to create a granulation solvent. The povidone is dispersed in the granulation solvent, followed by the addition of colorant and 17 $\beta$ -estradiol-3-acetate to the dispersion. The dispersion is slowly  
 10 sprayed into a blend of the lactose and microcrystalline cellulose. The resulting composition is then dried and milled to form a granulation, which is then combined with the croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. This blend is then compressed into tablets using appropriate tooling.

## 15 Example 2

### Capsules Containing 17 $\beta$ -Estradiol-3-Acetate and Norethindrone Acetate

Ingredient(s)	% w/w	mg/tablet
20 17 $\beta$ -estradiol-3-acetate	1.000	0.900
Norethindrone Acetate	1.000	0.900
Povidone, USP	1.800	1.620
Lactose Monohydrate, NF	58.698	52.828
Microcrystalline Cellulose, NF	35.000	31.500
25 Croscarmellose Sodium, NF	2.000	1.800
Magnesium Stearate, NF	0.500	0.450
Glacial Acetic Acid, USP	0.002	0.002
Alcohol, USP	-	QS
Purified Water, USP	-	QS

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Dosage units of the invention in the form of capsules having the above-described constituents are prepared as follows. First, glacial acetic acid, alcohol, and purified

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water are combined in a suitable vessel to create a granulation solvent. The povidone is dispersed in the granulation solvent, followed by the addition of  $17\beta$ -estradiol-3-acetate and norethindrone acetate to the resulting dispersion. The dispersion is slowly sprayed into a blend of the lactose and microcrystalline  
5 cellulose. The resulting composition is then dried and milled to form a granulation, which is then combined with the croscarmellose sodium and magnesium stearate. This blend is then used to fill capsules using appropriate equipment.

### 10 Example 3

Enhanced bioavailability of oral  $17\beta$ -estradiol when administered as its 3-acetate ester according to the invention.

15 A study was performed to compare the bioavailability of  $17\beta$ -estradiol and  $17\beta$ -estradiol-3-acetate tablets following oral administration to postmenopausal female volunteers. The study was an open-label, single-dose, randomized, crossover, bioavailability study in nine healthy postmenopausal women volunteers. Each  
20 volunteer received: A) one tablet of 1.152-mg  $17\beta$ -estradiol-3-acetate tablet (equivalent to 1.0 mg of  $17\beta$ -estradiol), prepared in a manner substantially similar to Example 1; and B) one tablet of 1-mg micronized  $17\beta$ -estradiol (Estrace® Tablets); each treatment was separated by a one-week washout period. Data from eight subjects were evaluable.

25 Mean serum estradiol concentrations following administration of one  $17\beta$ -estradiol-3-acetate tablet were higher than those following administration of one micronized  $17\beta$ -estradiol tablet. Mean estradiol and estrone pharmacokinetic parameters following administration of one  $17\beta$ -estradiol-3-acetate tablet and one estradiol tablet are summarized in Table 1. Comparison of treatments was based

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on ratio of least square means from analysis of variance and ratio of individual subject parameter values, e.g. ratio = (AUC<sub>treatment A</sub>)/(AUC<sub>treatment B</sub>). A summary of mean ratios is given in Table 2.

5 Following administration of treatment A, serum 17 $\beta$ -estradiol concentrations increased rapidly (T<sub>max</sub> = 2-3 hours), then decreased rapidly to relatively constant 17 $\beta$ -estradiol concentrations over 3 to 24 hours postdose. Following  
administration of micronized 17 $\beta$ -estradiol, serum 17 $\beta$ -estradiol increased slowly  
over the first six hours to relatively constant concentrations over 6 to 24 hours  
10 postdose.

C<sub>max</sub> values following administration of one 17 $\beta$ -estradiol-3-acetate tablet were two times higher than those following administration of one micronized 17 $\beta$ -estradiol tablet. Relative bioavailability as indicated by ratio of AUC values was  
15 15% higher for 17 $\beta$ -estradiol -3-acetate as compared to micronized 17 $\beta$ -estradiol.

Serum estradiol concentration-time profiles following administration of 17 $\beta$ -estradiol-3-acetate and micronized 17 $\beta$ -estradiol suggest differences in absorption. The shape of the profiles following 17 $\beta$ -estradiol-3-acetate administration indicate  
20 that it is rapidly absorbed and hydrolyzed to 17 $\beta$ -estradiol *in vivo* while the profile for estradiol administration indicates that 17 $\beta$ -estradiol itself is more slowly absorbed from micronized estradiol. Similarity of profiles at later times (> 6 hours) following 17 $\beta$ -estradiol-3-acetate administration and micronized 17 $\beta$ -estradiol administration suggests that disposition and elimination are not affected  
25 by administration of the 3-acetate ester of the naturally occurring hormone.

The reasons for the surprising improved bioavailability (higher C<sub>max</sub> and AUC values) seen with this example formulation of the invention are not clear but, without being bound by theory, may be related to the higher aqueous solubility

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characteristics of 17 $\beta$ -estradiol-3-acetate and a consequential effect on membrane permeability. Without being bound by theory it could also be due to an unexpected reduction in hepatic first pass metabolism when 17 $\beta$ -estradiol is administered orally as its 3-acetate ester.

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**Table 1.** Summary of 17 $\beta$ -Estradiol Pharmacokinetic Parameters Following Oral Administration of One 17 $\beta$ -estradiol -3-acetate and One 17 $\beta$ -estradiol Tablets (n=8);

Parameter	One 17 $\beta$ -Estradiol-3-acetate Tablet	One 17 $\beta$ -Estradiol Tablet
	Mean (%RSD)	Mean %RSD
C <sub>max</sub>	54.6 (48)	25.9 (24)
t <sub>max</sub>	1.9 (141)	10.1 (54)
AUC(0-t <sub>ldc</sub> )	913.8 (25)	793.6 (20)

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C<sub>max</sub> = Maximum serum concentration (pg/mL)                      t<sub>max</sub> = Time of C<sub>max</sub> (hr)  
AUC(0-t<sub>ldc</sub>) = Area under concentration-time profile (pg hr/mL) from time zero to time t<sub>ldc</sub>, time of last determinable concentration

CLAIMS

1. A pharmaceutical solid dosage unit for oral administration to a human female comprising a therapeutically effective amount of  $17\beta$ -estradiol-3-acetate and a pharmaceutically acceptable carrier, wherein the percent moisture of said solid dosage unit is less than or equal to 5%, and the amount of  $17\beta$ -estradiol-3-acetate is from 0.1 to 10 mg as estradiol equivalent.
2. The dosage unit according to claim 1, further comprising one or more pharmaceutically acceptable inhibitors of hydrolysis wherein the inhibitors of hydrolysis are selected from the group consisting of acetic acid, formic acid, propionic acid, lactic acid and tartaric acid .
3. The dosage unit according to claim 2, wherein the pharmaceutically acceptable inhibitor of ester hydrolysis is acetic acid.
4. The dosage unit according to claim 1, further comprising one or more additional steroids.
5. The dosage unit according to claim 4, wherein said one or more steroids have progestational activity.
6. The dosage unit according to claim 1, wherein the dosage unit is prepared by a granulation method.
7. The dosage unit according to claim 1, wherein the dosage unit is a tablet, capsule, powder, lozenge, or troche.

8. The dosage unit according to claim 1, wherein the dosage unit is a tablet or capsule.

9. The oral use of a solid dosage unit comprising a therapeutically effective amount of  $17\beta$ -estradiol-3-acetate and a pharmaceutically acceptable carrier for treating a human female having a deficiency of  $17\beta$ -estradiol, wherein the percent moisture of said dosage unit is less than or equal to 5%, and the amount of  $17\beta$ -estradiol-3-acetate is from 0.1 to 10mg as estradiol equivalent.

10. The use according to claim 9, wherein the solid dosage unit further comprises one or more pharmaceutically acceptable inhibitors of hydrolysis wherein the inhibitors of hydrolysis are selected from the group consisting of acetic acid, formic acid, propionic acid, lactic acid and tartaric acid .

11. The use according to Claim 9, wherein the solid dosage unit further comprises a pharmaceutically acceptable inhibitor of ester hydrolysis that is acetic acid.

12. The use according to Claim 9, wherein said dosage unit further comprises one or more additional medicaments.

13. The use according to Claim 9, wherein at least one additional medicament has progestational activity.

14. The use according to Claim 9, wherein the dosage unit is a tablet, capsule, powder, lozenge, troche or suspension.

15. The use according to Claim 13, wherein the dosage unit is a tablet or capsule.