(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 September 2012 (13.09.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/120365 A1

(51) **International Patent Classification**:
A61K 9/16 (2006.01) *A61K 31/585* (2006.01)
A61K 9/32 (2006.01) *A61K 47/26* (2006.01)
A61K 31/567 (2006.01)

(21) **International Application Number**:
PCT/IB2012/000432

(22) **International Filing Date**:
6 March 2012 (06.03.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
667/CHE/2011 7 March 2011 (07.03.2011) IN

(71) **Applicant** *(for all designated States except US)*: **AUROBINDO PHARMA LIMITED** [IN/IN]; Plot No. 2, Maitrivihar, Ameerpet, Andhrapradesh, 500038 Hyderabad (IN).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **SHAILENDRA, Mangde** [IN/IN]; Aurobindo Pharma Limited, Plot No. 2, Maitrivihar, Ameerpet, Andhrapradesh, 500038 Hyderabad (IN). **DINESH, Bilolikar** [IN/IN]; Aurobindo Pharma Limited, Plot No. 2, Maitrivihar, Ameerpet, Andhrapradesh, 500038 Hyderabad (IN). **MADHUSUDAN, Datta** [IN/IN]; Aurobindo Pharma Limited, Plot No. 2, Maitrivihar, Ameerpet, Andhrapradesh, 500038 Hyderabad (IN). **SIVAKUMARAN, Meenakshisunderam** [IN/IN]; Aurobindo Pharma Limited, Plot No. 2, Maitrivihar, Ameerpet, Andhrapradesh, 500038 Hyderabad (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2012/120365 A1

(54) **Title**: STABLE PHARMACEUTICAL COMPOSITION COMPRISING ETHINYL ESTRADIOL

(57) **Abstract**: The technical field of the present invention relates to a stable pharmaceutical composition comprising ethinyl estradiol. The present invention also relates to a process for preparation of a stable pharmaceutical composition comprising ethinyl estradiol. The present invention further relates to a stable pharmaceutical composition comprising ethinyl estradiol and progestogen.

STABLE PHARMACEUTICAL COMPOSITION COMPRISING ETHINYL ESTRADIOL

Field of the invention

The present invention relates to a stable pharmaceutical composition comprising ethinyl estradiol. The present invention also relates to a process for preparation of stable pharmaceutical composition comprising ethinyl estradiol. The present invention further relates to a stable pharmaceutical composition comprising ethinyl estradiol and progestogen.

Background of the invention

Oral contraceptives including the combination of gestagen and estrogen components are used for decades. Ethinyl estradiol is a synthetic estrogenic compound, chemically known as 19-nor-17α-pregna1,3,5(10)-triene-20-yne-3,17-diol.

Ethinylestradiol is currently marketed in the United States in combination with desogestrel (Kariva®, Desogen®, Cyclessa®, Mircette®); with drospirenone (Yasmin® and Yaz®); with levonorgestrel (Seasonique®, Loseasonique®, Seasonale®, Lybrel®); with norethindrone (Norinyl®, Ovcon-35®, Ovcon-50®); with norethindrone acetate (Femhrt®) and with norgestimate (Ortho Tricyclen®, Ortho Tricyclen Lo®).

These pharmaceutical compositions contain natural or synthetic hormones in low dose, as the daily dose of these active ingredients is extremely low i.e. 0.1 µg - 500 µg, which lead to serious formulation challenges, such as to achieve formulation reproducibility and the homogenous distribution of the active ingredients. On the other hand, the stability of the active ingredients causes problems, which influences the shelf life of the composition, and this may be related to the low dose of the active ingredient and to the interaction with the different excipients. This is a crucial parameter in the case of estrogen, particularly the ethinylestradiol containing oral contraceptives. There are

numbers of attempts to improve the stability of estrogen, especially ethinylestradiol containing pharmaceutical compositions

Following are the references that disclose stable composition of ethinyl estradiol and its combination with progestogen.

US Patent No. 4,115,563 relates to a solid pharmaceutical formulation comprising from 5 to 80 percent by weight of a pharmaceutically active steroid, 1 to 8 percent by weight of sodium starch glycolate and the remainder conventional excipients.

US Patent No. 4,154,820 relates to a stabilized therapeutic preparation exhibiting no oxidation and less than about 5% hydrolysis up to at least 24 months, consisting essentially of at least one alkali metal sulfate salt of a synthetic conjugated estrogen and an antioxidant, wherein the preparation is maintained at an alkalinity corresponding to a pH of not less than about 7.0.

US Patent No. 4,380,534 relates to a solid pharmaceutical composition containing less than 5 mg/dosage unit of a powdered microdose drug subject to changes in crystal form stability selected from ethinyl estradiol, the improvement comprising said powdered microdose drug being coated with a hydrophobic wax.

US Patent No. 4,383,992 relates to a water-soluble inclusion compound formed by complexing beta-cyclodextrin with a steroid compound having a molecular structure smaller than the inside dimension of the internal cavity of beta-cyclodextrin.

US Patent No. 4,727,064 relates to a method of producing a stabilized amorphous complex of a drug and a mixture of cyclodextrin, which comprises the steps of dissolving an intrinsically amorphous mixture of cyclodextrin derivatives which are water soluble and capable of forming inclusion complexes with drugs in water and solubilizing lipophilic drugs into the aqueous media to form a solution and form a solublized drug/cyclodextrin complex.

US Patent No. 4,877,774 relates a method for administering steroid hormones to patient needing supplemental steroid hormones by direct contact with mucosa or the conjunctiva comprising contacting the mucosa of said patient with an effective amount of a steroid hormone complexed with crystalline gamma-cyclodextrin.

US Patent No. 5,376,641 relates to water soluble compound formed by complexing branched beta cyclodextrin with a steroid having a molecular structure that can fit into the cavity of the branched beta cyclodextrin and form a complex with the branched beta cyclodextrin.

US Patent No. 5,134,127 relates to a pharmaceutically acceptable composition comprising a pharmaceutically acceptable carrier and a clathrate complex comprising a drug complexed to a cyclodextrin derivative a pharmaceutically acceptable cation; wherein said composition contains not more than 5 wt. % of underivatized cyclodextrin.

US Patent No. 5,382,434 relates to dry pharmaceutical preparations containing ultra-low doses of micronized steroidal medicinal agents in combination with a primary excipient having a high binding affinity and low demixing potential for the steroidal medicinal agent including spray-dried polyalcohols, granulated α-lactose monohydrate and mixtures thereof. The patent further discloses that the dry methods (dry-granulation and direct compression) are especially suitable for medicinal compounds which are sensitive to moisture or are unable to withstand the elevated drying temperatures associated with wet-granulation methods.

US Patent No. 5,543,157 relates to a pharmaceutical composition comprising an effective amount of active/cyclodextrin inclusion complex with pharmaceutical agent selected from the group consisting of estradiol; estriol; ethinylestradiol-3-methyl ether; ethisterone; and mixtures thereof, said complex being prepared by the kneading method and having a particle size of less than about 5 microns which provides for fast release of said pharmaceutical agent.

US Patent No. 5,547,948 relates a compressed tablet comprising a tablet core containing conjugated estrogens and a sugar coating in which said sugar coating incorporates a hormonal steroid and a release rate controlling amount of microcrystalline cellulose.

US Patent No. 5,798,338 discloses a composition comprising an effective amount of 17α-ethinylestradiol, and an amount of a β-cyclodextrin in the form of clathrate, effective in reducing the oxidative degradation of the 17α-ethinylestradiol. The patent discloses the use of clathrate of β-cyclodextrin for prevention of the oxidative degradation reactions of the active ingredient.

US Patent No. 5,928,668 relates to a method of dry blend compression of insoluble potent drug substances using a directly compressible, agglomerated excipient that is not a conventional spray dried polyalcohol or lactose. The patent further discloses that the estradiol and a number of other low-dose potent drugs precipitate in a variety of polymorphs and/or crystal habits on drying (during wet granulation process), which can affect the bioavailability of the drug.

US Patent No. 5,976,570 relates to a method for preparing solid pharmaceutical dosage units containing low dose active ingredients using a wet granulation technique which employs aqueous solvents and surfactants.

US Patent No. 6,156,341 relates to pharmaceutical agents that contain gallic acid ester as an antioxidant in combination with a steroidal active ingredient.

US Patent No. 6,958,326 relates to a pharmaceutical a composition comprising a granulated preparation comprising a complex between an estrogen and a cyclodextrin, the composition having a stability such that said estrogen is in an amount of at least 90% w/w in relation to the initial content of said estrogen after storage for 12 months at 40° C and 75% relative humidity (RH); and the composition being essentially free of polyvinylpyrrolidone.

US Patent Nos. 7,163,931 and 7,569,557 relates to a stable pharmaceutical product comprising an estrogen, comprising complexed estrogens or sensitive complexes between a cyclodextrin and an estrogen. The patent further discloses that the degradation of estrogens, such as ethinyl estradiol, in conventional products, is one of the most critical issues with regard to product shelf life.

US Publication No. 2005/0020554 relates to a method of preparing a pharmaceutical dosage form, the method comprising (a) encasing a pharmaceutical dosage form comprising an estrogen in a container essentially impervious to oxygen, and (b) purging the container with an inert gas, and pharmaceutical dosage forms made by the method thereof.

US Publication Nos. 2005/0207990, 2005/0220825, 2008/0175905 and 2009/0117183 disclose compositions comprising an estrogen in combination with a progestin.

Despite the achieved results as disclosed in above prior art references there is a need for such products of estrogen-gestagen combinations, which possess enhanced stability, homogenous distribution, and are easy to manufacture.

The inventors of the present invention have developed a stable composition comprising ethinyl estradiol as active ingredient and sucrose as stabilizer which provides better or comparative, content uniformity, dissolution profile and/or bioavailability w.r.t commercialized dosage forms. The inventors have surprisingly found that the composition comprising ethinyl estradiol with sucrose as stabilizer is stable against thermal degradation, hydrolysis and oxidation of ethinyl estradiol.

Objective of the Invention

The main objective of present invention is to provide a stable pharmaceutical composition comprising ethinyl estradiol and one or more pharmaceutically acceptable excipients.

Another objective of the present invention is to provide a process for the preparation of stable pharmaceutical composition comprising ethinyl estradiol having better or comparative dissolution properties, content uniformity and bioavailability w.r.t. commercially available dosage form.

Summary of the Invention

Accordingly, the present invention provides a stable pharmaceutical composition comprising ethinyl estradiol, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

In another embodiment, the present invention also provides a stable premix composition comprising ethinyl estradiol, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

In yet another embodiment, the present invention provides a stable pharmaceutical composition comprising ethinyl estradiol, progestogen, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

Detailed Description of the Invention

In another embodiment, one or more pharmaceutically acceptable excipients are selected from diluent, binder, disintegrant, stabilizers, surfactant, antioxidants, water soluble polymers, glidant and lubricant.

In another embodiment, progestogen is selected from drosperinone, levonorgestrel, desogestrel, norethindrone, norethindrone acetate, norgestimate, norgestrel, cyproterone.

In yet another embodiment, the present invention provides a stable pharmaceutical composition comprising ethinyl estradiol, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose or sucrose in mixture with other stabilizers.

In yet another embodiment, the present invention provides a stable pharmaceutical composition comprising ethinyl estradiol, drosperinone, a

stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

In yet another embodiment, the amount of drospirenone used may be in the range from about 1 to about 5 mg and the amount of ethinyl estradiol used may be in the range from about 0.01 to about 0.05 mg.

The stable pharmaceutical composition of the present invention is substantially free of surfactant.

The present invention further relates to a stable pharmaceutical composition comprising ethinyl estradiol, a stabilizer, an antioxidant, a surfactant and optionally one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

Ethinyl estradiol shows thermal degradation followed by hydrolysis and very much prone to oxidation also. The formulation of ethinyl estradiol with sucrose results in stable formulation.

- Sucrose is classified as a non-reducing sugar and doesn't get oxidized by mild oxidizing agent.
- Sucrose has a water activity of <0.8 which discourage the kinetic rates of many reaction.
- Sucrose when solubilized in water shows negative heat of enthalpy which works as a "coolant" preventing thermal degradation.
- Sucrose has high value of osmotic pressure which helps the carrier mediated transport of molecules across the cell membrane resulting in increased absorption.

The present invention further relates to a stable pharmaceutical composition comprising ethinyl estradiol, progestogen, a stabilizer, a water soluble polymer, an antioxidant, a surfactant and optionally one or more pharmaceutically acceptable excipients.

Suitable binders used according to the present invention are selected from the group comprising sucrose, cellulose and its derivatives including, ethyl

cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose and hydroxyethyl cellulose, carboxymethyl cellulose; starch and its derivatives; hydrocolloids; sugars; polyvinyl pyrrolidone, copovidone, methacrylic acid copolymers and the like or combination thereof. The amount of binder may range from about 1-40%, preferably 1-20% by weight of the dosage form.

Suitable diluents used according to the present invention are selected from sugars such as lactose, sucrose, dextrose; sugar alcohols such as mannitol, sorbitol, xylitol, lactitol; Starlac® (co-processed mixture of Starch and lactose), Microcelac® (co-processed mixture of microcrystalline cellulose and lactose), starch, corn starch, modified starches, pregelatinized starch, dibasic calcium phosphate, tribasic calcium phosphate, powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose and the like or combinations thereof. The amount of diluent may range from about 5-95%, preferably 10-70% by weight of the dosage form.

Suitable disintegrants used according to the present invention are selected from low-substituted hydroxypropyl cellulose; cross-linked polyvinylpyrrolidone; cross-linked sodium carboxymethylcellulose, sodium carboxymethylcellulose, microcrystalline cellulose; sodium starch glycolate; pregelatinized starch and the like or combinations thereof. The amount of disintegrant may range from about 1-30%, preferably 1-20% by weight of the dosage form.

Suitable lubricants used according to the present invention are selected from calcium stearate, glycerol behenate, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, vegetable oil, zinc stearate and the like or combinations thereof. The amount of lubricant may range from about 0.01-5%, preferably 0.1-2% by weight of the dosage form.

Suitable glidants of the present invention include calcium silicate, magnesium carbonate, magnesium oxide, magnesium silicate, talc, colloidal

silicon dioxide, starch and the like. The glidant may be used in the range of 0.01-5%, preferably 0.1-2% by weight of the dosage form.

Surfactants are compounds which are capable of improving the wetting of the drug and/or enhancing the dissolution. The surfactants can be selected from hydrophilic surfactants or lipophilic surfactants or mixtures thereof. The surfactants can be anionic, nonionic, cationic, and zwitterionic surfactants. Surfactants according to the present invention include, but not limited to, polyoxyethylene alkylaryl ethers such as polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether; polyethylene glycol fatty acid esters such as PEG monolaurate, PEG dilaurate, Polyethylene glycol 660 12- hydroxyl Stearate Ph.Eur. or Polyoxyl 15 hydroxystearate NF (Solutol HS 15), PEG distearate, PEG dioleate; polyoxyethylene sorbitan fatty acid ester such as polysorbate 40, polysorbate 60, polysorbate 80; sorbitan fatty acid mono esters such as sorbitan monolaurate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, polyoxyethylene castor oil derivates such as polyoxyl castor oil, polyoxyl hydrogenated castor oil, sodium lauryl sulphate, monooleate, monolaurate, monopalmitate, monostearate, sodium dioctyl sulfosuccinate (DOSS), lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, polyoxyethylene fatty acid glycerides, poloxamer, cremophore RH 40, and the like or combinations thereof. The surfactant may be used in the range of 0.001-5% by weight of the dosage form.

Antioxidants prevent the oxidative degradation of substance. Exemplary anti-oxidants include, but not limited to, ascorbic acid and its salts and derivatives, vitamin E, vitamin E acetate, tocopherols and their derivatives, citric acid, gallic acid ester, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), di-tert-butylphenol, tertiary butylhydroquinone, aromatic amines, phenolic acids, enzymatic antioxidants, flavonoids, N-acetylcysteine, mesna, glutathione, thiohistidine derivatives, triazoles; tannins, cinnamic acid, hydroxycinnamatic acids and their esters, their mixtures and the

like or combinations thereof. The antioxidant may be used in the range of 0.001-5% by weight of the dosage form.

Stabilizers used according to the present invention include sucrose, sucrose fatty acid esters, polyethylene glycol, polyvinyl alcohol, xanthan gum, maltodextrin, EDTA, poloxamer, trehalose and the like or combinations thereof.

Water soluble polymers according to the present invention include, but not limited to, polyethylene glycol, homopolymers and copolymers of N-vinyl lactams, especially homopolymers and copolymers of N-vinyl pyrrolidone, e.g. polyvinylpyrrolidone, copolymers of N-vinyl pyrrolidone and vinyl acetate e.g. copovidone, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene oxide, polyacrylates, methacrylate copolymers, methyl methacrylate, butyl methacrylate and the like or combinations thereof. The water soluble polymer may be used in the range of about 0.01 to 10% by weight of the dosage form.

The pharmaceutical composition according to the present invention may be prepared by any method known in the art such as melt extrusion, solid dispersion, solid solution, coprecipitation, wet granulation, melt granulation, dry granulation and/or direct compression.

In another embodiment, the present invention provides a stable pharmaceutical composition comprising:

a) ethinyl estradiol,

b) diluents selected from lactose, sucrose, corn starch and microcrystalline cellulose or mixtures thereof,

c) stabilizer selected from sucrose, sucrose fatty acid esters or mixtures thereof,

d) water soluble polymer selected from polyethylene glycol, methacrylate copolymers and copovidone or mixtures thereof,

e) antioxidant selected from vitamin E, vitamin E acetate, butylated hydroxyanisole and butylated hydroxytoluene,

f) surfactant selected from poloxamer, sodium lauryl sulfate and polysorbate or mixtures thereof.

In another embodiment, the present invention also provides a stable pharmaceutical composition comprising:

a) drospirenone and ethinyl estradiol as active ingredients,

b) diluents selected from lactose, sucrose, corn starch and microcrystalline cellulose or mixtures thereof,

c) stabilizer selected from sucrose, sucrose fatty acid esters or mixtures thereof,

d) disintegrant selected from corn starch, pregelatinized starch and croscarmellose sodium, surfactant selected from poloxamer, sodium lauryl sulphate and polysorbate,

e) antioxidant selected from vitamin E, vitamin E acetate, butylated hydroxyanisole and butylated hydroxytoluene,

f) surfactant selected from poloxamer, sodium lauryl sulfate and polysorbate or mixtures thereof,

g) lubricant selected from magnesium stearate, sodium stearyl fumarate and stearic acid, and

h) glidant selected from talc, colloidal silicon dioxide.

In a preferred embodiment, a stable pharmaceutical composition comprising ethinyl estradiol prepared by a process comprising the steps of:

a) blending ethinyl estradiol and sucrose along with one or more pharmaceutically acceptable excipients,

b) melting the blend of step (a) at 40-50°C with mixing till it liquefies in jacketed vessel,

c) mixing the melt of step (b) with one or more pharmaceutically acceptable excipients, and

d) cooling the blend of step (c) to room temperature and sifting the cooled blend.

In another preferred embodiment, a stable premix composition comprising ethinyl estradiol prepared by the process comprising the steps of:

a) blending ethinyl estradiol and sucrose along with one or more pharmaceutically acceptable excipients,

b) melting the blend of step (a) at 40-50°C with mixing till it liquefies in jacketed vessel,

c) mixing the melt of step (b) with one or more pharmaceutically acceptable excipients, and

d) cooling the blend of step (c) to room temperature and sifting the cooled blend.

The present invention further provides a stable pharmaceutical composition comprising progestogen and ethinyl estradiol prepared by the process comprising the steps of:

a) blending progestogen and ethinyl estradiol premix with one or more pharmaceutically acceptable excipients,

b) blending/lubricating the blend of step (a) with one or more extragranular pharmaceutically acceptable excipients, and

c) compressing the blend of step (b) into tablets or filling into capsules.

The present invention further provides a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending drospirenone, ethinyl estradiol along with one or more pharmaceutically acceptable excipients,

b) granulating the blend of step (a) with sucrose solution or dispersion and drying the wet granules,

c) compressing the granules into tablets or filling into capsules, and

d) optionally film coating the compressed tablet.

The present invention further provides a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending drospirenone along with one or more pharmaceutically acceptable excipients,

b) preparing solution/dispersion of sucrose and ethinyl estradiol optionally antioxidant in a suitable solvent,

c) granulating the blend of step (a) with solution/dispersion of step (b) and drying the wet granules,

d) blending/lubricating the granules with one or more extragranular pharmaceutically acceptable excipients, and

e) compressing the granules into tablets or filling into capsules.

The present invention further provides a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending one or more pharmaceutically acceptable excipients,

b) preparing solution/dispersion of sucrose, drospirenone and ethinyl estradiol in a suitable solvent,

c) granulating the blend of step (a) with solution/dispersion of step (b) and drying the wet granules,

d) blending/lubricating the granules with one or more extragranular pharmaceutically acceptable excipients, and

e) compressing the granules into tablets or filling into capsules.

The present invention further relates to a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending drospirenone along with one or more pharmaceutically acceptable excipients,

b) preparing solution/dispersion of sucrose, ethinyl estradiol and an antioxidant in a suitable solvent,

c) granulating the blend of step (a) with solution/dispersion of step (b) and drying the wet granules,

d) blending/lubricating the granules with one or more extragranular pharmaceutically acceptable excipients, and

e) compressing the granules into tablets or filling into capsules.

The present invention further relates to a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending one or more pharmaceutically acceptable excipients,

b) preparing solution/dispersion of ethinyl estradiol and an antioxidant in a suitable solvent,

c) granulating half the blend of step (a) with solution/dispersion of step (b) and drying the wet granules,

d) preparing solution/dispersion of drospirenone and sucrose in a suitable solvent,

e) granulating the remaining half of the blend of step (a) with solution/dispersion of step (d) and drying the wet granules,

f) blending/lubricating the granules of step (c) and step (e) with one or more extragranular pharmaceutically acceptable excipients, and

g) compressing the granules into tablets or filling into capsules.

The present invention further relates to a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending one or more pharmaceutically acceptable excipients,

b) preparing solution/dispersion of drospirenone, ethinyl estradiol and an antioxidant in a suitable solvent,

c) preparing solution/dispersion of sucrose in a suitable solvent and mixing with the solution/dispersion of step (b),

d) granulating the blend of step (a) with solution/dispersion of step (c) and drying the wet granules,

e) blending/lubricating the granules with one or more extragranular pharmaceutically acceptable excipients, and

f) compressing the granules into tablets or filling into capsules.

The present invention further relates to a stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending sucrose along with one or more pharmaceutically acceptable excipients,

b) preparing solution/dispersion of drospirenone, ethinyl estradiol, surfactant and an antioxidant in a suitable solvent,

c) preparing solution/dispersion of sucrose in a suitable solvent and mixing with the solution/dispersion of step (b),

d) granulating the blend of step (a) with solution/dispersion of step (c) and drying the wet granules,

e) blending/lubricating the granules with one or more extragranular pharmaceutically acceptable excipients, and

f) compressing the granules into tablets or filling into capsules.

In an embodiment of the present invention, the solvents used for dispersion /solution may be selected from isopropyl alcohol, methanol, ethanol, water, acetone, methylene chloride and the like or mixtures thereof.

"Dispersion" according to the present invention can be microdispersion or nanodispersion. The dispersion can be prepared and milled by any method known in the art.

The solid dosage form of the present invention may be uncoated or or optionally coated.

In yet another embodiment of the present invention, film coating composition comprises a solution / suspension of film coating polymers and one or more excipients such as such as plasticizers, opacifier, antisticking agent, colorants, sugars, pore forming agent, surfactants and the like.

Suitable film coating polymers used according to the present invention are selected from ethylcellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose and the like or mixtures thereof.

Suitable anti-sticking agents used according to the present invention are selected from talc, magnesium stearate and the like or a mixture thereof.

The following examples further exemplify the invention and are not intended to limit the scope of the invention. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

Examples 1-6: Preparation of Ethinyl estradiol premix

S. No	Ingredients	Qty (mg)					
		Example 1	**Example 2**	**Example 3**	**Example 4**	**Example 5**	**Example 6**
1	Ethinyl Estradiol	1.000	1.000	1.000	1.000	1.000	1.000
2	Sucrose	2.000	2.000	2.000	2.000	2.000	2.000
3	PEG 6000	0.500	0.500	-	-	-	0.500
4	Eudragit EPO	-	-	0.500	-	-	-
5	Vitamin E acetate	-	1.000	-	-	1.000	-
6	Poloxamer 188	-	-	-	0.500	0.500	-
7	Croscarmellose sodium	-	-	-	-	-	0.500
8	Anhydrous Lactose	6.500	5.500	6.500	6.500	5.500	6.000
	Total weight	**10.000**	**10.000**	**10.000**	**10.000**	**10.000**	**10.000**

The processing steps involved in manufacturing premix of ethinyl estradiol are given below:

a) ethinyl estradiol and sucrose were sifted separately and blended with one or more excipients from S. No. 3 to 7,

b) the blend of step (a) was melted at 40-50°C with mixing till it liquefies in jacketed vessel,

c) anhydrous lactose was mixed with the melt of step (b),

d) the blend of step (c) was cooled to room temperature and sifted.

Example 7

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol premix 10%	0.20
3	Lactose	65.60
4	Pregelatinized Starch	9.60
5	Talc	0.80
6	Magnesium Stearate	0.80
7	Methanol	q.s.
	Coating	
8	Opadry coating	4.00
9	Purified Water	q.s.
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) drospirenone, ethinyl estradiol premix, lactose, pregelatinized starch and talc were sifted separately and blended,

b) the blend of step (a) was lubricated with magnesium stearate,

c) the lubricated blend of step (b) was compressed into tablets, and

d) the compressed tablets obtained in step (c) were coated with Opadry coating.

Example 8

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol	0.02
3	Sucrose	10.00
4	Lactose monohydrate	49.58
5	Corn Starch	15.00
6	Talc	2.00
7	Magnesium Stearate	0.40
8	Purified water	q.s.
	Coating	
9	Opadry coating	4.00
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) drospirenone, lactose monohydrate and half the quantity of corn starch were sifted separately and blended,

b) sucrose was dissolved in purified water and ethinyl estradiol was dispersed in the sucrose solution,

c) the blend of step (a) was granulated using the dispersion of step (b) and the wet mass was dried, milled and sifted,

d) the granules of step (c) were blended with remaining quantity of corn starch, talc and the blend was lubricated with magnesium stearate,

e) the lubricated blend of step (d) was compressed into tablets,

f) the compressed tablets obtained in step (e) were coated with Opadry coating.

Example 9

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol	0.02

3	Sucrose	10.00
4	Lactose monohydrate	49.58
5	Corn Starch	15.00
6	Talc	2.00
7	Magnesium Stearate	0.40
8	Purified water	q.s.
	Coating	
9	Opadry coating	4.00
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) lactose and half the quantity of corn starch were sifted separately and blended,

b) sucrose was dissolved in purified water and drospirenone and ethinyl estradiol were dispersed in the sucrose solution,

c) the blend of step (a) was granulated using the dispersion of step (b) and the wet mass was dried, milled and sifted,

d) the granules of step (c) were blended with remaining quantity of corn starch, talc and the blend was lubricated with magnesium stearate,

e) the lubricated blend of step (d) was compressed into tablets,

f) the compressed tablets obtained in step (e) were coated with Opadry coating.

Example 10

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol	0.02
3	Sucrose	10.00
4	Vitamin E	0.08
5	Lactose monohydrate	49.50
6	Corn Starch	15.00
7	Talc	2.00
8	Magnesium Stearate	0.40

9	Purified water	q.s.
	Coating	
10	Opadry coating	4.00
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) drospirenone, lactose and half the quantity of corn starch were sifted separately and blended,

b) sucrose was dissolved in purified water and ethinyl estradiol and vitamin E were dispersed in the sucrose solution,

c) the blend of step (a) was granulated using the dispersion of step (b) and the wet mass was dried, milled and sifted,

d) the granules of step (c) were blended with remaining quantity of corn starch, talc and the blend was lubricated with magnesium stearate,

e) the lubricated blend of step (d) was compressed into tablets,

f) the compressed tablets obtained in step (e) were coated with Opadry coating.

Example 11

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol	0.02
3	Sucrose	10.00
4	Vitamin E	0.08
5	Lactose monohydrate	58.50
6	Corn Starch	15.00
7	Talc	2.00
8	Magnesium Stearate	0.40
9	Methanol	q.s.
10	Purified Water	q.s.
	Coating	
11	Opadry coating	4.00
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) lactose and half the quantity of corn starch were sifted separately and blended,

b) drospirenone, ethinyl estradiol and vitamin E were dissolved in methanol,

c) sucrose was dissolved in purified water and mixed with the solution of step (b),

d) the blend of step (a) was granulated using the dispersion of step (c) and the wet mass was dried, milled and sifted,

e) the granules of step (d) were blended with remaining quantity of corn starch, talc and the final blend was lubricated with magnesium stearate,

f) the lubricated blend of step (d) was compressed into tablets,

g) the compressed tablets obtained in step (e) were coated with Opadry coating.

Example 12

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol	0.02
3	Vitamin E	0.08
4	Poloxamer	0.50
5	Lactose monohydrate	49.00
6	Sucrose	10.00
7	Corn Starch	15.00
8	Talc	2.00
9	Magnesium Stearate	0.40
10	Purified Water	q.s.
	Coating	
11	Opadry coating	4.00
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) lactose, sucrose and half the quantity of corn starch were sifted separately and blended,

b) vitamin E and poloxamer were dissolved in purified water and drospirenone, ethinyl estradiol were dispersed in the solution,

c) the blend of step (a) was granulated using the dispersion of step (b) and the wet mass was dried, milled and sifted,

d) the granules of step (d) were blended with remaining quantity of corn starch, talc and the final blend was lubricated with magnesium stearate,

e) the lubricated blend of step (d) was compressed into tablets,

f) the compressed tablets obtained in step (e) were coated with Opadry coating.

Example 13

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.00
2	Ethinyl Estradiol	0.02
3	Vitamin E	0.08
4	Poloxamer	0.50
5	Lactose monohydrate	49.00
6	Sucrose	10.00
7	Corn Starch	15.00
8	Talc	2.00
9	Magnesium Stearate	0.40
10	Methanol	q.s.
11	Purified Water	q.s.
	Coating	
12	Opadry coating	4.00
	Total weight of the tablet	**84.00**

The processing steps involved in manufacturing drospirenone and ethinyl estradiol tablets are given below:

a) part of lactose, half the quantity of sucrose and half the quantity of corn starch were sifted separately and blended,

b) vitamin E, poloxamer, drospirenone and ethinyl estradiol were dissolved in methanol,

c) remaining half of the quantity of sucrose was dissolved in purified water and mixed with the solution of step (b),

d) the blend of step (a) was granulated using the dispersion of step (c) and the wet mass was dried, milled and sifted,

e) the granules of step (d) were blended with remaining quantity of lactose, remaining quantity of corn starch, talc and the final blend was lubricated with magnesium stearate,

f) the lubricated blend of step (e) was compressed into tablets,

g) the compressed tablets obtained in step (f) were coated with Opadry coating.

Examples 14: Preparation of Ethinyl estradiol premix

S. No	Ingredients	Qty/tab (mg)
1	Ethinyl Estradiol	0.020
2	Sucrose	0.329
3	Purified Water	q.s.
4	Anhydrous Lactose	1.095
5	Sucrose	0.365
6	Microcrystalline cellulose	0.365
	Total weight	**2.174**

The processing steps involved in manufacturing premix of ethinyl estradiol are given below:

a) lactose, sucrose and microcrystalline cellulose were sifted separately and blended,

b) ethinyl estradiol and sucrose were taken in vessel,

c) added purified water in step (b) and homogenized for 45-60 min using high speed homogenizer,

d) the blend of step (a) was granulated using the dispersion of step (c) and the wet mass was dried, milled and sifted.

Example 15

S. No	Ingredients	Qty/tab (mg)
1	Ethinyl Estradiol premix	2.160
2	Lactose	63.64
3	Pregelatinized Starch	9.600
4	Talc	0.800
5	Magnesium Stearate	0.800
	Coating	
6	Opadry coating	4.000
7	Purified Water	q.s.
	Total weight of the tablet	**81.000**

The processing steps involved in manufacturing ethinyl estradiol tablets are given below:

a) Ethinyl estradiol premix, lactose, pregelatinized starch and talc were sifted separately and blended,

b) the blend of step (a) was lubricated with magnesium stearate,

c) the lubricated blend of step (b) was compressed into tablets, and

d) the compressed tablets obtained in step (c) were coated with Opadry coating.

Example 16

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.000
2	Ethinyl Estradiol premix	2.160
3	Lactose	53.240
4	Corn starch	10.000
5	Pregelatinized Starch	10.000

6	Magnesium Stearate	0.800
	Coating	
7	Opadry coating	4.000
8	Purified Water	q.s.
	Total weight of the tablet	**84.000**

The processing steps involved in manufacturing ethinyl estradiol tablets are given below:

a) Drospirenone, ethinyl estradiol premix, lactose, corn starch and pregelatinized starch were sifted separately and blended,

b) the blend of step (a) was lubricated with magnesium stearate,

c) the lubricated blend of step (b) was compressed into tablets, and

d) the compressed tablets obtained in step (c) were coated with Opadry coating.

Example 17 -Comparative example without Sucrose

S. No	Ingredients	Qty/tab (mg)
1	Drospirenone	3.000
2	Ethinyl Estradiol	0.020
3	Lactose	56.180
4	Corn starch	10.000
5	Pregelatinized Starch	10.000
6	Magnesium Stearate	0.800
	Coating	
7	Opadry coating	4.000
8	Purified Water	q.s.
	Total weight of the tablet	**84.000**

The processing steps involved in manufacturing ethinyl estradiol tablets are given below:

e) Drospirenone, ethinyl estradiol, lactose, corn starch and pregelatinized starch were sifted separately and blended,

f) the blend of step (a) was lubricated with magnesium stearate,

g) the lubricated blend of step (b) was compressed into tablets, and

h) the compressed tablets obtained in step (c) were coated with Opadry coating.

Stability Data: Tablets prepared according to examples 15 and 17 were stored at 40°C/75% RH for six months and then tested by HPLC to determine the amount of impurities such as 6-keto ethinyl estradiol and related impurities. The stability data is given in table 1.

Table 1

	Example 15		**Example 17**	
	Initial	**6 Months**	**Initial**	**6 Months**
Assay	93.5	91.0	96.5	80.5
6-keto ethinyl estradiol	ND	0.34	ND	0.88
6-α Hydroxy ethinyl estradiol	0.04	0.05	0.03	0.06
6-β Hydroxy ethinyl estradiol	0.05	0.15	ND	0.31
Total impurities	0.34	1.16	0.81	3.68

Stability Data: Tablets prepared according to examples 16 and 17 were stored at 50°C/75% RH for 5 days and then tested by HPLC to determine the amount of impurities such as 6-keto ethinyl estradiol and related impurities. The stability data is given in table 1.

Table 2

	Example 16		**Example 17**	
	Initial	**5 days**	**Initial**	**5 days**
6-keto ethinyl estradiol	0.05	0.1	ND	0.15
6-α Hydroxy ethinyl estradiol	0.05	0.06	0.03	0.03
6-β Hydroxy ethinyl estradiol	0.01	0.07	ND	0.11
Total impurities	0.73	1.00	0.73	1.00

Claims:

1. A stable pharmaceutical composition comprising ethinyl estradiol, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

2. A stable premix composition comprising ethinyl estradiol, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

3. A stable pharmaceutical composition comprising ethinyl estradiol, progestogen, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose.

4. The composition of claim 1, wherein one or more pharmaceutically acceptable excipients are selected from diluent, binder, disintegrant, stabilizers, surfactant, antioxidants, water soluble polymers, glidant and lubricant.

5. A stable pharmaceutical composition comprising ethinyl estradiol, a stabilizer and one or more pharmaceutically acceptable excipients, wherein stabilizer is sucrose or sucrose in mixture with other stabilizers.

6. The composition of claim 3, wherein the diluent is selected from lactose, sucrose, dextrose; sugar alcohols such as mannitol, sorbitol, xylitol, lactitol; Starlac® (co-processed mixture of Starch and lactose), Microcelac® (co-processed mixture of microcrystalline cellulose and lactose), starch, corn starch, modified starches, pregelatinized starch, dibasic calcium phosphate, tribasic calcium phosphate, powdered cellulose, microcrystalline cellulose, silicified microcrystalline cellulose or combination thereof.

7. The composition of claim 3, wherein the binder is selected from cellulose and its derivatives including, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose and hydroxyethyl cellulose, carboxymethyl cellulose; starch and its derivatives; hydrocolloids; sugars; polyvinyl pyrrolidone, copovidone, methacrylic acid copolymers or combination thereof.

8. The composition of claim 3, wherein the antioxidant is selected from ascorbic acid and its salts and derivatives, vitamin E, vitamin E acetate, tocopherols and their derivatives, citric acid, gallic acid ester, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), di-tert-butylphenol, tertiary butylhydroquinone, aromatic amines, phenolic acids, enzymatic antioxidants, flavonoids, N-acetylcysteine, mesna, glutathione, thiohistidine derivatives, triazoles; tannins, cinnamic acid, hydroxycinnamatic acids and their esters, their mixtures and the like or combinations thereof.

9. A stable pharmaceutical composition comprising:

a) drospirenone and ethinyl estradiol as active ingredients,

b) diluents selected from lactose, sucrose, corn starch and microcrystalline cellulose or mixtures thereof,

c) stabilizer selected from sucrose, sucrose fatty acid esters or mixtures thereof,

d) disintegrant selected from corn starch, pregelatinized starch and croscarmellose sodium, surfactant selected from poloxamer, sodium lauryl sulphate and polysorbate,

e) antioxidant selected from vitamin E, vitamin E acetate, butylated hydroxyanisole and butylated hydroxytoluene,

f) surfactant selected from poloxamer, sodium lauryl sulfate and polysorbate or mixtures thereof,

g) lubricant selected from magnesium stearate, sodium stearyl fumarate and stearic acid, and

h) glidant selected from talc, colloidal silicon dioxide.

10. A stable pharmaceutical composition comprising ethinyl estradiol prepared by a process comprising the steps of:

a) blending ethinyl estradiol and sucrose along with one or more pharmaceutically acceptable excipients,

b) melting the blend of step (a) at 40-50°C with mixing till it liquefies in jacketed vessel,

c) mixing the melt of step (b) with one or more pharmaceutically acceptable excipients, and

d) cooling the blend of step (c) to room temperature and sifting the cooled blend.

11. A stable premix composition comprising ethinyl estradiol prepared by the process comprising the steps of:

a) blending ethinyl estradiol and sucrose along with one or more pharmaceutically acceptable excipients,

b) melting the blend of step (a) at 40-50°C with mixing till it liquefies in jacketed vessel,

c) mixing the melt of step (b) with one or more pharmaceutically acceptable excipients, and

d) cooling the blend of step (c) to room temperature and sifting the cooled blend.

12. A stable pharmaceutical composition comprising drospirenone and ethinyl estradiol prepared by the process comprising the steps of:

a) blending drospirenone, ethinyl estradiol along with one or more pharmaceutically acceptable excipients,

b) granulating the blend of step (a) with sucrose solution or dispersion and drying the wet granules,

c) compressing the granules into tablets or filling into capsules, and

d) optionally film coating the compressed tablet.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/000432

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/32 A61K31/567 A61K31/585 A61K47/26
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, BIOSIS, CHEM ABS Data, EMBASE, PASCAL, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 760 579 A (GEORGE REGINALD COSTLEY) 7 November 1956 (1956-11-07) examples 1-5	1-12
X	GB 888 631 A (UPJOHN CO) 31 January 1962 (1962-01-31) examples 1-3,6,7	1-12
X	GB 1 334 813 A (RICHARDSON MERRELL INC) 24 October 1973 (1973-10-24) example 1	1-12
X	DE 199 16 383 A1 (SCHERING AG [DE]) 5 October 2000 (2000-10-05) example 6 claim 9	1-12

☐ Further documents are listed in the continuation of Box C.

☒ 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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
11 May 2012	22/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Albrecht, Silke

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/000432

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 760579 A	07-11-1956	NONE	
GB 888631 A	31-01-1962	NONE	
GB 1334813 A	24-10-1973	BE 782321 A1	16-08-1972
		DE 2218016 A1	09-11-1972
		FR 2133862 A1	01-12-1972
		GB 1334813 A	24-10-1973
		ZA 7201930 A	27-12-1972
DE 19916383 A1	05-10-2000	AT 306907 T	15-11-2005
		AU 5058400 A	16-10-2000
		DE 19916383 A1	05-10-2000
		DK 1165055 T3	27-02-2006
		EP 1165055 A2	02-01-2002
		ES 2251377 T3	01-05-2006
		JP 2002540138 A	26-11-2002
		NO 20014726 A	14-11-2001
		WO 0057853 A2	05-10-2000