USE OF A GESTAGEN IN COMBINATION WITH AN ESTROGEN AND ONE OR MORE PHARMACEUTICALLY TOLERABLE EXCIPIENTS/ CARRIERS FOR LACTOSE-FREE ORAL CONTRACEPTIVE

Technical field of the invention

The present invention relates to the use of a gestagen in combination with an oestrogen and one or more pharmaceutically acceptable excipients/carriers for the preparation of a single-phase pharmaceutical formulation for lactose-free oral contraception. It makes it possible to improve the prophylaxis of lactose-intolerance in the case of a possible contributory factor, partly because the tests for lactose intolerance are complicated.

Prior art

Lactose intolerance, i.e. intolerance to milk sugar, is a disorder that primarily affects about 10 million people in Germany. The typical complaints in the case of lactose intolerance are abdominal pain, a bloated feeling, flatulence, nausea and diarrhoea, depending on the severity of the disorder. We basically distinguish between genetic lactose intolerance, caused for example by a congenital enzyme defect, and acquired lactose intolerance, the cause of which is still generally unknown. The diagnosis of lactose intolerance calls for a test on the breath for H_2 or for a biopsy on the small intestine. Lactose, which is a disaccharide and represents the carbohydrate in milk, is cleaved into monosaccharides by lactase in the small intestine, after which these monosaccharides are absorbed by the cells of the mucous membranes and transported further with the blood. Now, if lactose reaches the colon in the uncleaved or partially uncleaved state, owing to the absence or the reduced activity of lactase, then lactose is decomposed there by the resident bacteria into lactic acid, acetic acid, carbon dioxide, hydrogen and methane. The result is an osmotic pressure, which

intensifies the intestinal peristalsis, with consequent diarrhoea. At the same time, the resulting gases cause flatulence or cramps in the bowels. Patients who are affected are recommended to follow a lactose-free or a low-lactose diet (with less than 3 mg of lactose a day), depending on the severity of their lactose intolerance. A healthy adult on a normal diet has a daily lactose intake of 20-30 g. 100 g of cow's milk contain about 5 g of lactose. Owing to the method used for their production, various types of bread, baked goods, sausages, butter, margarine, chocolate and sweetener tablets also contain lactose.

The recommended treatment includes lactase-containing enzyme preparations, which are to be taken with food in order to stimulate the cleavage of lactose.

US 6,881,428 discloses the preparation of lactose-free milk by the incorporation of an enzyme (lactase) in the milk.

It is known from pharmaceutical technology to prepare oral contraceptives (OCs) exclusively with a lactose base. Owing to its outstanding properties, lactose is particularly suitable for use as a filler in such formulations. The products thus obtained are firm and stable and have the required disintegration properties. The steroid hormones used singly or in combination show a very favourable distribution over the various granulometric fractions when incorporated in a lactose granulate. It is virtually unknown for the granulate to undergo demixing, a process that would mean that the active substance is not distributed sufficiently uniformly in the core of the tablet in quantitative terms. It can be assumed that the active substance is uniformly distributed in an oral contraceptive with a lactose base even in the case of a very low dose range (down to 15 µg of ethinyloestradiol per unit). Lactose

can be easily granulated, and the granulate can be made into tablets without any problems. Direct tabletting, which would be feasible with a special lactose, has not been considered so far and is not used in practice, because the active substances in the various formulations would not be distributed uniformly in quantitative terms. Oral contraceptives with a low dose of the active substance have so far been produced by granulation, subsequent tabletting and in most cases a coating process.

WO 2005 / 030,175 discloses a composition containing norethisterone acetate, oestradiol and cellulose binders, where the pharmaceutical composition given as an example contains 45% of lactose.

WO 2005 / 030,176 discloses a composition with gestagens and cellulose binders, where the pharmaceutical composition given as an example similarly contains norethisterone acetate, oestradiol and 45% of lactose.

Description of the invention

The technical problem the present invention seeks to solve is to make the use of oral contraceptives possible both for women with lactose intolerance and for women who have not been able to use them owing to their lactose intolerance.

This is also expected to improve the prophylaxis of lactose intolerance in the case of a possible contributing factor, partly because the tests for lactose intolerance are complicated.

It has now been found that this technical problem is solved according to the invention by the use in combination with oestrogens and one or more pharmaceutically acceptable excipients/carriers, for

the preparation of a pharmaceutical formulation for lactose-free oral contraception. The gestagen is preferably dienogest, used in a dose of 2.0 mg or 1.5 mg, or chlormadinone acetate or levonorgestrel in an equivalent dose, and the oestrogen is preferably ethinyloestradiol in a dose of 0.030 mg, 0.020 mg or 0.015 mg, or it is oestradiol or oestradiol valerate in an equivalent dose. Ethinyloestradiol can also be used in the clathrate form.

Other gestagens can also be used according to the present invention.

The lactose-free oral contraceptives according to the invention are made with a cellulose base. The formulations are produced by granulation, tabletting or often coating.

In this method, which has not been used before for making low-dose oral contraceptives, celluloses are used as fillers, and the active substance is granulated with binders. The preferred binder is hydroxypropylcellulose (HPC), used in an amount of 1-5%, calculated on the core mass. However, hypromellose, maltodextrin, gelatine or starch mucilage can also be used as the binder. This has not been considered before because of problems, mainly with the distribution of the active substance, which occur in the case of celluloses with a very narrow granulometric spectrum.

To solve the technical problem in question, the following substances are chosen, possibly in combination: various kinds of microcrystalline cellulose (MCC) that differ from one another in their bulk density, particle size and moisture content (e.g. Avicel PH 101, Avicel PH 102 or Avicel PH 112) or combinations of microcrystalline cellulose and dibasic

calcium phosphate or mannitol, and at the same time the best value is chosen for the ratio between the amount of the binder (1-5%) and the total mass of the formulation (100%), since these measures surprisingly ensure a uniform distribution of the generally very low-dose gestagens and oestrogens over the various granulate fractions and later in the tablets. In the case of particularly low-dose ethinyloestradiol, the minimum possible dose of which at present is 15 µg per tablet, the active substance is sprayed on in the fluidized bed during granulation in the form of an ethanolic solution of ethinyloestradiol in order to improve its distribution.

The technical problem in question is also solved by the method proposed for making a single-phase pharmaceutical preparation for lactose-free oral contraception by using a combination of a gestagen and an oestrogen to prepare n x 21 daily dose units, followed by (after n x 21) up to 7 pill-free days or placebo-containing dose units, where n is 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17. Advantageous embodiments of the invention are specified in Claims 18-27.

Examples

Example 1

Active-substance combination: 2.0 mg of dienogest (DNG) and 0.030 mg of ethinyloestradiol (EO),

Example 2

Active-substance combination: 2.0 mg of chlormadinone acetate (CMA) and 0.030 mg of ethinyloestradiol.

Example 3

Active-substance combination: 0.125 mg of levonorgestrel (LNG) and 0.030 mg of ethinyloestradiol.

Example 4

Active-substance combination: 1.5 mg of dienogest and 0.015 mg of ethinyloestradiol, where 0.825 mg of the former and 0.015 mg of the latter are present in the film coating.

The detailed composition of the preparations mentioned in the examples is given in Table 1.

Table 2 shows a comparison of various cellulose formulations as regards the distribution of the active substances in the granulate and the tablet core according to the type of cellulose and the amount of binder used.

The uniform distribution of the active substances was ascertained by determining the amount of these substances in the different screening fractions (fine, medium and large particles) and by determining the CUT of the tablet core in different stages of the tabletting process (beginning, middle and end).

Fig. 1 shows the graphs for the release of the active substances from the cellulose-containing combination (2.0 mg of dienogest and 0.30 of ethinyloestradiol) in comparison with that from the lactose-containing combination (2.0 mg of dienogest and 0.030 mg of ethinyloestradiol), the data having been obtained by conducting a dissolution test in a drug release testing apparatus with a paddle, using water at 37°C as the dissolution medium and a stirring speed of 100 rpm. It can be seen that the lactose-free, cellulose-containing combination of active substances has the same type of release as the lactose-containing combination of active substances.

Fig. 2 shows the graphs for the release of the active substances from the cellulose-containing combination (2.0 mg of chlormadinone acetate and 0.30 mg of ethinyloestradiol) in comparison with that from the lactose-containing combination (2.0 mg of chlormadinone acetate and 0.030 mg of ethinyloestradiol), the data having been obtained by conducting a dissolution test in a drug release testing apparatus with a paddle, using sodium dodecyl sulphate at 37°C as the dissolution medium and a stirring speed of 75 rpm. It can be seen that the lactose-free, cellulose-containing combination of active substances has the same type of release as the lactose-containing combination of active substances.

Table 1

Formulation (core):	**1**	**2**	**3**	**4 (MR)***
Active substance	2 mg of DNG+0.03 mg of EO	2 mg of CMA+0.03 mg of EO	0.125 mg of LNG +0.03 mg of EO	0.675 mg of DNG
Filler	43.52 mg of MCC	43.52 mg of MCC	45.395 mg of MCC	58.425 mg of MCC
Matrix former	-	-	-	9 mg of hypromellose
Disintegrant	1.95 mg of croscarmellose sodium	1.95 mg of croscarmellose sodium	1.95 mg of croscarmellose sodium	15 mg of cornstarch
Binder	2 mg of HPC	2 mg of HPC	2 mg of HPC	6 mg of maltodextrin
Lubricant	0.5 mg of magnesium	0.5 mg of magnesium	0.5 mg of magnesium	0.9 mg of magnesium

	stearate	stearate	stearate	stearate

*0.825 mg of DNG and 0.015 mg of EO were introduced in addition in an active-substance layer as a film coating component

Table 2

	Batch No. 550907	Batch No. 621007	Batch No. 631007
Composition	2 mg of CMA, 0.03 mg of EO, 44.52 mg of Avicel PH 102, 1 mg of HPC, 1.95 mg of croscarmellose Na and 0.5 mg of Mg stearate	2 mg of CMA, 0.03 mg of EO, 28.52 mg of Avicel PH 102, 15 mg of Avicel PH 112, 2 mg of HPC, 1.95 mg of croscar-mellose Na and 0.5 mg of Mg stearate	2 mg of CMA, 0.03 mg of EO, 36.02 mg of Avicel PH 101, 7.5 mg of Avicel PH 112, 2 mg of HPC, 1.95 mg of croscar-mellose Na and 0.5 mg of Mg stearate
Amounts in the 3 screening fractions (fine, medium and Large)	Fine: 125% of CMA and 148% of EO Medium: 92% of CMA and 93% of EO Large: 79% of CMA and 52% of EO	Fine: 90.5% of CMA and 104.9% of EO Medium: 114.9% of CMA and 118.5% of EO Large: 125.9% of CAM and 116% of EO	Fine: 99.4% of CMA and 107.7% of EO Medium: 97.3% of CMA and 96.9% of EO Large: 111.9% of CMA and 102.5% of EO
CUT of the core in 3 stages (acceptance value). Theoretical: <15	Start: 2.75 of CMA and 3.78 of EO Middle: 4.59 of CMA and 5.33 of EO End: 4.68 of CMA and 4.62 of EO	Start: 3.89 of CMA and 4.20 of EO Middle: 7.15 of CMA and 8.59 of EO End: 3.58 of CMA and 6.71 of EO	Start: 2.27 of CMA and 9.65 of EO Middle: 3.74 of CMA and 3.01 of EO End: 7.12 of CMA and 9.24 of EO

Patent claims

1. Pharmaceutical composition for oral contraception containing a gestagen selected from the group consisting of 17α-cyanomethyl-17β-hydroxyestra-4,9-dien-3-one (dienogest), chlormadinone acetate and Levonorgestrel in combination with an estrogen selected from the group consisting of ethinylestradiol, and 17β-estradiol (estradiol) or estradiol valerate, characterized by the fact that no lactose is included.

2. Pharmaceutical composition according to Claim 1 wherein cellulose is used as fillers, characterized in that the gestagens and estrogens of claim 1 are granulated with binders.

3. Pharmaceutical composition according to Claim 2, characterized in that the cellulose is microcrystalline.

4. Pharmaceutical composition according to Claim 3, characterized in that hypromellose, maltodextrin, gelatine or starch mucilage are used as the binder.

5. Pharmaceutical composition according to any one of Claim 1, characterized in that the daily gestagen dose is equal or less than 2 mg of dienogest or an equivalent amount of chlormadinone acetate or Levonorgestrel.

6. Pharmaceutical composition according to any one of Claim 5, characterized in that the daily gestagen dose is 2 mg or 1.5 mg of dienogest or an equivalent amount of chlormadinone acetate or Levonorgestrel.

7. Pharmaceutical composition according to any one of Claim 1, characterized in that the daily estrogen dose is equal to or less than 0.030 mg of ethinylestradiol or an equivalent

amount of estradiol or estradiol valerate.

8. Pharmaceutical composition according to Claim 7, characterized in that the daily estrogen dose is 0.030 mg, 0.020 mg or 0.015 mg of ethinylestradiol or an equivalent amount of estradiol or estradiol valerate.