

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

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Technical field of the invention

The present invention relates to the use of a gestagen
in combination with an estrogen and one or more
pharmaceutically acceptable excipients/carriers for the
10 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
15 lactose intolerance are complicated.

Prior art

Lactose intolerance, i.e. intolerance to milk sugar, is
a disorder that primarily affects about 10 million
20 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
25 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 H₂ or for a biopsy on the
small intestine. Lactose, which is a disaccharide and
30 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
35 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
5 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
10 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
15 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
20 milk.

It is known from pharmaceutical technology to prepare oral contraceptives (OCs) exclusively with a lactose base. Owing to its outstanding properties, lactose is
25 particularly suitable for use as 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
30 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
35 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 ethinylestradiol per unit). Lactose can be easily granulated, and the granulate can be made

into tablets without any problems. Direct tableting, 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
5 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 tableting and in most case a coating process.

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

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

20 **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
25 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
30 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 of
35 gestagens in combination with estrogens 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 estrogen is preferably ethinylestradiol in a dose of 0.030 mg, 0.020 mg or 0.015 mg, or it is estradiol or estradiol valerate in an equivalent dose. Ethinylestradiol can also be used in the clathrate form.

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

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

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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 hydroxypropyl-cellulose (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 estrogens over the various granulate fractions and later in the tablets. In the case of particularly low-dose ethinylestradiol, 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 ethinylestradiol 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 estrogen to prepare $n \times 21$ daily dose units, followed by (after $n \times 21$) 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 ethinylestradiol (EO),

Example 2

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

Example 3

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

Example 4

Active-substance combination with modified regime (MR): 1.5 mg of dienogest and 0.015 mg of ethinylestradiol, 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.

5 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.

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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
15 of the tablet core in different stages of the tableting process (beginning, middle and end).

Fig. 1 shows the graphs for the release of the active substances from the cellulose-containing combination
20 (2.0 mg of dienogest and 0.030 of ethinylestradiol) in comparison with that from the lactose-containing combination (2.0 mg of dienogest and 0.030 mg of ethinylestradiol), the data having been obtained by conducting a dissolution test in a drug release testing
25 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
30 substances.

Fig. 2 shows the graphs for the release of the active substances from the cellulose-containing combination
35 (2.0 mg of chlormadinone acetate and 0.030 mg of ethinylestradiol) in comparison with that from the lactose-containing combination (2.0 mg of chlormadinone acetate and 0.030 mg of ethinylestradiol), 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 hypro-mellose
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 malto-dextrin
Lubricant	0.5 mg of magnesium stearate	0.5 mg of magnesium stearate	0.5 mg of magnesium stearate	0.9 mg of magnesium 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 and the meaning of MR is "modified regime".

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. Use of a gestagen in combination with an estrogen and one or more pharmaceutically acceptable excipients/
5 carriers, for the preparation of a single-phase pharmaceutical formulation for lactose-free oral contraception.
2. Use according to Claim 1, characterized in that
10 the gestagenic component is 17α -cyanomethyl- 17β -hydroxyestra-4,9-dien-3-one (dienogest), chlormadinone acetate or levonorgestrel.
3. Use according to Claims 1 or 2, characterized in
15 that the estrogenic component is a synthetic estrogen, a natural estrogen or an ester of the latter.
4. Use according to any one of Claims 1-3,
characterized in that the synthetic estrogen is
20 ethinylestradiol, and the natural estrogen is 17β -estradiol (estradiol) or estradiol valerate.
5. Use according to any one of Claims 1-4,
characterized in that the daily gestagen dose is equal
25 to or less than 2 mg of dienogest or an equivalent amount of chlormadinone acetate or levonorgestrel.
6. Use according to any one of Claims 1-5,
characterized in that the daily gestagen dose is 2 mg
30 or 1.5 mg of dienogest or an equivalent amount of chlormadinone acetate or levonorgestrel.
7. Use according to any one of Claims 1-6,
characterized in that the daily estrogen dose is equal
35 to or less than 0.030 mg of ethinylestradiol or an equivalent amount of estradiol or estradiol valerate.
8. Use according to any one of Claims 1-7,
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.

9. Use according to any one of Claims 1-8,
5 characterized in that the pharmaceutical formulation is prepared for use in the form of at least 21 daily dose units and up to 7 pill-free days or placebo-containing dose units of the pharmaceutical formulation containing one or more pharmaceutically acceptable excipients/
10 carriers.

10. Use according to any one of Claims 1-9, characterized in that the pharmaceutical formulation is prepared for use in the form of 21, 22, 23, 24 or 25
15 daily dose units of the pharmaceutical formulation, and 7, 6, 5, 4 or 3 pill-free days or placebo-containing daily dose units, so that the total number is equal to the 28 days of the menstrual cycle.

20 11. Use according to any one of Claims 1-10, characterized in that the pharmaceutical formulation is prepared for use in the form of at least $n \times 21$ daily dose units of the pharmaceutical formulation, where $n =$ 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and
25 17, and up to 7 pill-free days or placebo-containing dose units.

12. Use according to Claim 11, characterized in that the pharmaceutical formulation is prepared for use in
30 the form of 3, 4, 5, 6 or 7 pill-free days or daily placebo-containing dose units.

13. Use according to Claim 12, characterized in that pharmaceutical formulation is prepared for use in the
35 form of 84 daily dose units with a gestagen-estrogen combination and 7 pill-free days or daily placebo-containing dose units, so that the total number of days of the menstrual cycle per year is $4 \times (n \times 21 + 7)$, where $n = 4$.

14. Use according to any one of Claims 1-13, characterized in that the pharmaceutical formulation is in the form of tablets, film-coated tablets, sugar-coated tablets, capsules or powder.
15. Use according to any one of Claims 1-14, characterized in that the dosage form used is that of film-coated tablets, consisting of a tablet core with an amount of delayed-release gestagen forming a certain proportion of the total gestagen content, and a film coating with a non-delayed-release (fast release) gestagen forming a certain proportion of the total gestagen content, as well as a non-delayed-release (fast release) estrogen constituting the whole estrogen content.
16. Use according to Claim 15, characterized in that at least 10% and preferably 30% of the gestagen is released from the tablet core with a delay of more than 30 minutes, as found in a dissolution test with water at 37°C as the dissolution medium and a stirring speed of 50 rpm.
17. Use according to Claim 15 or 16, characterized in that the gestagen is dienogest or chlormadinone acetate, and the estrogen is ethinylestradiol.
18. Method for the preparation of a single-phase pharmaceutical formulation for lactose-free oral contraception, characterized in that it consists of a combination of a gestagen and an estrogen in the form of $n \times 21$ daily dose units, followed (after $n \times 21$) by up to 7 pill-free days or daily placebo-containing dose units, where $n = 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16$ and 17 .
19. Method according to Claim 18, characterized in

that the gestagenic component is 17 α -cyanomethyl-17 β -hydroxyestra-4,9-dien-3-one (dienogest), chlormadinone acetate or levonorgestrel.

- 5 20. Method according to Claims 18 and 19, characterized in that the estrogenic component is either a synthetic estrogen, a natural estrogen, or an ester of the latter.
- 10 21. Method according to Claims 18-20, characterized in that the synthetic estrogen is ethinylestradiol, and the natural estrogen is 17 β -estradiol (estradiol) or estradiol valerate.
- 15 22. Method according to Claims 18-21, characterized in that the daily gestagen dose is equal to or less than 2 mg of dienogest or an equivalent amount of chlormadinone acetate or levonorgestrel.
- 20 23. Method according to Claims 18-22, 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.
- 25 24. Method according to Claims 18-23, characterized in that daily estrogen dose is equal to or less than 0.030 mg of ethinylestradiol or an equivalent amount of estradiol or estradiol valerate.
- 30 25. Method according to Claims 18-24, characterized in that 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.
- 35 26. Method according to Claims 18-25, characterized in that the dosage form of the single-phase pharmaceutical preparation is that of film-coated tablets, consisting of a tablet core with an amount of delayed-release gestagen forming a certain proportion of the total

- amount of dienogest, chlormadinone acetate or levonorgestrel, and a film coating with a non-delayed-release (fast release) gestagen forming a certain proportion of the total amount of dienogest,
- 5 chlormadinone acetate or levonorgestrel, as well as non-delayed-release (fast release) ethinylestradiol or estradiol valerate, constituting the whole estrogen content.
- 10 27. Method according to Claims 18-26, characterized in that at least 10% and preferably 30% of the dienogest is released from the tablet core with a delay of more than 30 minutes, as found in a dissolution test with water at 37°C as the dissolution medium and a stirring
- 15 speed of 50 rpm.