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(54) **Titre :Pharmaceutical composition comprisingdrospirenone and contraceptive kit.**

(57) **Abrégé :**
The present invention relates to the field of pharmaceutical compositions and contraceptive methods. The present invention provides a pharmaceutical composition comprising drospirenone characterized by a slow dissolution rate of drospirenone in vitro and an improved pharmacokinetic profile. The use of the said composition in contraceptive methods and kits are also provided.

TITLE OF THE INVENTION

Pharmaceutical composition comprising drospirenone and contraceptive kit

FIELD OF THE INVENTION

The present invention relates to the field of contraceptive kits, compositions and methods.

DESCRIPTION OF THE RELATED PRIOR ART

Several contraceptives which comprise synthetic progestogens and no oestrogen are commercially available. These contraceptives called "progestogen-only contraceptives" encompass implants, uterine delivery systems and pills.

Progestogen-only Pills (POPs) have the advantage of avoiding the combined administration of estrogens as compared to traditional contraceptive combined pills.

However, POPs display several major drawbacks. Because of their low contraceptive reliability, POPs have to be taken each day at the same time without pill-free or placebo interval.

The bleeding patterns for women who take POP may be also altered deeply as compared to the natural menstrual cycle, since amenorrhea or unscheduled bleeding or spotting may occur.

It results that, in spite of their potential benefits, POPs are poorly used and are usually indicated for women who cannot tolerate estrogen, for women in post-partum period and for women who are breast-feeding (Amy, Tripathi, 2009, BMJ, 339, 563-568 ; Mandisk, 2008, Obstetric Medicine, 1,78-87).

Drospirenone (CAS: 67392-87-4; 6β, 7β,15β, 16β–dimethylen-3-oxo-17a-pregn4-ene-21,17-carbo-lactone) is a synthetic progestogen with a pharmacological profile very closely related to that of natural progesterone.

Drospirenone (or DRSP) is devoid of androgenic, glucocorticoid and antiglucocorticoid activity but does possess potent

antimineralocorticoid and antiandrogenic properties. It was shown that oral daily doses of at least 3 mg of drospirenone are able to inhibit ovulation over a single treatment cycle of 21 days. The combination of 3 mg drospirenone/30 µg ethinylestradiol provides a reasonable contraceptive safety margin by inhibiting ovulation with a low frequency of follicular maturation (Rosenbaum *et al.*, 2000, The European Journal of Contraception and Reproductive Health Care, 5,16-24).

Drospirenone (DRSP) is thus an appropriate progestin ingredient which may avoid the side-effects occurring with conventional synthetic progestogens such as weight gain and breast tension when combined with an estrogen for use as a contraceptive. DRSP is also likely to minimize fluid retention and to have neutral effects on metabolic and vascular risks (Blode *et al.*, 2000, The European Journal of Contraception and Reproductive Health Care, 5, 256-264; Sitruk-Ware, 2006, Human Reproduction Update, 12, 169-178). It has been also reported that drospirenone may treat moderate acne because of its well-established anti-androgenic properties.

Drospirenone as a contraceptive ingredient is available only in oral combined pills such as those marketed under the name of Yasmin® (3 mg DRSP/30 µg ethinylestradiol), Yaz® (3 mg DRSP/ 20 µg ethinylestradiol) and Yasminelle® (3 mg DRSP/ 20 µg ethinylestradiol). These pills comprise ethinylestradiol which acts to increase the ovulation inhibitory effect of drospirenone and to ensure contraception and cycle stability.

The patent application WO2008031631 describes combined oral contraceptives in which drospirenone is used as a progestative agent and ethinylestradiol is replaced by the phytoestrogen 8-prenylnaringenin. These contraceptives may consist in modified release formulations of 8-prenylnaringenin and drospirenone which may continuously distribute the active ingredients for the gastro-intestinal transit time of generally 12h-16h.

The commercially available contraceptives Yasmin®, Yaz® and Yasminelle® comprise drospirenone in a micronized form which promotes its rapid dissolution *in vitro* and ensures its good oral

bioavailability. It is also the case for Angeliq® which is a hormone replacement medicament combining drospirenone and estradiol.

However, such formulations are characterized by a high plasma concentration peak for drospirenone after oral intake.

High plasma concentrations are not preferred in patients treated with drospirenone because of a correlation between high C_{max} and certain undesirable side effects as well as poor general tolerance when hormonal levels fluctuate too much each and every day.

There is still a need in the art for novel contraceptive kits and for novel pharmaceutical compositions comprising drospirenone.

SUMMARY OF THE INVENTION

The present invention relates to a contraceptive kit comprising one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein , when orally administered under fasting conditions, one daily active dosage unit of said kit is adapted to provide a pharmacokinetic profile for drospirenone having the following features:

(i) a mean t_{max} of at least about 2.2 h and

(ii) a mean C_{max} which is less than about 30 ng/ml,

The present invention also relates to a contraceptive kit comprising one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein each daily active dosage unit comprises drospirenone in a form such that:

(i) no more than 50% of the drospirenone initially present in the said daily active dosage unit is dissolved within 30 minutes and

(ii) at least 50% of the said drospirenone is dissolved in a time range from 3 hours to 4 hours,

when the daily active dosage unit is subjected to an *in vitro* dissolution test USP XXIII Paddle Method, the percentages of drospirenone being related to the amount of drospirenone initially present in the said daily active dosage unit.

Each daily active dosage unit consists of a pharmaceutical composition comprising drospirenone, without estrogen.

Another object of the present invention is a pharmaceutical composition comprising drospirenone for use as a contraceptive.

A further object of the present invention is a contraceptive method for a female patient in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Particle size distribution

Figure 1 shows the cumulative distribution curve (cdf, filled diamonds) and the probability density function curve (pdf, filled squares) for drospirenone (DRSP) batch 080053. The distribution experimental data were obtained by laser diffraction method. X-coordinate: particle size (µm) in log scale. Left Y-coordinate: cumulative distribution in percentage. Right Y-coordinate: probability density function.

Figure 2: In vitro dissolution profiles

Figure 2 shows the *in vitro* dissolution profiles for tablet (A-3mg) obtained from DRSP batch 080053 as described in Example 1 (inventive, curve n°2) and comparative tablets, namely Yasminelle® (curve n°4), tablets CO1-3mg (curve n°3) and tablets CO2-3mg (curve n°1). Each tablet comprises 3 mg of DRSP. The *in vitro* dissolution profiles were determined by the USP XXIII Paddle Method as described in Example 2.

X-coordinate: time in hours, Y-coordinate: mean dissolution percentage of DRSP relating to the initial amount of DRSP contained in the tested tablet,

Figure 3a and Figure 3b: Mean drospirenone serum concentration versus time curves

Figure 3a shows DRSP plasma mean concentration versus time curves obtained after the oral administration of a single tablet of reference product i.e. Yasminelle® (empty squares) or after the oral administration of a single tablet obtained from DRSP batch 080053 as described in Example 1 (test product, filled squares). In both case, the

DRSP dosage was 3 mg. These clinical data were obtained during a monocentric, open, randomized, single-dose, two period crossover clinical trials conducted on 14 healthy female volunteers as described in Example 3 part 1. Each volunteer received in a random way an oral single dose of 1 tablet of the test product or one tablet of Yasminelle® on two single occasions, always under fasting conditions. Study periods were separated by a real wash-out phase of 7 days. In each study, blood samples were collected before the administration of the tablet (pre-dose, time 0) and at 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 12:00, 24:00, 48:00 and 72:00 hours post dosing for assaying the DRSP plasma concentration.

X-coordinate: time after the oral administration of the tablet (in hours). Y-coordinate: mean plasma concentration of DRSP in ng/ml (arithmetic mean).

Figure 3b shows DRSP plasma mean concentration versus time curves obtained after the oral administration of a single tablet of reference product i.e. Yasminelle® (empty squares) or after the oral administration of a single tablet CO1-3mg (filled diamonds) or after the oral administration of a single tablet CO2-3mg (filled squares) under fasting conditions (see Example 3, part 2)

X-coordinate: time after the oral administration of the tablet (in hours). Y-coordinate: mean plasma concentration of DRSP in ng/ml (arithmetic mean).

Figure 4a, 4b and 4c: Simulation based on pharmacokinetic results from clinical trial described in Example 3

Figure 4a and Figure 4b shows the experimental DRSP plasma mean concentration versus time curves obtained (i) for the oral administration of a single tablet of Yasminelle® (comparative, filled squares) and (ii) for the oral administration of a single tablet as described in Example 1 (A-3mg, invention, empty triangles). Both Yasminelle® tablet and tablet A-3mg contains 3 mg of DRSP. Figure 4a and 4b also shows the predicted mean DRSP plasma concentration versus time curve (invention, empty diamonds) obtained for the oral administration of a tablet similar to that described in Example 1 but containing 4 mg of

DRSP (tablet A-4mg). Such a curve was extrapolated from the experimental pharmacokinetic data obtained in the clinical trial described in Example 3, part 1.

X-coordinate: time after the oral administration of the tablet (in hours). Y-coordinate: mean plasma concentration of DRSP in ng/ml.

Figure 4c shows mean plasma DRSP concentration versus time curves resulting from the repeated administration of one tablet of Yasminelle® (curve n°1), that of one tablet A-3mg (curve n°3) and that of one tablet A-4mg (curve n°2), every 24 hours. These curves were obtained by extrapolation of experimental pharmacokinetic data obtained in the clinical trial described in Example 3.

X-coordinate: time after the oral administration of the first tablet (in hours). Y-coordinate: mean plasma concentration of DRSP in ng/ml.

Figure 5a and Figure 5b: In vitro dissolution profile and mean drospirenone serum concentration versus time curve for tablet comprising 4 mg of DRSP (B-4mg).

Figure 5a shows the mean *in vitro* dissolution profile for tablets obtained from DRSP batch N° PR100003 as described in Example 5 (see part 1). The tablet comprises 4mg of DRSP.

X-coordinate: time in hours, Y-coordinate: mean dissolution percentage of DRSP relating to the initial amount of DRSP contained in the tested tablet.

Figure 5b shows DRSP plasma mean concentration versus time curves obtained after the oral administration of a single tablet of reference product i.e. Yasminelle® (empty squares) or after the oral administration of a single tablet B-4mg (filled squares) under fasting conditions (see Example 5, part 2)

X-coordinate: time after the oral administration of the tablet (in hours). Y-coordinate: mean plasma concentration of DRSP in ng/ml.

Figures 6a et 6b: individual plasma levels of progesterone and estradiol in patients during treatment period and follow up period.

Figures 6a and 6b show the results of a clinical trial aiming to illustrate the contraceptive efficiency of the contraceptive compositions according to the invention. The methodology of the clinical trial is described in Example 4. Briefly, the treatment period comprises two

treatment cycles in which the subjects took one pill of 4 mg DRSP (tablet B-4mg) from day 1 to day 24 and one placebo tablet from day 25 to day 28 of each treatment cycle at a fixed hour. On day 5 and day 13 of the second cycle, the pill intake was delayed for 24 hours (i.e. that no pill was taken on day 5 and day 13 and that 2 pills were taken on day 6 and day 14, respectively). The complete study consisted of a 56-day treatment period and a 28-day post-treatment follow-up period. Pill corresponds to tablet B-4mg.

Figure 6a shows the variation of the individual plasma levels of progesterone during the treatment period and the follow-up period. X-coordinate: time in days after the first pill intake. Y-coordinate: progesterone level in ng/ml.

Figure 6b shows the variation of the individual plasma levels of estradiol during the treatment period and the follow-up period. X-coordinate: time in days after the first pill intake. Y-coordinate: estradiol level in pg/ml.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a contraceptive kit comprising a plurality of active daily dosage units. Each daily dosage unit consists of a pharmaceutical composition comprising drospirenone. In preferred embodiments, the said pharmaceutical composition comprises drospirenone, without estrogen. In other words, the contraceptive kit is preferably a progestogen-only contraceptive kit.

Drospirenone may be the sole contraceptive agent present within the pharmaceutical composition.

Said active daily dosage unit enables to prevent pregnancy when daily administered to a woman of child-bearing age over a period of 21 to 28 consecutive days.

The number of active daily dosage units comprised in the contraceptive kit may vary depending on the contraceptive method in which the contraceptive kit is intended to be used.

In order to disclose the contraceptive kit of the invention in a manner sufficiently clear and complete, (i) the pharmaceutical composition of the active daily dosage units of the said kit and (ii) the

contraceptive method for which the said kit is dedicated are fully-described in Chapter 1 and Chapter 2 hereunder. In Chapter 3, specific embodiments of the contraceptive kit of the invention are also described.

1. Pharmaceutical composition

The commercially available drospirenone-containing contraceptive pills comprise both ethinyl-estradiol and micronized drospirenone. According to EP1214076, the micronized form of drospirenone promotes its rapid dissolution *in vitro*. This rapid dissolution in vitro is claimed to be a necessary condition for obtaining a good bioavailability via the oral route. The rapid dissolution rate of drospirenone *in vitro* is assessed to be correlated to a rapid absorption *in vivo* of DRSP which avoids its degradation by gastric or intestine environments.

Several other patents and patent applications, such as WO2006128907, or WO2009138224, describe drospirenone compositions which exhibit a rapid dissolution of drospirenone *in vitro*.

Accordingly, the international application WO2006128907 teaches that surfactants may enhance the dissolution rate of non-micronized drospirenone having a specific surface area lower than 10 000 cm^2/g. the international application WO2009138224 describes that the dissolution rate of drospirenone may be significantly improved by co-milling drospirenone with an appropriate carrier so as to obtain drospirenone in amorphous state.

As mentioned in EP1214076, a rapid dissolution of drospirenone *in vitro* generally means that at least 70% of the drospirenone is dissolved within 30 minutes when the composition is subjected to an *in vitro* dissolution assay such as USP XXIII Paddle Method II.

Surprisingly, the Applicant went against this prejudice and showed, through *in vivo* pharmacokinetic assays, that a rapid dissolution of drospirenone *in vitro* is not required for obtaining a good oral bioavailability. In this respect, the Applicant conceived drospirenone-containing compositions with slow dissolution rate of drospirenone *in vitro* and which exhibit a similar mean AUC value (Area Under the Curve) as compared to Yasminelle® when orally administered to female patients.

Moreover, the Applicant managed to conceive DRSP-containing compositions which also display a significantly mean reduced C_{max} value (Maximum Plasma Concentration) associated with a delayed mean t_{max} value for drospirenone as compared to Yasminelle®.

The decrease of DRSP C_{max} is likely to improve the tolerance of DRSP-containing composition by reducing or avoiding side-effects, in particular those related to plasma level of potassium.

Drospirenone has anti-mineralocorticoid property which leads to an increase of potassium excretion and also, to an increase of potassium plasma level. It has been suggested that the C_{max} of drospirenone correlates to the C_{max} of potassium released after drospirenone administration. Such an increase of potassium plasma concentration after drospirenone administration may lead to hyperkalemia which is known to induce various disorders such as dizziness, palpitations, muscle weakness and even cardiac arrhythmia.

When orally administered, the DRSP-containing composition according to the invention induces a reduced plasmatic C_{max} for drospirenone. A reduced C_{max} for DRSP is expected to reduce the release of potassium in plasma. Consequently, in the case of the composition according to the invention, the tolerance for drospirenone may be improved especially for women who are predisposed to hyperkalemia, to women who suffers from kidney, liver or adrenal diseases and for women who are on daily, long-term treatment for a chronic condition with medications predisposing to hyperkalemia. Medications predisposing to hyperkalemia include, without being limited to, non steroidal anti-inflammatory drugs, potassium-sparing diuretics, potassium supplementation, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists and heparin.

Consequently, the DRSP-containing composition according to the invention may be particularly appropriate to prepare any oral medicament in which the mean C_{max} value for DRSP should be controlled in order to improve the tolerance for drospirenone. For example, the composition according to the invention may be used for preparing Hormone Replacement Therapy medicaments (HRT).

Since the DRSP-containing composition of the invention combined a reduced C_{max} with a delayed t_{max} and an $AUC_{0h\text{-}tlast}$ sufficient to provide a contraceptive effect, the said composition may be appropriate for use in progestogen-only pills.

As illustrated in Example 5, part 3, the Applicant showed that the compositions according to the invention provide an efficient and stable contraceptive drospirenone blood level when daily administered to a female patient. Thus, the co-administration of an oestrogen to ensure contraception and cycle stability is not required.

Since the mean C_{max} value is significantly reduced, the contraceptive composition of the invention provides a more stable plasma concentration of drospirenone i.e a DRSP plasma concentration with low fluctuations between two consecutive administrations. Such a feature may further reduce the incidence of unscheduled spotting and bleeding and, thus, may significantly improve the bleeding profile as compared to conventional POPs.

As described in Example 5, the applicant also showed the said composition remains contraceptive even when a placebo period is introduced in the contraceptive regimen and some daily pills are missed. It is thus expect that the said compositions will exhibit a higher contraceptive reliability than other progestogen only pills which will allow the patients to be a bit less compliant with treatment without risking unwanted pregnancy.

It is also expected that the contraceptive composition of the invention - which does not contain estrogen - will be as efficient as combined oral pill without inducing the side effects related to estrogen, in particular, without increasing the risk of cardiovascular events.

Thus, in some embodiments of the invention, the said pharmaceutical composition is appropriate to be used as an oral contraceptive. In some other specific embodiments, the pharmaceutical composition of the invention is used as a progestogen-only pill.

As used herein "progestogen-only contraceptive", or "progestogen-only pill" means a pill or a contraceptive which comprises progestogens as sole contraceptive agents and does not comprise any estrogen.

By "composition having an improved pharmacokinetic profile for drospirenone" as used herein is, thus, meant that the oral administration of a single daily dosage unit of said drospirenone-containing composition provides a pharmacokinetic profile for drospirenone characterized by a delayed mean t_{max} and a reduced mean C_{max} as compared to the administration of a single daily dosage unit of Yasminelle®.

The pharmacokinetic profile of Yasminelle® is described above in Example 3

In some aspect, the invention provides a pharmaceutical DRSP-containing composition characterized in that, when orally administered, a single daily dosage unit of said composition is adapted to provide a pharmacokinetic profile for DRSP having a mean C_{max} which is less than 85% of the mean C_{max} obtained after the oral administration of a single dosage unit of Yasminelle®.

The pharmaceutical DSRP-containing composition according to the present invention may further be characterized in that, when orally administered, a single daily dosage unit of said composition is adapted to provide a pharmacokinetic profile for DRSP having a mean t_{max} which is at least 150% of the mean t_{max} obtained after the oral administration of a single dosage unit of Yasminelle®

It goes without saying that the administration of a single dosage unit of the said composition provides a mean $AUC_{0h\text{-}tlast}$ which is sufficient to produce the pharmaceutical or the biological effect which is sought by the administration of drospirenone. Said pharmaceutical or biological effect generally refers to a contraceptive effect.

When the composition of the invention is used as a contraceptive, it may be further required that the mean $AUC_{0h\text{-}tlast}$ obtained upon the administration of a single daily dosage unit of said composition is at least 70% of the mean $AUC_{0h\text{-}tlast}$ obtained in the case of Yasminelle®

In other words, in some aspect of the invention, the daily dosage unit of the pharmaceutical composition according to the invention possesses a combination of physical and/or chemical features such that, when orally administered, the said daily dosage unit is adapted to provide a pharmacokinetic profile having the following characteristics:

- (i) a mean C_{max} which is no more than 85% of the mean C_{max} obtained after the oral administration of a single dosage unit of Yasminelle® and
- (ii) a mean t_{max} which is at least 150% of the mean t_{max} obtained after the oral administration of a single dosage unit of Yasminelle®

and, optionally, a mean $AUC_{0h\text{-}tlast}$ which is at least 70% of the mean $AUC_{0h\text{-}tlast}$ obtained after the oral administration of a single dosage unit of Yasminelle®.

In some embodiments, the mean $AUC_{0h\text{-}tlast}$ is at least 85% of the mean $AUC_{0h\text{-}tlast}$ obtained after the oral administration of a single dosage unit of Yasminelle®

In some embodiments, the pharmaceutical composition of the invention displays all the previous mentioned pharmacokinetic characteristics

The $AUC_{0h\text{-}tlast}$, the C_{max} and the t_{max} are determined based on the drospirenone plasma concentration versus time curve.

According to the present invention, for a given drospirenone-containing composition, the drospirenone plasma concentration versus time curve may be determined by following plasma drospirenone concentration over a period of about 72h after a single oral intake of one daily dosage unit of the said drospirenone-containing composition.

The single oral administration of the said drospirenone-containing composition is preferably performed in fasting conditions i.e. without food and not close to mealtime (i.e. in general, approximately 6h-10h after meal) since food ingestion may modify the absorption rate of drospirenone in the gastrointestinal tractus.

The t_{max} and C_{max} values refer to the maximum DRSP plasma concentration and the time to reach it, respectively, after the oral administration of a single daily dosage unit of the DRSP-containing composition of interest.

In other words, t_{max} and C_{max} refer to the characteristics of drospirenone plasma concentration peak observed after the oral intake of a single daily dosage unit of the composition of interest.

The $AUC_{0h\text{-}tlast}$ corresponds to the area obtained by integration of the drospirenone plasma concentration versus time over the interval [0h-tlast], the point "0h" referring to the oral intake of a single daily dosage unit of the composition of interest and the point "t_{last}" refers to the last time for which plasma concentration of DRSP can be quantifiable.

DRSP plasma concentration may be determined by well-known methods of the prior art. For example, an appropriate method of quantification comprises the extraction of DRSP from human plasma and then its quantification using liquid chromatography coupled with tandem mass spectrometry.

In a preferred embodiment, the one skilled in the art may adapt the analytical method described by Kirk et al (Rapid Communication in Mass Spectrometry, 2006;20:1247-1252). Such a method comprises a step of derivatization of drospirenone with Girard P hydrazine solution in order to increase the response of DRSP during the subsequent MS analysis. This method is generally appropriate to quantify DRSP in human EDTA plasma over a concentration range from about 0.25 to about 100 ng/ml.

As used herein, the mean $AUC_{0h\text{-}tlast}$, the mean C_{max} and the mean t_{max} refer to arithmetic mean values determined from individual pharmacokinetic data obtained for a group of healthy female volunteers of child-age bearing subjected to a single oral administration of one daily dosage unit of a drospirenone-containing composition.

The group of healthy female volunteers may comprise enough women to provide statistically confident pharmacokinetic results. Preferably, the said group comprises at least ten healthy women of child-age bearing.

As used herein, a healthy woman of child-age bearing refers to a pre-menopause Caucasian female between 18 and 40 years, with normal body weight and with no health problem, in particular, with no metabolism, renal, liver or gynaecologic disorders. A "normal body weight" refers to a body mass index (BMI) ranging from 18 to 29 kg/m^2.

Preferably, such volunteers do not have taken any hormone-containing compositions within 3 months prior the trial to determine the pharmacokinetic parameters of interest.

The mean C_{max}, t_{max} and $AUC_{0h\text{-}tlast}$ for Yasminelle® and for the drospirenone-containing composition according to the invention are determined for the same group of female patients. Between the administration of the single daily dosage unit of Yasminelle® and that of the DRSP-containing composition according to the invention, the female volunteers may be subjected to a washout period of at least 7 days.

The mean C_{max}, the mean t_{max} and the mean $AUC_{0h\text{-}tlast}$ for DRSP may be determined from raw individual pharmacokinetic data by well-known statistical methods of the prior art.

For example, all endpoints listed above may be determined in a model-independent way. The highest concentration really measured and the time at which it was registered after each dose in any given volunteer may be regarded as C_{max} and t_{max} respectively according to the algorithm of the program NC_PKP.sas.

The daily dosage unit of the DRSP containing-composition of the invention comprises at least 2 mg of drospirenone.

A daily amount of DRSP from 3 mg to 4.5 mg may be preferred when the composition of the invention is used as contraceptive.

As used herein, Yasminelle® is a combined oral pill commercialized by Bayer/Schering. The daily dosage unit of Yasminelle® is a coated tablet which comprises 3 mg of micronized drospirenone and ethinylestradiol betadex clathrate in an amount corresponding to 20 µg of ethinylestradiol. The tablet further comprises lactose monohydrate, maize starch and magnesium stearate as main excipients. The coating of the tablet comprises hypromellose, talc, titane oxide and iron oxide red.

As used herein, Yasminelle® (marketed under the name of Jasminelle® in France) refers to the pharmaceutical product covered by the French Marketing Authorization related to CIS number (Code d'Identification de Spécialité) 65052799 and revised on September, 17th, 2009.

In a preferred embodiment, the pharmacokinetic parameters (namely C_{max}, t_{max} and $AUC_{0h\text{-}tlast}$) are determined after the first oral administration of a single unit dosage of the DRSP-containing composition of interest, said first oral administration occurring in fasting conditions.

In a more general aspect, the present invention provides a pharmaceutical DRSP-containing composition characterized in that, when orally administered, a single daily dosage unit of said composition is adapted to provide a pharmacokinetic profile for DRSP having a mean C_{max} which is less than about 30 ng/ml. The said pharmaceutical DRSP-containing composition may be further characterized in that, when orally administered, a single daily dosage unit of said composition is adapted to provide a pharmacokinetic profile for DRSP having a mean t_{max} which is at least about 2.2 h.

It goes without saying that the administration of a single dosage unit of the said composition provides a mean $AUC_{0h\text{-}tlast}$ which is sufficient to produce the pharmaceutical or the biological effect which is sought by the administration of drospirenone.

When the composition of the invention is used as a contraceptive, it may be further required that the mean $AUC_{0h\text{-}tlast}$ obtained upon the administration of a single daily dosage unit of said composition is at least about 300 ng*ml/h

In other words, in some embodiments, the daily dosage unit of the pharmaceutical composition according to the invention possesses a combination of physical and/or chemical features such that, when orally administered, the said daily dosage unit is adapted to provide a pharmacokinetic profile having the following characteristics:

(i) a mean C_{max} which is less than about 30 ng/ml

(ii) a mean t_{max} of at least about 2.2 h

and, optionally, a mean $AUC_{0h\text{-}tlast}$ of at least about 300 ng*h/ml

In some embodiments, the pharmaceutical composition of the invention displays all the previous mentioned pharmacokinetic characteristics.

As used herein, the term "about" before a "specific value" defines a range from "the specific value minus 10% of the specific value" to "the specific value plus 10% of the specific value". For example, "about 50" defines a range from 45 to 55.

A mean $AUC_{0h\text{-}tlast}$ of at least about 300 ng*h/mL includes a mean $AUC_{0h\text{-}tlast}$ of at least about 310 ng*h/mL, at least about 320 ng*h/mL, at least about 330 ng*h/mL, at least about 340 ng*h/mL, at least about

350 ng*h/mL, at least about 360 ng*h/mL, at least about 370 ng*h/mL, at least about 380 ng*h/mL, at least about 390 ng*h/mL, at least about 400 ng*h/mL, at least about 410 ng*h/mL at least about 420 ng*h/mL, at least about 430 ng*h/mL.

In some embodiments, the mean $AUC_{0h\text{-}tlast}$ is at least about 350 ng*h/ml.

A mean t_{max} of at least about 2.2 h includes a mean t_{max} of at least about 2.5 h, of at least 3.0 h, of at least about 3.5 h, of at least 4h.

In a preferred embodiment the mean t_{max} does not exceed 6 hours in order to not significantly impair the bioavailability of DRSP. Thus, the mean t_{max} preferably ranges from 2.2h to 6h.

In some embodiments, a t_{max} ranging from 3.0 h to 4.0 h is preferred.

A mean C_{max} which is less than about 30 ng/ml includes a C_{max} less than about 28 ng/ml, less than about 26 ng/ml, less than about 24 ng/ml, less than about 22 ng/ml, less than about 20 ng/ml, less than about 19 ng/ml, less than about 18 ng/ml, less than about 17 ng/ml, less than about 16 ng/ml, less than about 15 ng/ml, less than about 14 ng/ml.

In some embodiments, the mean C_{max} ranges from 15 ng/ml to 30 ng/ml.

In other embodiments, the mean C_{max} ranges from 15 ng/ml to 26 ng/ml.

In certain embodiments, the daily dosage unit of the pharmaceutical composition according to the invention is adapted to provide a pharmacokinetic profile having the following characteristics:

(i) a mean C_{max} ranges from 15 ng/ml to 30 ng/ml,

(ii) a mean t_{max} ranges from 2.2 h to 6 h, and

(iii) optionally, a mean $AUC_{0h\text{-}tlast}$ of at least about 300 ng*h/ml,

when the said daily dosage unit is administered under fasting condition.

In a preferred embodiment, the pharmacokinetic parameters (namely C_{max}, t_{max} and $AUC_{0h\text{-}tlast}$) are determined after the first oral administration of a single unit dosage of the DRSP-containing composition of interest, said first oral administration occurring in fasting conditions.

The pharmaceutical composition of the invention is particularly appropriate to be used as a contraceptive, in particular, as an only-progestogen contraceptive.

The pharmaceutical composition of the invention may be also used for preparing any other medicaments for which the improvement of the DRSP tolerance may be sought.

Such medicaments include, without being limiting to, HRT medicament.

Without wishing to be bound by any theory, the Applicant believes that the *in vitro* dissolution rate of drospirenone is correlated to its pharmacokinetic profile *in vivo*.

A composition displaying a pharmacokinetic profile for drospirenone as fully-described above may exhibit a slow *in vitro* dissolution rate of drospirenone such that no more than 50% of drospirenone initially present in the said composition is dissolved within 30 minutes.

In one aspect, the present invention provides a pharmaceutical composition comprising drospirenone that is characterized by a slow dissolution rate of drospirenone *in vitro*.

As used herein, by "a slow dissolution rate of drospirenone *in vitro*" is meant that the release of drospirenone is such that no more than 50% of drospirenone initially present in the said composition is dissolved within 30 minutes when the said composition is subjected to a dissolution test.

As intended herein, no more than 50% of the drospirenone encompasses no more than 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10% of the drospirenone initially present in the contraceptive composition.

In some embodiments, no more than 40% of the drospirenone initially present in the composition is dissolved within 30 min.

As used herein, the percentage of drospirenone is related to the amount of drospirenone initially present in the said contraceptive composition.

The *in vitro* dissolution rate of drospirenone may be assessed by anyone of well-known methods described in the prior art.

The *in vitro* dissolution rate of drospirenone is preferably assessed by the USP XXIII Paddle Method. Briefly, a tablet consisting of the contraceptive composition comprising drospirenone to be tested is placed in 900 mL of water at 37°C (± 0.5°C). The dissolution test is performed using a USP dissolution test apparutus 2 at a stirring rate of 50 rpm.

In some embodiments of the invention, the pharmaceutical composition is a contraceptive composition.

As used herein, by "contraceptive composition" is meant a composition that may prevent pregnancy when daily administered in an effective amount to a female patient over a period of 21 to 28 consecutive days. The contraceptive composition may prevent pregnancy to occur by various biological effects. For example, the pregnancy may be prevented by the inhibition of ovulation, by the thickening of cervical mucus (which reduces the sperm viability and penetration) and/ or by prevent embryo implantation.

The term "drospirenone" refers to drospirenone itself, i.e. the chemical entity identified by the CAS registry Number 67392-87-4, solvates of drospirenone, and derivates or prodrugs of drospirenone

Drospirenone may be prepared by well-known methods described in the prior art, for example, described in US 4129564, WO9806738, EP11746101 or WO2006061309. The method described in WO2006061309 may be particularly suitable for preparing drospirenone.

It goes without saying that the method for preparing drospirenone may be performed so as to meet the Good manufacturing practice (GMP) requirements.

To ensure a good bioavailability of drospirenone, a significant amount of the drospirenone initially comprised in the contraceptive composition has to be released in a reasonable time range.

The Applicant showed that a good bioavailability of drospirenone was achieved in the case of compositions comprising drospirenone which had an *in vitro* dissolution rate of drospirenone such that at least 50% of the drospirenone initially present in the said compositions was dissolved in a time range from 3 hours to 4 hours.

Accordingly, an object of the present invention is a contraceptive composition comprising drospirenone wherein the *in vitro* dissolution rate of the said drospirenone is such that no more than 50% of the said drospirenone is dissolved within 30 minutes and such that at least 50% of the drospirenone is dissolved in a time range from 3 hours to 4 hours.

A time range from 3 hours to 4 hours encompasses a time range from 3,25 hours, to 3,5 hours, to 3,75 hours, to 4 hours.

At least 50% of the drospirenone encompasses at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, at least 88%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%.

In some embodiments, at least 60% of DRSP initially present is dissolved in a time range from 3 hours to 4 hours.

In some other embodiments, the said contraceptive composition is further characterized in that at least 70 % of the drospirenone is dissolved within 6 hours.

The applicant has shown that specific surface area of DRSP has a direct impact on the *in vitro* dissolution rate of drospirenone and its in vivo pharmacokinetic profile.

One way to obtain the DRSP-containing composition of the invention is to use drospirenone in a particle form having an appropriate specific surface area.

Drospirenone may be present in the pharmaceutical compositions of the invention in a non-micronized particle form.

It has been also shown that drospirenone in a particle form having a specific surface area from about 2000 cm^2/g to about 8500 cm^2/g may be suitable for obtaining the contraceptive compositions of the invention. The specific surface area may be experimentally determined using the BET method (gas adsorption method).

In some embodiments, the contraceptive composition of the invention comprises drospirenone in a particle form having a specific area from about 2000 cm^2/g to about 8500 cm^2/g.

Such a specific area range which includes values of about 2000 cm^2/g, 2500 cm^2/g, 3000 cm^2/g, 3500 cm^2/g, 4000 cm^2/g, 4500 cm^2/g, 5000 cm^2/g, 5500 cm^2/g, 6000 cm^2/g, 6100 cm^2/g, 6200 cm^2/g, 6300 cm^2/g,

6400 cm^2/g, 6500 cm^2/g, 6600 cm^2/g, 6700 cm^2/g, 6800 cm^2/g, 6900 cm^2/g, 7000 cm^2/g, 7500 cm^2/g, 8000 cm^2/g and 8500 cm^2/g.

Concerning the size particle distribution, drospirenone particles having a diameter greater than 200 µm shall be avoided in order to not drastically impair the *in vitro* dissolution rate and, thus, the *in vivo* bioavailability since such particles are poorly soluble.

Drospirenone may preferably have a d50 of less than 70 µm. In a preferred embodiment, the d50 of the drospirenone particles ranges from 10 µm to 60 µm.

A d50 ranges from about 10 µm to about 60 µm encompasses a d50 of 10 µm, of 15 µm, of 20 µm, of 25 µm, of 30 µm, of 35 µm, of 40 µm, of 45 µm, of 50 µm, of 55 µm and of 60 µm.

In some embodiments, the particle size distribution of the drospirenone present in the composition according to the invention is characterized by:

(i) a d90 particle size less than about 100 µm, and/or
(ii) a d50 particle size ranging from about 10 µm to about 60 µm and/or
(iii) a d10 particle size more than about 3 µm.

In some other embodiments, the d50 of drospirenone particles ranges from about 10 µm to about 30 µm. In such embodiments, the particle size distribution of the drospirenone present in the composition according to the invention is characterized by at least one of the following characteristics:

(i) a d90 particle size less than about 100 µm,
(ii) a d50 particle size ranging from about 10 µm to about 30 µm and
(iii) a d10 particle size more than about 3 µm.

As used herein, the term "about" before a "specific value" defines a range from "the specific value minus 10% of the specific value" to "the specific value plus 10% of the specific value". For example, "about 50" defines a range from 45 to 55.

As used herein, by "d90 particle size" is meant that the particle size distribution is such that at least 90% of the particles have a particle size diameter of less than the specified value.

As used herein, by "d50 particle size" is meant that the particle size distribution is such that at least 50% of the particles have a particle size diameter of less than the specified value.

As used herein, by "d10 particle size" is meant that the particle size distribution is such that at least 10% of the particles have a particle size diameter of less than the specified value

d90 particle size less than about 100 µm include d90 particle sizes less than about 90 µm, 80 µm, 70 µm, 60 µm, 55 µm, 50 µm, 45 µm, 40 µm, 38 µm, 36 µm, 34 µm, 32 µm, 30 µm, 28 µm, 26 µm, 24 µm, 22 µm, 20 µm.

d50 particle size values ranging from about 10 µm to about 30 µm include values of about 10 µm, 11 µm, 12 µm, 13 µm, 14 µm, 15 µm, 16 µm, 18 µm, 19 µm, 20 µm, 21 µm, 22 µm, 23 µm, 24 µm, 25 µm, 26 µm, 27 µm, 28 µm, 29 µm, 30 µm.

d10 particle size values more than about 3 µm include d10 particle size values more than about 3 µm, 3.5 µm 4.5 µm, 5 µm, 6 µm, 7 µm, 8 µm, 9 µm, 10 µm, 11 µm, 12 µm.

It goes without saying that d10 particle size value is smaller than d50 particle size value which is smaller than d90 particle value.

The drospirenone particle size distribution, in particular d90, d10 and d50 values, may be determined by well-kown methods of the prior art such as sieve analysis, laser diffraction methods, photoanalysis or optical counting methods. Laser diffraction methods are particularly preferred. As illustrated in the Example 1, the particle size distribution may be determined by laser diffraction in wet dispersion. The dispersant is preferably water.

In some embodiments, the pharmaceutical composition of the invention comprises drospirenone in a particle form having a particle size distribution having a combination of two characteristics selected from:

(i) a d90 particle size less than about 100 µm,

(ii) a d50 particle size ranging from about 10 µm to about 30 µm and

(iii) a d10 particle size more than about 3 µm.

In other words, the particle size distribution of DRSP display a combination of characteristics selected from characteristic (i) and

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characteristic (ii), characteristic (i) and characteristic (iii), and, characteristic (ii) and characteristic (iii).

In some other embodiments, the pharmaceutical composition of the invention comprising drospirenone in a non-micronized form having a particle size distribution characterized in that:

(i) d90 particle size is less than about 100 µm,

(ii) d50 particle size ranging from about 10 µm to about 30 µm and

(iii) d10 particle size is more than about 3 µm

In a preferred embodiment, the DRSP particle distribution is further characterized in that d90 particle size value is less than 50 µm and in that no particle has a size greater than 80 µm.

In some embodiments, the contraceptive composition of the invention comprises drospirenone in a particle form having a d90 particle size which ranges from about 20 µm to about 40 µm, a d50 particle size which ranges from about 10 µm to about 30 µm and a d10 which ranges from about 3 µm to about 9 µm and wherein no particle has a size greater than 80 µm, more preferably no particle has a size greater than 60 µm.

In some other embodiments, the contraceptive composition of the invention comprises drospirenone in a particle form having

(i) a d90 particle size which ranges from about 30 µm to about 40 µm,

(ii) a d50 particle size which ranges from about 15 µm to about 25 µm and

(iii) a d10 which ranges from about 5 µm to about 9 µm and wherein no particle has a size greater than 80 µm, more preferably no particle has a size greater than 60 µm.

For illustrative purpose, an appropriate particle size distribution of drospirenone according to the invention is shown in Figure 1.

In some other embodiments, the contraceptive composition of the invention comprises drospirenone in a particle form having a specific surface area from about 2000 cm^2/g to about 8000 cm^2/g and having a d50 particle size ranges from 10 µm to 60 µm.

To obtain drospirenone in a particle form having the specific surface area and/or the particle size distribution as described above, the one skilled in the art may use well-known methods of the prior art such as milling process optionally combined with sieve process.

For example, drospirenone, obtained by anyone of the synthesis methods described in the prior art, may be subjected to ball mill or hammer mill step optionally followed by a vibrating sieve steps. The subsequent vibrating sieve steps may remove finest and biggest particles of drospirenone which would impair the pharmacokinetic profile and the in vitro dissolution profile of drospirenone.

The one skilled in the art may adjust the parameters of the milling and sieve steps by routine experiments to obtain the appropriate particle form of drospirenone. Appropriate mills which may be used include fluid energy mill, ball mill or rod mill, hammer mill, cutting mill and oscillating granulator.

An appropriate particle form of drospirenone may be also prepared by crystallisation or precipitation process optionally combined with a sieve step in order to fully control the size of drospirenone particles. The precipitation process may comprise the steps of (i) dissolving drospirenone in a water-miscible solvent and then (ii) dispersing the resulting solution in cold water under stirring so that to induce the precipitation of drospirenone. The drospirenone particles may be then recovered by a filtration process.

The water-miscible solvents may be a solvent commonly used in crystallisation or precipitation process such as methanol, ethanol, isopropanol, dimethylformamide, tetrahydrofuran, dioxane or dimethyl sulfoxide, dimethylacetamide or acetone.

Such a process enables to obtain drospirenone essentially in crystallized form.

By routine experiments, the one skilled in the art may determine the parameters of the precipitation process to be used so as to obtain the appropriate form of drospirenone.

The one skilled in the art may adjust the parameters of the said precipitation process (such as the amounts of solvent, of water and optionally that of surfactant to be used) by routine experiments.

As described above, when the pharmaceutical composition of the invention is a contraceptive composition, the said composition may provide a pharmacokinetic profile of drospirenone such that the presence of an estrogenic compound to ensure the contraceptive efficiency of the said compositions is not required.

Accordingly, in preferred embodiments, the contraceptive composition of the invention does not comprise an estrogen, including phytoestrogen. As used herein, the term "estrogen" refers to compounds, such as ethinylestradiol, mestranol or the phytoestrogen 8-prenylnaringenin, that are able to bind and activate estrogen receptors. In other words, the DRSP is present in the contraceptive composition without estrogen, which means that DRSP is not associated with or combined with an estrogen as in the case of combined oral pill.

In some preferred embodiments, drospirenone is the sole contraceptive ingredient comprised in the contraceptive compositions i.e. the sole active ingredient able to prevent pregnancy when administered to a female patient of child-age bearing.

However, in some specific embodiments of the present invention, drospirenone may be combined with one or more progestogens.

The term "progestogen", as used herein, refers to any compound that binds and activates the progesterone receptor.

Progestogens include, but are not limited to, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17α-ethinyltestosterone and derivatives thereof, 17α-ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone acetate, levonorgestrel, norgestrel, d-17α -acetoxy-13β-ethyl-17α-a-ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene, desogestrel, etonorgestrel, norgestimate, norelgestromin, chlormadione and dienogest.

In some other embodiments, the drospirenone may be combined with one or more active ingredients which do not have contraceptive activities. Such active ingredients include, without being limited to,

antiemetic agents, vitamines such as folic acid, vitamine B12, vitamine D, minerals and oligo elements such as iron, iodine, selenium and others.

The contraceptive composition of the invention comprises drospirenone in an amount corresponding to a daily dosage which prevents pregnancy when the said contraceptive composition is administered to a woman over a single treatment period of 21 to 28 days.

As described in the Example 3 related to a clinical trial, the Applicant showed that the oral administration of a single daily dosage unit of a composition according to the invention and comprising 3 mg of DRSP enables to obtain a mean $AUC_{0h\text{-}tlast}$ value of 368 ng*h/ml, which corresponds to 88% of the mean $AUC_{0h\text{-}tlast}$ resulting from the oral administration of a single dose of Yasminelle®.

In a preferred embodiment, the pharmaceutical composition of the invention is a contraceptive composition which comprises drospirenone in an amount corresponding to a daily dose of at least 2 mg of drospirenone. At least 2 mg of drospirenone encompasses at least 3 mg of drospirenone, at least 3.5 mg of drospirenone, at least 4 mg of drospirenone.

In some embodiments, the active daily dosage unit which consists of the contraceptive composition as describes above may comprise a DRSP amount ranging from about 2 mg to about 6 mg.

A daily dose ranging from about 2 mg to about 6 mg encompasses daily doses of 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5.0 mg, 5.5 mg, 6 mg.

In a preferred embodiment, the contraceptive composition of the invention comprises DRSP in an amount corresponding to a daily dosage which ensures ovulation inhibition when the said contraceptive composition is administered to a woman over a single treatment period of 21 to 28 days.

Preferably, the daily dose of drospirenone ranges from about 3 mg to about 6 mg, more preferably from 3 mg to 4.5 mg. In some embodiments, the amount of drospirenone corresponds to a daily dose of about 4.0 mg.

However, the daily dose of drospirenone to be administered to a female patient in need thereof may also be adjusted depending on

individual factors such as the age, the body weight, the general health and the diet of the female patient. The said daily dose may also vary upon the drug interaction which may occur. The said daily dose may also vary upon the additional biological effect(s), other than the prevention of pregnancy, which may be sought through the administration of DRSP.

The daily dose of drospirenone to be daily administered to a female patient may be lower or higher than the doses previously mentioned. For example, a female patient in peri-menopause may require a higher or lower daily dosage of drospirenone, in order to improve her general conditions and, for example, in order to improve the regularity of her menstrual cycles.

The adjustment of the daily dosage may be routinely determined by practitioners.

In a preferred embodiment, the pharmaceutical composition of the invention further comprises one or more pharmaceutically acceptable excipients.

The pharmaceutical composition of the invention may be formulated according to standard methods such as those described in Remington: The Science and Practice of Pharmacy (Lippincott Williams & Wilkins; Twenty first Edition, 2005)

Pharmaceutically acceptable excipients that may be used to formulate the contraceptive composition of the invention are, in particular, described in the Handbook of Pharmaceuticals Excipients, American Pharmaceutical Association (Pharmaceutical Press; 6th Revised edition, 2009).

Examples of appropriate excipients include, but are not limited to, fillers, carriers, diluents, binders, anti-caking agents, plasticizers, disintegrants, lubricants, flavors, buffering agents, stabilizers, colorants, dyes, anti-oxidants, anti-adherents, softeners, preservatives and glidants.

In some embodiments, the contraceptive composition of the invention comprises one or more excipients selected from the group of binders, fillers, glidants and lubricants.

Examples of fillers include, without being limited to, lactose anhydrous, microcrystalline cellulose, starch, pregelatinized starch, modified starch, dibasic calcium phosphate dihydrate, calcium sulfate

trihydrate, calcium sulfate dihydrate, calcium carbonate, lactose, dextrose, sucrose, mannitol and sorbitol and combinations thereof.

Examples of lubricants include, without being limited to, magnesium stearate, calcium stearate, zinc stearate, talc, propylene glycol, PEG, stearic acid, vegetable oil, sodium benzoate, sodium lauryl sulfate, magnesium lauryl sulfate, mineral oil polyoxyethylene monostearate and combinations thereof.

Examples of binders include, without being limited to, starches, e.g., potato starch, wheat starch, corn starch; gums, such as gum tragacanth, acacia gum and gelatin; microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropylmethyl cellulose; polyvinyl pyrrolidone and combinations thereof.

Examples of glidants include silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

In a preferred embodiment, the pharmaceutical composition according to the invention do not comprises a significant amount of surfactant agent. A significant amount of a surfactant agent may impair the *in vitro* dissolution profile of DRSP by increasing its initial rate of dissolution. Surfactant agents include non-ionic surfactants such as polyoxyethylene sorbitan fatty acid esters and ionic surfactants such as sodium lauryl sulphate.

In some embodiments, the pharmaceutical composition of the invention comprises drospirenone, at least one binder and at least one filler wherein:

(i) the amount of drospirenone accounts for 1% to 10% by weight

(ii) the amount of the at least one binder accounts for 50% to 65% by weight and

(iii) the amount of the at least one filler accounts for 25% to 35% by weight,

the percentages by weight being related to the total weight of the said contraceptive composition.

In some embodiments, the said contraceptive composition further comprises at least one glidant and at least one lubricant wherein:

(iv) the amount of the at least one glidant accounts for 0.2% to 6% by weight and

(v) the amount of the at least one lubricant accounts for 0.2% to 0.6% by weight

the percentages by weight being related to the total weight of the said contraceptive composition.

It goes without saying that the drospirenone to be used may be in a particle form having the specific surface area and/or the d90, d10 and d50 particle sizes which are fully-described in the present specification.

The said contraceptive composition may optionally comprise additional excipients which may accounts for about 0.1 % to 10% by weight.

In some other embodiments, the contraceptive composition of the invention comprises drospirenone, at least one binder, at least one filler, at least one glidant, and at least on lubricant wherein:

(i) the at least one binder is microcrystalline cellulose

(ii) the at least one filler is anhydrous lactose

(iii) the at least one glidant is silicon dioxide and

(iv) the at least one lubricant is magnesium stearate.

The contraceptive composition according to the invention may be formulated in a galenic form suitable for oral administration. Such forms include, without being limited to, tablets, caplets, granules, pills, capsules, powders and suspension.

In preferred embodiments, the contraceptive composition is formulated in a solid form for oral administration such as tablets, capsules, granules, caplets and pills.

Such solid forms are particularly appropriate to be used as daily active dosage unit in the contraceptive kit according to the present invention.

When the pharmaceutical composition is formulated in solid forms such as tablets or pills, the said solid forms may be conveniently coated with a suitable film-forming agent such as hydroxypropylmethyl cellulose, hydroxypropyl cellulose or ethyl cellulose, to which a suitable excipient may optionally be added, e. g. a softener such as glycerol, propylene glycol, diethylphthalate or glycerol triacetate, a filler such as sucrose, sorbitol, xylitol, glucose or lactose, or a colorant such as titanium hydroxide, etc.

The pharmaceutical composition in the form of tablets, pills or granules may be prepared by conventional methods such as direct compression, dry granulation and wet granulation.

In some embodiments, the solid forms are obtained by direct compression.

A further object of the invention is to provide a method for preparing the contraceptive composition as described herein which comprises the steps consisting of:

(i) providing drospirenone in a particle form as fully-described previously in the present specification

(ii) providing one or more pharmaceutically acceptable excipients; and

(iii) mixing the drospirenone provided in step (i) with the one or more excipients provided in step (ii).

As fully-described above, the Applicant provides technical guidelines to obtain a composition comprising DRSP in a form such that:

(i) no more than 50% of the drospirenone initially present in the said composition is dissolved within 30 minutes and

(ii) at least 50% of the said drospirenone is dissolved in a time range from 3 hours to 4 hours,

when the composition is subjected to an *in vitro* dissolution test, the percentages of drospirenone being related to the amount of drospirenone initially present in the said composition.

A DRSP containing composition with such an *in vitro* dissolution profile or the in vivo pharmacokinetic profile fully-described above may be achieved by various other ways.

By routine experiments and in view of his general knowledge, the one skilled in the art may modify (i) the particle size distribution of DRSP and (ii) the amounts and the nature of excipients in order to obtain other alternative compositions displaying the *in vitro* dissolution profile and the *in vivo* pharmacokinetic profile described in the present application.

For example, the one skilled in the art may conceive a composition comprising (i) micronized DRSP together with (ii) a slow release agent in order to diminish the dissolution rate of said DRSP.

The one skilled in the art may also contemplate to combine (i) large particles of DRSP together with (ii) a surfactant and/or a wetting agent in order to ensure the dissolution of said DRSP.

In a general aspect, non-micronized and essentially crystallized form DRSP is preferably used for preparing the pharmaceutical composition of the invention.

2. Contraceptive methods

When orally administered, the pharmaceutical composition of the invention provides a significantly improved pharmacokinetic profile for drospirenone characterized by a similar $AUC_{[0h\text{-}tlast]}$, a delayed t_{max} and a reduced C_{max} as compared to that obtained with Yasminelle®.

In order to conceive contraceptive based on the said pharmaceutical composition, the presence of an estrogen such as ethinylestradiol or 8-prenylnaringenin is not required to ensure the ovulation inhibition and the cycle stability.

Moreover it is expected that such compositions may be more reliable than POPs described in the prior art.

The contraceptive compositions of the invention which do not comprise an estrogen are thus particularly appropriate to be used as progestogen-only contraceptive.

Accordingly, another object of the present invention is the use of the pharmaceutical composition as described herein for preparing a contraceptive progestogen-only pill or for preparing a contraceptive kit.

A further object of the present invention is to provide an oral contraceptive method for a female patient in need thereof characterized in that it comprises the step of administering active daily dosage units consisting of a pharmaceutical composition as fully-described herein to the said female patient over a period of several consecutive days preferably over a period of 21 to 28 days.

As used herein a contraceptive method relates to a method for preventing pregnancy.

As used herein, "an active daily dosage unit" means a dosage unit which is able to prevent pregnancy when daily administered to a female patient over a period selected from periods of 21 to 28 consecutive days.

In preferred embodiments, the active daily dosage unit is able to inhibit ovulation when daily administered to a female patient over a period selected from periods of 21 to 28 consecutive days

As used herein, a female patient refers to a woman of child-bearing age i.e. from the puberty to the menopause. Women of child-bearing age also include women in peri-menopause.

In a preferred embodiment, the said daily dosage units do not comprise an estrogen.

In some embodiments, the drospirenone is the sole contraceptive ingredient comprised in the said contraceptive composition.

The contraceptive method of the invention is generally performed for a period time corresponding to the average length of a menstrual cycle i.e. 28 days and may be iterated during several consecutive months, even, for several years.

In some embodiments, the contraceptive method of the invention consists in administering "continuously" daily dosage units of the invention. Such a method does not comprise a free-contraceptive period i.e. a period in which no contraceptive is administered.

In other embodiments, the contraceptive method of the invention comprises two consecutive phases:

- a first phase wherein active daily dosage units of the invention which do not comprise estrogen are administered to the female patient over a period of 21 to 27 consecutive days and
- a second phase wherein no contraceptive composition is administered to the female patient over a period of 1 to 7 consecutive days.

As used herein a period of 1 to 7 consecutive days include periods of 1 day, of 2 consecutive days, of 3 consecutive days, of 4 consecutive days, of 5 consecutive days, of 6 consecutive days, and of 7 consecutive days.

As used herein a period of 21 to 27 consecutive days include periods of 21 consecutive days, of 22 consecutive days, of 23 consecutive days, of 24 consecutive days, of 25 consecutive days, of 26 consecutive days, and of 27 consecutive days.

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As mentioned above, the duration of the first phase plus the second phase is preferably 28 days.

In the first phase, the composition of active daily dose units may remain constant, in particular in respect to the daily amount of drospirenone.

In some other embodiments, the composition of the active daily dose units may vary, in particular, in respect to the daily amount of drospirenone.

The second phase is a free-contraceptive period i.e. a phase during which no contraceptive ingredients is administered to the female patient. During the said second phase, daily placebo dosage units may be administered to the female patient. In some other cases, no pill is administered to the female patient.

Such a second phase may enable regular menstrual bleedings to occur and thus may enable to mimic the natural menstrual cycle.

Moreover, the said second phase is believed to enable the secretion of endogenous estradiol which may have some benefits on bone metabolism of the female patient.

As used herein, the term "active daily dosage unit" refers to physically discrete units suitable as unitary dosage which consists of a contraceptive composition as fully described hereabove in the present specification. As mentioned previously, the active daily dosage unit may generally comprise a drospirenone amount of about 3.0 mg to about 6.0 mg, more preferably, of about 3.5 mg to about 4.5 mg.

In some embodiments, the first phase of the contraceptive method lasts from 21 to 24 consecutive days and the second phase of the contraceptive method lasts from 4 to 7 consecutive days.

In some embodiments, the first phase of the contraceptive method lasts 24 consecutive days and the second phase of the contraceptive method lasts 4 consecutive days.

The contraceptive method of the invention may provide a high contraceptive efficiency without the disadvantages (i.e spottings, irregular bleedings...) observed for marketed progestogen-only contraceptive methods such as cerazette®.

The said contraceptive method may exhibit a higher reliability than other progestogen-only contraceptive methods by allowing the patients to be a bit less compliant with treatment (i.e. allowing episotic missing pills) without risking unwanted pregnancy (see Example 4 hereunder).

The contraceptive method of the invention is suitable for women of child-bearing age.

It should be noticed that the contraceptive method of the invention may be suitable for women whose health conditions is not compatible with high peak of drospirenone plasma concentration. Such women include, without being limited to, subjects with renal impairment, women predisposed to hyperkalemia and subjects who concomitantly take potassium sparing drugs.

The contraceptive method of the invention is also particularly suitable for women for whom the administration of estrogens is not recommended. Such women include, without being limited to, women predisposed to cardiovascular disorders, women who smoke and breast-feeding women.

3. Contraceptive kits

The present invention also provides a contraceptive kit based on the contraceptive compositions as fully-described in the present application. Such a kit is particularly suitable for use in the contraceptive methods as described above.

The said contraceptive kit comprises one or more packaging units. One or more packaging units includes, without being limited to, 1 packaging unit, 2 packaging units, 3 packaging units, 4 packaging units, 5 packaging units and 6 packaging units.

Each packaging unit comprises from 21 to 28 daily active dosage units. As fully described above, each daily active dosage unit consists of a contraceptive composition of the invention.

In some embodiments, the contraceptive kit comprises one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein each daily active dosage unit comprises drospirenone in a non-micronized particle form such that:

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(i) no more than 50% of the drospirenone initially present in the said daily active dosage unit is dissolved within 30 minutes and

(ii) at least 50% of the said drospirenone is dissolved in a time range from 3 hours to 4 hours,

when the daily active dosage unit is subjected to an *in vitro* dissolution test, the percentages of drospirenone being related to the amount of drospirenone initially present in the said daily active dosage unit

In other embodiments, the contraceptive kit comprises one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein the oral administration of a daily active dosage unit provides a pharmacokinetic profile for DRSP characterized by the following features:

(i) a mean t_{max} of at least about 2.2 h and

(ii) a mean C_{max} which is less than about 30 ng/ml,

In some embodiments, the oral administration of the said daily active dosage unit provides a pharmacokinetic profile further characterized by a mean AUC $_{0h\text{-}tlast}$ of at least 300 ng*ml/h, more preferably of at least 350 ng*ml/h.

As fully described above, the daily active dosage units preferably do not comprise any estrogen or estrogen derivative such as ethinyl estradiol, mestranol or 8-prenylnaringenin. In other words, the DRSP is preferably present in the daily active dosage units without estrogen.

In more preferred embodiments, DRSP is the sole contraceptive ingredient comprised within the daily active dosage units.

In some other embodiments, contraceptive kit comprises one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein:

(a) the amount of the drospirenone in each daily active dosage unit is at least 2 mg, without estrogen, and

(b) the oral administration of a daily active dosage unit provides a pharmacokinetic profile for DRSP characterized by the following features:

(i) a mean t_{max} ranges from 2.2 h to 6h and

(ii) a mean C_{max} which is less than about 30 ng/ml.

In other embodiments, the contraceptive kit comprises one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein

(a) the amount of drospirenone in each daily active dosage unit is at least 2 mg without estrogen, and

(b) each daily active dosage unit comprises drospirenone in a form such that:

(i) no more than 50% of the drospirenone initially present in the said daily active dosage unit is dissolved within 30 minutes and

(ii) at least 50% of the said drospirenone is dissolved in a time range from 3 hours to 4 hours,

when the daily active dosage unit is subjected to an *in vitro* dissolution test according to the USP XXIII Paddle Method, the percentages of drospirenone being related to the amount of drospirenone initially present in the said daily active dosage unit.

Each packaging unit optionally comprises from 1 to 7 daily dosage units of a pharmaceutically acceptable placebo.

In some embodiments, the contraceptive kit is characterized in that each packaging unit comprises 28 daily dosage units and no daily dosage unit of a pharmaceutically acceptable placebo. Such a contraceptive kit is particularly appropriate to perform the contraceptive method of the invention which consists in administering "continuously" DRSP without free-contraceptive period (see hereabove paragraph 2).

In other embodiments each packaging unit comprises:

- 21 to 27 active daily dosage units consisting of a contraceptive composition as fully described in the present application and
- optionally, 1 to 7 daily dosage units of a pharmaceutically acceptable placebo

Such a contraceptive kit is particularly appropriate to perform the contraceptive method of the invention which comprises

- a first phase wherein active daily dosage units of the invention which do not comprise estrogen are administered to the female patient over a period of 21 to 27 consecutive days followed by
- a second phase wherein no contraceptive composition is administered to the female patient over a period of 1 to 7 consecutive days.

In some other embodiments, each packaging unit of the kit comprises 24 daily dosage units comprising an effective amount of a contraceptive composition as described herein and, optionally, 4 daily dosage units of a pharmaceutically acceptable placebo.

The packaging unit as described above may have one of the conventional forms usually used for oral contraceptives.

For example, the packaging unit may be a conventional blister pack comprising the appropriate number of dosage units in a sealed blister pack with a cardboard, paperboard, foil or plastic backing and enclosed in a suitable cover. Each blister container may be conveniently numbered or marked in order to facilitate compliance.

The packaging unit may contain daily dosage units in the order in which they are to be taken, i.e. starting with the first of the at least 21 dosage units that contain the combination of drospirenone optionally followed by 7 or less empty blisters or by 7 or less dosage units that comprise a pharmaceutically acceptable placebo.

The kit of the invention may comprise other appropriate components such as instructions for use.

The following examples are illustrative and are not intended to limit the scope of the invention as claimed.

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EXAMPLES

Example 1: Preparation of tablets

a. Preparation of drospirenone

Drospirenone was prepared according to a process similar to that described in WO2006/061309. In order to obtain DRSP with an appropriate particle size distribution, DRSP was subjected to an additional process of precipitation as mentioned in the present application.

Five batches of DRSP were prepared by variants of the above-mentioned precipitation process.

The analysis of the particle size distribution of each batch was performed by laser diffraction method in wet dispersion (Helos sensor, Sympatec with the wet disperser Quixel). The dispersant used was water. The full particle dispersion was ensured by ultrasonication.

The specific area was determined by BET method. The results obtained are shown in table 1.

Table 1: particle size distribution parameters and specific area of DRSP batches

	DRSP Batch				
	PR100003	**080169**	**080204**	**080257**	**080053**
d50 (µm)	22.4	24.5	13.1	12.6	19.8
d90 (µm)	37.4	37.1	24.8	23.4	34.2
d10 (µm)	5.9	2.9	4.4	5.3	7.2
d99 (µm)	56.1	48.9	34.5	35.3	44.8
Specific area (m^2/g)	0.26	0.45	0.83	0.77	0.63

The cumulative distribution function and the probability density function for batch 080053 are shown in Figure 1.

b. <u>Preparation of tablets according to the present invention</u>

The tablets are prepared by direct compression. The composition of tablets is described hereunder.

Table 2: composition of tablets (A-3mg, inventive)

Material	mg/tablet	(%)
Drospirenone (Batch 080053)	3.00	4.74
Microcrystalline cellulose 102	36.48	57.60
Anhydrous lactose DCL21	20.16	31.83
Silicon dioxide	3.36	5.31
Magnesium stearate	0.33	0.53
TOTAL	**63.33**	**100.00**

Example 2: In vitro dissolution profiles

a. Comparaison of tablets A-3mg (inventive) with Yasminelle® (comparative)

The rate of dissolution of drospirenone from the tablets prepared in Example 1 (A-3mg) was determined by the USP XXIII Paddle Method using a USP Dissolution Test Apparatus 2 including 6 covered glass vessels and 6 paddles.

Tablets were placed in 900 ml water at a temperature of 37°C± (0.5°C) and stirred at 50 rpm. The amount of drospirenone released in water was measured over several hours. The mean percentages of DRSP released (which were related to the amount of drospirenone initially present in the each tablet) were calculated and plotted versus time in order to provide the *in vitro* dissolution profile of DRSP.

The *in vitro* dissolution profile of tablets A-3mg (inventive) is shown in Figure 2 (see curve n°2).

Figure 2 also provides the dissolution profile obtained for Yasminelle® tablets which comprised micronized DRSP (comparative) (see curve n°4).

It appears that the initial dissolution rate for tablets obtained in Example 1 (A-3mg) was significantly reduced as compared to that of Yasminelle® tablet since only about 22% of DRSP initially present in tablets were released within 30 min (versus almost 100% for Yasminelle® in 30 min). The final dissolution percentage of DRSP from tablets obtained in Example 1 was more than 80%. As described in Example 3, Part 1, such an *in vitro* dissolution profile is correlated with an improved pharmacokinetic profile as compared to Yasminelle®.

b. Examples of other in vitro dissolution profiles

In order to illustrate the correlation between the in vitro dissolution profile of drospirenone and its pharmacokinetic profile upon oral administration, two other types of DRSP-containing tablets (comparative) were prepared. The composition of these tablets is distinct from that of tablet A-3 mg. Each tablet comprises 3 mg of DRSP in a non-micronized form.

The first type of tablet (CO1-3mg) provides a rapid dissolution in vitro since about 60% of DRSP initially present in tablets were released within 30 min according to the USP XXIII Paddle Method (see curve n°3, Figure 2).

The second type of tablet (CO2-3mg) displays a very low dissolution rate of DRSP in vitro. No more than of 5% of DRSP initially present in tablets were released within 30 min and no more than about 40% of the said DRSP was dissolved within 4 hours (see curve n°1, Figure 2).

Example 3: Pharmacokinetic studies

Part 1: Evaluation of the pharmacokinetics parameters for the composition according to the invention (tablet A-3mg) as compared to Yasminelle®

Objectives:

The main objective of the present trial was to assess the bioavailability of an oral test preparation containing drospirenone 3.0 mg (tablets described in Example 1 obtained from batch 080053 (i.e. A-3mg), called hereunder "test product" hereunder) as compared to a market standard (YASMINELLE®, Schering AG, called hereunder "reference product") after oral administration of a single dose of drospirenone 3.0 mg under fasting conditions in two different periods, 7 days apart. Yasminelle® comprises 3.0 mg DRSP in micronized form and 0.030 mg of ethinylestradiol.

In order to investigate the relative bioavailability of the products, the 90% confidence intervals for the intra-individual ratios (test vs. reference) for the endpoint(s) (AUC0-tlast and Cmax of drospirenone) were determined.

The secondary objective of the present trial was to investigate the safety of both preparations on the basis of safety clinical and laboratory examinations (at the beginning and at the end of the trial) and registration of adverse events and/or adverse drug reactions.

Methodology:

The study was conducted as a monocentric, open, randomized, single-dose, two-period crossover trial in healthy female volunteers, with duration of hospitalization of approximately 12 h - 13 h after dosing on day 1 and with a real wash-out period of 7 days.

Subjects (planned and analyzed):

- planned for completion: 10
- enrolled: 19
- screened only: 5
- randomized: 14
- drop-outs: 0
- completed as per protocol: 14
- data set for pharmacokinetic analysis: 14
- data set for statistical analysis: 14
- data set for safety analysis: 14

Diagnosis and main criteria for inclusion:	[1] female Caucasian [2] age between 18 and 40 years [3] physically and mentally healthy as judged by means of a medical, standard laboratory and gynecological examination [4] non-smokers since at least 6 months (confirmed by urine cotinine test) [5] use of an effective non-hormonal method of contraception List of accepted contraceptive methods - combination of two barrier methods (female/male condoms, diaphragms, spermicides) - intrauterine device (inert or copper-releasing IUD) - existing sterilization (female tubal occlusion)

Duration of treatment:

Each volunteer received in a random way an oral single dose of 1 tablet of the test product or 1 of the reference drug on two single occasions, always under fasting conditions.

Both study periods were separated by a real wash-out phase of at least 7 days.

Blood sampling points in each study period:

Pre-dose, and 0:30, 1:00, 1:30, 2:00, 3:00, 4:00, 5:00, 6:00, 8:00, 12:00, 24:00, 48:00 and 72:00 hours post dosing with separation of plasma.

For each endpoint, the quantification of DRSP in plasma was performed according to an analytical method adapted from Kirk et al., Rapid Communications in mass Spectrometry, 2006, 20:1247-1252.

Briefly, Drospirenone was extracted from human EDTA plasma using a solid-phase extraction procedure with HLB 60 mg Oasis cartridges and afterwards derivatized with Girard-P solution, then injected into a liquid chromatograph equipped with a tandem mass spectrometry detector. This method enables the determination of drospirenone in human EDTA plasma over the range 0.25 to 100.40 ng/mL.

Criteria for evaluation:

Pharmacokinetics:

Primary endpoints: AUC0-tlast and Cmax of drospirenone

Secondary endpoint: t_{max} of drospirenone

Additional endpoints: not planned

Safety

Adverse events, clinical and laboratory screening parameters.

Statistical methods:

For pharmacokinetic endpoints:

- parametric method (ANOVA-log) for AUC0-tlast and Cmax of drospirenone
- covariates in the model: sequence, treatment, period, volunteer within sequence
- non-parametric method (Hauschke et al. 1990) t_{max} of drospirenone
- 90% confidence interval for the ratios (test vs. reference) for AUC0-tlast and Cmax of drospirenone

For evaluation of safety:

- descriptive statistical evaluation only.

Bioavailability:

The 90% confidence intervals of log-transformed values were calculated for the intra-individual ratio test vs. reference for AUC0-tlast and Cmax of drospirenone a then only interpreted in a descriptive way and not compared with

the usual acceptance ranges for the respective parameters (CPMP/EWP/QWP/1401/98, July 2001) as the current trial did not have the aim of proving bioequivalence). The 90% confidence interval was calculated for the intra-individual ratio for the difference of t_{max} (test-reference) and descriptively assessed.

RESULTS

Pharmacokinetics:

A total number of 14 volunteers completed the trial according to the protocol. The samples of 14 volunteers were analyzed and 14 volunteers were subject to statistical evaluation. The endpoints of the analysis of drospirenone after an oral single dose of 1 tablet (=drospirenone 3.0 mg) of the test preparation or 1 film-coated tablet (=0.03 mg/3 mg ethinyl estradiol and drospirenone) of the reference product of the 14 volunteers who were subject to pharmacokinetic and statistical evaluation are summarized in table 3 hereunder.

Table 3: Pharmacokinetic endpoints (primary, secondary, and additional) of drospirenone for test product (TEST) and reference product (REFERENCE).

TEST (N=14)						
Variable	geom.mean	arithm.mean	SD	CV	range	median
AUC0-tlast [ng*h/mL]	360.96	368.55	75.83	20.6	234.72 - 482.91	359.33
AUC0-inf [ng*h/mL]	452.93	462.00	93.26	20.2	312.60 - 624.12	463.65
AUCres [%]	19.12	20.04	6.62	33.0	12.13 - 33.70	17.70
Cmax [ng/mL]	16.46	17.36	5.50	31.6	6.39 - 27.79	17.41
tmax	-	3.57	1.01	28.3	2.00 - 5.00	3.50
MRT [h]	-	44.08	9.69	22.0	33.64 - 64.18	40.89
$t^{1/2}$ [h]	-	31.87	6.29	19.7	24.59 - 44.43	29.42
REFERENCE (N=14)						
Variable	geom.mean	arithm.mean	SD	CV	range	median
AUC0-tlast [ng*h/mL]	414.60	418.58	60.46	14.4	337.80 - 527.81	397.70
AUC0-inf [ng*h/mL]	503.65	509.25	77.76	15.3	386.08 - 654.48	510.74
AUCres [%]	17.12	17.58	4.18	23.8	11.19 - 27.61	18.47
Cmax [ng/mL]	34.91	35.43	6.32	17.8	24.30 - 45.96	35.24
tmax	-	1.57	0.55	35.0	1.00 - 3.00	1.50
MRT [h]	-	38.81	6.45	16.6	29.68 - 56.00	39.39
$t^{1/2}$ [h]	-	29.78	4.41	14.8	25.21 - 43.30	28.47

The 90% confidence intervals for the intra-individual ratios (test/reference) for $AUC_{0\text{-tlast}}$ and C_{max} of drospirenone, as well as differences (test-reference) for t_{max} of drospirenone are presented in table 4 hereunder.

Table 4: 90% confidence intervals of drospirenone

Variable	Point estimator	confidence limits***	ANOVA-log (%)
AUC0-tlast (ratio test/reference)	0.8706*	0.8081 - 0.9380*	11.1%
Cmax (ratio test/reference)	0.4715*	0.3930 - 0.5658*	27.6%
tmax [h] (difference test-reference)	1.7650**	1.5000 - 2.5000**	-
* : parametric confidence interval ** : non-parametric confidence interval *** : 14 volunteers subjected to statistical evaluation			

The concentration-time curves of drospirenone after administration of an oral single dose of 1 tablet of the test preparation and tablet of the reference product are to be found in Figure 3a for both preparations (arithmetic means).

The evaluation of bioavailability of the primary endpoints AUC0-tlast and Cmax of drospirenone was based on a parametric method (ANOVA-log).

The 90%-confidence interval calculated by means of ANOVA-log for the first primary endpoint, intra-individual ratio (T/R) of AUC0-tlast of was between 0.8081 and 0.9380. The 90%-confidence interval calculated by means of ANOVAlog for the second primary endpoint intra-individual ratio (T/R) of Cmax of drospirenone was between 0.3930 and 0.5658.

Concerning the secondary endpoint t_{max} the 90%-confidence interval for the intra-individual differences was between 1.5000 and 2.5000 hours. The point estimator for the difference of t_{max} of drospirenone was 106 minutes (the concentration maxima after administration of the test preparation being observed later).

It is well known in the art that drospirenone isomerizes into a biologically inactive isomer in acidic conditions, including in the acidic conditions that are encountered in the human stomach.

When conducting the present pharmacokinetics study, assays for detecting the eventual presence of the inactive isomer of drospirenone in the plasma of the treated women have been performed. The results have

shown that the amount of the inactive isomer of drospirenone in the plasma samples collected from the clinically tested women subjects was below the detectable level (< 1 ng/ml), which means that the pharmaceutical composition that has been used is adapted to release the full amount of drospirenone in its biologically active form to the target organs.

Safety:

The test formulation and the reference drug were well tolerated. Seventeen non-serious adverse events (AEs) were registered in 11 subjects in the course of the trial:

- nine AEs were observed in 8 subjects after administration of test product
- eight AEs were observed in 7 subjects after administration of reference drug.

All adverse events were assessed as not serious. All adverse events were assessed as possible related by the investigator. All AEs resolved completely within relative short frame time. The results of laboratory screening gave no indications for adverse events or adverse drug reactions.

CONCLUSIONS

Based on $AUC_{0\text{-tlast}}$ of drospirenone, the extent of absorption of the test product is similar to that of the reference product but the rate of absorption is significantly delayed resulting in increased t_{max} and decreased C_{max}. The tolerability of test product and the reference product was similarly good.

Part 2: Evaluation of other comparative tablets CO1-3mg et CO2-3mg as compared to Yasminelle ®

The main objective of this second trial was to further illustrate the correlation between in vitro dissolution profile and pharmacokinetics parameters for oral tablets comprising DRSP.

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The oral test tablets were tablet CO1-3mg and tablet CO2-3mg which display a rapid in vitro dissolution rate for DRSP and a very slow dissolution rate for DRSP, respectively (see Example 2b).

The reference product was Yasminelle®. The methodology for this second trial was similar to that of the trial described in part 1 hereabove.

Briefly, the bioavailability of two oral test preparations (namely CO1-3mg and CO2- 3mg) as compared to that of the market standard (JASMINELLE, Schering AG) was assessed after oral administration of a single tablet in each case (corresponding to 3 mg of DRSP) under fasting conditions in three different periods, 7 days apart. In order to investigate the relative bioavailability of the products, the 90% confidence intervals for the intraindividual ratios (CO1-3mg vs. reference product and CO2-3mg vs. reference product) for the endpoint(s) ($AUC_{0\text{-tlast}}$ and C_{max} of drospirenone) were determined.

The study was conducted as a monocentric, open, randomized, single-dose, three-period crossover trial in healthy female volunteers, with duration of hospitalization of approximately 12 h - 13 h after dosing.

Each volunteer received in a random way an oral single dose of drospirenone 3.0 mg (either 1 test tablet CO1-3mg or 1 test tablet CO2-3mg or 1 film-coated tablet of Yasminelle®) on three single occasions under fasting conditions.

The three study periods were separated by a real wash-out phase of between 7 days and 10 days.

Subjects (planned and analyzed):

- planned for completion: 10
- enrolled: 18
- screened only: 4
- randomized: 14
- drop-outs: 0
- completed as per protocol: 14
- data set for pharmacokinetic analysis: 14
- data set for statistical analysis: 14
- data set for safety analysis: 14

RL

RESULTS

The concentration-time curves of drospirenone after administration of an oral single dose of 1 tablet of each product (namely, CO1-3mg, CO2-3mg and Yasminelle®) are to be found in Figure 3b (arithmetic means).

For reminder, CO1-3mg displayed a rapid dissolution rate for DRSP in vitro (about 60% within 30 min). As expected, the pharmacokinetic profile obtained for CO1-3mg is very close to that of Yasminelle® except for C_{max}. Interestingly, the mean Cmax of CO1-3mg was 30 ng/ml versus 36 ng/ml for Yasminelle®. The $AUC_{0h\text{-}tlast}$ for CO1-3mg was similar to that of Yasminelle® (410.58 ng*h/ml versus 440.14 ng*h/ml).

On the other hand, CO2-3 mg displays a very low dissolution rate of DRSP in vitro since no more than of 5% of DRSP initially present in tablets were released within 30 min and no more than about 40% of the said DRSP was dissolved within 4 hours. As expected, said composition displays a reduced C_{max} and a delayed t_{max} as compared to Yasminelle®. However, the mean AUC of said composition was low. Said composition may be not appropriate to be used as progestogen-only pill since it may provide a low contraceptive reliability.

These pharmacokinetics results combined with *in vitro* results described in Example 2 illustrate the correlation between the *in vitro* dissolution rate of DRSP and its pharmacokinetics profile (in particular for C_{max} and t_{max}), upon oral administration.

Example 4: Simulation curves based on experimental data obtained in the clinical trial described in Example 3, Part 1.

The DRSP mean plasma concentration versus time curves, which is expected to be obtained from the oral administration of one tablet described in table 2 but containing 4 mg of DRSP from batch 80053 (namely, A-4mg), was extrapolated from experimental data obtained in the clinical trial described in Example 3 with the assumption that the DRSP plasma concentration is proportional to the administered oral amount of DRSP.

The resulting curve for tablet A-4mg is shown in Figure 3a and Figure 4a and compared with that obtained with Yasminelle® and with the tablet A-3mg described in table 2.

As illustrated in Figure 4a and 4b, increasing the DRSP amount from 3 mg to 4 mg in the tablet described in table 2 is expected not to modify the t_{max} which may remain significantly delayed as compared to that of Yasminelle®. C_{max} is expected to be increased but to remain significantly lower than that of Yasminelle® (no more than 60 % that of Yasminelle ®). Interestingly, the mean plasma concentration is expected to be higher than that of Yasminelle® after the concentration peak.

Figure 4c shows the mean DRSP plasma concentration versus time curves which are expected to result from the repeated administration every 24 hours of one tablet of Yasminelle® (curve n°1), that of one tablet A-3mg (curve n°3) and that of one tablet A-4mg (curve n°2).

The curves obtained for the compositions of the invention (namely curves n°3 and n°2) show less difference between mean C_{max} and mean C_{min} (minimal DRSP concentration) than Yasminelle® composition. The repeated administration of the compositions of the invention is thus expected to provide more stable DRSP plasma concentration with lower C_{max} than Yasminelle®. Such a fact is expected to improve the bleeding profile and to reduce the side effects of DRSP when the compositions of the invention are used as contraceptive.

In the case of tablet A-4mg, it should be underlined that the mean plasma concentration is expected to be higher than that obtained of Yasminelle® for the time period between t_{max} and the time of the next tablet intake, which provides a higher contraceptive reliability.

Thus, Tablet A-4mg is expected to be appropriate to be used as progestogen-only pill.

Example 5: Another example of composition according to the invention

Part 1: In vitro dissolution profile

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Tablets (B-4mg) were prepared as described in Example 1 from DRSP batch N° PR100003. Each tablet comprises 4.0 mg of DRSP and excipients in a similar amount to that described in Table 1. The tablets (B-4mg) were further coated with a suitable film-forming agent, as described in the specification.

The resulting tablets were subjected to a dissolving in vitro test as described in Example 2. The mean *in vitro* dissolution profile of said tablets is shown in Figure 5a.

The initial dissolution rate for DRSP was significantly reduced as compared to Yasminelle® since only about 22% of DRSP initially present in tablets were released within 30 min. However, about 66% and about 77% of DRSP initially present in tablets were released within 4h and 6h respectively.

The in vitro dissolution profile for tablets B-4mg was similar to that of tablet A-3mg (see example 1). Such a fact illustrates that the specific area of DRSP does not significantly impair its in vitro dissolution if the said DRSP displays appropriate d50, d90 and d10.

Part 2: Evaluation of the pharmacokinetics parameters for the composition according to the invention (tablet B-4mg) as compared to Yasminelle®

a. Methodology

The pharmacokinetics parameters for tablet B-4mg were determined as described in Example 1, part 1.

Briefly, the bioavailability of the test preparation (namely B-4mg) as compared to that of the market standard (JASMINELLE, Schering AG) was assessed after oral administration of a single tablet in each case under fasting conditions in three different periods, 7 days apart.

The DRSP oral dose was 3 mg for Yasminelle® versus 4 mg for tablet B-4mg (inventive).

In order to investigate the relative bioavailability of the products, the 90% confidence intervals for the intraindividual ratios (B-4mg versus Yasminelle®) for the endpoint(s) ($AUC_{0\text{-}tlast}$ and C_{max} of drospirenone) were determined.

4✓

The study was conducted as a monocentric, open, randomized, single-dose, three-period crossover trial in healthy female volunteers, with duration of hospitalization of approximately 12 h - 13 h after dosing.

Each volunteer received in a random way an oral single dose of drospirenone (either one test tablet B-4mg or one tablet of Yasminelle®) on two single occasions under fasting conditions.

Both study periods were separated by a real wash-out phase of between 7 days and 10 days.

Subjects (planned and analyzed):
- planned for completion: 10
- enrolled: 15
- screened only: 5
- randomized: 10
- drop-outs: 0
- completed as per protocol: 10
- data set for pharmacokinetic analysis: 10
- data set for statistical analysis: 10
- data set for safety analysis: 10

b. Results

Yasminelle® and the test product were well-tolerated by all the patients.

The concentration-time curves of drospirenone after administration of an oral single dose of 1 tablet of each product (namely, tablet B-4mg and Yasminelle®) are to be found in Figure 5b (arithmetic means). The results of said trial are further shown in table 5 hereunder.

Table 5: Pharmacokinetic endpoints of drospirenone for tablet B-4mg (TEST) and Yasminelle® (REFERENCE)

TEST (N=10)						
Variable	**geom.mean**	**arithm.mean**	**SD**	**CV**	**range**	**median**
AUC0-tlast [ng*h/mL]	428.07	438.85	104.53	23.8	320.74 – 634.58	419.05
Cmax [ng/mL]	18.96	19.81	6.14	31.0	12.42 – 30.17	19.40
tmax [h]	-	3.900	0.876	22.5	3.000 – 5.000	4.000
REFERENCE (N=10)						
Variable	**geom.mean**	**arithm.mean**	**SD**	**CV**	**range**	**median**
AUC0-tlast [ng*h/mL]	386.68	394.88	90.22	22.8	271.57 – 615.65	391.49
Cmax [ngh/mL]	32.52	32.85	4.85	14.8	23.97 – 42.80	33.39

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tmax [h]	-	1.700	0.979	54.1	1.000 – 4.000	1.500

The pharmacokinetics profile for DRSP obtained after the oral administration of one tablet B-4mg correlated with the DRSP pharmacokinetics profile expected on the basis of simulations (see Example 4).

As expected, mean t_{max} for tablet B-4mg was significantly delayed as compared to that of Yasminelle® (3.9 h versus 1.7 h). Furthermore, the mean C_{max} obtained for tablet B-4mg was significantly lower than that of Yasminelle® (19.8 versus 32.9 ng*h/ml).

Mean C_{max} for tablet B-4mg corresponded to about 58% of Yasminelle® C_{max} whereas, in Example 1, mean C_{max} for tablet A-3mg corresponded to 49% of that of Yasminelle® : the increase of DRSP dose in tablets did not induce a significant change in mean C_{max} values.

On the other hand, the increase of DRSP dose significantly improved the mean $AUC_{0h\text{-}tlast}$ since the mean $AUC_{0h\text{-}tlast}$ for tablet B-4mg was 111% of Yasminelle. In Example 1, the mean $AUC_{0h\text{-}tlast}$ for tablet A-3mg was only 86% of that of Yaminelle®.

In other words, the present results clearly show that compositions of the invention enable to obtain a high value of mean $AUC_{0h\text{-}tlast}$ combined with a low mean C_{max} and a delayed mean t_{max} for DRSP as compared to Yasminelle®.

The repeated administration of tablets B-4mg every 24 hours will certainly provide a DRSP plasma concentration profile similar to that expected for tablet A-4mg (see figure 4C, curve n°2).

To conclude, pharmaceutical tablets of the invention, such that tablet A-4mg and tablet B-4mg, are likely to be appropriate to be used as contraceptive-only pills. Such contraceptives are expected to have a good tolerance and to prevent the occurrence of side-effects related to high and fluctuated DRSP plasma concentrations

Part 3: Evaluation of the contraceptive efficiency of the pharmaceutical composition according to the invention

The aim of the study is to illustrate that a contraceptive pill according to the invention which comprises DRSP as the sole

contraceptive agent and which is administered upon a 24/4 regimen enables to inhibit ovulation even in the case of episodic delayed of pill.

The contraceptive pill is made of 24 tablets B-4mg as defined in Example 5, Part 2 hereabove and 4 placebo tablets.

a. Methodology

The study was an open-label monocentric trial.

Subjects eligible for the study were aged 20-30 years, had a body mass index < 30 kg/m², regular menstrual cycles (at least 4 regular cycles in the past 6 months) and were willing to use condoms during the entire duration of the study. Excluded were subjects with a (suspected) pregnancy, active or past thromboembolic disorder, present or past severe hepatic disease, carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia, undiagnosed vaginal bleeding, use of liver enzyme-inducing drugs and other drugs.

A total of 20 women were enrolled in this trial and performed the two treatment cycles and the follow-up cycle.

Table 6 : Parameters of enrolled patients

	Age	Weight (kg)	BMI (Kg/m²)	Systolic blood pressure (mmHg)	Diatolic blood pressure (mmHg)	Heart rate (beats/mm)
Mean ± Std dev	24.6 ± 2.4	60.28± 7.95	22.76 3.19	110.3 ± 10.3	64.1 ± 7.0	65.4 ± 5.7
Median	24.5	59.1	22.39	115.0	62.5	64.0
Min, Max	20 ; 29	50.0 ; 79.2	18.1 ; 30.0	90 ; 120	50 ; 80	58 ; 80

Subject received daily treatment with tablets containing 4 mg DRSP with a 24/4 regimen during two cycles. The subjects started treatment on the 1st day of the cycle (i.e. .the first day of onset of vaginal bleeding) following the screening visit. The subjects took one tablet of 4 mg DRSP from day 1 to day 24 and one placebo tablet from day 25 to day 28 of each treatment cycle at a fixed hour, with the exception of day 5 and day 13 of the second cycle. On these two days, the tablet intake was delayed for 24 hours (i.e. that no pill was taken on day 5 and day 13

and that 2 tablets were taken on day 6 and day 14, respectively). The complete study consisted of a 56-day treatment period and a 28-day post-treatment follow-up period. After informed consent was obtained, subjects underwent a gynecological examination and a general medical examination, 12-lead ECG, hematology, biochemistry and urinalysis laboratory tests. After compliance with the eligibility criteria was confirmed, and after performing a urine pregnancy test with a negative result on the first day of onset of vaginal bleeding, the subject was included in the study and started to take the study medication.

Blood sampling for hormonal determination (progesterone, 17-beta-estradiol, FSH and LH) was performed every 3 days from day 1 to day 84 and assessments of weight, blood pressure and heart rate were performed at each visit. Serum progesterone, 17-beta-estradiol, FSH and LH concentrations were measured with validated commercial in vitro diagnostic kits (VIDAS, ELFA Biomerieux). Internal controls were included in each set of samples.

Two urine pregnancy tests were performed during the study:

- at the visit on day 1 of the first cycle in order to verify the exclusion criterion "pregnant woman" just before starting the study treatment: the subject was to be excluded if this test was positive.
- at the visit on day 7 of the follow-up cycle.

The occurrence of ovulation during treatment was determined on the basis of serum progesterone concentration, using the criteria of Landgren et al. Thus, an ovulation was judged to have occurred in case of progesterone concentrations > 5.04 ng/ml- sustained for at least 2 consecutive progesterone samples.

b. Results

Figures 6a and 6b show the plotted individual values for plasma progesterone levels and plasma estradiol levels, respectively.

For all the women, progesterone level values were systematically lower than 5.04 ng/ml during all the treatment period (including placebo period). The maximum value of progesterone was observed to be 3 ng/mL for a sole woman and for only one time during the treatment periods (including placebo period).

These results show that during the 2 cycles, no ovulation occurred. Conversely, upon cessation of treatment, during the 28-day follow-up cycle, the progesterone levels increased above 5.04 ng/mL in 17 out of 20 women showing a return of ovulation. The minimum time to the first level of progesterone to be above 5,04 ng/mL was on day 15 after the last placebo tablet.

During the 2 cycles under treatment, the mean estradiol levels were significantly lower in comparison with those measured during the follow-up cycle.

Noticeably, the secretion of estradiol is not totally inhibited during the treatment period.

To conclude, these data confirm that the composition of the invention, when used as a POP upon a 24/4 regimen provided reliable inhibition of ovulation even in the presence of placebo period. This ovulation inhibition was maintained even if the intake of the tablet was delayed for 24 hours in two separate times within one cycle.

In view of these experimental data, it is expected that the only-progestogen contraceptive of the invention exhibits similar reliability and efficiency as traditional combined pill such as Yasmine® with less side-effects on cardiovascular system.

Example 6: another example composition according to the invention

Tablets comprising 4 mg of drospirenone (C-4mg) are prepared by direct compression. The composition of tablets is described hereunder.

Table 7: Composition of tablets (C-4mg, inventive)

Material	mg/tablet
Drospirenone (PR100311)	4.00
Microcrystalline cellulose PH102	33.02
Anhydrous lactose PS =20%, <45 µm	17.50
Silicon dioxide	0.29
Magnesium stearate	0,33

Coating (Opadry II 85F18422 white)	1.65
TOTAL	**56.75**

DRSP batch PR100311 is characterized by a specific area of 0.66 m^2/g. The in vitro dissolution rate and the pharmacokinetic parameters for these tablets were determined as described in Example 2 and Example 3, respectively.

Table 8: In vitro DRSP dissolution rate and DRSP pharmacokinetic profile for tablets C-4mg

In vitro Dissolution	% of DRSP dissolved within 30 min	45.8
	% of DRSP dissolved within 4h	88.3
Pharmacokinetics	Mean C_{max} (ng/ml)	26
	Mean t_{max} (h)	3.6
	Mean $AUC_{0\text{-}tlast}$ (ng*h/mL)	643

CLAIMS

1. A contraceptive kit comprising one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein

(a) each daily active dosage unit comprises drospirenone in an amount of at least 2 mg, without estrogen, and

(b) a single daily active dosage unit, when orally administered under fasting conditions, is adapted to provide a pharmacokinetic profile for drospirenone having:

(ii) a mean t_{max} ranges from 2.2 h to 6h and

(ii) a mean C_{max} which is less than about 30 ng/ml

2. A contraceptive kit according to claim 1 wherein the said pharmacokinetic profile for drospirenone has a $AUC_{0h\text{-}tlast}$ which is at least 300 ng.h/ml, preferably at least 350 ng.h/ml.

3. A contraceptive kit according to anyone of claims 1 and 2 wherein the mean C_{max} ranges from 15 ng/ml to 30 ng/ml.

4. A contraceptive kit comprising one or more packaging units wherein each packaging unit comprises 21 to 28 daily active dosage units and wherein

(a) the amount of drospirenone in each daily active dosage unit is at least 2 mg without estrogen, and

(b) each daily active dosage unit comprises drospirenone in a form such that:

(i) no more than 50% of the drospirenone initially present in the said daily active dosage unit is dissolved within 30 minutes and

(ii) at least 50% of the said drospirenone is dissolved in a time range from 3 hours to 4 hours,

when the daily active dosage unit is subjected to an *in vitro* dissolution test according to the USP XXIII Paddle Method, the

percentages of drospirenone being related to the amount of drospirenone initially present in the said daily active dosage unit

5. The contraceptive kit according to anyone of claims 1 to 4 wherein the drospirenone is the sole contraceptive ingredient.

6. The contraceptive kit according to anyone of claims 1 to 5 wherein the amount of drospirenone in each daily active unit dosage ranges from about 2.0 mg to about 6.0 mg, preferably from about 3.0 mg to about 4.5 mg.

7. The contraceptive kit according to anyone of claims 1 to 6 wherein the one or more packaging units further comprise from 1 to 7 daily dosage units of a pharmaceutically acceptable placebo

8. The contraceptive kit according to anyone of claims 1 to 7 wherein each packaging unit comprises 24 daily active dosage units.

9. The contraceptive kit according to claim 8 further comprising 4 daily placebo dosage units.

10. A contraceptive method for a female patient in need thereof comprises the step of administering active daily dosage units as defined in anyone of claims 1 to 9 to said female patient over a period of 21 to 28 consecutive days.

11. A contraceptive method according to claim 10 comprising two phases:

- a first phase wherein active daily dosage units are administered to the female patient over a period of 21 to 27 consecutive days, followed by
- a second phase wherein no contraceptive is administered to the female patient over a period of 1 to 7 consecutive days.

12. The contraceptive method according to claim 11 wherein daily placebo dosage units are administered during the said second phase

13. The contraceptive method according to claim 11 or claim 12 wherein the first phase lasts 24 consecutive days and the second phase lasts 4 consecutive days.

14. A pharmaceutical composition comprising drospirenone wherein:

(a) a daily active dosage unit of said composition comprises an amount of drospirenone of at least 2mg, without estrogen, and

(b) a single daily active dosage unit, when orally administered under fasting conditions, is adapted to provide a pharmacokinetic profile for drospirenone having:

(ii) a mean t_{max} ranges from 2.2 h to 6h, and

(ii) a mean C_{max} which is less than about 30 ng/ml

for use as a contraceptive for a female patient in need thereof.

15. A pharmaceutical composition comprising drospirenone wherein:

(a) a daily active dosage unit of said composition comprises an amount of drospirenone of at least 2mg, without estrogen, and

(b) the said daily active dosage unit comprises drospirenone in a form such that:

(i) no more than 50% of the drospirenone initially present in the said daily active dosage unit is dissolved within 30 minutes, and

(ii) at least 50% of the said drospirenone is dissolved in a time range from 3 hours to 4 hours,

when the daily active dosage unit is subjected to an *in vitro* dissolution test according to the USP XXIII Paddle Method, the percentages of drospirenone being related to the amount of drospirenone initially present in the said daily active dosage unit, for use as a contraceptive for a female patient in need thereof.

16. A pharmaceutical composition according to claim 14 or claim 15 wherein the daily dosage units of the composition are administered as defined in anyone of claims 10 to 13.

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ORIGINAL

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14 DEC. 2012

PAR PROCURATION

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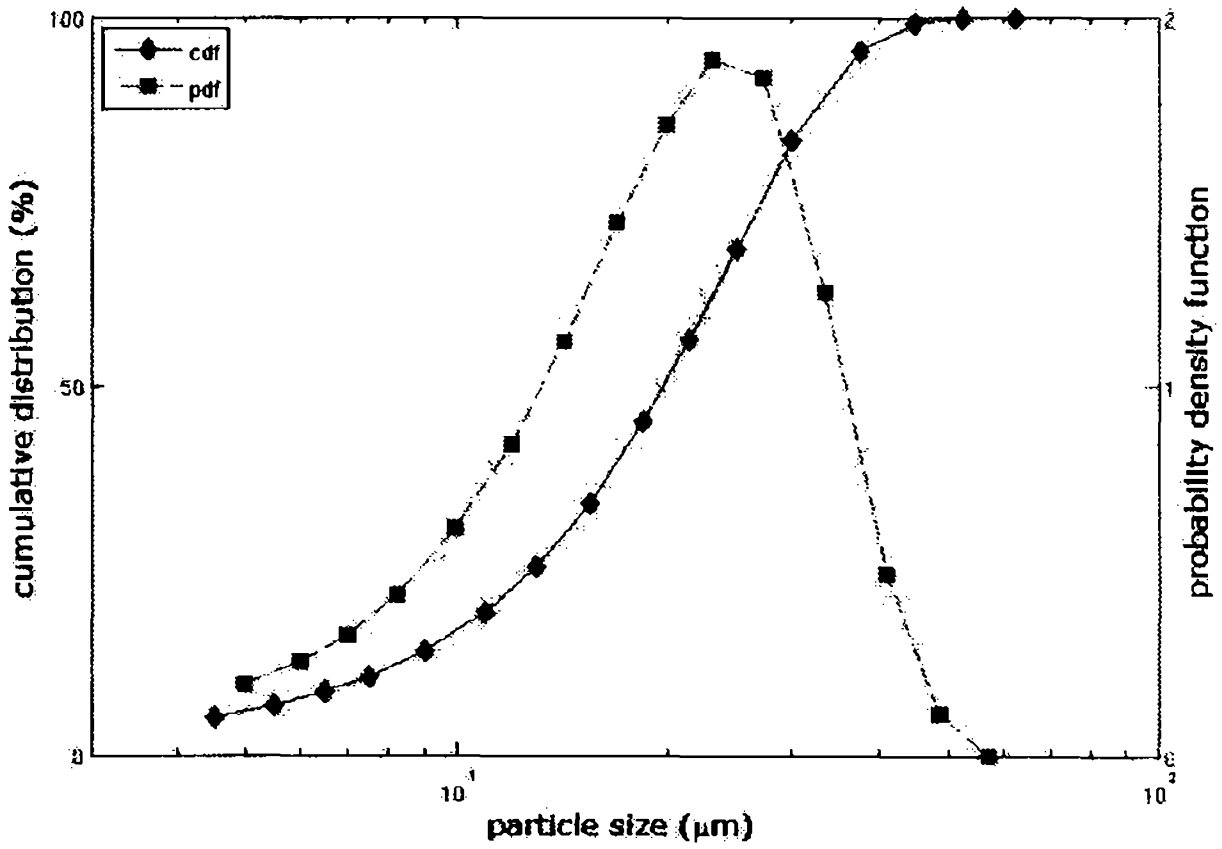

Figure 1

14 DEC. 2012

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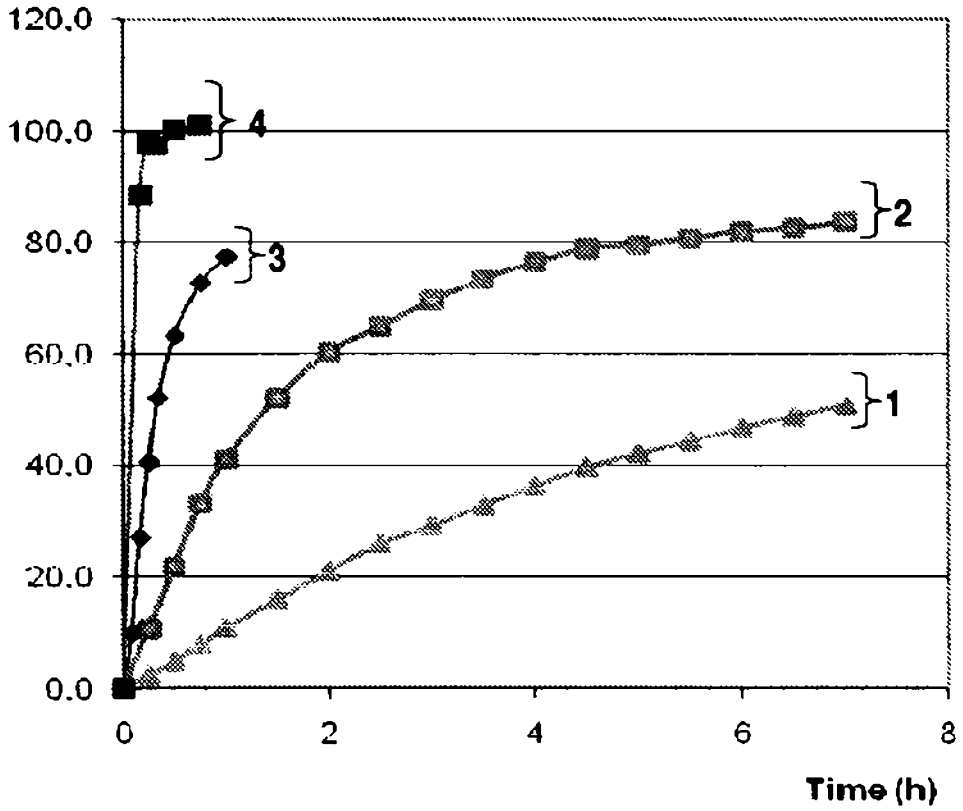

Figure 2

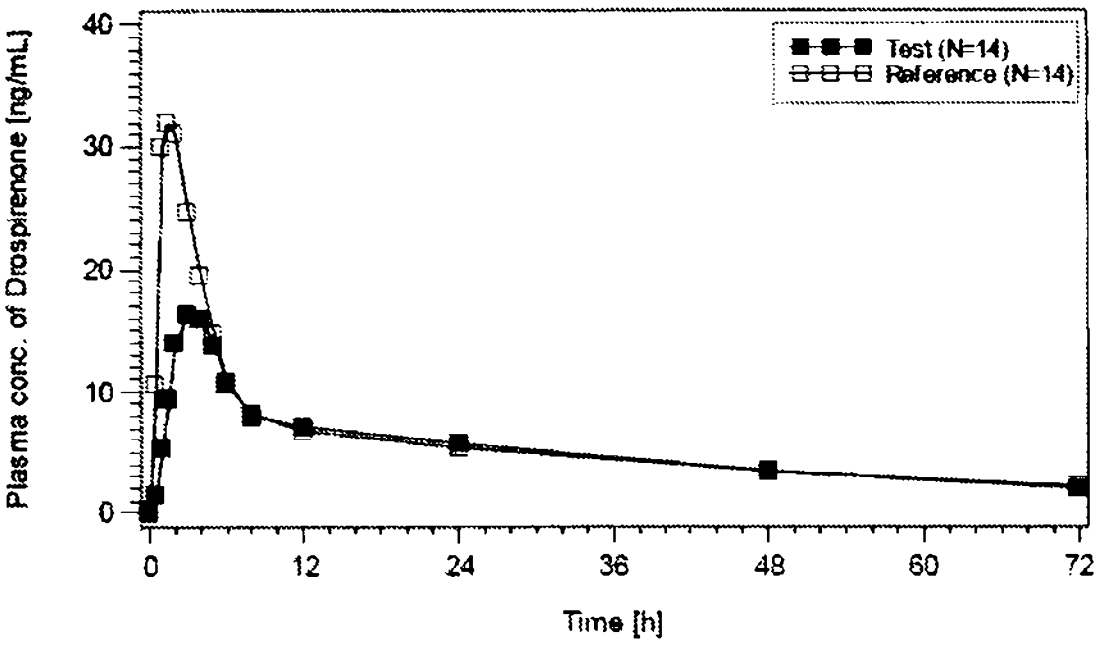

Figure 3a

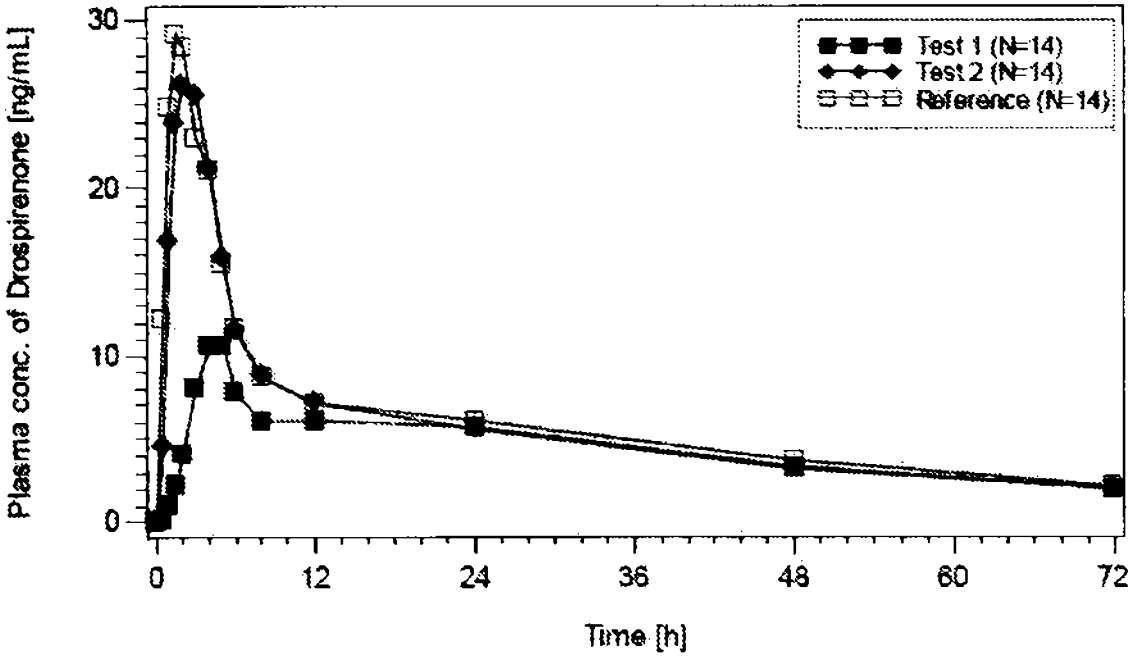

Figure 3b

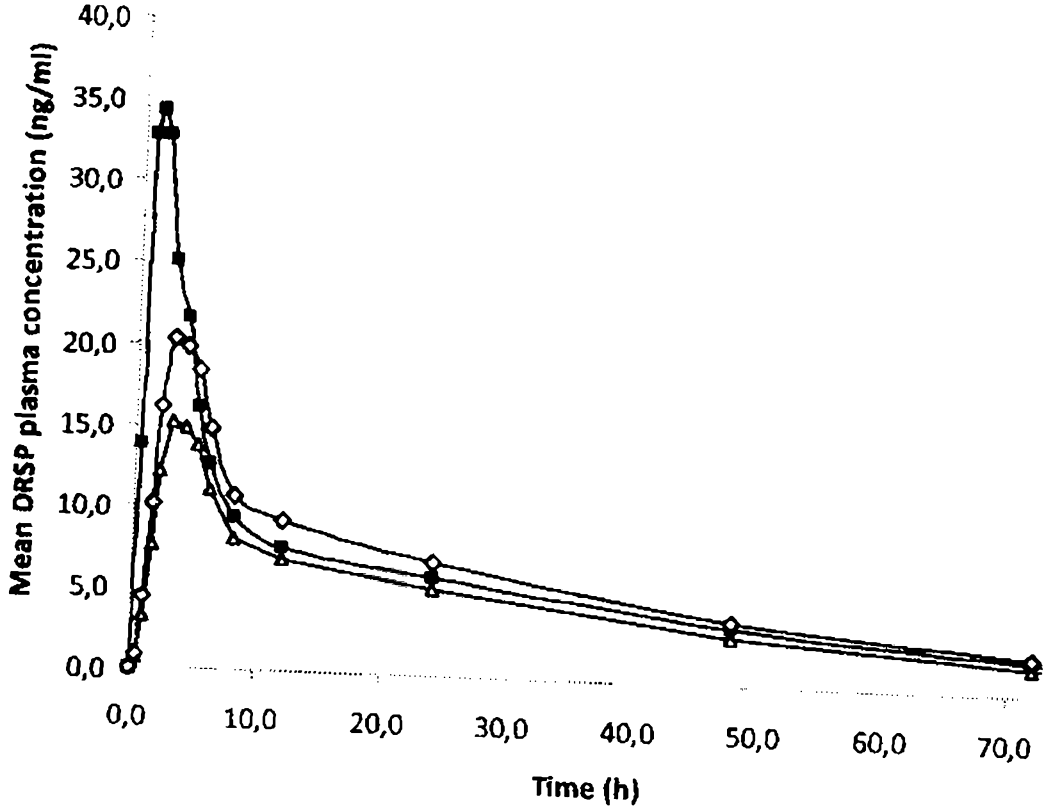

Figure 4a

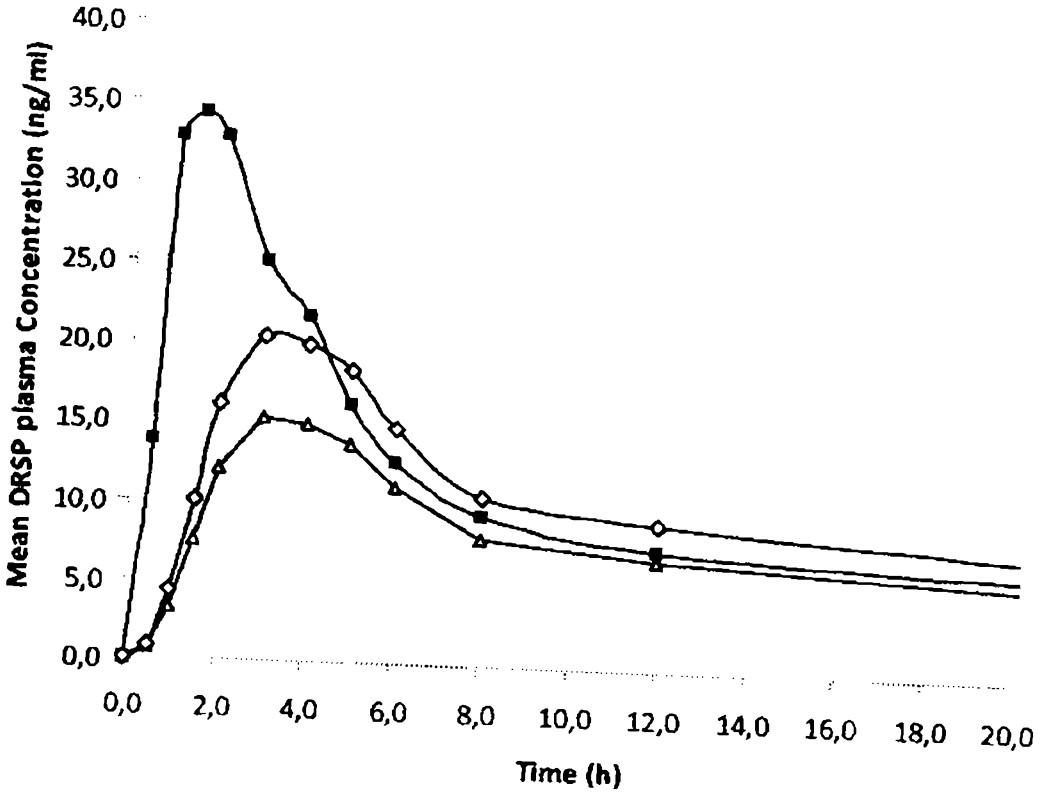

Figure 4b

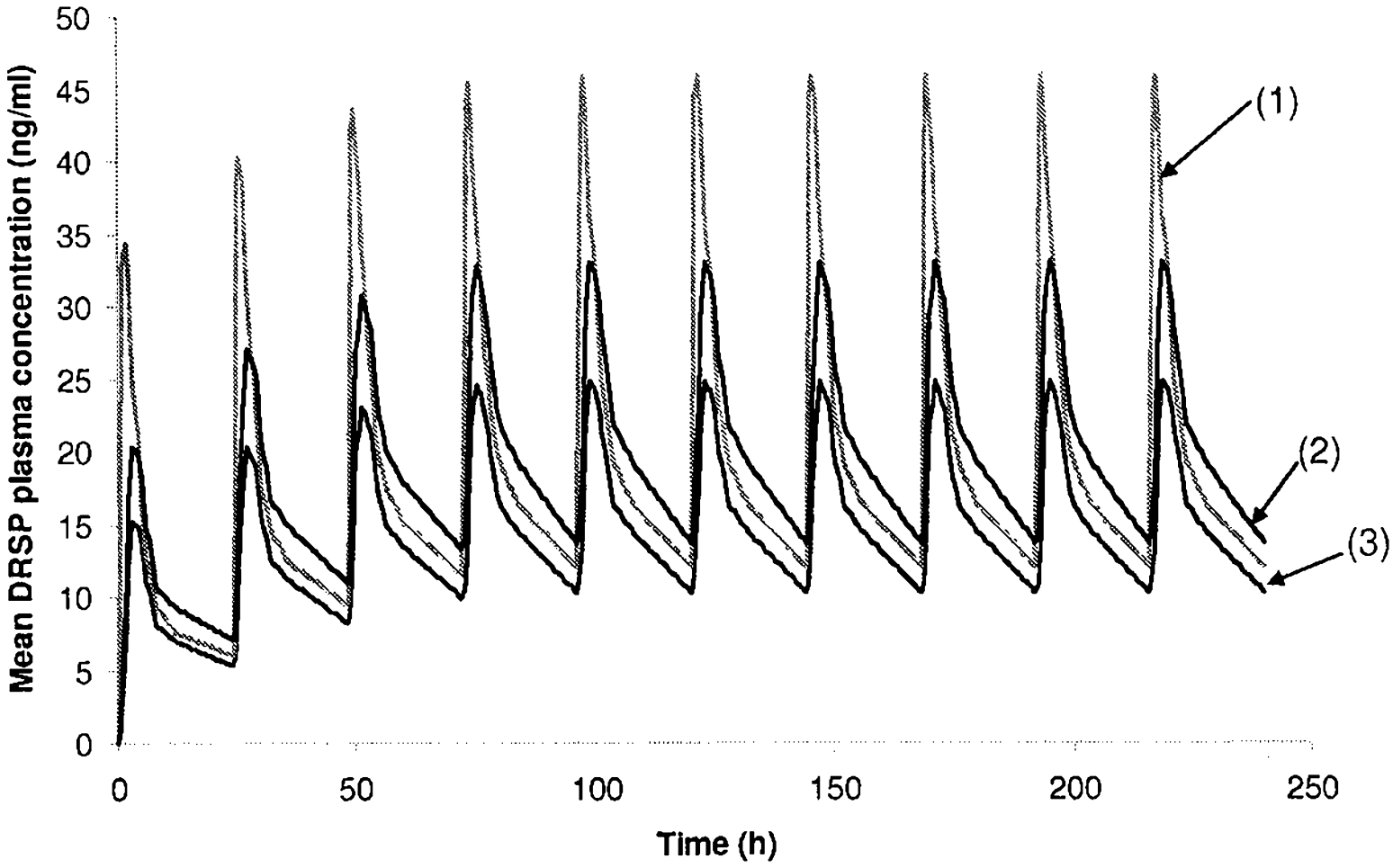

Figure 4c

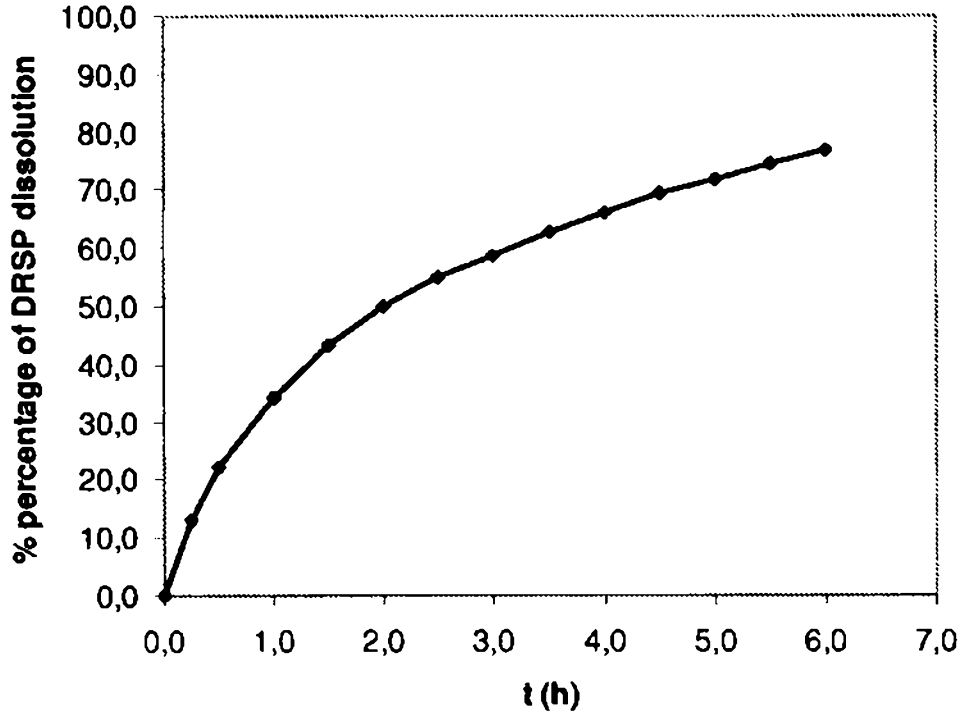

Figure 5a

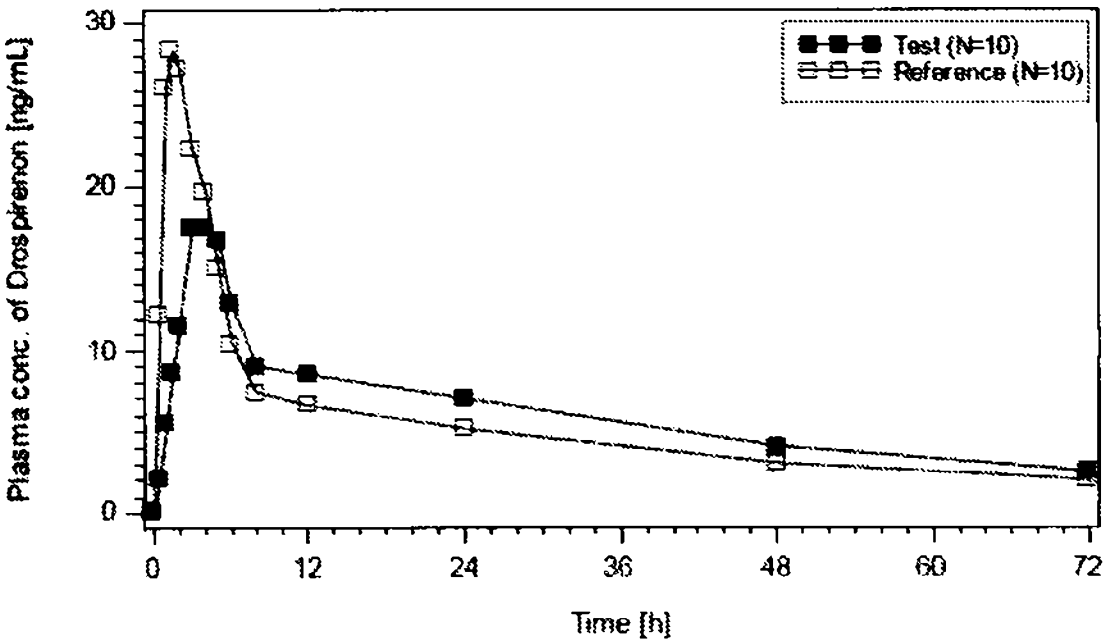

Figure 5b

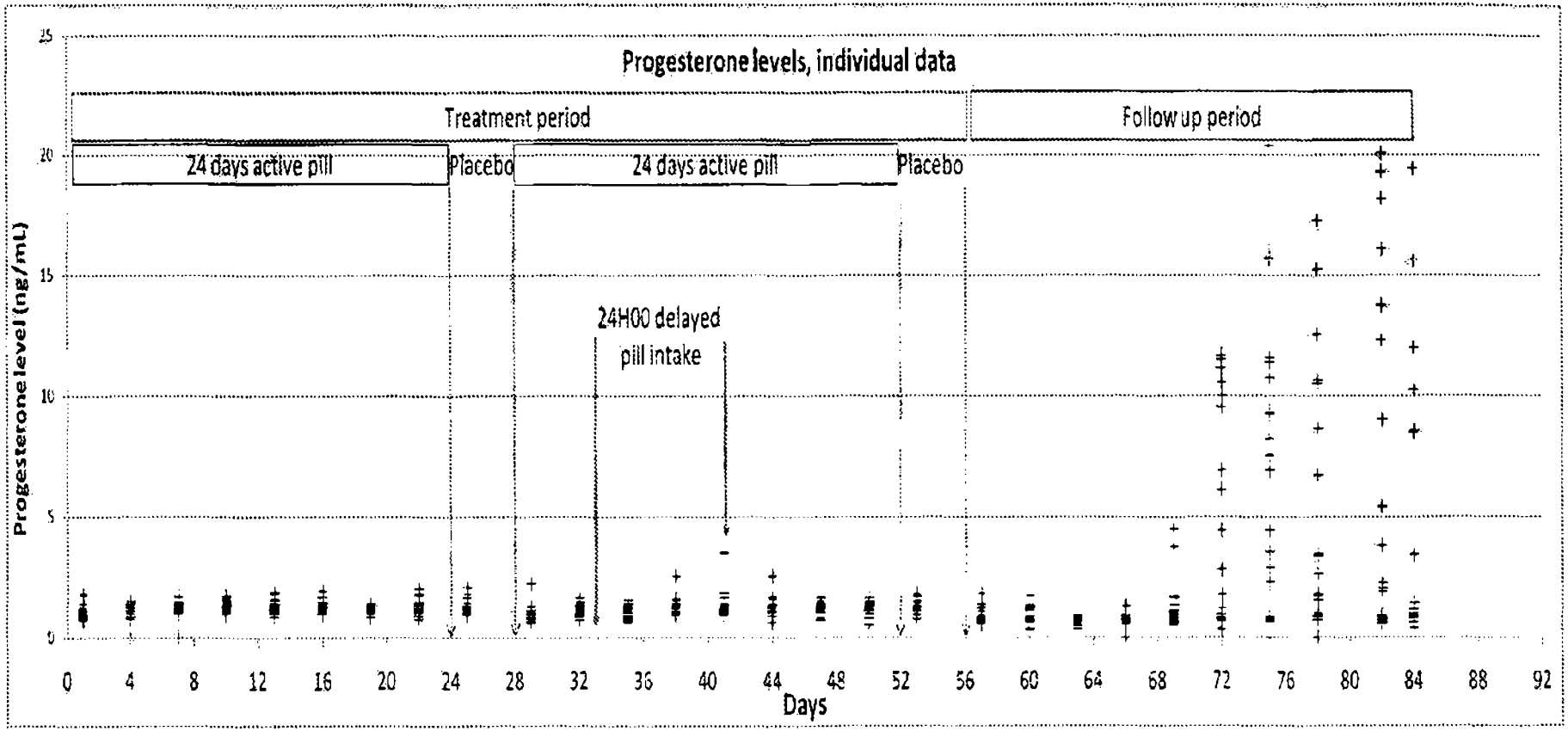

Figure 6a

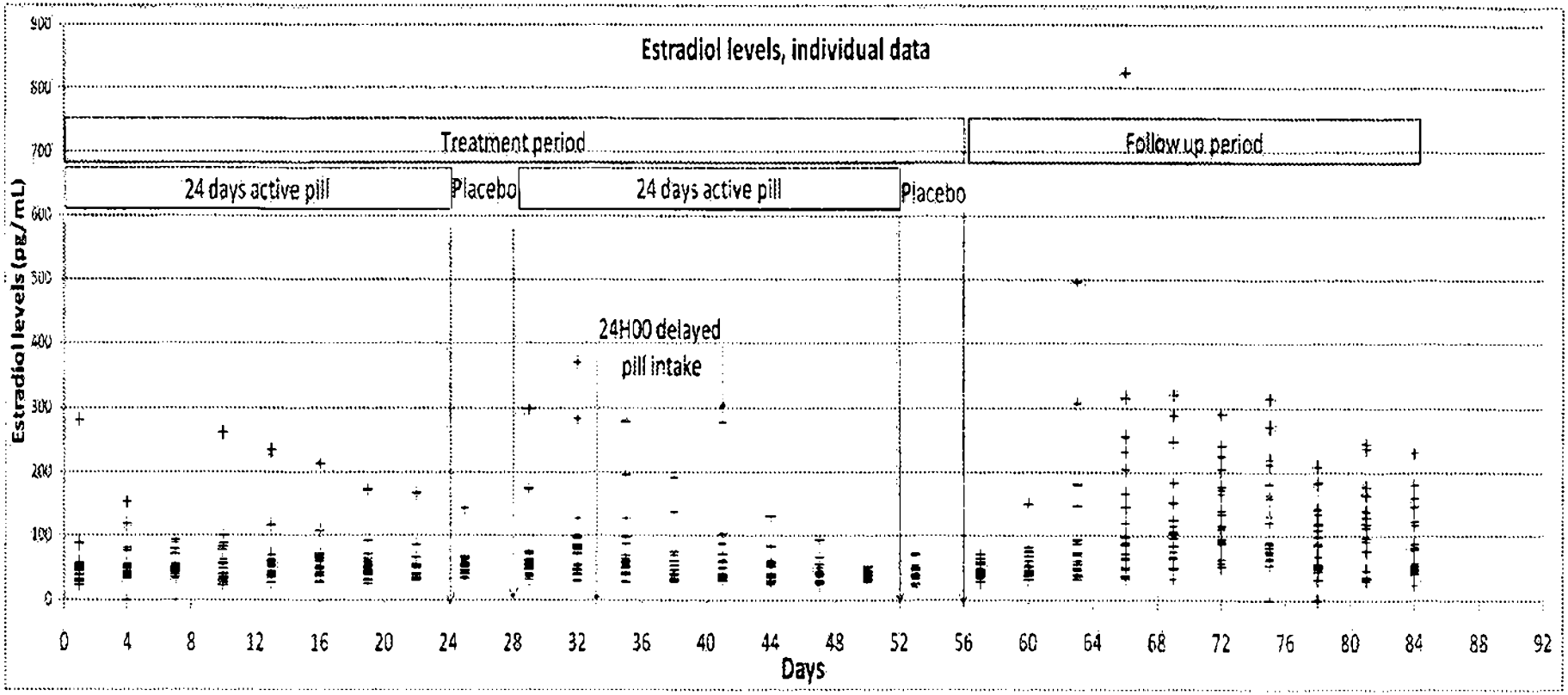

Figure 6b