EXHIBIT 1004

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Boissonneault et al.

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(54) **CHEWABLE ORAL CONTRACEPTIVE**

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Related U.S. Application Data

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(52) **U.S. Cl.** **424/439**; 424/400; 424/440; 424/441; 424/464; 424/484; 424/489; 514/841; 514/843

(58) **Field of Search** 424/400, 439, 424/440, 441, 464, 484, 489; 514/841, 843

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,960,911	A		6/1976	Suschitzky et al.
4,036,983	A		7/1977	Rutherford et al.
4,038,413	A		7/1977	Suschitzky et al.
4,136,162	A		1/1979	Fuchs et al.
4,512,986	A		4/1985	Reel et al.
4,684,534	A		8/1987	Valentine
5,135,744	A		8/1992	Alexander et al.
5,569,456	A		10/1996	Gorinskyt
5,576,014	A		11/1996	Mizumoto et al.
5,747,480	A	*	5/1998	Gast 514/170

* cited by examiner

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(57) **ABSTRACT**

The present invention relates to a chewable, palatable oral contraceptive tablet, comprising an oral contraceptive agent, a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, as well as use of these tablets in a method of human female oral contraception, and in a method of enhancing compliance with a human female oral contraceptive regimen.

60 Claims, No Drawings

CHEWABLE ORAL CONTRACEPTIVE

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation-in-part of U.S. patent application Ser. No. 09/286,908, filed Apr. 6, 1999.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not Applicable.

REFERENCE TO MICROFICHE APPENDIX

Not Applicable.

BACKGROUND OF THE INVENTION

The present invention generally relates to an oral contraceptive delivery system, and in particular an oral contraceptive delivery system involving novel alternate dose forms to improve compliance.

The efficacy of oral contraceptives tends to be particularly patient compliance dependent, largely due to the lack of a disease state or symptoms to remind a human female patient (sometimes referred to simply as "patient" or "woman") to take a pill. The single most significant reason for failure with oral contraceptives is use, rather than method, failure. That is, unless the contraceptives are used according to the prescribed regimen, the contraceptives can fail to effectively help a patient avoid pregnancy. Further, in order to be most effective in preventing pregnancy and maintaining menstrual cycle control, proper compliance with an oral contraceptive dosage regimen requires that the oral contraceptives be taken at about the same time each day.

Various attempts have been made to improve patient compliance with contraceptive regimens. For example, it has been suggested that progestin rods can be inserted subdermally. This procedure has been described, for example, in U.S. Pat. No. 5,756,115. This technique has the significant disadvantage of requiring a surgical incision, a procedure that is highly disfavored by a relatively large segment of the patient population.

As another example, it has been suggested that DEPO-PROVERA® (Pharmacia, Inc.) medroxyprogesterone acetate can be injected subcutaneously every three months. This technique has been described, for example, in U.S. Pat. No. 4,639,439. This procedure has the disadvantage of requiring an injection via hypodermic needle, which is also a procedure that is disfavored by many patients.

In many cases, the patient prefers to carry the contraceptive pills on her person as a matter of lifestyle or personal discretion. This is especially true for younger patients, and it is not uncommon for such patients to exchange pills. Members of this population tend to view portable packaging of the pills, immediate access to the pills, and ease of pill use as significant benefits.

Prior proposed solutions to the compliance problem have tended to focus primarily or exclusively on optimizing compliance packaging, rather than on changes to the dosage form. It has been suggested that instead of being packaged in vials, contraceptive pills can be packaged in 21 or 28 day blister packages. It has also been suggested that the size of these packages can be reduced to improve portability and confidentiality.

Although oral contraceptive pills provided in a small blister package are somewhat more convenient to carry and to conceal, they are not necessarily easy to ingest. Access to water to facilitate contraceptive pill taking remains a problem. Most medications are typically stored in a medicine cabinet and therefore are likely to be near a water source. On the contrary, oral contraceptive pills are often carried on the person and a source of water is not always available when it is time to take the oral contraceptive pill. Additionally, a certain segment of the patient population will have trouble swallowing pills, irrespective of access to water.

The present invention provides an improved oral contraceptive tablet. The technology encompassed in the invention involves a chewable, palatable oral contraceptive tablet that has appropriate size and hardness for blister packaging and compliant use.

BRIEF SUMMARY OF THE INVENTION

One aspect of the present invention relates to a chewable, palatable oral contraceptive tablet, comprising an oral contraceptive agent, a chewable carrier suitable for human consumption, and not comprising a ferrocene compound.

Another aspect of this invention relates to a method of human female oral contraception, the method comprising providing a chewable, palatable oral contraceptive tablet comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablet to a human female.

Yet another aspect of this invention relates to a method of enhancing compliance with a human female oral contraceptive regimen involving oral contraceptive tablets, the method comprising providing chewable, palatable oral contraceptive tablets comprising a contraceptively effective amount of an oral contraceptive agent, and a chewable carrier suitable for human consumption, and not comprising a ferrocene compound, and administering the tablets to the human female in accordance with the contraceptive regimen.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Not Applicable.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to chewable, palatable oral contraceptive tablets for administering an oral contraceptive agent to human females. The tablets of this invention may simply be chewed, and therefore are easy for a patient to ingest, even in the absence of a liquid. The oral contraceptive agent formulation of this invention improves dosage regimen compliance, and thereby enhances the desired contraceptive effect of the oral contraceptive. This invention also includes methods for administering the oral contraceptive formulations to a woman.

Definitions

The articles "a" and "an" are used herein to refer to one or more than one (i.e., to at least one) of the grammatical objects of the article. By way of example, "an element" means one element or more than one element.

The term "oral contraceptive agent," as used herein, refers to any compound or combination of compounds which, when administered orally, prevents pregnancy.

The term "estrogen," as used herein, refers to any natural or synthetic compound which exhibits an effect on the

female reproductive organs in a manner similar to the natural female hormone estrogen. Examples of an estrogen include, but are not limited to, ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate.

The term "progestin," as used herein, refers any natural or synthetic compound which exhibits a progestational effect on the female reproductive organs. Examples of a progestin include, but are not limited to, norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne and nesterone.

The term "palatable," as used herein, means that the tablet of this invention has a taste, mouth feel, chewability, texture, aroma, and lack of grittiness and bad aftertaste that makes the tablet agreeable to a woman to chew.

A tablet is "chewable," as used herein, such that when the tablet is chewed, it breaks into smaller pieces that can be swallowed. This is in contrast to gum, for example, which does not break into smaller pieces when chewed.

Description of the Invention

The first aspect of the invention relates to a chewable, palatable oral contraceptive tablet comprising an oral contraceptive agent, a chewable carrier suitable for human consumption and not comprising a ferrocene compound. The tablet of this invention expressly does not contain a ferrocene compound. Ferrocene compounds are used in the treatment of anemia and it should not be assumed that all patients desiring an oral contraceptive agent are anemic. Administering ferrocene compounds when they are not needed can lead to iron poisoning. Additionally, ferrocene compounds may not be palatable when chewed.

In principle, virtually any oral contraceptive agent used in human medicine could be employed in accordance with the principles of the present invention. The oral contraceptive agent may be an estrogen, a progestin, or a combination of an estrogen and a progestin. In one embodiment, the oral contraceptive agent is an estrogen selected from the group consisting of ethinyl estradiol, estradiol, estradiol valerate, and estradiol acetate. Preferably, the estrogen is ethinyl estradiol.

In another embodiment, the oral contraceptive agent is a progestin selected from the group consisting of norethindrone, norethindrone acetate, desogestrel, levonorgestrel, ethynodiol diacetate, norgestrel, norgestimate, gestodene, drospirenone, trimegestone, levodesogestrel, gestodyne, and nesterone. Preferably, the progestin is norethindrone.

The dosage of the oral contraceptive agent employed would tend to be that conventionally used in the art for the particular oral contraceptive agent selected. The proportion of the oral contraceptive agent in the tablet may be a pharmaceutically effective trace amount to about 10% by weight. Thus, the quantity of oral contraceptive agent per tablet may be varied as desired, typically about 10 micrograms to about 5 milligrams, but the lower and upper dosages may be reduced or increased. Examples of approximate dosage ranges of oral contraceptive agents in milligrams per tablet are summarized in Table 1.

TABLE 1

Examples of Dose Ranges of Oral Contraceptive Agents (milligrams per tablet)

Description	Examples	Broad	Intermediate	Preferred
Progestin	Norethindrone,	0.1 to 2.5	0.25 to 2.0	0.4 to 1.5
	Norethindrone acetate	0.1 to 2.5	0.25 to 2.0	0.4 to 1.5
	Desogestrel	0.05 to 0.5	0.1 to 0.3	0.1 to 0.2
	Levonorgestrel	0.025 to 1.5	0.025 to 1.0	0.05 to 0.6
	Ethynodiol diacetate	0.5 to 2.5	0.75 to 1.25	0.9 to 1.1
	Norgestrel	0.05 to 3.0	0.05 to 2.0	0.1 to 1.2
	Norgestimate	0.1 to 0.5	0.15 to 0.35	0.18 to 0.25
	Gestodene	0.03 to 0.15	0.05 to 0.10	0.06 to 0.075
	Drospirenone	1.0 to 5.0	2.0 to 4.0	2.5 to 3.5
	Trimegestone	0.05 to 0.5	0.1 to 0.3	0.1 to 0.2
Estrogen	Ethinyl Estradiol,	0.01 to 0.075	0.015 to 0.05	0.020 to 0.050
	Estradiol	0.5 to 4.0	1 to 3	1.5 to 2.5
	Estradiol valerate	0.5 to 5.0	1.5 to 3.5	1.9 to 3.0
	Estradiol acetate	0.5 to 5.0	1.5 to 3.5	1.8 to 3.0

In one preferred embodiment, the tablet comprises estrogen in the form of ethinyl estradiol in an amount of about 10 micrograms to about 75 micrograms. In another preferred embodiment, the tablet comprises progestin in the form of norethindrone in an amount of about 0.1 milligram to about 2.5 milligrams.

The invention also includes a tablet in which the oral contraceptive agent is a combination of an estrogen and a progestin. Preferably, the estrogen is ethinyl estradiol and the progestin is norethindrone. In a more preferred embodiment, the amount of ethinyl estradiol in the tablet is about 10 micrograms to about 75 micrograms and the amount of norethindrone in the tablet is about 0.1 milligram to about 2.5 milligrams.

The tablets of this invention can be used in conjunction with an oral contraceptive regimen. The regimen can comprise administering tablets on a daily basis for multiple consecutive days. As such, throughout the duration of the regimen the amount of oral contraceptive agent in the oral contraceptive tablets may remain constant, thereby comprising a uniphasic regimen. Additionally, the amount of oral contraceptive agent in the oral contraceptive tablets may vary throughout the duration of the regimen, thereby comprising a multiphasic regimen. In tablets comprising an estrogen and a progestin, the ratio of the estrogen to the progestin can be constant throughout the duration of the regimen. Additionally, the ratio of the estrogen to the progestin in the oral contraceptive tablets can vary throughout the regimen.

It is also possible to form placebo tablets which otherwise correspond in composition to the tablet of the present invention but are free of the oral contraceptive agent.

The oral contraceptive agent may be present in a carrier either in a dissolved or a uniformly suspended state. A carrier comprises all but the active oral contraceptive agent or agents and includes an inactive ingredient or a combination of one or more inactive ingredients. The carrier imparts chewable and palatable characteristics to the tablet and must be suitable for human consumption, that is, free of harmful amounts of any toxins or components that are adverse to humans. All ingredients in the carrier should be generally recognized as safe (GRAS), as determined by the Food and Drug Administration (FDA) or the Flavor and Extract Manufacturers' Association (FEMA). The carrier selected for the invention must be chewable and should not confer a disagreeable taste to the tablet. Thus, the carrier itself must be palatable. The primary ingredient of a carrier is one or more diluents. Non-limiting examples of diluents that can be used in accordance with this invention include microcrystalline cellulose, corn starch, modified starch, calcium carbonate, dicalcium phosphate, and poly-alcohol sugars such as dextrose, mannitol, sorbitol, xylitol, lactose, sucrose, and fructose. Many other diluents or other ingredients suitable as components of carriers for a chewable, palatable oral contraceptive tablet are available and would be well known to those skilled in the art in view of the present disclosure.

In another aspect of the invention, the tablet optionally further comprises at least one of a flavor agent, a sweetener, and a color agent. A flavor agent can be used to enhance the taste of the tablet, making the tablet more palatable than a tablet without a flavor agent. Spray dried flavor agents are preferred because they are easy to incorporate into a chewable tablet. Non-limiting examples of preferred flavor agents impart the following flavors: strawberry, wild berry, spearmint, wintergreen, black cherry, orange, orange cream, and lemon. The flavoring agents are readily available from many commercial sources. Exemplary compounds suitably used in preparing flavors are listed in G. Burdock, Ed., Fenaroli's Handbook of Flavor Ingredients, 3rd edition, Volumes I and II, CRC Press, New York, 1995. Other flavors and flavoring agents suitable for the tablet would be well known to those skilled in the art in view of the present disclosure.

A sweetener can also be used to enhance to taste of the tablet, making the tablet more palatable than a tablet without a sweetener. Sweeteners include natural sugars and artificial sugar substitutes. Non-limiting examples of sweeteners that can be used in accordance with this invention include aspartame, sucralose, xylitol, sorbitol, mannitol, dextrose, sucrose, and fructose. Non-limiting examples of the amount of flavor agents or sweeteners that can be used in the tablet composition of the present invention are listed in Table 2. The amounts in Table 2 are given as percentage of the total tablet weight.

TABLE 2

Sweetener and Flavor Amounts Used in Chewable Oral Contraceptive Formulations

Ingredient Type	Examples	Broad	Intermediate	Preferred
Sweetener	Aspartame	0.02 to 1.0%	0.02% to 0.2%	0.03% to 0.05%
	Sucralose	0.01 to 0.5%	0.01% to 0.1%	0.02 to 0.04%
Flavor Agent	Spearmint	0.5 to 5%	1 to 3%	1.5 to 2.5%
	Wintergreen	0.5 to 5%	1 to 3%	1.5 to 2.5%
	Wild berry	0.1 to 3%	0.2 to 1%	0.3 to 0.5%

Optionally, a color agent may be added to aid in tablet identification and to enhance the visual appearance of the tablet. A visually pleasing color enhances patient acceptance and thereby compliance with an oral contraceptive regimen. The color agent may be any that are well known to those in the tablet-making art in view of the present disclosure, and could be used in any amount to impart the desired color.

The tablet can be manufactured by standard pharmaceutical techniques of solid dose formulation, such as granulation and compression. These processes are well known to those skilled in the art of making tablets (See Lieberman, Lachman, and Schwartz, *Pharmaceutical Dosage Forms*, Volume 1, New York, 1989). During the granulation process, other ingredients typically used in tablet formulation for human consumption can be included, such as binders, lubricants, anti-adherents, glidants, disintegrants and fillers or other optional ingredients that do not adversely affect chewability or palatability of the tablet or its active oral contraceptive agent ingredient(s).

Binders aid the formation of granulated particles of active oral contraceptive agents and carrier ingredients. Non-limiting examples of binders include glucose, acacia, guar gum, gelatin, simple syrup, sucrose, sorbitol, starch, alginic acid, alginate salts, polyethylene glycol, polyvinylpyrrolidone, polymethacrylates, pregelatinized starch, and celluloses such as methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and ethylcellulose. A solution of binder is prepared (concentrations dependent on the particular binder used), and the binder solution is mixed with the other excipients to form the wet granulation. A binder such as polyvinylpyrrolidone (Povidone) is typically used in a solution of about 3% to about 15% by weight and is added to the other tablet ingredients resulting in a final formulation concentration of about 2% to about 5%. Similarly, cellulose derivatives are typically used in granulating solutions of about 5% to about 10% by weight and concentrations would be known to one skilled in the art of making tablets using wet granulation in view of the present disclosure.

Disintegrants facilitate breakup of the tablet after administration during chewing. Non-limiting examples of disintegrants include crospovidone, croscarmellose sodium, starches, corn starch, potato starch, modified corn starch, sodium starch glycolate, and pregelatinized starch. Disintegrants can be included in the tablet formulation in amounts generally less than about 25% of the tablet weight, preferably less than about 20%, and more preferably about 1 to about 20% (natural starches such as corn or potato starch), about 5 to about 10% (pregelatinized starch), and about 3 to 8% (modified corn starch). Crospovidone and croscarmellose sodium are used at levels of about 5% or lower.

As a final step in the manufacture of the tablet, a lubricant, an anti-adherent, and a glidant can be added to the tablet

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