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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

THERAPEUTICSMD, INC., **Plaintiff,** **v.** **AMNEAL PHARMACEUTICALS, INC., AMNEAL PHARMACEUTICALS, LLC, and AMNEAL PHARMACEUTICALS OF NEW YORK LLC,** **Defendants.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiff TherapeuticsMD, Inc. ("TherapeuticsMD"), by its undersigned attorneys, for its Complaint against defendants Amneal Pharmaceuticals, Inc. ("Amneal Inc."), Amneal Pharmaceuticals, LLC ("Amneal LLC"), and Amneal Pharmaceuticals of New York LLC ("Amneal NY") (together, "Amneal" or "Defendants"), alleges as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, arising from Amneal's filing of Abbreviated New Drug Application ("ANDA") No. 214293 ("Amneal's ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of TherapeuticsMD's BIJUVA® drug product ("Amneal's Proposed Product") before the expiration of United States Patent No. 10,806,740 (the "'740 patent"), owned by TherapeuticsMD.

The Parties

2. Plaintiff TherapeuticsMD is a women's healthcare company committed to creating and commercializing innovative products to support women from pregnancy prevention through menopause. TherapeuticsMD focuses on, and invests heavily in, the development and commercialization of health solutions that enable new standards of care for women. TherapeuticsMD is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business at 951 Yamato Rd., Suite 220, Boca Raton, Florida 33431.

3. On information and belief, Defendant Amneal Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807.

4. On information and belief, Defendant Amneal LLC is a limited liability company organized and existing under the laws of the State of Delaware, having a principal place of business at 400 Crossing Boulevard, Bridgewater, New Jersey 08807. On information and belief, Amneal LLC is a wholly owned subsidiary of Amneal Inc.

5. On information and belief, Defendant Amneal NY is a limited liability company organized and existing under the laws of the State of Delaware, having a place of business at 400

Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is a wholly owned subsidiary of Amneal LLC.

The Patent-in-Suit

6. On October 20, 2020, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '740 patent, entitled, "Natural Combination Hormone Replacement Formulations and Therapies" to TherapeuticsMD as assignee of the inventors. A copy of the '740 patent is attached hereto as Exhibit A.

The BIJUVA® Drug Product

7. TherapeuticsMD holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for estradiol and progesterone capsules (NDA No. 210132), which it sells under the trade name BIJUVA®. BIJUVA® is an FDA-approved medication indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

8. The claims of the '740 patent cover, *inter alia*, pharmaceutical compositions and formulations comprising estradiol and progesterone.

Jurisdiction and Venue

9. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

10. TherapeuticsMD received a letter from Amneal no earlier than March 17, 2020, notifying TherapeuticsMD that Amneal had submitted ANDA No. 214293 ("Amneal's First Notice Letter"). Each page of Amneal's Notice Letter bears the address 400 Crossing Boulevard, 3rd Floor, Bridgewater, NJ 08807.

11. Attached to Amneal's First Notice Letter was a document entitled "Amneal Pharmaceuticals, LLC Detailed Factual and Legal Basis of Non-Infringement and/or Invalidity" ("Amneal's Detailed Statement").

12. On information and belief, one or more acts related to Amneal's preparation of Amneal's ANDA and the preparation of Amneal's written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Amneal's Paragraph IV Certification(s)"), set forth in Amneal's ANDA were conducted in this District and/or will be conducted in the District.

13. On information and belief, upon FDA approval of Amneal's ANDA, Amneal intends to commercially manufacture, import, market, offer for sale, and/or sell Amneal's Proposed Product throughout the United States including in this Judicial District.

14. On information and belief, Amneal is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District. This Judicial District is a likely destination for the generic drug products described in ANDA No. 214293. On information and belief, Amneal also prepares and/or aids in the preparation and submission of ANDAs to the FDA.

15. The Court has personal jurisdiction over Amneal LLC by virtue of, *inter alia*, its continuous and systematic contacts with the State of New Jersey. On information and belief, Amneal LLC's principal place of business is in Bridgewater, New Jersey. On information and belief, Amneal LLC is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business I.D. No. 0600211542. On information and belief, Amneal LLC is registered with the State of New Jersey's Department

of Health as a drug manufacturer and wholesaler, under Registration No. 5002991. On information and belief, Amneal LLC purposefully has conducted and continues to conduct business in this Judicial District.

16. This Court has personal jurisdiction over Amneal NY because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its affiliate, agent, and/or alter ego, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler; and (2) maintains extensive and systematic contacts with the State of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC. On information and belief, Amneal NY has a place of business at 400 Crossing Blvd., Third Floor, Bridgewater, New Jersey 08807. On information and belief, Amneal NY is registered with the State of New Jersey's Department of Health as a drug manufacturer and wholesaler, under Registration No. 5003663. On information and belief, Amneal NY purposefully has conducted and continues to conduct business in this Judicial District.

17. This Court has personal jurisdiction over Amneal Inc. because, *inter alia*, it: (1) has purposefully availed itself of the privilege of doing business in New Jersey, including directly or indirectly through its subsidiaries, agents, and/or alter egos, Amneal LLC, a company that has its principal place of business in the State of New Jersey and holds licenses with the State of New Jersey as a pharmacy wholesaler, and Amneal NY, a company that has a place of business in the State of New Jersey and is registered with the State of New Jersey as a drug manufacturer and wholesaler; and (2) maintains extensive and systematic contacts with the State

of New Jersey, including the marketing, distribution, and/or sale of generic pharmaceutical drugs in New Jersey including through, directly or indirectly, Amneal LLC and/or Amneal NY.

18. On information and belief, Amneal Inc.'s executive offices are located in Bridgewater, New Jersey. On information and belief, Amneal Inc. owns or leases numerous properties throughout New Jersey for the purposes of manufacturing, research and development, warehousing, and packaging. (*See* Amneal Pharmaceuticals, Inc. Securities and Exchange Commission Form 10-K (for the fiscal year ended December 31, 2019) ("Amneal Inc. Form 10-K") at 34.)

19. On information and belief, Amneal Inc. regularly and continuously transacts business within New Jersey, including by making pharmaceutical products for sale in New Jersey and selling pharmaceutical products in New Jersey. On information and belief, Amneal Inc. derives substantial revenue from the sale of those products in New Jersey and has availed itself of the privilege of conducting business within New Jersey. Amneal Inc.'s 10-K filing states, "[t]he Company's Generics segment includes over 200 product families covering an extensive range of dosage forms and delivery systems . . . . [and] 113 products either approved but not yet launched or pending FDA approval." (Amneal Inc. Form 10-K at 5.) On information and belief, Amneal Inc. derives substantial revenue from selling generic pharmaceutical products throughout the United States, including in this Judicial District.

20. This Court has personal jurisdiction over Amneal because, *inter alia*, it has committed an act of patent infringement under 35 U.S.C. § 271(e)(2), and has sent notice of that infringement to TherapeuticsMD. On information and belief, Amneal intends a future course of conduct that includes acts of patent infringement in New Jersey. These acts have led and will continue to lead to foreseeable harm and injury to TherapeuticsMD in New Jersey and in this

Judicial District. For example, on information and belief, Amneal will work towards the regulatory approval, manufacturing, use, importation, marketing, sale, offer for sale, and distribution of generic pharmaceutical products, including Amneal's ANDA Product, throughout the United States, including in New Jersey and in this Judicial District, before the expiration of the '740 patent.

21. In Amneal's First Notice Letter, Amneal stated that the name and address of its agent in the United States authorized to accept written notice requesting access under its Office of Confidential Access is Lars Taavola, Esq., Amneal Pharmaceuticals, LLC, 400 Crossing Boulevard, 3rd Floor, Bridgewater, NJ 08807. By naming Mr. Taavola in Bridgewater, NJ as its agent in connection with this action, Amneal has consented to jurisdiction in New Jersey.

22. Amneal LLC has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g.*, *TherapeuticsMD, Inc., v. Amneal Pharmaceuticals, Inc., et al.*, No. 20-5256 (D.N.J.); *Cubist Pharmaceuticals LLC v. Amneal Pharmaceuticals, LLC, et al.* No. 19-15439 (D.N.J.); *Senju Pharmaceutical Co., et al. v. Amneal Pharmaceuticals LLC et al*., No. 18-05571 (D.N.J.); *BTG International Limited, et al. v. Actavis Laboratories FL, Inc., et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.)*; Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*; No. 12-05064 (D.N.J.).

23. Amneal LLC has further availed itself of the jurisdiction of this Court by initiating litigation in this Judicial District. *See, e.g., Amneal Pharmaceuticals LLC v. Reckitt Benckiser Pharmaceuticals, Inc., et al.*, No. 15-08864 (D.N.J.).

24. Amneal NY has previously been sued in this Judicial District, has availed itself of New Jersey courts through its assertion of counterclaims in suits brought in New Jersey, and has not challenged personal jurisdiction. *See, e.g., TherapeuticsMD, Inc., v. Amneal Pharmaceuticals, Inc., et al.*, No. 20-5256 (D.N.J.); *BTG International Limited et al. v. Actavis Laboratories FL, Inc.. et al.*, No. 15- 05909 (D.N.J.); *Shire Pharmaceutical Development Inc., et al. v. Amneal Pharmaceuticals LLC, et al.*, No. 15-02865 (D.N.J.)*; Novo Nordisk Inc., et al. v. Amneal Pharmaceuticals, LLC, et al.*, No. 13-04915 (D.N.J.); *Luitpold Pharmaceuticals, Inc. v. Amneal Pharmaceuticals, LLC, et al.*; No. 12-05064 (D.N.J.).

25. Venue is proper in this Judicial District pursuant to 28 U.S.C. §§ 1391 and/or 1400(b).

Acts Giving Rise To This Suit

26. Pursuant to Section 505 of the FFDCA, Amneal's ANDA seeks FDA approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of 1 mg/100 mg (estradiol/progesterone) capsules before the '740 patent expires.

27. On information and belief, following FDA approval of Amneal's ANDA, Amneal will make, use, offer to sell, or sell Amneal's Proposed Product throughout the United States, or import such generic products into the United States.

28. On information and belief, the proposed label or proposed package insert for Amneal's Proposed Product will state that it is indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

29. On information and belief, in connection with the filing of its ANDA as described above, Amneal provided Amneal's Paragraph IV Certification(s) alleging, *inter alia*, that the claims of United States Patent Nos. 8,633,178; 8,846,648; 8,846,649; 8,987,237; 8,993,548; 8,993,549; 9,006,222; 9,114,145; 9,114,146; 9,301,920; 10,052,386; 10,206,932; 10,639,375;

and 10,675,288 are unenforceable, and/or will not be infringed by the activities described in Amneal's ANDA.

30. No earlier than March 17, 2020, TherapeuticsMD received Amneal's written notice of its first Paragraph IV Certification(s). Amneal's First Notice Letter alleged, *inter alia*, that the claims of United States Patent Nos. 8,633,178; 8,846,648; 8,846,649; 8,987,237; 8,993,548; 8,993,549; 9,006,222; 9,114,145; 9,114,146; 9,301,920; 10,052,386; and 10,206,932 are invalid and/or will not be infringed by the activities described in Amneal's ANDA. Amneal's First Notice Letter informed TherapeuticsMD that Amneal seeks approval to market Amneal's Proposed Product before United States Patent Nos. 8,633,178; 8,846,648; 8,846,649; 8,987,237; 8,993,548; 8,993,549; 9,006,222; 9,114,145; 9,114,146; 9,301,920; 10,052,386; and 10,206,932 expire.

31. No earlier than July 17, 2020, TherapeuticsMD received Amneal's written notice of its second Paragraph IV Certification(s) ("Amneal's Second Notice Letter"). Amneal's Second Notice Letter alleged, *inter alia*, that the claims of United States Patent Nos. 10,639,375 and 10,675,288 are invalid and/or will not be infringed by the activities described in Amneal's ANDA. Amneal's Second Notice Letter informed TherapeuticsMD that Amneal seeks approval to market Amneal's Proposed Product before United States Patent Nos. 10,639,375 and 10,675,288 expire.

Count I: Infringement of the '740 Patent

32. TherapeuticsMD repeats and realleges the allegations of the preceding paragraphs as if fully set forth herein.

33. Amneal, by the submission of its Paragraph IV Certification(s) as part of its ANDA to the FDA, has indicated that it seeks approval to engage in the commercial

manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '740 patent.

34. Amneal's ANDA has been pending before the FDA since at least March 16, 2020, the date that Amneal sent Amneal's Notice Letter to TherapeuticsMD.

35. Amneal's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Amneal's Proposed Product, before the expiration of the '740 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A).

36. There is a justiciable controversy between TherapeuticsMD and Amneal as to the infringement of the '740 patent.

37. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will infringe one or more claims of the '740 patent under 35 U.S.C. § 271(a) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States.

38. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will induce infringement of one or more claims of the '740 patent under 35 U.S.C. § 271(b) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, upon FDA approval of Amneal's ANDA, Amneal will intentionally encourage acts of direct infringement with knowledge of the '740 patent and knowledge that its acts are encouraging infringement.

39. Unless enjoined by this Court, upon FDA approval of Amneal's ANDA, Amneal will contributorily infringe one or more claims of the '740 patent under 35 U.S.C. § 271(c) by making, using, offering to sell, selling, and/or importing Amneal's Proposed Product in the United States. On information and belief, Amneal has had and continues to have knowledge that

Amneal's Proposed Product is especially adapted for a use that infringes one or more claims of the '740 patent and that there is no substantial non-infringing use for Amneal's Proposed Product.

40. TherapeuticsMD will be substantially and irreparably damaged and harmed if Amneal's infringement of the '740 patent is not enjoined.

41. TherapeuticsMD does not have an adequate remedy at law.

42. This case is exceptional and TherapeuticsMD is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff TherapeuticsMD respectfully requests the following relief:

(A) A Judgment that Amneal has infringed the '740 patent by submitting ANDA No. 214293;

(B) A Judgment that Amneal has infringed, and that Amneal's making, using, offering to sell, selling, or importing Amneal's Proposed Product will infringe one or more claims of the '740 patent;

(C) An Order that the effective date of FDA approval of ANDA No. 214293 be a date which is not earlier than the later of the expiration of the '740 patent, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(D) Preliminary and permanent injunctions enjoining Amneal and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Amneal's Proposed Product until after the expiration of the '740 patent, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Amneal, its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from practicing any of the claimed inventions of the '740 patent, or from actively inducing or contributing to the infringement of any claim of the '740 patent, until after the expiration of the '740 patent, or any later expiration of exclusivity to which TherapeuticsMD is or becomes entitled;

(F) A Judgment that the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product will directly infringe, induce, and/or contribute to infringement of the '740 patent;

(G) To the extent that Amneal has committed any acts with respect to the claimed inventions of the '740 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding TherapeuticsMD damages for such acts;

(H) If Amneal engages in the commercial manufacture, use, offer for sale, sale, and/or importation into the United States of Amneal's Proposed Product before the expiration of the '740 patent, a Judgment awarding damages to TherapeuticsMD resulting from such infringement, together with interest;

(I) A Judgment declaring that the '740 patent remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding TherapeuticsMD its attorneys' fees incurred in this action;

(K) A Judgment awarding TherapeuticsMD its costs and expenses incurred in this action; and

(L) Such further and other relief as this Court may deem just and proper.

Dated: October 23, 2020

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULES 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *TherapeuticsMD, Inc., v. Amneal Pharmaceuticals, Inc., et al.*, Civil Action No. 20-5256 (FLW)(TJB) (D.N.J.) is related to the matter in controversy because the matter in controversy involves the same parties and because Defendants are seeking FDA approval to market generic versions of the same pharmaceutical products.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: October 23, 2020

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EXHIBIT A

US010806740B2

(12) **United States Patent**
Persicaner et al.

(10) **Patent No.: US 10,806,740 B2**
(45) **Date of Patent: *Oct. 20, 2020**

(54) **NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES**

(71) Applicant: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(72) Inventors: **Peter H. R. Persicaner**, Boca Raton, FL (US); **Brian A. Bernick**, Boca Raton, FL (US); **Julia M. Amadio**, Boca Raton, FL (US)

(73) Assignee: **TherapeuticsMD, Inc.**, Boca Raton, FL (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/512,046**

(22) Filed: **Oct. 10, 2014**

(65) **Prior Publication Data**

US 2015/0031654 A1 Jan. 29, 2015

Related U.S. Application Data

(63) Continuation-in-part of application No. 13/843,428, filed on Mar. 15, 2013, which is a continuation-in-part of application No. 13/684,002, filed on Nov. 21, 2012, now Pat. No. 8,633,178.

(60) Provisional application No. 61/661,302, filed on Jun. 18, 2012, provisional application No. 61/662,265, filed on Jun. 20, 2012, provisional application No. 61/889,483, filed on Oct. 10, 2013.

(51) **Int. Cl.**

A61K 31/57	(2006.01)
A61K 31/565	(2006.01)
A61K 9/48	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/57*** (2013.01); ***A61K 9/4858*** (2013.01); ***A61K 31/565*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Dennis J Parad

(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP

(57) **ABSTRACT**

Pharmaceutical formulations for co-administering estradiol and progesterone are provided herein. In some embodiments, the formulation comprises solubilized estradiol, suspended progesterone, and a medium chain (C6-C12) oil.

17 Claims, 8 Drawing Sheets

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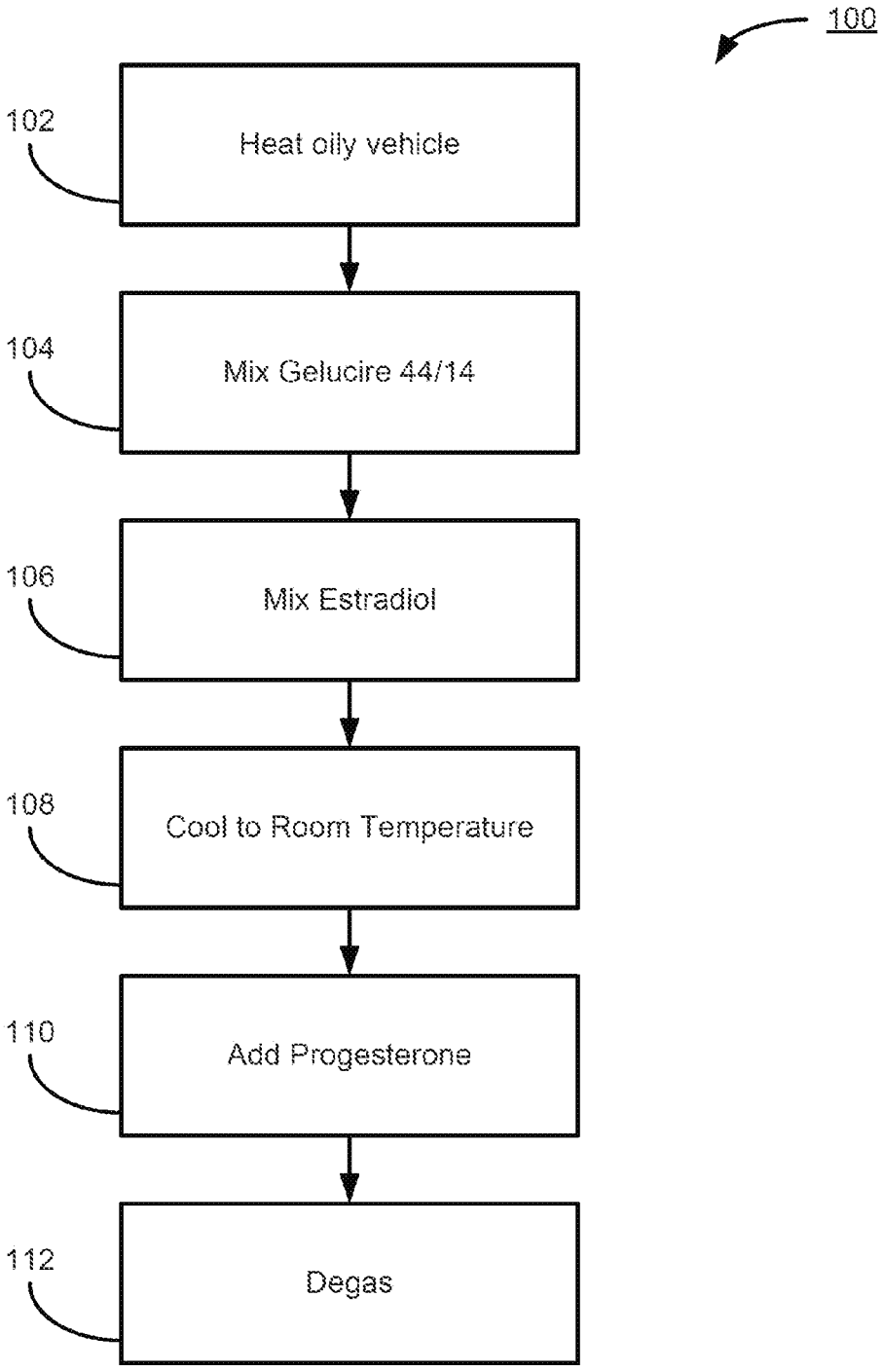

100
102
Heat oily vehicle
104
Mix Gelucire 44/14
106
Mix Estradiol
108
Cool to Room Temperature
110
Add Progesterone
112
Degas

FIG. 1

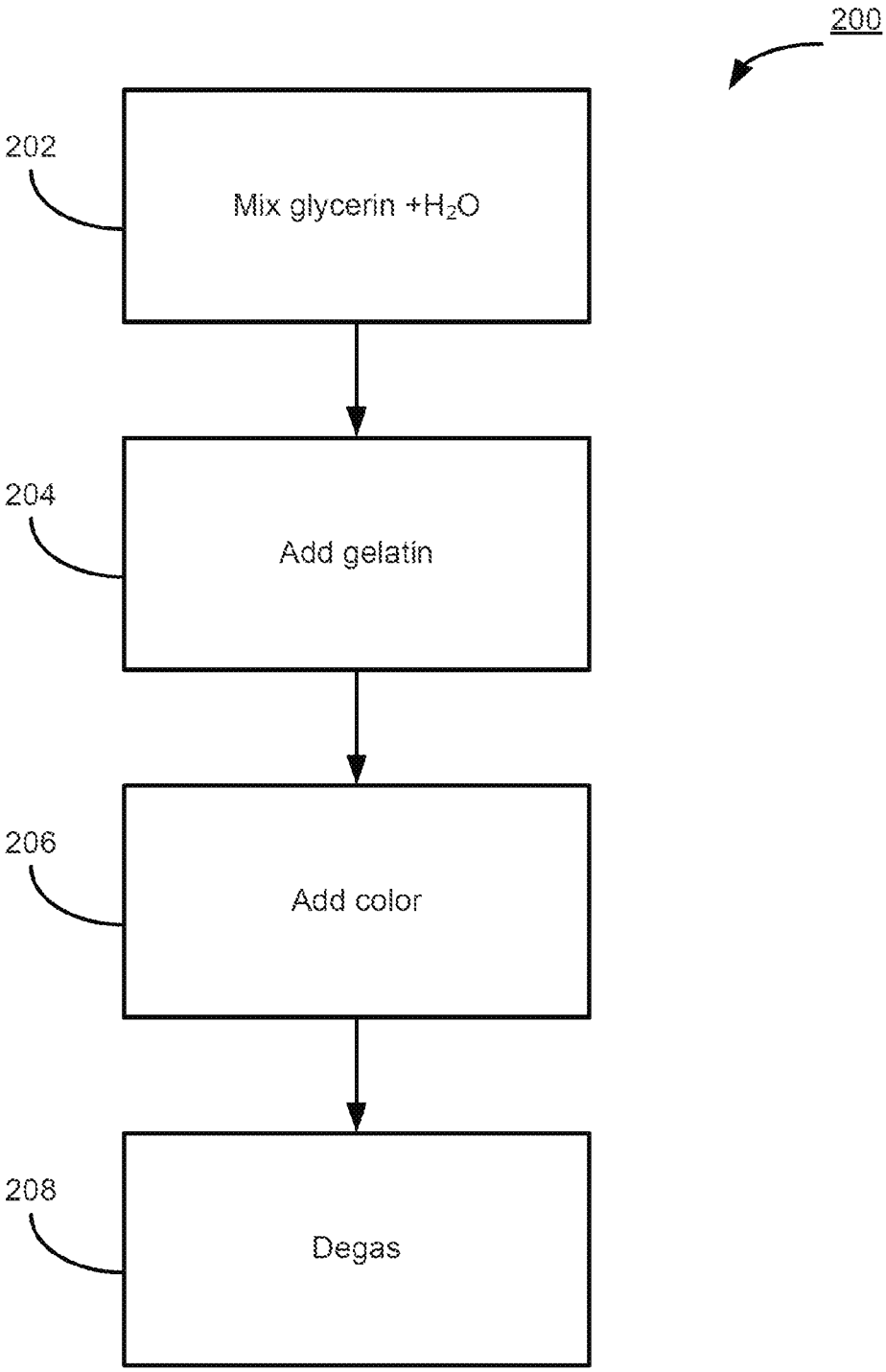

200
202
Mix glycerin +H_2O
204
Add gelatin
206
Add color
208
Degas

FIG. 2

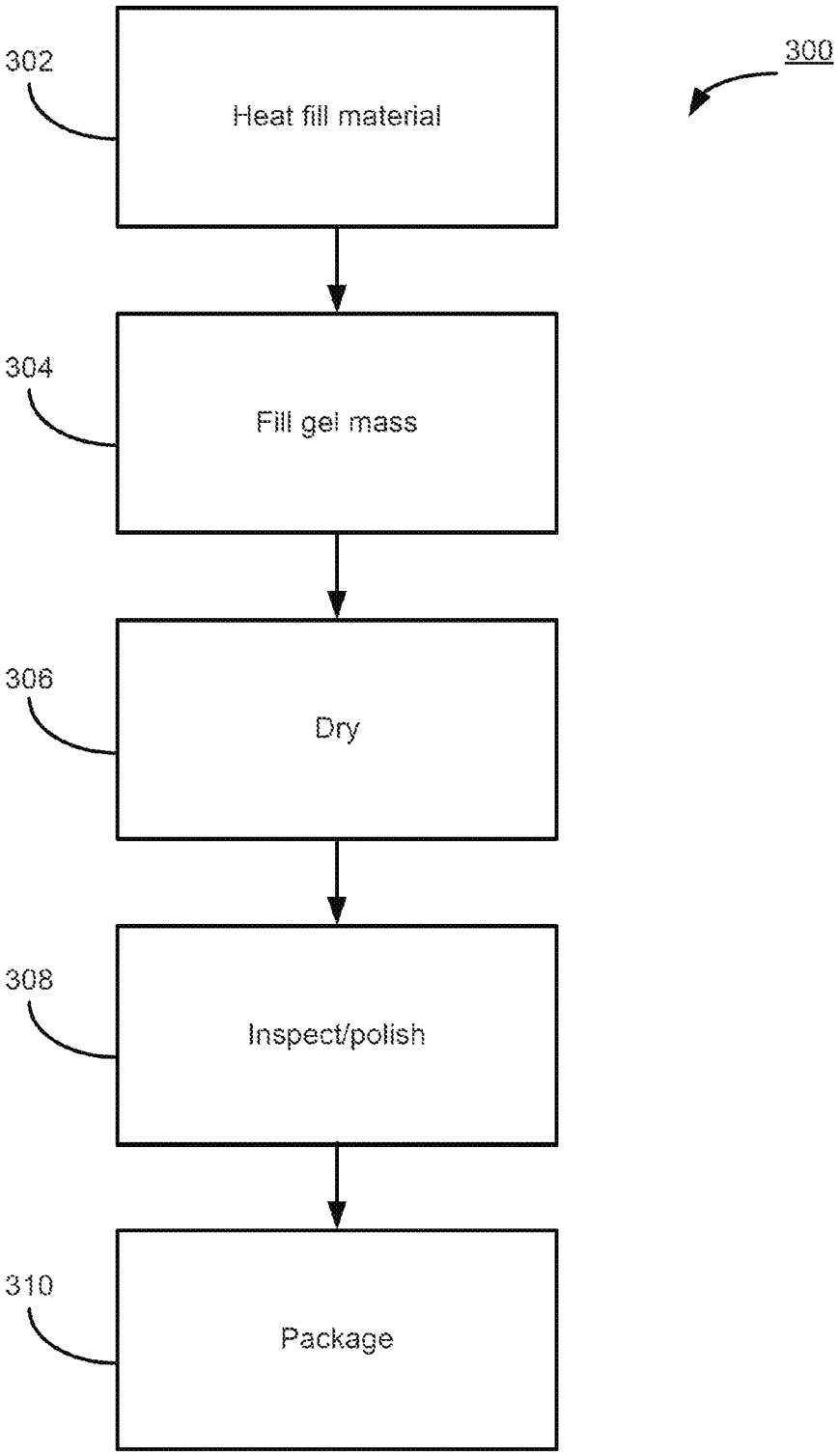

300
302
Heat fill material
304
Fill gel mass
306
Dry
308
Inspect/polish
310
Package

FIG. 3

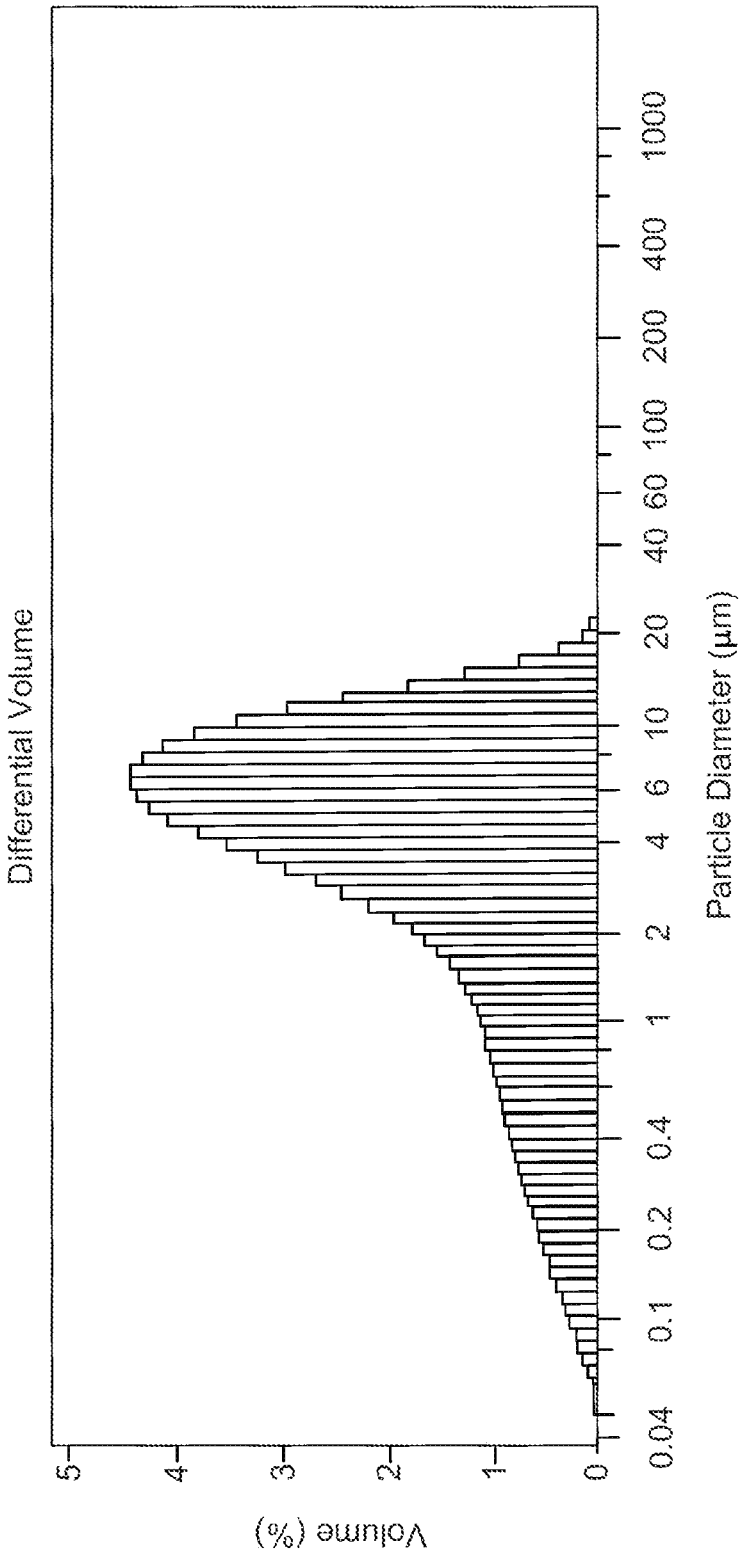

Differential Volume
Volume (%)
0
1
2
3
4
5
Particle Diameter (µm)
0.04
0.1
0.2
0.4
1
2
4
6
10
20
40
60
100
200
400
1000

FIG. 4

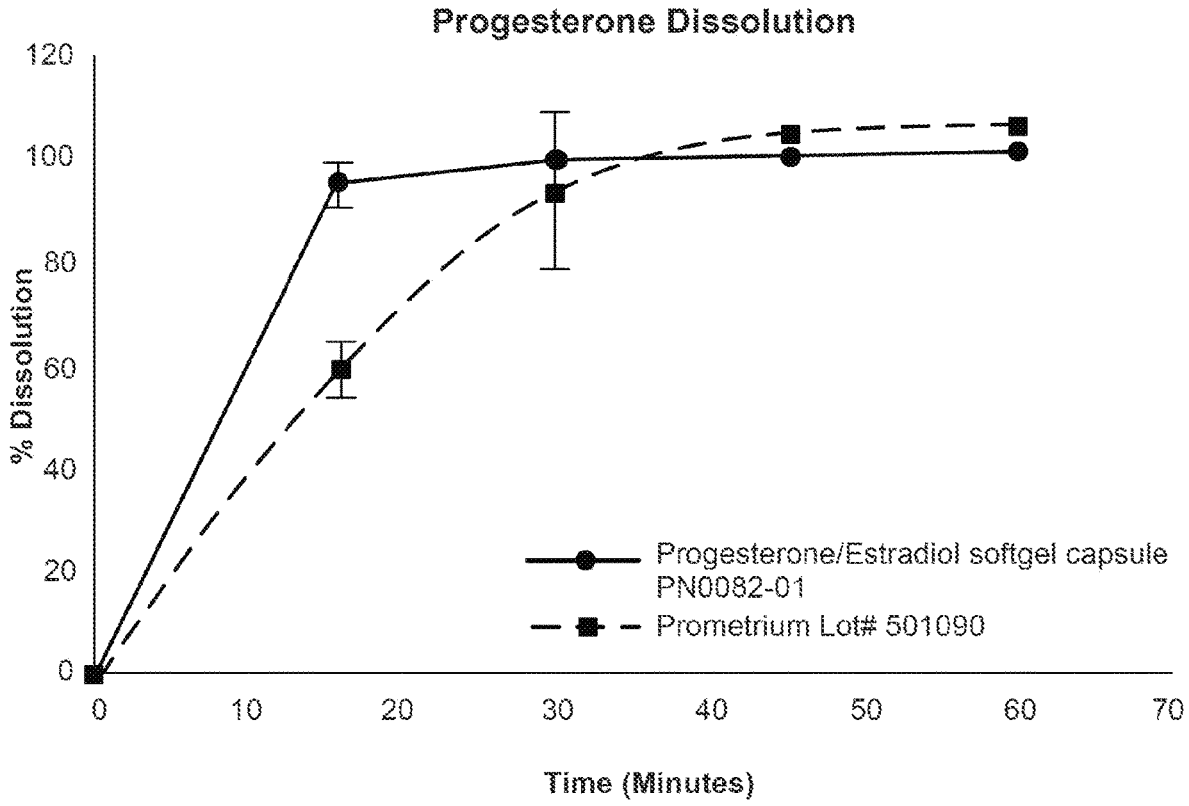

Progesterone Dissolution
120
100
80
60
40
20
0
% Dissolution
0
10
20
30
40
50
60
70
Time (Minutes)
Progesterone/Estradiol softgel capsule PN0082-01
Prometrium Lot# 501090

FIG. 5

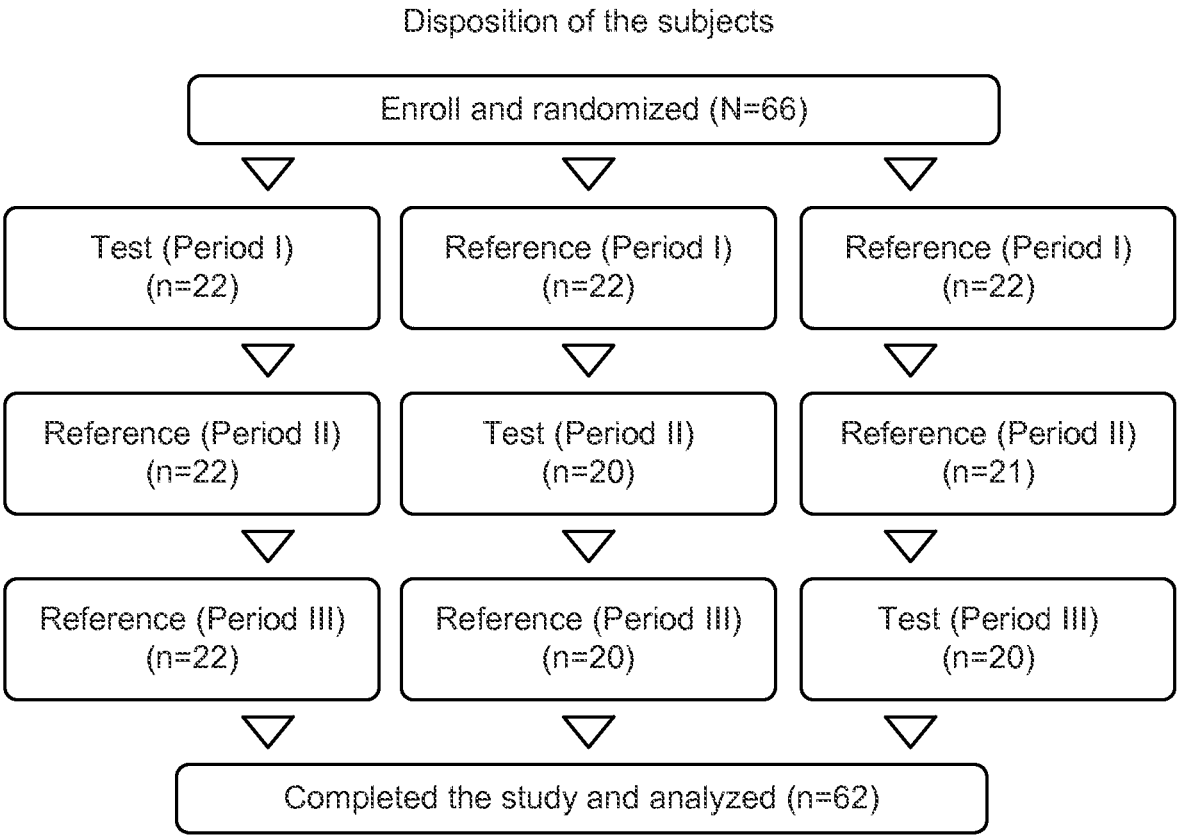
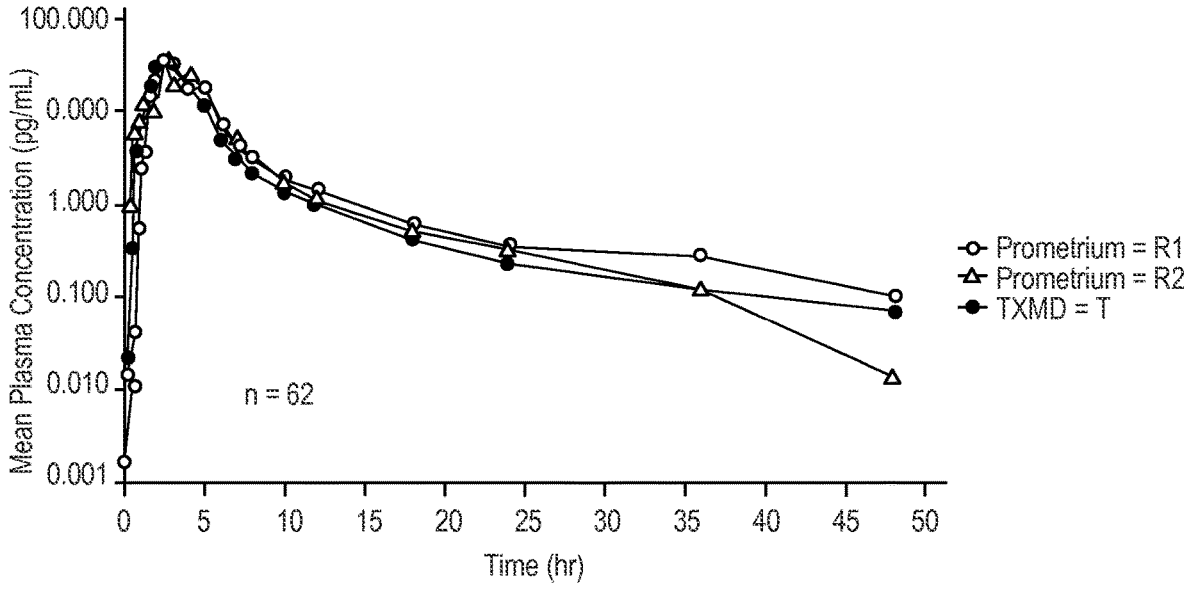

Disposition of the subjects
Enroll and randomized (N=66)
Test (Period I) (n=22)
Reference (Period I) (n=22)
Reference (Period I) (n=22)
Reference (Period II) (n=22)
Test (Period II) (n=20)
Reference (Period II) (n=21)
Reference (Period III) (n=22)
Reference (Period III) (n=20)
Test (Period III) (n=20)
Completed the study and analyzed (n=62)

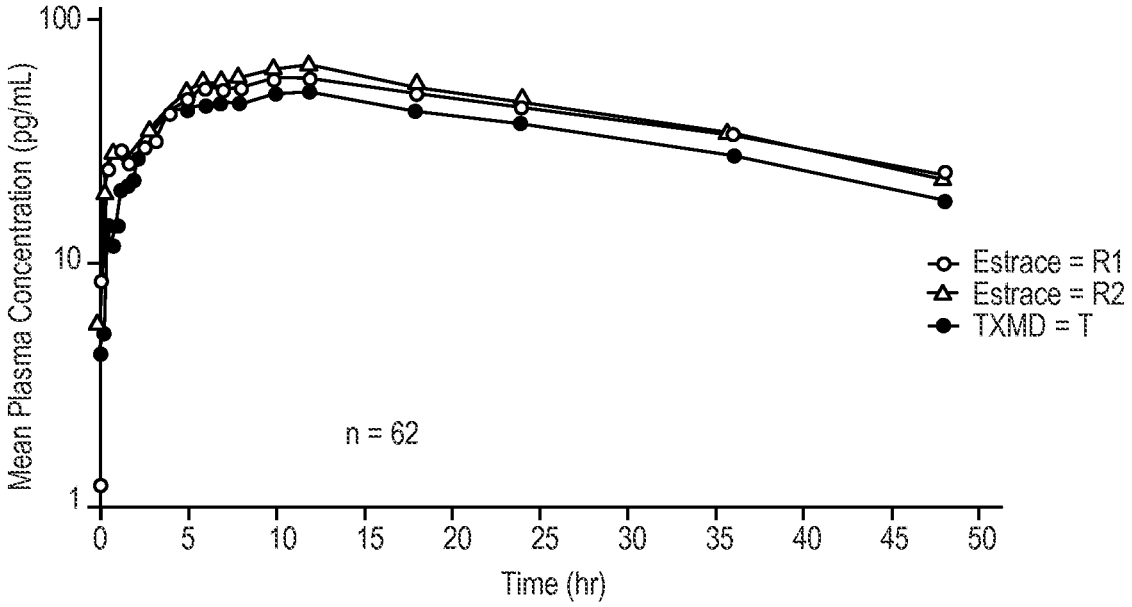
FIG. 6



95% Upper Confidence Limit for PK Parameter

Parameter	Point estimate T/R Ratio	Within Subject Std. Deviation	Upper 95% Confidence Bound
C_{max}	1.16	1.179	-0.785
AUC_{0-1}	1.05	0.956	-0.542

FIG. 7



95% Confidence Interval for PK Parameter

Parameter	Point estimate T/R Ratio	Within Subject Std. Deviation	Upper 95% Confidence Bound
C_{max}	0.88	0.344	-0.040
AUC_{0-1}	0.93	0.409	-0.089

FIG. 8

NATURAL COMBINATION HORMONE REPLACEMENT FORMULATIONS AND THERAPIES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 13/843,428, filed on Mar. 15, 2013, which is a continuation-in-part of U.S. application Ser. No. 13/684,002, filed on Nov. 21, 2012, which claims priority to U.S. Provisional Application Ser. No. 61/661,302, filed on Jun. 18, 2012, and to U.S. Provisional Application Ser. No. 61/662,265, filed on Jun. 20, 2012; and also claims priority to U.S. Provisional Application Ser. No. 61/889,483, filed Oct. 10, 2013; the contents of each of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

This application relates to natural estrogen and progesterone replacement therapies, with formulations provided for each estradiol and progesterone alone and in combination for the treatment of pre, peri-menopausal, menopausal and post-menopausal females in relation to the treatment of Estrogen- and Progesterone-deficient states, each as herein below defined.

BACKGROUND OF THE INVENTION

Hormone Replacement Therapy (HRT) is a medical treatment that involves the use of one or more of a group of medications designed to increase hormone levels in women who lack adequate hormone production. HRT can mitigate and prevent symptoms caused by diminished circulating estrogen and progesterone hormones regardless as to whether the subject is pre-menopausal, peri-menopausal, menopausal or post-menopausal. However, specific symptomatic states can exist during each stage of menopausal progression.

HRT is presently available in various forms. One therapy involves administration of low dosages of one or more estrogens. Another involves administration of progesterone or a chemical analogue, called a progestin. Progesterone administration acts, among treating other disease states, to mitigate certain undesirable side effects from estrogen administration including, for example, endometrial hyperplasia (thickening) and reducing the incidence of endometrial cancer.

Timing for dosage administration is often varied cyclically, with estrogens taken daily and progesterone taken for approximately two weeks of every month; a method often referred to as "Cyclic-Sequential" or "Sequentially-Combined HRT." This method is intended to mimic the natural menstrual cycle and typically causes menstruation similar to a period after the progesterone is stopped. This regimen is most typically used in peri-menopausal or newly menopausal women as the alternative continuous method often results in irregular bleeding in such women. An alternate method, a constant dosage with both estrogen and progesterone taken daily, is called "Continuous-Combined HRT." This method usually results in no menstruation and is used most often after a woman has been menopausal for some time.

Estrogen, in its various forms, and progesterone, in its various forms, are used in HRT via a variety of administered dosage forms including, for example, via tablets, capsules and patches.

"Bio-identical" or "body-identical" hormones, which are identical in chemical structure to the hormones naturally produced by human bodies, can be used and are often referred to as Natural Hormone Replacement Therapy, or NHRT.

These natural or bio-identical hormones are formulated from various ingredients to match the chemical structure and effect of estradiol, estrone, or estriol (the 3 primary estrogens) as well as progesterone that occurs naturally in the human body (endogenous).

Currently, bio-identical estradiol is available in both branded and generic FDA approved versions. FDA-approved bio-identical progesterone for HRT is available as the branded stand-alone drug commercially identified as PROMETRIUM® (progesterone, USP) (Abbott Laboratories, Abbott Park, Ill.), with a generic authorized by the innovator, and generic products provided by Teva (Israel) and Sofgen Americas, Inc. (New York). PROMETRIUM® was approved for sale in the United States on May 14, 1998 under NDA # N019781. According to the prescribing information approved for this product (Rev June 2009) ("PROMETRIUM® prescribing information"), PROMETRIUM® comprises synthetic progesterone that is chemically identical to progesterone of human ovarian origin. Capsules comprise 100 mg or 200 mg of micronized progesterone. The inactive ingredients include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, and yellow and red dyes.

Other products such as PREMPRO® (conjugated estrogens/medroxyprogesterone acetate tablets) and PREMPHASE® (conjugated estrogens plus medroxyprogesterone acetate tablets) (Wyeth Laboratories, a division of Pfizer, Inc., New York) provide both continuous-combined and cyclic-sequential products containing PREMARIN® (estrogen derived from mare's urine) and synthetic medroxyprogesterone acetate. Other products are available. However, no FDA approved product exists on the market today with combination bio-identical estradiol and bio-identical progesterone.

BRIEF SUMMARY OF THE INVENTION

In one aspect, pharmaceutical formulations for co-administering estradiol and progesterone to a mammal in need thereof are provided. In some embodiments, the pharmaceutical formulation comprises: solubilized estradiol, suspended progesterone, and a medium chain (C6 to C12) oil.

In some embodiments, the medium chain oil comprises medium chain fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the medium chain fatty acids are predominantly: C6 to C12 fatty acids, C6 to C10 fatty acids, C8 to C12 fatty acids, or C8 to C10 fatty acids. In some embodiments, the medium chain oil comprises a glyceride containing a C6-C12 fatty acid. In some embodiments, the glyceride is a mixture of mono- and diglycerides. In some embodiments, the fatty acid is predominantly a C8 to C10 fatty acid. In some embodiments, the fatty acids are predominantly saturated fatty acids. In some embodiments, the fatty acids are predominantly unsaturated fatty acids. In some embodiments, the medium chain oil comprises CAPMUL® MCM.

In some embodiments, the pharmaceutical formulation further comprises one or more surfactants, e.g., one or more non-ionic surfactants. In some embodiments, the surfactant comprises lauroyl polyoxyl-32-glycerides. In some embodiments, the surfactant comprises GELUCIRE® 44/14.

In some embodiments, the pharmaceutical formulation further comprises solubilized progesterone, wherein at least

50% (e.g., at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or about 100%) of the total progesterone is solubilized.

In some embodiments, the pharmaceutical formulation is in a hard capsule, a soft capsule, or a tablet for oral administration. In some embodiments, the hard capsule or soft capsule comprises gelatin, glycerol, and coloring agents.

In some embodiments, the pharmaceutical formulation comprises:

30 to 35 wt % progesterone;

0.1 to 0.4 wt % estradiol;

55 to 75 wt % medium chain oil; and

0.5 to 10 wt % non-ionic surfactant.

In some embodiments, the pharmaceutical formulation comprises about 2 mg estradiol and about 200 mg progesterone.

In some embodiments, a pharmaceutical formulation as described herein (e.g., comprising solubilized estradiol, suspended progesterone, and a medium chain (C6-C12) oil), when administered to a human subject, produces:

(a) one or more progesterone-related parameters selected from: (i) an area under the curve $(AUC)_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; (ii) an $AUC_{(0-\infty)}$ for progesterone that is from 105 ng·hr/ml to 164 ng·hr/ml; and (iii) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; and

(b) one or more estrogen-related parameters selected from: (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·hr/ml to 1755 pg·hr/ml; (ii) an $AUC_{(0-\infty)}$ for estradiol that is from 1968 pg·hr/ml to 3075 pg·hr/ml; and (iii) a C_{max} for unconjugated estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the formulation to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml and a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml. In some embodiments, administration of the formulation to the subject produces both an $AUC_{(0-t)}$ for unconjugated estradiol that is from 1123 pg·hr/ml to 1755 pg·hr/ml and a C_{max} for unconjugated estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, when the formulation is administered to a human subject, the formulation further produces one or more of the following:

(i) an $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/ml to 11370 pg·hr/ml;

(ii) an $AUC_{(0-\infty)}$ for estrone sulfate that is from 9596 pg·hr/ml to 14994 pg·hr/ml; or

(iii) a C_{max} for estrone sulfate that is from 341 pg/ml to 533 pg/ml.

In some embodiments, administration of the formulation to the subject produces both an $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/ml to 11370 pg·hr/ml and a C_{max} for estrone sulfate that is from 341 pg/ml to 533 pg/ml.

In some embodiments, when the formulation is administered to a human subject, the formulation further produces one or more of the following:

(i) an $AUC_{(0-t)}$ for total estrone that is from 161 pg·hr/ml to 252 pg·hr/ml;

(ii) an $AUC_{(0-\infty)}$ for total estrone that is from 171 pg·hr/ml to 267 pg·hr/ml; or

(iii) a C_{max} for total estrone that is from 28 pg/ml to 44 pg/ml.

In some embodiments, administration of the formulation to the subject produces both an $AUC_{(0-t)}$ for total estrone that is from 161 pg·hr/ml to 252 pg·hr/ml and a C_{max} for total estrone that is from 28 pg/ml to 44 pg/ml.

In some embodiments, the progesterone and the estradiol in the pharmaceutical formulation demonstrate comparable bioavailability to their individual drug references of PROMETRIUM® and ESTRACE®, respectively ("Referenced Products"), when said formulation is administered to a human subject.

In some embodiments, the progesterone and the estradiol in said formulation demonstrate about 80% to about 125% of the C_{max} and/or AUC of their individual references of PROMETRIUM® and ESTRACE®, respectively, when said formulation is administered to a human subject.

In some embodiments, when administered to a human subject, the formulation produces one or more of the following:

(i) an $AUC_{(0-t)}$ for progesterone comparable to the $AUC_{(0-t)}$ for progesterone obtained with PROMETRIUM®;

(ii) an $AUC_{(0-\infty)}$ for progesterone comparable to the $AUC_{(0-\infty)}$ for progesterone obtained with PROMETRIUM®; or

(iii) a C_{max} for progesterone comparable to the C_{max} for progesterone obtained with PROMETRIUM®.

In some embodiments, when administered to a human subject, the formulation produces one or more of the following:

(i) an $AUC_{(0-t)}$ for unconjugated estradiol comparable to the $AUC_{(0-t)}$ for progesterone obtained with ESTRACE®;

(ii) an $AUC_{(0-\infty)}$ for unconjugated estradiol comparable to the $AUC_{(0-\infty)}$ for progesterone obtained with ESTRACE®; or

(iii) a C_{max} for unconjugated estradiol comparable to the C_{max} for progesterone obtained with ESTRACE®.

In some embodiments, when administered to a human subject, the formulation produces one or more of the following:

(i) an $AUC_{(0-t)}$ for unconjugated estrone comparable to the $AUC_{(0-t)}$ for progesterone obtained with ESTRACE®;

(ii) an $AUC_{(0-\infty)}$ for unconjugated estrone comparable to the $AUC_{(0-\infty)}$ for progesterone obtained with ESTRACE®; or

(iii) a C_{max} for unconjugated estrone comparable to the C_{max} for progesterone obtained with ESTRACE®.

In some embodiments, when administered to a human subject, the formulation produces one or more of the following:

(i) an $AUC_{(0-t)}$ for total estrone comparable to the $AUC_{(0-t)}$ for progesterone obtained with ESTRACE®; or

(ii) an $AUC_{(0-\infty)}$ for total estrone comparable to the $AUC_{(0-\infty)}$ for progesterone obtained with ESTRACE®.

In another aspect, methods of treating a subject having one or more symptoms of estrogen deficiency (e.g., one or more symptoms of menopause) are provided. In some embodiments, the method comprising administering to the subject an effective amount of a pharmaceutical formulation as described herein. In some embodiments, the subject is female. In some embodiments, the subject is a woman having a uterus.

In yet another aspect, methods of effecting hormone replacement therapy in a woman in need thereof are provided. In some embodiments, the method comprises orally administering to the woman an effective amount of a pharmaceutical formulation as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate the present disclosure and, together with the description, further

serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the disclosed embodiments.

FIG. **1** illustrates an exemplary manufacturing process of a fill material in accordance with various embodiments of the invention;

FIG. **2** illustrates an exemplary manufacturing process of a softgel material in accordance with various embodiments of the invention;

FIG. **3** illustrates an exemplary manufacturing process in accordance with various embodiments of the invention;

FIG. **4** illustrates a graph of the particle distribution obtained in Example 10; and

FIG. **5** illustrates a dissolution study of a formulation in accordance with various embodiments of the invention.

FIG. **6** illustrates a flow chart of subject disposition for a study comparing the bioavailability of a 17β-estradiol and progesterone combination formulation to the bioavailability of co-administered PROMETRIUM® and ESTRACE®.

FIG. **7** illustrates pharmacokinetic parameters for progesterone for the combination formulation (T) versus co-administered PROMETRIUM® and ESTRACE® (R1 and R2).

FIG. **8** illustrates pharmacokinetic parameters for free estradiol for the combination formulation (T) versus co-administered PROMETRIUM® and ESTRACE® (R1 and R2).

DETAILED DESCRIPTION OF THE INVENTION

Frequently, higher recommended oral dosages of pharmaceuticals are necessary to treat a given disease state because many active ingredients are not completely absorbed by a patient in need of treatment. In other words, a better-absorbed dosage form of a medicament such as, for example, progesterone or estradiol, or dosage forms that provide greater consistency of absorption of progesterone or estradiol among subjects, alone or in combination with estradiol, may be able to be administered at dosage strengths lower than presently recommended, potentially resulting in a reduced or minimized side effect profile, among other potential benefits.

I. DEFINITIONS

The term "area under the curve" ("AUC") refers to the area under the curve defined by changes in the blood concentration of an active pharmaceutical ingredient (e.g., estradiol or progesterone), or a metabolite of the active pharmaceutical ingredient, over time following the administration of a dose of the active pharmaceutical ingredient. "$AUC_{0-\infty}$" is the area under the concentration-time curve extrapolated to infinity following the administration of a dose. "AUC_{0-t}" is the area under the concentration-time curve from time zero to time t following the administration of a dose, wherein t is the last time point with measurable concentration.

The term "C_{max}" refers to the maximum value of blood concentration shown on the curve that represents changes in blood concentrations of an active pharmaceutical ingredient (e.g., progesterone or estradiol), or a metabolite of the active pharmaceutical ingredient, over time.

The term "T_{max}" refers to the time that it takes for the blood concentration an active pharmaceutical ingredient (e.g., estradiol or progesterone), or a metabolite of the active pharmaceutical ingredient, to reach the maximum value.

Collectively AUC, C_{max} and, optionally, T_{max} are the principal pharmacokinetic parameters that can characterize the pharmacokinetic response of a particular drug product, such as progesterone or estradiol, in an animal, especially a mammal, including human, subject.

An "active pharmaceutical ingredient" (API), as used herein, means the active compound or compounds used in formulating a drug product. APIs are generally safe for administering to animals, especially mammals, including humans, according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

The term "bioavailability" has the meaning as defined in 21 C.F.R. § 320.1(a): the rate and extent to which an API or active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the API or active ingredient or active moiety becomes available at the site of action. For example, bioavailability can be measured as the amount of API in the blood (serum or plasma) as a function of time. Pharmacokinetic (PK) parameters such as AUC, C_{max}, or T_{max} may be used to measure and assess bioavailability.

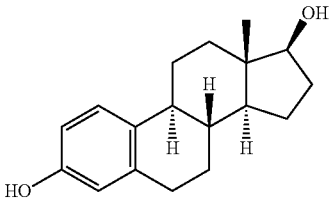
The term "bioequivalent" has the meaning as defined in 21 C.F.R. § 320.1(e): the absence of a significant difference in the rate and extent to which the API or active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. In practice, two products are considered bioequivalent if the 90% confidence interval of the AUC, C_{max}, or optionally T_{max} is within 80.00% to 125.00%.

As used herein, the term "comparable," as used with reference to comparing a bioavailability characteristic (including but not limited to area under the curve (AUC), C_{max}, or T_{max}) for a test composition, means that the test composition has a value for the bioavailability characteristic that is from 80% to 125% of the value of the bioavailability characteristic of a reference composition. In some embodiments, the reference composition is a commercially available progesterone composition (e.g., progesterone in a peanut oil, e.g., PROMETRIUM®) or a commercially available estradiol composition (e.g., a micronized estradiol tablet, e.g., ESTRACE®). In some embodiments, the reference composition is a co-administration of a commercially available progesterone composition (e.g., PROMETRIUM®) and a commercially available estradiol composition (e.g., ESTRACE®). In some embodiments, the reference composition is a combination formulation comprising progesterone and estradiol as provided herein. Thus, in some embodiments, a test composition is "comparable" to a reference combination formulation comprising progesterone and estradiol as provided herein when the test composition has

a value for a bioavailability characteristic (e.g., $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max}, and/or T_{max} for one or more analytes, e.g., progesterone, unconjugated estradiol, unconjugated estrone, or total estrone) that is from 80% to 125% of the value of the bioavailability characteristic of the reference combination formulation.

The term "bio-identical hormone" or "body-identical hormone" refers to an active pharmaceutical ingredient that is structurally identical to a hormone naturally or endogenously found in the human body (e.g., estradiol and progesterone).

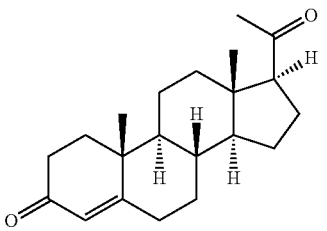
The term "estradiol" refers to (17β)-estra-1,3,5(10)-triene-3,17-diol. Estradiol is also interchangeably called 17β-estradiol, oestradiol, or E2, and is found endogenously in the human body. As used herein, estradiol refers to the bio-identical or body-identical form of estradiol found in the human body having the structure:



As used herein, unless specified, estradiol includes estradiol in anhydrous and hemihydrate forms. For the purposes of this disclosure, the anhydrous form or the hemihydrate form can be substituted for the other by accounting for the water or lack of water according to well-known and understood techniques.

The term "solubilized estradiol" means that the estradiol or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein. Solubilized estradiol may include estradiol that is about 80% solubilized, about 85% solubilized, about 90% solubilized, about 95% solubilized, about 96% solubilized, about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. In some embodiments, the estradiol is "fully solubilized" with all or substantially all of the estradiol being solubilized or dissolved in the solubilizing agent. Fully solubilized estradiol may include estradiol that is about 97% solubilized, about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The term "progesterone" refers to pregn-4-ene-3,20-dione. Progesterone is also interchangeably called P4 and is found endogenously in the human body. As used herein, prostergone refers to the bio-identical or body-identical form of progesterone found in the human body having the structure:



The term "solubilized progesterone" means that the progesterone or a portion thereof is solubilized or dissolved in the solubilizing agents or the formulations disclosed herein disclosed herein. In some embodiments, the progesterone is "partially solubilized" with a portion of the progesterone being solubilized or dissolved in the solubilizing agent and a portion of the progesterone being suspended in the solubilizing agent. The term "partially solubilized progesterone," as used herein, means progesterone which is in any state of solubilization up to but not including about 100%, e.g., about 1% solubilized, about 5% solubilized, about 10% solubilized, about 15% solubilized, about 20% solubilized, about 30% solubilized, about 40% solubilized, about 50% solubilized, about 60% solubilized, about 70% solubilized, about 80% solubilized, about 85% solubilized, about 90% solubilized, about 95% solubilized, or about 98% solubilized. In other embodiments, the progesterone is "fully solubilized" with all or substantially all of the progesterone being solubilized or dissolved in the solubilizing agent, e.g., at least about 98% solubilized, about 99% solubilized or about 100% solubilized. Solubility can be expressed as a mass fraction (% w/w, which is also referred to as wt %).

The terms "micronized progesterone" and "micronized estradiol," as used herein, include micronized progesterone and micronized estradiol, respectively, having an X50 particle size value below about 15 microns and/or having an X90 particle size value below about 25 microns. The term "X50," as used herein, means that one-half of the particles in a sample are smaller in diameter than a given number. For example, micronized progesterone having an X50 of 5 microns means that, for a given sample of micronized progesterone, one-half of the particles have a diameter of less than 5 microns. Similarly, the term "X90" means that ninety percent (90%) of the particles in a sample are smaller in diameter than a given number.

The terms "uniform distribution," "uniform dispersal," and "uniformly dispersed," as used with reference to estradiol or progesterone, means at least one of uniform dispersion, solubility, or lack of agglomeration of estradiol or progesterone in a dissolution test compared to a reference product (e.g., PROMETRIUM® or ESTRACE®, respectively) at a similar dosage strength and the same USP dissolution apparatus.

The terms "solubilizer" and "solubilizing agent" refer to any substance or mixture of substances that may be used to solubilize or to enhance the solubility of an active pharmaceutical ingredient (e.g., estradiol or progesterone). For example and without limitation, suitable solubilizing agents include medium chain oils and other solvents and co-solvents (e.g., surfactants) that solubilize or dissolve an active pharmaceutical ingredient to a desirable extent. Solubilizing agents suitable for use in the formulations disclosed herein are pharmaceutical grade solubilizing agents (e.g., pharmaceutical grade medium chain oils). It will be understood by those of skill in the art that other excipients or components can be added to or mixed with the solubilizing agent to enhance the properties or performance of the solubilizing agent or resulting formulation. Examples of such excipients include, but are not limited to, surfactants, emulsifiers, thickeners, colorants, flavoring agents, etc. In some embodiments, the solubilizer or solubilizing agent is a medium chain oil and, in some other embodiments, the medium chain oil is combined with a co-solvent(s) or other excipient(s).

The term "medium chain" is used to describe the aliphatic chain length of fatty acid containing molecules. As used herein, "medium chain" means any medium chain carbon-

containing substance, including C4-C18, and including C6-C12 substances, fatty acid esters of glycerol, fatty acids, and mono-, di-, and tri-glycerides of such substances. In some embodiments, "medium chain" refers to fatty acids, fatty acid esters, or fatty acid derivatives that contain fatty acid aliphatic tails or carbon chains that contain between 6 (C6) and 14 (C14) carbon atoms. As non-limiting examples, C6-C14 fatty acids, C6-C12 fatty acids, and C8-C10 fatty acids are all medium chain fatty acids and may be used in instances in which this specification calls for use of medium chain fatty acids, e.g., medium chain fatty acid esters of glycerol or other glycols. Examples include, without limitation, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, and derivatives thereof.

The term "oil," as used herein, may be any pharmaceutically acceptable oil, such as an organic oil other than peanut oil, that would suspend and/or solubilize any suitable progesterone or estradiol, starting material, or precursor, including micronized progesterone or estradiol as described herein. In some embodiments, oils may include, for example and without limitation, medium chain fatty acids, generally of the group known as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof.

The term "medium chain oil" refers to an oil wherein the composition of the fatty acid fraction of the oil is substantially or predominantly medium chain (e.g., C6 to C14) fatty acids, i.e., the composition profile of fatty acids in the oil is substantially medium chain. As used herein, "substantially" or "predominantly" means that between 20% and 100% (inclusive of the upper and lower limits) of the fatty acid fraction of the oil is made up of medium chain fatty acids. In some embodiments, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the fatty acid fraction of the oil is made up of medium chain fatty acids. It will be understood by those of skill in the art that the medium chain oils suitable for use in the formulations disclosed herein are pharmaceutical grade (e.g., pharmaceutical grace medium chain oils). Examples of medium chain oils include, for example and without limitation, medium chain fatty acids, medium chain fatty acid esters of glycerol (e.g., for example, mono-, di-, and triglycerides), medium chain fatty acid esters of propylene glycol, medium chain fatty acid derivatives of polyethylene glycol, and combinations thereof.

II. FORMULATIONS

In one aspect, this disclosure relates to pharmaceutical formulations for co-administering estradiol and progesterone to a human subject in need thereof. In some embodiments, the formulation comprises estradiol, progesterone, and a medium chain oil (e.g., a C6-C12 oil). In some embodiments, a pharmaceutical formulation comprising progesterone and estradiol as described herein demonstrates comparable bioavailability to their individual drug references of PROMETRIUM® and ESTRACE®, respectively, when the formulation is administered to a human subject or a population of subjects.

Another aspect of the present disclosure includes a pharmaceutical formulation of micronized progesterone, micronized progesterone with partially solubilized progesterone and fully solubilized progesterone, wherein the formulation may provide increased progesterone bioavailability in a treated subject compared to the bioavailability provided by PROMETRIUM® when administered at equal dosage strengths.

Additional objects of the present disclosure includes: providing increased patient compliance secondary to ease of use; providing increased physician adoption secondary to ease of use/instruction with less worry of side effects from inappropriate usage; providing decreased side-effects from erroneous use (decreased irregular bleeding); providing better efficacy/control of symptoms secondary to appropriate use; reducing the metabolic and vascular side effects of the commonly used synthetic progestins when administered alone or in combination with an estrogen (norethindrone acetate, medroxyprogesterone acetate, etc.) including, for example, stroke, heart attacks, blood clots and breast cancer.

Formulations of Estradiol and Progesterone

In some embodiments, a pharmaceutical formulation for use as described herein comprises solubilized estradiol without progesterone; micronized progesterone without estradiol; micronized progesterone with partially solubilized progesterone; solubilized estradiol with micronized progesterone; solubilized estradiol with micronized progesterone in combination with partially solubilized progesterone; or solubilized estradiol with solubilized progesterone. The underlying formulation concepts provided herein may be used with other natural or synthetic forms of estradiol and progesterone. Unless otherwise specified, "natural," as used herein with reference to hormones discussed herein, means bio-identical or body-identical hormones formulated to match the chemical structure and effect of those that occur naturally in the human body (endogenous). An exemplary natural estrogen is estradiol (also described as 17β-estradiol and E2) and a natural progestin is progesterone. Micronization specifications, aspects and embodiments are further defined herein.

Other aspects of the present disclosure further provide: more uniform dissolution of progesterone, and reduced intra- and inter-patient blood level variability in formulations of progesterone of the present disclosure, typically in combinations with solubilized estradiol, when compared to equal dosages of PROMETRIUM®). Blood level variability is also compared at equal sampling times following administration. Not to be limited by theory, these aspects are believed to be influenced by the percentage of solubilized progesterone in a respective formulation wherein such more uniform dissolution of progesterone, and lower intra- and inter-patient blood level variability, are influenced by a greater proportion of solubilized progesterone relative to total progesterone. A reduced food effect with the present formulations comprising progesterone may also be implicated.

According to the PROMETRIUM® prescribing information, clinical trials have shown significant patient variability. For example, a clinical trial involving post-menopausal women who were administered PROMETRIUM® once a day for five days resulted in the mean PK parameters listed in the following table:

TABLE 1

	PROMETRIUM Capsules Daily Dose		
Parameter	100 mg	200 mg	300 mg
C_{max} (ng/ml)	17.3 +/− 21.9	38.1 +/− 37.8	60.6 +/− 72.5
T_{max} (hr)	1.5 +/− 0.8	2.3 +/− 1.4	1.7 +/− 0.6
AUC_{0-10} (ngxhr/ml)	43.4+/− 30.8	101.2 +/− 66.0	175.7 +/− 170.3

In particular illustrative aspects and embodiments of this invention, it is possible, though not necessary, to reduce the standard deviations in one or more of these PK parameters.

More uniform dissolution of progesterone in a formulation of the present disclosure compared to the dissolution of PROMETRIUM® at equal dosage strengths and using the same USP apparatus can be determined using standard techniques established for API dissolution testing, including that which is described in the examples below.

Reduced intra- and inter-patient variability of progesterone formulated pursuant to the present disclosure compared to PROMETRIUM can be demonstrated via a fed bio-study such as that described below.

Exemplary dosage strengths for estradiol for use in the formulations described herein include, without limitation, 0.125, 0.25, 0.375, 0.50, 0.625, 0.75, 1.00, 1.125, 1.25, 1.375, 1.50, 1.625, 1.75 and 2.00 mg. Exemplary dosage strengths for progesterone for use in the formulations described herein include, without limitation, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 and 400 mg. These dosage strengths for each of estradiol and progesterone can be administered in formulations described herein either alone or in combination.

In some embodiments, estradiol is solubilized. Estradiol solubilization helps ensure high content uniformity and enhanced stability. Solubilized estradiol may include estradiol that is approximately 80% to 100% soluble in a solubilizing agent, including specifically embodiments that are: 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% soluble in a solubilizing agent. Solubility may be expressed as a mass fraction (% w/w, also referred to as wt %).

In some embodiments, the composition comprises micronized progesterone. Progesterone active pharmaceutical ingredient may be micronized via any one of the multiple methods typically utilized by the ordinarily skilled artisan. In various embodiments, micronized progesterone has an X50 particle size value of less than about 15 microns, less than about 10 microns, less than about 5 microns and/or less than about 3 microns. In various embodiments, micronized progesterone has an X90 particle size value of less than about 25 microns, less than about 20 microns, and/or less than about 15 microns.

Particle size may be determined in any suitable manner. For example, a Beckman Coulter LS 13 320 Laser Diffraction Particle Size Analyzer (the "Beckman Device") may be used to determine particle size. As described above, particle size may be represented by various metrics, for example, through an X50 particle size, and/or X90 particle size, or similar descriptions of particle size.

The Beckman Device may be used with various modules for introducing a sample for analysis. The Beckman Device may be used with the LS 13 320 Universal Liquid Module ("ULM"). The ULM is capable of suspending samples in the size range of 0.017 μm to 2000 μm. The ULM is a liquid based module that allows for delivery of the sample to the sensing zone. The ULM recirculates the sample through the Beckman Device. The ULM comprises two hoses, one for fluid delivery and another for waste. The total volume used may be 125 mL or less. A sample mass of from about 1 mg to about 10 g may be used. The ULM may interact with the Beckman Device via pins that fit into slots on the ULM. The ULM may use a variety of suspension fluids, for example, water, butonol, ethanol, chloroform, heptanes, toluene, propanol, COULTER Type 1B Dispersant ("Coulter 1B"), and a variety of other suspension fluids. Surfactants may also be used, though pump speed should be adjusted to prevent excessive bubbling. Coulter 1B may comprise one or more of acetaldehyde, ethylene oxide, and/or 1,4-dioxane. The Beckman Device may be configured to use a variety of optical theories, including the Fraunhofer optical model and the Mie Theory.

The Beckman Device may comprise software to control the Beckman Device while the ULM is in use. The software may control, for example, pump speed, use of de-bubble routine, rinse routine, sonicate routine, and fill routine, among others. Parameters regarding the sample run may also be configured. For example, run length may be set. Though any suitable run length may be used, in various embodiments, a time period of 30 seconds to 120 seconds, and preferably between 30 seconds and 90 seconds may be used.

The Beckman Device may be used with the LS 13 320 Micro Liquid Module ("MLM"). The MLM is capable of suspending samples in the size range of 0.4 μm to 2000 μm. The MLM is a liquid based module that allows for delivery of the sample to the sensing zone. The MLM includes a stirrer. The total volume used may be 12 mL or less. The MLM may use a variety of suspension fluids, both aqueous and non-aqueous.

In some embodiments, the progesterone is solubilized. Fully solubilized progesterone formulations or partially solubilized progesterone formulations, in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95% is solubilized, appear to provide improved PK-related properties.

In some embodiments, the estradiol and the progesterone are both in the solubilizing agent. In some embodiments, the estradiol and the progesterone are both uniformly dispersed in the pharmaceutical formulation.

In accordance with various aspects and embodiments, the solubility proportion (i.e., the proportion of a solute that enters solution) is notable. The weight ratio of estradiol to the weight of the entire solution is also notable due to the intended dose amounts, discussed herein. In particular, it is desirable to obtain a target dosage of estradiol in an amount of solution that may be readily administered via a capsule. For example, if it is desired to have a dose of estradiol in a capsule of between about 0.125 mg to about 2 mg, it would also be desirable to have a total solution weight to be between about 250 mg to about 400 mg, preferably about 300 mg to about 350 mg and more preferably about 325 mg. In various embodiments, the following weight ratios of estradiol to total solution are from about 0.125/50 mg to about 0.125/1000 mg, from about 1 mg:500 mg to about 1 mg:50 mg; from about 1 mg:250 mg to about 1 mg:60 mg; from about 1 mg:100 mg to about 1 mg:66 mg; from about 2 mg/50 mg to about 2 mg/1000 mg. In various embodiments, the target for single dose product is 325 mg, and a target fill weight for a combination product (e.g., two or more sterol APIs) is 650 mg.

In illustrative embodiments, total progesterone, i.e., dissolved and micronized, is 20 to 50 wt %, e.g., 30 to 35 wt %; estradiol is 0.1 to 0.8 wt %, e.g., 0.15 to 0.35 wt %.

Solubilizing Agents

In various embodiments, the solubilizing agent is selected from at least one of a solvent or co-solvent. Suitable solvents and co-solvents include any mono-, di- or triglyceride and glycols, and combinations thereof.

In some embodiments, formulations of the present disclosure (e.g., estradiol and progesterone formulations) are prepared via blending with a pharmaceutically acceptable oil; generally, the oil comprises at least one medium chain

fatty acid such as medium chain fatty acids consisting of at least one mono-, di-, or triglyceride, or derivatives thereof, or combinations thereof. Optionally added are other excipients including, for example and without limitation, antioxidants, lubricants and the like. Sufficient oil is used to form a suspension of micronized progesterone or, in the alternative, solubilize progesterone.

In illustrative embodiments of the invention, oils used to solubilize estradiol and to suspend, partially solubilize, or fully solubilize progesterone include medium chain fatty acid esters (e.g., esters of glycerol, polyethylene glycol, or propylene glycol) and mixtures thereof. In illustrative embodiments, the medium chain fatty acids are C6 to C14 or C6 to C12 fatty acids. In illustrative embodiments, the medium chain fatty acids are saturated, or predominantly saturated, e.g., greater than about 60% or greater than about 75% saturated.

Mixtures of medium chain fatty acid glycerides, e.g., C6-C12, C8-C12, or C8-C10 fatty acid mono- and diglycerides or mono-, di-, and triglycerides are very well suited for dissolving estradiol; good results have been obtained with an oil that is predominantly a mixture of C8-C10 saturated fatty acid mono- and diglycerides. Longer chain glycerides appear to be not as well suited for dissolution of estradiol. On the other hand, high solubility of progesterone has been obtained in mixtures that are predominantly medium chain fatty acid triglycerides.

Pharmaceutically acceptable oils include, without limitation, the use of at least one of caproic fatty acid; caprylic fatty acid; capric fatty acid; tauric acid; myristic acid; linoleic acid; succinic acid; glycerin; mono-, di-, or triglycerides and combinations and derivatives thereof; a polyethylene glycol; a polyethylene glycol glyceride (GELUCIRE®, a polyethylene glycol glyceride); GATTEFOSSE SAS, Saint-Priest, France); a propylene glycol; a caprylic/capric triglyceride (MIGLYOL® (caprylic/capric triglyceride) SASOL Germany GMBH, Hamburg; MIGLYOL® includes MIGLYOL® 810, 812, 816 and 829); a caproic/caprylic/capric/lauric triglyceride; a caprylic/capric/linoleic triglyceride; a caprylic/capric/succinic triglyceride; propylene glycol monocaprylate; propylene glycol monocaprate; (CAPMUL® PG-8 (propylene glycol monocaprylate) and 10; the CAPMUL® MCM (medium chain mono- and diglycerides) brands are owned by ABITEC, Columbus Ohio); propylene glycol dicaprylate; propylene glycol dicaprylate; medium chain mono- and di-glycerides (CAPMUL® MCM); a diethylene glycol mono ester (including 2-(2-Ethoxyethoxy)ethanol: TRANSCUTOL® (diethylene glycol monoethyl ether); esters of saturated coconut and palm kernel oil and derivatives thereof; triglycerides of fractionated vegetable fatty acids, and combinations and derivatives thereof.

Illustrative examples of mono- and diglycerides of medium chain fatty acids include, among others, CAPMUL® MCM, CAPMUL® MCM C10, CAPMUL® MCM C8, and CAPMUL® MCM C8 EP. These oils are C8 and C10 fatty acid mono- and diglycerides. Illustrative examples of oils that are triglycerides of medium chain fatty acids include, among others, MIGLYOL® 810 and MIGLYOL® 812.

Illustrative examples of oils that are medium chain fatty acid esters of propylene glycol include, among others, CAPMUL® PG-8, CAPMUL® PG-2L EP/NF, CAPMUL® PG-8 NF, CAPMUL® PG-12 EP/NF and CAPRYOL™. Other illustrative examples include MIGLYOL® 840.

Illustrative examples of oils that are medium chain fatty acid esters of polyethylene glycol include, among others, GELUCIRE® 44/14 (PEG-32 glyceryl laurate EP), which is polyethylene glycol glycerides composed of mono-, di- and triglycerides and mono- and diesters of polyethylene glycol. Without intending to be bound to any particular mechanism, it appears that at least in formulations comprising small amounts of GELUCIRE®, e.g., 10 wt % or less, the primary function of this oil is as a non-ionic surfactant.

These illustrative examples comprise predominantly medium chain length, saturated, fatty acids, specifically predominantly C8 to C12 saturated fatty acids.

In accordance with various embodiments, the formulations of the present disclosure do not include peanut oil.

It will be understood that commercially available fatty acid esters of glycerol and other glycols are often prepared from natural oils and therefore may comprise components additional to the fatty acid esters that comprise the predominant (by weight) component(s) and that therefore are used to characterize the product. Such other components may be, e.g., other fatty acid triglycerides, mono- and diesters, free glycerol, or free fatty acids. So, for example, when an oil/solubilizing agent is described herein as a saturated C8 fatty acid mono- or diester of glycerol, it will be understood that the predominant component of the oil, i.e., >50 wt % (e.g., >75 wt %, >85 wt % or >90 wt %) are caprylic monoglycerides and caprylic diglycerides. For example, the Technical Data Sheet by ABITEC for CAPMUL® MCM C8 describes CAPMUL® MCM C8 as being composed of mono and diglycerides of medium chain fatty acids (mainly caprylic) and describes the alkyl content as ≤1% C6, ≥95% C8, ≤5% C10, and ≤1.5% C12 and higher.

By way of further example, MIGLYOL® 812 is generally described as a C8-C10 triglyceride because the fatty acid composition is at least about 80% caprylic (C8) acid and capric (C10) acid. However, it can also comprise small amounts of other fatty acids, e.g., less than about 5% of caproic (C6) acid, lauric (C12) acid, and myristic (C14) acid.

Specifically, a product information sheet for MIGLYOL® by SASOL provides the composition of fatty acids as follows:

TABLE 2

MIGLYOL ® Fatty Acid Composition

Fatty acid	MIGLYOL ® 810	MIGLYOL ® 812	MIGLYOL ® 818	MIGLYOL ® 829	MIGLYOL ® 840
Caproic acid (C6:0)	max. 2.0	max. 2.0	max. 2	max. 2	max. 2
Caprylic acid (C8:0)	65.0-80.0	50.0-65.0	45-65	45-55	65-80
Capric acid (C10:0)	20.0-35.0	30.0-45.0	30-45	30-40	20-35
Lauric acid (C12:0)	max. 2	max. 2	max. 3	max. 3	max. 2

TABLE 2-continued

MIGLYOL ® Fatty Acid Composition					
Fatty acid	MIGLYOL ® 810	MIGLYOL ® 812	MIGLYOL ® 818	MIGLYOL ® 829	MIGLYOL ® 840
Myristic acid (C14:0)	max. 1.0	max. 1.0	max. 1	max. 1	max. 1
Linoleic acid (C18:2)	—	—	2-5	—	—
Succinic acid	—	—	—	15-20	—

Where certain embodiments of this invention are described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in C8-C10 triglycerides, and a thickening agent, it will be understood that the fatty acid esters component of the formulation may be, e.g., MIGLYOL® 812 or a similar product.

By way of further illustration, GELUCIRE® 44/14 is generally described as lauroyl polyoxyl-32 glycerides, i.e., polyoxyethylene 32 lauric glycerides (which is a mixture of mono-, di-, and triesters of glycerol and mono- and diesters of PEGs) because the fatty acid composition is 30 to 50% lauric acid and smaller amounts of other fatty acids, e.g., up to 15% caprylic acid, up to 12% capric acid, up to 25% myristic acid, up to 25% palmitic acid, and up to 35% stearic acid. The product may also contain small amounts of non-esterified glycols. Where certain embodiments of this invention are described as described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising C8 to C18 fatty acid esters of glycerol and polyethylene glycol, it will be understood that the thickening agent component of the formulation may be, e.g., GELUCIRE® 44/14 or a similar product.

Similarly, where certain embodiments of this invention are as described as comprising (or consisting essentially of) a capsule shell, estradiol solubilized in triglycerides, and a thickening agent that is a non-ionic surfactant comprising PEG-6 stearate, ethylene glycol palmitostearate, and PEG-32 stearate, it will be understood that the thickening agent component of the formulation may be, e.g., TEFOSE® 63 or a similar product.

In addition to the oils referenced above, other solubilizers include, for example and without limitation, glyceryl mono- and di-caprylates, propylene glycol and 1,2,3-propanetriol (glycerol, glycerin, glycerine).

Anionic and/or non-ionic surfactants can be used in other embodiments of the presently disclosed formulations containing estradiol, progesterone or a combination thereof. In certain embodiments, a non-ionic surfactant is used. Exemplary non-ionic surfactants may include, for example and without limitation, one or more of oleic acid, linoleic acid, palmitic acid, and stearic acid esters or alcohols. In further embodiments, the non-ionic surfactant may comprise polyethylene sorbitol esters, including polysorbate 80, which is commercially available under the trademark TWEEN 80® (Sigma Aldrich, St. Louis, Mo.). Polysorbate 80 comprises approximately 60%-70% oleic acid with the remainder comprising primarily linoleic acids, palmitic acids, and stearic acids. Polysorbate 80 may be used in amounts ranging from about 5 to 50%, and in certain embodiments, about 30% of the formulation total mass.

In various other embodiments, the non-ionic surfactant is selected from one or more of glycerol and polyethylene glycol esters of fatty acids, for example, lauroyl macrogol-32 glycerides and/or lauroyl polyoxyl-32 glycerides, commercially available as GELUCIRE®, including, for example, GELUCIRE® 44/11 and GELUCIRE® 44/14. These surfactants may be used at concentrations greater than about 0.01%, and typically in various amounts of about 0.01%-10.0%, 10.1%-20%, and 20.1%-30%. In certain examples, below, GELUCIRE® 44/14 is used as a surfactant in amounts of 1 to 10 wt %. See, e.g., Tables 13-17, below. Other non-ionic surfactants include, e.g., LABRASOL® PEG-8 Caprylic/Capric Glycerides (Gattefosse) and LABRAFIL® corn/apricot oil PEG-6 esters (Gattefosse).

Other Excipients

In other embodiments, a lubricant is used. Any suitable lubricant may be used, such as for example lecithin. Lecithin may comprise a mixture of phospholipids.

In additional embodiments, an antioxidant is used. Any suitable antioxidant may be used such as, for example and without limitation, butylated hydroxytoluene.

For example, in various embodiments, a pharmaceutical formulation comprises about 20% to about 80% carrier by weight, about 0.1% to about 5% lubricant by weight, and about 0.01% to about 0.1% antioxidant by weight.

The choice of excipient will, to a large extent, depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Excipients used in various embodiments may include colorants, flavoring agents, preservatives and taste-masking agents. Colorants, for example, may comprise about 0.1% to about 2% by weight. Preservatives may comprise methyl and propyl paraben, for example, in a ratio of about 10:1, and at a proportion of about 0.005% and 0.05% by weight.

As is with all oils, solubilizers, excipients and any other additives used in the formulations described herein, each is to be non-toxic and pharmaceutically acceptable.

Formulation and Administration

In some embodiments, combinations of solubilizing agents (e.g., two or more oils or combinations of one or more oils and one or more surfactants) are used to form estradiol and progesterone compositions. Various ratios of these solubilizing agents (e.g., oils or surfactants) can be used. CAPMUL® MCM and a non-ionic surfactant, e.g., GELUCIRE® 44/14 (lauroyl macrogol-32 glycerides EP; lauroyl polyoxyl-32 glycerides NF; lauroyl polyoxylglycerides (USA FDA IIG)), can be used at ratios of about 99:1 to 2:1, including, for example and without limitation: 60:40, 65:35, 70:30, 75:25, 80:10, 80:15, 85:20, 90:10, and 98:1. The ratios of oil (e.g., medium chain fatty acid esters of monoglycerides and diglycerides) to non-ionic surfactant can be significantly higher. For example, in certain examples, below, CAPMUL® MCM and GELUCIRE® were used in ratios of up to about 65:1, e.g., 8:1, 22:1, 49:1, 65:1 and 66:1. See, e.g., Tables 20-24, below. Thus, useful ratios can be 8:1 or greater, e.g., 60 to 70:1. Among other combina-

tions, these solubilizers, as defined herein, and combinations thereof, can be used to form combination estradiol and progesterone formulations of the present disclosure.

In illustrative embodiments, estradiol or progesterone is soluble in the oils at room temperature, although it may be desirable to warm the oils up until they are in a liquid state. In illustrative embodiments, the oil or oil/surfactant is liquid at between room temperature and about 50° C., e.g., at or below 50° C., at or below 40° C., or at or below 50° C. In illustrative embodiments, GELUCIRE® 44/14 is heated to about 65° C. and CAPMUL® MCM is heated to about 40° C. to facilitate mixing of the oil and non-surfactant, although such heating is not necessary to dissolve the estradiol or progesterone. In illustrative embodiments, the solubility of estradiol in the oil (or oil/surfactant) is at least about 0.5 wt %, e.g., 0.8 wt % or higher, or 1.0 wt % or higher. However, much higher solubility can be achieved. For example, as shown in Example 4, below, estradiol is stable in solution in CAPMUL® MCM at 12 mg/g (which is approximately equal to 12 mg/ml). As shown in Example 19, such solubility is favored over results observed in longer chain and unsaturated fatty acid esters.

High solubility of estradiol has been obtained in 2-(2-Ethoxyethoxy)ethanol, e.g., TRANSCUTOL® and in Propylene glycol monocaprylate, e.g., CAPRYOL™ 90 (Gattefosse).

In some embodiments, progesterone is fully solubilized using, for example and without limitation, sufficient amounts of: TRANSCUTOL® and MIGLYOL®; TRANSCUTOL®, MIGLYOL® and CAPMUL® PG 8 and/or PG 10; CAPMUL® MCM; CAPMUL® and a non-ionic surfactant; and CAPMUL® MCM and GELUCIRE®.

Combinations of these oils can produce partially solubilized progesterone, depending upon the desired unit dosage amount of progesterone. The greater the amount of progesterone per unit dosage form, the less progesterone may be solubilized. The upward limit of dosage strength per unit dose it generally limited only by the practical size of the final dosage form.

In illustrative embodiments of the invention, the selected oil does not require excessive heating in order to solubilize progesterone or estradiol. For example, when the formulation comprises medium chain fatty acid mono- and diglycerides (e.g., CAPMUL® MCM) and polyethylene glycol glycerides (e.g., GELUCIRE®) as a surfactant, the oil and/or the surfactant can be warmed up, e.g., to about 65° C. in the case of the surfactant and less in the case of the oil, to facilitate mixing of the oil and surfactant. The estradiol can be added at this temperature or at lower temperatures as the mixture cools or even after it has cooled as temperatures above room temperature, e.g., about 20° C., are not required to solubilize the estradiol in preferred oils. The progesterone can also be added as the mixture cools, e.g., to below about 40° C. or to below about 30° C., even down to room temperature.

As a non-limiting example, an illustrative embodiment of a pharmaceutical composition of the invention comprises solubilized estradiol, progesterone at least 75% of the progesterone being solubilized (the balance being micronized as discussed elsewhere herein), and an oil, wherein the oil is medium chain fatty acid mono- and diesters of glycerol, with or without surfactant. In certain embodiments, a specification for progesterone is set at >80% solubilized, <20% micronized or >85% solubilized, <15% micronized. Specific examples of such illustrative embodiments, with GELUCIRE® as surfactant, in which at least about 85% of the progesterone can be solubilized, include, e.g., the following four formulations:

TABLE 3

Formulation A—P:50/E2:0.25:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.17	0.26
CAPMUL ® MCM, NF	65.49	98.24
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 4

Formulation B—P:50/E2:0.5:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	50.00
Estradiol Hemihydrate	0.35	0.52
CAPMUL ® MCM, NF	65.32	97.98
GELUCIRE ® 44/14, NF	1.00	1.50
Total	100.00	150.00

TABLE 5

Formulation C—P:100/E2:0.5:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.17	0.52
CAPMUL ® MCM, NF	65.49	196.48
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 6

Formulation D—P:100/E2:1:

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	100.00
Estradiol Hemihydrate	0.34	1.03
CAPMUL ® MCM, NF	65.32	195.97
GELUCIRE ® 44/14, NF	1.00	3.00
Total	100.00	300.00

TABLE 7

Formulation E—P:200/E2:2:		
Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate	0.34	2.06
CAPMUL ® MCM, NF	65.32	391.94
GELUCIRE ® 44/14, NF	1.00	6.00
Total	100.00	600.00

*Note:
1.00 mg Estradiol equivalent to 1.03 mg Estradiol Hemihydrate.

In general terms, the above formulations comprise 30 to 35 wt % progesterone, 0.1 to 0.4 wt % estradiol (or estradiol hemihydrate), 55 to 75 wt % of an oil that is predominantly medium chain fatty acid mono- and diglycerides, such as CAPMUL® MCM, and 0.5 to 10 wt % non-ionic surfactant, such as GELUCIRE® 44/14. The above formulations may be modified to comprise excipients, e.g., gelatin such as Gelatin 200 Bloom, glycerin, coloring agents such as Opatint red and white, and, optionally, MIGLYOL® 812.

Estradiol solubilization helps ensure high content uniformity and enhanced stability. Fully solubilized progesterone formulations or partially solubilized progesterone formulations in which at least about 50% of the progesterone, e.g., 75%, 80%, 85%, 90%, or >95%, is solubilized appear to provide improved PK-related properties.

Pharmaceutical formulations as described herein can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid preparation can comprise one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton Pa. ("Remington's").

In some embodiments, the pharmaceutical formulations described herein are prepared and administered as filled capsules, typically soft capsules of one or more materials well known in the art including, for example and without limitation, soft gelatin capsules. Micronized progesterone, as described herein, may also be prepared for administration in tablets or other well-known orally administered dosage forms using standard techniques.

In some embodiments, in which the carrier is a medium fatty acid ester of a glycol and which comprise a non-ionic surfactant as described herein, the formulations are in liquid form, i.e., not gels, hard fats or other solid forms.

In general, the type of composition is selected based on the mode of administration. A pharmaceutical composition (e.g., for oral administration or delivery by injection) can be in the form of a liquid (e.g., an elixir, syrup, solution, emulsion or suspension). Alternatively, a pharmaceutical composition as described herein can take the form of a pill, tablet, or capsule containing the liquid oil, and thus, the composition can contain any of the following: a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such a starch, gum acacia, polyvinylpyrrolidone, gelatin, cellulose and derivatives thereof. The composition can also be formulated into a suppository disposed, for example, in a polyethylene glycol (PEG) solubilizing agent.

Administration of the formulations described herein can be carried out via any of the accepted modes of administration. Thus, administration can be, for example, intravenous, topical, subcutaneous, transcutaneous, transdermal, intramuscular, oral, intra-joint, parenteral, intra-arteriole, intradermal, intraventricular, intracranial, intraperitoneal, intralesional, intranasal, rectal, vaginal, or by inhalation. In some embodiments, a composition as described herein is administered orally. For example, a pharmaceutical composition as described herein can be administered via capsules such as soft capsules. In some embodiments, a pharmaceutical composition as described herein is administered once daily.

According to various embodiments described herein, a 28-day or monthly regimen of capsules can be packaged in a single kit (e.g., a blister pack) having administration days identified to improve compliance and reduce associated symptoms, among others. One or more of the capsules may contain no estradiol, for example, and/or no progesterone. Capsules that comprise no estrogen or progesterone API may be referred to as placebos. A blister pack can have a plurality of scores or perforations separating blister pack into 28 days. Each day may further comprise a single blister or a plurality of blisters. In various embodiments, each unit dose may contain micronized and/or partially solubilized, or fully solubilized progesterone and/or solubilized estradiol in amounts as set forth herein above, although other dose ranges may be contemplated. In addition, kits having other configurations are also contemplated herein. For example, without limitation, kits having such blister packs may contain any number of capsules.

As referenced above, the formulations of the present disclosure are generally orally administered, typically via, for example, capsules such as soft capsules. The present formulations can also be used to form transdermal patches using standard technology known in the art. Solubilized formulations of the present invention can also be formulated for intraperitoneal administration using techniques well known in the art.

In some embodiments, the pharmaceutical formulations disclosed herein are useful in treating conditions in subjects caused, at least in part, by estrogen deficiency, particularly for women with a uterus. For example, in some embodiments, the formulations disclosed herein are useful for the treatment of an animal, especially a mammal, including humans, for menopause; for endometrial hyperplasia; for secondary amenorrhea; as a method of treatment for preterm birth, when said animal has a shortened cervix, and other disease states or conditions treated with supplemental progesterone or estrogen. In some embodiments, a formulation as disclosed herein is useful for treating one or more symptoms of menopause such as vaginal atrophy, vaginal dryness, watery discharge, skin dryness, osteoporosis, thin bones, painful fractures, incontinence, urinary frequency, urinary urgency, urinary tract infections, temperature dyregulation (e.g., feeling unusually hot or cold or temperature swings), dysfunctional bleeding, rapid heartbeat, migraine, breast tenderness or swelling, breast atrophy, decreased skin elasticity, back pain, joint pain, muscle pain, fatigue, decreased libido, dyspareunia, vasomotor symptoms (e.g., flushing, hot flashes), irritability, memory loss, mood disturbance, depression, anxiety, sleep disturbance, and sweating. Thus, in some embodiments, the present disclosure provides methods of treating such a condition by administering to the subject a composition comprising estra-

diol and progesterone as described herein. As used herein, the term "treatment," or a derivative thereof, contemplates partial or complete inhibition of the stated disease state when a formulation as described herein is administered prophylactically or following the onset of the disease state for which such formulation is administered. For the purposes of the present disclosure, "prophylaxis" refers to administration of the active ingredient(s) to an animal, especially a mammal, to protect the animal from any of the disorders set forth herein, as well as others.

Bioavailability Properties

The pharmaceutical formulations of the present disclosure can be formulated to provide desirable pharmacokinetic parameters in a subject (e.g., a female subject) to whom the composition is administered. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for progesterone in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for estradiol in the subject. In some embodiments, a pharmaceutical composition as described herein produces desirable pharmacokinetic parameters for one or more metabolites of progesterone or estradiol in the subject, for example estrone or total estrone.

In certain embodiments, combination formulations of the present disclosure exhibit bioavailability properties that are comparable to the bioavailability properties of the components of the combination formulation when individually formulated (e.g., progesterone in a peanut oil, e.g., PROMETRIUM®, and a micronized estradiol tablet, e.g., ESTRACE®). In certain embodiments, a composition is within the scope of the invention if it has a value for a pharmacokinetic parameter that is about 80% to about 125% of the value of the pharmacokinetic parameter for a reference composition when said formulation is administered to a human subject.

Following the administration of a composition comprising progesterone and estradiol to a subject, the concentration and metabolism of progesterone or estradiol can be measured in a sample (e.g., a plasma sample) from the subject. Progesterone is metabolized to pregnanediols and pregnanolones, which are then conjugated to glucuronide and sulfate metabolites that are excreted or further recycled. Estradiol is converted reversibly to estrone, and both estradiol and estrone can be converted to the metabolite estriol. In postmenopausal women, a significant proportion of circulating estrogens exist as sulfate conjugates, especially estrone sulfate. Thus, estrone can be measured with respect to "estrone" amounts (excluding conjugates such as estrone sulfate) and "total estrone" amounts (including both free, or unconjugated, estrone and conjugated estrone such as estrone sulfate).

The pharmaceutical formulations of the present disclosure can be characterized for one or more pharmacokinetic parameters of progesterone, estradiol, or a metabolite thereof following administration of the composition to a subject or to a population of subjects. These pharmacokinetic parameters include AUC, C_{max}, and T_{max}.

In certain embodiments, a composition is within the scope of the invention if it has a C_{max} value that is about 80% to about 125% of the C_{max} value of the reference composition. C_{max} is well understood in the art as an abbreviation for the maximum drug concentration in serum or plasma of the test subject. In certain embodiments, a composition is within the scope of the invention if it has a T_{max} value that is about 80% to about 125% of the T_{max} value of the reference composition. T_{max} is well understood in the art as an abbreviation for the time to maximum drug concentration in serum or plasma of the test subject. In vivo testing protocols for determining a C_{max} and/or T_{max} value can be designed in a number of ways.

In certain embodiments, a composition is within the scope of the invention if it has an AUC value that is about 80% to about 125% of the AUC value of the reference composition. AUC is a determination of the area under the curve (AUC) plotting the serum or plasma concentration of drug along the ordinate (Y-axis) against time along the abscissa (X-axis). AUCs are well understood, frequently used tools in the pharmaceutical arts and have been extensively described, for example in "Pharmacokinetics Processes and Mathematics," Peter E. Welling, ACS Monograph 185; 1986.

Any of a variety of methods can be used for measuring the levels of progesterone, estradiol, estrone, or total estrone in a sample, including immunoassays, mass spectrometry (MS), high performance liquid chromatography (HPLC) with ultraviolet fluorescent detection, liquid chromatography in conjunction with mass spectrometry (LC-MS), tandem mass spectrometry (MS/MS), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). It will be understood by a person of skill in the art that the sensitivity of the assay used will correlate with the level of quantification that can be detected, and that a more sensitivity assay will enable lower levels of quantification of progesterone, estradiol, estrone, or total estrone. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured using a validated LC-MS/MS method. Methods of measuring hormone levels are well described in the literature.

The levels of progesterone, estradiol, estrone, or total estrone can be measured in any biological sample, e.g. a tissue or fluid such as blood, serum, plasma, or urine. In some embodiments, the sample is blood or plasma. In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 0.0, 0.10, 0.20, 0.05, 0.30, 0.35, 0.40, 0.45, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, or 48 hours after dosing, or any other appropriate time period that is common or useful in determining the levels of each of the hormones. Generally, assays to determine the levels of progesterone, estradiol, estrone, or total estrone are measured one or more times every 5, 10, 15, 20, 30, 60, 120, 360, 480, 720, or 1440 minutes after administration, or combinations thereof (e.g., the first measurements are taken every 15 minutes for the first hour, followed by every 120 minutes thereafter). In some embodiments, the levels of progesterone, estradiol, estrone, or total estrone are measured about 48 hours after dosing. In embodiments, the timing of such measurements are designed to accurately measure C_{max}, T_{max}, or AUC. Timing can be adjusted based on the given circumstances (i.e., one formulation may cause a more rapid C_{max}, in which case the initial times would be clustered closer together, closer to time zero, or both to ensure accurate measurement of C_{max}, T_{max}, and AUC).

In some embodiments, the values for C_{max}, T_{max}, and/or AUC represent a number of values taken from all the subjects in a patient test population and are, therefore, mean values averaged over the entire test population. Alternatively, the C_{max} value, T_{max} value, and/or AUC test/AUC control ratio may be determined for each subject, then averaged.

In some embodiments, administration of the pharmaceutical formulation as disclosed herein (e.g., a pharmaceutical formulation comprising solubilized estradiol, suspended

progesterone, and a medium chain (C6-C12) oil) to a subject produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;

(ii) an $AUC_{(0-\infty)}$ for estradiol that is from 1968 pg·hr/ml to 3075 pg·hr/ml; or

(iii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the formulation to the subject produces both an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml, and a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml.

In some embodiments, administration of the formulation to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml;

(ii) an $AUC_{(0-\infty)}$ for progesterone that is from 105 ng·hr/ml to 164 ng·hr/ml; or

(ii) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the composition to the subject produces both an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml, and a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the formulation to the subject produces, in a plasma sample from the subject,

(i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;

(ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;

(iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; or

(iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the pharmaceutical formulation to the subject produces, in a plasma sample from the subject, one, two, three or more parameters selected from:

(i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml;

(ii) a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml;

(iii) an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; or

(iv) a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml.

In some embodiments, administration of the pharmaceutical formulation to the subject produces both parameters (i) and (ii). In some embodiments, administration of the formulation to the subject produces both parameters (i) and (iii). In some embodiments, administration of the formulation to the subject produces both parameters (i) and (iv). In some embodiments, administration of the formulation to the subject produces both parameters (ii) and (iii). In some embodiments, administration of the formulation to the subject produces both parameters (ii) and (iv). In some embodiments, administration of the formulation to the subject produces both parameters (iii) and (iv). In some embodiments, administration of the formulation to the subject produces all of parameters (i), (ii), and (iii). In some embodiments, administration of the formulation to the subject produces both parameters (i), (iii), and (iv). In some embodiments, administration of the formulation to the subject produces both parameters (ii), (iii), and (iv). In some embodiments, administration of the formulation to the subject produces all of parameters (i), (ii), (iii), and (iv).

In some embodiments, administration of the pharmaceutical formulation to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/ml to 11370 pg·hr/ml;

(ii) an $AUC_{(0-\infty)}$ for estrone sulfate that is from 9596 pg·hr/ml to 14994 pg·hr/ml; or

(ii) a C_{max} for estrone sulfate that is from 341 pg/ml to 533 pg/ml.

In some embodiments, administration of the pharmaceutical composition to the subject further produces, in a plasma sample from the subject, one or more parameters selected from:

(i) an $AUC_{(0-t)}$ for total estrone that is from 161 pg·h/ml to 252 pg·h/ml;

(ii) an $AUC_{(0-\infty)}$ for total estrone that is from 171 pg·hr/ml to 267 pg·hr/ml; or

(ii) a C_{max} for total estrone that is from 28 pg/ml to 44 pg/ml.

In some embodiments, the pharmaceutical composition is administered to a population of subjects in need thereof, and mean parameters are determined for samples (e.g., plasma samples) from the subjects administered the composition. Thus, in some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml, a mean $AUC_{(0-\infty)}$ for estradiol that is from 1968 pg·hr/ml to 3075 pg·hr/ml, or a mean C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml, a mean $AUC_{(0-\infty)}$ for progesterone that is from 105 ng·hr/ml to 164 ng·hr/ml, or a mean C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/ml to 11370 pg·hr/ml, a mean $AUC_{(0-\infty)}$ for estrone sulfate that is from 9596 pg·hr/ml to 14994 pg·hr/ml, or a mean C_{max} for estrone sulfate that is from 341 pg/ml to 533 pg/ml. In some embodiments, administration of the composition to a population of subject produces, in plasma samples from the subjects, one or more of a mean $AUC_{(0-t)}$ for total estrone that is from 161 pg·h/ml to 252 pg·h/ml, a mean $AUC_{(0-t)}$ for total estrone that is from 171 pg·hr/ml to 267 pg·hr/ml, or a mean C_{max} for total estrone that is from 28 pg/ml to 44 pg/ml.

In some embodiments, method of treating a subject are provided. In some embodiments, the method comprises administering to the subject a pharmaceutical composition as described herein, wherein administration of the pharmaceutical composition produces, in a plasma sample from the subject, one or more parameters selected from: an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·h/ml to 1755 pg·h/ml; an $AUC_{(0-\infty)}$ for estradiol that is from 1968 pg·hr/ml to 3075 pg·hr/ml; a C_{max} for estradiol that is from 52 pg/ml to 81 pg/ml; an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/ml to 150 ng·hr/ml; an $AUC_{(0-\infty)}$ for progesterone that is from 105 ng·hr/ml to 164 ng·hr/ml; a C_{max} for progesterone that is from 71 ng/ml to 112 ng/ml; an $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/ml to 11370 pg·hr/ml; an $AUC_{(0-\infty)}$ for estrone sulfate that is from 9596 pg·hr/ml to 14994 pg·hr/ml; a C_{max} for estrone sulfate that is from 341 pg/ml to 533 pg/ml; an $AUC_{(0-t)}$ for total estrone that is from 161 pg·h/ml to 252 pg·h/ml; an $AUC_{(0-\infty)}$ for total estrone

that is from 171 pg·hr/ml to 267 pg·hr/ml; and a C_{max} for total estrone that is from 28 pg/ml to 44 pg/ml.

III. EXAMPLES

The following examples are offered to illustrate, but not to limit, the claimed subject matter.

Example 1

Estradiol Solubility

In various experiments, suitable solvents were determined for providing sufficient solubility to make 2 mg of estradiol in a 100 mg fill mass, with a desired goal of achieving ~20 mg/g solubility for estradiol. Initial solubility experiments were done by mixing estradiol with various solvents, saturate the solution with the estradiol, equilibrate for at least 3 days and filter the un-dissolved particles and analyzing the clear supernatant for the amount of estradiol dissolved by HPLC.

Estradiol solubility experiments were performed. From this list at least one item (e.g. propylene glycol) is known to be unsuitable for encapsulation in more than 20% w/w concentration.

TABLE 8

Ingredient	Solubility (mg/g)
PEG 400	105*
Propylene Glycol	75*
Polysorbate 80	36*
TRANSCUTOL ® HP	141
CAPMUL ® PG8	31.2

*Literature reference—Salole, E.G. (1987) The Physicochemical Properties of Oestradiol, J Pharm and Biomed Analysis, 5, 635-640.

In further solubility studies, estradiol was soluble at least 6 mg/gm MIGLYOL® TRANSCUTOL® in ratios of 81:19 to 95:5, in MIGLYOL®; ethanol at 91:11, and in MIGLYOL®:CAPMUL® PG8 at 88:11, but not in MIGLYOL: TRANSCUTOL at 96:4, MIGLYOL®:LABRASOL® at 70:30 to 80:20, or MIGLYOL®:CAPMUL® PG8 at 86:14.

Example 2

It was desired to achieve 50 mg of progesterone suspended in a medium that can also solubilize 2 mg estradiol in a total capsule fill mass of 200 mg. In order to achieve this formulation, the required solubility of estradiol needs to be ~10 mg/g. A total fill weight of 200 mg was considered suitable for a size 5 oval soft gelatin capsule.

Additional solubility studies were performed to find solvent mixtures that might possibly be more suitable for soft gelatin encapsulation. Solubility studies were conducted with CAPMUL® PG8 and CAPMUL® MCM by mixing estradiol with various solvent systems and as before by analyzing for the amount of estradiol dissolved by HPLC after filtration. Results of these experiments are presented in Table 9. It can be seen from these results that mixtures containing MIGLYOL®:CAPMUL® PG8 at 50%; and also CAPMUL® MCM alone or in combination with 20% Polysorbate 80 can achieve sufficient solubility to meet the target of 10 mg/g. CAPMUL® PG8 mixed with MIGLYOL® at the 15 and 30% level did not provide sufficient solubility.

TABLE 9

Ingredient	Solubility (mg/g)
MIGLYOL ®:CAPMUL ® PG8 (85:15)	4.40
MIGLYOL ®:CAPMUL ® PG8 (70:30)	8.60
TRANSCUTOL:MIGLYOL ® 812: CAPMUL PG8 (5:65:28)	>12
TRANSCUTOL ®:MIGLYOL ® 812: CAPMUL ® PG8 (5:47:47)	>12
MIGLYOL ®:CAPMUL ® PG8 (50:50)	14.0
CAPMUL ® MCM	19.8
Polysorbate 80:CAPMUL ® MCM (20:80)	15.0

Example 3

Additional studies were performed to assess the stability of estradiol (4-6 mg) in solvent mixtures, as reported in Table 10. MIGLYOL® 812 with 4% TRANSCUTOL®precipitated on Hot/Cold cycling after 96 hours, while estradiol solubilized in MIGLYOL®:CAPMUL® blends at 30 and 50% or in CAPMUL® MCM alone, did not precipitate under the same conditions for a minimum of 14 days.

TABLE 10

Formulation	Estradiol (mg/g)	Results Hot/Cold Cycling
TRANSCUTOL ®: MIGLYOL ® 812 (4:96)	4	Crystallizes after 96 hours
MIGLYOL ® 812: CAPMUL ® PG8 (70:30)	6	Clear, after 14 days
MIGLYOL 812: CAPMUL ® PG8 (50:50)	6	Clear, after 14 days
TRANSCUTOL ®:MIGLYOL ® 812:CAPMUL ® PG8 (5:80:15)	6	Clear, after 14 days
CAPMUL ® MCM	6	Clear, after 14 days

As shown in Table 11 below, it was found that 12 mg estradiol solubilized in MIGLYOL®:CAPMUL® PG8 50:50, CAPMUL® MCM, and in mixtures of TRANSCUTOL®: MIGLYOL®: CAPMUL® PG8 are stable and do not precipitate for at least 12 days.

TABLE 11

Formulation	Estradiol (mg/g)	Results Hot/Cold Cycling
MIGLYOL ® 812: CAPMUL ® PG8 (50:50)	12	Clear, after 12 days
TRANSCUTOL ®: MIGLYOL ® 812: CAPMUL ® PG8 (5:65:28)	12	Clear, after 12 days
TRANSCUTOL ®: MIGLYOL ® 812: CAPMUL ® PG8 (5:47:47)	12	Clear, after 12 days
CAPMUL ® MCM	12	Clear, after 12 days

Example 4

In addition to determining physical stability of the estradiol solutions over time, it is necessary to determine if the fill material will be stable during the encapsulation process. One way to test these preparations is with the addition of water to the fill mass. As can be seen in Table 12, estradiol solutions at a concentration of 6 mg/g in Polyethylene Glycol 400 and CAPMUL® MCM are able to absorb a

minimum of 7% water without recrystallization, whereas the same concentration in MIGLYOL® 812:CAPMUL® PG8 (75:25) precipitates.

Estradiol solutions at a concentration of 12 mg/g in Polyethylene Glycol 400 and CAPMUL® MCM are able to absorb a minimum of 7% water without recrystallization. All CAPMUL® PG8 containing formulations turned hazy on the addition of water. However, it should be noted that estradiol recrystallization was not observed, and the addition of water to CAPMUL® PG 8 alone (without any estradiol) also turns hazy on the addition of water.

TABLE 12

Formulation	Estradiol (mg/g)	Results after addition of 7% water
MIGLYOL ® 812:CAPMUL ® PG8 (75:25)	6	Precipitated
MIGLYOL ® 812:CAPMUL ® PG8 (50:50)	12	Hazy
TRANSCUTOL ®:MIGLYOL ® 812:CAPMUL ® PG8 (5:65:28)	12	Hazy
CAPMUL ® MCM	12	Clear
TRANSCUTOL ®:MIGLYOL ® 812:CAPMUL ® PG8 (5:47:47)	12	Hazy
Polyethylene Glycol 400	12	clear

Example 5

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 13

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Triglyceride of caprylic/capric acid (e.g., MIGLYOL ® 812)	qs
Diethylene Glycol Monoethylether (TRANSCUTOL ® HP)	65.00
Liquid lecithin	1.63
Butylated Hydroxytoluene	0.13
Total Fill Weight	325

Example 6

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 14

Ingredient	Mg/Capsule
Estradiol Hemihydrate	2.00
Monoglycerides/diglycerides of capric acid (e.g., CAPMUL ® MCM)	qs
Liquid lecithin	1.63
Polysorbate 80	97.5
Total Fill Weight	325

In an exemplary embodiment, a capsule is provided containing a fill material comprising:

TABLE 15

Ingredient	Mg/Capsule	% w/w	Amount/Batch
Estradiol Hemihydrate	2.03	0.62	20.2 g
Monoglycerides/diglycerides of capric acid (e.g., CAPMUL ® MCM)	322.97	99.38	3.23 kg
Total		100	3.25 kg

The above formulation is prepared as follows: estradiol is added to CAPMUL® MCM and mixed until dissolved.

Example 7

Progesterone Solubility

In various embodiments, both estradiol and progesterone may be dissolved in a solvent. In various embodiments, the solubility of both estradiol and progesterone will be such that a therapeutically effective dose may be obtained in a reasonably sized mass, generally considered to be between 1 mg and 1200 mg, preferably suitable for encapsulation in a size 3 to 22 oval or oblong capsule. For example, in various embodiments, 50 mg to 100 mg of progesterone may be dissolved in a volume of solvent; i.e., the solubility would be 50 mg to 100 mg per capsule. MIGLYOL® was attempted, and while it can be considered a good carrier for progesterone, it alone did not provide a desirable level of solubilization of estradiol (e.g., solubility of 12 mg/g may be desirable in various embodiments). Thus, MIGLYOL® may be used in embodiments comprising a suspension of progesterone, though MIGLYOL®, standing alone, is not desirable for use in embodiments having fully solubilized progesterone and/or estradiol.

As can be seen in Table 16, the solubility of progesterone in CAPMUL® MCM is ~73 mg/g. Therefore, by suspending 200 mg progesterone in 400 mg of solvent, part of the dose (~14%) is already dissolved and the remaining is still a suspension. In some aspects and embodiments, it is desired to minimize the partial solubility of progesterone in the formulation in order to minimize the possibility of recrystallization.

Based on 73 mg/g solubility, the capsule size required to make a capsule of 50 mg solubilized progesterone would be 685 mg. Therefore, it was shown that it would be feasible to make a 50 mg progesterone and 2 mg estradiol solubilized formulation. MIGLYOL® had the lowest solubility, but that solvent is unable to dissolve the estradiol, therefore under further experiments, it was decided to proceed with the second lowest or CAPMUL® MCM. It has also been found that 2 mg of estradiol may also be dissolved in 685 mg of CAPMUL® MCM.

TABLE 16

Ingredient	Progesterone Solubility (mg/g)
CAPMUL ® MCM	73.4
CAPMUL ® PG8	95
MIGLYOL ® 812	27.8
CAPMUL ® MCM: GELUCIRE ® 44/14 (9:1)	86.4
CAPMUL ® MCM: GELUCIRE 44/14 (7:3)	70.5
CAPMUL ® MCM: GELUCIRE ® 44/14 (6:3)	57.4

In addition, it has been found that the solubility of progesterone in a solvent of CAPMUL® MCM in combination with GELUCIRE® 44/14 in a 9:1 ratio increases the solubility to approximately 86 mg/g. Therefore, in various embodiments, progesterone and/or estradiol may be dissolved in a CAPMUL® MCM and GELUCIRE® 44/14 system, wherein the ratio of CAPMUL® MCM to GELUCIRE® 44/14 is 9:1.

TABLE 17

Ingredient	Progesterone Solubility (mg/g)
CAPMUL ® MCM: GELUCIRE 44/14 (9:1)	86.4
CAPMUL ® MCM: GELUCIRE ® 44/14 (7:3)	70.5
CAPMUL ® MCM: GELUCIRE ® 44/14 (6:4)	57.4

Example 8

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized progesterone and estradiol comprising:

TABLE 18

Ingredient	Mass (mg)	% w/w	Qty/Capsule (mg)
Progesterone, USP, micronized	50.00	7.14	50.00
Estradiol Hemihydrate, USP	2.03	0.29	2.03
CAPMUL ® MCM, NF		82.57	577.97
GELUCIRE ® 44/14, NF		10.0	70.00
TOTAL		100.00	700.00

A capsule such as that shown in Table 18 may be manufactured in any suitable manner. For the purposes of this Example, mixing may be facilitated by an impellor, agitator, or other suitable means. Also for the purposes of this Example, heating and/or mixing may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing and/or heating for the purposes of this Example may be performed in any suitable vessel, such as a stainless steel vessel.

For example, CAPMUL® MCM may be heated to between 30° C. to 50° C., more preferably from 35° C. to 45° C., and more preferably to 40° C.+/−2° C. GELUCIRE® 44/14 may be added to the CAPMUL® MCM and mixed until dissolved. The addition may occur all at once or may occur gradually over a period of time. Heat may continue to be applied during the mixing of the GELUCIRE® 44/14 and the CAPMUL® MCM.

Heat may be removed from the GELUCIRE® 44/14 and CAPMUL® MCM mixture. Estradiol Hemihydrate may be added to the mixture. The addition may occur all at once or may occur gradually over a period of time. Micronized progesterone may then be added to the GELUCIRE® 44/14, CAPMUL® MCM and Estradiol Hemihydrate mixture until dissolved. The addition may occur all at once or may occur gradually over a period of time.

Example 9

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 19

Ingredient	mg/ Capsule	%	Function
Micronized Progesterone	200.00	30.77	Active
Medium Chain Triglyceride (MIGLYOL ® 812 or equivalent)	qs	qs	Carrier
Lecithin Liquid	1.63	0.25	Lubricant/ Emulsifier
Butylated Hydroxytoluene (also referred to as "BHT")	0.13	0.02	Antioxidant

The above formulation is prepared as follows: MIGLYOL® is heated to about 45° C. GELUCIRE® 44/14 is added and mixed until dissolved. BHT is added and mixed until dissolved. Progesterone is suspended and passed through a colloid mill. The resultant fill mass can be used for encapsulation.

In an exemplary embodiment, a capsule is provided containing a fill material having partially solubilized progesterone comprising:

TABLE 20

Ingredient	Qty/ Capsule (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
Micronized Progesterone, USP	200.00	33.33	Active	2.0
Monoglycerides/ diglycerides/triglycerides of caprylic/capric acid (CAPMUL ® MCM)	394.0	65.67	Carrier	3.94
Lauroyl polyoxyl-32-glycerides (GELUCIRE ® 44/14 or equivalent)	6.0	1	Lubricant/ Emulsifier	0.06
Total	600.00 mg	100		6.0 kg

For suspensions of progesterone and partially solubilized progesterone, GELUCIRE® 44/14 may be added at 1% to 2% w/w to increase viscosity. The above formulation is prepared as follows: CAPMUL® MCM is heated to about 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Progesterone is added and the mixture is passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 10

In an exemplary embodiment, a capsule is provided containing a fill material having suspended progesterone comprising:

TABLE 21

Ingredient	%	mg/ Capsule	Function
Micronized Progesterone	30.77	200.00	Active
Medium Chain Triglyceride (MIGLYOL ® 812 or equivalent)	65.93	428.55	Carrier

TABLE 21-continued

Ingredient	%	mg/ Capsule	Function
Lauroyl polyoxyl-32-glycerides (GELUCIRE ® 44/14 or equivalent)	3.00	19.50	Suspending Agent
Butylated Hydroxytoluene	0.03	1.95	Antioxidant
Total	100	650	

In various embodiments, amounts of MIGLYOL® may be present in a range from about 35-95% by weight; GELUCIRE® 44/14 from about 0.5-30% by weight; and BHT from about 0.01-0.1% by weight.

Example 11

For the purposes of this Example, a particle size analysis is conducted by using the Beckman Device. A sample API comprising micronized progesterone in accordance with various embodiments is provided for analysis.

Approximately 0.01 g of a sample API in accordance with various embodiments was combined with Coulter 1B and 10 mL of deionized water. Sonication was performed for 15 seconds. The Beckman Device, equipped with a ULM, performed analysis for 90 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 4.279 μm, an X75 of 7.442 μm, and an X25 of 1.590 μm. The Beckman Device also yielded that the mean particle size is 4.975 μm, the median particle size is 4.279 μm, the mode particle size is 6.453 μm, and the standard deviation is 3.956 μm. A graph of the particle distribution obtained is shown in FIG. **4**.

Example 12

A formulation sample having approximately 200 mg of micronized progesterone and 2 mg of estradiol was dispersed with oil. The Beckman Device, equipped with a MLM, performed analysis for 60 seconds. The Beckman Device was configured to use the Fraunhofer optical model. The Beckman Device yielded that the sample has an X50 of 11.0 μm, an X75 of 17.3 μm, and an X25 of 5.3 μm. The Beckman Device also yielded that the mean particle size is 11.8 μm, the median particle size is 11.04 μm, the mode particle size is 13.6 μm, and the standard deviation is 7.8 μm.

Example 13

In order to increase the solubility of progesterone in the final solution, GELUCIRE® 44/14 was added at about 10% w/w.

TABLE 22

Quantitative Formula: Batch Size 10,000 capsules

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (kg)
1.	Progesterone, USP, micronized	50.00	7.14	50.00	0.50
2.	Estradiol Hemihydrate, USP	2.03	0.29	2.03	0.02
3.	CAPMUL ® MCM, NF		82.57	577.97	5.78
4.	GELUCIRE ® 44/14, NF		10.0	70.00	0.70
		Total:	100.00	700.00	7.00

TABLE 22-continued

Quantitative Formula: Batch Size 10,000 capsules

An example of the final formulation is provided in Table 22. The manufacturing process is as follows. CAPMUL® MCM is heated to 40° C. GELUCIRE® 44/14 is heated to 65° C. and added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and mixed until dissolved.

Example 14

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 23

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	50.00	25.000	50.00	500.00
2.	Estradiol Hemihydrate	0.25	0.129	0.26	2.58
3.	CAPMUL ® MCM, NF		73.371	146.74	1467.42
4.	GELUCIRE ® 44/14, NF		1.500	3.00	30.00
		Total:	100.00	200.00 mg	2000.00

The manufacturing process is as follows. CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation.

Example 15

In an exemplary embodiment, a capsule is provided containing a fill material having fully solubilized estradiol and partially solubilized progesterone comprising:

TABLE 24

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
1.	Progesterone, USP, micronized	200.00	33.33	200.0	2000.0
2.	Estradiol Hemihydrate	2.00	0.35	2.07	20.7

TABLE 24-continued

Item No.	Ingredient(s)	Label Claim (mg)	% w/w	Qty/ Capsule (mg)	Amount/ Batch (g)
3.	CAPMUL ® MCM, NF		65.32	391.93	3919.3
4.	GELUCIRE ® 44/14, NF		1.00	6.0	60.0
		Total:	100.00	600.0 mg	6000.0

The manufacturing process is as follows. CAPMUL® MCM is heated to 65° C. GELUCIRE® 44/14 is added and mixed until dissolved. Heat is removed. Estradiol is added and mixed until dissolved. Micronized progesterone is then added and dispersed. The mixture is then passed through a colloid mill. The resultant fill mass can be used for encapsulation. Alternatively, GELUCIRE® 44/14 is heated to 65 C and CAPMUL® MCM is heated to 40 C+/−5 C to achieve mixing of the oil and the surfactant before heat is removed; estradiol is added while the mixture is cooling; progesterone is added when the mixture has dropped below about 4° C.; the mixture is then passed through a colloid mill, e.g., three times.

Example 16

Study 352—Progesterone and Estradiol Combination Study Under Fed Conditions

This following study protocol was used to establish bio-availability and bioequivalence parameters for a combination product of the present disclosure comprising progesterone (200 mg) and estradiol (2.0 mg) as prepared via the process described in Example 14 and compared to 200 mg of PROMETRIUM® (Catalent Pharmaceuticals, St. Petersburg, Fla. (and 2.0 mg of ESTRACE® (estradiol vaginal cream, USP, 0.01%) (Bristol-Myers Squibb Co. Princeton, N.J.), administered to twenty-four (24) normal healthy, adult human post-menopausal female subjects under fed conditions.

The pharmaceutical formulation of the invention used in these PK studies had substantially the following formula as shown in Table 25:

TABLE 25

Ingredient(s)	Amount (% w/w)	Qty/Capsule (mg)
Progesterone, USP, micronized	33.33	200.00
Estradiol Hemihydrate, USP	0.35	2.07
Micronized CAPMUL MCM, NF, USP	65.32	391.93
GELUCIRE 44/14, NF	1.00	6.00
Total	100.00	600

The Study Design: An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover study. The subjects were housed in the clinical facility from at least 11.00 hours pre-dose to at least 48.00 hours post-dose in each period, with a washout period of at least 14 days between the successive dosing days.

Subjects were fasted for at least about 10.00 hours before being served a high-fat, high-calorie breakfast, followed by dosing, then followed by a 04.00 hour, post-dose additional period of fasting. Standard meals were provided at about 04.00, 09.00, 13.00, 25.00, 29.00, 34.00 and 38.00 hours post-dose, respectively. Water was restricted at least about 01 hour prior to dosing until about 01 hour post-dose (except for water given during dosing). At other times, drinking water was provided ad libitum. Subjects were instructed to abstain from consuming caffeine and/or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least about 24.00 hours prior to dosing and throughout the study, grapefruit and\or its juice and poppy containing foods for at least about 48.00 hours prior to dosing and throughout the study.

Subjects remained seated upright for about the first 04.00 hours post-dose and only necessary movements were allowed during this period. Thereafter subjects were allowed to ambulate freely during the remaining part of the study. Subjects were not allowed to lie down (except as directed by the physician secondary to adverse events) during restriction period.

Subjects were instructed not to take any prescription medications within 14 days prior to study check in and throughout the study. Subjects were instructed not to take any over the counter medicinal products, herbal medications, etc. within 7 days prior to study check-in and throughout the study.

After overnight fasting of at least about 10.00 hours, a high-fat high-calorie breakfast was served about 30 minutes prior to administration of investigational product(s). All subjects were required to consume their entire breakfast within about 30 minutes of it being served, a single dose of either test product (T) of Progesterone 200 mg & Estradiol 2 mg tablets or the reference product (R) PROMETRIUM® (Progesterone) soft gel Capsule 200 mg and ESTRACE® (Estradiol) Tablets 2 mg (according to the randomization schedule) were administered with about 240 mL of water under fed condition, at ambient temperature in each period in sitting posture. A thorough mouth check was done to assess the compliance to dosing.

All dosed study subjects were assessed for laboratory tests at the end of the study or as applicable.

In each period, twenty-three (23) blood samples were collected. The pre-dose (10 mL) blood samples at −01.00, −00.50, 00.00 hours and the post-dose blood samples (08 mL each) were collected at 00.25, 00.50, 00.67, 00.83, 01.00, 01.33, 01.67, 02.00, 0.50, 03.00, 04.00, 05.00, 06.00, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 48.00 hours in labeled K2EDTA—vacutainers via an indwelling cannula placed in one of the forearm veins of the subjects. Each intravenous indwelling cannula was kept in situ as long as possible by injecting about 0.5 mL of 10 IU/mL of heparin in normal saline solution to maintain the cannula for collection of the post-dose samples. In such cases, blood samples were collected after discarding the first 0.5 mL of heparin containing blood. Each cannula was removed after the 24.00 hour sample was drawn or earlier or if blocked.

At the end of the study, the samples were transferred to the bio-analytical facility in a box containing sufficient dry ice to maintain the integrity of the samples. These samples were stored at a temperature of −70° C.±20° C. in the bio-analytical facility until analysis.

Progesterone (corrected and uncorrected), estradiol (unconjugated), total estrone, and estrone sulfate in plasma samples is assayed using a validated LC-MS/MS method.

The pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were calculated on data obtained from 24 subjects for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 26, below, for progesterone.

TABLE 26

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmaco-	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
kinetic Parameter	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product(R)
C_{max}	47.0	43.0	81.0 ± 82.8	117.7 ± 173.7
AUC_{0-t}	107.6	97.8	163.9 ± 136.5	191.1 ± 241.7
$AUG_{0-\infty}$	110.7	110.0	173.5 ± 143.0	207.1 ± 250.3

*Estimate of Least Square Mean used to calculate Geometric Mean

Example 17

Study 351—Progesterone and Estradiol Combination Study Under Fasting Conditions

Fasted studies using the above protocol and test and reference products were also conducted. However, rather than the high-fat meal prior to administration of the test and reference drug, each subject fasted for a period of at least twelve (12) hours prior to dose administration.

The pharmacokinetic parameters C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were calculated on data obtained from 23 subjects under fasting conditions for the test product and reference product. In general, bioavailability of progesterone and estradiol were similar but bioequivalence was not established.

Corrected pharmacokinetic profile summaries are presented in Table 27, below, for progesterone.

TABLE 27

Summary of Primary Pharmacokinetic Profile of Test Product (T) versus Reference Product (R) for Progesterone (Corrected)

Pharmaco-	Geometric Mean*		Arithmetic Mean ± Standard Deviation	
kinetic Parameter	Test Product (T)	Reference Product (R)	Test Product (T)	Reference Product(R)
C_{max}	2.3	3.0	2.9 ± 2.3	3.9 ± 3.4
AUC_{0-t}	8.4	10.9	11.2 ± 8.7	14.5 ± 11.0
$AUG_{0-\infty}$	12.9	17.2	15.1 ± 9.0	19.6 ± 10.2

*Estimate of Least Square Mean used to calculate Geometric Mean

The data indicate good (i.e., low) inter-patient and intra-patient variability relative to PROMETRIUM.

Example 18

Methods of manufacture in accordance with various embodiments are shown in FIGS. **1-3**. With reference to FIG. **1**, method of fill material **100** is shown. Step **102** comprises heating an oily vehicle carrier to 40° C.±5° C. Heating may be accomplished through any suitable means. The heating may be performed in any suitable vessel, such as a stainless steel vessel. The oily vehicle may be any oily vehicle described herein, for example, CAPMUL® MCM.

Step **104** comprises mixing GELUCIRE® 44/14 with the oily vehicle. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **102** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Mixing may be performed in any suitable vessel, such as a stainless steel vessel.

Step **106** comprises mixing estradiol into the mixture of the oily vehicle and GELUCIRE® 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **106** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2.

Step **108** comprises cooling to room temperature. Cooling may be allowed to occur without intervention or cooling may be aided by application of a cooling system.

Step **110** comprises mixing micronized progesterone into the mixture of oily vehicle, estradiol and GELUCIRE® 44/14. Mixing may occur in a steel tank or vat. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **110** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step **112** comprises degasing. The resulting mixture from step **112** may comprise a fill material suitable for production into a softgel capsule.

With reference to FIG. **2**, softgel capsule, i.e. gel mass, production **200** is shown. Step **202** comprises mixing glycercin with water. The water used in step **202** may be purified by any suitable means, such as reverse osmosis, ozonation, filtration (e.g., through a carbon column) or the like. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **202** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Heating may be performed until the temperature reaches 80° C.±5° C.

Step **204** comprises the addition of gelatin to the glycerin water mixture. Mixing may be facilitated by an impellor, agitator, or other suitable means. Step **204** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. A vacuum may be drawn in step **204** to de-aerate.

Step **206** comprises addition of a coloring agent such as a dye. A coloring agent may comprise products sold under the trademark OPATINT or other suitable agent. Step **206** may be performed under an inert or relatively inert gas atmosphere, such as nitrogen gas N2. Step **208** comprises degasing. The resulting mixture from step **208** may comprise a gel capsule material suitable for use as a gel capsule in production of a softgel capsule.

With reference to FIG. **3**, softgel capsule assembly process **300** is shown. Step **302** comprises heating the fill material. The fill material may be heated to any suitable temperature. In various embodiments, the fill material is heated to 30° C.+/−3° C. Fill material may be heated in a fill hopper. A fill hopper may comprise a device configured to hold a volume of the fill material and/or to dispense the fill material in controlled volumes.

Step **304** comprises filling a gel mass. A gel mass may be taken from the gel capsule material produced in step **208** of FIG. **2**. Filling may be performed by injecting, placing, or otherwise disposing the fill material within a volume defined by the gel capsule material. The filling may occur in an encapsulator. The spreader boxes may be a temperature of 55° C.+/−10° C. The wedge temperature may be 38° C.+/−3°

C. The drum cooling temperature may be 4° C.+/−2° C. The encapsulator may be lubricated using MIGLYOL® **812** or other suitable lubricant. Step **304** thus produces one or more softgel capsules. Filling may comprise producing a ribbon of thickness 0.85 mm±0.05 mm using spreader box knobs. The fill material may be injected into the gel to produce a fill weight having target weight±5% (i.e., 650±33 mg and 325±16.3 mg).

Step **306** comprises drying the softgel capsules. Drying may be performed in a tumble dryer, tray dryer, or combinations thereof. For example, drying may be performed in a tumble drying basket for between about 10 minutes and about 120 minutes. Drying may continue in a drying room for about 24 hours to about 72 hours. Step **308** may comprise inspection and/or polishing. Polishing may be performed with isopropyl alcohol. Step **310** may comprise packaging. Packaging may be accomplished through any suitable means. Packaging may comprise packing softgel capsules into a blister pack, bottle, box, pouch, or other acceptable packaging.

Example 19

I. Solubility of Estradiol in Soy Bean Oil, Peanut Oil, and Safflower Oil

Data was obtained visually by making the mixtures described below, sonicating the mixtures, and then seeing if a clear solution resulted. If a clear solution was achieved, it was an indication of solubility at the level studied.

Procedures and Results:

Step 1.

0.3% of Estradiol suspension in each oil was prepared by adding 30 mg Estradiol to solvent and QS to 10 g. Samples were mixed on vortex for 2 hours, heated at 50° C. for 30 minutes and then mixed for 1 hour more. All samples were still in suspension form.

Step 2.

Each sample was diluted to 0.24% (by adding 2.5 g more oil) and mixed for 2 hours and heated at 50° C. for 30 min and mixed again for one hour. All the samples were still cloudy. Samples were kept at room temperature overnight to see if they precipitate or if un-dissolved API settles out. After 20 hours at room temperature, it was observed that all samples still had un-dissolved API.

Step 3.

Each sample was diluted to 0.2% (by adding 2.5 g more oil) and mixed 2 for hours and heated at 50° C. for 30 min and mixed again for one hour. All the samples were still slightly cloudy, indicating that the estradiol was not completely dissolved.

TABLE 28

Ingredient	Estradiol Solubility (mg/g)	Estradiol Solubility (% w/w)
Peanut Oil	<2	<0.2
Safflower Oil	<2	<0.2
Soy Bean Oil	<2	<0.2

The solubility of estradiol in all three oils was less than 2 mg/g (0.2% w/w). This level of solubility is significantly below the solubility that the present inventors have discovered can be achieved in other oils, e.g., medium chain fatty acid esters, such as the mono/diglycerides, propylene glycol esters, and polyethylene glycol esters discussed above.

In sum, if no heat is used to dissolve estradiol in safflower oil, it will not go into solution. Given that the estradiol did not dissolve at 50° C., oils such as safflower oil will not be useful in the methods of the invention using medium chain fatty acid esters as described hereinabove.

II. Solubility in Safflower Oil

In a separate experiment, 50 g of safflower oil was heated to 85-88° C. and 60 mg estradiol was added, mixed until fully dissolved (1 hr), and allowed to cool to room temperature. The solubility achieved was 1.0 mg/ml. Addition of progesterone to a sample of the estradiol solution did not affect the solubility of estradiol.

Unsaturated fats are prone to oxidation, i.e., rancidity. Peroxides are intermediates formed during oxidation and the Peroxide Value is an indicator of extent of oxidation. The US Pharmacopeia specification for Peroxide Value of safflower oil is 10 max. Heating the oil, e.g., to 85° C., has been shown to increase the Peroxide Value. In contrast, medium chain fatty acid glycols, such as CAPMUL® MCM and MYGLYOL® 812, which comprise saturated C8-C10 fatty acid esters, have much lower Peroxide Values, e.g., on the order of 1 or less.

Example 20

Dissolution

Dissolution studies were performed using a formulation of this invention comparing the dissolution of progesterone to the dissolution of PROMETRIUM® and comparing the dissolution of estradiol to the dissolution of ESTRACE®. In one study, a formulation of the invention in capsules comprising 200 mg of progesterone and 2 mg estradiol was used. In a second study, a formulation of the invention in capsules comprising 50 mg of progesterone and 2 mg estradiol was used. The two formulations comprised:

The dissolution study was performed using a USP dissolution apparatus (reciprocating cylinder) ("USP Apparatus 3"). The apparatus was set to 30 dips per minute. 250 mL of a solution of 0.1N HCl with 3% sodium lauryl sulfate was used at 37° C.

In both studies, progesterone was dissolved faster, and with smaller standard deviations, from the capsules of the invention than from PROMETRIUM®. Dissolution of estradiol was comparable but marginally slower from the capsules of the invention than from ESTRACE®. For illustrative purposes, a graph showing progesterone dissolution from the 200 mg progesterone capsule of the invention and from PROMETRIUM® is attached as FIG. **5**.

Both capsules of the invention were stable on storage in white HDPE bottles. Positive stability data were obtained with the 200 mg progesterone formulation over 6 months (>6 months data unavailable) and with the 50 mg progesterone formulation over 3 months (>3 months data unavailable).

Example 21

Study 459—Combination Study Under Fed Conditions—Pharmacokinetics of the First Combination 17β-Estradiol/Progesterone Capsule in Clinical Development for Hormone Therapy

The objective of this study was to evaluate the pharmacokinetic and oral bioavailability of a combination capsule

of 17β-estradiol/progesterone in comparison to co-administration of the individual products ESTRACE® and PROMETRIUM®.

Subjects and Study Design:

An open label, balanced, randomized, single-dose, 2-treatment, 3-period, 3-sequence, crossover, partial-replicate, reference-scaled, oral, relative bioavailability study compared the bioavailability of an investigational 2-mg 17β-estradiol/200-mg progesterone combination capsule, without peanut oil (formulated in a manner similar to that set forth in Table 24), with that of co-administered 200-mg PROMETRIUM® (progesterone) and 2-mg ESTRACE® (17β-estradiol) tablets in healthy postmenopausal women aged 40-65 yrs (N=66). Key inclusion criteria for subjects included a BMI 18.50 to 29.99 kg/m^2 who were nonsmokers or ex-smokers (no smoking in the last 3 months). Key exclusion criteria for subjects included consuming grapefruit juice or poppy-containing foods within 48 hours before and throughout the study, use of any hormonal agent within 14 days before the study, and use of menopausal hormone therapy within 6 months before dosing.

Patients were randomly assigned sequentially to 1 of 3 dosing sequences of the same dose of the combination capsule (Test, T) and reference products (Reference, R): TRR, RTR, or RRT. 66 subjects were randomized and 62 (94.0%) completed the study (FIG. **6**). Subjects had a mean age of 49.5±5.6 years (range 40 to 64) and a mean BMI of 24.8±3.1 kg/m^2 (range 18.7-29.9).

After consuming a high-fat, high-calorie breakfast, each woman received a single dose of the combination (Test) capsule in 1 period of the study and single doses of the co-administered products (Reference) in each of the 2 remaining periods. Plasma was collected pre-dose and at specified intervals over 48 h after dosing to determine progesterone, free (unconjugated) estradiol, and free and total (conjugated+free) estrone concentrations. The primary (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) and secondary (t_{max}, $t_{1/2}$, and K_e) PK parameters for each analyte were determined for each subject during each period by non-compartment analyses using baseline-adjusted concentrations. Statistical analyses were conducted using the Scaled Average Bioequivalence (BE) method for highly variable drugs to determine whether the combination Test capsule had progesterone and estradiol bioavailability similar to that of the co-administered Reference products. This method is applicable when the within-subject coefficient of variation (CV) for the reference product is ≥30%. For any PK parameter with CV<30%, the BE method based on 90% CI must be used.

Results: All AUC and C_{max} parameters met BE criteria for all analytes, except C_{max} for total estrone (Table 29). The extent of estradiol and progesterone absorption for the Test capsule appeared to be similar to that for the ESTRACE® and PROMETRIUM® tablets, respectively (Table 29), while the rate of estradiol absorption for the Test capsule appeared to be faster than that for ESTRACE®, respectively (Table 30). Semilogarithmic plots of AUC over time for each analyte are presented in FIGS. **7** and **8**. Pharmacokinetic data (C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$) for progesterone, estradiol, free estrone, and total estrone is presented in Tables 31-34. For Tables 31-34, "Test Product (T)" refers to the progesterone+estradiol pharmaceutical composition, while "Reference product (R1)" and "Reference product (R2)" refer to co-administered PROMETRIUM® (progesterone) and ESTRACE® (estradiol).

The bioequivalent outcomes for progesterone should allow the Test capsule to bridge to the safety data for PROMETRIUM®. A bridge to the safety data for the ESTRACE® tablet should also be viewed as having been established because the only parameter for which the Test capsule failed to meet BE criteria was the C_{max} for just 1 estradiol-related analyte (total estrone). The extent of estradiol absorption, reflecting the total amount of estradiol delivered by the Test capsule, is the most critical safety measure.

TABLE 29

Scaled Average Bioequivalence Analyses for Each Analyte

Analyte/Parameter	Test-to-Ref Ratio	CV %	95% Upper Confidence Bound	Meets BE Criteria†
Progesterone				
$AUC_{(0-t)}$	1.05	122.2	−0.5422	Yes
$AUC_{(0-inf)}$	0.94	116.4	−0.4941	Yes
C_{max}	1.16	173.7	−0.7850	Yes
Unconjugated estradiol				
$AUC_{(0-t)}$	0.93	42.6	−0.0888	Yes
$AUC_{(0-inf)}$	0.83	47.4	−0.0625	Yes
C_{max}	0.88	35.4	−0.0399	Yes
Analyte/Parameter	**Test-to-Ref Ratio**	**CV %**	**90% Confidence Interval**	**Meets BE Criteria**
Unconjugated estrone				
$AUC_{(0-t)}$	0.89	18.0	0.848-0.938	Yes
$AUC_{(0-inf)}$	0.88	26.3	0.834-0.933	Yes
C_{max}	0.93	23.3	0.873-0.991	Yes

TABLE 29-continued

Scaled Average Bioequivalence Analyses for Each Analyte

Total estrone				
$AUC_{(0-t)}$	1.06	29.7	0.982-1.115	Yes
$AUC_{(0-inf)}$	1.06	29.7	0.985-1.114	Yes
C_{max}	1.75	35.9	0.3438*	No

*95% Upper Confidence Bound

†Scaled Average Bioequivalence requires Test-to-Reference ratio between 0.800 and 1.250 and the 95% upper confidence bound on the linearized statistic is ≤0. Unscaled Average Bioequivalence requires that the 90% confidence interval on the Test-to-Reference ratio is entirely within 0.800 and 1.250.
BE = Bioequivalence;
CV % = coefficient of variance.

TABLE 30

T_{max} for Each Analyte

Analyte/Parameter	Test	Reference 1	Reference 2
Progesterone	3.00 (0.83-10.0)	3.00 (1.00-12.0)	4.00 (0.67-18.0)
Unconjugated estradiol	9.00 (0.50-36.0)	10.0 (0.50-35.1)	10.0 (0.25-36.6)
Unconjugated estrone*	5.50 (0.83-36.0)	8.00 (1.67-18.0)	10.0 (1.67-18.0)

TABLE 31

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R1, R2) for Progesterone (Corrected)

PK Parameter	N	Test Product (T)	N	Reference Product (R1)	N	Reference Product (R2)
C_{max} (ng/mL) Arithmetic Mean ± SD	62	89.2222 ± 149.7309	62	72.7228 ± 101.8885	62	69.7590 ± 87.0777
C_{max} (ng/mL) Geometric Mean	62	35.0996	62	30.6904	62	29.7178
$AUC_{(0-t)}$ (ng · hr/mL) Arithmetic Mean ± SD	62	120.0869 ± 164.1385	62	125.9406 ± 152.3483	62	111.5867 ± 113.3200
$AUC_{(0-t)}$ (ng · hr/mL) Geometric Mean	62	63.3952	62	61.5312	62	58.5421
$AUC_{(0-\infty)}$ (ng · hr/mL) Arithmetic Mean ± SD	57	131.3817 ± 172.4806	57	142.1332 ± 160.4853	56	126.6006 ± 117.2665
$AUC_{(0-\infty)}$ (ng · hr/mL) Geometric Mean	57	72.1098	57	79.9008	56	75.7201

TABLE 32

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R1, R2) for Estradiol (Corrected)

PK Parameter	N	Test Product (T)	N	Reference Product (R1)	N	Reference Product (R2)
C_{max} (pg/mL) Arithmetic Mean ± SD	62	64.7902 ± 50.9833	62	69.1286 ± 33.0484	62	73.4236 ± 43.4077
C_{max} (pg/mL) Geometric Mean	62	56.1068	62	62.2189	62	64.5362
$AUC_{(0-t)}$ (pg · hr/mL) Arithmetic Mean ± SD	62	1403.7333 ± 763.8136	62	1508.2206 ± 876.7390	62	1658.2502 ± 976.5556
$AUC_{(0-t)}$ (pg · hr/mL) Geometric Mean	62	1224.2031	62	1239.6990	62	1413.7331

TABLE 32-continued

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R1, R2) for Estradiol (Corrected)

PK Parameter	N	Test Product (T)	N	Reference Product (R1)	N	Reference Product (R2)
$AUC_{(0-\infty)}$ (pg · hr/mL) Arithmetic Mean ± SD	60	2459.4394 ± 4498.2737	60	2842.8805 ± 4582.6502	57	2110.9591 ± 1175.3995
$AUC_{(0-\infty)}$ (pg · hr/mL) Geometric Mean	60	1658.0281	60	1879.6716	57	1796.6988

TABLE 33

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R1, R2) for Total Estrone (Corrected)

PK Parameter	N	Test Product (T)	N	Reference Product (R1)	N	Reference Product (R2)
C_{max} (pg/mL) Arithmetic Mean ± SD	61	35.4289 ± 17.0856	61	19.8716 ± 7.4485	61	19.9048 ± 8.0288
C_{max} (pg/mL) Geometric Mean	61	31.9856	61	18.3037	61	18.4035
$AUC_{(0-t)}$ (pg · hr/mL) Arithmetic Mean ± SD	61	201.7524 ± 94.2081	61	182.7729 ± 88.8386	61	199.8295 ± 94.9392
$AUC_{(0-t)}$ (pg · hr/mL) Geometric Mean	61	182.7135	61	165.3741	61	182.1279
$AUC_{(0-\infty)}$ (pg · hr/mL) Arithmetic Mean ± SD	61	213.2402 ± 104.6011	60	193.6387 ± 100.5831	56	203.0289 ± 81.4884
$AUC_{(0-\infty)}$ (pg · hr/mL) Geometric Mean	61	191.4769	60	173.4694	56	187.8867

TABLE 34

Summary of Pharmacokinetic Parameters of Test Product (T) versus Reference Product (R1, R2) for Estrone Sulfate

PK Parameter	N	Test Product (T)	N	Reference Product (R1)	N	Reference Product (R2)
C_{max} (pg/mL) Arithmetic Mean ± SD	62	426.5492 ± 179.3303	62	455.5107 ± 189.4486	62	467.2302 ± 207.4373
C_{max} (pg/mL) Geometric Mean	62	391.6591	62	416.8218	62	425.6676
$AUC_{(0-t)}$ (pg · hr/mL) Arithmetic Mean ± SD	62	9096.0907 ± 4377.2730	62	10156.0282 ± 5140.5831	62	10507.3557 ± 5183.1289
$AUC_{(0-t)}$ (pg · hr/mL) Geometric Mean	62	8043.8229	62	8872.7467	62	9204.9744
$AUC_{(0-\infty)}$ (pg · hr/mL) Arithmetic Mean ± SD	61	11994.9695 ± 6678.5468	62	13445.9048 ± 8699.4068	62	14066.2362 ± 7563.2370
$AUC_{(0-\infty)}$ (pg · hr/mL) Geometric Mean	61	10264.7576	62	11273.4294	62	11936.6967

For the test product pharmaceutical formulation, pharmacokinetic data ranges for AUC and C_{max} are presented in Table 35 below.

TABLE 35

pK Ranges for the Test Product (T) Pharmaceutical Formulation

	C_{max}	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$
Progesterone	71 ng/mL to 112 ng/mL	96 ng · hr/mL to 150 ng · hr/mL	105 ng · hr/mL to 164 ng · hr/mL
Estradiol	52 pg/mL to 81 pg/mL	1123 pg · hr/mL to 1755 pg · hr/mL	1968 pg · hr/mL to 3075 pg · hr/mL
Estrone sulfate	341 pg/mL to 533 pg/mL	7277 pg · hr/mL to 11370 pg · hr/mL	9596 pg · hr/mL to 14994 pg · hr/mL
Total estrone	28 pg/mL to 44 pg/mL	161 pg · hr/mL to 252 pg · hr/mL	171 pg · hr/mL to 267 pg · hr/mL

CONCLUSION

The combination 17β-estradiol/progesterone capsule demonstrated similar bioavailability of its constituents to their individual respective references of ESTRACE® and PROMETRIUM®, when given together under fed conditions. This new capsule could represent an interesting development in hormone therapy, as no approved hormone therapy to date has been able to 1) combine natural progesterone with 17β-estradiol as an oral formulation, and 2) provide progesterone without peanut oil, a known allergen. The efficacy and safety of this new capsule combining 17β-estradiol with progesterone will be evaluated in phase 3 clinical trials.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present disclosure without departing from the spirit or scope of the disclosure. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

Likewise, numerous characteristics and advantages have been set forth in the preceding description, including various alternatives together with details of the structure and function of the devices and/or methods. This disclosure is intended as illustrative only and as such is not intended to be exhaustive. It will be evident to those skilled in the art that various modifications may be made, especially in matters of structure, materials, elements, components, shape, size and arrangement of parts including combinations within the principles of the disclosure, to the full extent indicated by the broad general meaning of the terms in which the appended claims are expressed. To the extent that these various modifications do not depart from the spirit and scope of the appended claims, they are intended to be encompassed therein.

What is claimed is:

1. A pharmaceutical formulation for administering estradiol and progesterone to a female subject in need thereof, comprising:

17β-estradiol, wherein at least about 80% of the estradiol in the formulation is solubilized;

suspended progesterone;

a solubilizing agent comprising a medium chain oil comprising fatty acid esters of glycerol, polyethylene glycol, or propylene glycol, or mixtures thereof, wherein the fatty acid esters are predominantly esters of C6 to C12 fatty acids; and

a surfactant comprising at least one of lauroyl macrogol-32 glycerides, lauroyl polyoxyl-32 glycerides, or lauroyl polyoxylglycerides,

wherein the surfactant is present in the formulation in an amount from 0.01 wt % to 10 wt % and the ratio of the medium chain oil to the surfactant is 8:1 or greater; and

wherein when administered to a female subject, the formulation produces:

(a) one or more progesterone-related pharmacokinetic parameters selected from: (i) an area under the curve $(AUC)_{(0-t)}$ for progesterone that is from 96 ng·hr/mL to 150 ng·hr/mL; (ii) an $AUC_{(0-\infty)}$ for progesterone that is from 105 ng·hr/mL to 164 ng·hr/mL; and (iii) a C_{max} for progesterone that is from 71 ng/mL to 112 ng/mL; or

(b) one or more stradiol-related pharmacokinetic parameters selected from: (i) an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·hr/mL to 1755 pg·hr/mL; (ii) an $AUC_{(0-\infty)}$ for estradiol that is from 1968 pg·hr/mL to 3075 pg·hr/mL; and (iii) a C_{max} for unconjugated estradiol that is from 52 pg/mL to 81 pg/mL.

2. The pharmaceutical formulation of claim **1**, wherein administration of the formulation to the female subject produces both an $AUC_{(0-t)}$ for estradiol that is from 1123 pg·hr/mL to 1755 pg·hr/mL and a C_{max} for unconjugated estradiol that is from 52 pg/mL to 81 pg/mL.

3. The pharmaceutical formulation of claim **1**, wherein administration of the formulation to the female subject produces both an $AUC_{(0-t)}$ for progesterone that is from 96 ng·hr/mL to 150 ng·hr/mL and a C_{max} for progesterone that is from 71 ng/mL to 112 ng/mL.

4. The pharmaceutical formulation of claim **1**, wherein when administered to the female subject, the formulation further produces one or more of the following:

(i) an $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/mL to 11370 pg·hr/mL;

(ii) an $AUC_{(0-\infty)}$ for estrone sulfate that is from 9596 pg·hr/mL to 14994 pg·hr/mL; or

(iii) a C_{max} for estrone sulfate that is from 341 pg/mL to 533 pg/mL.

5. The pharmaceutical formulation of claim **4**, wherein administration of the formulation to the female subject produces both an $AUC_{(0-t)}$ for estrone sulfate that is from 7277 pg·hr/mL to 11370 pg·hr/mL and a C_{max} for estrone sulfate that is from 341 pg/mL to 533 pg/mL.

6. The pharmaceutical formulation of claim **1**, wherein when administered to the female subject, the formulation further produces one or more of the following:

(i) an $AUC_{(0-t)}$ for total estrone that is from 161 pg·hr/mL to 252 pg·hr/mL;

(ii) an $AUC_{(0-\infty)}$ for total estrone that is from 171 pg·hr/mL to 267 pg·hr/mL; or

(iii) a C_{max} for total estrone that is from 28 pg/mL to 44 pg/mL.

7. The pharmaceutical formulation of claim **6**, wherein administration of the formulation to the female subject produces both an $AUC_{(0-t)}$ for total estrone that is from 161 pg·hr/mL to 252 pg·hr/mL and a C_{max} for total estrone that is from 28 pg/mL to 44 pg/mL.

8. The pharmaceutical formulation of claim **1**, wherein at least 50% of the fatty acid esters in the oil have a fatty acid chain length of C6-C12.

9. The pharmaceutical formulation of claim **1**, wherein at least 90% of the fatty acid esters in the oil have a fatty acid chain length of C6-C12.

10. The pharmaceutical formulation of claim **1**, wherein the medium chain oil is present in the formulation in an amount from 55 wt % to 75 wt %.

11. The pharmaceutical formulation of claim **1**, wherein the medium chain oil is a mixture of mono- and diglycerides of capric and caprylic acid.

12. The pharmaceutical formulation of claim **1**, wherein the medium chain oil comprises a mixture of mono- and diglycerides of capric and caprylic acid, and the surfactant comprises lauroyl polyoxyl-32 glycerides.

13. The pharmaceutical formulation of claim **1**, wherein the formulation comprises progesterone in an amount from 30 wt % to 35 wt %, estradiol in an amount from 0.01 wt % to 0.04 wt %, the medium chain oil in an amount from 55 wt % to 75 wt %, and the surfactant in an amount from 0.01 wt % to 10 wt %.

14. The pharmaceutical formulation of claim **1**, wherein the ratio of the medium chain oil to the surfactant is from 60:1 to 70:1.

15. A method of treating a subject having one or more symptoms of estrogen deficiency, the method comprising administering to the subject an effective amount of the pharmaceutical formulation of claim **1**.

16. The method of claim **15**, wherein the subject is female.

17. The method of claim **15**, wherein the subject is a woman having a uterus.

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