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(57) Abstract

The present invention discloses a novel solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid, and a fatty acid ester of glycerol or propylene glycol. In another aspect, the present invention discloses a pharmaceutical composition comprising the solution of the invention. In another aspect, the present invention discloses a gelatin capsule filled with the composition of the present invention.

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PHARMACEUTICAL COMPOSITION

The present invention relates to certain pharmaceutical compositions comprising 4-aza steroids and/or 6-aza steroids. In particular, the present invention relates to solutions comprising a steroid 5-alpha reductase inhibitor.

Pharmaceutically active compounds can be delivered in a variety of forms, for example in a soft gelatin capsule. Methods for preparation of soft gelatin capsules are well known. See, for example, J.P. Stanley, *Soft Gelatin Capsules, Ch. 13 - Part Two in: The Theory and Practice of Industrial Pharmacy*, eds. L. Lachman et. al., 3 rd Ed., pp. 398-412, 1986, and W.R. Ebert, *Soft Elastic Gelatin Capsules: A Unique Dosage Form*, Pharmaceutical Technology, Vol. 1, No. 5.

The choice of excipients is important in order to ensure good solubility and good bioavailability of the pharmaceutically active compound. See For example, A. Matso, *Excipients Commonly Used in Soft Gelatin Capsules: Their Analysis and Usefulness*, Novel Drug Formulation Systems and Delivery Devices International Seminar, pp. 76-81,(1991). K. Hutchison, *Encapsulation in Softgels for Pharmaceutical Advantage*, Spec. Pub. - R. Soc. Chem., Vol. 138, pp 86-97, (1993), M.S. Patel et. al., *Advances in Softgel Formulation Technology*, Manufacturing Chemist, August 1989, and I.R. Berry, *Improving Bioavailability with Soft Gelatin Capsules*, Drug & Cosmetic Industry, pp. 32, 102-108, (September, 1983). Particular issues with respect to formulation of hydrophobic pharmaceutically active compounds has been described, for example in K. Hutchison, *Formulation of Softgels For Improved Oral Delivery of Hydrophobic Drugs*, Spc. Pub. - R. Soc. Chem., Vol. 161, pp 133-147 (1995).

Liquid filled hard gelatin capsules have also been utilized. See, for example, D. Cade et. al., *Liquid Filled and Sealed Hard Gelatin Capsules*, Drug Development and Industrial Pharmacy, 12(11-13): 2289-2300, (1986).

Aza steroids are an important class of pharmaceutically active compounds. In particular there are 4-aza steroids and 6-aza steroids known to be inhibitors of

the enzyme testosterone 5-alpha-reductase (hereinafter "5AR inhibitors"). Such compounds are thought to be useful in the treatment of benign prostatic hyperplasia, prostate cancer and other diseases. See, for example, U.S. Pat. Nos. 4,377,584 (Rasmusson et al.), 4,220,775 (Rasmusson et al.), 4,732,897 (Cainelli et al.), 4,760,071 (Rasmusson), 4,845,104 (Carlin et al.), 4,859,681 (Rasmusson), 5,302,589 (Frye et al.), 5,438,061 (Bergman et al.), 5,543,406 (Andrews et al.), 5,565,467 (Batchelor et al.), and WO 95/07926 (Batchelor et al.). One such 5AR inhibitor, finasteride, is commercially available from Merck & Co., Inc. as PROSCAR™. These pharmaceutically active compounds are not easy to dissolve. These solubility challenges can affect bioavailability possibly resulting in reduced or unpredictable bioavailability.

A mixture of glyceride esters, commercially available from Abitec (P.O. Box 569, Columbus, Ohio) as Capmul™ MCM, has been used for dissolving bile duct stones. See, for example, "Cholesterol Stones Dissolved Harmlessly," Medical World News, page 28 (1978), U. Leuschner and D. Landgraf, "Dissolution of Biliary Duct Stones with Mono-Octanoin," The Lancet, 2 p 8133 (1979), and J.L. Thistle et al., "Monooctanoin, a Dissolution Agent for Retained Cholesterol Bile Duct Stones: Physical Properties and Clinical Application," Gastroenterology 78, pp 1016-1022 (1980).

Esters of glycerol and/or propylene glycol have been used in a variety of formulations. See, for example, U.S. Pat. Nos. 4,316,917 (Antoshkiw et. al.) and 4,343,823 (Todd et. al.).

Briefly, in one aspect, the present invention discloses a novel solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid, and a fatty acid ester of glycerol or propylene glycol. The fatty acids are preferably carboxylic acids containing from 6 to 12 carbon atoms. Preferably, the ester is a monoester.

In another aspect, the present invention discloses a pharmaceutical composition comprising the solution of this invention. The composition of this invention is particularly suitable for use as a fill formulation for gelatin capsules.

In another aspect, the present invention discloses a gelatin capsule filled with the composition of the present invention.

The composition of this invention has improved bioavailability over standard tablets or suspensions .

Some of the steroids useful in this invention are potent teratogens. Converting the steroid from a free powder to a solution early in the manufacturing process provides a safer process. There is less risk in working with the solution than with the free solid.

Also, some of these steroids are prone to oxidation. Gelatin capsule formulations can be much more resistant to oxidation due to the low oxygen permeation of typical gelatin shells. See, for example, F.S. Hom et al., *Soft Gelatin capsules II: Oxygen Permeability Study of Capsule Shells*, J. Pharm. Sci., Vol. 64 (No. 5), pp 851-887 (1975).

The esters useful in this invention preferably are derived from carboxylic acids containing from 6 to 12 carbon atoms. Particularly preferred are those esters derived from caprylic acid (8 carbon atoms). While mono, di, and tri-esters are all useful in this invention, monoesters are preferred. In addition, the ester may be part of a mixture comprising differing carbon atom content in the esters and/or comprising a mixture of monoglycerides, diglycerides, and triglycerides. Commercially available esters are often such mixtures. For example Capmul ™ MCM and PG-8 (both available from Abitec Corporation, Janesville, Wisconsin) are such mixtures. The composition of Capmul™ MCM is a mixture of fatty acid esters of glycerol and is approximately 95% monoester, 1% glycerin, 2% free fatty acid, and less than 0.5% water and is derived from approximately 85% caprylic acid and 15% capric acid (all percentages are weight percents). PG-8 is a mixture of fatty

acid esters of propylene glycol and is approximately 96% monoester, .05% diester, 1.3% free propylene glycol, and is derived from caprylic acid.

The aza steroids useful in this invention can be any pharmaceutically active aza steroid or pharmaceutically acceptable solvate thereof. Preferred classes of aza steroids are the 4-azasteroid class and the 6-azasteroid class of 5AR inhibitors. For example, any of the 5AR inhibitors disclosed in the above cited patents. Particularly preferred aza steroids are the 4-aza steroids. Particularly preferred 4-aza steroids include finasteride, 17-beta-N-(2,5,-bis(trifluoromethyl))-phenylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one which is the steroid that is disclosed in U.S. Pat. No. 5,565,467 (Batchelor et al.), and 17-beta-N-1-(3,4-methylenedioxy-phenyl)-cyclohexylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one and 17-beta-N-(1-(p-chlorophenyl))cyclopentylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one which are both disclosed in WO 95/07926 (Batchelor et al.). These steroids can be prepared by well-known methods, for example as described in the above cited patents.

The aza steroid is preferably present in the range of from 0.0025 to 2.5% by weight of the solution of this invention, more preferably from 0.025 to 1.5 % by weight of the solution of this invention.

It may also be useful to include an anti-oxidant in the composition. Suitable anti-oxidants include butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), and ascorbic acid. A particularly preferred anti-oxidant is butylated hydroxytoluene. Antioxidants may be used alone or in combination. The antioxidant or mixture of antioxidants is preferably from 0.001 to 0.5% by weight of the composition of this invention.

The pharmaceutical composition of the present invention is particularly useful as a fill formulations for gelatin capsules, most preferably for soft gelatin capsules.

Experimental

In the following experiments, a pharmaceutically active 4-aza steroid was utilized in various solubility studies. The pharmaceutically active steroid utilized was 17-beta-N-(2,5,-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5-alpha-androst-1-ene-3-one. This steroid is described in the '467 patent and can be prepared by known methods including the methods described in the '467 patent.

The solubility of the steroid was determined by suspending an excess amount of the steroid in about 1 mL of various aqueous and organic media. The resulting suspension was tumbled in a Vankel® rotating water bath maintained at 25°C and protected from light. At the end of an equilibration time, usually between 1 and 12 days, excess solid was removed by filtercentrifugation through 0.22μ filters. The resulting supernatant was then assayed for steroid concentration against an external standard. The concentration of steroid in the supernatant was determined by HPLC analyses using a Hewlett Packard 1090 Series II/M with a DOS Chem Station. The HPLC conditions are summarized below in Table 1. The results of the solubility in various aqueous media is summarized in Table 2, and in various organic media is summarized in Table 3. Table 4 summarizes the solubility in various compositions containing a complexing agent (2-hydroxypropyl-beta-cyclodextrin). Table 5 summarizes the solubility in various oils and in Capmul™ MCM. Table 6 summarizes the results of the solubility in mixtures of Capmul™ MCM and polyethylene glycol having an average molecular weight of 400 (PEG 400). In the following Tables and experiments, Mili Q™ plus water is a reverse osmosis water, CMC is carboxy methyl cellulose, THF is tetrahydrofuran, DMSO is dimthylsulfoxide, PG is propylene glycol, Labrafil™ is a mixture of unsaturated polyglycolyzed gylcerides obtained by partial alcoholysis of corn oil or apricot kernel oil, consisting of glycerides and polyethylene glycol esters, SDS is sodium dodecyl sulfate, "model duodenum bile salts" is a mixture of sodium glycocholate, sodium glycochenodesoxycholate, sodium glycodesoxycholate, sodium taurocholate, sodium taurochenodesoxycholate, sodium taurodesoxycholate, sodium chloride, lecithin, and phosphate buffer, Tween 80 is polyoxyethylene(20)sorbitan

monooleate, the polyethylene glycol 400 was purchased form Union Carbide, Molescusol™ is 2-hydroxypropyl-beta-cyclodextrin, and Intralipid is a mixture of soy bean oil, phospholipids, glycerin USP, and water for injection. Unless stated otherwise, all % are by weight, for example, "v/v" means % by volume.

Table 1. HPLC Conditions

Column	250 x 4.6 mm Zorbax Rx C18
Mobile Phase	A. 0.1% v/v TFA B. 0.05% v/v TFA in Acetonitrile
Percent Composition	40%B-95%B in 20 minutes (10 min hold)
Flow rate	1.0 mL/minute
Detection wavelength	210/240
Oven Temperature	35°C

Table 2. Solubility in Aqueous Media

Medium	Concentration (mg/mL)
Milli Q® plus water	< 0.0039
0.1N HCl	< 0.0039
0.5% CMC	< 0.0039
1% Labrafil®	highly degraded
0.02% SDS	< 0.0039
0.01% docusate sodium	< 0.0039
0.1% Tween 80	< 0.0039
0.1% Tween 80/0.02% SDS	< 0.0039
Model duodenum bile salts	0.0386

Table 3. Solubility in Organic Media

Medium	Concentration (mg/mL)
Propylene glycol	6.21
Polyethylene glycol 400	3.27
PEG 400, 0.1% Tween 80	3.91
Propylene carbonate	6.24
Ethyl acetate	14.49
THF	225.44
Acetonitrile	7.44
Acetone	46.97
DMSO	130.40
Benzyl Alcohol	>34
Ethanol	45.59
70% aqueous ethanol	2.73
Isopropanol	29.98

Table 4. Solubility in 2-Hydroxypropyl-β-cyclodextrin Solutions

Medium	Concentration (mg/mL)
10% Molecusol®	0.03
20% Molecusol®	0.12
40% Molecusol®	0.79
40% Molecusol®, 25% PEG400, 5%PG	0.08
40% Molecusol®, 50% aqueous PEG 400	0.56

Table 5. Solubility in Various Oil Base Systems

Medium	Concentration (mg/mL)
Sesame oil	0.52
Safflower oil	0.39
Soybean oil	0.44
Cottonseed oil	0.53
Corn oil	0.56
Castor oil	2.01
Olive oil	0.44
Peanut oil	0.46
Mineral oil	0.007
1% Span 20, cotton seed oil	0.62
10% benzyl alcohol, cottonseed oil	2.77
Intralipid® 20%	0.009
Capmul™ MCM	28.24

Table 6. Solubility in mixtures of Capmul™ MCM and PEG

Capmul™ MCM (%) in PEG400	Concentration (mg/mL)
10	6.95
25	10.01
50	14.11
100	28.24

The solubility data show that these types of steroids are very difficult to dissolve. The data also show that solubility in Capmul™ MCM is significantly higher than in the other systems which were tested.

Capmul™ MCM was then used to prepare fill formulations suitable for use in gelatin capsules. For manufacture of 0.01, 0.05, 0.5, 2.5, 5.0, and 10.0 mg soft-gelatin capsules, Capmul™ MCM was heated to approximately 26-28°C. Then butylated Hydroxytoluene NF is added and the mixture is stirred until dissolved. Then the steroid was added and mixed, and the temperature of the mixture was maintained and monitored to ensure that it did not exceed 40°C, until dissolved. The solution was deaerated prior to encapsulation.

The gelatin was prepared by blending gelatin NF, glycerin USP, sorbitol special and purified water USP. The resulting mixture was heated in a pressurized reactor to melt the gelatin. The gelatin was then maintained in the molten state until used for encapsulation.

Encapsulation was performed using a rotary die process. The heated gelatin was fed to an encapsulation machine where it entered two spreader boxes which cast the gelatin on a cooling drum, thus forming two gelatin ribbons. Each gelatin ribbon was lubricated with Fractionated Coconut Oil on the internal side and Fractionated Coconut Oil with 0.1% Lecithin NF on the external side. The Fractionated Coconut Oil prevents the gelatin from sticking to equipment and the Lecithin NF prevents the capsules from sticking together after manufacture, prior to drying. The ribbons were then conveyed to the encapsulation roller. Die cavities to

form the capsules are located on the circumference of the two adjacent rollers, which rotate and pull the gelatin ribbons between them. The fill solution was injected, by a metered positive-displacement pump, between the gelatin ribbons forcing them to expand and fill the die cavities. As the capsules were filled, they were simultaneously shaped, sealed and cut from the gelatin ribbon by the encapsulation rollers. The capsules were then conveyed to the rotating basket dryer.

The capsules were dried by tumbling in a rotating basket dryer to remove sufficient moisture to allow handling. They were then transferred onto trays and allowed to dry until the moisture level of the fill solution was not more than 2% (w/w). Drying time is the time required to reach the 2% moisture level.

Six batches were prepared containing 0.01, 0.05, 0.5, 2.5, 5.0, or 10.0 mg of steroid, 0.035 mg of butylated hydroxytoluene NF, and sufficient Capmul™ MCM to make a total fill composition of 350 mg, except the 10 mg capsule was made with a total fill of 500 mg.

These compositions were evaluated for relative bioavailability using standard methods. Volunteers were randomized to receive drug in either a soft gelatin capsule of the present invention or in a conventional tablet. Plasma samples were collected and pharmaco kinetic parameters (AUC, C_{max}, T_{max}) were compared between the treatment groups. The relative bioavailability from the soft gelatin capsule of this invention was 80% to 90% compared to 10% to 20% for the same amount of steroid in a tablet.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any novel feature or combination of features described herein and may include, by way of example and without limitation, one or more of the following claims.

Claims

What is claimed is:

1. A solution comprising a therapeutically effective amount of a pharmaceutically active aza steroid, and a fatty acid ester of glycerol or propylene glycol.

2. The solution of Claim 1 wherein said steroid is a 4-aza or a 6-aza steroid.

3. The solution of Claim 2 wherein said steroid is a 17-beta-substituted carbonyl-4-azaandrost-1-en-3-one or a 17-beta-substituted carbonyl-6-azaandrost-4-en-3-one.

4. The solution of Claim 3 wherein said steroid is a 17-beta-substituted carbonyl-4-azaandrost-1-en-3-one.

5 The solution of Claim 4 wherein said steroid is 17-beta-N-(t-butyl)carbamoyl-4-aza-5-alpha-androst-1-en-3-one, 17-beta-N-(2,5,-bis(trifluoromethyl))-phenylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one, 17-beta-N-1-(3,4-methylenedioxy-phenyl)-cyclohexylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one, or 17-beta-N-(1-(p-chlorophenyl))cyclopentylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one.

6. The solution of Claim 5 wherein said steroid is 17-beta-N-(2,5,-bis(trifluoromethyl))phenylcarbamoyl-4-aza-5-alpha-androst-1-en-3-one.

7. The solution of any of claims 1 - 6 wherein said steroid is from 0.0025 % to 2.5 % by weight of said solution.

8. The solution of claim 7 wherein said steroid is from 0.025 % to 1.5 % by weight of said solution.

9. The solution of any of claims 1-8 wherein said ester is derived from carboxylic acids which contain from 6 to 12 carbon atoms.

10. The solution of claim 9 wherein said ester is derived from carboxylic acids which contain 8 carbon atoms.

11. The solution of any of claims 1 - 10 wherein said ester is a monoester.

12. A pharmaceutical composition comprising the a solution according to any previous Claim .

13. The composition of claim 12 further comprising an antioxidant.

14. The composition of claim 13 wherein said antioxidant is butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid, or mixtures thereof.

15. The composition of claim 13 or 14 wherein said antioxidant is from 0.001 % to 0.5 % by weight of said composition.

16. A liquid filled gelatin capsule comprising the composition of any of claims 12 - 15.

17. The gelatin capsule of claim 16 wherein said capsule is a soft gelatin capsule.