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54 CONTROLLED RELEASE DELIVERY SYSTEM FOR NASAL APPLICATIONS

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If no classification is finished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

ABSTRACT

This invention relates to a pernasally administrable preparation for the controlled release of sexual hormones to the systemic circulation, in particular to a formulation which enables its active ingredient to be absorbed in a sustained manner providing a better bioavailability at very low doses and longer duration of action.

Controlled release delivery system for nasal applications

Field of the Invention

The present invention relates to a formulation for the controlled release of sexual hormones to the systemic circulation after nasal application.

Description of the Related Art

Nasal drug delivery offers many advantages that include rapid adsorption due to abundant capillary vessels, fast onset of action, avoidance of hepatic first-pass metabolism, utility for chronic medication and ease of administration.

It is known that, in contrast to large and/or ionized molecules, lipophilic pharmaceutical compounds having a sufficiently low molecular weight in general are readily adsorbed by the mucous membrane of the nose. For such drugs it is possible to obtain pharmacokinetic profiles similar to those obtained after intravenous injection.

However, maintaining constant in vivo therapeutic drug concentrations for an extended period of time has been problematic because of the rapid mucociliary clearance of the therapeutic agent from the site of deposition resulting in a short span of time available for absorption and of the presence of enzymes that may cause degradation in the nasal cavity.

A lot of efforts have been made to overcome these limitations including the use of bioadhesive systems that increase residence time in the nasal cavity, the use of enhancers to improve permeability of the nasal membrane or the use of stabilizers that prevent degradation of drugs.

Thus in GB 1987000012176 the use of bioadhesive microspheres has been proposed by Illum, and in PCT/GB98/01147 the use of in-situ gelling pectin formulations by WEST Pharmaceuticals.

Investigations on the nasal absorption of sexual steroids, rather small and lipophilic compounds, have shown that they are readily absorbed by the mucous membrane of the nose and are found very quickly in serum. Due to this fact, to the short half-life of the compounds and to limited possibilities for formulating nasal application forms with sustained release their use in clinical practice has been limited up to now because hormone replacement therapy, in general, is a long-term application.

Several formulations were proposed for these drugs. Thus, in the case of testosterone, which is nearly water-insoluble and somewhat better in vegetable oil, Hussain et al., "Testosterone 17β-N,N-dimethylglycinate hydrochloride: A prodrug with a potential for nasal delivery of testosterone", J. Pharmaceut. Sci. 91(3): 785-789 (2002), concluded that it would be an ideal candidate for nasal administration, if its solubility in water could be increased. He proposed to use a water-soluble pro-drug, testosterone 17β-N,N-dimethylglycinate, and found serum levels equal to intravenous administration with peak plasma concentrations within 12 min (25 mg dose) and 20 min (50 mg dose), respectively, and elimination half-lives of about 55 min. It must be mentioned that this speed is not necessary/desirable because sex hormone replacement is not an emergency therapy.

Ko et al., "Emulsion formulations of testosterone for nasal administration", J. Microencaps., 15(2): 197-205 (1998), proposed the use of charged testosterone submicron O/W emulsion formulations (water/Tween80, soybean oil/Span80) based on the hypothesis that increased absorption is possible upon solubilisation of the drug and/or prolongation of the formulation residence time in the nose. He found a higher relative bioavailability of the positively (55%) and negatively (51%) charged emulsion compared to the neutral one (37%). Tmax was observed in every case at about 20 min after administration. It is difficult to discuss these results because Ko did not take blood samples before application and thus it is not possible to evaluate the differences in the decrease of serum levels, although from a graph it seems that after intravenous application (hydroalcoholic solution) the level shows the longest elimination half time. In practice, however, such an

emulsion is not suitable because the droplet size (430 nm) is not acceptable for nasal application.

The solubility of progesterone in water and oil is somewhat comparable to that of testosterone, but investigators have had different approaches:

Cicinelli et al., "Progesterone administration by nasal spray", Fertil Steril 56(1): 139-141 (1991), "Nasally-administered progesterone: comparison of ointment and spray formulations", Maturitas 13(4): 313-317 (1991), "Progesterone administration by nasal sprays in menopausal women: comparison between two different spray formulations", Gynecol Endocrinol 6(4): 247-251 (1992), "Effects of the repetitive administration of progesterone by nasal spray in postmenopausal women", Fertil Steril, 60(6): 1020-1024 (1993) and "Nasal spray administration of unmodified progesterone: evaluation of progesterone serum levels with three different radioimmunoassay techniques", Maturitas 19(1): 43-52 (1994), showed that progesterone, dissolved in almond oil (20 mg/ml) and administered by nasal spray, lead to higher bioavailability than that provided by progesterone dissolved in dimethicone or a PEG-based ointment. After nasal application of progesterone in almond oil Cmax levels were observed after 30 to 60 minutes, decreasing significantly 6 to 8 hours after single administration.

Steege et al. "Bioavailability of nasally administered progesterone", Fertil Steril, 46(4): 727-729 (1986), dissolved progesterone in polyethylene glycol (200 mg/ml) and found Tmax at 30 min. The duration of serum levels was at least 8 hours but with high variations.

When progesterone was formulated in ethanol/propylene glycol/water however Tmax was only 5.5 min (Kumar et al, "Pharmacokinetics of progesterone after its administration to ovariectomized rhesus monkeys by injection, infusion, or nasal spraying", Proc. Natl. Acad. Sci. U.S.A., 79: 4185-9 (1982)).

Provasi et al., "Nasal delivery progesterone powder formulations comparison with oral administration", Boll. Chim. Farm. 132(10): 402-404 (1993), investigated powder mixtures (co-ground and co-lyophilized progesterone/cyclodextrin)

containing progesterone and also found Tmax within 2-5 min and a serum level decrease already in about 20 min.

These results are quite similar to that found for testosterone (see above) and for an already marketed aqueous nasal spray containing estradiol, formulated in cyclodextrin (Aerodiol®). Maximum plasma levels are reached within 10-30 minutes decreasing to 10% of the peak value after 2 hours already. Again, this speed is not necessary for sex hormone replacement therapy and not desirable in view of the short elimination half-time of hormones.

Apart from the "liberation/adsorption" problem shown above, in connection with sexual hormones and bioavailability, nearly exclusively the crucial liver metabolism and the short half-life are discussed, although a problem is also the high protein-binding. Approximately 40% of circulating plasma testosterone e.g. binds to sex hormone binding globulin (SHBG) - in men 2%, in women up to 3% remains unbound (free) - and the remainder binds to albumin and other proteins. The fraction bound to albumin dissociates easily and is presumed to be biologically active, whereas the SHBG fraction is not. The amount of SHBG in plasma however determines the distribution of testosterone in free and bound forms, where free testosterone concentrations determine (limit) the drug's half-life.

Accordingly, there is a constant need for a sexual hormone drug formulation system that is therapeutically effective when administered to the nose of a patient and is safe, stable and easily manufactured.

Summary of the invention

The inventor made intensive studies of various sexual hormone drug formulations and, as a result, surprisingly found that the incorporation of the drug into a special lipophilic or partly lipophilic system not only leads to a higher bioavailability in general caused by sustained serum levels in plasma, but also to a more favourable serum level profile.

The invention comprises a formulation for nasal application comprising a) at least one sexual hormone drug; b) at least one lipophilic or partly lipophilic carrier; and c) a compound or a mixture of compounds having surface tension decreasing activity, an amount effective for in situ generation of an emulsion upon contact of the formulation with water.

Preferably, the lipophilic carrier comprises an oil.

More preferably, said oil is a vegetable oil.

Most preferably, said oil is castor oil.

A preferred embodiment of the invention is characterized in that the amount of oil comprises between 30% and 98% by weight, preferably between 60 and 98% by weight, more preferably between 75% and 95% by weight, even more preferably between 85% and 95% by weight and most preferably around 90% by weight of the formulation.

A further embodiment is characterized in that component (c) comprises at least one surfactant selected from the group consisting of lecithin, fatty acid ester of polyvalent alcohols, of sorbitanes, of polyoxyethylensorbitans, of polyoxyethylene, of sucrose, of polyglycerol and/or at least one humectant selected from the group consisting of sorbitol, glycerine, polyethylene glycol, and macrogol glycerol fatty acid ester, or a mixture thereof.

Most preferably, component (c) comprises an oleoyl macrogolglyceride or a mixture of oleoyl macrogolglycerides.

Preferably, component (c) is comprised within the formulation in an amount of from 1 to 20% by weight, preferably 1 to 10% by weight, more preferably 1 to 5% by weight, and most preferably at around 4% by weight.

A further embodiment comprises a viscosity regulating agent.

Preferably, it is preferred that said viscosity regulating agent comprises a thickener or gelling agent selected from the group consisting of cellulose and cellulose derivatives, polysaccharides, carbomers, polyvinyl alcohol, povidone, colloidal silicon dioxide, cetyl alcohols, stearic acid, beeswax, petrolatum, triglycerides and lanolin, or a mixture thereof.

Most preferably, said viscosity increasing agent is colloidal silicon dioxide.

Preferably, the viscosity regulating agent is comprised within the formulation in an amount of from 0.5 to 10% by weight, preferably 0.5 to 5% by weight, more preferably 1 to 3% by weight, and most preferably at around 3% by weight.

In a preferred embodiment, the sexual hormone drug is testosterone.

Preferably, it is preferred that the sexual hormone drug is comprised within the formulation in an amount of from 0.5 to 6% by weight, preferably 2 to 4% by weight, more preferably 0.5 to 2% by weight, and most preferably at around 2% by weight.

Brief description of drawing

Figure 1 shows the serum levels of free testosterone at baseline and after nasal application of testosterone.

Detailed description of the invention

The resultant formulation is chemically and physically stable and can be a suspension or a solution of the pharmacologically active substance. Preferably it is filled into a preservative-free, airless multi-dose device able to accurately deliver doses of the above formulation, also at higher viscosities.

Once at the absorption site, the drug or the drug particles should be efficiently trapped at the deposition site and be absorbed at a predictable rate across the

mucous membrane of the patient, thereby limiting possible deactivation by metabolizing enzymes and/or protein-binding.

As used herein the following terms are defined as follow:

The term "sexual hormone drug" shall mean at least one sexual hormone (such as testosterone) or at least one biologic pro-drug of a sexual hormone (such as androstenedione, progesterone, 17-α-hydroxyprogesterone) or at least one derivative of a sexual hormone (such as mestanolone and 4-chloro-1-dehydromethyltestosterone) or a combination thereof. In a preferred embodiment the sexual hormone drug is testosterone.

The sexual hormone drug is comprised within the formulation in an amount of from 0.5 to 6% by weight, preferably 2 to 4% by weight, more preferably 0.5 to 2% by weight, and most preferably at around 2% by weight

The drug of this invention may be introduced into the formulation also in a processed form such as microspheres, liposomes etc.

The term "lipophilic carrier" shall comprise, but not limited to, a vegetable oil such as castor oil, soybean oil, sesame oil or peanut oil, fatty acid ester such as ethyl- and oleyloleat, isopropylmyristate, medium chain triglycerides, glycerol esters of fatty acids, or polyethylene glycol, phospholipids, white soft paraffin, or hydrogenated castor oil. Particularly useful is castor oil.

The incorporation of the drug is also possible into an oil mixture.

The particular amount of oil that constitutes an effective amount is dependent on the particular viscosity regulating agent (see below) used in the formulation. It is therefore not practical to enumerate specific amounts for use with specific formulations of the invention. Generally, however, the lipophilic part can be present in a formulation in an amount between 30% and 98% by weight, preferably between 60 and 98% by weight, more preferably between 75% and

95% by weight, even more preferably between 85% and 95% by weight and most preferably around 90% by weight of the formulation.

Componentn (C) shall comprise at least a surfactant such as, but not limited to, lecithin, fatty acid ester of polyvalent alcohols, of sorbitanes, of polyoxyethylensorbitans, of polyoxyethylene, of sucrose, of polyglycerol and/or at least one humectant such as sorbitol, glycerine, polyethylene glycol, or macrogol glycerol fatty acid ester. Particularly useful, however, are oleoyl macrogolglycerides (such as Labrafil M 1944 CS, as available from Gattefossé (Franco)).

The incorporation of the drug is also possible into a surfactant mixture.

The particular amount of surfactant that constitutes an effective amount is dependent on the particular oil or oil mixture (see above) used in the formulation. It is therefore not practical to enumerate specific amounts for use with specific formulations of the invention. Generally, however, the surfactant can be present in a formulation in an amount of from 1 to 20% by weight, preferably 1 to 10% by weight, more preferably 1 to 5% by weight, and most preferably at around 4% by weight.

The term "viscosity regulating agent" shall mean a thickener or gelling agent. Examples are, but not limited to, cellulose and derivatives thereof, polysaccharides, carbomers, polyvinyl alcohol, povidone, colloidal silicon dioxide, cetyl alcohols, stearic acid, beeswax, petrolatum, triglycerides or lanolin. Particularly useful however is colloidal silicon dioxide (such as Acrosil 200, as availble from Degussa).

The incorporation of the drug is also possible into a mixture of thickeners or gelling agents.

The particular amount of thickener/gelling agent that constitutes an effective amount is dependent on the particular oil or oil mixture (see above) used in the formulation. It is therefore not practical to enumerate specific amounts for use

with specific formulations of the invention. Generally, however, the thickener/gelling agent(s) can be present in a formulation in an amount from 0.5 to 10% by weight, preferably 0.5 to 5% by weight, more preferably 1 to 3% by weight, and most preferably at around 3% by weight.

The formulation according to this invention may also be processed into powder form, e.g. by lyophilization or spray-drying.

Generally the formulations of the invention can be prepared very easily by conventional methods, i.e.:

- Emulsion

The thickener or gelling agent is added to a sufficient amount of water and dispersed with high speed mixing and, if necessary, a surfactant (mixture 1). In a second container water and/or the lipophilic carrier are introduced and, if necessary, a surfactant (mixture 2). To mixture 2 the hormone is added very carefully avoiding introducing air. Mixture 2 is added to mixture 1, if necessary pH and tonicity are adjusted and the final mixture is homogenised and sterilised.

- Water-free formulation

Lipophilic carrier and emulsifier are filled into a stirrer vessel and about 75% of the viscosity regulating agent is mixed in. The hormone is added under stirring until a homogenous dispersion of the active ingredient is obtained. Then the formulation is adjusted to the necessary viscosity with the rest of the viscosity regulating agent.

The formulation is preferably filled into a preservative-free, airless nasal spray device such as the COMOD system available from Ursatec.

By "higher availability" is meant that after a single application a serum level of sexual hormone significantly higher than baseline is maintained for 6 hours, more preferably for 8 hours and most preferably for at least 10 hours.

Because sexual hormones are nearly not soluble in water liberation from the formulation is the speed-limiting step for adsorption. It has been surprisingly found that the incorporation of a sexual hormone drug such as testosterone in an oily formulation containing a suitable surfactant according to the invention leads of to physiologic serum levels and to a steady, sustained action of the hormone over time.

On one hand, the release of the hormone is sustained due to its solubility in the oily carrier and to the viscosity of the formulation remaining on the mucous membrane for a prolonged duration of time.

On the other hand, upon contact of the formulation with the humidity of the mucous membrane the drug's precipitation is hindered by the surfactant's property to form oil drops containing the drug. Thus by adding a suitable surfactant to the formulation the dissolution pattern of the hormone becomes more favourable and effective because there is no big variability in dissolution ensuring bioequivalence.

EXAMPLE

- **Typical formulation**

The formulation shown below was selected considering the serum level of the active ingredient achieved but it also exhibits a skin care property which is important for long term applications.

Table 1 Most preferred formulation

Compound	Amount per container	Delivery per spray
Testosterone	2%	≈ 2.8 mg
Aerosil® 200	3%	≈ 4.2 mg
Labrafil® M 1944 CS	4%	≈ 5.6 mg
Castor oil, refined grade	91%	≈ 127.4 mg

- **Typical serum level**

Comparing different formulations (see Figure 1) containing testosterone it is obvious that Cmax is clearly decreased in the special oily formulation of this invention, which is desirable in view of toxicological considerations. Further the level of unbound testosterone is very constant over at least 10 hours mimicking the physiologic daily rhythm of testosterone release.

The dotted line shows the serum level after application of 1 spray per nostril once of the most preferred formulation (see Table 1).

It can be concluded that the formulation for nasal application of this invention is different from conventional formulations, especially to those for sustained release, as it is mimicking the physiologic daily rhythm of testosterone release. It is also avoiding supra- and sub-normal testosterone levels, which is pleasant for the patient and a demand for hormone replacement therapy. As shown in Figure 1 (upper line), a simple nasal spray containing testosterone is unsatisfactory in this sense.

The features disclosed in the foregoing description, in the claims and/or in the drawings may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

Claims

1. An oil-based formulation for nasal application comprising
   (a) at least one sexual hormone drug;
   (b) at least one lipophilic or partly lipophilic carrier comprising at least one oil in an amount of between 60% and 98% by weight of the formulation; and
   (c) a compound or a mixture of the compounds having surface tension decreasing activity, in an amount effective for in situ generation of an emulsion upon contact of the formulation with water.

2. The formulation according to claim 1, wherein said oil is a vegetable oil.

3. The formulation according to claim 2, wherein said oil is castor oil.

4. The formulation according to any of claims 1 to 3, wherein the amount of oil comprises between 75% and 95% by weight of the formulation.

5. The formulation according to any of claims 1 to 3, wherein the amount of oil comprises between 85% and 95% by weight of the formulation.

6. The formulation according to any of claims 1 to 3, wherein the amount of oil comprises around 90% by weight of the formulation.

7. The formulation according to any of the preceding claims, wherein component (c) comprises at least one surfactant selected from the group consisting of lecithin, fatty acid ester of polyvalent alcohols, of sorbitanes, of polyoxyethylenesorbitans, of polyoxyethylene, of sucrose, of polyglycerol and/or at least one humectant selected from the group consisting of sorbitol, glycerine, polyethylene glycol, and macrogol glycerol fatty acid ester, or a mixture thereof.

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8. The formulation according to claim 7, wherein component (c) comprises an oleoyl macrogolglyceride or a mixture of oleoyl macrogolglycerides.

9. The formulation according to claim 7 and 8, wherein component (c) is comprised within the formulation in an amount of from 1 to 20% by weight.

10. The formulation according to claim 7 and 8, wherein component (c) is comprised within the formulation in an amount of from 1 to 10% by weight.

11. The formulation according to claim 7 and 8, wherein component (c) is comprised within the formulation in an amount of from 1 to 5% by weight.

12. The formulation according to claim 7 and 8, wherein component (c) is comprised within the formulation in an amount of around 4% by weight.

13. The formulation according to any of the preceding claims, further comprising a viscosity regulating agent.

14. The formulation according to claim 13, wherein said viscosity regulating agent comprises a thickener or gelling agent selected from the group consisting of cellulose and cellulose derivatives, polysaccharides, carbomers, polyvinyl alcohol, povidone, colloidal silicon dioxide, cetyl alcohols, stearic acid, beeswax, petrolatum, triglycerides and lanolin, or a mixture thereof.

15. The formulation according to claim 14, wherein said viscosity increasing agent is colloidal silicon dioxide.

16. The formulation according to any of the claims 13 to 15, wherein the viscosity regulating agent is comprised within the formulation in an amount of from 0.5 to 10% by weight.

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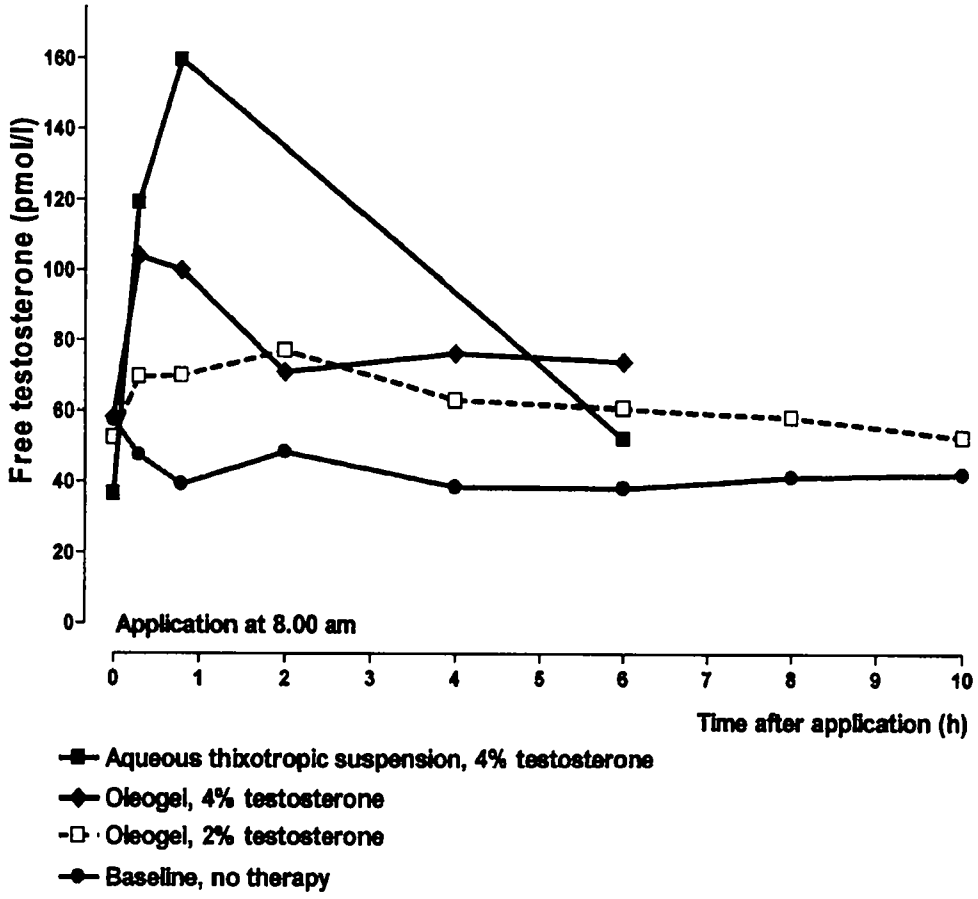

Free testosterone (pmol/l)
160
140
120
100
80
60
40
20
0
Application at 8.00 am
0
1
2
3
4
5
6
7
8
9
10
Time after application (h)
Aqueous thixotropic suspension, 4% testosterone
Oleogel, 4% testosterone
Oleogel, 2% testosterone
Baseline, no therapy

Figure 1