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STEROID FORMULATIONS FOR NASAL ADMINISTRATIONS

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(57) Claim

1. A substantially non-stinging aqueous anti-inflammatory steroid formulation suitable for intranasal administration, which formulation comprises:

an anti-inflammatory steroid in an amount between ~~about~~ 0.01% and ~~about~~ 0.05% (w/v);

propylene glycol in an amount between ~~about~~ 2% and ~~about~~ 10% (w/v);

PEG 400 in an amount between ~~about~~ 10% and ~~about~~ 25% (w/v);

polysorbate 20 in an amount between ~~about~~ 1% and ~~about~~ 4% (w/v); and water.

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Complete Specification for the invention entitled:

AQUEOUS STEROID FORMULATIONS FOR NASAL ADMINISTRATION

The following statement is a full description of this invention, including the best method of performing it known to : us

AQUEOUS STEROID FORMULATIONS FOR NASAL ADMINISTRATION

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to aqueous anti-inflammatory steroid formulations suitable for nasal administration, and to methods for treating inflammation of the nasal mucosa by intranasal administration of said formulations.

Related Disclosure

Aqueous formulations of anti- inflammatory steroids such as flunisolide suitable for nasal administration are commercially available, for example under the trademark Nasalide® (see, for example, U.K. Patent No. 1525181). However, currently available formulations, while safe and effective, are known to cause stinging upon administration in some cases, which is a side effect particularly undesirable when treating nasal inflammation. The novel formulations of the invention are suitable for nasal administration of anti-inflammatory steroids without causing stinging.

DETAILED DESCRIPTION AND PREFERRED EMBODIMENTS

One aspect of the invention is a substantially non-stinging aqueous anti-inflammatory steroid formulation suitable for nasal administration, which formulation comprises: an anti-inflammatory steroid in

an amount between ~~about~~ 0.01% and ~~about~~ 0.05% (w/v); propylene glycol in an amount between ~~about~~ 2% and ~~about~~ 10% (w/v); PEG 400 in an amount between ~~about~~ 10% and ~~about~~ 25% (w/v); polysorbate 20 in an amount between ~~about~~ 1% and ~~about~~ 4% (w/v); and water.

Suitably, an effective amount of a preservative, preferably between ~~about~~ 0.02% and ~~about~~ 0.08% (w/v); an effective amount of a stabilizer, preferably between ~~about~~ 0.005% and ~~about~~ 0.05%; an effective amount of an antioxidant, preferably between ~~about~~ 0.001% and ~~about~~ 0.05%; and a pH buffering agent sufficient to adjust the pH of the resulting solution to between ~~about~~ 3.5 and ~~about~~ 7, are also present to enhance stability and preservability.

A preferred subgenus of the invention is the formulation wherein said anti-inflammatory steroid is flunisolide, particularly in an amount of about 0.025% (w/v).

A preferred class is the formulation wherein said preservative is benzalkonium chloride in an amount between ~~about~~ 0.02% and ~~about~~ 0.08% (w/v); said stabilizer is disodium EDTA in an amount between ~~about~~ 0.005% and ~~about~~ 0.05% (w/v); and said antioxidant is BHT in an amount between ~~about~~ 0.001% and ~~about~~ 0.05% (w/v); especially the formulation which further comprises sorbitol in an amount between ~~about~~ 0.001% and ~~about~~ 5% (w/v). A preferred subclass is the formulation wherein said pH buffering agent comprises a citrate buffer such as: citric acid in an amount between ~~about~~ 0.001% and ~~about~~ 0.05% (w/v); and sodium citrate dihydrate in an amount between ~~about~~ 0.001% and ~~about~~ 0.05% (w/v).

A preferred species is the non-stinging aqueous anti-inflammatory steroid formulation suitable for nasal administration, which formulation comprises:

flunisolide hemihydrate in an amount of about 0.025% (w/v);

propylene glycol in an amount of about 5% (w/v);

PEG 400 in an amount of about 20% (w/v);

polysorbate 20 in an amount of about 2.50% (w/v);

benzalkonium chloride in an amount of about 0.035% (w/v);

disodium EDTA in an amount of about 0.01% (w/v);

BHT in an amount of about 0.01% (w/v);

citric acid in an amount of about 0.005% (w/v);

sodium citrate dihydrate in an amount of about 0.00765% (w/v);

sorbitol in an amount of about 2.00% (w/v); and

water, wherein the pH of the resulting solution is adjusted to about 5.2.

Another aspect of the invention is a method of treating inflammation of the nasal mucosa without inducing stinging, which method comprises intranasally administering to a subject in need thereof a substantially non-stinging aqueous anti-inflammatory steroid formulation as described above.

A further aspect of the invention is the use of the steroid formulation as described above in the treatment of inflammation of the nasal musosa.

The compositions of this invention have very satisfactory nasal acceptability, particularly as shown by their lack of, or low level of, nasal stinging.

The compositions of this invention provide good drug solubility, and this solubility is retained with varying temperature.

The compositions of this invention provide excellent pumping characteristics, so reducing the need to overcome pump clogging with washing and rinsing procedures.

The compositions of this invention are also stable and preservable.

From these advantages, it is clear that the compositions of this invention provide very attractive nasal steroid formulations.

DEFINITIONS

As used herein, the term "anti-inflammatory steroid" refers to a steroid compound which is pharmaceutically acceptable, and which is known to be useful in reducing inflammation. Particularly suitable anti-inflammatory steroids are flunisolide and beclomethasone. Dexamethasone or hydrocortisone might also be used. Flunisolide is most advantageously used in the form of the hemihydrate, as that form is non-hygroscopic and is thus easiest to handle during formulation. Flunisolide is commercially available, and can be prepared as described in U.S. Pat. No. 4,273,710. Beclomethasone is also commercially available, and can be prepared as described in G.B. Pat. No. 912,378.

Propylene glycol refers to 1,2-propanediol. Propylene glycol is available commercially.

Polyethylene glycol 400 refers to commercially available mixtures of polymers of average molecular weight about 400 of the form $H-(OCH_2CH_2)_n-OH$, where the average value of n is between 8.2 and 9.1. Polyethylene glycol 400 is abbreviated herein as "PEG 400".

Polysorbate 20 refers to commercially available polyoxyethylene-sorbitan monolaurates having about 20 oxyethylene units per sorbitan unit, for example Tween® 20.

The term "BHT" refers to butylated hydroxytoluene, which is a commercially available preservative/anti-oxidant.

The term "BHA" refers to butylated hydroxyanisole, which is a commercially available preservative/anti-oxidant.

The term "preservative" refers to a compound or mixture of compounds used in a formulation which is useful for reducing or eliminating microbial growth in a formulation. A preservative must be pharmaceutically acceptable at the concentrations used, and should not interfere with the action of the active compound in the formulation. An "effective amount" of a preservative is that amount necessary to prevent the growth of microorganisms in the formulation. The effective amount may be determined using the USP-BP modified double blind assay. Exemplary preservatives include, without limitation, BHA, BHT, benzalkonium chloride, thimerosal, potassium sorbate, methylparaben, propylparaben, sodium benzoate and the like. Presently preferred preservatives are benzalkonium chloride and thimerosal, particularly benzalkonium chloride.

The term "antioxidant" refers to a compound or mixture of compounds used in a formulation which is useful for preventing the oxidation of active compound(s) in a formulation. A antioxidant must be pharmaceutically acceptable at the concentrations used, and should not interfere with the action of the active compound in the formulation. An "effective amount" of an antioxidant is that amount necessary to prevent undue oxidation of the active compound under normal storage conditions. Presently preferred antioxidants are BHA, and BHT, particularly BHT.

The term "stabilizer" refers to a compound used in a formulation to prevent chemical degradation by means other than oxidation or microbial digestion. An "effective amount" of an oxidant is that amount necessary to prevent unacceptable degradation of the active compound. The presently preferred stabilizer is disodium EDTA.

The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and includes:

(i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;

(ii) inhibiting the disease, i.e., arresting its development; or

(iii) relieving the disease, i.e., causing regression of the disease.

ADMINISTRATION

The compositions of the invention are advantageously administered intranasally by means of a "non-propellant" type aerosol or atomizer, especially using a pump-type dispenser. For example, the Calmar Mark II nasal pump (Calmar-Albert GmbH) and the Pfeiffer pump (Ing.-erich Pfeiffer GmbH & Co. KG) are generally useful.

Preferably, the aerosol pump will deliver a spray in which less than 1% of the droplets are below 16 µm in diameter. This minimizes the amount of composition which reaches the lungs.

Sufficient amounts of the composition will be administered to give effective nasal anti-inflammatory action with the steroid concerned.

PREPARATION

The compositions of this invention may be prepared in any convenient manner. Suitably the steroid is dissolved in the solubilizers (propylene glycol, PEG 400 and polysorbate 20) before the required water is added. Any desired excipients may suitably be dissolved in the water prior to adding to the steroid solution. The pH of the final solution is adjusted to suitable levels, for example, between 3.5 and 7.

Preferred compositions of the invention may be prepared as follows:

The desired amounts of propylene glycol, PEG 400, and polysorbate 20 are mixed well in an appropriate vessel. To this mixture is added the desired amount of flunisolide (preferably in the form of the hemihydrate), and BHT. The resulting mixture is heated to 50-55°C and mixed until the flunisolide and BHT dissolve.

The desired amount of sorbitol (e.g., as a 70% solution) is mixed with citric acid and sodium citrate (in the proper proportions for obtaining the desired buffer), benzalkonium chloride (e.g. as a 50% solution), edetate disodium, and water, to form a solution which is approximately 90% water. This solution is then mixed with the flunisolide solution and the pH measured and adjusted with HCl solution or NaOH solution as appropriate.

The resulting solution is brought to final volume with purified water, filtered through a 3 micron filter, and packaged.

EXAMPLE 1

(Example Formulations)

The following are representative compositions of the invention. The compositions are prepared as described in the Preparation above.

(I)

Compound	amount%(w/v)
flunisolide hemihydrate	0.025
propylene glycol	5.0
PEG 400	20.0
polysorbate 20	2.50
benzalkonium chloride	0.035
disodium EDTA	0.01
BHT	0.01
citric acid	0.005
sodium citrate·$2H_2O$	0.00765
sorbitol	2.00
water qs	100.0
pH	5.2

(II)

Compound	amount%(w/v)
flunisolide hemihydrate	0.01
propylene glycol	2.0
PEG 400	10.0
polysorbate 20	1.0
benzalkonium chloride	0.03
disodium EDTA	0.01
BHT	0.01
citric acid	0.005
sodium citrate·$2H_2O$	0.00765
sorbitol	2.00
water qs	100.0
pH	5.3

(III)

Compound	amount%(w/v)
beclomethasone	0.05
propylene glycol	10.0
PEG 400	25.0
polysorbate 20	4.0
benzalkonium chloride	0.03
disodium EDTA	0.01
BHT	0.01
citric acid	0.005
sodium citrate·$2H_2O$	0.00765
sorbitol	5.00
water qs	100.0
pH	5.2

EXAMPLE 2

(Nasal Acceptability)

The following example illustrates a procedure for assaying the nasal acceptability of various compositions. The formulations were prepared as in Example 1. Formulation C is a vehicle according to this invention.

Eighteen volunteers were randomly divided into two groups. Group 1 received formulations A, B, and D. Group 2 received formulations A, C, and E. The tests were performed by applying one spray to each nostril, with a rest period of 4 hours between administrations of different formulations.

The following parameters were recorded, both immediately and 15 minutes after administration: nasal stinging, taste, other sensations, and willingness to use the spray three times daily. The formulations tested were as follows:

	amount%(w/v)				
Compound	A	B	C	D	E
propylene glycol	20.0	7.0	5.0	0.0	0.0
PEG 3350	15.0	0.0	0.0	0.0	0.0
PEG 400	0.0	40.0	20.0	15.0	0.0
polysorbate 20	0.0	0.0	2.50	3.5	3.5
*benzalkonium Cl	0.02	0.02	0.02	0.02	0.02
disodium EDTA	0.01	0.01	0.01	0.01	0.01
BHA	0.002	0.002	0.002	0.002	0.002
citric acid	0.005	0.005	0.005	0.005	0.005
Na citrate	0.0077	0.0077	0.0077	0.0077	0.0077
sorbitol	0.0	3.0	2.0	2.0	2.0
water qs	100.0	100.0	100.0	100.0	100.0
pH	5.3	5.3	5.3	5.3	5.3

*50% solution

The results indicated superior nasal acceptability for compositions C, D, and E.

EXAMPLE 3

(Accelerated Stability)

The stability of formulations was investigated as follows:

Six formulations were prepared as set out below for testing. Ten mL of each formulation was filled and sealed in amber glass ampoules and stored at 80°C (1/2 month), 60°C (1.5 months), and 15°C for the period of time stated. In addition, 25 mL of each solution was filled in 1 oz round high density polyethylene bottles and screw capped. These bottles were stored at 50°C (2, 3, 8, and 10 months), 40°C (8 and 10 months), and room temperature (RT) (8 and 10 months). At the end of the appropriate time period, the steroid content was determined using HPLC, and the pH of the solution measured. The results are normalized against the 15°C data for the appropriate time periods.

	amount%(w/v)						
Composition 1	2	3	4	5	6	7
PG	20.0	5.0	5.0	0.0	5.0	5.0	0.0
PEG 3350	15.0	0.0	0.0	0.0	0.0	0.0	0.0
PEG 400	0.0	20.0	20.0	15.0	20.0	20.0	15.0
PS 20	0.0	2.5	2.5	3.5	2.5	2.5	3.5
BHA	0.01	0.01	0.01	0.01	0.0	0.0	0.0
BHT	0.0	0.0	0.0	0.0	0.01	0.01	0.01
citrate	0.01	0.01	0.02	0.01	0.02	0.01	0.02
water qs	100.0	100.0	100.0	100.0	100.0	100.0	100.0

In addition, each formulation contained 0.025% flunisolide, 2% sorbitol, 0.01% EDTA, and 0.04% benzalkonium chloride. Composition 1 corresponds to Composition A of Example 2. Compositions 2, 3, 5, and 6 are equivalent to Composition C of Example 2, and are according to the invention. Compositions 4 and 7 are equivalent to Composition D of Example 2.

The results indicated that the formulations of the invention (Compositions 2, 3, 5, and 6) display superior stability as compared to other compositions (1, 4, and 7) in this assay.

EXAMPLE 4

(Preservative Efficacy)

The compositions listed below are tested for preservative efficacy using the USP-BP modified double challenge test.

Composition	amount%(w/v) A	B	C	D	E
flunisolide	0.025	0.025	0.025	0.025	0.025
propylene glycol	20.0	7.0	5.0	0.0	0.0
PEG 3350	15.0	0.0	0.0	0.0	0.0
PEG 400	0.0	40.0	20.0	15.0	0.0
polysorbate 20	0.0	0.0	2.50	3.5	3.5
disodium EDTA	0.01	0.01	0.01	0.01	0.01
BHA	0.002	0.002	0.002	0.002	0.002
citrate buffer	0.01	0.01	0.01	0.01	0.01
sorbitol	0.0	3.0	2.0	2.0	2.0
water qs	100.0	100.0	100.0	100.0	100.0
pH	5.3	5.3	5.3	5.3	5.3

In addition, each composition is prepared with 0.01, 0.02, 0.025, 0.03, 0.035, or 0.04 %(w/v) benzalkonium chloride. These compositions correspond to compositions A-E of Example 2. Composition C is according to the invention.

Compositions A-E are prepared according to Example 1, added to culture media, and the resulting test media directly inoculated with challenge organisms. After incubation for 14 days, the test media are inoculated again. The number of colony forming units is recorded over the remaining 14 days of the test.

The results indicated that Compositions A and B were effectively preserved with 0.01% benzalkonium chloride and Composition C was effectively preserved with 0.03% benzalkonium chloride, whereas Composition D required more than 0.04% benzalkonium chloride, and Composition E was not effectively preserved with any concentration of benzalkonium chloride tested.

EXAMPLE 5

(Toxicology)

No adverse reactions were seen in a one month intranasal toxicity study in rabbits with Composition (I) from Example 1 above.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:
~~WHAT IS CLAIMED~~:

1. A substantially non-stinging aqueous anti-inflammatory steroid formulation suitable for intranasal administration, which formulation comprises:

an anti-inflammatory steroid in an amount between ~~about~~ 0.01% and ~~about~~ 0.05% (w/v);

propylene glycol in an amount between ~~about~~ 2% and ~~about~~ 10% (w/v);

PEG 400 in an amount between ~~about~~ 10% and ~~about~~ 25% (w/v);

polysorbate 20 in an amount between ~~about~~ 1% and ~~about~~ 4% (w/v); and water.

2. A formulation according to Claim 1, which is a stable, effectively preservable, substantially non-stinging aqueous anti-inflammatory steroid formulation suitable for intranasal administration, which formulation comprises:

an anti-inflammatory steroid in an amount between ~~about~~ 0.01% and ~~about~~ 0.05% (w/v);

propylene glycol in an amount between ~~about~~ 2% and ~~about~~ 10% (w/v);

PEG 400 in an amount between ~~about~~ 10% and ~~about~~ 25% (w/v);

polysorbate 20 in an amount between ~~about~~ 1% and ~~about~~ 4% (w/v);

an effective amount of preservative;

an effective amount of antioxidant;

an effective amount of stabilizer;

water; and

pH buffering agent sufficient to adjust the pH of the resulting solution to between ~~about~~ 3.5 and ~~about~~ 7.

3. The formulation of Claim 2 which comprises:

preservative in an amount between ~~about~~ 0.02% and ~~about~~ 0.08% (w/v);

antioxidant in an amount between ~~about~~ 0.001% and ~~about~~ 0.05% (w/v); and

stabilizer in an amount between ~~about~~ 0.005% and ~~about~~ 0.05% (w/v).

4. The formulation of Claims 1, 2 or 3 wherein said anti-inflammatory steroid is flunisolide.

5. The formulation of Claims 1, 2, 3 or 4 which further comprises sorbitol in an amount between ~~about~~ 0.001% and ~~about~~ 5% (w/v).

6. A formulation according to Claim 2 which is a stable, effectively preservable, substantially non-stinging aqueous anti-inflammatory steroid formulation suitable for intranasal administration, which formulation comprises:

flunisolide hemihydrate in an amount of about 0.025% (w/v);

propylene glycol in an amount of about 5% (w/v);

PEG 400 in an amount of about 20% (w/v);

polysorbate 20 in an amount of about 2.50% (w/v);

benzalkonium chloride in an amount of about 0.035% (w/v);

disodium EDTA in an amount of about 0.01% (w/v);

BHT in an amount of about 0.01% (w/v);

citric acid in an amount of about 0.005% (w/v);

sodium citrate dihydrate in an amount of about 0.00765% (w/v);

sorbitol in an amount of about 2.00% (w/v); and

water, wherein the pH of the resulting solution is adjusted to about 5.2.

7. Use of a formulation according to any one of the Claims 1-6 in treating inflammation of the nasal mucosa without inducing stinging.

8. A process for preparing the formulation of Claim 1, which process comprises dissolving the stated ingredients in water.

9. A formulation substantially as hereinbefore described with reference to Example 1(I).

10. A formulation substantially as hereinbefore described with reference to Example 1(II).

11. A formulation substantially as hereinbefore described with reference to Example 1(III).

12. Use of a formulation substantially as hereinbefore described with reference to Example 1(I) in treating inflammation of the nasal mucosa without inducing stinging.

13. Use of a formulation substantially as hereinbefore described with reference to Example 1(II) in treating inflammation of the nasal mucosa without inducing stinging.

14. Use of a formulation substantially as hereinbefore described with reference to Example 1(III) in treating inflammation of the nasal mucosa without inducing stinging.

DATED this 11th day of January, 1991.

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