TIXOCORTOL PIVALATE SUSPENSION, COLLUTORIUM BASED ON IT AND PACKAGING CONTAINING IT

The subject of the present invention is a tixocortol pivalate suspension, in the form of a collutorium, and a container containing this suspension, the packaging additionally comprising a metering pump.

Several compositions based on tixocortol (or (11β)-11,17-dihydroxy-21-mercaptopregn-4-ene-3,20-dione) are already known, in particular in the pivalate form, for the local treatment of inflammatory states, in particular ear, nose and throat conditions. These compositions can be nebulized so as to be dispensed in the throat.

A pressurized packaging equipped with a metering valve and comprising a tixocortol pivalate suspension in isopropyl myristate is known, the propellant gas being dichlorodifluorocarbon (F12, CFC). The volume of the collutorium discharged is on average 180 µl.

The ban on the use of CFCs has caused the suppression of the metering valve associated with propellant gas. The packaging has been replaced by a packaging with a metering pump, the composition remaining identical. During use, the patient compresses the air in the pump's chamber, which makes it possible to deliver about 50 µl of suspension.

This solution is, however, not satisfactory for several reasons. First of all, the suspension does not make it possible to deliver a sufficient volume of collutorium (50 µl against 180 µl previously). Next, this suspension is relatively viscous, which does not make it possible to obtain good coverage of the area to be treated. Furthermore, this type of product does not make it possible to obtain droplets of controlled size which will not enter into the bronchi but will be delivered into the buccopharyngeal cavity.

It is not possible to adjust the volume to 180 µl with isopropyl myristate, the taste being unacceptable.

The aim of the invention is therefore to provide a suspension which is stable to storage and which can be easily delivered in the form of a collutorium having an appropriate droplet volume and size.

The document WO-A-9720578 describes a tixocortol pivalate suspension in an aqueous vehicle free of preservative, for the treatment of ocular and ophthalmic pathologies.

The document WO-A-9531964 describes a fluticasone propionate composition having a particle size of less than 12 µm, in suspension in an aqueous solution comprising a surfactant and a buffering agent, intended to be administered into the bronchi.

The document WO-A-9511669 describes a loteprednol etabonate composition in suspension in an aqueous solution comprising a polymer and a nonionic surfactant and an isotonicity agent (glycerol).

None of the above documents teaches or suggests the present invention.

Thus, the invention provides an aqueous suspension of tixocortol pivalate comprising:

(a) tixocortol pivalate in suspension, having a particle size such that its average size D50 is between 0.5 and 20 µm;

(b) a surfactant;

(c) a viscosity agent; and

(d) the balance as water and conventional adjuvants.

The invention also provides a collutorium based on the suspension defined above, and having a volume of between 100 and 300 µl.

The invention also provides a packaging comprising a container containing the suspension defined above, provided with a metering pump.

Finally, the invention provides a method of preparing the suspension defined above, comprising the following steps:

(1) preparation of the aqueous solution with the balance of water, the surfactant, the viscosity agent and optionally the second active ingredient;

(2) suspension of the tixocortol pivalate in said solution.

The invention is now described in greater detail in the description which follows.

Tixocortol pivalate

The active ingredient is in micronized form, and it has a particle size such that its average size D50 (D50, size below which 50% by volume of the particles exist) is between 0.5 and 20 µm, preferably between 1 and 10 µm. Preferably, the size of the particles may be such that the value of D90 (D90, size below which 90% by volume of the particles exist) is less than 10 µm.

The active ingredient is prepared by conventional methods. The crystals are reduced to the desired size by methods which are also conventional, for example micronization.

The active ingredient in micronized form is also commercially available, for example from PPG (Avrillé, France).

The suspension according to the invention will comprise, by weight relative to the final volume of the suspension (in % m/v, that is to say in grams per 100 ml of suspension) for example from 0.05 to 10% m/v, in particular from 0.1 to 5% m/v, advantageously from 0.1 to 0.5% m/v, of tixocortol pivalate.

Second active ingredient

The suspension advantageously comprises a second active ingredient, in particular an antiseptic. This antiseptic may be chlorhexidine (in particular in saline form). Preferably, the antiseptic is chlorhexidine digluconate.

Preferably, the second active ingredient is itself soluble in the aqueous solution.

Chlorhexidine digluconate is available in the form of an aqueous solution, for example at a dose of 20% m/v.

The suspension according to the invention will comprise, by weight relative to the final volume of the suspension (in % m/v) for example from 0.05 to 10% m/v, in particular from 0.1 to 5% m/v, advantageously from 0.1 to 0.5% m/v of chlorhexidine digluconate (expressed in dry form).

Other active ingredients may also be present.

Surfactant, wetting agent

The surfactant is a wetting agent which may be selected from pharmaceutically acceptable surfactants. By way of example, there may be mentioned sorbitan trioleate, monooleate or monolaurate, or their polyoxyethylenated derivatives (polysorbate 20, 40, 60, 80); natural or synthetic lecithin; polyoxyethylenated oleyl, stearyl or lauryl fatty ethers; polyoxyethylene-polyoxypropylene block copolymers; diethylene glycol dioleate; tetrahydrofurfuryl oleate, ethyl oleate, glyceryl monooleate, glyceryl monolaurate; PEG400 to PEG4000; and quaternary ammonium derivatives. These surfactants are commercially available, for example under the names Pluronic, Poloxamer, Tween. The surfactants wetting agents preferred in the invention are the quaternary ammonium derivatives, in particular the cyclic derivatives comprising the nitrogen atom quaternized in the ring or otherwise. By way of example, there may be mentioned picolinium, benzalkonium and cetylpyridinium, the latter being preferred. The counter-ion may be any conventional counter-ion, for example chloride. Mixtures are also appropriate.

The suspension according to the invention will comprise, by mass relative to the final volume of the suspension (in % m/v) for example from 0.005 to 2.5%

m/v, in particular from 0.01 to 0.5% m/v, advantageously from 0.01 to 0.05% m/v of surfactant.

Viscosity agent

The object of the viscosity agent is to adjust the viscosity of the solution and in fine of the suspension. This viscosity agent (or thickening agent) may be chosen from water-soluble polymers (such as polyvinylpyrrolidone PVP, polyvinyl alcohol PVA; cellulose derivatives such as hydroxypropyl-methylcellulose HPMC, hydroxymethylcellulose HMC, hydroxyethylcellulose HEC, hydroxypropylcellulose HPC, carboxymethylcellulose CMC; (cyclo)dextrin, and the like) and polyols and derivatives thereof. The latter class comprises for example glycerol, sorbitol and maltitol. The latter class is preferred, and glycerol will be more particularly preferred. It has, in addition, sweetening and demulcent (emollient) properties. Mixtures are appropriate.

A solution which is relatively only slightly viscous will be preferred. The viscosity of the suspension, measured according to the capillary tube method (Ph. Eur. 2-2-9), is advantageously between 1.2 and 2 mPa.s, preferably between 1.4 and 1.8 mPa.s (the viscosity of pure water being 1.03 mPa.s).

The slightly viscous suspension makes it possible to obtain better coverage of the area to be treated, and better adherence at the level of the upper airways. Furthermore, this viscosity makes it possible to slow down the sedimentation of the particles of active ingredient.

The suspension according to the invention will comprise, by weight relative to the final volume of the suspension (in % m/v) for example from 1 to 50% m/v, in particular from 5 to 30% m/v, advantageously from 10 to 20% m/v of viscosity agent.

Adjuvants

Conventional adjuvants may be added to the composition. Among these adjuvants, there may be mentioned sweetening agents, flavorings, buffers,

preservatives and the like. These adjuvants, as well as their quantities, are standard and known to persons skilled in the art.

As sweetening agent, there may be used in particular aspartame, sodium saccharinate, potassium acesulfame, sodium cyclamate or ammonium glycyrrhizinate. Potassium acesulfame will be preferred. The content of sweetening agent is for example from 0.025 to 0.5% m/v, in particular from 0.025 to 0.05% m/v, advantageously from 0.05 to 0.25% m/v of sweetening agent. The flavor modifier (flavoring) may be present in solution or in suspension. Mixtures are appropriate.

Suspension

This suspension exhibits good properties as regards:

- the speed of sedimentation (stability)
- variation in the size and shape of the tixocortol pivalate particles under the effect of temperature cycles.
- ability to be resuspended.

As regards the speed of sedimentation, the degree of sedimentation at room temperature is greater than 90% after 45 min, that is to say that the height of the sedimentation front is 90% of the initial total height.

As regards the variation in the size and shape of the tixocortol pivalate particles under the effect of temperature cycles, no modification is noted. After a cycle 50°C for 1 h, 5°C for 1 h, 50°C for 1 h, 5°C for 1 h, 50°C for 1 h, there is no difference with a control sample stored at room temperature.

As regards the ability to be resuspended, the present invention offers excellent results. After standing for 24 h at room temperature, 2 to 4 inversions of the cylinder are sufficient for the preparation to become homogeneously resuspended. Thus, the user will not have to shake the vial for several

minutes before use, but a few inversions of the vial will be sufficient.

The suspension comprises the active ingredient, still in micronized form, the aggregation or flocculation being minimal. Thus, the size of the particles of active ingredient in suspension is in general at most five times, preferably twice, the initial size.

The suspension according to the invention exhibits good resistance to microbial contamination.

The suspension is prepared by any appropriate method. A typical method comprises the following steps, for example carried out at room temperature:

- preparation of an aqueous solution with water, the antiseptic agent (chlorhexidine digluconate), the surfactant (cetylpyridinium), the adjuvants;
- solubilization/dispersion of the viscosity agent (glycerol); and
- suspension (dispersion and then homogenization) of the tixocortol pivalate.

It is also possible to use a two-stage method, the first stage comprising the preparation of the aqueous solution with all the water-soluble or water-dispersible ingredients, and then the suspension of the tixocortol pivalate.

The materials used are standard and known to persons skilled in the art.

Collutorium

The collutorium is provided in the form of an aerosol of droplets.

The volume of collutorium dispensed is in general between 100 and 300 µl, preferably between 150 and 220 µl, advantageously about 180 µl.

The droplets have an average size (D'50) such that these droplets do not penetrate into the bronchi, but on the contrary remain in the areas of the throat intended to receive the anti-inflammatory treatment, namely the laryngeal and rhinopharyngeal region. It

should be noted that in general the temperature does not modify the particle size of the spray. D'50 is in general between 20 and 500 µm, advantageously between 50 and 200 µm, preferably about 100 µm.

The suspension and the collutorium based on it are intended in particular for the treatment of inflammations of the laryngeal, buccopharyngeal and rhinopharyngeal regions, in particular angina, laryngitis and rhinopharyngitis. A dose will comprise in general a quantity of tixocortol pivalate of between 0.2 and 1.2 mg, in particular of about 0.6 mg. A dose will comprise in general a quantity of chlorhexidine digluconate of between 0.05 and 0.6 mg, in particular of about 0.18 mg.

Packaging

The packaging comprises a container and a metering pump.

The metering pump is adapted to deliver appropriate volumes of droplets of suspension in the form of a collutorium. Such a metering pump is commercially available.

The following examples illustrate the invention without limiting it.

Example 1.

A composition having the following percentage composition (in m/v) is prepared:

Ingredient	Quantity
Tixocortol pivalate	0.333 g
Chlorhexidine digluconate	0.143 g
Polysorbate 80	0.050 g
Glycerol	15 g
Adjuvants (flavoring and sweetener)	0.7 g
Water	qs 100 ml

In a first instance, there is prepared an aqueous solution with water, the solution containing 20% m/v of chlorhexidine digluconate, the polysorbate 80 and the adjuvants, by mixing at room temperature.

In a second instance, the glycerol is dispersed therein.

Finally, the tixocortol pivalate is suspended therein by dispersion and then homogenization.

Example 2.

A composition having the following percentage composition (in m/v) is prepared:

Ingredient	Quantity
Tixocortol pivalate	0.333 g
Chlorhexidine digluconate	0.143 g
Cetylpyridinium chloride	0.025 g
Glycerol	15 g
Adjuvants (flavoring and sweetener)	0.7 g
Water	qs 100 ml

The procedure is carried out in the same manner as in Example 1 but replacing polysorbate 80 with cetylpyridinium chloride.

Example 3.

A container is filled with the suspensions of Examples 1 or 2, and then a metering pump is seamed onto the body of the container. The dose delivered is 180 µl of collutorium, corresponding to 0.6 mg and 0.257 mg of tixocortol pivalate and of chlorhexidine digluconate, respectively. The droplets of the collutorium have a size of about 100 µm.

CLAIMS

1. Aqueous suspension of tixocortol pivalate comprising:

(a) tixocortol pivalate in suspension, having a particle size such that its average size D50 is between 0.5 and 20 µm;

(b) a surfactant;

(c) a viscosity agent; and

(d) the balance as water and conventional adjuvants.

2. The suspension according to claim 1, in which the tixocortol pivalate has a particle size such that its average size D50 is between 1 and 10 µm.

3. The suspension according to claim 1 or 2, in which the tixocortol pivalate has a particle size such that its average size D90 is less than 10 µm.

4. The suspension according to any one of claims 1 to 3, in which the surfactant is a quaternary ammonium derivative.

5. The suspension according to claim 4, in which the quaternary ammonium derivative is cetylpyridinium.

6. The suspension according to any one of claims 1 to 5, in which the viscosity agent is glycerol.

7. The suspension according to any one of claims 1 to 6, comprising, in % by mass per volume of the suspension:

(a) from 0.05 to 10% m/v of tixocortol pivalate in suspension, having a particle size such that its average size D50 is between 0.5 and 20 µm;

(b) from 0.005 to 2.5% m/v of a surfactant;

(c) from 1 to 50% m/v of a viscosity agent; and

(d) the balance as water and conventional adjuvants.

8. The suspension according to any one of claims 1 to 7, comprising, in % by mass per volume of the suspension:

(a) from 0.1 to 5% m/v of tixocortol pivalate;

(b) from 0.01 to 0.5% m/v of a surfactant;

(c) from 5 to 30% m/v of a viscosity agent; and

(d) the balance as water and conventional adjuvants.

9. The suspension according to any one of claims 1 to 8, comprising, in % by mass per volume of the suspension:

(a) from 0.1 to 0.5% m/v of tixocortol pivalate;

(b) from 0.01 to 0.05% m/v of a surfactant;

(c) from 10 to 20% m/v of a viscosity agent; and

(d) the balance as water and conventional adjuvants.

10. The suspension according to any one of claims 1 to 9, which has a viscosity of between 1.2 and 2 mPa.s.

11. The suspension according to any one of claims 1 to 10, which has a viscosity of between 1.4 and 1.8 mPa.s.

12. The suspension according to any one of claims 1 to 11, comprising, in addition:

(e) an antiseptic.

13. The suspension according to claim 12, in which the antiseptic is chlorhexidine.

14. The suspension according to claim 12 or 13, comprising, in % by mass per volume of the suspension:

(e) from 0.05 to 10% m/v of antiseptic.

15. The suspension according to claim 12, 13 or 14, comprising, in % by mass per volume of the suspension:

(e) from 0.1 to 5% m/v of antiseptic.

16. The suspension according to claim 1, having the following percentage composition: 0.333 g of tixocortol pivalate, 0.143 g of chlorhexidine digluconate, 0.025 g of cetylpyridinium chloride, 15 g of glycerol, 0.7 g of adjuvants and the quantity of water necessary to reach a volume of 100 ml.

17. The suspension according to any one of claims 1 to 16, for the treatment of inflammations of the laryngeal, buccopharyngeal and rhinopharyngeal region.

18. A collutorium based on a suspension according to any one of claims 1 to 17, having a delivered volume of between 100 and 300 µl.

19. The collutorium according to claim 18, having a delivered volume of between 150 and 220 µl.

20. The collutorium according to claim 18 or 19, in which the droplets have a particle size such that its average size D'50 is between 20 and 500 µm.

21. The collutorium according to claim 18, 19 or 20, whose droplets have a particle size such that its average size D'50 is between 50 and 200 µm.

22. The collutorium according to any one of claims 18 to 21, comprising between 0.2 and 1.2 mg of tixocortol pivalate.

23. A packaging comprising a container containing the suspension according to any one of claims 1 to 17, provided with a metering pump.

24. A method of preparing the suspension according to any one of claims 1 to 17, comprising the following steps:

(1) preparation of the aqueous solution with the balance of water, the surfactant, the viscosity agent and optionally the second active ingredient;

(2) suspension of the tixocortol pivalate in said solution.

25. The method according to claim 24, in which stage (1) comprises two substages, the first substage comprising the preparation of an aqueous solution with the balance of water, the surfactant and optionally the second active ingredient, the second substage comprising the solubilization/dispersion of the viscosity agent.

26. A method of preparing a collutorium according to any one of claims 18 to 22, comprising the action of a metering pump of the packaging according to claim 23.