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(54) **Title**: ORAL SUSPENSION OF DEXAMETHASONE ACETATE -TASTE MASKING COMPOSITION OF DEXAMETHASONE

(57) **Abstract**: The present invention is a pharmaceutically acceptable composition in the form of suspension for the oral delivery of dexamethasone acetate in which the active ingredient is homogenously dispersed in a pharmaceutically acceptable aqueous carrier -vehicle. The present invention relates to a method for taste masking the bad taste of dexamethasone, provide a pharmaceutical composition comprising a specific ester of dexamethasone (dexamethasone acetate), in a therapeutically effective amount in a aqueous, compatible, stable media vehicle and a suspending agent The inventive formulation comprising dexamethasone acetate dispersed in an aqueous, compatible, between about 0.4 mg/ml to about 40 mg/ml, more preferably between 0.4 mg/ml to about 10mg/ml,more preferably 4 mg/ml. The aqueous vehicle may further consist of glycerin and propylene glycol. The inventive composition, comprises more than one pharmaceutical excipients.

ORAL SUSPENSION OF DEXAMETHASONE ACETATE –TASTE MASKING COMPOSITION OF DEXAMETHASONE

DESCRIPTION

The invention related to a immediate release pharmaceutical formulation for oral administration comprising an effective amount of dexamethasone acetate in an aqueous ,pharmaceutically acceptable vehicle and a suspending agent

Dexamethasone ,a corticosteroid ,used in inflammatory and autoimmune disorders, usually formulated into tablets and liquid formulations for oral delivery. Commercially available oral liquid formulations of dexamethasone comprising soluble salts of dexamethasone esters, for example dexamethasone sodium phosphate. However the bad taste of these solutions ,extensively described in the literature ,results in poor patient compliance . Provided that the bad taste of dexamethasone and its soluble esters are dose dependent it is a considerable problem for the patient to comply especially in case of therapies require high doses of dexamethasone.

Furthermore the bad (bitter) taste and aftertaste of these liquid oral dosage forms is difficult to be masked , without alter the release rate of the active ingredient and using the already known taste masking techniques , that can be found in the literature and are known to the skilled person.

The problem is to create a palatable, stable, immediate release oral liquid dosage form of dexamethasone especially when high therapeutic doses of dexamethasone are needed

Dexamethasone acetate (the insoluble acetate ester of dexamethasone) has been previously used in formulations for local administration –including ophthalmic formulations-,as well as in parenteral (intramuscular) formulations , but it has not been previously used in oral liquid formulations for immediate release dosage forms

After many experiments we surprisingly found that dexamethasone acetate can be used for the preparation of a suspension of dexamethasone ,in which dexamethasone acetate has the attribute to mask the bad and exceptionally bitter taste of dexamethasone .This attribute becomes perceptible particular when high doses of the said active ingredient are needed to be administered.. Moreover by the use of specific excipients that are known to the skilled person it can be prepared a immediate release ,stable formulation ,with components mutually compatible and stable during the shelf life of the product as it is determined from the rules governing the medicinal products for human use.

Dexamethasone acetate possess specific advantages compared to other dexamethasone esters for this specific purpose

a) Immediate release of the active ingredient dexamethasone in the low pH of the gastric fluids (1-2), according to the literature

b) Low solubility. Dexamethasone acetate does not dissolved in the aqueous conditions of the mouth cavity, and the interactions between the bitter molecule of dexamethasone and the taste buds of the tongue are prevented.

The formulation of the present invention is a palatable, oral aqueous suspension of dexamethasone in which dexamethasone is in the form of the its acetate ester and in concentration between about 0.4 mg/ml to about 40 mg/ml , more preferably between 0.4 mg/ml to about 10mg/ml,more preferably 4 mg/ml

The present invention is an aqueous suspension in which dexamethasone is dispersed in a medium-vehicle, that comprised mainly from water and may include propylene glycol and glycerin . Dexamethasone acetate is evenly dispersed in the liquid aqueous vehicle. The suspension has homogeneity so the active ingredient is uniformly dispersed, but undissolved in the vehicle-aqueous medium. The medium can also comprise other pharmaceutical excipients that are mutually compatible at room temperature and they can form a pharmaceutically acceptable oral liquid preparation.

The aqueous vehicle serves as the external phase for the suspensions. In our case and as it is previously described , the vehicle may comprised of water ,glycerin , propylene glycol and mixtures there of. The water comprising from about 30 to about 70% of the vehicle. Glycerin may comprise up to 50 % of the vehicle. The vehicle may also contain propylene glycol up to 20% of the vehicle.

Purified water that is the main ingredient of the vehicle component, comprising from about 30 to about 70% (w/w) of the formulation. In the present embodiment Water concentration is about 30% to 40% (w/w) in the final formulation

The particle size is very important for the bio availability of the product .In case of smaller particle size the active surface area is increased and the dissolution time is also increased .On the other hand the increased surface area may result in some agglomeration affecting the stability of the suspension or increase the oxidation and hydrolysis of the active compound resulting in faster degradation of dexamethasone. Dexamethasone acetate of the inventive formulation has a median particle size of 1μm to about 30 μm, more preferably about 3 μm to about 15 μm . The particle size can be achieved using established methods well known to the skilled person like air jet milling, ball milling, mortal milling or any other approved method to decrease the particle size. For example dexamethasone acetate particles of the disclose formulation were micronised using Jet Mil 50 (Jet Pharma S.A.)

The viscosity may be about 80 to about 2000 cps ,more preferably about 100 to about 500 cps,most preferably about 100 to 150cps. In the inventive formulation there is no crystalline growth during a heat cool study for three days at a temperature range of 8°C to about 45°C.The active ingredient particles maybe crystals that neither dissolve or grow substantially when the sample is heated to 45 °C and cooled to room temperature repeatedly

The size of the particles may be measured using light scattering device ,sedimentation methods, or any other methods known to the skilled person .For example Matersizer 2000 manufactured by Malvern instruments Ltd ,Malvern U.K. the maybe used to measure the particle size.

Pharmaceutical excipients are pharmaceutically approved components of virtually all the pharmaceutical formulations. Excipients serve many different and wide purposes during the process of formulation as well as in the final formulation it self. The inventive pharmaceutical suspension may comprise at least one of the additional component excipient selected form the following groups of excipients: surface active agents ,dispersing agents , sweetening agents, flavoring agents, coloring agents, buffers, salts, preservatives, oily vehicles, wetting agents, demulcents, spreading agents, stabilizers, antioxidants, antibiotic ,antifungal agents .

In the present formulation , due to the insoluble nature of dexamethasone acetate a wetting agent was necessary in order to ensure the homogenously dispersion of the active ingredient in the aqueous based vehicle. Poloxamer 188 found to be effective , in concentrations at about 0.05 to 0.5% without create excessive foaming and without alter the taste of the inventive composition .

Spreading agents like maltitol, mannitol, polyethylene glycol, and sorbitol can be added to the vehicle components in order to adjust the spreadability of the final suspension. In the present embodiment of the invention and due to the low concentration of Xantham Gum and the low viscosity of the suspension there is no need to adjust spreadability .Notwithstanding the use of such spreading agents cannot be excluded in other embodiments of the present invention where the higher viscosity could be higher. Especially sorbitol and mannitol also serve as an immediate on set sweetener and for this purpose used also in the present invention. In the present embodiment it has been used sorbitol solution 70% (w/w) in concentration less than 20% (w/w) ,even more less than 15%(w/w),to about 10 to 15% (w/w) of the final formulation

The suspension of the present invention may contain EDTA. EDTA is a chelating agent that creates stable complexes with metals ions (alkaline earth , mainly Ca^{2+} and Zn^{2+}) .The involvement of these metals in traces in catalyzing the auto oxidation, is an obvious possibility and has been reported in the literature. EDTA is useful as an antioxidant, sequestering metal ions that otherwise catalyze autoxidation reactions. E.D.T.A. can also be serve as a preservative.

The stability of the suspension can be increased by the incorporation in the suspension a small amount of nitrogen- containing compound ,such as niacinamide, creatinine and derivatives there of , like n-methylcreatinine .These compounds usually act as stabilizers for the ester and prevents the precipitates for long period of time

In addition to these stabilizers and since a certain proportion of any decomposition evidenced is due to oxidative degradation , it is desirable to include to these formulations , a small amount of antioxidant .Suitable antioxidants include , both inorganic and organic compounds .Organic antioxidants, such as Sodium Citrate penicillamine , pyridinesulfinic acid , thiourea and sodium formaldehyde sulfoxylate are acceptable .Inorganic antioxidants such as sodium sulfite ,sodium metabisulfite, sodium hypophosphite are acceptable. In the present embodiment the inventive suspension contains sodium metabisulfite

Suspending agents is another group of excipients. These agents usually added for obtain the desired viscosity and flow to the formulation. As thickening can be used a group of different compounds like xantham gum or carbomers. This depends on the desired viscosity of the final formulation. Xantham gum is active and keep its properties in a wide range of pH, thus it appears more advantageous than other suspending agents. The inventive formulation may contain xantham gum in a concentration from about 0.1% (w/w) at about 0.3% ,more preferably between 0.1 to 0.25 ,most preferably 0.17% (w/w).

Even though it is well described in the literature that the acetate ester of dexamethasone is more stable in low pH values (acidic conditions) there is a further need to determine with more accuracy the pH values in which the suspension remain stable ,avoiding the ester degradation and further interactions between suspension components. For these reasons we proceed in one month accelerated stability studies. A sample of the suspension that is described in the present embodiment of the invention divided in 6 amber glass vials of 100ml volume. pH was adjusted with NaOH. Finally it was prepared six suspension of the said formulation with pH values of 3.8, 4.0 ,4.2, 4.6, 5.0 ,5.2 ,5.4 και 5.6.Dexamethasone acetate was measured by HPLC (High Pressure Liquid Chromatography)Measurements showed that the optimal pH is 4 9 (percentage of degradation less than 1%)

In addition to those stabilizers and antioxidants other substances can be included to the present formulation .A bacteriogical preservative for example , like sodium benzoate , methyl-paraben, propyl paraben, butyl-paraben , other antimicrobial agents can also be used in concentration and limits described in the pharmaceutical literature .

The inventive formulation may comprise sweeteners for making the inventive formulation even more palatable. The present invention comprise at least one sweetener immediate onset and at least one sweetener delayed on set .The present invention comprise aspartame and neohesperidin. The present embodiment of the invention comprised of sorbitol solution (70%) in a concentration less than 20% (w/w) more preferably less than 15% (w/w),at about 10 to 15% of the final formulation.
Other organoleptic agents include coloring and flavoring agents and masking agents and can be incorporated to the inventive formulation for making it even more palatable.

As it is previously mentioned the components are pharmaceutically compatible, that means that do not interact or separate in the preparation ,keep their properties and are stable during the shelf life of the product as it is determined by the regulatory storage stability testing of the preparation (as indicated by accelerated 3 month intervals stability studies in stress conditions $\Theta=40^0C$,RH=75%)

The shelf life of the product may be six ,twelve, eighteen ,twenty four months, thirty or thirty six months as it can be determined by according to the regulatory stability

testing of the final formulation and described by the rules governing the medicinal products for human use.

The following examples further illustrate the invention, but should not be construed as limiting the invention by any manner.

In describing embodiments of the present invention has been used specific terminology common and well known to the skilled of the art person. However this invention is not intended to be limited of the specific terminology. Each specific element includes all the technical equivalents which operates in a similar manner to accomplish a similar purpose. The above described embodiments of the invention may be modified or varied, and elements added or omitted, without changing the teaching of the invention, as it is well understood from the skilled in the art person.

EXAMPLE 1

[0037]The dexamethasone acetate suspension contain the following ingredients

TABLE 1

Composition of oral dexamethasone acetate suspension

INGREDIENTS	4mg/ml
Dexamethasone acetate	0.38
Poloxamer 188.	0.13
Glycerine	43.7
Propylene Glycol	4.48
Edetate disodium	0.17
Aspartame	0.09
Mint Flavor (Tagasago Peppermint flavor 10324199)	0.11
Xantham Gum	0.17
Sodium Metabisulfite	0.17
Sorbitol solution 70 %	11.25
Creatinine	0.17
Neohesperidin dihydrochalcone	0.02
Purified water	38.90
Citric acid q.s. pH = 3.80 - 4.20	(about 3.60 mg for pH = 4.00)

[0038] A small sample of volunteers(5 volunteers) evaluate the dexamethasone formulation for taste and flavour

Sensory Perception in different samples of Dexamethasone formulation

Product Description	Initial Taste	After Taste
Dex/ne acetate suspension 4 mg/ml	Sweet, Mint Flavor	No bitterness perceived
Dexamethasone Sodium Phosphate Sol 4mg/ml CASSO	Sweet, Mint Flavour	Delayed bitter taste, Persistent for long time

1.A pharmaceutical composition for the oral delivery comprising a effective amount of dexamethasone acetate .

2. A pharmaceutical composition of the claim 1 for taste masking the bitter taste and after taste of dexamethasone .

3. The pharmaceutical composition of the claim 1 where in the dexamethasone acetate is suspended.

4. The pharmaceutical composition of the claim 3 further comprising a pharmaceutically acceptable vehicle and a suspending agent

5. The composition of the claim 1 containing dexamethasone acetate between 0.4 mg/ml to about 40 mg/ml of dexamethasone acetate.

6. The pharmaceutical composition of the claim 1 wherein the dexamethasone acetate has a particle size between 1 to 30μm, more preferably between 3 to 15 μm

7. The pharmaceutical composition of the claim 4 where the suspending agent is xantham gum .

8. The pharmaceutical composition of the claim 4 where the vehicle is water, glycerine or propylene glycol and mixtures there of.

9. The pharmaceutical composition of the claim 3 where further comprising pharmaceutical excipients.

10. The pharmaceutical composition of the claim 8 further comprising a wetting agent

11 .The pharmaceutical composition of the claim 8 further comprising a spreading agent

12. The pharmaceutical composition of the claim 8 further comprising a stabilizer

13. The pharmaceutical composition of the claim 8 further comprising a preservative
14. The pharmaceutical composition of the claim 8 further comprising a sweetener

15. The pharmaceutical composition of the claim 8 further comprising a delay on set sweetener

16. The pharmaceutical composition of the claim 8 further comprising a flavouring agent

17. The pharmaceutical composition of the claim 3 having pH between 3.8 to 6, more preferably 4 to 5
18. The pharmaceutical composition of the for oral delivery comprising from about 0.1to about 10 mg/ml of dexamethasone acetate ,about 30-70 % water (w/w) ,up to 50% glycerin ,up to 10% propylene glycol, up to 20% sorbitol, up to about 3%

surfactant, up to about 15% surfactant (poloxamer 188) and up to about 1% of a suspending agent (Xantham gum)

19.A pharmaceutical composition for oral delivery comprising:

a. 0.38 (w/w) dexamethasone acetate
b. 0.13% (w/w) Poloxamer 188
c. 43.7 (w/w) Glycerin
d. 4.48 % (w/w) Propylene glycol
e. 0.17 % (w/w) EDTA
f. 0.09% (w/w)Aspartame
g. 0.17% (w/w) Xantham gum
h. 11.25% (w/w) Sorbitol sol. 70%
i. 0.17% (w/w) Sodium Metabisulfite
j. 0.17% (w/w) Creatinine
k. 0.02% (w/w) Neohesperidin dihydrochalcone
l. 0.11% (w/w) Mint Flavor (Mint Flavor-Tagasago Peppermint Flavor 10324199)
m. 38.90% (w/w) Purified Water
n. Citric acid q.s. pH = 3.80 - 4.20

20. The pharmaceutical composition of the claim 18,where the pH is between 3.8 and 6.