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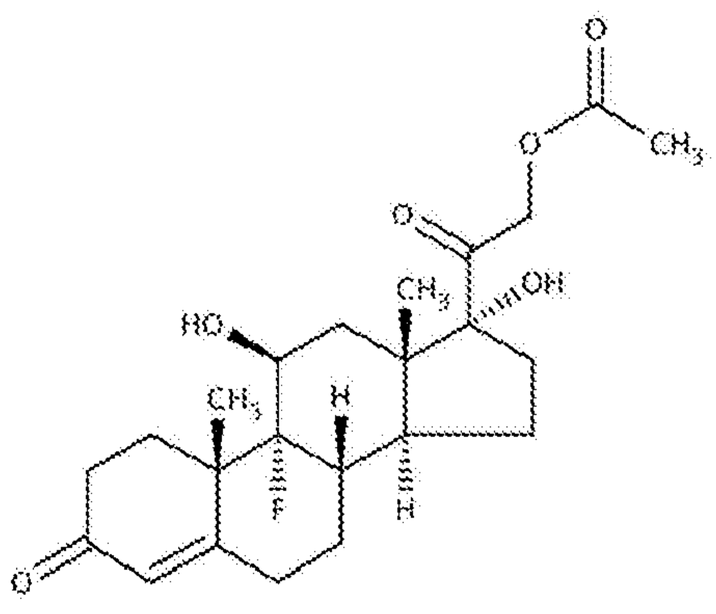
Title: **Stable liquid suspension composition of fludrocortisone**

Field of the Invention

The present invention contemplates a stable liquid suspension composition of fludrocortisone or its pharmaceutically acceptable salts thereof. The present invention contemplates more particularly a stable liquid composition of fludrocortisone or its pharmaceutically acceptable salts thereof suitable for oral administration.

Background of the Invention

Fludrocortisone (9-a-fluorocortisol): A synthetic analog of aldosterone that acts on the kidney so as to conserve sodium and excrete potassium. This definition includes derivatives of fludrocortisone, such as fludrocortisone acetate (which goes by the brand name Florinef®. Fludrocortisone in the form of its acetate salt has the chemical name 9-fluoro-11β,17,21-trihydroxypregn-4-ene-3,20-dione 21-acetate; its molecular formula is C23H31FO6, and its molecular weight is 422.493. The structural formula is shown below;



Fludrocortisone is prescribed for partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease and for the treatment of salt-losing adrenogenital syndrome.

The usual dose is 0.1 mg of fludrocortisone acetate daily, although dosage ranging from 0.1 mg three times a week to 0.2 mg daily has been employed. In the event transient hypertension develops as a consequence of therapy, the dose should be reduced to 0.05 mg daily. Fludrocortisone acetate is preferably administered in conjunction with cortisone (10 mg to 37.5 mg daily in divided doses) or hydrocortisone (10 mg to 30 mg daily in divided doses).

Products comprising fludrocortisone are marketed under the trade name FLORINEF®. Various tablet formulations of fludrocortisone have been approved for marketing, for instance, conventional compressed instant release (IR) tablets comprising 0.1 mg of active ingredient. These are administered once, twice or three times daily.

In terms of pharmaceutical formulations, the major market is solid oral formulations or dosage forms because of ease of manufacturing, storage, stability etc. However on the other hand, there are a huge number of patients who have difficulties swallowing, for example children and aged people. Also some patients with mental disorders or nauseated patients struggle with administration of such formulations. There are also certain situations when patients may be travelling and have very little or no access of water. In all such cases, the solid formulations appears to be non viable and may result in patient non compliance and/or medication error. This may lead to discontinuation of medication.

In absence of any oral liquid formulation available in the market, hospitals & dispensaries generally follow a practice of preparing extemporaneous suspensions from available solid formulations and triturating the same followed by adding water and, if required, syrup to make it palatable. For fludrocortisone such practice is followed by crushing commercially available tablet formulation and mixing with water and syrup or some sweetener to prepare a palatable oral suspension for the patient.

However, the pharmacy practice of dispensing extemporaneous suspensions from solid formulations can create medication errors in terms of accurate dosing. This could lead to potentially fatal conditions especially for a drug of this type which falls in low therapeutic index as in the case for fludrocortisone.

Thus the practice of dispensing extemporaneous suspensions of the drug is very unsafe and may result in adverse effects.

Furthermore, preparing extemporaneous suspension may result in degradation of the active ingredients, if the active ingredient is sensitive to water or any other solvent exposure which may result in a decrease in concentration of the active ingredient in extemporaneous suspension and patient may get less dose compared to the prescribed one for effective treatment.

To overcome these problems an oral liquid formulation is required.

In a liquid formulation, stability is the biggest challenge compared to solid formulations. This is because in liquid formulations, the active ingredient will remain in a dissolved state in solvent vehicle (which is usually water or a medium comprised mostly of water) and water or the solvent medium is usually the reason for the instability. The solvent medium such as water may lead to degradation of the active ingredient. This is a potential issue for fludrocortisone.

Formation of foam during the preparation of liquid formulation is also a quite common problem and interferes with development of stable and effective liquid formulation. The severity of foam formation depends on nature of active ingredients as well as other excipients used in the preparation.

Still a need exists for stable liquid pharmaceutical composition of fludrocortisone which overcome all the problems discussed above. There is a need for oral administration formulations that do not have any stability or dose uniformity issue. Inventors of the present invention have addressed these issues and provided stable liquid pharmaceutical composition suitable for oral administration comprising fludrocortisone or pharmaceutically acceptable salts thereof.

Summary of the Invention

The present invention relates a stable liquid suspension composition comprising fludrocortisone or its pharmaceutically acceptable salt thereof present in the range from 0.001 mg/ml to 1 mg/ml, a vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof, a cellulose based suspending agent, an anti foaming agent, at least one preservative and one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

In an embodiment, said stable liquid suspension composition comprises;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone or its pharmaceutically acceptable salt thereof,
b) 0.01 to 5% w/v of a vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof,
c) 0.1 to 10 % w/v of a cellulose based suspending agent,
d) 0.005 to 1 % w/v of an anti-foaming agent,
e) 0.008% w/v to 0.5% w/v of a preservative, and

f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

In certain embodiments, the stable liquid suspension composition comprises;

g) 0.001 mg/ml to 1 mg/ml of fludrocortisone acetate,
h) 0.01 to 5% w/v of glycerol,
i) 0.1 to 10 % w/v of HPMC (hydroxypropyl methylcellulose) E4M,
j) 0.005 to 1 % w/v of simethicone,
k) methyl parahydroxybenzoate (methyl paraben) and ethyl parahydroxybenzoate (ethyl paraben),
l) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, anti flavouring agent.

The stable liquid suspension is formulated in water or an aqueous medium including water.

One more aspect of the present invention is to provide process for preparing said stable liquid suspension composition comprising steps of;

a) adding preservative in water and stirring,,
b) adding a cellulose based suspending agent to the solution of step a) optionally with continuous stirring,
c) adding antifoaming agent to the solution produced in step b), optionally with continuous stirring,
d) adding sweetener to the solution produced in step c), optionally with continuous stirring,
e) dispersing fludrocortisone acetate in a mixture of vehicle and purified water,
f) adding the dispersion produced in step e) in to the suspension produced in step d) to get an homogenous suspension, optionally with continuous stirring,
g) adding buffering agent to the suspension produced in step f) to adjust the pH to from 3 to 5, and
h) adding purified water to make the final volume.

In any one or more of the above steps, where indicated as optional, continuous stirring may be employed in order to ensure good dissolution or suspension of the relevant component.

Detailed description of the Invention

Stable liquid pharmaceutical composition of fludrocortisone or its pharmaceutically acceptable salt thereof is the invention as further described herein.

The invention provides a stable liquid suspension composition comprising fludrocortisone or its pharmaceutically acceptable salt thereof present in the range from about 0.001 mg/ml to 1 mg/ml. The composition includes a vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof, a cellulose based suspending agent, an anti foaming agent, at least one preservative and one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

The term "pharmaceutically-acceptable salts" as used herein includes salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. Suitable pharmaceutically-acceptable acid addition salts of fludrocortisone may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicyclic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, alginic, β-hydroxybutyric, malonic, galactaric and galacturonic acid. The preferred salt form for the present invention is acetic and the fludorocortisone is in the form of fludorcortisone acetate.

The term "about" as and where used in this specification means ±10% of the mentioned value. However when the term “about” is used in connection with pH, it should be considered as ±2 unit of the pH value.

The terms “formulation” and “composition” are intended to have the same meaning and are used interchangeably throughout this specification. The term "suspension" as used herein refers to a system in which small solid particles are essentially uniformly dispersed in a liquid medium.

The term "stable suspension", as used herein describes a suspension that shows no separation after being stored for at least 1 week at ambient temperature.

To keep liquid suspension composition of present invention stable for longer period of time, the pH also plays a role. It is typically necessary to carefully control the pH of the liquid suspension. As per one embodiment, pH of the composition should be from 3 to 5, preferably the pH is from 3.8 to 4.2, and ideally about 4.

The stable liquid suspension composition of the present invention is chemically and physically stable without any precipitation or crystallization. This was demonstrated in a stability study. Another benefit is that the composition overcame the problem of unpleasant taste.

A stable liquid suspension composition according to the present invention shows good stability and reproducibility even after long-term storage. This means that a liquid composition can be stored for a few days or a week or longer without significant degradation.

The stable liquid suspension composition of present invention, even though being in the form of a suspension also offers an advantage of uniform dosing, physical stability. It also reduces the chances of medication error or over dosage. The stable liquid suspension composition of the present invention, as described herein remains stable for longer period during stability studies performed at different temperature and humidity condition.

Fludrocortisone acetate is a synthetic adrenocortical steroid possessing very potent mineralcorticoid properties and high glucocorticoid activity. It is used for its mineralcorticoid effects. It is a white to pale yellow, odourless or almost odourless, crystalline powder. Practically insoluble in water; soluble 1 in 50 in alcohol, 1 in 50 in chloroform; slightly soluble in ether.

As per one embodiment, fludrocortisone to be used in the form of fludrocortisone acetate. The fludrocortisone acetate to be used in the range from 0.001 mg/ml to 1 mg/ml, preferably in the range from 0.005 mg/ml to 0.08 mg/ml, more preferably from 0.008 mg/ml to 0.05 mg/ml. In a most preferred embodiment, the fludrocortisone acetate is present in the range from 0.008 mg/ml to 0.02 mg/ml.

In certain embodiments, a stable liquid suspension composition comprises fludrocortisone present in the range from 0.001 mg/ml to 1 mg/ml, a vehicle for fludrocortisone, a cellulose based suspending agent, an anti foaming agent, at least one preservative and one or more inactive excipients. The liquid suspension is a suspension in water or a mixture of water and a co-solvent. Preferably, the liquid suspension is a suspension in water.

The stable liquid suspensions of the invention remain stable and uniform when appropriate excipients are selected and are used at specific and effective concentrations. Two of the main excipients that play role in stabilizing the pharmaceutical composition of present invention are suspending agent and vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof.

As fludrocortisone is insoluble in water, an appropriate vehicle is required to disperse fludrocortisone acetate before preparing the final composition. Many vehicles are unsuitable for producing compositions of fludorocortisone. The inventors of the present invention tried many vehicles and surprisingly found that appropriate stability is observed when the vehicle is selected from one or more of: polyethylene glycol, glycerol and propylene glycol. Further in a preferred embodiment, glycerol is used as a vehicle for dispersing fludrocortisone acetate. The amount of the vehicle for dispersing fludrocortisone acetate is used in the range from 0.01 to 5% w/v, and is preferably in the range from 0.05 to 1% w/v.

In certain preferred embodiments, the suspending agent is cellulose based, in a preferred embodiment, HPMC (hydroxypropyl methylcellulose), microcrystalline cellulose or Avicel® RC-591 (microcrystalline cellulose/ sodium carboxymethyl cellulose). As per more preferred embodiment, the suspending agent is HPMC (hydroxypropyl methylcellulose) also known as hypromellose.

Hypromellose is a solid, and is a slightly off-white to beige powder in appearance and may be formed into granules. The compound forms colloids when dissolved in water. This non-toxic ingredient is combustible and can react vigorously with oxidising agents. HPMC is available in different grades commercially based on the viscosity for the product measured at 2% in water at 20°C. Different grades available are HPMC followed by K100 LV, K4M, K15M, K100M, E15 LV, E50 LV, E4M, F50 LV, F4M code. In a preferred embodiment, the HPMC with low viscosity grade are preferred, including HPMC K100LV, HPMCE4M, HPMC E50LV and HPMC E15LV. In a most preferred embodiment, the suspending agent is HPMC E4M.

The concentration of the suspending agent is also important. This impacts the final stability and physical characteristic of composition. As per one embodiment, the % of suspending agent is in the range from 0.1 to 10 % w/v, more preferably in the range from 0.25 to 5 % w/v and most preferred is 0.5 to 2.5 % w/v.

A substance used to reduce foam formation in liquid dosage compositions is called anti foaming agents also called as Defoamer. Commonly in process of manufacturing or when reconstituting of liquid dosage have this problem of foam formation forms needs it due to undesirable and disruptive Anti-foaming agents. These are effective to reduce foam by lowering surface tension and cohesive binding of the liquid phase.

A defoamer or an anti-foaming agent is a chemical additive that reduces and hinders the formation of foam in industrial process liquids. The terms anti-foam agent and defoamer are often used interchangeably. Generally a defoamer is insoluble in the foaming medium and has surface active properties. An essential feature of a defoamer product is a low viscosity and a facility to spread rapidly on foamy surfaces. It has affinity to the air-liquid surface where it destabilizes the foam lamellas. This causes rupture of the air bubbles and breakdown of surface foam. Entrained air bubbles are agglomerated, and the larger bubbles rise to the surface of the bulk liquid more quickly.

In certain embodiments, the anti-foaming agent for the present invention can be selected from one or more of: polydimethylsiloxane, simethicone, other silicones, stearates, alcohols and glycols. The anti-foaming agent may be of more than one of the above agents. In a preferred embodiment, the anti foaming agent is simethicone.

In an embodiment, the anti foaming agent is present in the range from 0.005 to 1 % w/v. In a preferred embodiment, anti foaming agent is present in the range from 0.01 to 0.5 % w/v. In a more preferred embodiment, anti foaming agent is present in the range from 0.01 to 0.1 % w/v. In a most embodiment, anti foaming agent is present in the range from 0.02 to 0.08 % w/v.

In certain embodiments, suitable preservative for present invention can be selected from one or more of: methyl parahydroxybenzoate (methyl paraben), ethyl parahydroxybenzoate (ethyl paraben), propyl parahydroxybenzoate (propyl paraben), butyl parahydroxybenzoate (butyl paraben), isobutyl parahydroxybenzoate (isobutyl paraben), isopropyl parahydroxybenzoate (isopropyl paraben), benzyl parahydroxybenzoate (benzyl paraben), Sodium Benzoate,

Benzoic acid, Potassium Sorbate and combinations thereof. In one embodiment the preservative is present in the range from about 0.001 %w/v to about 0.5 %w/v.

The present stable liquid suspension composition of present invention contains one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent and flavoring agent.

In certain embodiments, suitable buffer for present invention is selected from one or more of: Citric Acid monohydrate, Sodium Citrate, Sodium Dihydrogen Phosphate, Disodium Phosphate, Trometamol (Tris), Disodium hydrogen phosphate anhydrous, Hydrochloric Acid, Ascorbic Acid, Sodium Ascorbate and anhydrous, monohydrate or dehydrate forms thereof. The buffer can be single or any combination of above listed buffer. In a preferred embodiment, combination of Disodium hydrogen phosphate anhydrous and Citric Acid monohydrate is to be used.

In certain embodiments, suitable sweetener for present invention is selected from one or more of: acesulfame potassium, sucralose, cyclamate, saccharin, saccharin sodium and aspartame or mixtures thereof. In a preferred embodiment, sucralose is to be used. The liquid pharmaceutical composition of the present invention can be prepared in absence of sweetener. However to make it more palatable and easily acceptable by patient especially children, very small amount of sweetener can be added. Sweetener for the present invention can be used in the range from about 0.01 %w/v to 0.5 % w/v.

In certain embodiments, the liquid pharmaceutical composition may further comprise anti oxidants.

Suitable antioxidants for the composition of the present invention can be selected from one or more of: consisting of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, beta-carotene, alpha-tocopherol, propyl gallate, gentisic acid sodium ascorbate, sodium bisulfite, sodium metabisulfite, monothioglycero, cysteine, thioglycolate sodium, acetone sodium bisulfite, ascorbate (sodium/acid), bisulfite sodium, cystein/cysteinate HCl, dithionite sodium (Na hydrosulfite, Na sulfoxylate), gentisic acid, gentisic acid ethanolamine, glutamate monosodium, formaldehyde sulfoxylate sodium, metabisulfite potassium, metabisulfite sodium, monothioglycerol (thioglycerol), propyl gallate, sulfite sodium, tocopherol alpha and thioglycolate sodium. The antioxidant may be a mixture of more than one of the above agents.

In certain embodiments the vehicle or solvent for making the final volume of the composition can be selected from one or more of: glycerine, alcohols, propylene glycol, polyethylene glycol, purified water, ethanol and isopropyl alcohol. The vehicle or solvent may include mixtures of the above agents. Preferably purified water is used as a solvent.

In one embodiment of the present invention, said stable liquid suspension composition comprises;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone or its pharmaceutically acceptable salt thereof,
b) vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof,
c) a cellulose based suspending agent,
d) an anti foaming agent,
e) at least one preservative and
f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

The stable liquid composition of fludrocortisone or its pharmaceutically acceptable salt thereof is to be used for partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison's disease. It can also be used for the treatment of salt-losing adrenogenital syndrome.

In another embodiment, said stable liquid suspension composition comprises;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone or its pharmaceutically acceptable salt thereof,
b) vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof selected from polyethylene glycol, glycerol and propylene glycol, or mixtures thereof,
c) a cellulose based suspending agent selected from HPMC (hydroxypropyl methylcellulose), microcrystalline cellulose, Avicel® RC-591 (microcrystalline cellulose/ sodium carboxymethyl cellulose) or mixtures thereof
d) an anti foaming agent selected from polydimethylsiloxane, simethicone, other silicones, stearates, alcohols, glycols or combinations thereof,
e) a preservative selected from methyl parahydroxybenzoate (methyl paraben), ethyl parahydroxybenzoate (ethyl paraben), propyl parahydroxybenzoate (propyl paraben), butyl parahydroxybenzoate (butyl paraben), isobutyl parahydroxybenzoate (isobutyl

paraben), isopropyl parahydroxybenzoate (isopropyl paraben), benzyl parahydroxybenzoate (benzyl paraben), sodium benzoate, benzoic acid, potassium sorbate and combinations thereof, and

f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

In another embodiment, said stable liquid suspension composition comprises;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone acetate,
b) 0.01 to 5% w/v of glycerol,
c) 0.1 to 10 % w/v of HPMC (hydroxypropyl methylcellulose) E4M,
d) 0.005 to 1 % w/v of simethicone,
e) methyl parahydroxybenzoate (methyl paraben) and ethyl parahydroxybenzoate (ethyl paraben),
f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

In another embodiment, said stable liquid suspension composition comprises;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone acetate,
b) 0.05 to 1% w/v of glycerol,
c) 0.25 to 5 % w/v of HPMC (hydroxypropyl methylcellulose) E4M,
d) 0.01 to 0.5 % w/v of simethicone,
e) methyl parahydroxybenzoate (methyl paraben) and ethyl parahydroxybenzoate (ethyl paraben),
f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

In another embodiment, the stable liquid suspension composition is prepared by

a) adding preservative in water and stirring,
b) adding a cellulose based suspending agent in step a) with continuous stirring,
c) adding antifoaming agent in step b) with continuous stirring,
d) adding sweetener to step c) with continuous stirring,
e) dispersing fludrocortisone acetate in mixture of vehicle and purified water,
f) adding dispersion of step e) in to step d) with continuous stirring to get homogenous suspension,

g) adding buffering agent to step f) to adjust pH to from 3 to 5 and

h) adding purified water to make final volume.

In another embodiment, the stable liquid suspension composition is prepared by

a) adding methyl parahydroxybenzoate (methyl paraben) and ethyl parahydroxybenzoate (ethyl paraben) in water and stirring till dissolve it,

b) adding HPMC (hydroxypropyl methylcellulose) E4M in step a) with continuous stirring,

c) adding simethicone in step b) with continuous stirring,

d) adding sucralose to step c) with continuous stirring,

e) dispersing fludrocortisone acetate in mixture of glycerol and purified water,

f) adding dispersion of step e) in to step d) with continuous stirring to get homogenous suspension,

g) adding citric acid monohydrate and disodium hydrogen phosphate anhydrous to step f) to adjust pH in between 3 to 5 and

h) adding purified water to make final volume.

The invention is further illustrated by the following examples, which are by no means intended to limit the scope of the invention but are given by way of illustration.

Examples

Example 1: Fludrocortisone acetate Suspension 0.05 mg/5ml

Ingredients	**gm/100ml**
Fludrocortisone acetate	0.0010095*
Methyl parahydroxybenzoate	0.18
Ethyl parahydroxybenzoate	0.020
Simethicon PD30	0.060
HPMC E4M Premium	1.00
Sucralose	0.020
Glycerol	0.100
Caramel flavor	0.040
Citric acid monohydrate	Q.S. to pH 3 to 5
Disodium hydrogen phosphate anhydrous	Q.S. to pH 3 to 5

Purified water	Up to 100 ml

*value after potency correction as per COA.

Process:

1. Add and dissolve methyl parahydroxybenzoate and ethyl parahydroxybenzoate into 60 ml purified water with the aid of heating at above 90^0C to get a clear, colourless solution. Keep aside till temperature reaches 60 -70^0C.
2. Add HPMC E4M in step 1 when temperature reaches 60-70^0C and keep aside to cool at room temperature.
3. Add simethicon PD30 and stirr for 20- 30 minutes,
4. Add sucralose to step 3 and stir for 10-15 minutes using.
5. Separately disperse fludrocortisone acetate in glycerol and add 5ml of purified water and form uniform dispersion.
6. Add dispersion of step 5 into step 4 and mix to get homogeneous suspension.
7. Add citric acid monohydrate and disodium hydrogen phosphate anhydrous and mix to get homogeneous suspension to adjust pH in between 3-5.
8. Add caramel flavor to suspension and mix it.
9. Make up to volume with purified water and stir for 10 minutes to get homogeneous suspension.

Physical observations: The composition of Example 1 was observed after storing for 24 hrs at room temperature. No any sedimentation or colour change observed, hence further stability studies at different temperature/humidity and time duration was planned.

Example 2: Comparative examples

	2A	**2B**	**2C**
Ingredients	**gm/100ml**	**gm/100ml**	**gm/100ml**
Fludrocortisone acetate	0.0010095*	0.0010095*	0.0010095*
Methyl parahydroxybenzoate	0.18	0.18	0.18
Ethyl parahydroxybenzoate	0.020	0.020	0.020
Simethicon PD30	0.060	0.060	0.060
Carmellose sodium (Cekol® 2000 P)	1.00	-	0.25
Aluminium Mg Silicate (Veegum®)	-	1.00	0.50
Sucralose	0.020	0.020	0.020
Glycerol	0.100	0.100	0.100
Caramel flavor	0.040	0.040	0.040
Citric acid monohydrate	Q.S. to pH 3 to 5	Q.S. to pH 3 to 5	Q.S. to pH 3 to 5
Disodium hydrogen phosphate	Q.S. to	Q.S. to	Q.S. to

anhydrous	pH 3 to 5	pH 3 to 5	pH 3 to 5
Purified water	Up to 100 ml	Up to 100 ml	Up to 100 ml

Procedure: As per Example 1

Physical observations: The composition of Example 2 (2A, 2B and 2C) was observed after storing for 24 hrs at room temperature. There are sedimentation as well as slight color change was observed in all three composition. Therefore no further stability studies were conducted.

Example 3: Fludrocortisone acetate Suspension 0.05 mg/5ml

Ingredients	**gm/100ml**
Fludrocortisone acetate	0.0010095*
Methyl parahydroxybenzoate	0.20
Simethicon PD30	0.060
HPMC E15 LV	1.00
Sucralose	0.020
Propylene glycol	0.150
Caramel flavor	0.040
Citric acid monohydrate	Q.S. to pH 3 to 5
Disodium hydrogen phosphate anhydrous	Q.S. to pH 3 to 5
Purified water	Up to 100 ml

*value after potency correction as per COA.

Procedure: As per Example 1

Physical observations: The composition of Example 3 was observed after storing for 24 hrs at room temperature. There are very little sedimentation was observed but that was redisersible on shaking. No further stability conducted.

Example 4: Stability study of Example 1

Stability study of composition of Example 1 filled in amber colour glass bottle were performed at different temperature and relative humidity conditions for 6 months and results are as described below;

Results of stability study at 25°C/60%RH and 30°C/65%RH

Stability station		Initial	25°C/60%RH				30°C/65% RH
Storage condition		**RT**	**1M**	**2M**	**3M**	**6M**	**6M**
Description		Opaque white suspension					
pH		4.0	4.13	4.13	4.16	4.11	4.09
Assay (%w/w)	**Fludrocortisone acetate (95.0% to 105.0%)**	100.5%	100.2	98.3	94.6	93.4	87
Assay (%w/w)	**MHB (95.0% to 105.0%)**	100.1%	100.5	99.9	99.6	97.1	95.2
	EHB (95.0% to 105.0%)	97.4%	98.6	98.6	96.7	97.6	95.5
Related substances (%w/w)	**Fludrocortisone : NMT 4.0%**	0.171 (RRT:0.623)	0.600 (0.605)	1.707 (0.596)	2.546 (0.589)	5.297	7.301
	SMUI: NMT 1.0 %	0.122 (RRT: 0.851)	0.335 (0.861)	0.701 (0.852)	1.023 (0.846)	1.984	2.745
	Total Impurity	0.293	0.935	2.408	3.569	7.281	10.259
Dissolution Profile (Media: 0.01 N HCl, 500ml, 75 rpm, paddle)	**45 Min**	95.8	94.2	93.7	90.7	86.9	87.6

Result of stability study at 2-8°C

Stability station		Initial	2-8°C			
Storage condition		**RT**	**1M**	**2M**	**3M**	**6M**
Description		Opaque white suspension				
pH		4.0	4.18	4.2	4.04	4.12
Assay (%w/w)	**Fludrocortisone acetate (95.0% to 105.0%)**	100.5	100.2	99.7	98.4	98.0
Assay (%w/w)	**MHB (95.0% to 105.0%)**	100.1	101.9	99.6	98.4	97.0
	EHB (95.0% to	97.4	100.3	98.1	96.9	97.5

	105.0%)					
Related substances (%w/w)	**Fludrocortisone : NMT 4.0%**	0.171 (RRT:0.623)	0.213 (0.607)	0.448 (0.596)	0.537 (0.589)	1.245
	SMUI: NMT 1.0 %	0.122 (RRT: 0.851)	0.041 (0.865)	0.148 (0.853)	0.178 (0.846)	0.372
	Total Impurity	0.293	0.254	0.596	0.715	1.617
Dissolution Profile (Media: 0.01 N HCl, 500ml, 75 rpm, paddle)	**45 Min**	96.8	97.8	96.7	95.0	96.8

After performing stability study, it was observed that the liquid suspension composition of Example 1 shows good stability for 6 months storage when stored in the condition of 2-8°C.

Claims

1. A stable liquid suspension composition comprising fludrocortisone or its pharmaceutically acceptable salt thereof present in the range from 0.001 mg/ml to 1 mg/ml, vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof, a cellulose based suspending agent, an anti foaming agent, at least one preservative and one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent

2. The stable liquid suspension composition of claim 1, comprising;
0.001 mg/ml to 1 mg/ml of fludrocortisone or its pharmaceutically acceptable salt thereof,
0.01 to 5% w/v of a vehicle for dispersing fludrocortisone or its pharmaceutically acceptable salt thereof,
0.1 to 10 % w/v of a cellulose based suspending agent,
0.005 to 1 % w/v of an anti-foaming agent,
a preservative, optionally in an amount of from 0.001% w/v to 0.5% w/v, and
one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

3. The stable liquid suspension composition according to claim 1 or 2, wherein fludrocortisone is in the form of fludrocortisone acetate.

4. The stable liquid suspension composition according to any preceding claim, wherein the pH is in the range from 3 to 5.

5. The stable liquid suspension composition according to any preceding claim, wherein liquid suspension is to be stored at condition of 2-8°C.

6. The stable liquid suspension composition according to any preceding claim, wherein vehicle for fludrocortisone or its pharmaceutically acceptable salt thereof is selected from polyethylene glycol, glycerol and propylene glycol.

7. The stable liquid suspension composition according to any preceding claim, wherein suspending agent is selected from HPMC (hydroxypropyl methylcellulose),

microcrystalline cellulose, and microcrystalline cellulose/sodium carboxymethyl cellulose.

8. The stable liquid suspension composition according to any preceding claim, wherein anti foaming agent is selected from polydimethylsiloxane, simethicone, other silicones, stearates, alcohols and glycols.

9. The stable liquid suspension composition according to any preceding claim, wherein preservative is selected from methyl parahydroxybenzoate (methyl paraben), ethyl parahydroxybenzoate (ethyl paraben), propyl parahydroxybenzoate (propyl paraben), butyl parahydroxybenzoate (butyl paraben), isobutyl parahydroxybenzoate (isobutyl paraben), isopropyl parahydroxybenzoate (isopropyl paraben), benzyl parahydroxybenzoate (benzyl paraben), sodium benzoate, benzoic acid, potassium sorbate and combinations thereof.

10. The stable liquid suspension composition according to claim 1, wherein sweetener is selected from acesulfame potassium, sucralose, cyclamate, saccharin, saccharin sodium and aspartame or mixtures thereof.

11. The stable liquid suspension composition of claim 1, comprising;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone acetate,
b) 0.01 to 5% w/v of glycerol,
c) 0.1 to 10 % w/v of HPMC (hydroxypropyl methylcellulose) E4M,
d) 0.005 to 1 % w/v of simethicone,
e) methyl parahydroxybenzoate (methyl paraben) and ethyl parahydroxybenzoate (ethyl paraben),
f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

12. The stable liquid suspension composition of claim 1 comprising;

a) 0.001 mg/ml to 1 mg/ml of fludrocortisone acetate,
b) 0.05 to 1% w/v of glycerol,
c) 0.25 to 5 % w/v of HPMC (hydroxypropyl methylcellulose) E4M,
d) 0.01 to 0.5 % w/v of simethicone,

e) methyl parahydroxybenzoate (methyl paraben) and ethyl parahydroxybenzoate (ethyl paraben),

f) one or more inactive excipients selected from buffering agent, sweetener, anti oxidant, coloring agent, and flavouring agent.

13. A process for preparing a stable liquid suspension composition, comprising the steps of;

a) adding preservative in water and stirring until dissolved,

b) adding a cellulose based suspending agent in step a) with continuous stirring,

c) adding antifoaming agent in step b) with continuous stirring,

d) adding sweetener to step c) with continuous stirring,

e) dispersing fludrocortisone acetate in mixture of vehicle and purified water,

f) adding dispersion of step e) in to step d) with continuous stirring to get homogenous suspension,

g) adding buffering agent to step f) to adjust pH in between 3 to 5 and adding purified water to make final volume.