STABLE PHARMACEUTICAL COMPOSITIONS OF CALCITRIOL

The present invention provides a stable clear colorless liquid composition comprising Calcitriol with butylated hydroxy toluene and/or butyl hydroxyl anisole; further this invention provides innovative liquid composition of Calcitriol.
STABLE PHARMACEUTICAL COMPOSITIONS OF CALCITRIOL

PRIORITY

This patent application claims priority to Indian patent application number 201641000206 filed on Jan 04, 2016, the contents of which are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to stable clear colorless liquid pharmaceutical compositions of calcitriol with butylated hydroxy toluene and/or butylated hydroxy anisole.

BACKGROUND OF THE INVENTION

Calcitriol, also known as 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, 1α, 25-dihydroxycholecalciferol, or 1α, 25-dihydroxyvitamin D3, is the biologically active form of vitamin D3 which promotes intestinal calcium transport and bone calcium resorption. Calcitriol was first identified by Michael F. Holick in work published in 1971. The preparation, isolation, identification and biological activity of 1,25-dihydroxycholecalciferol (Calcitriol) are disclosed in U.S. patent No. 3,697,559.

Calcitriol increases blood calcium levels ([Ca^{2+}]) by promoting absorption of dietary calcium from the gastrointestinal tract and increasing renal tubular reabsorption of calcium, thus reducing the loss of calcium in the urine.

Calcitriol is approved in US as injection, oral capsule, oral solution and topical ointment. Calcitriol is supplied commercially as Rocaltrol® (calcitriol) capsules (Roche Labs) provide a solid tablets and solution for oral administration, while Calcijex® (calcitriol) (Abbvie) provides a solution for intravenous administration, which is particularly useful for chronic renal dialysis patients and topical ointment by Galderma Labs.
Calcitriol is commercially available as ampoules and vials. The headspace of the calcitriol ampoule is filled with nitrogen gas to provide an inert atmosphere. However, even in the airtight ampoule, the solution retains some oxygen and the reaction of the metal ascorbate antioxidant with the residual oxygen ultimately causes the clear solution to turn yellow. Since drug products are periodically inspected for discoloration, a significant amount of therapeutically useful product is discarded due to antioxidant discoloration. Disadvantages of ampoules are sealed glass ampoules must be broken open in order to access the medication, exposing the health care provider to risk of injury from broken glass. Glass fragments can enter the solution as the ampoule is broken, often requiring the use of a sterile filter, with additional effort and expense, to remove the solution from the open ampoule. Breaking the ampoule is usually done in a non-sterile environment, increasing the risk of both microbial and blood contamination. The ampoule has broken glass edges which are difficult to sterilize before the needle is inserted. Once the ampoule is broken the entire contents must be used or, if only a part of the contents are used, the remainder must be discarded.

U.S. patent No. 6,051,567 and its family equivalent patents U.S. patent No. 6,265,392 and U.S. patent No. 6,247,169 claims a stable aqueous formulations comprising Calcitriol, polysorbate 20, sodium ascorbate, hydrochloric acid or sodium hydroxide to adjust the pH, water for injection and in a sealed vessel, having no more than about 2.0% of oxygen in the headspace of the container. Though sodium ascorbate is used as an antioxidant in the composition and head space maintained with less than 2.0% oxygen, the composition gets degraded and does not provide the required potency to the product.

U.S. patent No. 6,211,169 patent disclose liquid Calcitriol formulations for intravenous administration. The invention relates to a calcitriol solution, and a method for preparing the solution, which is suitable for packaging into vials. This composition though present in vials uses sodium ascorbate as antioxidant in the finished product composition.
WO 2016103722 patent application disclose vitamin D₃ derivatives for treating different diseases.

U.S. patent application No. 20150045333 disclose stable liquid emulsion composition comprising vitamin D or a salt thereof, with sorbate and benzoate.

As per Pack insert details, commercially available Calcitriol injection is mentioned as colorless to yellow aqueous solution. Though they are colorless solution but would turn to yellow solution after coming in contact with environment. The color change is also affecting the appearance with reduced EDTA content and with reduced potency.

Therefore, even though there are many formulations for calcitriol known in the art, all or almost all of them suffer from limited stability when Calcitriol is in solution, particularly over extended periods. From the above draw backs of commercially available product and prior art disclosures it is evident that Calcitriol undergoes degradation by light and oxygen and during their compositions as a dosage form due to the head space oxygen and other environmental factors.

It was surprisingly found that Calcitriol with alternate antioxidants other than the metal ascorbate produced stable liquid clear colorless composition with maximum potency, no reduction in EDTA content even after autoclaving the product. Thus, there is still a need to provide improved compositions of Calcitriol with greater stability that gives maximum potency till end of shelf life.

**SUMMARY OF THE INVENTION**

The inventive subject matter is drawn to stable pharmaceutical liquid compositions and methods for Calcitriol in which calcitriol has significantly increased stability over prolonged periods of time.

The object of the present invention is to prepare stable clear, colorless pharmaceutical liquid compositions of Calcitriol with antioxidants other than metal ascorbate.
Another object of the present invention is to prepare stable clear, colorless pharmaceutical liquid compositions of Calcitriol with antioxidants butylated hydroxy toluene and/or butylated hydroxy anisole with maximum potency even after storing the product for one month and autoclaving at 121 °C for 15 minutes.

Another object of the present invention is to prepare stable clear, colorless pharmaceutical liquid compositions of Calcitriol which remains clear, colorless during the shelf life of the product.

Aspects of the present invention relate to a stable clear, colorless pharmaceutical liquid composition comprising Calcitriol or its pharmaceutically acceptable salt thereof, with antioxidant other than metal ascorbate and other suitable excipients.

Another aspect relates to a stable clear, colorless pharmaceutical liquid composition comprising Calcitriol or its pharmaceutically acceptable salt thereof; with antioxidant other than metal ascorbate is butylated hydroxy toluene and butylated hydroxy anisole; and other suitable excipients.

The pharmaceutical liquid composition of above aspect is clear, colorless during shelf life and is suitable for autoclaving at 121 °C for 15 minutes.

The pharmaceutical liquid composition of above aspect, wherein suitable excipients include, solubilizer or surfactant comprising selected from polyoxyethylene sorbitan monooleate (polysorbate 80), sorbitan monooleate, polyoxyethylene sorbitan monolaurate (polysorbate 20), lecithin, polyoxyethylene- polyoxypolyylene copolymers (pluronics) or any mixtures thereof; antioxidant is selected from ascorbic acid, tocopherol, acetylcysteine, monothioglycerol, butylhydroxy toluene, butylhydroxy anisole, cystein, methionine, propyl gallate, thioglycolate sodium, and mixtures thereof; buffering agent selected from sodium phosphate monobasic or dibasic or any mixtures thereof; complexing agent such as sodium edetate (EDTA); tonicity
contributing agent selected from sodium chloride, dextrose, sucrose, fructose, and mixtures thereof.

The pharmaceutical liquid composition of above aspect, comprising:

- a) Calcitriol or its pharmaceutically acceptable salt thereof;
- b) butylated hydroxy toluene, butylated hydroxy anisole, any mixtures thereof;
- c) polysorbate 20 or any mixtures thereof;
- d) sodium phosphate monobasic and dibasic sodium phosphate;
- e) sodium edetate;
- f) sodium chloride; and
- g) water for injection.

The pharmaceutical composition of above aspects has about 95% potency of Calcitriol and about 100% potency of EDTA after autoclaving at 121°C for 15 minutes.

The pharmaceutical composition of above aspects is clear and colorless and has about 93% potency of Calcitriol and about 100% potency of EDTA after autoclaving at 121°C for 15 minutes for 1 month storage.

The pharmaceutical liquid composition according to above aspect, wherein said composition comprises from about 0.01 mcg/ml to about 10 mcg/ml of Calcitriol.

The pharmaceutical composition according to above aspect, wherein said composition comprises from about 0.05 mcg/ml to about 5 mcg/ml of Calcitriol.

Various objects, features, aspects and advantages of the inventive subject matter will become more apparent from the following detailed description of preferred embodiments.
The present invention relates to stable clear colorless liquid pharmaceutical compositions of calcitriol and process of preparing the same.

The term "active ingredient or drug" refers to a substance that has a physiological effect when ingested or otherwise introduced into the body, in particular or a chemical substance used in the treatment, cure, prevention, or diagnosis of disease or used to otherwise enhance physical or mental well-being.

The term "pharmaceutically acceptable" refers to substances that are useful in preparing a pharmaceutical composition that are generally non-toxic and not biologically undesirable, and includes materials acceptable for veterinary use and/or human pharmaceutical use.

Pharmaceutically acceptable salts are those forms of compounds, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "excipient" or "pharmaceutically acceptable excipient" means a component of a pharmaceutical product that is not a pharmacologically active ingredient, such as filler, diluent, carrier, preservative, etc. The excipients that are useful in preparing pharmaceutical compositions are generally safe, non-toxic, and neither biologically nor otherwise undesirable, and are acceptable for veterinary use as well as human pharmaceutical use. The term includes both one and more than one such excipients.

The term "composition" is intended to encompass a combination including active ingredients and pharmaceutically acceptable excipients, as well as any product which results, directly or indirectly, from combination, complexation, or aggregation of any two or more of the
ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions involving one or more of the ingredients.

The terms "formulation" or "dosage form" or "composition" refers to finished pharmaceutical products that are suitable for administration, including, but not limited to, injections, etc.

The term "optional" or "optionally" means that the subsequently described element, component or circumstance may or may not be present, so that the description includes instances where the element, component, or circumstance is included and instances where it is not.

The term "stable" or "stability" as used herein includes both physical and chemical stability. The term "physical stability" refers to maintenance of the form of active agents, such as crystalline or amorphous, and the term "chemical stability" relates to a limited formation of impurities.

"Carrier" or "vehicle" as used herein refers to pharmacologically inert materials that provide a more or less fluid matrix, suitable for topical drug administration. Carriers and vehicles useful herein include any such materials known in the art, which are nontoxic and do not interact with other components of a pharmaceutical formulation or drug delivery system in a deleterious manner. The topical formulations of the present invention are particularly suitable for parenteral administration. Formulations suitable for parenteral dosage forms such as injectables such as intravenous, intramuscular or subcutaneous, implants and the like. Other parenteral ingredients used in the formulation are generally those commonly used and recognized by persons skilled in the art of parenteral formulations.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to modulate the formation or progression of a malaria infection in a host.

The term "Calcitriol" includes the compound Calcitriol, pharmaceutically acceptable salts and esters thereof, and any polymorphs, solvates and hydrates thereof.
The term "antioxidant" or "antioxidants" includes individual antioxidant or a combination or mixtures of antioxidant.

Aspects of the present invention relate to innovative stable liquid pharmaceutical compositions of Calcitriol with antioxidants selected from butylated hydroxy toluene (BHT) and/or butylated hydroxy anisole (BHA) and suitable excipients.

Another aspect relates to liquid compositions which are suitable for autoclaving at 121°C for 15 minutes. The compositions were found to be stable subsequent to autoclaving and provided the required potency.

In another aspect, a storage stable liquid pharmaceutical composition is contemplated that includes Calcitriol in a therapeutically effective amount. As used herein, the term "storage stable clear colorless liquid pharmaceutical composition" refers to a liquid pharmaceutical composition in which Calcitriol is dissolved in a solvent or solvent system, and in which at least 90% of the pharmaceutically active ingredient remain in an undegraded state after storage of the composition over one month after autoclaving at 121°C for 15 minutes.

Another aspect relates to a composition which is suitable for autoclaving, wherein the commercially available compositions are unable to withstand heat and undergoes degradation to lose its potency.

In comparison with the prior available compositions and its concern with stability the present invention has overcome those concerns and the advantage of the present invention is use of antioxidants BHA and/or BHT, which stabilizes the active ingredient Calcitriol and provides potency of about 95%. Further the disodium EDTA content is also highly stable.

In one more aspect, the composition comprises a stable liquid composition comprising a substantially aqueous solvent system suitable for injection, an antioxidant, wherein the Calcitriol is present in the composition at a therapeutically effective concentration. For example in one
aspect of the inventive subject matter, Calcitriol will be present at a concentration of about 0.01 mcg/ml to about 10 mcg/ml between 0.1 mg/ml to 10.0 mg/ml, and typically between about 0.05 mcg/ml to about 5 mcg/ml, inclusive.

In one more aspect, the present inventive composition is a clear colorless stable liquid composition even after storage for longer duration without any change in color, potency and EDTA content of the composition.

In one more aspect, the pharmaceutical composition is clear colorless stable liquid composition and has about 93% potency of Calcitriol and about 100% potency of EDTA after autoclaving at 121°C for 15 minutes after 1 month.

In another aspect, the antioxidant in such compositions has as a single and predominant component butylated hydroxy anisole and/or butylated hydroxy toluene. Thus, the antioxidant in compositions essentially consists of butylated hydroxy anisole and/or butylated hydroxy toluene. However, in few other aspects, the composition may also include one or more additional antioxidants that are compatible and provide good stability with Calcitriol, and especially suitable antioxidants include propyl gallate, ascorbic acid, acetylcysteine, monothioglycerol and the like or any mixtures thereof. As can be seen from the initial experimental data, the chemical stability of Calcitriol can be greatly increased by appropriate choice of the antioxidants.

Another aspect relates to a liquid composition further comprises of excipients. Another aspect relates to excipients such as solubilizer or surfactant comprising selected from Polyoxyethylene sorbitan monooleate (polysorbate 80), Sorbitan monooleate Polyoxyethylene sorbitan monolaurate (polysorbate 20), Polyoxyethylene sorbitan monopalmitate, Polyoxyethylene sorbitan trioleate, Lecithin, Polyoxyethylene- polyoxypropylene copolymers (Pluronics) or any mixtures thereof. Examples of solubilizer or surfactants include, but not limited to Polyoxyethylene sorbitan monooleate (polysorbate 80), Sorbitan monooleate Polyoxyethylene sorbitan monolaurate (polysorbate 20) and the like or any mixtures thereof.
Another aspect relates to antioxidant selected from ascorbic acid, tocopherol, acetylcysteine, monothioglycerol, butylated hydroxy toluene, butylated hydroxy anisole, cystein, methionine, propyl gallate, thioglycolate sodium, and mixtures thereof. Examples of antioxidants include but not limited to acetylcysteine, monothioglycerol, butylated hydroxy toluene, butylated hydroxy anisole, cystein and the like or any mixtures thereof.

Another aspect relates to buffers include citric acid buffer, acetic acid buffer, maleic acid buffer, phosphoric acid buffer, succinic acid buffer, and tartaric acid buffer and the ester forms of same. Examples of buffers include but not limited to acid salt of the above buffers viz., sodium citrate, sodium phosphate, sodium acetate, sodium tartrate or any mixtures thereof.

Another aspect relates to complexing agent is selected from sodium ethylene diamine tetra acetic acid (EDTA), disodium EDTA, calcium disodium EDTA, Diethylenetriaminepenta acetic acid (DTPA) and the like or any mixtures thereof. Examples of complexing agents include but not limited to sodium ethylene diamine tetra acetic acid (EDTA), disodium EDTA, calcium disodium EDTA and the like or any mixtures thereof.

Another aspect relates to tonicity contributing agent include but not limited to sodium chloride, dextrose, sucrose, fructose, mannitol, calcium chloride, potassium chloride, sodium lactate and mixtures thereof. Examples of tonicity contributing agent include but not limited to sodium chloride, dextrose, sucrose, or any mixtures thereof. The concentration of tonicity contributing agents used is as available in the general art to provide required osmolality.

Another aspect relates to process of preparing the Calcitriol composition:

1) Water for injection was collected in a container and nitrogen was purged to reduce the dissolved oxygen content to less than 1 PPM.

2) required quantity of polysorbate 20 was collected in another container, to this BHA and BHT was added and dissolved.

3) calcitriol was added and dissolved in step 2 mixture and added to step 1 container mixture having water for injection.
4) EDTA, sodium chloride, dibasic sodium phosphate, anhydrous and monobasic sodium phosphate were added and dissolved individually under nitrogen cover.

5) pH of the solution was checked and final volume was made up to 100%.

6) the above solution was filtered through 0.22 µ filter.

7) filtered product was then filled into suitable containers & closure system under Nitrogen atmosphere.

The pharmaceutical compositions of the present invention can be used to treat patient suffering from a disease sensitive to the treatment with Calcitriol, in the management of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe chronic renal failure, significantly reduce elevated parathyroid hormone levels. Reduction of PTH has been shown to result in an improvement in renal osteodystrophy via various routes of administration such as intravenous, intramuscular, or subcutaneous injection.

A stability assessment was evaluated up to 6 months after storage at 25±5°C and 40±5°C till 3 months and the following tests were executed: pH appearance (colour, clarity/opalescence, particles; by visual inspection), pH, assay (by HPLC) and purity (by HPLC).

It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.
The following examples serve to provide further appreciation of the invention but not meant in any to restrict the effective scope of the invention.

### Examples 1-3: Liquid compositions of calcitriol

<table>
<thead>
<tr>
<th>S. No</th>
<th>Ingredients</th>
<th>Example-1</th>
<th>Example-2</th>
<th>Example-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Calcitriol</td>
<td>1 mcg/mL</td>
<td>1 mcg/mL</td>
<td>1 mcg/mL</td>
</tr>
<tr>
<td>2</td>
<td>Polysorbate 20</td>
<td>4 mg/mL</td>
<td>4 mg/mL</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>3</td>
<td>BHA</td>
<td>0.003 mg/mL</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>BHT</td>
<td>0.02 mg/mL</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>Monothioglycerol</td>
<td>--</td>
<td>0.2 mg/mL</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>L-Cystiene HCl</td>
<td>--</td>
<td>--</td>
<td>0.3 mg/mL</td>
</tr>
<tr>
<td>7</td>
<td>EDTA</td>
<td>1.1 mg/mL</td>
<td>1.1 mg/mL</td>
<td>1.1 mg/mL</td>
</tr>
<tr>
<td>8</td>
<td>Sodium chloride USP/BP/Ph.Eur</td>
<td>1.5 mg/mL</td>
<td>1.5 mg/mL</td>
<td>1.5 mg/mL</td>
</tr>
<tr>
<td>9</td>
<td>Dibasic sodium phosphate anhydrous USP/Ph.Eur</td>
<td>7.6 mg/mL</td>
<td>7.6 mg/mL</td>
<td>7.6 mg/mL</td>
</tr>
<tr>
<td>10</td>
<td>Monobasic Sodium phosphate monohydrate USP/Ph.Eur</td>
<td>1.8 mg/mL</td>
<td>1.8 mg/mL</td>
<td>1.8 mg/mL</td>
</tr>
<tr>
<td>11</td>
<td>Water for Injection</td>
<td>QS to 1 mL</td>
<td>QS to 1 mL</td>
<td>QS to 1 mL</td>
</tr>
</tbody>
</table>

### Manufacturing process:

1) Water for injection was collected in a container and nitrogen was purged to reduce the dissolved oxygen content to less than 1 PPM.

2) required quantity of polysorbate 20 was collected in another container, to this BHA and BHT was added and dissolved.

3) calcitriol was added and dissolved in step 2 mixture and added to step 1 container mixture having water for injection.

4) EDTA, sodium chloride, dibasic sodium phosphate, anhydrous and monobasic sodium phosphate were added and dissolved individually under nitrogen cover.
5) pH of the solution was checked and final volume was made up to 100%.
6) the above solution was filtered through 0.22 µ filter.
7) filtered product was then filled into suitable containers & closure system under Nitrogen atmosphere.

5

**Example 4**: Stability data of composition of calcitriol. (Example -1)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Raw material</th>
<th>Initial</th>
<th>3M LT</th>
<th>6M LT</th>
<th>3M ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Description</strong></td>
<td>A clear colorless solution</td>
<td>A clear colorless solution</td>
<td>A clear colorless solution</td>
<td>A clear colorless solution</td>
</tr>
<tr>
<td>2</td>
<td><strong>pH</strong></td>
<td>6.08</td>
<td>7.36</td>
<td>7.32</td>
<td>7.35</td>
</tr>
<tr>
<td>3</td>
<td><strong>Assay of Calcitriol</strong></td>
<td>102.0</td>
<td>100.0</td>
<td>98.2</td>
<td>93.2</td>
</tr>
<tr>
<td>4</td>
<td><strong>Related substances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a) 1-Beta Calcitriol</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>b) Trans-Calcitriol</td>
<td>0.049</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>c) Pre Calcitriol</td>
<td>3.41</td>
<td>3.76</td>
<td>3.56</td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td>d) Any un specified impurity</td>
<td>0.34</td>
<td>0.31</td>
<td>0.21</td>
<td>2.57</td>
</tr>
<tr>
<td></td>
<td>e) Total (Excluding Pre calcitriol)</td>
<td>1.09</td>
<td>0.53</td>
<td>0.21</td>
<td>2.71</td>
</tr>
</tbody>
</table>

*ND- Not detected*
We Claim:

1. A stable clear, colorless pharmaceutical liquid composition comprising:
   Calcitriol or its pharmaceutically acceptable salt thereof, with antioxidant other than metal ascorbate and other suitable excipients.

2. A stable clear, colorless pharmaceutical liquid composition comprising;
   Calcitriol or its pharmaceutically acceptable salt thereof;
   with antioxidant other than metal ascorbate is butylated hydroxy toluene and butylated hydroxyl anisole; and other suitable excipients.

3. The pharmaceutical liquid composition of claim 1, wherein suitable excipients include, solubilizer or surfactant comprising selected from polyoxyethylene sorbitan monoooleate (polysorbate 80), sorbitan monooleate, polyoxyethylene sorbitan monolaurate (polysorbate 20), lecithin, polyoxyethylene- polyoxypropylene copolymers (pluronics) or any mixtures thereof; antioxidant is selected from ascorbic acid, tocopherol, acetylcysteine, monothioglycerol, butylhydroxy toluene, butylhydroxyl anisole, cystein, methionine, propyl gallate, thioglycolate sodium, and mixtures thereof;
   buffering agent selected from sodium phosphate monobasic or dibasic or any mixtures thereof;
   complexing agent such as sodium edetate (EDTA);
   tonicity contributing agent selected from sodium chloride, dextrose, sucrose, fructose, and mixtures thereof.

4. The pharmaceutical liquid composition of claim 1, comprising
   Calcitriol or its pharmaceutically acceptable salt thereof;
   butylated hydroxy toluene, butylated hydroxyl anisole, any mixtures thereof;
   polysorbate 20 or any mixtures thereof;
   sodium phosphate monobasic and dibasic sodium phosphate;
   sodium edetate;
   sodium chloride; and
water for injection.

5. The pharmaceutical composition of claims 1 and 4, has about 95% potency of Calcitriol and about 100% potency of EDTA after autoclaving at 121°C for 15 minutes.

6. The pharmaceutical liquid composition according to claim 1, wherein said composition comprises from about 0.01 mcg/ml to about 10 mcg/ml of Calcitriol.

7. The pharmaceutical composition according to claim 4, wherein said composition comprises from about 0.05 mcg/ml to about 5 mcg/ml of Calcitriol.

8. The pharmaceutical liquid compositions comprising Calcitriol, solubilizer/surfactant, antioxidants and one or more tonicity contributing agent substantially as herein described.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/59, A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Pateer, IPO Internal Dat abase

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>WO 03 047595 A1 (NOVACEA INC [US]) 12 June 2003 c1 aims 1, 19, 21; examples 1-2, table 2; para 0 067</td>
<td>1-3</td>
</tr>
<tr>
<td>Y</td>
<td>para 0 067</td>
<td></td>
</tr>
<tr>
<td>Y</td>
<td>US 20060292080 A1 (CONNET ECS AUS TRAL I A PTY LTD [AU]) 28 December 2006 claim 13, para 0 0671-[0070], [0072], table 2</td>
<td>4-8</td>
</tr>
<tr>
<td>Y</td>
<td>US 20050101576 A1 (NOVACEA INC) 12 May 2005 abstract; claims 7, 28-32; para 0 0831, [0163-0164]</td>
<td>4-8</td>
</tr>
<tr>
<td>Y</td>
<td>US 20060189586 A1 (CLELAND JEFFREY L [US]) 24 August 2006 claims 1-8; para 0 0251, [0069]; table 2</td>
<td>4-8</td>
</tr>
<tr>
<td>Y</td>
<td>WO2 008027532 A2 (COHEN RAKEFET [IL]; FOX MI CHALEL [IL]) 06 March 2008 claims 1, 12; para 0 0281, [0033], [0050]</td>
<td>4-8</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Date of the actual completion of the international search 21-03-2017
Date of mailing of the international search report 21-03-2017

Name and mailing address of the ISA/Indian Patent Office Plot No. 32, Sector 14, Dwarka, New Delhi-110075
Facsimile No.

Authorized officer
Abha S Kumar Bhoi
Telephone No. +91-1125300200

Form PCT/ISA/210 (second sheet) (January 2015)
<table>
<thead>
<tr>
<th>Citation</th>
<th>Pub. Date</th>
<th>Family</th>
<th>Pub. Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EP 1461044 A4</td>
<td>09-10-2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2005515996 A</td>
<td>02-06-2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2469119 A1</td>
<td>12-06-2003</td>
</tr>
<tr>
<td>us 2006292080 A1</td>
<td>28-12-2006</td>
<td>US 8263580 B2</td>
<td>11-09-2012</td>
</tr>
<tr>
<td>Wo 2008027532 A2</td>
<td>06-03-2008</td>
<td>US 2008064669 A1</td>
<td>13-03-2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012046253 A1</td>
<td>23-02-2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2010502624 A</td>
<td>28-01-2010</td>
</tr>
</tbody>
</table>