

**NOVEL TOPICAL CREAM COMPOSITIONS FOR DIABETIC FOOT
TREATMENT AND PROCESS FOR PREPARATION THEREOF**

FIELD OF THE INVENTION

5 The present invention relates to topical compositions for Diabetic foot treatment.

The present invention specifically relates to novel topical cream composition comprising Curcuma nano drop and pharmaceutically acceptable excipients.

10 The present invention specifically relates to novel topical cream composition for the treatment of diabetic foot comprising Curcuma nano drop having curcuminoids (curcumin, bisdemethoxycurcumin and demethoxycurcumin) and non-curcuminoids (Turmerones especially Aromatic Turmerones (AR- Turmerones)).

15 The present invention also relates to process for the preparation of novel topical cream composition.

BACKGROUND OF THE INVENTION

20 Diabetes mellitus is among the most common disorder in developed and developing countries, and the disease is increasing rapidly in most parts of the world. It is characterized by high blood sugar levels caused either due to inadequate production of insulin or due to inability of body cell to respond to insulin. As per WHO, currently over 382 million people are affected globally and diabetes will emerge as 7th leading cause of death in 2030. As the diabetes capital of the world with 50 million people suffering from type-2 diabetes, India
25 has a challenge to face. However, medical experts feel that timely awareness, detection and right management can go a long way in helping patients lead a normal life. Hence there is a need to develop the convenient, cost effective, efficient and with minimal side-effects medication that can control the Diabetes mellitus.

30 The Scientific name of Curcumin is *Haridra (Curcuma longa) Rhizome*, a traditional Chinese herb, also known as turmeric, safflower, or yellow ginger, has curcumin as its main phenolic compound. Its rhizome (underground stem) is used as a culinary spice and

traditional medicine. Historically, turmeric was used in Ayurveda and other traditional Indian medical systems, as well as Eastern Asian medical systems such as traditional Chinese medicine. In India, it was traditionally used for disorders of the skin, upper respiratory tract, joints, and digestive system. Curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. Curcumin is a major component of turmeric, and the activities of turmeric are commonly attributed to curcuminoids.

Diabetic foot ulcers are among the most common complications of patients who have diabetes mellitus which is not well controlled. It is usually the result of poor glycemic control, underlying neuropathy, peripheral vascular disease, or poor foot care. It is also one of the common cause for osteomyelitis of the foot and amputation of lower extremities. Unlike most diseases and disorders, DFUs will not arise as a result of a single pathological consequence. Among the various factors, neuropathy and peripheral vascular diseases (PVD) are the most common causes of DFUs. Prolonged/excessive glucose deposition in blood leads to the damage of peripheral nerves (peripheral neuropathy). Depending on the type of damaged nerve, neuropathy may be sensory, motor or autonomic. Sensory neuropathy leads to loss of sensation on the surface of the foot.

Curcumin (diferuloylmethane) is the main curcuminoid present in turmeric and responsible for its yellow color. Curcumin has been shown to possess significant anti-inflammatory, anti-oxidant, anti-carcinogenic, anti-mutagenic, anti-coagulant and anti-infective effects. Curcumin has also been shown to have significant wound healing properties. Curcumin is a natural polyphenolic substance that has been used since ancient times in Ayurveda for its healing properties, as it reduces inflammation and acts on several healing stages. Several research studies for curcumin delivery at the wound site reported the effectiveness of curcumin in eradicating reactive oxygen species and its ability to enhance the deposition of collagen, granulation tissue formation, and finally, expedite wound contraction.

Curcumin found to exhibit various biological activities in treating DFUs via various mechanisms such as inhibition of activity of matrix metalloproteinases and proinflammatory

cytokines (TNF- α , IL-1 β ; decreased inflammation and ECM degradation). It also inhibits mitogen activated protein kinases and suppression of lectin-like oxidized low density lipoprotein receptor-1 (LOX-1) up regulation (decreased nerve damage). Curcumin increases the levels of anti-oxidant enzymes (SOD, Glutathione peroxidase (GPx))
5 (decreased oxidative stress) and eNOS (decreased vascular occlusion). It also increases the levels of HO-1, VEGF, TGF- β 1 (promote angiogenesis) and SDF-1 α , HIF-1 α (vasculogenesis) (Gowthamarajan et al., Trop Med Surg 2015, 3:1).

Curcumin is a bright yellow chemical produced by *Curcuma longa* plants. It is the
10 principal curcuminoid of turmeric (*Curcuma longa*), a member of the ginger family, Zingiberaceae. Curcumin, chemically described as (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadien-3,5-dione. It is a yellowish crystalline, odorless powder, poorly soluble in water, petroleum ether, and benzene, soluble in ethyl alcohols, glacial acetic acid, and in propylene glycol, very soluble in acetone and ethyl ether.

15 Diabetic Foot Ulcers (DFU) are a severe complication of diabetes that involves chronic non-healing wounds, often leading to infections and lower-limb amputations. Curcumin has shown promising therapeutic potential in managing DFUs due to its multifunctional properties. Here's how it contributes to DFU healing:

20 1. Modulation of Inflammation

- Chronic inflammation is a hallmark of DFUs. Curcumin inhibits nuclear factor-kappa B (NF- κ B) activation, reducing the levels of pro-inflammatory cytokines (e.g., TNF- α , IL-6, IL-1 β) that impair wound healing.

2. Promotion of Angiogenesis

- 25 • Curcumin enhances angiogenesis by upregulating vascular endothelial growth factor (VEGF) and improving microvascular blood flow, which are often compromised in diabetic patients. This is critical for delivering oxygen and nutrients to the wound site.

3. Antioxidant Properties

- 30 • DFUs are exacerbated by oxidative stress. Curcumin scavenges reactive oxygen species (ROS) and enhances the activity of antioxidant enzymes, reducing oxidative damage in the wound environment.

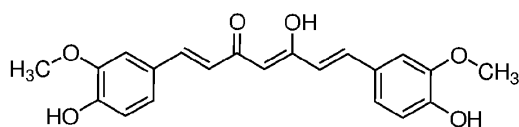
4. Improvement in Collagen Synthesis

- Curcumin promotes fibroblast proliferation and increases collagen deposition, improving wound closure and tensile strength. This addresses the impaired extracellular matrix remodeling seen in DFUs.

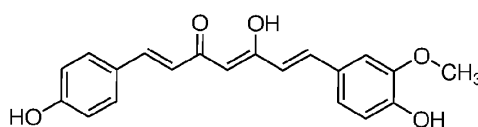
5. Antimicrobial Action

- DFUs are prone to infections by multidrug-resistant pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Curcumin's broad-spectrum antimicrobial activity can help prevent and manage infections in DFUs.

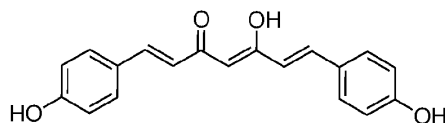
Curcuminoids are phenolic compounds extracted from the dried rhizomes of *Curcuma longa* (Turmeric) having potent anti-inflammatory and anti-oxidant properties. Curcuma drops having 95% Curcuminoids (Curcumin, Demethoxycurcumin & Bisdemethoxycurcumin) & non-curcuminoids prepared using patented C3 CURA augmented absorption technology. It is soluble and bioavailable form providing potent anti-inflammatory and pain relieving effects.



Curcumin



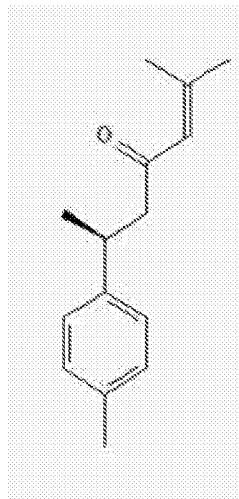
Demethoxycurcumin



Bisdemethoxycurcumin

Non-curcuminoids are basically all other biologically active compounds of turmeric excluding curcuminoids. The immunomodulatory and chemo-preventive activities of α -turmerone, a non-curcuminoid, was revealed with regards to its potency to be equivalent to

curcuminoids (Yue GGL et al, 2010). Aromatic-turmerone, a non-curcuminoid, has shown to possess potent anti-inflammatory, anti-oxidative and anti-platelet properties (S Toden et al, 2017).



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Non-curcuminoids are isolated from the mother liquor after isolation of Curcumin from oleoresin is known as curcumin removed turmeric oleoresin (CRTO) and it has shown antimicrobial properties (*Jayaprakasha et al, 2001*).

10 Curcuma Drops used in the present invention are manufactured using the technology disclosed in Patent no. PCT/IN2019/050780.

IN 1853/DEL/2008 discloses a topical formulation comprising turmeric or extracts thereof such as curcumin or curcuminoids along with excipients wherein the formulation is
15 non-staining and includes (a) a specialized base solution (SBS) (b) a specialized solubilizer (SS) in specific concentrations.

WO 2023/278876 A1 discloses composition suitable for topical application, comprising: (i) a curcuminoid compound of Formula I and/or a salt thereof as an active
20 pharmaceutical ingredient (API) in a range of from 0.001% w/w to 0.2% w/w; and (ii) an oil solvent system in an amount of at least 8% w/w, wherein % w/w is compared to the overall weight of the pharmaceutical composition. (iii) a surfactant system in a range of from 1.6% w/w to 16% w/w, said surfactant system comprising a non-ionic surfactant and a fatty acid;

wherein the oil solvent system is in a range of from 8% w/w to 32% w/w, said oil solvent system comprising isopropyl myristate, benzyl alcohol, diethylene glycol monoethyl ether, and dimethicone.

5 None of the prior-art disclosed the cream compositions of present application. The present inventors have focussed on safe, easy to use, soothing novel cream for all ages of diabetic patients to treat effectively. The novel cream composition of present invention itself as a non-sticky cream, thus, increasing compliance. Topical cream is a new methodology among the present management procedures for the diabetics.

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide a topical composition.

15 Another objective of the present invention is to provide novel topical cream composition comprising Curcuma nano drop and pharmaceutically acceptable excipients.

20 Another objective of the present invention is to provide a novel topical cream composition for the treatment of diabetic foot comprising Curcuma nano drop having curcuminoids (curcumin, bisdemethoxycurcumin and demethoxycurcumin) and non-curcuminoids (Turmerones especially Aromatic Turmerones (AR- Turmerones)).

Yet another objective of the present invention is to provide a process for the preparation of novel cream composition.

SUMMARY OF THE INVENTION

25 Accordingly, the present invention relates to a novel topical composition.

30 One embodiment of the present invention provides a novel topical cream composition comprising Curcuma nano drop and pharmaceutically acceptable excipients.

Another embodiment of the present invention provides a novel topical cream composition for the treatment of diabetic foot comprising Curcuma nano drop having

curcuminoids (curcumin, bisdemethoxycurcumin and demethoxycurcumin) and non-curcuminoids (Turmerones especially Aromatic Turmerones (AR- Turmerones)).

Another embodiment of the present invention provides a novel topical cream
5 composition for the treatment of Diabetic Foot comprising Curcuma nano drop, wherein the cream having pH of 4 to 6 and Viscosity of 2000 to 10000 cps.

Another embodiment of the present invention provides a novel cream composition comprising Curcuma nano drop and pharmaceutically acceptable excipients selected from
10 cream bases, humectants, emulsifiers, emollients, solubilizers, antifoaming agents, chelating agents, Permeation enhancers, thickening agents, preservatives, buffering agents and solvents.

Yet another embodiment of the present invention provides a topical cream
15 composition comprising:

- a) 0.001% to 0.5% (w/w) of Curcuma Nano drop,
- b) 5% to 30% (w/w) of cream bases,
- c) 1% to 20% (w/w) of humectants,
- d) 1% to 30% (w/w) of emulsifiers,
- 20 e) 0.1% to 15% (w/w) of antifoaming agents,
- f) 0.1% to 5% (w/w) of preservatives,
- g) 40% to 80% (w/w) of solvent, and
- h) 10% to 50% (w/w) of other pharmaceutically acceptable excipients.

25 Yet another embodiment of the present invention provides a topical cream composition comprising:

- a) 0.001% to 0.5% (w/w) of Curcuma Nano drop,
- b) 5% to 30% (w/w) of light mineral oil (light liquid paraffin),
- c) 1% to 10% (w/w) of propylene glycol,
- 30 d) 1% to 5% (w/w) of glycerin,
- e) 0.1% to 15% (w/w) of dimethicone,
- f) 0.1% to 5% (w/w) of phenoxy ethanol,

- g) 40% to 80% (w/w) of purified water, and

Yet another embodiment of the present invention provides a topical cream composition comprising:

- 5 a) 0.001% to 0.5% (w/w) of Curcuma Nano drop,
b) 5% to 30% (w/w) of light mineral oil (light liquid paraffin),
c) 1% to 10% (w/w) of propylene glycol,
d) 1% to 5% (w/w) of glycerin,
e) 1% to 10% (w/w) of cetyl alcohol,
10 f) 1% to 10% (w/w) of stearyl alcohol,
g) 1% to 10% (w/w) of cetostearyl alcohol,
h) 1% to 10% (w/w) of glycerol monostearate,
i) 1% to 5% (w/w) of sorbitan monostearate,
j) 0.1% to 5% (w/w) of sodium lauryl sulphate,
15 k) 1% to 5% (w/w) of dimethicone,
l) 0.01% to 1% (w/w) of disodium edetate,
m) 0.1% to 5% (w/w) of phenoxy ethanol,
n) 0.01% to 1% (w/w) of citric acid monohydrate, and
o) 40% to 80% (w/w) of purified water.

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Yet another embodiment of the present invention provides a topical cream composition comprising:

- a) 0.001% to 0.5% (w/w) of Curcuma Nano drop,
b) 5% to 30% (w/w) of light mineral oil (light liquid paraffin),
25 c) 1% to 10% (w/w) of propylene glycol,
d) 1% to 5% (w/w) of glycerin,
e) 1% to 10% (w/w) of cetyl alcohol,
f) 1% to 10% (w/w) of stearyl alcohol,
g) 1% to 10% (w/w) of cetostearyl alcohol,
30 h) 1% to 10% (w/w) of glycerol monostearate,
i) 1% to 5% (w/w) of sorbitan monostearate,
j) 0.1% to 5% (w/w) of sodium lauryl sulphate,

- k) 1% to 5% (w/w) of dimethicone,
- l) 0.01% to 1% (w/w) of disodium edetate,
- m) 0.1% to 5% (w/w) of phenoxy ethanol,
- n) 0.01% to 1% (w/w) of citric acid monohydrate,
- 5 o) 0.3-0.8% (w/w) of Vitamin E TPGS and
- p) 40% to 80% (w/w) of purified water.

In yet another embodiment, the present invention provides a process for preparation of curcuma nano drops solution with a uniformly interspersed particle formulation comprising an ultrafine and a fine particle comprising a curcuminoid and a non-curcuminoid solution which is manufactured by:

- a) mixing non-ionic solubilizer and emulsifier and a Curcumin removed turmeric oleoresin under heating,
- b) adding Curcumin to the mixture under stirring to form a uniform solution,
- 15 c) Cooling the solution and adding Ethanol,
- d) Sonicating the final solution to obtain a uniformly interspersed particle formulation of curcuma nano drops solution comprising an ultrafine and a fine particle comprising a curcuminoid and a non-curcuminoid.

20 In yet another embodiment, the present invention provides the use of curcuma nano drops solution to prepare topical cream.

In yet another embodiment, the present invention provides a process for preparing topical cream, the process comprising steps of:

- 25 a) adding all excipients under stirring and heating at 50-70°C until it dissolves completely,
- b) adding curcuma drops into main manufacturing vessel under stirring,
- c) adding purified water to main manufacturing vessel and continue to mix for 15 minutes,
- 30 d) adding moisturizer to main manufacturing vessel under stirring and continue mixing for 1 hour,
- e) homogenizing for 60 minutes to get uniform pale-yellow colour cream.

In yet another embodiment, the present invention provides a process for preparing topical cream, the process comprising steps of:

- a) adding light mineral oil, cetyl alcohol, stearyl alcohol, glycerol mono stearate, glycerine, cetostearyl alcohol, sorbitan monostearate in a suitable vessel under heating at 65-70°C and heat until a clear liquid is obtained,
- b) adding disodium EDTA, sodium lauryl sulphate, propylene glycol, phenoxy ethanol into a suitable vessel containing purified water under stirring and heating at 50-70°C until it dissolves completely,
- c) adding step b) to step a) contents in main manufacturing vessel under stirring and heating at 65-70°C for 20 minutes,
- d) adding curcuma drops into main manufacturing vessel under stirring,
- e) adding Purified water to main manufacturing vessel and continue to mix for 15 minutes,
- f) adding Dimethicone to main manufacturing vessel under stirring and continue mixing for 1 hour,
- g) dissolving citric acid monohydrate in purified water and adjusting the pH (Target pH - 4.00 to 6.00),
- h) transferring solution into main manufacturing vessel and stir for 15 minutes to obtain uniform pH and viscosity build up, and
- i) homogenizing for 60 minutes to get uniform pale-yellow colour cream.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1: The wound healing percentage, 75% (38) of patients exhibited a range of responses ranging from 70% to 99%.

Figure 2: The average wound size at the start of the treatment and at the end of the treatment with a mean wound size reduction of 4.8 cm ($p < 0.05$)

Figure 3: Significant reduction in the average VAS score for pain from 8 to 3 ($p < 0.05$)

Figure 4: 45-year-old male patient with initial wound size of 8cm on day 0 experienced 96% wound healing at end of treatment.

Figure 5: 54-year-old female patient with initial wound size of 5cm on day 0 experienced 95% wound healing at end of treatment.

DETAILED DESCRIPTION OF THE INVENTION

The term "comprising", which is synonymous with "including", "containing", or "characterized by" here is defined as being inclusive or open-ended, and does not exclude additional, unrecited elements or method steps, unless the context clearly requires
5 otherwise.

The present invention provides a novel topical cream composition comprising Curcuma nano drop and pharmaceutically acceptable excipients.

10 The present invention provides a novel topical cream composition for the treatment of diabetic foot comprising Curcuma nano drop having curcuminoids (curcumin, bisdemethoxycurcumin and demethoxycurcumin) and non-curcuminoids (Turmerones especially Aromatic Turmerones (AR- Turmerones)).

15 Another embodiment of the present invention provides a novel topical cream composition for the treatment of Diabetic Foot comprising Curcuma nano drop, wherein the cream having pH of 4 to 6 and Viscosity of 2000 to 10000 cps.

The present invention provides a novel cream composition comprising Curcuma nano
20 drop and pharmaceutically acceptable excipients selected from cream bases, humectants, emulsifiers, emollients, solubilizers, antifoaming agents, chelating agents, Permeation enhancers, thickening agents, preservatives, buffering agents and solvents.

The curcuminoids, non-curcuminoids used in the present invention is Curcuma Nano
25 drop and the concentration of Curcuma Nano drop is in the range of 0.001% to 0.5% (w/w) of the total weight of the composition.

Cream bases used in the present invention are selected from and not limited to white
30 soft paraffin, light mineral oil (light liquid paraffin), liquid paraffin, hard paraffin, shea butter, cocoa butter, lanolin, beeswax, carnauba, lanolin, microcrystalline wax, and the like, either singly or mixtures thereof.

The concentration of cream bases is in the range of 5% to 30% (w/w) of the total weight of the composition.

Humectant used in the present invention are selected from and not limited to
5 glycerin, hyaluronic acid, propylene glycol, sorbitol or mixtures thereof.

The concentration of humectants is in the range of 1% to 20% (w/w) of the total weight of the composition.

10 Emulsifiers used in the present invention are selected from and not limited to cetyl alcohol, stearyl alcohol, cetostearyl alcohol, sucrose stearate, polysorbates laureth-4, potassium cetyl sulphate, Olivem 900 or mixtures thereof.

The concentration of emulsifiers is in the range of 1% to 30% (w/w) of the total
15 weight of the composition.

Emollient used in the present invention are selected from and not limited to glycerol monostearate, urea, ammonium lactate, salicylic acid, urea, vitamins A, D, and E, mixtures thereof.

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The concentration of emollients is in the range of 1% to 10% (w/w) of the total weight of the composition.

Solubilizers used in the present invention are selected from and not limited to
25 sorbitan monostearate, sodium lauryl sulfate, sodium laureth sulfate, or mixtures thereof.

The concentration of Solubilizers is in the range of 0.1% to 10% (w/w) of the total weight of the composition.

30 Anti-foaming agents used in the present invention are selected from and not limited to Dimethicone, cetostearyl alcohol, insoluble oils (castor oil), stearates, polydimethylsiloxanes and other silicones derivatives, ether and glycols or mixtures thereof.

The concentration of anti-foaming agents is in the range of 0.1% to 15% (w/w) of the total weight of the composition.

5 Chelating agents used in the present invention are selected from and not limited to EDTA, Disodium edetate or mixtures thereof.

The concentration of chelating agents is in the range of 0.01% to 5% (w/w) of the total weight of the composition.

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Permeation enhancers used in the present invention are selected from and not limited to Vitamin E TPGS, dimethyl isosorbide, isopropyl myristate, diethylene glycol monoethyl ether (e.g., TRANSCUTOL HP brand diethylene glycol monoethyl ether), ethyl alcohol, ethyl oleate, isostearyl alcohol, oleyl alcohol, polyethylene glycol, N-methyl-2-pyrrolidone, 15 dimethyl sulfoxide, or propylene carbonate or combination thereof.

The concentration of Permeation enhancers is in the range of 1% to 10% (w/w) of the total weight of the composition.

20 Thickening agents used in the present invention are selected from and not limited to Sepineo-P-600 (Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer/Isohexadecane & Polysorbate 80), carrageenan, xanthan gum, epicatechin, alginic acid, gelatin, polysaccharide, gelling agent, pectin or mixtures thereof.

25 The concentration of Thickening agents is in the range of 1% to 10% (w/w) of the total weight of the composition.

Preservatives used in the present invention are selected from and not limited to, phenoxy ethanol, sodium benzoate, potassium sorbate, methylparaben, propylparaben, 30 benzyl alcohol, sorbic acid, benzoic acid, diazolidinyl urea or mixtures thereof.

The concentration of preservatives is in the range of 0.1% to 5% (w/w) of the total

weight of the composition.

Buffering agents used in the composition of the present invention include, but are not limited to citric acid monohydrate, citric acid anhydrate or mixtures thereof.

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The concentration of pH adjusting agents is in the range of 0.01% to 1% (w/w) of the total weight of the composition.

10 Solvents used in the composition of the present invention include, but are not limited to purified water, castor oil, oleyl alcohol or mixtures thereof.

The concentration of solvents is in the range of 40% to 80% (w/w) of the total weight of the composition.

15 The curcuma nano drops of the present invention preparing using below process (C3 CURA augmented absorption technology):

1. Weigh and dispense required quantity of Polyoxyl 35 Hydrogenated castor oil and Curcumin Removed Turmeric Oleoresin (CRTO) into suitable manufacturing vessel and heat it between 80°C to 120°C under stirring.
- 20 2. Add curcumin powder to manufacturing vessel containing Polyoxyl 35 Hydrogenated castor oil and CRTO under stirring at 5000-6000 RPM and maintain at this temperature until dark brown color solution is observed and allow it to cool to room temperature.
3. Add sucralose to separate vessel containing ethanol under stirring at 2000-3000 RPM until solution is clear.
- 25 4. Add sucralose solution of step 3 to step 2 under continuous stirring at 5000-6000 RPM for 30 to 60 minutes.
5. Add taste masking flavour to manufacturing vessel under stirring for 5 to 15 minutes after addition.
6. Check and record the pH.
- 30 7. Carry out the sonication using Sonicator (Ultrasonic processor, Hielscher, Germany) for a duration until the required energy level is imparted as per the parameters mentioned below to obtain soluble and therapeutically safe curcuma nano drop formulation.

Sonotrode	As per batch size
Energy level	50000 w/s
Amplitude	30 – 70%
Temperature cut off	Not more than 40°C
On time	20-30 seconds
Off time	20-30 seconds

All the actives and excipients used in the present application are procured from the commercial sources. The details are as given below:

S.No.	Active/Auxiliary materials	Commercial source	Detailed address of source
1	Curcuma	Mane Kancor Ingredients Private Limited or Plant Lipids	Mane Kancor Ingredients Ltd and Kancor Ingredients Ltd), Sy.No.278/1, Kanakkankadavu Road, Angamaly South, Angamaly, Ernakulam District, Kerala-683573, India Plant lipids (P) Ltd, Kolenchery, Cochin-682311
2	Light Mineral oil (Light Liquid Paraffin)	Raj Petro Specialities Pvt Ltd.	73/1B, Vaikkadu Village, Manali, Chennai, Tamil Nadu - 600103

- 5 The present invention is illustrated in detail but not limiting to, the following examples. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

Example 1

- 10 Each gram of Cream contains: Haridra (*Curcuma longa*) Rhizome extract 0.05 mg

S. No.	Ingredient Name	Qty (mg/ gm)	% w/v
1	Curcuma Nano drop	0.050	0.005
2	Light Mineral oil (Light Liquid Paraffin)	80.000	8.000
3	Propylene glycol	50.000	5.000
4	Sucrose stearate	60.000	6.000
5	Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer/Isohexadecane & Polysorbate 80 (Sepineo-P-600)	25.000	2.500
6	Glycerin	20.000	2.000
7	Dimethicone	10.000	1.000
8	Phenoxy ethanol	7.000	0.700
9	Purified water	747.950	74.795

MANUFACTURING PROCESS

1. Check the cleanliness and dryness of all the manufacturing containers, equipment and accessories.
- 5 2. Add Light Mineral oil (Light liquid paraffin) to sucrose stearate in a suitable vessel under heating at 65-70°C and heat until a clear liquid is obtained. Transfer it to the main manufacturing vessel. Rinse the vessel with Purified water.
3. Transfer propylene glycol in a suitable vessel containing Purified water under heating at 70°C. Transfer it to the main manufacturing vessel. Rinse the vessel with Purified water.
- 10 4. Add Step 3 to Step 2 under stirring at 700 RPM for 10 minutes. Rinse the vessel with Purified water.
5. Add Glycerine to Step 4 under heating at 45 - 50°C and stirring at 700 RPM for 5 minutes. Rinse the vessel with Purified water.
6. Add Dimethicone to Step 5 in main manufacturing vessel under stirring at 800-1000 RPM for 10 minutes. Rinse the vessel with Purified water.
- 15 7. Add Phenoxy ethanol to step 6 in main manufacturing vessel under heating at 25 -30°C and stirring at 1200 RPM for 5 minutes. Rinse the vessel with Purified water.

8. Sepineo P 600 was added to step-7 in main manufacturing vessel under stirring at 3000 RPM for 10 minutes. Rinse the vessel with Purified water.
9. Add Curcumin nanodrops to the step 8 in main manufacturing vessel under stirring at 500-700 RPM for 5 minutes. Rinse the vessel with Purified water.
- 5 10. Add Purified water to main manufacturing vessel and continue to mix for 15 minutes at 500 – 700 RPM, stir for 15 minutes to obtain uniform pH and viscosity build up. A smooth pale-yellow colour cream will be obtained.
11. Perform homogenization at 2000 – 3000 RPM for 60 minutes to get uniform pale-yellow colour cream.
- 10 12. Check and Record the pH and viscosity from top, middle and bottom portion.
13. Pack the Cream as per procedure.

Example 2

Each gram of Cream contains: Haridra (*Curcuma longa*) Rhizome extract 0.05 mg

S. No.	Ingredient Name	Qty (mg/gm)	% w/w
1	Curcuma Nano drop	0.050	0.005
2	Light Mineral oil (Light Liquid paraffin)	80.000	8.000
3	Propylene Glycol	50.000	5.000
4	Cetyl Alcohol	40.000	4.000
5	Stearyl Alcohol	40.000	4.000
6	Cetostearyl alcohol	20.000	2.000
7	Glycerol monostearate	40.000	4.000
8	Sorbitan Monostearate	20.000	2.000
9	Sodium lauryl sulphate	5.000	0.500
10	Glycerin	20.000	2.000
11	Dimethicone	10.000	1.000
12	Disodium edetate	1.000	0.100
13	Phenoxy ethanol	7.000	0.700
14	Citric acid monohydrate	1.000	0.100

15	Purified Water	665.95	66.595
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MANUFACTURING PROCESS:

1. Check the cleanliness and dryness of all the manufacturing containers, equipment and accessories.
- 5 2. Add Light Mineral Oil, Cetyl alcohol, Stearyl alcohol, Glycerol Mono Stearate, Glycerine, Cetostearyl alcohol, Sorbitan monostearate in a suitable vessel under heating at 65-70°C and heat until a clear liquid is obtained. Transfer it to the main manufacturing vessel. Rinse the vessel with Purified water.
- 10 3. Add Disodium EDTA, Sodium lauryl sulphate, Propylene glycol, Phenoxy ethanol into a suitable vessel containing Purified water under stirring at 500 -700 RPM and heating at 50-70°C until it dissolves completely. Rinse the vessel with Purified water.
4. Add Step 3 to Step 2 contents in main manufacturing vessel under stirring at 1500 - 2500 RPM and heating at 65-70°C for 20 minutes.
- 15 5. Add Curcuma drops into main manufacturing vessel under stirring at 500 - 700 RPM for 10 minutes. Rinse the vessel with Purified water .
6. Add Purified water to main manufacturing vessel and continue to mix for 15 minutes at 500 – 700 RPM.
7. Add Dimethicone to main manufacturing vessel under stirring at 30 – 50 RPM and continue mixing for 1 hour. Dissolve Citric acid monohydrate in Purified water and adjust the pH (Target pH - 4.00 to 6.00). Rinse vessel with purified water and transfer rinsing solution into main manufacturing vessel and stir for 15 minutes to obtain uniform pH and viscosity build up. A smooth pale-yellow colour cream will be obtained.
- 20 8. Perform homogenization at 2000 – 3000 RPM for 60 minutes to get uniform pale-yellow colour cream.
- 25 9. Check and Record the pH and viscosity from top, middle and bottom portion.
10. Pack the Cream as per procedure.

Example 3

Each gram of Cream contains: Haridra (*Curcuma longa*) Rhizome extract 0.05 mg

S. No.	Ingredient Name	Qty (mg/gm)	% w/w
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1	Curcuma Nano drop	0.050	0.005
2	Light Mineral oil (Light Liquid paraffin)	80.000	8.000
3	Propylene Glycol	50.000	5.000
4	Vitamin E TPGS	3.000	0.3000
5	Cetyl Alcohol	40.000	4.000
6	Stearyl Alcohol	40.000	4.000
7	Cetostearyl alcohol	20.000	2.000
8	Glycerol monostearate	40.000	4.000
9	Sorbitan Monostearate	20.000	2.000
10	Sodium lauryl sulphate	5.000	0.500
11	Glycerin	20.000	2.000
12	Dimethicone	10.000	1.000
13	Disodium edetate	1.000	0.100
14	Phenoxy ethanol	7.000	0.700
15	Citric acid monohydrate	1.000	0.100
16	Purified Water	662.95	6.595

MANUFACTURING PROCESS:

1. Check the cleanliness and dryness of all the manufacturing containers, equipment and accessories.
- 5 2. Add Light Mineral Oil, Cetyl alcohol, Stearyl alcohol, Glycerol Mono Stearate, Glycerine, Cetostearyl alcohol, Sorbitan monostearate in a suitable vessel under heating at 65-70°C and heat until a clear liquid is obtained. Transfer it to the main manufacturing vessel. Rinse the vessel with Purified water.
- 10 3. Add Disodium EDTA, Sodium lauryl sulphate, Propylene glycol, Vitamin E TPGS, Phenoxy ethanol into a suitable vessel containing Purified water under stirring at 500 - 700 RPM and heating at 50-70°C until it dissolves completely. Rinse the vessel with Purified water.
4. Add Step 3 to Step 2 contents in main manufacturing vessel under stirring at 1500 - 2500 RPM and heating at 65-70°C for 20 minutes.
- 15 5. Add Curcuma drops into main manufacturing vessel under stirring at 500 - 700 RPM for

10 minutes. Rinse the vessel with Purified water.

6. Add Purified water to main manufacturing vessel and continue to mix for 15 minutes at 500 – 700 RPM.
7. Add Dimethicone to main manufacturing vessel under stirring at 30 – 50 RPM and continue mixing for 1 hour. Dissolve Citric acid monohydrate in Purified water and adjust the pH (Target pH - 4.00 to 6.00). Rinse vessel with purified water and transfer rinsing solution into main manufacturing vessel and stir for 15 minutes to obtain uniform pH and viscosity build up. A smooth pale-yellow colour cream will be obtained.
8. Perform homogenization at 2000 – 3000 RPM for 60 minutes to get uniform pale-yellow colour cream.
9. Check and Record the pH and viscosity from top, middle and bottom portion.
10. Pack the Cream as per procedure.

Physicochemical properties of cream product of present application:

S.No	Test Parameter	Results
1.	Description	Yellow colour cream
2.	Odour	Complies
3.	pH	4.78
4.	Viscosity	4860 cps
5.	Asssay	
	a. Total curcuminoids (0.05 mg/g)	123.5
	b. Phenoxy ethanol (7.0 mg/g)	97.7
6.	Microbiological quality	
a	<i>Staphylococcus aureus</i>	Absent/g
b	<i>Salmonella sp</i>	Absent/g
c	<i>Escherichia coli</i>	Absent
d	Total microbial plate count	< 10 CFU/g
e	Total Yeast and mould count	< 10 CFU/g

The composition of the present application complies all the parameters.

Efficacy data:

Applicant has performed clinical studies to evaluate the efficacy and safety of cream composition of present application in the treatment and prevention of Diabetic Foot Ulcers (DFUs).

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The study encompassed both male and female individuals aged 20 to 80 years, comprising of 36 males and 14 females, diagnosed with either Type 1 or Type 2 diabetes and undergoing therapy for glycemic control utilizing available diabetes drugs, including insulin. All patients consistently applied cream composition of present application over the entire 12-week treatment duration.

75% (38) of patients exhibited a range of wound healing response ranging from 70% to 99% (**Figure 1**). The average wound size at the start of the treatment was 6.63 cm, and 1.83 cm at the end of the treatment with a mean wound size reduction of 4.8 cm ($p < 0.05$) (**Figure 2**). There was significant reduction in the average VAS score for pain from 8 to 3 ($p < 0.05$) (**Figure 3**). In a trial conducted by application of curcumin cream lead to a significant reduction in the size of diabetic ulcers at five weeks. 45-year-old male patient with initial wound size of 8cm on day 0 experienced 96% wound healing at end of treatment (**Figure 4**). 54-year-old female patient with initial wound size of 5cm on day 0 experienced 95% wound healing at end of treatment (**Figure 5**).

The cream of the present application contributed to wound healing by reducing the average wound size by 4.8 cm, oxidative stress, suppressing inflammatory activities, and facilitating the proliferation and remodelling stages. The average VAS score for pain also reduced from 8 to 3. Moreover, the observations revealed that more than 90% healing was achieved for 23 (46%) patients in the present study, with noticeable changes in the length, width, and depth of the ulcers. No major side effects were reported. The cream of the present application demonstrated good tolerability in all patients.

Therefore, this study concludes that cream of the present application led to a significant reduction in the size of diabetic ulcers and reduced pain and clinically effective in the management of diabetic foot ulcer.

WE CLAIM:

1. A novel topical cream composition comprising Curcuma nano drop and pharmaceutically acceptable excipients wherein the concentration of Curcuma nano drop is in the range of 0.001% to 0.5% (w/w) of the total weight of the composition.
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2. The cream composition as claimed in claim 1, wherein said Curcuma nano drop comprising curcuminoids having curcumin, bisdemethoxycurcumin and demethoxycurcumin, non-curcuminoids having Turmerones especially AR Turmerone.
- 10 3. The cream composition as claimed in claim 1, wherein the cream having pH of 4 to 6 and Viscosity of 2000 to 10000 cps.
4. The cream composition as claimed in claim 1, wherein said pharmaceutically acceptable excipients selected from cream bases, humectants, emulsifiers, emollients, solubilizers,
15 antifoaming agents, chelating agents, Permeation enhancers, thickening agents, preservatives, buffering agents and solvents.
5. The cream composition as claimed in claim 4, wherein said cream bases are selected from white soft paraffin, light mineral oil (light liquid paraffin), liquid paraffin, hard paraffin,
20 shea butter, cocoa butter, lanolin, beeswax, carnauba, lanolin, microcrystalline wax, and the like, either singly or mixtures thereof, present in the range of 5% to 30% (w/w) of the total weight of the composition.
6. The cream composition as claimed in claim 4, wherein said humectant is selected from
25 glycerin, hyaluronic acid, propylene glycol, sorbitol or mixtures thereof, present in the range of 1% to 20% (w/w) of the total weight of the composition.
7. The cream composition as claimed in claim 4, wherein said emulsifiers are selected from cetyl alcohol, stearyl alcohol, cetostearyl alcohol, sucrose stearate, polysorbates laureth-4,
30 potassium cetyl sulphate, Olivem 900 or mixtures thereof, present in the range of 1% to 30% (w/w) of the total weight of the composition.

8. The cream composition as claimed in claim 4, wherein said emollient is selected from glycerol monostearate, urea, ammonium lactate, salicylic acid, urea, vitamins A, D, and E, mixtures thereof, present The concentration of emollients is in the range of 1% to 10% (w/w) of the total weight of the composition.
- 5
9. The cream composition as claimed in claim 4, wherein said solubilizers are selected from sorbitan monostearate, sodium lauryl sulfate, sodium laureth sulfate, or mixtures thereof, present in the range of 0.1% to 10% (w/w) of the total weight of the composition.
- 10
10. The cream composition as claimed in claim 4, wherein said anti-foaming agents are selected from Dimethicone, cetostearyl alcohol, insoluble oils (castor oil), stearates, polydimethylsiloxanes and other silicones derivatives, ether and glycols or mixtures thereof, present in the range of 0.1% to 15% (w/w) of the total weight of the composition.
- 15
11. The cream composition as claimed in claim 4, wherein said chelating agents are selected from and not limited to EDTA, Disodium edetate or mixtures thereof, present in the range of 0.01% to 5% (w/w) of the total weight of the composition.
- 20
12. The cream composition as claimed in claim 4, wherein said permeation enhancers are selected from and not limited to Vitamin E TPGS, dimethyl isosorbide, isopropyl myristate, diethylene glycol monoethyl ether (e.g., TRANSCUTOL HP brand diethylene glycol monoethyl ether), ethyl alcohol, ethyl oleate, isostearyl alcohol, oleyl alcohol, polyethylene glycol, N-methyl-2-pyrrolidone, dimethyl sulfoxide, or propylene carbonate or combination thereof, present in the range of 1% to 10% (w/w) of the total weight of the composition.
- 25
13. The cream composition as claimed in claim 4, wherein said thickening agents are selected from Sepineo-P-600 (Acrylamide/Sodium Acryloyldimethyl Taurate Copolymer/Isohexadecane & Polysorbate 80), carrageenan, xanthan gum, epicatechin, alginic acid, gelatin, polysaccharide, gelling agent, pectin or mixtures thereof, present in the range of 1% to 10% (w/w) of the total weight of the composition.
- 30
14. The cream composition as claimed in claim 4, wherein said preservative are selected

from phenoxy ethanol, sodium benzoate, potassium sorbate, methylparaben, propylparaben, benzyl alcohol, sorbic acid, benzoic acid, diazolidinyl urea or mixtures thereof, present in the range of 0.1% to 5% (w/w) of the total weight of the composition.

- 5 15. The cream composition as claimed in claim 4, wherein said buffering agents include citric acid monohydrate, citric acid anhydrate or mixtures thereof, present in the range of 0.01% to 1% (w/w) of the total weight of the composition.

- 10 16. The process for the preparation of composition as claimed in claim 1, wherein said process comprising steps of:

- a) adding all excipients under stirring and heating at 50-70°C until it dissolves completely,
- b) adding curcuma drops into main manufacturing vessel under stirring,
- c) adding purified water to main manufacturing vessel and continue to mix for 15
- 15 minutes,
- d) adding moisturizer to main manufacturing vessel under stirring and continue mixing for 1 hour,
- e) homogenizing for 60 minutes to get uniform pale-yellow colour cream.

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