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(54) **Title**: A MEDICINAL CREAM MADE USING CLOBETASOL PROPIONATE AND INCORPORATING A BIOPOLYMER AND A PROCESS TO MAKE IT

(57) **Abstract**: The present invention is directed to a composition for treating skin inflammation (Dermatitis), skin regeneration & rejuvenation and wound healing containing a Chitosan component used for the treatment of skin regeneration & rejuvenation and wound healing, Clobetasol Propionate used in treating skin inflammations, a cream base containing any of the ingredients selected from a group comprising primary and secondary emulsifiers, waxy materials, co-solvents, acids, preservatives, buffering agents, anti-oxidants, chelating agents and humectants, and purified water. The invention has the advantage that it reduces blood clotting time, increases epithelial effect, and provides faster relief from infection and inflammation. The invention also provides an integrated unit-dose or a single-dose therapy hitherto unavailable in prescription dermaceutical formulations. Furthermore, the invention is ad-equately stable/efficacious at ambient conditions and does not need special temperature control during transportation/ storage.

A Medicinal Cream Made Using Clobetasol Propionate and incorporating a biopolymer and a process to make it

Background Of The Invention

Dermatitis is an inflammation of the skin. Dermatitis actually refers to a number of skin conditions that inflame the skin. Dermatitis is characterized by skin that may be red, swollen, blistered, scabbed, scaly, oozing, or itchy. Some types of dermatitis are caused by allergies, while the majority does not have any known causes.

There are many types of dermatitis that require clinical care by a physician or other healthcare professional. The following are some of the examples of Dermatitis: Atopic Dermatitis (Eczema), Contact Dermatitis, Dermatitis Herpetiformis, Generalized Exfoliative Dermatitis and Seborrheic Dermatitis.

Wounds are heterogeneous and the wound healing process is of a multifactorial nature, influenced by many factors and compounds, introduced externally. Throughout history, humans have searched for materials to promote wound healing. A great variety of preparations and products have been used, ranging from hot oils, papyri and waxes of the Egyptians to the cotton and gauze tissues, which are still used. Until the 1960s, there had been a minimum of research and development into wound management products, and very few of the products

have been shown to be of great benefit. Fishermen in ancient China first recognized a therapeutic application for chitin for its natural wound healing properties. More recently a number of scientific studies have been conducted to investigate how chitin and its chitosan derivative may modulate wound healing. Since the understanding of wound-healing biology has advanced, it may now be the time when the rational design of effective drug formulations to promote healing is a real possibility.

In order to understand the field of wound healing relative to the use of compounds or agents, a few statements have to be made. The definition of wound pharmacology is the study of agents and their actions in wound environment. Three classes of agents can be discussed; drugs, biologics and special biologics such as those produced by biotechnology. Conventional drugs can be categorized by route of administration (topical, systemic or both). The kinetics are relatively easy to study and can serve as a guide for development of more complex agents. In contrast, biologics are naturally occurring synthetic or modified proteins and carbohydrates. There are generally large molecules that possess an increased complexity and a pleiotropic effect.

In current dermatological therapy there are some unmet medical needs, which have to be addressed. For example, Dermatological conditions are often caused by allergy accompanied by inflammation, tissue damage, irritation and itching.

Numerous treatments both topical and systemic are currently employed for the treatment of above skin inflammations. Topical and systemic inflammatory treatment compositions typically employ corticosteroids in a base component. The active ingredients typically comprise Corticosteroids such as Clobetasol Propionate ,Betamethasone dipropionate, Beclomethasone dipropionate, Hydrocortisone, Clobetasone butyrate, Halobetasol propionate, Mometasone furoate, Halcinonide, Fluocinonide, Triamcinolone acetonide, Fluticasone propionate, Amcinonide, Hydrocortisone acetate, Diflorasone diacetate, Prednicarbate and like .

Chitosan is a biopolymer with skin regeneration and rejuvenation properties due to its unique physical nature. Chitosan acts as a biocatalyst in accelerating the wound healing. Due to its positive charge it couples with negatively charged blood cells and aids in clotting of blood. It also helps in controlling the microbial mobility because of its charge and prevents spread of infections. As a micro-film forming bio material, Chitosan helps in reducing the width of the wound, controls the oxygen permeability at the site, and absorbs wound discharge, which is very much essential for faster wound healing. It also reduces the itching by providing a soothing effect.

Therefore the combination of Chitosan with steroids is a unique and novel since these combinations are not available globally and presented in patient friendly cream formulations.

Brief Description Of Figures

Figure 1 shows the film formed when using the formulation of the present invention.

Brief Summary Of The Invention

The present invention is directed to a composition for treating skin inflammation (Dermatitis), skin regeneration & rejuvenation and wound healing containing

a) A Chitosan component which is an unbranched binary polysaccharides consisting of the two units N-acetyl-D-glucosamine and D-glucosamine used for the treatment of skin regeneration & rejuvenation and wound healing.

b) Corticosteroids like Clobetasol Propionate used in treating skin inflammations.

c) A cream base containing primary and secondary emulsifiers, waxy materials, co-solvents, acids, preservatives, buffering agents, anti-oxidants, chelating agents and humectants.

d) Water

The active ingredients a Chitosan component, a corticosteroid are incorporated in cream base for use in treating skin inflammation due to allergy & itching, & wounds on human skin involving contacting human skin with the above identified composition.

Detailed Description Of The Invention

Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients are understood as being modified in all instances by the term "about".

The active compound which may be employed in the present invention are topical corticosteroids like Clobetasol Propionate and a biopolymer for treating skin inflammation and wounds.

Examples of suitable biopolymer, which may be used, include, but are not limited to Chitosan and the like.

Examples of suitable topical Corticosteroids, which may be used, include, but are not limited to, Clobetasol Propionate, and like.

These actives require a base component to be used in the pharmaceutical composition that uses the actives, since the actives cannot, by themselves, be deposited directly on to human skin due to their harshness.

The base component usually contains primary and secondary emulsifiers, waxy materials, co-solvents, acids, and preservatives, buffering agents, anti oxidants, chelating agents, humectants and the like.

Chitosan

Chitosan is an un-branched binary polysaccharide consisting of the two units N-Acetyl-D-glucosamine and D-glucosamine linked in β (1, 4) manner.

The chemical name of Chitosan is Poly-β- (1, 4)-2-Amino-2-deoxy-D-glucose.

Chitosan is produced by partial deacetylation (Not less than 70 %) of Chitin, which is extracted from the shells of shrimp and crab.

Chitosan finds its application in various areas including Pharmaceutical, Cosmetics and Food industry. It is official available in USP/NF as an excipient.

It is used as a film forming, mucoadhesive and viscosity-increasing agent.
It is also used as a binder and disintegrating agent in tablet formulations.

Chitosan generally absorbs moisture from the atmosphere / environment and the amount absorbed depends upon the initial moisture content, temperature and relative humidity of the environment.

It is regarded as a non-toxic and non-irritant material. It is biocompatible with both healthy and infected skin and has been shown to be biodegradable as it is derived from shrimps and crabs.

Chitosan due to its unique physical property accelerates wound healing and wound repair. It is positively charged and soluble in acidic to neutral solution. Chitosan is bioadhesive and readily binds to negatively charged surfaces such as mucosal membranes. Chitosan enhances the transport of polar drugs across epithelial surfaces. Chitosan's property allows it to rapidly clot blood, and has recently gained approval in the USA for use in bandages and other hemostatic agents.

Chitosan is hypoallergenic, and has natural anti-bacterial properties, further supporting its use. A therapeutic application for chitin was first recognized by fishermen in ancient China who revered it for its natural wound healing properties. More recently a number of scientific studies have been conducted to investigate how chitin and its chitosan derivative may modulate wound healing.

As a micro-film forming biomaterial, Chitosan helps in reducing the width of the wound, controls the oxygen permeability at the site, absorbs wound discharge and gets degraded by tissue enzymes which are very much required for healing at a faster rate. It also reduces the itching by providing a soothing effect. It also acts like a moisturizer.

Wound repair is a complex process involving an integrated response by many different cell types controlled by a variety of growth factors. During the initial inflammatory phase fibroblasts start to enter the wound where they synthesize and later remodel new extracelluar matrix material of which collagen is the main component. The dermal response is only one aspect of cutaneous wound repair however, the outermost and vital barrier layer, the epidermis which is composed of several layers of keratinocytes must also be restored. In injured skin, basal layer keratinocytes migrate from the wound edge and from injured epidermal appendages (hair follicles and sweat glands) into the defect, moving over the newly formed dermal scaffolding. They proliferate, stratify and differentiate to produce a neo-epidermis to cover the wound and restore the skin's barrier function.

Topical Corticosteroids

Topical corticosteroids are a powerful tool for treating skin diseases.

Corticosteroids include drugs like Clobetasol Propionate ,Betamethasone dipropionate, Beclomethasone dipropionate, Hydrocortisone, Clobetasone butyrate, Halobetasol propionate, Mometasone furoate, Halcinonide, Fluocinonide, Triamcinolone acetonide, Fluticasone propionate, Amcinonide, Hydrocortisone acetate, Diflorasone diacetate, Prednicarbate, etc. Understanding the correct use of these agents will result in the successful management of a variety of skin problems. Topical corticosteroids have anti inflammatory, antipruritic and vasoconstrictive properties.

Corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor Arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Topical corticosteroids are classified by their potency, ranging from weak to extremely potent. They include weak potent steroids, moderate potent steroids, potent steroids, very potent steroids and extremely potent steroids.The high potency steroids include Clobetasol Propionate, Betamethasone Dipropionate, Betamethasone Valerate, Diflorasone Diacetate, Halobetasol Propionate, Desoximetasone, Diflorasone Diacetate, Fluocinonide, Mometasone Furoate, Triamcinolone Acetonide, etc. Low potency topical steroids include Desonide, Fluocinolone acetate, and Hydrocortisone, etc.

Topical corticosteroid is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid responsive dermatoses.

Clobetasol Propionate

Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity. Clobetasol Propionate is a synthetic corticosteroid with anti- inflammatory activity Chemically, Clobetasol Propionate is (11β, 16β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1, 4-diene-3, 20-dione, with the empirical formula $C_{25}H_{32}ClFO_5$, and a molecular weight of 466.98 g/mol. Clobetasol Propionate is a white to cream-colored crystalline powder insoluble in water.

Pharmacology

Like other topical corticosteroids, Clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation Such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A2.

Pharmacokinetics

The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption. Studies performed with Clobetasol propionate cream (emollient) indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

Indications

Clobetasol propionate cream (emollient) is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond two consecutive weeks is not recommended, and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

In the treatment of moderate to severe plaque-type psoriasis, Clobetasol propionate cream (emollient) applied to 5-10% of body surface area can be used up to 4 consecutive weeks. The total dosage should not exceed 50 g per week. When dosing for more than 2 weeks, any additional benefits of extending

treatment should be weighed against the risk of HPA suppression. Treatment beyond 4 consecutive weeks is not recommended.

Most of the topical products are formulated as either creams or ointments. A cream is a topical preparation used for application on the skin. Creams are semi-solid emulsions, which are mixtures of oil and water in which APIs (Active Pharmaceutical Ingredients) are incorporated. They are divided into two types: oil-in-water (O/W) creams which compose of small droplets of oil dispersed in a continuous water phase, and water-in-oil (W/O) creams which compose of small droplets of water dispersed in a continuous oily phase. Oil-in-water creams are user-friendly and hence cosmetically acceptable as they are less greasy and more easily washed with water. An ointment is a viscous semisolid preparation containing APIs, which are used topically on a variety of body surfaces. The vehicle of an ointment is known as ointment base. The choice of a base depends upon the clinical indication of the ointment, and the different types of ointment bases normally used are:

- Hydrocarbon bases, e.g. hard paraffin, soft paraffin
- Absorption bases, e.g. wool fat, bees wax

Both above bases are oily and greasy in nature and this leads to the undesired effects like difficulty in applying & removal from the skin. In addition this also leads to staining of the clothes. Most of the topical products are available as cream formulation because of its cosmetic appeal.

The acidic scale of pH is from 1 to 7, and the base scale of pH is from 7 to 14. Human skins pH value is some where between 4.5 and 6. Newborn baby's skin pH is closer to neutral (pH 7), but it quickly turns acidic. Nature has designed this probably to protect young children's skin, since acidity kills bacteria. As people become older, the skin becomes more and more neutral, and won't kill as many bacteria as before. This is why the skin gets weak and starts having problems. The pH value goes beyond 6 when a person actually has a skin problem or skin disease. This shows that it is necessary to choose topicals that have a pH value close to that of skin of a young adult.

A slight shift towards the alkaline pH would provide a better environment for microorganisms to thrive. Most of the topical products are available as creams. Active compounds in cream formulations are available in ionized state, whereas in case of ointments these are present in non -ionized state. Generally, the cream formulations are the first choice of the formulators in design and development of topical dosage forms, as the cream formulations are cosmetically elegant, and also as the active compound is available in ionized state, and the drug can penetrate the skin layer fast which makes the formulation totally patient friendly.

Rationale for the Use of Clobetasol Propionate and Chitosan Combination

In current dermatological therapy there are some unmet medical needs, which have to be addressed. For example, Dermatological conditions are often caused by allergy accompanied by inflammation, irritation and itching.

Numerous topical treatments are currently employed for the treatment of skin inflammations. However there is no effective therapy for protecting the skin, skin regeneration & rejuvenation, controlling superficial wounds .To meet this need and to bring affordable and safe therapy to the dispersed segment of population across all countries/communities, a therapy with unique combination of Chitosan, a biopolymer with skin regeneration & rejuvenation, wound healing properties with Clobetasol Propionate is proposed as a novel cream.

Clobetasol Propionate provides much wanted rapid relief of the pruritus. Therapy with only Clobetasol Propionate is recommended for severe eczematic eruptions to provide instant relief to patients from itching and burning. Also the monotherapy with Clobetasol Propionate will help in avoiding the allergenic response to antifungals and antibacterials.

The inclusion of Chitosan in the formulation takes care of many attributes, which are considered to be very much essential in treating skin ailments.

The combination of Chitosan with Clobetasol Propionate is unique and novel since this is not available commercially across the globe. The concept of the

combination is justified by considering the Physical, Chemical and Therapeutic properties of Chitosan with Clobetasol Propionate. As Chitosan is a film forming, biocompatible, non-allergenic biopolymer, it protects the skin by acting as a barrier.

In a therapy, Clobetasol Propionate takes care of the inflammation. But the issues like skin protection, mobility of pathogens from one site to another, etc are not addressed so far. This present invention will fill this gap by an innovative technology of incorporating Chitosan and tapping the required benefits of skin protection (by way of film forming property), immobilization of pathogenic microbes (due to its cationic electrostatic property) and wound healing.

Chitosan is regarded as a non-toxic and non-irritant material. It is biocompatible with both healthy and infected skin and has been shown to be biodegradable as it is derived from shrimps and crabs.

Another reason of great biomedical interest is chemical similarity of Chitosan to GlycosAminoGlycans (GAGs). GAGs like Heparin, Heparin sulfate, Hyaluronic acid and Keratin sulfate are all derivatives of 2-amino-2-deoxy-D-glucose) and present in all parts of human body. GAGs are essential building blocks of macromolecular frame work of connective and other tissues. Fetal wounds are

known to heal without scars and this has been attributed to fetal skins being rich in hyaluronic acid (Hyaluronan).

Chitosan/Polyglucosamine is structurally similar to hyaluronan and is expected to assist scarless wound healing. Heparin enhances mitogen by induction and stabilization of fibroblast growth stimulating factor (FGF). Polyglucosamine may promote tissue growth and wound healing by forming complexes with heparin and acting to prolong the half-life of the growth factors.

Chitosan is hypoallergenic, and has natural anti-bacterial properties, further supporting its use.

As a film forming biomaterial, Chitosan helps in reducing the width of the wound, controls the oxygen permeability at the site, absorbs wound discharge and gets degraded by tissue enzymes which are very much required for healing at a faster rate. It also reduces the itching by providing a soothing effect. It also acts like a moisturizer.

The novel cream of the present invention, are most stable/efficacious at ambient conditions and does not need special temperature control during transportation/storage – hence will go a long way in achieving the objectives.

During dermatological conditions, currently available therapies do not address the issues like protecting the skin, arresting the bleeding etc. The unique innovative formulation of the present invention takes care of the skin conditions by treating them along with controlling the superficial bleeding at the site. It is well understood that if the superficial bleeding is left untreated, it will lead to secondary microbial infections. The present invention advantageously provides a solution to this unmet need.

The invention has the following embodiments:

Embodiment 1: A novel dermaceutical cream for topical treatment of skin inflammations, and for related wound healing, wherein said cream comprises Clobetasol Propionate, and a biopolymer provided in a cream base, said cream base comprising at least one of each of a primary and a secondary emulsifier, a waxy material, a co-solvent, a preservative, an acid, and water, preferably purified water.

Embodiment no. 2: A novel dermaceutical cream as disclosed in the embodiment no. 1, wherein said cream further comprising any of a group comprising a buffering agent, an antioxidant, a chelating agent, a humectant, or any combination thereof.

Embodiment no. 3: A novel dermaceutical cream as disclosed in the embodiment no. 1 wherein

- said Clobetasol Propionate is added in an amount between about 0.001% (w/w) and about 5% (w/w), preferably between about 0.01 % (w/w) and about 1% (w/w), and most preferably about 0.05% (w/w) and,
- said biopolymer is in the form of chitosan, added in an amount between about 0.01% (w/w) and about 2.5% (w/w)by weight, and added in an amount preferably from about 0.01% (w/w) to about 2.0% (w/w) and most preferably about 0.5% (w/w) said chitosan being US pharmacopeia conformant with regard to its functional excipient category and selected from any grades such as Long Chain, Medium Chain & Short Chain, and has a molecular weight in the range between 50 kDa to 5000 kDa,
- said primary and secondary emulsifiers are selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Cetyl alcohol, Stearyl alcohol, Isopropyl Myristate, Polysorbate-80, Span-80 and the like from about 1% (w/w) to 25% (w/w); said waxy materials is selected from a group comprising White Soft Paraffin, Liquid Paraffin, Hard Paraffin and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 30% (w/w); said co-solvent is selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400, Isopropyl Myristate and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 50% (w/w); said acid is selected from a group comprising HCl, H_2SO_4, HNO_3,

Lactic acid and the like, or any combination thereof, and added in an amount from about 0.005% (w/w) to 1% (w/w); said preservative is selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid, Phenoxyethanol, Benzyl alcohol and the like, or any combination thereof, and added in an amount from about 0.02% (w/w) to 0.5% (w/w); said water is added in the amount in the range of 10% (w/w) to 75% (w/w), preferably purified water.

Embodiment no. 4: A novel cream as disclosed in the embodiment no. 1 and the embodiment no. 2, further comprising a buffering agent which is selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like, or any combination thereof, and added in an amount from about 0.05% (w/w) to 1% (w/w).

Embodiment no. 5: A novel cream as disclosed in the embodiment no. 1, 2, or 3, further comprising an antioxidant which is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, either singly or any combination thereof, to form a proportion from about 0.001% (w/w) to 5% (w/w),.

Embodiment no. 6: A novel cream as disclosed in the embodiments 1 to 4, further comprising a chelating agent which is selected from a group comprising

Disodium EDTA and the like, or any combination thereof, and added in an amount from about 0.05% (w/w) to 1% (w/w).

Embodiment no. 7: A novel cream as disclosed in the embodiments 1 to 6, further comprising a humectant which is selected from a group comprising Glycerin, Propylene Glycol, Sorbitol, and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 20% (w/w).

Embodiment no. 8: A process of making a cream is disclosed, said process comprising the steps of providing Clobetasol Propionate, and chitosan as a biopolymer in a cream base comprising at least one of each of a primary and a secondary emulsifier, a waxy material, a co-solvent, a preservative, an acid, and water, preferably purified water, and mixing all the ingredients together to form a homogeneous cream.

Embodiment no. 9: A process of making a cream as disclosed in the embodiment no. 8, wherein the ingredients further comprise any of a group comprising a buffering agent, an antioxidant, a chelating agent, a humectant, or any combination thereof.

Embodiment no. 10: A process of making a cream as disclosed in embodiments 7 or 8, wherein said Clobetasol Propionate is provided in an amount between about 0.001% (w/w) to about 5% (w/w) by weight, preferably from about 0.01% (w/w)

to about 1% (w/w) by weight and most preferably about 0.05 % (w/w) by weight, and,

- said chitosan is being provided in an amount between about 0.01% (w/w) to about 2.5% (w/w) by weight, preferably from about 0.01% (w/w) to about 2.0% (w/w) by weight and most preferably about 0.5% (w/w) by weight (Molecular Weight – 50 kDa to 5000 kDa).
- said primary and secondary emulsifier is selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Cetyl alcohol, Stearyl alcohol, Isopropyl Myristate, Polysorbate-80, Span-80 and the like from about 1% (w/w) to 25% (w/w),
- said waxy material is selected from a group comprising White Soft Paraffin, Liquid Paraffin, Hard Paraffin and the like from about 5% (w/w) to 30% (w/w),
- said co-solvent is selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400, Isopropyl Myristate and the like from about 5% (w/w) to 50% (w/w),
- said acid is selected from a group comprising such as HCl, H_2SO_4, HNO_3, Lactic acid and the like from about 0.005% (w/w) to 1% (w/w),
- said preservatives are selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid, Phenoxyethanol, Benzyl alcohol and the like from about 0.05% (w/w) to 0.5% (w/w),

- said water is added in the amount in the range of 10% (w/w) to 75% (w/w), preferably purified water,
- said buffering agents are selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like from about 0.05% (w/w) to 1% (w/w),
- said antioxidant is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, either singly or any combination thereof, to form a proportion from about 0.001% (w/w) to 5% (w/w),
- said chelating agents are selected from a group comprising Disodium EDTA and the like from about 0.05% (w/w) to 1% (w/w),
- said humectants are selected from a group comprising Glycerin, Propylene Glycol, Sorbitol, and the like from about 5% (w/w) to 20% (w/w),

and combining/mixing the above ingredients to make a pharmaceutically acceptable cream.

Embodiment no. 11: A novel cream as disclosed in any of the foregoing embodiments, wherein chitosan has a molecular weight range of 50 kDa to 5000 kDa.

The present invention will be further elucidated with reference to the accompanying examples, which are however not intended to limit the invention in any way whatever.

Examples

Table No.1: Clobetasol Propionate(0.05%) + Chitosan Cream

S.No	Name of the Material	Qty (% w/w)
1	Clobetasol Propionate	0.05
2	Chitosan	0.5
3	Methylparaben	0.2
4	Propylparaben	0.02
5	Cetostearyl Alcohol	7.2
6	Cetomacrogol 1000	1.8
7	White Soft Paraffin	20
8	Liquid Paraffin	10
9	Titanium Dioxide	1
10	Lactic Acid	0.05
11	Propylene Glycol	48
12	Purified Water	11.17

Table No.2: Clobetasol Propionate (0.05%) + Chitosan Cream

S.No	Name of the Material	Qty (% w/w)
1	Clobetasol Propionate	0.05
2	Chitosan	0.5
3	Methylparaben	0.2
4	Propylparaben	0.02
5	Isopropyl myristate	5.0
6	Chlorocresol	0.1
7	Cetostearyl Alcohol	8.5
8	Cetomacrogol 1000	2.5
9	White Soft Paraffin	8.5
10	Liquid Paraffin	5.0
11	Lactic Acid	0.25
12	Propylene Glycol	35.00
13	Purified Water	35.00

The therapeutic efficacy of topically applied innovative anti-inflammatory cream with chitosan is due to the pronounced activity of the active Clobetasol Propionate- corticosteroid against skin inflammations - dermatitis & allergic conditions, the unique ability of actives to penetrate intact skin and skin regeneration & rejuvenation, wound healing and soothing properties of Chitosan.

According to another embodiment of the present invention, there is also provided a process for treating skin inflammations and for skin regeneration & rejuvenation with wound healing involving contacting human skin with the above-disclosed composition.

Experimental Data:

API-stability experiments were carried out (see tables 3 - 11) using the product of the present invention Clobetasol propionate 0.05% cream and reference market product currently available. Tests were carried out to observe (or measure as appropriate) the physical appearance of the product, the pH value and assay of the API over a period of time. Tests were also carried out to assess the stability by subjecting the product to stress studies such as autoclave test and oxidative degradation test. Animal subjects are used to determine the Preclinical studies such as blood clotting studies, Skin inflammatory Studies & human subjects are used to determine the clinical studies such as Skin blanching study, Clinical efficacy studies.

The product used for the Stability Studies, Autoclave and Oxidative degradation tests contained approximately 5.0% extra API (overages). It was packaged in an aluminum collapsible tube. The details of the analysis on commercially available comparable product (Clobetasol Propionate creams) are provided in the tables 13 and 14 as appropriate.

It is apparent from tables 3 -11 that on all counts, the pH value, the physical appearance, and stability, the product of the present invention is quite good.

Table 12 provides reference dates for commercially available creams of Clobetasol propionate and used for analysis.

The present invention will be further elucidated with reference to the accompanying example containing the composition and stability studies data, which are however not intended to limit the invention in any way whatever.

The tests were carried out on Clobetasol propionate cream prepared according to the invention packed in collapsible aluminium tubes and containing Clobetasol propionate 0.05% (w/w).

Table 3: Description test, Batch No. CPC-39

Measured parameter: Physical appearance **Method of measurement:** Observation by naked eye **Best value of measured parameter:** Homogeneous white to off white viscous cream **(C indicates that the results comply with the initial state)**

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	Homogeneous white to off white viscous cream	C	C	C	C	-	-	-	-	-
30°C 65% RH		-	-	C	C	C	C	C	C	C
25°C 60% RH		-	-	C	C	C	C	C	C	C
Temp. cycling		C	-	-	-	-	-	-	-	-
Freeze thaw		C	-	-	-	-	-	-	-	

Table 4: Description test, Batch No. CPC-40

Measured parameter: Physical appearance **Method of measurement:** Observation by naked eye **Best value of measured parameter:** Homogeneous white to off white viscous cream **(C indicates compliance with initial state)**

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	Homogeneous white to off white viscous cream	C	C	C	C	-	-	-	-	-
30°C 65% RH		-	-	C	C	C	C	C	C	C
25°C 60% RH		-	-	C	C	C	C	C	C	C
Temp. cycling		C	-	-	-	-	-	-	-	-
Freeze thaw		C	-	-	-	-	-	-	-	

Table 5: Description test, Batch No. CPC-41

Measured parameter: Physical appearance **Method of measurement:** Observation by naked eye **Best value of measured parameter:** Homogeneous white to off white viscous cream **(C indicates compliance with initial state)**

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	Homogeneous white to off white viscous cream	C	C	C	C	-	-	-	-	-
30°C 65% RH		-	-	C	C	C	C	C	C	C
25°C 60% RH		-	-	C	C	C	C	C	C	C
Temp. cycling		C	-	-	-	-	-	-	-	-
Freeze thaw		C	-	-	-	-	-	-	-	

Table 6: pH test, Batch No. CPC-39

Measured parameter: pH **Limit of measured parameter:** 4.0 – 7.0

Method of measurement: Digital pH meter

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	4.83	4.89	4.87	4.87	4.73	-	-	-	-	-
30°C 65% RH		-	-	4.88	4.75	4.87	4.86	5.00	4.90	4.77
25°C 60% RH		-	-	4.96	4.72	4.83	4.82	5.03	4.82	4.75
Temp. cycling		4.81	-	-	-	-	-	-	-	-
Freeze thaw		4.83	-	-	-	-	-	-	-	-

Table 7: pH test, Batch No. CPC-40

Measured parameter: pH **Limit of measured parameter:** 4.0 – 7.0

Method of measurement: Digital pH meter

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	4.86	4.88	4.88	4.82	4.78	-	-	-	-	-
30°C 65% RH		-	-	4.85	4.83	4.83	4.85	4.72	4.78	4.61
25°C 60% RH		-	-	4.67	4.63	4.73	4.84	4.92	4.80	4.69
Temp. cycling		4.85	-	-	-	-	-	-	-	-
Freeze thaw		4.88	4.88	4.82	4.78	-	-	-	-	-

Table 8: pH test, Batch No. CPC-41

Measured parameter: pH **Limit of measured parameter:** 4.0 – 7.0

Method of measurement: Digital pH meter

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	4.71	4.66	4.79	4.82	4.78	-	-	-	-	-
30°C 65% RH		-	-	4.88	4.88	4.86	4.76	4.86	4.81	4.64
25°C 60% RH		-	-	4.87	4.86	4.78	4.70	4.87	4.73	4.58
Temp. cycling		4.69	-	-	-	-	-	-	-	-
Freeze thaw		4.73	-	-	-	-	-	-	-	-

Table 9: Assay % test, Batch No. CPC-39

Measured parameter: Assay (%) **Limit of measured parameter:** 90 – 110 %

Method of measurement: HPLC method

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	104.85	104.49	103.79	103.97	103.27	-	-	-	-	-
30°C 65% RH		-	-	104.16	104.08	103.83	103.44	102.94	101.80	101.93
25°C 60% RH		-	-	104.24	104.20	104.05	103.47	102.75	102.55	102.36
Temp. cycling		104.63	-	-	-	-	-	-	-	-
Freeze thaw		103.98	-	-	-	-	-	-	-	-

Table 10: Assay % test, Batch No. CPC-40

Measured parameter: Assay (%) **Limit of measured parameter:** 90 – 110 %

Method of measurement: HPLC method

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	104.35	104.24	103.98	103.80	103.63	-	-	-	-	-
30°C 65% RH		-	-	104.21	103.95	103.50	102.94	102.50	102.12	101.69
25°C 60% RH		-	-	104.19	103.80	103.63	102.89	125.70	102.40	101.40
Temp. cycling		104.45	-	-	-	-	-	-	-	-
Freeze thaw		104.31	-	-	-	-	-	-	-	-

Table 11: Assay % test, Batch No. CPC-41

Measured parameter: Assay (%) **Limit of measured parameter:** 90 – 110 %

Method of measurement: HPLC method

Condition	Initial	1st Mth	2nd Mth	3rd Mth	6th Mth	9th Mth	12th Mth	18th Mth	24th Mth	36th Mth
40°C 75% RH	104.78	104.15	103.32	103.02	102.98	-	-	-	-	-
30°C 65% RH		-	-	104.06	104.24	103.77	103.75	102.64	102.38	101.58
25°C 60% RH		-	-	104.29	104.01	103.57	103.46	103.25	102.57	102.42
Temp. cycling		104.98	-	-	-	-	-	-	-	-
Freeze thaw		105.26	-	-	-	-	-	-	-	-

Table No. 12: Product Details

Sample No	Mfg Date	Expiry Date
Present invention	May'2011	Apr'2014
Market product	Jun'2011	Nov'2012

Table 13: Autoclave analysis (%) test

Measured parameter: Assay (%) **Method of measurement:** HPLC method

S.No	Name of the Products	Analysis-I (%)			Analysis-II (%)			Average Drop of Analysis-I and Analysis – II (%)
		Initial	After Autoclave	Drop	Initial	After Autoclave	Drop	
1	Present Invention	104.86	105. 05	-0.19	105.12	104.56	0.56	0.18
2	Market product	100.56	98.56	2.33	100.16	98.29	1.87	2.1

Table No. 14: Oxidative analysis (%) Test
Measured parameter: Assay (%)
Method of measurement: HPLC Method

S.No	Name of the Products and Details	Analysis-I (%)		
		Initial	After Oxidation	Degradation in %
1	Present invention	104.86 %	105. 48 %	-0.62
2	Market Product	100.56 %	98.89 %	1.67

Inference from Table 13: The assay results of Autoclave analysis (121°C applied for 15 Minutes) indicate that the commercially available sample of Clobetasol propionate cream (S. No. 2) show more percentage drop in API content than for the product of the present invention (S. No. 1).

Inference from Table 14: The above Assay results of Oxidative degradation analysis (10% Hydrogen peroxide Solution at 60°C for 1 hour) indicate that the Market sample of Clobetasol propionate cream (S. No. 2) show significantly higher API degradation (indicated by the percentage drop in API content) than for the product of the present invention (S. No. 1).

From the above data, it is evident that product of the present invention is quite stable at ambient conditions and also at elevated temperature & humid conditions of storage. Also the autoclave studies & Oxidative degradation studies further confirm the stability of the product. The stability of the product is further ascertained by the shelf-life prediction of the formulation using Arrhenius plot of degradation employing Nova-LIMS software.

Method of Application of the Cream

Apply a thin layer of Clobetasol Propionate cream USP 0.05% (w/w) to the affected areas with once or twice daily and rub in gently and completely wash hands after each application.

Clobetasol Propionate Cream USP 0.05% (w/w) is a super high potency topical corticosteroid; therefore, treatment should be limited to 2 consecutive weeks and amounts greater than 50 grams per week should not be used.

Experiments

Experiments were carried out with the cream in laboratory as well as various CROs using suitable animal models and human voluntaries. The following aspects were tested – Blood clotting time, film forming, skin inflammatory, acute dermal irritation, vasoconstrictor effect and clinical efficacy.

A. Blood Clotting

Blood clotting time was observed in both groups of animals, untreated control group and the test group of animals treated with the product of the present invention. Statistically significant decrease in the blood clotting time in treated group animals was observed when compared with that of the control group

animals. The mean percent reduction of 34.96% was observed for the blood clotting time using the product of the present invention.

B. Film Forming Properties

It was found that chitosan does not lose its film forming property in the presence of the excipients used for cream preparations in the present invention.

It is evident that the properties of chitosan when used in formulations containing the excipients used in the current invention are not compromised in any way. This has been achieved through a careful selection of excipients.

C. Diffusion Study

Diffusion study was done to performed drug release studies using Keshary Chein apparatus. The percentage of drug release was found in the invention cream compared with the reference market product 44.40% and 34.36% at the end of 8 hours respectively. The results indicated that the invention product had higher release rate compared to the market reference product and their release rates were found to be 0.071/hr for invention product and 0.041/hr for reference market product.

D. Skin inflammatory Study

The Skin inflammatory Study was concluded statically that the Croton oil application in to ear of rats has produced 70% edema in control group. The

present invention formulations of Clobetasol Propionate Cream and market Cream have reduced the edema produced by croton oil. The highest reduction in edema is by Clobetasol Propionate Cream (invention) (13.20±2.84). The market Cream has reduced the edema by 39.12±11.15 only. The percentage of protection is highest with present invention Cream of Clobetasol Propionate Cream (81.36%) compared to market product (44.77%).

Table No. 15: Effect of different formulations of Clobetasol propionate cream on croton oil induced skin edema.

GROUP	Number of animals	EDEMA % (MEAN±SEM)	p value	Protection (%)
Control	10	70.84±3.41	-	-
Clobetasol Propionate Cream	10	13.20±2.84	.000	81.36
Conventional Market Product	10	39.12±11.15	.021	44.77

E. Vasoconstrictor In-vivo Bioequivalence Study

Skin Blanching study of the Clobetasol propionate cream of the present invention comparing reference market product was determined through a randomized double blind Parallel group. The 90% CI value found to be a 97.63-102.975 it's within the limit range hence the invention Cream formulation are bioequivalent with the Market cream.

Further a pilot bioequivalence study was done by comparison of vasoconstriction effect on present invention Cream of Clobetasol propionate with the reference

market cream. The results showed that the test product of Clobetasol propionate and the reference market cream tend towards bioequivalent.

F. Acute dermal irritation study

The primary skin irritation is the production of reversible damage in the skin. Topical exposure of chemicals, drugs etc., can lead to the adverse skin effects. According to the severity and reversibility of effects, the products can be distinguished into irritant or corrosive. So the experimental study was performed to assess the possible hazard likely to arise from exposure of this topical formulation to the human skin. Thus primary skin irritation study was carried out for the newly formulated dermal cream - Clobetasol Propionate Cream (invention) to determine its irritant response to the skin after single exposure. From the experimental study it was concluded that the formulation of Clobetasol Propionate Cream (invention) scored the primary skin irritation index of 0. Hence the Clobetasol Propionate Cream (invention) is non-irritant and dermal-friendly.

G. Clinical trial

A randomized, parallel group, double blinded active controlled clinical trial comparing efficacy of Clobetasol propionate 0.05% cream

a) Visual Analog Scale score clearly indicates that severity of wound is lesser in test group.

b) Summary statistics of Global Score Index data shows that, 40 % of study population has normal, clear skin with no evidence of eczema from the

group received test product cream where as only 10 % with reference product conventional cream

c) Summary statistics of patient's compliance confirmed that 60 % of study population has achieved score zero i.e. absence of signs of itching or indication of pain from the group, that received innovated cream, but only 20% of study population achieved with reference product conventional cream.

d) Physician global evaluation score (PGES) shows that 80 % population from group, that received invention product cream achieved good and excellent results but only 20 % achieved good and excellent results with conventional market product.

Based on the statistical results obtain from this study it is concluded that, Clobetasol propionate 0.05 % cream of invention and reference market Cream of (Clobetasol propionate 0.05 %) are clinically equivalent.

Results and Discussion

It is evident that the properties of chitosan when used in formulations containing the excipients used in the current invention are not compromised in any way. This has been achieved through a careful selection of excipients. For example, our experiments show that widely used excipients such as xanthan gum or carbomer precipitate in combination with chitosan due to cationic, anionic interactions. The

therapeutic impact, as observed from the testing, of the addition of chitosan to the cream, is shown in the following table by considering various aspects of therapeutic cure of a compromised skin condition:

Table No. 16

Therapeutic aspect	**Existing creams**	**Products of the present invention**
1. Blood Clotting time	None explicitly claimed	Statistically significant reduction in clotting time as evidenced by pre-clinical animal trials
2. Immobilization of microbes	None explicitly claimed	Expected to immobilize the surface microbes because of the cationic charge of chitosan
3.Micro-Film Forming Property	None explicitly claimed	Its Having an Excellent film forming activity (see figure 1)
4.Diffusion Study	None explicitly claimed	Invention product had higher release rate compared to the market reference product
5. Skin inflammatory Study	Standards as per Existing Products	Highest Percentage of reduction in Skin inflammatory of in-vivo animal studies
6. Vasoconstrictor In-vivo Bioequivalence study	Standards as per Existing Products	Statically bioequivalent with the healthy human voluntaries
7. Acute dermal irritation study	Standards as per Existing Products	The study shows that the formulation of present invention is non-irritant and dermal-friendly when applied to the skin
8. Clinical Efficacy Study	Standards as per Existing Products	Statically Clinical equivalent with the market product in human voluntaries

The therapeutic efficacy of topically applied cream of the present invention is due to the pronounced anti-inflammatory pruritic manifestations of corticosteroid responsive dermatoses & soothing properties of chitosan.

It is evident from the foregoing discussion that the present invention offers the following advantages and unique aspects over the currently available dermaceutical compositions for anti-inflammatory and pruritic manifestations of corticosteroid responsive dermatoses of the skin:

1. The cream of the present invention incorporates a skin-friendly biopolymer in the form of chitosan provides enhanced therapeutic outcomes.
2. The cream of the present invention incorporates a biopolymer without compromising the stability of the cream matrix and without adversely affecting the functioning of known active pharmaceutical ingredients. This has been achieved through a careful selection of functional excipients to bypass undesirable aspects of physiochemical compatibility/stability and bio-release.
3. The cream of the present invention provides an integrated unit-dose or a single-dose therapy hitherto unavailable in prescription dermaceutical formulations.
4. The novel cream of the present invention is adequately stable / efficacious at ambient conditions and does not need special temperature control during transportation/storage – hence will go a long way in achieving these social objectives.

While the above description contains much specificity, these should not be

construed as limitation in the scope of the invention, but rather as an exemplification of the preferred embodiments thereof. It must be realized that modifications and variations are possible based on the disclosure given above without departing from the spirit and scope of the invention. Accordingly, the scope of the invention should be determined not by the embodiments illustrated, but by the appended claims and their legal equivalents.

Claims:

1. A dermaceutical cream for topical treatment of skin inflammations, and for related wound healing, wherein said cream comprises Clobetasol Propionate, and a biopolymer provided in a cream base, said cream base comprising at least one of each of a primary and a secondary emulsifier, a waxy material, a co-solvent, a preservative, an acid, and water, preferably purified water.

2. A dermaceutical cream as claimed in claim 1, characterized in that said cream further comprising any of a group comprising a buffering agent, an anti-oxidant, a chelating agent, a humectant, or any combination thereof.

3. A dermaceutical cream as claimed in claims 1 or 2, characterized in that
   - said Clobetasol Propionate is added in an amount between about 0.001% (w/w) and about 5% (w/w), preferably between about 0.01 % (w/w) and about 1% (w/w), and most preferably about 0.05% (w/w) and,
   - said biopolymer is in the form of chitosan, added in an amount between about 0.01% (w/w) and about 2.5% (w/w) by weight, and added in an amount preferably from about 0.01% (w/w) to about 2.0% (w/w) and most preferably about 0.5% (w/w), said chitosan being US pharmacopeia conformant with regard to its functional excipient

category and selected from any grades such as Long Chain, Medium Chain & Short Chain, and has a molecular weight in the range between 50 kDa to 5000 kDa,

- said primary and secondary emulsifiers are selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Cetyl alcohol, Stearyl alcohol, Isopropyl Myristate, Polysorbate-80, Span-80 and the like from about 1% (w/w) to 25% (w/w);
- said waxy materials is selected from a group comprising White Soft Paraffin, Liquid Paraffin, Hard Paraffin and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 30% (w/w);
- said co-solvent is selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400, Isopropyl Myristate and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 50% (w/w);
- said acid is selected from a group comprising HCl, H_2SO_4, HNO_3, Lactic acid and the like, or any combination thereof, and added in an amount from about 0.005% (w/w) to 1% (w/w);
- said preservative is selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid, Phenoxyethanol, Benzyl alcohol and the like, or any combination

thereof, and added in an amount from about 0.02% (w/w) to 0.5% (w/w);

- said water is added in the amount in the range of 10% (w/w) to 75% (w/w), preferably purified water.

4. A dermaceutical cream as claimed in any of claims 1 to 3, characterized in that it further comprises a buffering agent which is selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like, or any combination thereof, and added in an amount from about 0.05% (w/w) to 1% (w/w).

5. A dermaceutical cream as claimed in any of claims 1 to 4, characterized in that it further comprises an anti-oxidant, wherein said anti-oxidant is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, either singly or any combination thereof, to form a proportion from about 0.001% (w/w) to 5% (w/w),

6. A dermaceutical cream as claimed in any of claims 1 to 5, characterized in that it further comprises a chelating agent which is selected from a group comprising Disodium EDTA and the like, or any combination thereof, and added in an amount from about 0.05% (w/w) to 1% (w/w).

7. A dermaceutical cream as claimed in any of claims 1 to 6, characterized in that it further comprises a humectant which is selected from a group comprising Glycerin, Propylene Glycol, Sorbitol, and the like, or any

combination thereof, and added in an amount from about 5% (w/w) to 20% (w/w).

8. A process of making a dermaceutical cream, characterized in said process comprises the steps of providing Clobetasol Propionate, and chitosan as a biopolymer in a cream base comprising at least one of the components selected from a group comprising a primary and a secondary emulsifier, a waxy material, a co-solvent, a preservative, an acid, and water, preferably purified water, and mixing all the ingredients together to form a homogeneous cream.

9. A process as claimed in claim 8, characterized in that the list of components further comprises any of the components selected from a group comprising a buffering agent, an antioxidant, a chelating agent, a humectant, or any combination thereof.

10. A process as claimed in any of claims 7 to 9, characterized in that

- said Clobetasol Propionate is provided in an amount between about 0.001% (w/w) to about 5% (w/w) by weight, preferably from about 0.01% (w/w) to about 1% (w/w) by weight and most preferably about 0.05 % (w/w) by weight, and,
- said chitosan is being provided in an amount between about 0.01% (w/w) to about 2.5% (w/w) by weight, preferably from about 0.01% (w/w) to

about 2.0% (w/w) by weight and most preferably about 0.5% (w/w) by weight (Molecular Weight – 50 kDa to 5000 kDa).

- said primary and secondary emulsifier is selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Cetyl alcohol, Stearyl alcohol, Isopropyl Myristate, Polysorbate-80, Span-80 and the like from about 1% (w/w) to 25% (w/w),
- said waxy material is selected from a group comprising White Soft Paraffin, Liquid Paraffin, Hard Paraffin and the like from about 5% (w/w) to 30% (w/w),
- said co-solvent is selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400 and the like from about 5% (w/w) to 50% (w/w),
- said acid is selected from a group comprising such as HCl, H_2SO_4, HNO_3, Lactic acid and the like from about 0.005% (w/w) to 1% (w/w),
- said preservatives are selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid, Phenoxyethanol, Benzyl alcohol and the like from about 0.02% (w/w) to 0.5% (w/w),
- said water is added in the amount in the range of 10% (w/w) to 75% (w/w), preferably purified water,

- said buffering agents are selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like from about 0.05% (w/w) to 1% (w/w),
- said antioxidant is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, either singly or any combination thereof, to form a proportion from about 0.001% (w/w) to 5% (w/w),
- said chelating agents are selected from a group comprising Disodium EDTA and the like from about 0.05% (w/w) to 1% (w/w),
- said humectants are selected from a group comprising Glycerin, Propylene Glycol, Sorbitol, and the like from about 5% (w/w) to 20% (w/w),

and combining/mixing the above ingredients to make a pharmaceutically acceptable cream.

11. A dermaceutical cream as claimed in any of claims 1 to 7, wherein said chitosan has a molecular weight range of 50 kDa to 5000 kDa.

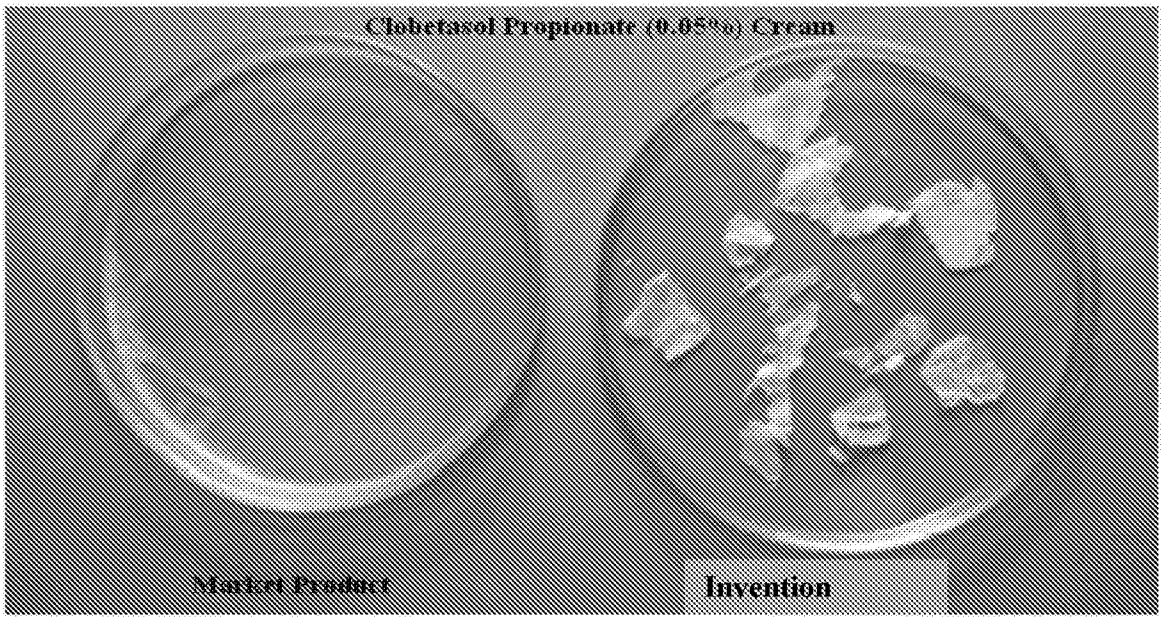
Clobetasol Propionate (0.05%) Cream
Market Product
Invention

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053257

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/36 A61K9/107 A61K31/573 A61P17/02
ADD.

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)
EPO-Internal, BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/109425 A2 (VANANGAMUDI SULUR SUBRAMANIAM [IN]; SRINIVASAN MADHAVAN [IN]; CHULLIEL) 30 September 2010 (2010-09-30) page 7, lines 11-19 page 12, line 5 - page 13, line 9 page 13, line 13 - page 14, line 7 page 29; table 7 claims -----	1-11
X	WO 2012/017372 A1 (VANANGAMUDI SULUR SUBRAMANIAM [IN]; SRINIVASAN MADHAVAN [IN]; CHULLIEL) 9 February 2012 (2012-02-09) page 15, lines 7-17 page 27, line 16 - page 28, line 15 page 32, line 9 - page 34, line 10 page 70; table 9 -----	1-11

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[X] Further documents are listed in the continuation of Box C.

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20 September 2016	28/09/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	van de Wetering, P

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053257

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SENYIGIT T ET AL: "Different approaches for improving skin accumulation of topical corticosteroids", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 380, no. 1-2, 1 October 2009 (2009-10-01), pages 155-160, XP026715213, ISSN: 0378-5173, DOI: 10.1016/J.IJPHARM.2009.07.018 [retrieved on 2009-07-25] page 156, right-hand column, paragraph 2.1.-2.2. -----	8-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/053257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010109425 A2	30-09-2010	EP 2411014 A2	01-02-2012
		US 2012022019 A1	26-01-2012
		WO 2010109425 A2	30-09-2010
WO 2012017372 A1	09-02-2012	NONE	