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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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(54) Title: A MEDICINAL FUSIDIC ACID CREAM MADE USING SODIUM FUSIDATE, A CORTICOSTEROID, AND AN ANTIFUNGAL AGENT, AND INCORPORATING A BIOPOLYMER, AND A PROCESS TO MAKE IT

(57) Abstract: The present invention is directed to a medicinal composition for treating skin inflammations, fungal/bacterial skin infections and related wounds, and also other skin wounds including those caused by burns. The cream also causes skin rejuvenation through an epithelisation process. The cream comprises a) a biopolymer in the form of Chitosan, b) active Pharmaceutical Ingredients (APIs), in the form of fusidic acid that has been generated in situ from sodium fusidate, Mometasone furoate & Miconazole nitrate, c) a cream base containing primary and secondary emulsifiers, waxy materials, co-solvents, acids, preservatives, buffering agents, anti oxidants, chelating agents, and humectants, and d) water. The active ingredients, namely chitosan, Mometasone furoate, Miconazole nitrate and fusidic acid, are incorporated in cream base for use in treating skin inflammations, fungal/bacterial skin infections with allergy & itching, & wounds on human skin involving contacting human skin with the above identified composition. Fusidic acid of the cream is made in situ from Sodium Fusidate as the starting raw material, under oxygen- free environment.

A medicinal fusidic acid cream made using sodium fusidate, a corticosteroid, and an antifungal agent, and incorporating a biopolymer, and a process to make it

Field Of Invention

The present invention relates to primary and secondary bacterial skin infections, skin inflammations, fungal skin infections and wounds including burn wounds. In particular it relates to a cream incorporating fusidic acid and a biopolymer in the form of chitosan, a corticosteroid in the form of Mometasone Furoate, and an antifungal agent in the form of Miconazole nitrate, and the process of making it and using it in treating these infections, inflammations and wounds. Furthermore the Fusidic acid in the said cream has been created in situ using Sodium Fusidate as the starting Active Pharmaceutical Ingredient (API).

Background of invention:

Numerous treatments, both topical and systemic, are available for the primary and secondary skin infection caused by sensitive Gram +ve organisms such as Staphylococcus aureus, Streptococcus spp etc. Topical and systemic bacterial infection treatment compositions typically employ at least one active pharmaceutical ingredient (API) in combination with a base component. In the cream form, the APIs typically comprise an antibiotic/antibacterial such as Fusidic acid and the like.

In the currently available Fusidic acid creams, Fusidic acid in fine powder form is used as source API. The small particle size enhances its dermal contact by providing a large specific surface area and penetration, and provides a smooth feel on application to skin. However, a serious shortcoming of the fine size of Fusidic acid particles is that it presents an enormous surface area for contact and reaction with molecular Oxygen during manufacture, handling, and processing of the cream. This has serious implications to its chemical stability and results in rapid reduction in potency of the API (Fusidic acid) in the final cream formulation.

Degradation due to oxidation is a major cause of instability of currently available Fusidic acid creams. Table 1 show that the degradation in the API samples (Fusidic acid) exposed to oxygen ranged between 7.7 % and 11% for conditions ranging from room temperature to 45 ^{o}C when analysed at three months of exposure period at the above conditions.

It is known that greater the exposure time of Fusidic acid as the raw API to Oxygen, greater the limitations on stabilising Fusidic acid in a formulation. However, there is no published data on the stability of Fusidic acid over a period of time.

As an alternative to Fusidic acid, Sodium Fusidate is known to have been used to make dermaceutical medicaments for topical application. However, these are in the form of ointment rather than cream. Drawbacks of ointments over creams are

well known and it's generally preferable to use creams rather than ointments for topical application.

Several aspects of Fusidic acid as an API are known:

- It is thermolabile
- It is available in cream formulations
- It can be obtained from Sodium Fusidate by dissolving the latter in an aqueous phase and adding acid to the solution, whereby Fusidic acid precipitates. However, the Fusidic acid precipitate is difficult to process into a cream form first due to its coarse and uneven particle size and second retrieving Fusidic acid from wet cake involves drying and further handling which deteriorates the Fusidic acid due to exposure to oxygen
- The stability of the API in a Fusidic acid cream is unreliable due to the thermolabile nature of Fusidic acid

Stabilization of medicaments containing Fusidic acid against oxidation involves observing a number of stringent precautionary procedures during manufacture and storage. These include:

- replacing Oxygen in pharmaceutical containers with inert gases such as Nitrogen, Carbon dioxide, Helium and the like
- avoiding contact of the medicament with heavy metal ions which catalyze oxidation,

- storing the API at reduced temperatures throughout its shelf life before processing

In practice this means stricter controls during the manufacture as well as storage of such API (storing it typically at 2°C to 8°C in air-tight containers throughout their shelf life).

There is therefore a need to provide a process of making a Fusidic acid cream in which Fusidic acid will be of greater stability than the stability of the Fusidic acid in the conventional creams, particularly at the time of the manufacture of the cream, and which will sustain its stability at an acceptable level throughout its shelf life.

Next, let us look at the types of skin disorders and the methods of treatment available for them. Skin disorders can be broadly categorized as those arising from bacterial forms or fungi. Antifungal or antibacterial compositions are traditionally applied as lotions, creams or ointments. Furthermore in many instances, it is difficult to ascertain whether the skin condition is due to a bacterial agent or a fungus.

One approach to treating skin disorders is through elimination by trial and error. Antibacterial or antifungal compositions are applied in turn and response monitored and treatment modified. A major disadvantage of this approach is that treatment needs to be applied many times a day during the treatment period. This

is greatly inconvenient and also not cost effective for a majority of human population, particularly in the under-developed nations.

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There are several treatments available to treat skin disorders caused by bacteria or fungi. Typically, such compositions use steroids, antibacterial agents or antifungal agents, (or a fixed dose combination of these) and focus on these pharmaceutically active ingredients. The composition of such formulations is such as to enhance their physical/chemical/bio-release profile.

Many skin disorders caused by inflammation and fungal/bacterial attacks lead to itching and subsequent scratching, which, among other causes, can in turn lead to serious and complicated secondary infections. The conventionally available treatments do not focus on skin healing or rejuvenation; normally these two aspects are left to heal naturally.

The word healing as related to compromised skin conditions (cuts, wounds, infections, inflammations, abrasions, etc.) are not only about prevention, control, elimination of the source cause such as bacteria or fungi but also to restore the skin to its pre-infection state.

The current approaches of skin treatment can be broadly categorized into two stages, a. healing b. restoration of skin to pre-ailment state. The healing part comprises elimination, to the best possible extent, of the root cause of the

disorder. This may be elimination of bacteria or fungi causing the infection through a suitable treatment of antibacterial or antifungal agents or reducing the inflammation through steroid treatment. While this treatment is under way, the ongoing compromised condition of the skin continues to be susceptible to secondary infections which can be of quite serious nature. In the case of scratched or wounded skin, it is important for blood clotting to occur quickly as it reduces chances of secondary infections. The focus of such treatments, which are administered through creams, lotions, ointments is on the action of active pharmaceutical ingredients. Cream bases or ointment bases are merely viewed as carriers to take APIs to the sites of disorder.

However, the aspect of restoring the skin back to its pre-disorder state is almost completely left to nature. Therefore one key drawback of the existing skin treatment approaches is that they run the risk of secondary infections due to slow blood clotting and wound healing process.

Furthermore, from the study of the prior art several lacking aspects of the existing prescription derma products used for topical treatment of skin disorders. This is manifested by the fact that the cream base matrix or the ointment base has been overlooked for any potential therapeutic benefits. In particular none of the available prior art suggests that:

- Topical skin formulations can deliver skin healing or regeneration beyond the activity of the main APIs such that the therapeutic outcome of the main APIs is enhanced.
- The addition of biologically active polymers (the so-called biopolymers) is a complex process in which the stability of the formulations could be compromised if the right biopolymer or naturally interacting formulation excipients or process parameters are not well thought through and optimized to enhance and complement therapy outcomes at the drug design stage itself.
- Incorporation of a functionally bio-active excipient polymer in cream matrix while retaining the functional stability of the API in a *single dose format* of dermaceutical cream involves resolution of problems specific to the physical stability of cream matrix.

A look at some of the existing patents illustrates the above points. Fusidic acid has been used in cream form. The PCT application WO 2009063493 discloses a combination therapy of a topical antibiotic and a topical steroid for the treatment of inflammatory dermatoses associated with secondary bacterial infections. In particular it relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, psoriasis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin. In

particular it claims to relate to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in prevention of infection in cases of dermatitis, especially atopic dermatitis sufferers who are at risk of getting secondary bacterial infection.

The application claims to derive inventiveness on the assertion that the then existing prior art failed to disclose the composition comprising a combination of fusidic acid with corticosteroids especially Mometasone or Halobetasol. The inventors of WO 2009063493 apparently surprisingly found that antibiotic action of fusidic acid and the anti-inflammatory effect of corticosteroid, such as Mometasone both play important roles in reducing S. aureus and improving patient's symptoms and signs of skin inflammatory infections. The inventors of WO 2009063493 also apparently surprisingly found that antibiotic action of fusidic acid and the anti-inflammatory effect of a corticosteroid such as Halobetasol, both play important roles in prevention of secondary bacterial infections in patients with non-infected dermatoses and in treatment of infected steroid responsive dermatoses such as secondarily infected dermatoses including secondarily infected contact dermatitis, allergic contact dermatitis, atopic dermatitis, psoriasis and other corticosteroid responsive dermatoses (CRD) with secondary bacterial infections of skin.

Let us now look at the way the various active ingredients such as Mometasone Furoate and Miconazole Nitrate are used conventionally.

The invention disclosed in WO 2009063493 relates to a combination therapy of a topical antibiotic and a topical steroid for the treatment of inflammatory dermatoses associated with secondary bacterial infections. In particular the present invention relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in treatment of infected eczema's such as secondarily infected dermatitis, including secondarily infected contact dermatitis, psoriasis, allergic contact dermatitis and atopic dermatitis with secondary bacterial infections of skin. In particular the present invention also relates to topical pharmaceutical compositions comprising a combination of fusidic acid and corticosteroid such as Mometasone furoate useful in prevention of infection in cases of dermatitis, especially atopic dermatitis sufferers who are at risk of getting secondary bacterial infection

EP1787652 relates to a composition with antifungal properties, against foot fungus. The invention comprises the use of Melaleuca Alternifolia essential oil in combination with at least one component chosen from the group consisting of miconazole nitrate, benzoic acid and sodium benzoate. EP1787652 claims novelty on the assertion that the composition according to this invention has an improved antifungal effect and can be used for both preventive and therapeutic applications. Apparently it is advantageous if the composition comprises 2 to 8% by weight of Melaleuca Alternifolia essential oil and 0.5 to 1% by weight of a benzoate

compound relative to the total composition. At this concentration an optimum level is achieved between antifungal activity and economic use of Melaleuca Alternifolia essential oil and benzoate compound.

US 20020009422 relates to a tanning product that treat tinea versicolor and promote tanning. The product includes the active ingredients tolnaftate and miconazole nitrate. US 20020009422 claims novelty on the assertion that the product manages to overcome few problem faced by conventionally used therapeutic like unpleasant smell, dry and rough skin caused by the conventional treatment. The applicant has devices a system for treating tinea versicolor which consists of three systems; a body wash having a mixture of a shampoo, an exfoliate and tolnaftate cream; a tanning lotion and anti-fungal topical having mixture of a lotion, a tanning bronzer and a miconazole nitrate; and body spray having a mixture of a liquid tan enhancing body spray and tolnaftate cream.

US 4911932 describes a skin care composition having improved effectiveness in preventing and treating acute inflammatory skin conditions. The composition consists of miconazole nitrate and zinc oxide. US 4911932 claims novelty on the assertion that the formulation is an improved skin care compositions, which can be used for the prevention and treatment of diaper rash. According to the applicant, the improvement in the formulation is achieved

because of the synergistic combination of active ingredients, 0.25% of miconazole nitrate and zinc oxide. The composition of the invention may be added in either aqueous or oleaginous media. A thickener or stabilizer is added to prevent settling of the synergistic combinations and the resulting non-uniformity of the finished product upon standing.

CN 1931164 deals with the nanometer miconazole nitrate emulsion medicine which consist of surfactant, oil, miconazole nitrate and distilled water. The application claims novelty on the assertion that the nanometer miconazole nitrate emulsion has high skin permeability, no contamination to clothing, high dissolubility of miconazole nitrate, raised bioavailability of miconazole nitrate, delayed metabolism time and wide medicine market foreground.

US 5,461,068 pertains to improved formulations for topical treatment of fungal diseases, and more particularly to solutions of imidazole derivatives such as miconazole nitrate of sufficient strength and stability for pharmaceutical use The said composition can accommodate a therapeutically significant concentration of the antifungal agents; thereby increasing the stability of the antifungal agents in solution for extended periods of time. The solvent system comprises a primary carboxylic acid, a polar solvent, a solubilizer, a non-ionic or amphoteric surfactant, and water, in which imidazole derivatives can be dissolved.

US 6,001,864 deals with an antifungal composition wherein an imidazole-type antifungal compound in the form of miconazole nitrate is combined with a quaternary ammonium salt. It is claimed that the miconazole nitrate is more potentiated active and has higher therapeutic effect. The composition is effective against both Trichophyton and Candida. The applicant also claims on the bases that combination disclosed in the present application has never been used before.

It is evident from the above example and other similar sources that the existing prior art does not teach or suggest the use of fusidic acid, mometasone furoate, Miconazole nitrate and chitosan in a single product. Furthermore none of the above citations teaches or suggests:

- Use of the cream base matrix as a functional element of the cream rather than a mere carrier for the main APIs
- Use a known bio-polymer as a functional excipient along with anti bacterial agent Sodium Fusidate
- Providing far superior healing effects as micro-film forming, blood clotting, supporting epidermal growth, microbial electrostatic immobilization take effect simultaneously rather than one after the other as would be the case in conventional single-drug therapy
- Improve overall medicinal properties of the cream, complimenting the API used in the cream matrix

There is therefore a need for a single-dose API topical treatment that will be provided in a cream base, which cream base provides therapeutical value complementary to that provided by the main APIs and serves the purpose over and above that of being a mere carrier or delivery mechanism.

Objects and advantages of invention

It is therefore one object of the present invention to provide a process of making a medicinal cream which contains Fusidic acid as the active API but which has greater stability of the API than the Fusidic acid manufactured using other means, throughout its shelf life, and also containing Mometasone furoate as a steroid, Miconazole nitrate as an antifungal using a functional cream base that contains chitosan that will provide an effective treatment against bacterial infections and also help actively heal the skin rejuvenate.

Another object of the present invention is to provide a medicinal cream that is effective in treatment of skin inflammations, bacterial/fungal skin infections, wounds including burn wounds.

Further objects of the present invention are to provide prescription medicinal formulations for topical skin treatment that:

- Can deliver skin healing or regeneration beyond the activity of Sodium Fusidate, Mometasone furoate & Miconazole nitrate such that the therapeutic outcome of the main APIs are enhanced.

- Contain biologically active polymers (the so-called biopolymers) without compromising the stability of the formulations could be compromised if the right biopolymer is not selected.
- Incorporate a functionally bio-active excipient polymer in cream matrix while retaining the functional stability of the API in a single dose format

Brief Description Of Figures:

Figure 1 – Non-homogeneous nature of creams containing chitosan with non-compatible excipient such as carbomer

Figure 2 – Film formation using chitosan

Summary of invention

The present invention is directed to a medicinal composition for treating skin inflammations, fungal/bacterial skin infections and related wounds, and also other skin wounds including those caused by burns. The cream also causes skin rejuvenation through an epithelisation process. The cream comprises:

a) a biopolymer in the form of Chitosan

b) active Pharmaceutical Ingredients (APIs), in the form of fusidic acid that has been generated in situ from sodium fusidate, Mometasone furoate & Miconazole nitrate

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, namely chitosan, Mometasone furoate, Miconazole nitrate and fusidic acid, are incorporated in cream base for use in treating skin inflammations, fungal/ bacterial skin infections with allergy & itching, & wounds on human skin involving contacting human skin with the above identified composition.

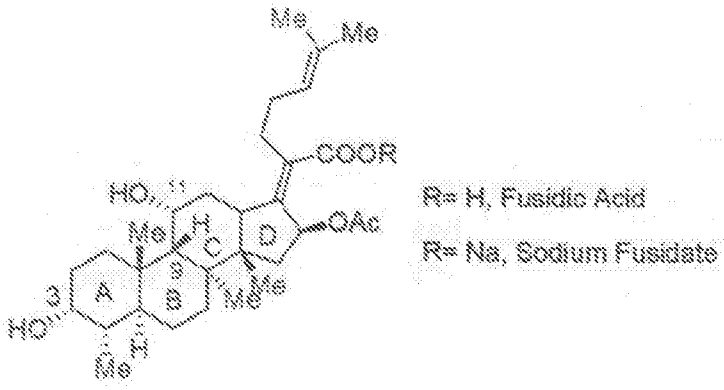
The invention also discloses a process to make the medicinal cream containing Fusidic acid which is formed in situ from Sodium Fusidate as the starting raw material, wherein Sodium Fusidate is converted into Fusidic acid under oxygen-free environment created using inert gas, preferably nitrogen, and chitosan. The cream produced by the process of the present invention has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic acid. The cream produced by the process of the present invention contains Fusidic acid as the API that has been formed in situ from Sodium Fusidate, Mometasone furoate & Miconazole nitrate in a cream base comprising a preservative, an acid, a co-solvent, an emulsifier and a waxy material along with water, preferably purified water. The cream produced by the process of the present invention further optionally contains an ingredient selected from a group comprising, a buffering agent, an anti oxidant, a chelating agent, and a humectant, or any combination thereof.

Detailed description of invention:

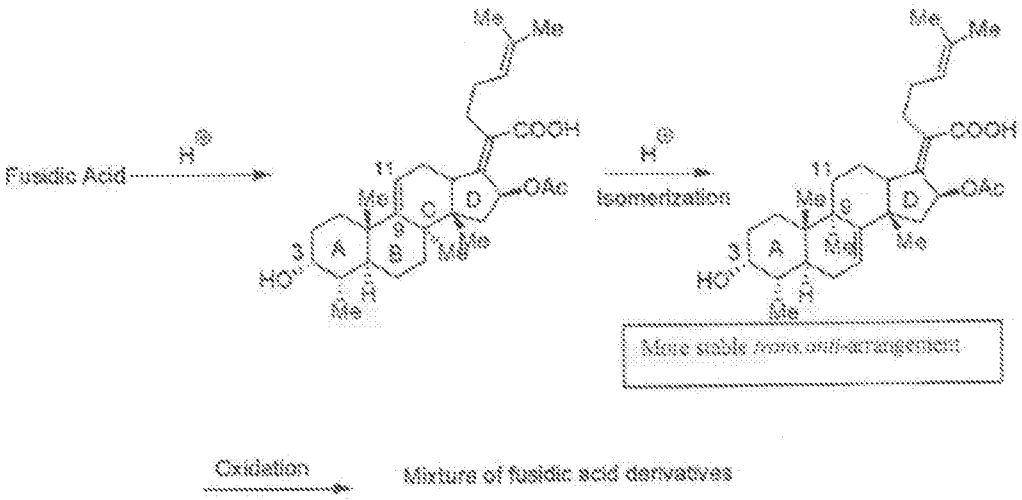
We discussed earlier the known aspects of the topical preparations that have Fusidic acid and Sodium Fusidate as the APIs. It is evident from the current state of knowledge that:

- Creams containing Fusidic acid that is made using Sodium Fusidate as starting API are not available.
- Creams containing Fusidic acid that are made using Sodium Fusidate as starting API along with Mometasone Furoate as a steroid, and Miconazole nitrate as antifungal are not available.
- There is no published data on the stability of Sodium Fusidate as the API.
- Sodium Fusidate is not considered to be inherently more stable as an API than Fusidic acid.
- Creams containing chitosan and fusidic acid which has been created in situ from sodium fusidate is not commercially available.

In the face of this, it has been surprisingly discovered that Sodium Fusidate as an API is significantly more stable than Fusidic acid and that Fusidic acid deteriorates more rapidly than Sodium Fusidate. A look at the chemical structures of sodium fusidate and fusidic acid reveals some interesting facts.



It is noticed that one of the most remarkable features of the fusidic acid structures is the unusual stereochemistry of the cyclopentanoperhydrophenanthrene ring system which differs fundamentally from that of other tetracyclic triterpenes and sterols. In contrast to the usual *trans,anti,trans* arrangement of A, B, and C ring systems of sterols, fusidic acid has very labile *trans,sys,trans* arrangement of these rings which forces ring B into a boat conformation. To relieve this strain, fusidic acid readily undergoes acid mediated dehydration of C-11 hydroxy group to generate a C9-C11 double bond which on further isomerization followed by oxidization in the presence of oxygen leads to a mixture of biologically inactive fusidic acid derivatives.



In the solid state, carboxylic acid functional group present in the fusidic acid facilitates the above process more readily upon storage. Whereas in the case of sodium fusidate such carboxylic acid promoted decomposition is not feasible. So, sodium fusidate has superior solid state stability when compared to fusidic acid. This discovery of the inventor has also been corroborated through stability assessment of sodium fusidate and fusidic acid.

There is no published data on the stability of Sodium Fusidate as the API. The applicant carried out experiments on Sodium Fusidate to evaluate its stability. It can be seen from Table 2 that the degradation of Sodium Fusidate over a temperature range of room temperature to 45 °C ranged between 2.45 % and 6%.

Tables 1 and 2 also show the comparison between the stability of the Fusidic acid and Sodium Fusidate as raw APIs. The study was carried out using an in-house HPLC method developed by the applicant, which the applicant believes is a true stability-indicating method as opposed to the titration method suggested in British Pharmacopoeia (BP). This is because the BP method does not differentiate between the intact API and the degraded form.

Stability analysis of fusidic acid:

Tab1e 1: Results Of 3-Month-Old Fusidic Acid (API) Analysis By Stability Indicating HPLC Method And Titration Method

S.No	Conditions	*Initial (%)	Fusidic Acid Assay (%)		Percentage Drop (%)		Remarks
			Titration	HPLC	Titration	HPLC	
1	RT (Open)	100.6	99.21	92.93	1.39	7.67	API analysed After 3 Months
2	RT (Closed)		99.02	94.37	1.58	6.23	
3	45°C (Open)		98.52	89.52	2.08	11.08	
4	45°C (Closed)		99.10	92.12	1.50	8.48	

Name of the Sample: **FUSIDIC ACID BP** Pack: **Open & Closed Petri dish**

Stability analysis of sodium fusidate:

Tab1e 2 : Results Of 3 Months Old Sodium Fusidate (API) Analysis By Stability Indicating HPLC Method And Titration Method

Name of the Sample: **Sodium Fusidate BP** Pack: Open & Closed Petri dish

S.No	Conditions	*Initial (%)	Sodium Fusidate Assay(%)		Percentage (%)		Remarks
			Titration	HPLC	Titration	HPLC	
1	RT (Open)	98.7	97.71	96.25	0.99	2.45	API analysed After 3 Months
2	RT (Closed)		98.85	97.67	-0.15	1.03	
3	45°C (Open)		97.07	92.65	1.63	6.05	
4	45°C (Closed)		97.16	92.96	1.54	5.74	

In both studies the * Initial denotes the results of the samples tested at the time of receipt of the API from the supplier.

It can be observed from Tables 1 and 2 that:

- In the case of Fusidic Acid, there is about 7.7% loss in 3 Months at room temperature (open condition) and about 11% loss in 3 Months at 45°C (open condition).
- In the case of Sodium Fusidate, there is about 2.5% loss in 3 Months at room temperature (open condition) and about 6% loss in 3 Months at 45°C (open condition).

The data thus shows that Sodium Fusidate as an API is more stable than Fusidic acid.

The applicants explored the possibility of making a cream (rather than an ointment) containing chitosan, Mometasone Furoate, Miconazole nitrate and

Sodium Fusidate (rather than Fusidic acid) as the starting raw material. Although Sodium Fusidate has been used in dermaceutical applications, it has not been possible to make creams that use Sodium Fusidate. This is because of the inherent alkalinity of Sodium Fusidate (pH 7.5 to 9), which means it cannot be used in a cream form therefore all products manufactured using Sodium Fusidate as starting material are ointments. A dermaceutical cream that uses Sodium Fusidate would exploit the benefit of the fact that Sodium Fusidate is more stable than Fusidic acid and it would also provide a cream formulation which is far superior in its application qualities than an ointment. It would thus fill an existing need for a cream that has better stability than currently available creams containing Fusidic acid.

The applicant therefore surprisingly discovered that in order to achieve greater stability of the API in a dermaceutical cream, Sodium Fusidate rather than Fusidic acid may be used as the starting API during the cream's manufacture. Using Sodium Fusidate as starting material eliminates the drawback associated with the manufacture and storage of existing Fusidic acid creams.

The applicant has also discovered that the Fusidic acid cream prepared using Sodium Fusidate as the starting API and Mometasone Furoate as a steroid, and Miconazole nitrate as an antifungal showed good chemical stability and efficacy

The application discloses a process of making a cream containing a biopolymer - Chitosan, Mometasone Furoate as a steroid, and Miconazole nitrate as an

antifungal, and Fusidic acid (the API) that has been prepared using Sodium Fusidate as the starting API, in which Fusidic acid forms in-situ under totally oxygen-free environment created using inert gas, preferably nitrogen, by slow addition of an acid, into a molecular dispersion form (due to the presence of a co-solvent) at the intermediate stage, and which Fusidic acid regenerates as an extremely fine dispersion when added to a final cream base, thereby resulting in a finely and homogeneously dispersed Fusidic acid in the final cream. All these operations are performed in an environment free of atmospheric oxygen created using inert gas, preferably nitrogen.

The cream made using the process of the present invention contains Fusidic acid as the API that has been formed in situ from Sodium Fusidate, a biopolymer – Chitosan, Mometasone Furoate as a steroid, and Miconazole nitrate as an antifungal in a cream base comprising a preservative, an acid, a co-solvent, an emulsifier and a waxy material along with water, preferably purified water.

The active compounds Sodium Fusidate, Mometasone Furoate & Miconazole nitrate which may be employed in the process of the present invention as starting APIs are well known in the art of treating bacterial primary & secondary bacterial skin infections, skin inflammations and fungal skin infections.

The active compounds Sodium Fusidate Mometasone Furoate & Miconazole nitrate require a base component to be used in the pharmaceutical composition

that uses the compound, since the compound cannot, by themselves, be deposited directly on to human skin due to their harshness.

The base component usually contains a biopolymer, primary and secondary emulsifiers, waxy materials, co-solvents, acids, preservatives, purified water and the like.

The cream base of the cream made using the process of the present invention optionally further comprises an ingredient selected from a group comprising a buffering agent, an anti oxidant, a chelating agent, and a humectant, or any combination thereof.

The present invention provides a process to make a novel cream that has been produced using Sodium Fusidate as the starting raw material, and which cream contains Fusidic acid of high therapeutic efficacy and of chemical stability that is generally superior to the commercially available creams containing Fusidic acid.

As a further inventive feature of the present invention, the Fusidic acid cream made using the process of the present invention has been manufactured in a totally oxygen free environment under purging with inert gas and applying vacuum, the inert gas being preferably nitrogen. Under these conditions, the Sodium Fusidate is converted in situ into Fusidic acid and to which Mometasone Furoate as a steroid, and Miconazole nitrate as an antifungal are added. The cream of the

present invention is used in the treatment of bacterial skin infections fungal infections and inflammations.

From the study of the prior art several lacking aspects of the existing topical treatment formulations in the field of prescription medications are evident. The prior art does not teach or suggest that:

- Topical skin formulations can deliver skin healing or regeneration beyond the activity of the main APIs such that the therapeutic outcomes of the main APIs are enhanced.
- The addition of biologically active polymers (the so-called biopolymers) is a complex process in which the stability of the formulations could be compromised if the right biopolymer is not selected.
- Incorporation of a functionally bio-active excipient polymer in cream matrix while retaining the functional stability of the API in a single dose format of dermaceutical cream involves resolution of problems specific to the physical stability of cream matrix.

Examples of suitable topical antibacterial agents, which may be used, include, but are not limited to Neomycin Sulphate, Sodium Fusidate, Calcium Mupirocin, Gentamycin, Silver Sulphadiazine, Ciprofloxacin, Framycetin Sulphate, Quinidochlor, Povidone-Iodine, Sisomicin, Nitrofural and the like.

Examples of Corticosteroids, which may be used, include, but are not limited to Betamethasone Valerate, Fluticasone Propionate, Mometasone Furoate, Dexamethasone Acetate, Hydrocortisone Acetate, Clobetasol Propionate, Beclomethasone Dipropionate, Betamethasone Dipropionate and the like.

Examples of Antifungals, which may be used, include, but are not limited to Miconazole Nitrate, Terbinafine Hydrochloride, Ketoconazole, Clotrimazole and the like.

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

Chitosan

Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). It is known to have a number of commercial uses in agriculture and horticulture, water treatment, chemical industry, pharmaceuticals and biomedics.

It's known properties include accelerated blood clotting. However, it is not known to a person skilled in the art that chitosan's behaviour with a pharmaceutical active ingredient such as an antibacterial or antifungal agent needs to be treated with caution.

It is known to have film forming, mucoadhesive and viscosity-increasing properties and it has been 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, squids 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 properties allow it to rapidly clot blood, and it has recently gained approval in the USA for use in bandages and other hemostatic agents.

Chitosan is nonallergenic, and has natural anti-bacterial properties, further supporting its use. 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. It is also useful in treatment of routine minor cuts and wounds, burns, keloids, diabetic ulcers and venous ulcers. Chitosan used in the present invention comes in various molecular weights ranging from 1kdal to 5000kdal.

Chitosan is discussed in the US Pharmacopoeia forum with regard to its functional excipient category. Since chitosan is basically a polymer, it is available in various grades depending upon the molecular weight. The various grades of chitosan include chitosan long chain, chitosan medium chain & chitosan short chain. The grades long, medium & short chain directly corresponds to the molecular weight of the chitosan.

Generally the long chain grade has a molecular weight in the range of 500,000-5,000,000 Da, the medium chain grade has a molecular weight in the range of 1,00,000-2,000,000 Da and the short chain grade has a molecular weight in the range of 50,000-1,000,000 Da.

The molecular weight of the chitosan plays an important role in the formulation. Higher molecular weight chitosan imparts a higher viscosity to the system and lower molecular weight chitosan imparts a lower viscosity to the system. However

the medium chain grade chitosan delivered an optimum level of viscosity to the formulation. Since the dosage form is a cream, appropriate levels of viscosity is required to achieve a good spreadability over the skin.

The inventors finalized the chitosan medium chain grade for the present invention since it imparted the required rheologic properties to the cream without compromising the therapeutic activity of the actives, ie Sodium Fusidate, Mometasone Furoate & Miconazole nitrate as the starting actives and chitosan. The concentration of chitosan medium chain grade was carefully arrived based on several in house trials and Preclinical animal studies for efficacy.

Topical Anti-fungals

Topical anti-fungals are intended to target skin for fungal infections caused by fungi such as Tinea pedis, Tinea cruris, and Tinea corporis. Typical antifungal agents include drugs like Clotrimazole, Ketoconazole, Miconazole nitrate, Terbinafine Hydrochloride etc. Fungal infections are generally manifested with itching at the site. Anti-fungals act by altering the permeability of the fungal membrane by inhibiting the synthesis of sterols.

Miconazole Nitrate

Miconazole Nitrate is an antifungal agent with similar antimicrobial activity to ketoconazole. Chemically, Miconazole Nitrate is 1-[2-(2,4-Dichlorophenyl)-2-

[(2,4- dichlorophenyl)methoxy]ethyl]-1H-imidazole with the empirical formula $C_{18}H_{14}Cl_4N_2C.HNO_3$, and a molecular weight of 479.15.

Miconazole Nitrate is a White or almost white, crystalline or micro-crystalline powder, freely soluble in methanol; slightly soluble in ethanol (95%) and in chloroform; very slightly soluble in water and in ether. It is administered by intravenous infusion in the treatment of severe systemic fungal infections including candidiasis, coccidioidomycosis, cryptococcosis, paracoccidioidomycosis, and infections due to Pseudeliescheria boydii. Miconazole may be given by mouth for the treatment of oral and intestinal candidiasis.

It has been given prophylactically to patients at high risk of opportunistic fungal infections. In fungal meningitis, intravenous treatment may be supplemented with intrathecal injections of Miconazole. Miconazole nitrate is used locally for treating various fungal skin infections.

Pharmacology

Miconazole nitrate is a synthetic antifungal agent which inhibits the growth of the common dermatophytes, Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum, the yeast-like fungus, Candida albicans, and the organism responsible for tinea versicolor (Malassezia furfur).

Mechanism of Action: Miconazole nitrate inhibits biosynthesis of ergosterol, damaging the fungal cell wall membrane, which increases permeability causing leaking of nutrients

Pharmacokinetics: Absorption of Miconazole nitrate is negligible by topical route. Miconazole nitrate is widely distributed to body tissues; penetrates well into inflamed joints, vitreous humor of eye, and peritoneal cavity, but poorly into saliva and sputum; crosses blood-brain barrier but only to a small extent Protein binding of Miconazole nitrate is about 91% to 93%. Miconazole nitrate is metabolized in liver and is excreted in feces (~50%) and urine (<1% as unchanged drug)

Indications: For topical application in the treatment of tinea pedis (athlete's foot), tinea cruris, and tinea corporis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum, in the treatment of cutaneous candidiasis (moniliasis), and in the treatment of tinea versicolor.

Topical Corticosteroids

Topical corticosteroids are a powerful tool for treating skin diseases. Corticosteroids include drugs such as Betamethasone dipropionate, Beclomethasone dipropionate, , Clobetasol propionate, Clobetasone butyrate, Halobetasol propionate, Mometasone furoate, Halcinonide, Fluocinonide,

Triamcinolone acetonide, Fluticasone propionate, Amcinonide, Hydrocortisone acetate, Diflorasone diacetate, Prednicarbate, etc.

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 Betamethasone Dipropionate, Betamethasone Valerate, Diflorasone Diacetate, Clobetasol Propionate, Halobetasol Propionate, Desoximetasone, Diflorasone Diacetate, Fluocinonide, Mometasone Furoate, Triamcinolone Acetonide, etc. Low potency topical steroids include Desonide, Fluocinolone acetate, and Hydrocortisone acetate, etc.

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

Mometasone Furoate

Mometasone Furoate is a synthetic corticosteroid with anti- inflammatory activity Chemically, Mometasone Furoate is 9α,21-dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate), with the empirical formula $C_{27}H_{30}CI_2O_6$, and a molecular weight of 521.4.

Mometasone Furoate is a white to off-white powder practically insoluble in water, slightly soluble in octanol, and moderately soluble in ethyl alcohol. It is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid- responsive dermatoses.

Pharmacology

Mometasone Furoate is a medium-potency synthetic corticosteroid with antiinflammatory, antipruritic, and vasoconstrictive properties. Mometasone Furoate depresses formation, release, and activity of endogenous mediators of inflammation, including prostaglandins, kinins, histamine, liposomal enzymes, and complement system; modifies body's immune response.

Mometasone Furoate have been shown to have a wide range of inhibitory effects on multiple cell types (e.g. mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (e.g. histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma and in skin lesions.

Mechanism Of Action:

Unbound Mometasone Furoate cross cell membranes and bind with high affinity to specific cytoplasmic receptors. Inflammation is decreased by diminishing the release of leukocytic acid hydrolases, prevention of macrophage accumulation at

inflamed sites, interference with leukocyte adhesion to the capillary wall, reduction of capillary membrane permeability, reduction of complement components, inhibition of histamine and kinin release, and interference with the formation of scar tissue. The antiinflammatory actions of Mometasone Furoate are thought to involve phospholipase A_2 inhibitory proteins, lipocortins, which control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes. Mometasone furoate has been shown in vitro to exhibit a binding affinity for the human glucocorticoid receptor which is approximately 12 times that of dexamethasone, 7 times that of triamcinolone acetonide, 5 times that of budesonide, and 1.5 times that of fluticasone.

Pharmacokinetics

Absorption: Compared with IV administration, bioavailability of an inhaled dose of Mometasone Furoate is less than 1%. Mean C max ranged from 94 to 114pcg/mL and the time to C max ranged from about 1 to 2.5 h.

Distribution: The in vitro protein binding of Mometasone Furoate was found to be from 98% to 99%.

Metabolism: Mometasone Furoate is primarily and extensively metabolized in the liver by the CYP3A4 isozyme to multiple metabolites.

Elimination: Terminal t ½ of Mometasone Furoate is about 5 h. Excretion up to 7 days is primarily in the feces (74%) and, to a lesser amount, in the urine (8%).

Indications: Mometasone Furoate is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Topical Anti-bacterials

Topical Anti-bacterials are intended to target skin for bacterial infections caused by Staphylococcus aureus, Staphylococcus epidermidis, Methicillin Resistance Staphylococcus Aureus (MRSA) etc.

Anti-bacterials act by inhibiting cell wall synthesis by combining with bacterial ribosomes and interfering with mRNA ribosome combination.

In another hypothesis it is believed that anti-bacterials induce ribosomes to manufacture peptide chains with wrong amino acids, which ultimately destroy the bacterial cell.

Sodium Fusidate

Sodium Fusidate belongs to the group of medicines known as *antibiotics.*
It is used to treat bacterial infections, such as infections of the joints and bones by killing or stopping the growth of the bacteria responsible.

The molecular formula of Sodium Fusidate is C31H47. The chemical name is 3µ,11µ,16ß-Trihydroxy 29-nor-8µ, 9ß, 13µ, 14ß-dammara-17(20) [10,21-cis], 24-

dien-21-oic acid 16-acetate, sodium salt. It is a white colour crystalline powder soluble in one part of water at 20 ^{o}C.

Pharmacology & Mechanism of Action

Sodium Fusidate inhibits bacterial protein synthesis by interfering with amino acid transfer from aminoacyl-sRNA to protein on the ribosomes. Sodium Fusidate may be bacteriostatic or bactericidal depending on inoculum size.

Although bacterial cells stop dividing almost within 2 minutes after contact with the antibiotic in vitro, DNA and RNA synthesis continue for 45 minutes and 1 to 2 hours, respectively. Sodium Fusidate is virtually inactive against gram-negative bacteria. The differences in activity against gram-negative and gram-positive organisms are believed to be due to a difference in cell wall permeability.

Mammalian cells are much less susceptible to inhibition of protein synthesis by Sodium Fusidate than sensitive bacterial cells. These differences are believed to be due primarily to a difference in cell wall permeability.

Indications: Sodium Fusidate is indicated for the treatment of primary and secondary skin infections caused by sensitive strains of S. aureus, Streptococcus species and C. minutissimum. Primary skin infections that may be expected to respond to treatment with Sodium Fusidate topical include: impetigo contagiosa,

erythrasma and secondary skin infections such as infected wounds and infected burns.

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.

The pH of the Chitosan Cream with antibacterial agent – Sodium Fusidate, Mometasone Furoate as a steroid, Miconazole nitrate as an antifungal of the present invention is from about 3 to 6. On the other hand, ointments that are commercially available are greasy and cosmetically non elegant. Furthermore, as

the active compound in an ointment is in non-ionized form, the penetration of skin is slow.

It is essential that the active drug penetrates the skin for the optimum bio-dermal efficacy. The particle size of the active drug plays an important role here. It is necessary that the active drug is available in colloidal or molecular dispersed state for the product being highly efficacious form. Also this is to be achieved in the safe pH compatible environment of skin (4.0 to 6.0). To achieve all these, it is essential to choose proper vehicles or co-solvents for the dissolution or dispersion of the drug. The product of the present invention is highly efficacious due to the pronounced antibacterial & wound healing activity of the active ingredients, which are available in ultra micro-size, colloidal form, which enhances skin penetration.

Rationale for combining fusidic acid made from sodium fusidate, mometasone furoate, Miconazole nitrate and chitosan:

Numerous topical treatments are currently employed for the treatment of bacterial and fungal infections and reduce skin imflammation. However there is no effective single-dose therapy for protecting the skin, controlling superficial bleeding, wounds and burns. 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

rejuvenation properties with Sodium Fusidate, a corticosteroid in the form of mometasone furoate, and an antifungal in the form of Miconazole nitrate is proposed as a novel cream.

Topical Sodium Fusidate & Miconazole nitrate have profound efficacy in primary & secondary bacterial/fungal skin infections of varied etiology due to their antibacterial/antifungal properties. A drawback of the monotherapy with any topical antibacterial/antifungal has been the relatively slow onset of the effect.

By employing fusidic acid along with mometasone furoate and Miconazole nitrate & chitosan in a formulation, the properties of antibacterial, antifungal, and anti-imflammatory agents as well as chitosan are optimized. As chitosan is film forming, biocompatible, non-allergenic material it helps in protecting the skin by acting as a barrier. It further controls the superficial bleeding caused by scratching and also arrests the mobility of pathogens due to its cationic charge.

The properties of Sodium Fusidate, Mometasone furoate, Miconazole nitrate and chitosan's skin regenerative aspects are well exploited in the present invention and the maximum therapeutic benefit is passed on to the patient thereby aiding in faster healing. This ensures that the patient would benefit for the treatment of skin inflammations, wounds, burns with bacterial and fungal infections.

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 Sodium Fusidate, Mometasone furoate, Miconazole nitrate 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 used in combination with fusidic acid made in situ from Sodium Fusidate, Mometasone furoate & Miconazole nitrate.

Other Inventive Aspects Of The Present Invention:

Another inventive aspect of the present invention is that the addition of a functional excipient in the cream base is not a straight forward process of mere addition. The inventor has found that the compatibility of the functional excipient such as chitosan with other agents in the cream is of critical importance. This is because incompatibility would compromise the stability of the final product. As examples, the inventors have found that well known excipients such as Xanthan Gum and carbomer which have been variously used as stabilizing agents, cannot be used in combination with functional biopolymers such as chitosan.

Excipients for topical dosage forms include Polymers, Surfactants, Waxy Materials, and Emulsifiers etc. Polymers are used as gelling agents, suspending agents, viscosity builders, release modifiers, diluents, etc. Surfactants are used as wetting agents, emulsifiers, solubilising agents release enhancers, etc.

Generally polymers & surfactants may or may not possess ionic charge. They may be anionic or cationic or non-ionic in nature. If anionic excipients are included in

the formulation they interact with cationic formulation excipients and produce products which are not homogenous, aesthetically not appealing and give rise to unwanted by products, possible allergens, impurities, toxic substances etc due to incompatibility.

Since the dosage is for the treatment of ailing patients, these incompatibilities in the products cannot be accepted and these add more complication to the patients.

The inventors carefully screened the excipients which included the polymers and surfactants for developing a formulation. A thorough study was performed after screening the short listed excipients. The possible interactions between the excipients were given much focus and detailed experiments were done.

To quote some examples about the anionic-cationic interaction in the cream dosage form the inventors made some formulations of Sodium Fusidate, Mometasone Furoate & Miconazole nitrate (see tables 3 – 7) containing Xanthan Gum & Chitosan, Acrylic acid polymer & Chitosan, Sodium Lauryl Sulphate & Chitosan, Docusate Sodium & Chitosan and Gum Arabic & Chitosan. The results clearly indicated the occurrence of interactions which was very much visible and seen as lumps into the entire system. The final product was also not aesthetically appealing without homogeneity. The attached Figure 1 clearly explains the interaction between chitosan and unsuitable anionic excipients. Based on the observations and thorough knowledge about the excipients, the inventors arrived at a robust formula without any possible interactions.

Table 3: Fusidic Acid, Mometasone furoate, Miconazole nitrate Cream incorporating Chitosan and Xanthan Gum

S.No	Ingredients	% (w/w)
1	Sodium Fusidate (equ. to make Fusidic Acid 2% w/w)	2.08
2	Mometasone Furoate	0.1
3	Miconazole Nitrate	2
4	Chitosan	0.25
5	Lactic acid	0.1
6	Xanthan Gum	1.0
7	White soft Paraffin	12.5
8	Cetostearyl Alcohol	12.5
9	Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)	1
10	Polysorbate 80	2
11	Benzoic Acid	0.2
12	Disodium Edetate	0.1
13	Disodium Hydrogen Orthophosphate anhydrous	0.5
14	Propylene Glycol	47
15	Butylated Hydroxy Toluene	0.01
16	1 M Nitric Acid Solution	4
17	Purified water	15

Table 4: Fusidic acid, Mometasone furoate, Miconazole nitrate cream incorporating chitosan and acrylic acid polymer

S.No	Ingredients	% (w/w)
1	Sodium Fusidate (Equ. To make Fusidic Acid 2% w/w)	2.08
2	Mometasone Furoate	0.1
3	Miconazole Nitrate	2
4	Chitosan	0.25
5	Lactic acid	0.1
6	Acrylic Acid Polymer	0.75
7	White soft Paraffin	12.5
8	Cetostearyl Alcohol	12.5
9	Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)	1
10	Polysorbate 80	2
11	Benzoic Acid	0.2
12	Disodium Edetate	0.1
13	Disodium Hydrogen Orthophosphate anhydrous	0.5
14	Propylene Glycol	47
15	Butylated Hydroxy Toluene	0.01
16	1 M Nitric Acid Solution	4
17	Purified water	15

Table 5:Fusidic acid, Mometasone furoate, Miconazole nitrate cream incorporating chitosan & sodium lauryl sulphate

S.No	Ingredients	% (w/w)
1	Sodium Fusidate (equ. To make Fusidic acid 2% w/w)	2.08
2	Mometasone Furoate	0.1
3	Miconazole Nitrate	2
4	Chitosan	0.25
5	Lactic acid	0.1
6	Sodium Lauryl Sulphate	1.0
7	White soft Paraffin	12.5
8	Cetostearyl Alcohol	12.5
9	Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)	1
10	Polysorbate 80	2
11	Benzoic Acid	0.2
12	Disodium Edetate	0.1
13	Disodium Hydrogen Orthophosphate anhydrous	0.5
14	Propylene Glycol	47
15	Butylated Hydroxy Toluene	0.01
16	1 M Nitric Acid Solution	4
17	Purified water	15

Table 6: Fusidic acid, Mometasone furoate, Miconazole nitrate cream incorporating chitosan and docusate sodium

S.No	Ingredients	% (w/w)
1	Sodium Fusidate (equ. To make Fusidic acid 2% w/w)	2.08
2	Mometasone Furoate	0.1
3	Miconazole Nitrate	2
4	Chitosan	0.25
5	Lactic acid	0.1
6	Docusate Sodium	1.0
7	White soft Paraffin	12.5
8	Cetostearyl Alcohol	12.5
9	Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)	1
10	Polysorbate 80	2
11	Benzoic Acid	0.2
12	Disodium Edetate	0.1
13	Disodium Hydrogen Orthophosphate anhydrous	0.5
14	Propylene Glycol	47
15	Butylated Hydroxy Toluene	0.01
16	1 M Nitric Acid Solution	4
17	Purified water	15

Table 7: Fusidic Acid, Mometasone furoate, Miconazole nitrate acid cream incorporating chitosan and gum arabic

S.No	Ingredients	% (w/w)
1	Sodium Fusidate (equ. To make Fusidic acid 2% w/w)	2.08
2	Mometasone Furoate	0.1
3	Miconazole Nitrate	2
4	Chitosan	0.25
5	Lactic acid	0.1
6	Gum Arabic	1.0
7	White soft Paraffin	12.5
8	Cetostearyl Alcohol	12.5
9	Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)	1
10	Polysorbate 80	2
11	Benzoic Acid	0.2
12	Disodium Edetate	0.1
13	Disodium Hydrogen Orthophosphate anhydrous	0.5
14	Propylene Glycol	47
15	Butylated Hydroxy Toluene	0.01
16	1 M Nitric Acid Solution	4
17	Purified water	15

The above products (tables 3 to 7) are examples of products that do not form homogeneous creams, but produce non-homogeneous creams of the type illustrated in figure 1. Yet the proportions stated in these examples are the ones that a person skilled in the art may use based currently available knowledge. Only after a thorough and extensive trials and errors would it be possible to arrive at right types and proportions of excipients.

As we have also discussed earlier, in a therapy, Fusidic acid provides relief against bacterial infections, Mometasone furoate provides relief against skin inflammations, Miconazole nitrate provides relief against fungal infections However, the aspects such as like skin protection, bleeding at the site, mobility of

pathogens from one site to another, etc are not addressed so far in a single dose therapy that includes fusidic acid generated in situ from sodium fusidate.

This present invention with its single-dose application fills this gap by incorporating chitosan and tapping the required benefits of skin protection (by way of film forming property), stopping the bleeding (by way of blood clotting property) and immobilization of pathogenic microbes (due to its cationic electrostatic property).

Therapeutic value addition by incorporation of a functional excipient in the form of a chitosan which is a biopolymer in the cream matrix is an integrated sub-set of the following functional attributes of the biopolymer:

- formation of a micro-film on the skin surface
- accelerated blood clotting as compared to creams that do not contain film-forming biopolymers
- electrostatic immobilisation of surface microbes due to cationic charge of the biopolymer
- significant enhancement of the skin epithelisation or regeneration which is of particular help in skin damage caused by severe infections as well as wounds and burns

The inventive efforts involved in developing the platform technology covered by incorporation of a functional biopolymer in prescription dermaceutical products rest:

- in identification of the complementary therapeutic value that such incorporation delivers
- in identification of issues related to physio-chemical stability of the product resulting from the incorporation of the biopolymer
- in providing a single dose format where the bacterial skin infection, fungal skin infection & inflammation has been identified

The importance of a single dose treatment, particularly in the underdeveloped countries cannot be overemphasized. In absence of access to a general physician in most parts of south Asia or Africa, let alone a skin specialist, a single dose formulation dramatically increases chances of eliminating root cause of the skin disorder while also allowing the skin to regenerate.

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.

Further, with ever increasing pressures on medical support systems and the attendant scarcity/high cost of the same, there is an emergent need all across the globe to address the following issues in such cases –

- Patients waiting too long for treatment
- Staying unnecessarily long when they get to hospital
- Having to come back more often than they need to

Reducing the length of stay is a key underlying problem to be tackled in most cases. The present invention with its single-dose therapy reduces the overall treatment time of a serious skin disorder significantly.

Details of the medicinal cream of the present invention and processes of manufacturing it:

These are provided in the form of various embodiments that describe the product of the present invention and the processes to make it.

Preferred embodiment no. 1: A medicinal cream for topical treatment of bacterial skin infections, fungal skin infections, inflammations and for related wound healing including burns wound, wherein said cream comprises an antibacterial agent, Sodium Fusidate, an antifungal agent in the form of Miconazole nitrate, a corticosteroid in the form of Mometasone furoate and a biopolymer in the form of chitosan provided in a cream base, said cream base

comprising at least one of each of a preservative, a primary and a secondary emulsifier, a waxy material, a co-solvent, an acid, and water, preferably purified water.

Embodiment no. 1: A medicinal cream as disclosed in the preferred 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. 2: A novel dermaceutical cream as disclosed in the preferred embodiment no 1 and the embodiment no. 1, wherein

- said Fusidic acid is present in an amount from about 0.1% (w/w) to about 25% (w/w), preferably from about 0.5% (w/w) to about 5%(w/w), and more preferably about 2.00 % (w/w), and in which the amount of said Sodium Fusidate used to form in situ said Fusidic acid is in the range between about 0.1% (w/w) to about 25% (w/w), preferably from about 0.5% (w/w) to about 5% (w/w) and more preferably about 2.08 % (w/w), and
- said **Mometasone Furoate** is added from about 0.005% to about 2.5% by weight, preferably from about 0.05% to about 1.00% by weight, and most preferably from about 0.1% by weight, and
- said Miconazole Nitrate is added from about 0.5% to about 5.0% by weight, preferably from about 0.5% to about 3.0% by weight, and most preferably about 2.0% by weight; and

- said chitosan is added in an amount between about 0.01% and about 1% by weight, preferably from about 0.01% w/w to about 0.5% w/w and most preferably about 0.25% w/w,

- said primary and secondary emulsifiers are selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Polysorbate-80, Span-80 and the like and added in an amount from about 1% (w/w) to 20% (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 0.5% (w/w); said preservative is selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid and the like, or any combination thereof, and added in an amount from about 0.05% (w/w) to 0.5% (w/w); said water is added in the amount in the range of 20% (w/w) to 75% (w/w), preferably 30% (w/w) to 50% (w/w), more preferably 35% (w/w) to 45% (w/w), preferably purified water.

Embodiment no.3: A novel medicinal cream as disclosed in the preferred embodiment no 1 and embodiment 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 0.001% (w/w) to 1.00% (w/w).

Embodiment no. 4: A novel medicinal cream as disclosed in the preferred embodiment no 1 and embodiments 2 and 3 further comprising an antioxidant which is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, or any combination thereof, and added in an amount from about 0.001% (w/w) to 1 % (w/w).

Embodiment no. 5: A novel medicinal cream as disclosed in the preferred embodiment no 1 and embodiments nos.2 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.6: A novel medicinal cream as disclosed in the preferred embodiment no 1, and embodiments nos. 2 to 5 further comprising a humectant which is selected from a group comprising Glycerin, Sorbitol, Propylene Glycol and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 50% (w/w).

Embodiment no. 7 : A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments nos. 1 to 6 wherein sodium fusidate is converted in-situ under totally oxygen free environment by slow addition of an acid, into Fusidic acid of a molecular dispersion form (due to the presence of a co-solvent) at the intermediate stage, and which Fusidic acid regenerates into an extremely finely dispersed form when added to a final cream base, thereby resulting in a finely and homogeneously dispersed Fusidic acid in the final cream; all operations of converting sodium fusidate into Fusidic acid carried out preferably in an environment free of atmospheric oxygen.

Embodiment no. 8: A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments no. 1 to 7 wherein said conversion of Sodium Fusidate into said Fusidic acid and the following formation of said Fusidic acid in a finely dispersed form in the final cream base take place in an oxygen-free environment.

Embodiment no. 9: A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments no. 7 and 8 wherein said oxygen-free environment comprises a gaseous environment formed of inert gas selected from a group comprising carbon dioxide, nitrogen, helium and the like.

Preferred embodiment 2: The preferred embodiment of the invention discloses a process to make a dermaceutical cream containing Fusidic acid, said process

comprising the step of using sodium fusidate as the raw API and converting it in situ into Fusidic acid under oxygen-free environment in a cream base.

Embodiment No. 10: In an embodiment of the present invention the process of making the composition is disclosed, wherein the step of converting the sodium fusidate in situ into Fusidic acid of the preferred embodiment no. 2 comprises the steps of:

a. heating purified water in the range from 5% (w/w) to 40% (w/w), preferably 5% (w/w) to 30% (w/w), more preferably 7% (w/w) to 15% (w/w), in a water-phase vessel to 70 °C to 80 °C,

b. adding to said water-phase vessel a preservative, selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid and the like, either singly or any combination thereof, in an amount between 0.05% (w/w) and 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.2% (w/w), more preferably Benzoic acid,

c. mixing the mixture using an agitator at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

d. adding waxy materials, selected from a group comprising white soft paraffin, liquid paraffin, hard paraffin and the like, either singly or any combination thereof, in an amount between 5% (w/w) and 20% (w/w), preferably 15% (w/w), more preferably12.5% (w/w), to an oil-phase vessel and melting said wax by heating to 70 °C to 80 °C,

e. adding to said oil-phase vessel of a primary emulsifier, preferably in the form of a non ionic surfactant, selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, either singly or any combination thereof, wherein Cetostearyl alcohol is added in an amount between 1% (w/w) and 15% (w/w), preferably 15% (w/w), more preferably 12.5% (w/w), and Cetomacrogol-1000 is added in an amount between 0.1% (w/w) and 5% (w/w), preferably 1% (w/w), more preferably 0.5% (w/w), and optionally a secondary emulsifier selected from a group comprising Polysorbate-80, Span-80 and the like, preferably Polysorbate-80, in an amount between 1 and 5% w/w, more preferably 2% w/w and mixing the mixture thoroughly, preferably using an agitator, at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

f. transferring under vacuum in the range of minus 1000 to minus 300 mm of mercury and at 70 °C to 80 °C the contents of the water-phase and oil-phase vessels to a mixing vessel and mixing the mixture thoroughly, preferably using an agitator, at 10 to 50 RPM to form an emulsion,

g. cooling said emulsion to 45 °C preferably by circulating cold water, preferably at 8 °C to 15 °C from a cooling tower in the jacket of said mixing vessel,

h. in a first API-vessel adding a co-solvent, selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400 and the like, either singly or any combination thereof, in an amount between 5% (w/w) and 40% (w/w), preferably 30% (w/w), more preferably 25% (w/w),

preferably propylene glycol, subjecting the contents of said API-vessel to inert gas flushing, said inert gas being preferably nitrogen, and adding sodium fusidate to the mixture, said sodium fusidate added in an amount between 0.1% (w/w) and about 25% (w/w), preferably from about 0.5% (w/w) to about 5% (w/w) and more preferably about 2.08 % (w/w), and dissolving said sodium fusidate in the mixture,

i. adjusting the pH of the mixture in said first API-vessel of step h to below 2 by using an acid, selected from a group comprising acids such as HCl, H_2SO_4, HNO_3, Lactic acid and the like, either singly or any combination thereof, preferably Nitric acid in an amount from about 0.005% (w/w) to 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.25% (w/w),

j. adding in a second API-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 10% (w/w), heating to 60°C and dissolving Mometasone Furoate in it by continuous mixing.

k. adding in a third API-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 13% (w/w) and dispersing Miconazole nitrate in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill,

l. transferring the contents of said first API-vessel of step i to the mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas being preferably nitrogen,

m. transferring the contents from said second API-vessel of step j to said mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

n. transferring the contents of the colloid milled Miconazole nitrate from the third API – vessel of step k to the said mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenising the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

o. in a biopolymer-mixing vessel adding an acid, selected from a group comprising acids such as HCl, H2So4, HNO3, Lactic acid and the like, either singly or any combination thereof, preferably Lactic acid to form a from about 0.005% (w/w) to 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.1% (w/w), and purified water from about 0.1% (w/w) to 10% (w/w), preferably 8% (w/w), more preferably 5% (w/w) to form a mixture and dissolving a biopolymer, preferably Chitosan in an amount between about 0.01% w/w and about 1% w/w, preferably from about 0.01% w/w to about 0.5% w/w and most preferably about 0.25% w/w,

p. transferring the contents of the biopolymer-mixing vessel of step o to the mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas being preferably nitrogen,

q. cooling the contents of the mixing vessel of step g to 30 °C to 37 °C using circulation of cooled water from a cooling tower at 8 °C to 15 °C into the jacket of mixing vessel,

r. turning off the agitator and the homogenizer and removing the mixture of the mixing vessel of step q to a storage container.

Embodiment No. 11: In an embodiment of the present invention, the co-solvent of step h of the embodiment no. 10 above also serves as a humectant. However, in another embodiment of the invention, an additional humectant may be added, in the step a of embodiment 7,selected from a group comprising Glycerin, Sorbitol, Propylene glycol and the like, either singly or any combination thereof, to form a from about 5% (w/w) to 40% (w/w), preferably 30% (w/w), more preferably 25% (w/w).

Embodiment No. 12: In another embodiment of the present invention the process described in embodiment no. 11 further incorporates adding a chelating agent, after the step of adding a preservative, selected from a group comprising Disodium EDTA and the like, either singly or any combination thereof, to form a from about 0.01% (w/w) to 1% (w/w), preferably 0.5% (w/w), more preferably 0.1% (w/w).

Embodiment No. 13: In yet another embodiment of the present invention the process described in embodiments no. 11 and 12 further incorporate a buffering agent after the step of adding chelating agent selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the

like from about 0.01% (w/w) to 2.00% (w/w), preferably 1.5% (w/w), more preferably 1% (w/w).

Embodiment No. 14: In a further embodiment of the present invention the process described in embodiments no. 11 to 13 further incorporate an anti oxidants in the step h of embodiment 10 selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like from about 0.001% (w/w) to 5% (w/w), preferably 0.1% (w/w), more preferably 0.01% (w/w).

Embodiment No. 15: Yet another process of making the composition as per the said earlier preferred embodiments & embodiments is disclosed, said process comprises the steps of:

a. heating purified water in the range from 5% (w/w) to 40% (w/w), preferably 5% (w/w) to 30% (w/w), more preferably 7% (w/w) to 15% (w/w) in a water-phase vessel to 70 °C to 80 °C,
b. adding to said water-phase vessel a preservative, selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid and the like, either singly or any combination thereof, added in an amount between 0.05% (w/w) and 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.2% (w/w), the preferred preservative being Benzoic acid,
c. optionally adding to said water-phase vessel of step b a chelating agent, or buffering agent , or a humectants added in combination thereof, wherein

said chelating agent is preferably Disodium edetate, added in an amount preferably between 0.01 and 1 %, more preferably 0.1%, said buffering agent is preferably Di Sodium Hydrogen Ortho Phosphate, added in an amount preferably 0.01% (w/w) to 2.00% (w/w), preferably 1.5% (w/w), more preferably 1% (w/w) and said humectant is preferably Propylene Glycol, added in an amount preferably 5% (w/w) to 60% (w/w), more preferably 48.5% (w/w),

d. mixing the mixture of said water-phase vessel of step c using an agitator at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

e. adding to an oil-phase vessel an emulsifying wax, preferably Cetostearyl alcohol, in an amount preferably between 1 and 15 %, more preferably 12.5 % and a waxy material, preferably white soft paraffin, in an amount preferably between 5 and 20 %, more preferably 12.5 %, and melting them by heating to 70 °C to 80 °C,

f. adding to said oil phase vessel a non ionic surfactant or emulsifier, in an amount preferably between 1 and 5 %, more preferably 2 % of Polysorbate 80 and 1% of Cetomacrogol 1000, and mixing the mixture thoroughly using an agitator at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

g. transferring the contents of the water-phase vessel of step d and oil-phase vessel of step f to a mixing vessel under vacuum conditions in the range of

minus 1000 to minus 300 mm of mercury and at 70 ^{o} C to 80 ^{o} C and mixing the mixture at 10 to 50 RPM to form an emulsion,

h. cooling the emulsion of said mixing vessel to 45 ^{o} C preferably by circulating cold water at a temperature between 8 and 15 ^{o}C from cooling tower in the jacket of the mixing vessel,

i. adding in a first API-vessel a co-solvent selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400adding propylene glycol, or any mixture thereof, in an amount preferably between 5% (w/w) and 30% (w/w), more preferably 25% (w/w), and optionally adding and dissolving an antioxidant, selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, or any combination thereof, added in an amount preferably between 0.001% (w/w) and 0.1 % (w/w), more preferably 0.01 % (w/w) Butylated Hydroxy Toluene in it by continuous mixing,

j. subjecting the contents of said first API-vessel to inter gas flushing, said inert gas preferably being nitrogen and adding Sodium Fusidate to the mixture and dissolving it in the mixture, said sodium fusidate being added in an amount between 0.1% (w/w) and about 25% (w/w), preferably between 0.5% (w/w) and about 5% (w/w) and more preferably about 2.08 % (w/w),

k. adjusting the pH of the mixture in said first API-vessel of step j to below 2 by using an acid, selected from a group comprising acids such as HCL, H_2SO_4 , HNO_3 , lactic acid and the like, either singly or any combination thereof,

preferably Nitric acid in an amount preferably between 0.005% (w/w) and 0.5 % (w/w), preferably 0.3 % (w/w), more preferably 0.25% (w/w),

l. adding in a second API-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 10% (w/w), heating to 60°C and dissolving Mometasone Furoate in it by continuous mixing.

m. adding in a third API-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 13% (w/w) and dispersing Miconazole nitrate in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill

n. transferring the contents of said first API-vessel of step k to said mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas preferably being nitrogen,

o. transferring the contents of the said second API-vessel of step l to said mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

p. transferring the contents of the colloid milled Miconazole nitrate from the third API – vessel of step m to the said mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenising the mixture at 1000

to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

q. in a biopolymer-mixing vessel adding an acid, selected from a group comprising acids such as HCl, H_2So_4, HNO_3, Lactic acid and the like, either singly or any combination thereof, preferably Lactic acid to form a from about 0.005% (w/w) to 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.1% (w/w), and purified water from about 0.1% (w/w) to 10% (w/w), preferably 8% (w/w), more preferably 5% (w/w) to form a mixture and dissolving the said biopolymer, Chitosan in an amount between about 0.01% and about 1% by weight, preferably from about 0.01% w/w to about 0.5% w/w and most preferably about 0.25% w/w,

r. transferring the contents of the biopolymer mixture of step q to the mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas being preferably nitrogen,

s. cooling the contents of said mixing vessel of step h to 30 ^{o} C to 37 ^{o} C using circulation of cooled water from cooling tower at 8 ^{o} C to 15 ^{o} C into the jacket of mixing vessel,

t. turning off the agitator and the homogenizer and removing the mixture of the mixing vessel of step s to a storage container.

The co-solvent of step i also serves as a humectant. However, in an embodiment of the invention, an additional humectant may be added, selected from a group comprising Glycerin, Sorbitol, Propylene glycol and the like, either singly or any combination thereof, to form a from about 5% (w/w) to 40% (w/w), preferably 30% (w/w), more preferably 25% (w/w).

Embodiment no. 16: A method of treating primary & secondary bacterial & fungal skin infections and inflammations said method comprising applying of a cream containing at least one corticosteroid Mometasone furoate, one antifungal Miconazole nitrate and Fusidic acid which is made in situ under oxygen-free environment using Sodium Fusidate, wherein said cream comprises Fusidic acid made using Sodium Fusidate, a cream base containing a preservative, primary and secondary emulsifiers, waxy materials, co-solvents, acids, and water.

Embodiment no. 17 : A method of treating primary & secondary bacterial & fungal skin infections and inflammations said method comprising applying of a cream as described in the preferred embodiment 1 and any of embodiments 1 to 9. The cream obtained using the process of the present invention is homogenous and white to off white in colour and viscous in consistency. The pH of the product made using the process of the present invention is from about 3 to 6. On the other hand, Sodium Fusidate ointments that are commercially available are greasy and cosmetically non elegant.

It is essential that the active drug penetrates the skin for the optimum bio-dermal efficacy. The particle size of the active drug plays an important role here. It is necessary that the active drug is available in a finely dispersed form for the product to be being efficacious. Also this is to be achieved in the safe pH compatible environment of skin (4.0 to 6.0). To achieve all these, it is essential to choose proper vehicles or co-solvents for the dissolution or dispersion of the drug.

The product of the present invention is efficacious due to the pronounced antibacterial activity of the regenerated Fusidic acid, antifungal activity of the Miconazole nitrate, anti-inflammatory activity of the Mometasone furoate which are available in reduced particle size than the conventional products, and in a finely dispersed form.

Tests for determination of particle size of fusidic acid were carried out on several products available in the market containing fusidic acid and also on the present invention. An optical microscope (Carl Zeiss Axio Star Plus 2x to 100x magnification) was used. Table 8A provides the results.

Table 8A (Particle Size Distribution of Fusidic Acid) (All sizes in µm)

PARTICLE SIZE DISTRIBUTION								
S.No	**Invention**	**A**	**C**	**D**	**F**	**G**	**J**	**K**
1	1.64	9.88	15.02	17.83	17.74	16.47	28.52	23.9
2	0.34	13.58	14.73	22.17	19.9	22.94	28.36	24.74
3	0.49	39.58	13.54	11.65	15.9	10.72	23.98	19.07
4	0.24	5.23	9.32	24.69	19.9	18.87	21.97	5.94
5	0.65	8.87	12.54	18.19	14.91	21.75	31.49	5.75
6	2.52	19.27	32.69	27.52	8.84	10.42	24.41	15.63
7	0.77	19.1	11.72	22.1	16.2	29.48	41.35	18.5
8	1.55	7.46	13.05	25.01	17.74	17.74	33.91	16.15
9	1.06	24.82	14.01	17.46	7.93	12.59	10.21	27.69
10	0.89	20.1	6.9	16.83	16.2	10.31	11.88	5.75
11	0.66	15.32	10.42	18.75	14.91	19.65	13.55	10.27
12	1.78	29.24	12.54	19.01	15.9	18.87	20.12	8.15
13	1.46	12.36	8.96	20.68	13.9	7.29	24.32	14.22
14	0.7	7.23	6.07	18.19	18.43	10.72	4.17	17.62
15	0.95	17.27	14.91	24.69	18.78	22.94	13.28	23.39
16	0.65	25.62	15.02	9.8	17.08	9.43	20.23	22.88
17	1.04	15.25	28.55	11.65	7.93	11.07	30.92	25.08
18	0.73	15.21	22.36	16.96	16.2	8.87	13.25	7.08
19	1.36	35.25	10.25	11.22	8.84	15.36	28.12	11.56
20	1.22	21.31	9.68	15.36	9.23	9.65	28.16	32.63
AVR	**1.035**	**18.09**	**14.11**	**18.48**	**14.82**	**15.25**	**22.61**	**16.8**
MAX	**2.52**	**39.58**	**32.69**	**27.52**	**19.9**	**29.48**	**41.35**	**32.63**
MIN	**0.24**	**7.23**	**6.07**	**9.8**	**7.93**	**7.29**	**4.17**	**5.75**
CV	**0.536**	**0.511**	**0.474**	**0.269**	**0.272**	**0.398**	**0.411**	**0.483**

It can be seen from the results that the size of the fusidic acid particles is considerably smaller than that of fusidic acid in existing products. Whereas the maximum particle size observed for fusidic acid of the present invention is less than 3µm, the maximum particle size observed for existing creams varies between

19 µm to 42 µm, with a majority of them having the maximum particle size between 30 µm and 40 µm. The average size of the fusidic acid particles in the present invention has been found to approximately 1 µm whereas that for the existing creams varies between 14 µm to 22 µm. Equally importantly, the minimum particle size observed was approx. 0.25 µm whereas the minimum particle size observed for existing creams ranged between 4 µm and 10 µm. The cream of the present invention is therefore physically distinct from any of the existing creams and easily distinguishable.

Table 8B – Sample data for test results of table 8A

Sample description	
Sodium Fusidate + Mometasone Furoate Cream + biopolymer (present invention)	**Mfg.Date:** June 2010; **Exp.Date:** May 2012
Sample A	Mfg.Date : Aug'09; Exp.Date: Jul'11
Sample C	Mfg.Date : Jul'09; Exp.Date: Jun'11
Sample D	Mfg.Date : Jul'09; Exp.Date: Jun'11
Sample F	Mfg.Date : Aug'09; Exp.Date: Jul'11
Sample G	Mfg.Date : Aug'09; Exp.Date: Jul'11
Sample J	Mfg.Date : Dec'09; Exp.Date: Nov'11
Sample K	Mfg.Date : Dec'09; Exp.Date: Nov'11

The reduced particle size of the fusidic acid of the present invention is of particular significance as it has been achieved without compromising the stability of fusidic acid. In contrast with this, products such as those disclosed in WO2007087806 by Leo Pharma have employed mechanical means such as mortar and pestle to mechanically grind fusidic acid for adding to a cream base. Although WO2007087806 is silent on the particle size achieved, it will be known to a

person skilled in the art that its particle size of fusidic acid cannot be finer than that of the present invention. Moreover, the stability of the fusidic acid in creams produced by the teachings of WO2007087806 or indeed fusidic acid creams that employ grinding of fusidic acid in presence of oxygen cannot be as good as that of the present invention as evidenced by the data included in Table 8A.

The inventor has screened different co-solvents such as Propylene Glycol, Hexylene Glycol, PolyEthyleneGlycol-400 & the like and dissolved the Sodium Fusidate in one of above co-solvents varying from about 5% (w/w) to 40% (w/w) under inert gas purging and under vacuum and converted to Fusidic acid in-situ by adding an acid such as HCl, H_2SO_4, HNO_3, Lactic acid and the like from about 0.005% (w/w) to about 0.5% (w/w) under stirring and obtained Fusidic acid in more stabilized and solution form, which makes our final product in a cream base which easily penetrates the skin and highly efficacious, and also highly derma compatible by having a pH of about 3.0 to about 6.0.

The stability of the product is confirmed by the stability studies performed for 6 months as per ICH guidelines and a comparison of stress studies done for in-house product with those on samples of commercially available comparable products.

Experimental Data:

API-stability experiments were carried out (see tables 9 - 11) using the product of the present invention and products currently commercially 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 oxydative degradation test. Further, in vitro antimicrobial zone of inhibition studies and preclinical studies such as blood clotting studies & burns wound healing studies were also carried out over a period of time. Each gram of product of the present invention used for the tests contained Sodium Fusidate as the starting raw material in the amount required to produce approximately 2% (w/w) Fusidic acid, 0.1% (w/w) Mometasone furoate & 2%(w/w) Miconazole nitrate in the finished product.

The product used for the Stability Studies tests contained approximately 10% extra API (overages). The product of the present invention used for studies contained Fusidic acid cream prepared using Sodium Fusidate as starting material. It was packaged in an aluminium collapsible tube and each gram of the product contained 20.8 mg of Sodium Fusidate (in conformance with BP), which is equivalent to 20 mg of Fusidic acid (BP conformant) and appropriate amount of steroids and antifungals as mentioned below.

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It is apparent from tables 10 - 12 that on all counts, the pH value, the physical appearance, and stability, the product of the present invention is quite good.

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 composition of the final cream is given in the table 9 below.

Example-: Table 9 Fusidic acid 2.0% (equivalent of Sodium Fusidate 2.08% w/w) + Mometasone Furoate (0.1% w/w) + Miconazole nitrate (2% w/w) + Chitosan 0.25% (w/w) Cream

S.No	Ingredients	Specification	% (w/w)
1	Sodium Fusidate (equ. to make Fusidic Acid 2% w/w)	BP	2.08
2	Mometasone Furoate	USP	0.1
3	Miconazole Nitrate	IP	2
4	Chitosan	USP/NF	0.25
5	Lactic acid	IP	0.1
6	White soft Paraffin	IP	12.5
7	Cetostearyl Alcohol	IP	12.5
8	Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)	USP	1
9	Polysorbate 80	IP	2
10	Benzoic Acid	IP	0.2
11	Disodium Edetate	IP	0.1
12	Disodium Hydrogen Orthophosphate anhydrous	IP	0.5
13	Propylene Glycol	IP	48
14	Butylated Hydroxy Toluene	IP	0.01
15	1 M Nitric Acid Solution	IP	4
16	Purified water	IP	15

PRODUCT: SODIUM FUSIDATE + MOMETASONE FUROATE + MICONAZOLE NITRATE CREAM

PACK: Aluminum Collapsible tube

Composition Each gm contains: i) Sodium Fusidate BP equivalent to Fusidic Acid BP 2.0 % ii) Mometasone Furoate USP 0.1 % iii) Miconazole Nitrate IP 2.0 %

Table 10: Description Test, Batch No. SMN-04

Measured parameter: Physical appearance

Best value of measured parameter: Homogeneous White to off White Viscous cream; **Method of measurement:** Observation by naked eye

Conditions	**Initial**	**1st Month**	**2nd Month**	**3rd Month**
40°C 75% RH	Homogenous White to off White viscous cream	same as initial	same as initial	same as initial
30°C 65% RH	-	Do	Do	Do
25°C 60% RH	-	Do	Do	Do
Temp cycling	-	Do	-	-
Freezthaw	-	Do	-	-

Table 11: Assay (%) Test, Batch No. SMN-04

Measured parameter: Assay (%); **Limits of measured parameter:** 90-110

Method of measurement: HPLC Method

Conditions	**Assay (%)**	***Initial***	**1st Month**	**2nd Month**	**3rd Month**
40°C 75% RH	i) Fusidic acid	109.77	109.66	109.44	109.28
	ii) Mometasone Furoate	107.16	107.11	107.08	107.02
	iii) Miconazole Nitrate	108.56	108.46	108.35	108.21
30°C 65% RH	i) Fusidic acid	-	109.68	109.61	109.22
	ii) Mometasone Furoate	-	107.15	107.12	107.05
	iii) Miconazole Nitrate	-	108.55	108.40	108.23
25°C 60% RH	i) Fusidic acid	-	109.54	109.45	109.25
	ii) Mometasone Furoate	-	107.15	107.08	107.05
	iii) Miconazole Nitrate	-	108.55	108.42	108.38
Temperature cycling	i) Fusidic acid	-	109.66	-	-
	ii) Mometasone Furoate	-	107.11	-	-
	iii) Miconazole Nitrate	-	108.25	-	-
Freezthaw	i) Fusidic acid	-	108.51	-	-
	ii) Mometasone Furoate	-	107.05	-	-
	iii) Miconazole Nitrate	-	108.15	-	-

Table 12: pH Test, Batch No. SMN-04
Measured parameter: pH; **Limits of measured parameter:** 5-7
Method of measurement: Digital pH Meter

Conditions	Initial	1st Month	2nd Month	3rd Month
40°C 75% RH	4.22	4.21	4.21	4.20
30°C 65% RH	-	4.21	4.21	4.20
25°C 60% RH	-	4.21	4.20	4.20
Temperature cycling	-	4.19	-	-
Freezthaw	-	4.18	-	-

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. This is a major advantage over the currently available Fusidic acid creams. 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.

The antimicrobial/antibacterial activity of the product is confirmed by the in vitro Zone of Inhibition studies for the product. The results obtained clearly indicate the statistical significance.

A comparison of table 10 with tables 3 to 7 will illustrate the difference in the products that would be based on the conventional drug design and the innovative approach adopted in the present invention.

Method Of Application Of The Cream:

The cream is applied after thorough cleansing and drying the affected area. Sufficient cream should be applied to cover the affected skin and surrounding

area. The cream should be applied two – four times a day depending upon the skin conditions for the full treatment period, even though symptoms may have improved.

Experiments:

Experiments were carried out with the cream in laboratory as well as using suitable animal models inflicted with excision wounds. Four aspects were tested – wound contraction, epithelisation, blood clotting time, and film forming. These aspects together would suggest that the microbes were immobilized thereby leading to effective wound healing.

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A. Wound Contraction:

Excision wound healing activity of the cream of the present invention was determined through animal testing. An excision wound 2.5 cm in diameter was inflicted by cutting away full thickness of the skin. The amount of contraction of the wound observed over a period indicated that the cream of present invention provides significantly improved wound contraction than a control(untreated wound).

B. Period Of Epithelisation:

Epithelisation of the wound occurred within shorter number of days using the cream of the present invention as compared to the days taken for epithelisation

using the conventional cream Therefore one benefit of the cream of the present invention is that it facilitates significantly faster epithelisation of the skin than a control (untreated wound).

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C. 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 50-60% was observed for the blood clotting time using the product of the present invention.

Film Forming Properties:

It is evident from figure 1 that chitosan does not lose its film forming property in the presence of the excipients used for cream preparations in the present invention.

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 animal testing, of the addition of chitosan to Sodium Fusidate an antibacterial agent, Mometasone furoate a corticosteroid & Miconazole nitrate an antifungal is shown in the following table by considering various aspects of therapeutic cure of a compromised skin condition:

Table 13

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. Immobilisation of microbes	None explicitly claimed	Expected to immobilise the surface microbes because of the cationic charge of chitosan
3. Epidermal growth support	None explicitly claimed	It is well known that chitosan possesses properties that have significant complimentary action on epidermal growth. This functional aspect of chitosan is preserved in the product of the present invention
4. Micro-film forming	None explicitly claimed	Yes (see figure 2)
5. Overall wound healing medicinal effect	Standard as per existing products	Provides statistically significant superior healing properties

Wound healing studies were carried out on animals and using the cream of the present invention and the results were found to be statistically significant for the invention for wound healing & epithelisation when compared against a control (untreated wound).

It is evident that the film forming ability of the chitosan incorporated in the cream allows better access of the antibacterial agent, Sodium Fusidate to the infected area and results in better functioning of these API.

The therapeutic efficacy of topically applied cream of the present invention is due to the pronounced antibacterial / antifungal activity of the Sodium Fusidate & Miconazole nitrate against the organisms responsible for skin infections, pronounced antiinflammatory activity of the Mometasone furoate against inflammations, the unique ability of actives to penetrate intact skin and wound healing & soothing properties of chitosan.

It is further evident that the ability of the cream of the present invention to achieve statistically significant level of epithelisation as well as wound contraction is surprisingly greater than the currently available therapies.

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 bacterial/fungal infections, inflammations and for wound healing of the skin:

1. The cream of the present invention incorporates a skin-friendly biopolymer in the form of chitosan provides enhanced therapeutic outcomes. This is evident from the reduced blood clotting time,

increased epithelial effect, and faster relief from infection and inflammation and wound contraction.

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 physio-chemical compatibility/stability and bio-release.
3. The cream of the present invention provides an integrated uni-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.

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

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 medicinal cream for topical treatment of bacterial skin infections, fungal skin infections, inflammations and for wound healing including burns wound, said cream containing Fusidic acid as an antibacterial, Mometasone furoate as a corticosteroid, Miconazole nitrate as an antifungal, and a biopolymer, preferably chitosan, in a cream base containing at least one of each of a primary and secondary emulsifier, a preservative, a waxy material, a co-solvents, an acid, and water characterized in that said fusidic acid is manufactured in situ under oxygen free environment using Sodium Fusidate so that average particle size of said fusidic acid in said cream is less than 4µm.

2. A medicinal cream as claimed in claim 1, wherein said cream base comprises a preservative, an acid, a co-solvent, an emulsifier and a waxy material along with water, preferably purified water.

3. A novel dermaceutical cream as claimed in claim 1, wherein

- said Fusidic acid is present in an amount from about 0.1% (w/w) to about 25% (w/w), preferably from about 0.5% (w/w) to about 5%(w/w), and more preferably about 2.00 % (w/w), and in which the amount of said Sodium Fusidate used to form in situ said Fusidic acid is in the range between about 0.1% (w/w) to about 25% (w/w), preferably from about 0.5% (w/w) to about 5% (w/w) and more preferably about 2.08 % (w/w), and

- said mometasone furoate is added from about 0.005% to about 2.5% by weight, preferably from about 0.005% to about 1.00% by weight, and most preferably about 0.1% by weight, and

- said miconazole nitrate is added from about 0.5% to about 5.0% by weight, preferably from about 0.5% to about 3.0% by weight, and most preferably about 2.0% by weight; and

- said chitosan is added in an amount between about 0.01% (w/w) and about 1% (w/w), preferably from about 0.01% w/w to about 0.5% w/w and most preferably about 0.25% w/w,

- said primary and secondary emulsifiers are selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Polysorbate-80, Span-80 and the like and added in an amount from about 1% (w/w) to 20% (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 0.5 % (w/w); said preservative is selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid and the like, or any combination thereof, and added in an amount from about

0.05% (w/w) to 0.5% (w/w); said water is added in the amount in the range of 5% (w/w) to 40% (w/w), preferably 15% (w/w) to 30% (w/w), more preferably 7% (w/w) to 15% (w/w), preferably purified water.

4. A novel medicinal cream as claimed in claims 1 and 3 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 0.001% (w/w) to 1.00% (w/w).

5. A novel medicinal cream as claimed in claims 1, 3, and 4 further comprising an antioxidant which is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, or any combination thereof, and added in an amount from about 0.001% (w/w) to 1% (w/w).

6. A novel medicinal cream as claimed in claims 1 and 3 to 5 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).

7. A novel medicinal cream as claimed in claims 1 and 3 to 6 further comprising a humectant which is selected from a group comprising Glycerin, Sorbitol, Propylene Glycol and the like, or any combination thereof, and added in an amount from about 5% (w/w) to 50% (w/w).

8. A novel dermaceutical cream as claimed in claims 1 and 3 to 7, wherein sodium fusidate is converted in-situ under totally oxygen free environment by slow addition of an acid, into Fusidic acid of a molecular dispersion form (due to the presence of a co-solvent) at the intermediate stage, and which Fusidic acid regenerates into an extremely finely dispersed form when added to a final cream base, thereby resulting in a finely and homogeneously dispersed Fusidic acid in the final cream; all operations of converting sodium fusidate into Fusidic acid carried out preferably in an environment free of atmospheric oxygen.

9. A novel dermaceutical cream as claimed in claims 1 to 8 wherein said conversion of Sodium Fusidate into said Fusidic acid and the following formation of said Fusidic acid in a finely dispersed form in the final cream base takes place in an oxygen-free environment.

10. A novel dermaceutical cream as claimed in claim 9 wherein said oxygen-free environment comprises a gaseous environment formed of inert gas selected from a group comprising carbon dioxide, nitrogen, helium and the like.

11. A process to make fusidic acid, mometasone furoate, Miconazole nitrate cream as claimed in claim 8 wherein the step of using sodium fusidate as the raw active pharmaceutical ingredient and converting said sodium fusidate in

situ into fusidic acid under oxygen-free environment in a cream base comprises the steps of:

a. heating purified water in the range from 5% (w/w) to 40% (w/w), preferably 5% (w/w) to 30% (w/w), more preferably 7% (w/w) to 15% (w/w), in a water-phase vessel to 70 °C to 80 °C,

b. adding to said water-phase vessel a preservative, selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid and the like, either singly or any combination thereof, in an amount between 0.05% (w/w) and 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.2% (w/w), more preferably Benzoic acid,

c. mixing the mixture using an agitator at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

d. adding waxy materials, selected from a group comprising white soft paraffin, liquid paraffin, hard paraffin and the like, either singly or any combination thereof, in an amount between 5% (w/w) and 20% (w/w), preferably 15% (w/w), more preferably12.5% (w/w), to an oil-phase vessel and melting said wax by heating to 70 °C to 80 °C,

e. adding to said oil-phase vessel of a primary emulsifier, preferably in the form of a non ionic surfactant, selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, either singly or any combination thereof, wherein Cetostearyl alcohol is added in an amount between 1% (w/w) and 15% (w/w), preferably 15% (w/w), more preferably 12.5% (w/w), and Cetomacrogol-1000 is added in an amount between 0.1%

(w/w) and 5% (w/w), preferably 1% (w/w), more preferably 0.5% (w/w), and optionally a secondary emulsifier selected from a group comprising Polysorbate-80, Span-80 and the like, preferably Polysorbate-80, in an amount between 1 and 5% w/w, more preferably 2% w/w and mixing the mixture thoroughly, preferably using an agitator, at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

f. transferring under vacuum in the range of minus 1000 to minus 300 mm of mercury and at 70 °C to 80 °C the contents of the water-phase and oil-phase vessels to a mixing vessel and mixing the mixture thoroughly, preferably using an agitator, at 10 to 50 RPM to form an emulsion,

g. cooling said emulsion to 45 °C preferably by circulating cold water, preferably at 8 °C to 15 °C from a cooling tower in the jacket of the mixing vessel,

h. in a first API-vessel adding a co-solvent, selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400 and the like, either singly or any combination thereof, in an amount between 5% (w/w) and 40% (w/w), preferably 30% (w/w), more preferably 25% (w/w), preferably propylene glycol, subjecting the contents of said API-vessel to inert gas flushing, said inert gas being preferably nitrogen, and adding sodium fusidate to the mixture, said sodium fusidate added in an amount between 0.1% (w/w) and about 25% (w/w), preferably from about 0.5% (w/w) to about 5% (w/w) and more preferably about 2.08 % (w/w), and dissolving said sodium fusidate in the mixture,

i. adjusting the pH of the mixture in said first API-vessel of step h to below 2 by using an acid, selected from a group comprising acids such as HCl, H_2SO_4, HNO_3, Lactic acid and the like, either singly or any combination thereof, preferably Nitric acid in an amount from about 0.005% (w/w) to 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.25% (w/w),

j. adding in a second API-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 10% (w/w), heating to 60°C and dissolving Mometasone Furoate in it by continuous mixing,

k. adding in a thirdAPI-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 13% (w/w) and dispersing Miconazole nitrate in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill,

l. transferring the contents of said first API-vessel of step i to the mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas being preferably nitrogen,

m. transferring the contents from said second API-vessel of step j to said mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

n. transferring the contents of the colloid milled Miconazole nitrate from the third API – vessel of step k to the said mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenising the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

o. in a biopolymer-mixing vessel adding an acid, selected from a group comprising acids such as HCl, H2So4, HNO3, Lactic acid and the like, either singly or any combination thereof, preferably Lactic acid to form a from about 0.005% (w/w) to 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.1% (w/w), and purified water from about 0.1% (w/w) to 10% (w/w), preferably 8% (w/w), more preferably 5% (w/w) to form a mixture and dissolving a biopolymer, preferably Chitosan in an amount between about 0.01% w/w and about 1% w/w, preferably from about 0.01% w/w to about 0.5% w/w and most preferably about 0.25% w/w,

p. transferring the contents of the biopolymer-mixing vessel of step o to the mixing vessel of step g with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas being preferably nitrogen,

q. cooling the contents of the mixing vessel of step g to 30 ^{o}C to 37 ^{o}C using circulation of cooled water from a cooling tower at 8 ^{o}C to 15 ^{o}C into the jacket of mixing vessel,

r. turning off the agitator and the homogenizer and removing the mixture of the mixing vessel of step q to a storage container.

12. A process to make fusidic acid cream as claimed in claim 2 further wherein a humectant is added to the mixing vessel of step a in claim 11 said humectant being selected from a group comprising Glycerin, Sorbitol, Propylene glycol and the like, either singly or any combination thereof, to form a from about 5% (w/w) to 40% (w/w), preferably 30% (w/w), more preferably 25% (w/w).

13. A process to make fusidic acid cream as claimed in any of claims 2 and 12 further wherein a chelating agent is added to the step a of claim 11, said chelating agent being selected from a group comprising Disodium EDTA and the like, either singly or any combination thereof, to form a from about 0.01% (w/w) to 1% (w/w), preferably 0.5% (w/w), more preferably 0.1% (w/w).

14. A process to make fusidic acid cream as claimed in any of claims 2, 12, and 13 further wherein a buffering agent is added to the step a of claim 11, said buffering agent being selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like from about 0.001% (w/w) to 1.00% (w/w), preferably 0.05% (w/w), more preferably 0.5% (w/w).

15. A process to make fusidic acid cream as claimed in any of claim 2,12 to 14, further wherein an anti oxidants is added to step h of claim 11, said anti oxidant being selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like from about 0.001% (w/w) to 5% (w/w), preferably 0.1% (w/w), more preferably 0.01% (w/w).

16. A process to make a cream as claimed in claims 2 to 10, said process comprising the steps of:

a. heating purified water in the range from 5% (w/w) to 40% (w/w), preferably 5% (w/w) to 30% (w/w), more preferably 7% (w/w) to 15% (w/w) in a water-phase vessel to 70 °C to 80 °C,

b. adding to said water-phase vessel a preservative, selected from a group comprising Methylparaben, Propylparaben, Chlorocresol, Potassium sorbate, Benzoic acid and the like, either singly or any combination thereof, added in an amount between 0.05% (w/w) and 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.2% (w/w), the preferred preservative being Benzoic acid,

c. optionally adding to said water-phase vessel of step b a chelating agent, or buffering agent , or a humectants added in combination thereof, wherein said chelating agent is preferably Disodium edetate, added in an amount preferably between 0.01 and 1 %, more preferably 0.1%, said buffering agent is preferably Di Sodium Hydrogen Ortho Phosphate, added in an amount preferably 0.01% (w/w) to 2.00% (w/w), preferably 1.5% (w/w),

more preferably 1% (w/w) and said humectant is preferably Propylene Glycol, added in an amount preferably 5% (w/w) to 60% (w/w), more preferably 48.5% (w/w),

d. mixing the mixture of said water-phase vessel of step c using an agitator at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

e. adding to an oil-phase vessel an emulsifying wax, preferably Cetostearyl alcohol, in an amount preferably between 1 and 15 %, more preferably 12.5 % and a waxy material, preferably white soft paraffin, in an amount preferably between 5 and 20 %, more preferably 12.5 %, and melting them by heating to 70 °C to 80 °C,

f. adding to said oil phase vessel a non ionic surfactant or emulsifier, in an amount preferably between 1 and 5 %, more preferably 2 % of Polysorbate 80 and 1% of Cetomacrogol 1000, and mixing the mixture thoroughly using an agitator at 10 to 50 RPM while maintaining the temperature of the mixture at 70 °C to 80 °C,

g. transferring the contents of the water-phase vessel of step d and oil-phase vessel of step f to a mixing vessel under vacuum conditions in the range of minus 1000 to minus 300 mm of mercury and at 70 °C to 80 °C and mixing the mixture at 10 to 50 RPM to form an emulsion,

h. cooling the emulsion of said mixing vessel to 45 °C preferably by circulating cold water at a temperature between 8 and 15 °C from cooling tower in the jacket of the mixing vessel,

i. adding in a first API-vessel a co-solvent selected from a group comprising Propylene Glycol, Hexylene Glycol, PolyEthylene Glycol-400adding propylene glycol, or any mixture thereof, in an amount preferably between 5% (w/w) and 30% (w/w), more preferably 25% (w/w), and optionally adding and dissolving an antioxidant, selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, or any combination thereof, added in an amount preferably between 0.001% (w/w) and 0.1 % (w/w), more preferably 0.01 % (w/w) Butylated Hydroxy Toluene in it by continuous mixing,

j. subjecting the contents of said first API-vessel to inter gas flushing, said inert gas preferably being nitrogen and adding Sodium Fusidate to the mixture and dissolving it in the mixture, said sodium fusidate being added in an amount between 0.1% (w/w) and about 25% (w/w), preferably between 0.5% (w/w) and about 5% (w/w) and more preferably about 2.08 % (w/w),

k. adjusting the pH of the mixture in said first API-vessel of step j to below 2 by using an acid, selected from a group comprising acids such as HCL, H_2SO_4 , HNO_3 , lactic acid and the like, either singly or any combination thereof, preferably Nitric acid in an amount preferably between 0.005% (w/w) and 0.5 % (w/w), preferably 0.3 % (w/w), more preferably 0.25% (w/w),

l. adding in a second API-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 10% (w/w),

heating to 60°C and dissolving Mometasone Furoate in it by continuous mixing,

m. adding in a thirdAPI-vessel propylene glycol in an amount between 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 13% (w/w) and dispersing Miconazole nitrate in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill,

n. transferring the contents of said first API-vessel of step k to said mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas preferably being nitrogen,

o. transferring the contents of the said second API-vessel of step l to said mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

p. transferring the contents of the colloid milled Miconazole nitrate from the third API – vessel of step m to the said mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenising the mixture at 1000 to 3000 RPM under vacuum, preferably of a magnitude between minus 1000 and minus 300 mm of mercury,

q. in a biopolymer-mixing vessel adding an acid, selected from a group comprising acids such as HCl, H_2So_4, HNO_3, Lactic acid and the like, either singly or any combination thereof, preferably Lactic acid to form a

from about 0.005% (w/w) to 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.1% (w/w), and purified water from about 0.1% (w/w) to 10% (w/w), preferably 8% (w/w), more preferably 5% (w/w) to form a mixture and dissolving the said biopolymer, Chitosan in an amount between about 0.01% and about 1% by weight, preferably from about 0.01% w/w to about 0.5% w/w and most preferably about 0.25% w/w,

r. transferring the contents of the biopolymer mixture of step q to the mixing vessel of step h with continuous stirring at 10 to 50 RPM and homogenizing the mixture at 1000 to 3000 RPM under inert gas flushing and under vacuum of minus 1000 to minus 300 mm of mercury, said inert gas being preferably nitrogen,

s. cooling the contents of said mixing vessel of step h to 30 ^{o}C to 37 ^{o}C using circulation of cooled water from cooling tower at 8 ^{o}C to 15 ^{o}C into the jacket of mixing vessel,

t. turning off the agitator and the homogenizer and removing the mixture of the mixing vessel of step s to a storage container.

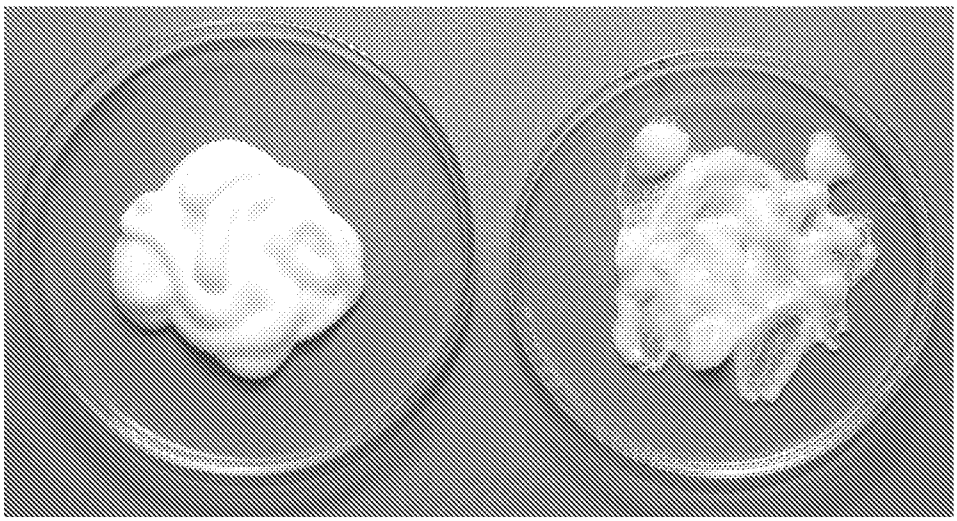

Figure 1

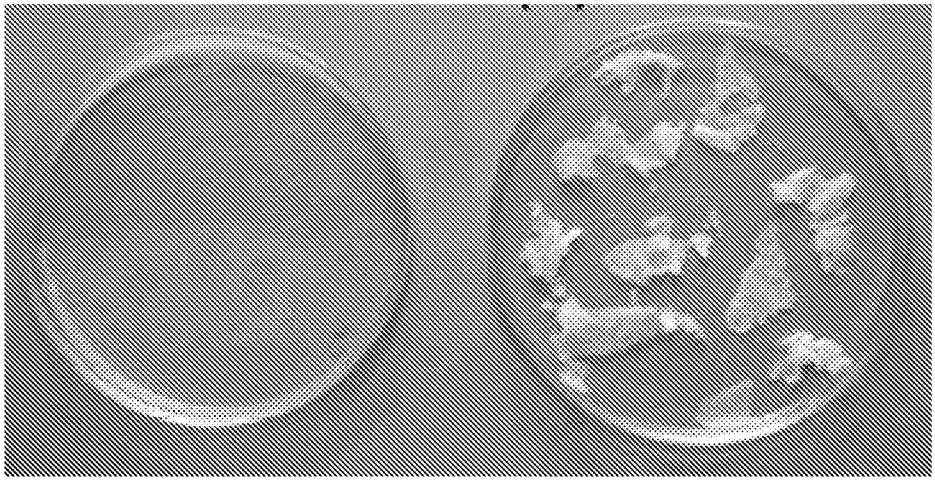

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/056128

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/06 A61K31/56 A61K31/573 A61K31/722 A61K31/575
A61K31/415 A61K31/58
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 practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/106503 A1 (VANANGAMUDI SULUR SUBRAMANIAM [IN]; SRINIVASAN MADHAVAN [IN]; CHULLIEL) 23 September 2010 (2010-09-23) page 1, line 1 - page 32, last line; figures 1-13; tables 1-6 -----	1-16
Y	WO 2009/063493 A2 (GLENMARK PHARMACEUTICALS LTD [IN]; SEN NILENDU [IN]; GOLE KUSUM DINKAR) 22 May 2009 (2009-05-22) page 7, lines 3-8 page 8, lines 4-11 page 12, lines 12-16 page 13, line 15 page 16, line 23 - page 18, line 7; claims 1-22; examples 1-8; tables 1-6, 1A-6A -----	1-16

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 January 2012	24/01/2012

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2010/056128

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/45645 A1 (IVREA INC [US]; CATTANEO MAURIZIO V [US]; DEMIERRE MARIE FRANCE [US]) 28 June 2001 (2001-06-28) page 9, lines 2-14 page 10, lines 17-27 page 13, lines 7-15 page 20, line 1; claims 1-31	1-16
Y	RAVI KUMAR M N V: "A review of chitin and chitosan applications", REACTIVE & FUNCTIONAL POLYMERS, ELSEVIER SCIENCE PUBLISHERS BV, NL, vol. 46, no. 1, 1 November 2000 (2000-11-01), pages 1-27, XP004224437, ISSN: 1381-5148, DOI: 10.1016/S1381-5148(00)00038-9 page 9, right-hand column, paragraph 3 - page 10, right-hand column, paragraph 2 page 21, right-hand column, paragraphs 2,4	1-16
Y	RAMSAY C A ET AL: "The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate", JEADV. JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 7, no. SUPPL. I, 1 July 1996 (1996-07-01), pages S15-S22, XP002582785, ISSN: 0926-9959, DOI: 10.1016/0926-9959(96)00032-3 [retrieved on 2002-10-11] abstract page 16, right-hand column, paragraph 2 - page 21, right-hand column, paragraph 3	1-16
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