Abstract:
The invention discloses a dermaceutical cream containing Fluticasone Propionate as a corticosteroid, an antifungal agent in the form of Clotrimazole and an antibacterial agent in the form of Fusidic acid, which Fusidic acid is formed in situ from Sodium Fusidate as the starting raw material, wherein Sodium Fusidate is converted into Fusidic acid under oxygen-free environment. The cream 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 of the present invention contains Fusidic acid as the API that has been formed in situ from Sodium Fusidate, Fluticasone Propionate and Clotrimazole, in a cream base comprising a preservative, an acid, a co-solvent, emulsifiers and a waxy material along with water, preferably purified water.
A DERMACEUTICAL CREAM MADE USING SODIUM FUSIDATE, CLOTRIMAZOLE AND FLUTICASONE PROPIONATE

A Novel Dermaceutical Cream Made Using Sodium Fusidate, Clotrimazole And Fluticasone Propionate, A Process To Make The Same, And A Method Of Treatment Using It

Field Of Invention

The present invention relates to primary & secondary bacterial skin infections and inflammations and in particular it relates to the single dose treatment using a cream containing a corticosteroid in the form of Fluticasone Propionate and an antifungal agent in the form of Clotrimazole an antibacterial agent in the form of Fusidic acid wherein the Fusidic acid has been made using Sodium Fusidate as the starting Active Pharmaceutical Ingredient (API).

Background Of The Invention

Use of steroids to alleviate inflammation, irritation and itching caused by skin ailments is well known. It is also well known that use of steroids compromises patient's immune system and exposes them to bacterial and fungal infections. Single dose therapies containing steroids, antifungals and antibacterials are well known.

Numerous single dose treatments, both topical and systemic, are currently employed for the treatment of above skin inflammations. Topical and systemic inflammatory treatment compositions typically employ a combination of corticosteroids in a base component. The active ingredients typically comprise
Corticosteroids such as Betamethasone Valerate, Fluticasone Propionate, Mometasone Furoate, Dexamethasone Acetate, Hydrocortisone Acetate, Clobetasol Propionate, Beclomethasone Dipropionate, Betamethasone Dipropionate and the like.

Fungal infections sometimes follow the use of antibiotics, which kill nonpathogenic as well as pathogenic bacteria, thereby providing a free field in the body for fungal invasion.

Numerous treatments both topical and systemic are currently employed for the treatment of fungal infections. Topical and systemic fungal infections, treatment compositions typically employ antifungal agents as active ingredients in a base component.

The active ingredients typically comprise antifungal agents such as Miconazole Nitrate, Terbinafine Hydrochloride, Ketoconazole, Clotrimazole and the like.

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 °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 Fusidic acid cream in which Fusidic acid will be of greater stability at the time of the manufacture of the cream, and which will sustain its stability at an acceptable level throughout its shelf life.

There's a need to provide dermaceutical cream containing Mometasone furoate as a steroid, clotrimazole as an antifungal, and an antibacterial in the form of Fusidic acid, and in which Fusidic acid will be of greater stability at the time of the manufacture of the cream, and which will sustain its stability at an acceptable level throughout its shelf life.

20 Objects And Advantages Of The Invention

It is therefore one object of the present invention to provide a cream which contains Fusidic acid as the active API but which has greater stability of the API throughout its shelf life.
It is a further objective of the present invention to provide a dermaceutical cream containing at least one steroid, and an antibacterial agent in the form of Fusidic acid, in which Fusidic acid will be of greater stability at the time of the manufacture of the cream, and which will sustain its stability at an acceptable level throughout its shelf life.

**Brief Summary Of The Invention**

The invention discloses a dermaceutical cream containing Fluticasone Propionate as a corticosteroid, an antifungal agent in the form of Clotrimazole and an antibacterial agent in the form of Fusidic acid, which Fusidic acid is formed in situ from Sodium Fusidate as the starting raw material, wherein Sodium Fusidate is converted into Fusidic acid under oxygen-free environment. The cream 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 of the present invention contains Fusidic acid as the API that has been formed in situ from Sodium Fusidate, Fluticasone Propionate and Clotrimazole, in a cream base comprising a preservative, an acid, a co-solvent, emulsifiers and a waxy material along with water, preferably purified water.
Detailed Description Of The 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 are made using Sodium Fusidate as starting API are not available.

- Creams containing Fusidic acid that are made using Sodium Fusidate along with a corticosteroid in the form of Fluticasone Propionate as starting APIs are not available.

- Creams containing Fusidic acid that are made using Sodium Fusidate along with corticosteroid in the form of Fluticasone Propionate and Clotrimazole as antifungal agent are also 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.

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, and, 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 UPLC 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:**

**Table 1: Results Of 3 Months Old Fusidic Acid (API) Analysis By Stability Indicating HPLC Method And Titration Method**

<table>
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<tr>
<th>S.No</th>
<th>Conditions</th>
<th>Initial (%)</th>
<th>Fusidic Acid Assay (%)</th>
<th>%age Drop (%)</th>
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Name of Sample: **FUSIDIC ACID BP**; Pack: Open (O) & Closed (C) Petri dish
Stability Analysis of Sodium Fusidate:

Table 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

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<th>S.No</th>
<th>Conditions</th>
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</table>

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 applicant explored the possibility of making a cream (rather than an ointment) using Sodium Fusidate (rather than Fusidic acid) and a corticosteroid in the form of such as Fluticasone Propionate. 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 and steroids 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 and steroids.

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 found
that the stability of the cream of the present invention over the entire shelf life of
the product is within acceptable level. This is strikingly advantageous over
existing creams contain fusidic acid as APIs, which have a life of one month once
the tube has been opened. The applicant has also discovered that the Fusidic acid
and steroids cream prepared using Sodium Fusidate as the starting APIs showed
good chemical stability, and efficacy.

The application discloses a cream containing Steroids in the form of Fluticasone
Propionate 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 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.

The cream of the present invention contains Fusidic acid as the API that has been
formed in situ from Sodium Fusidate, a steroid in the form of Fluticasone
Propionate in a cream base comprising an acid, a preservative, a co-solvent,
emulsifiers and a waxy material along with water, preferably purified water.
The cream base of the present invention optionally further comprises an ingredient selected from a group comprising a buffering agent, an antioxidant, a chelating agent, and a humectant, or any combination thereof.

The present invention provides 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.

The Fusidic acid and steroid cream of the present invention has been manufactured in a totally oxygen free environment under purging with inert gas and applying vacuum. Under these conditions, the Sodium Fusidate is converted in situ into Fusidic acid. The cream of the present invention is used in the treatment of bacterial skin infections and inflammations.

The pH of the product of the present invention is between 3 and 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 anti-inflammatory, antibacterial activity of the steroid and regenerated Fusidic acid which is 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 by Carl Zeiss (Axio Star Plus 2x to 100x magnification) was used for this purpose. Table 2A provides the results. 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 3μη, the maximum particle size observed for existing creams varies between 19 μη to 42 μη, with a majority of them having the maximum particle size between 30 μη and 40 μη. The average size of the fusidic acid particles in the present invention has been found to be approximately 1 μη whereas that for the existing creams varies between 14 μη to 22 μη. Equally importantly, the minimum particle size observed was approx. 0.28 μη whereas the minimum particle size observed for existing creams ranged between 4 μη and 10 μη. The cream of the present invention is therefore physically distinct from any of the existing creams and easily distinguishable.
Table 2A (Particle Size Distribution of Fusidic Acid)

(All sizes in µη)

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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 any fusidic acid creams

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<tr>
<td>Sample G</td>
<td>Aug'09</td>
<td>Jul'11</td>
</tr>
<tr>
<td>Sample J</td>
<td>Dec'09</td>
<td>Nov'11</td>
</tr>
<tr>
<td>Sample K</td>
<td>Dec'09</td>
<td>Nov'11</td>
</tr>
</tbody>
</table>
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 2A.

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 between 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 HC1, H2SO4, HNO3, Lactic acid and the like between 0.005% (w/w) and 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 present invention discloses the following embodiments.

15 **Preferred embodiment 1**

A novel dermatceutical cream containing Fluticasone Propionate as a corticosteroid, Clotrimazole as antifungal agent and Fusidic acid which is made in situ by conversion of sodium fusidate under oxygen-free environment, and a cream base containing at least one of each of a preservative, a primary and secondary emulsifiers, a waxy material, a co-solvent, an acid, and water, preferably purified water.
Embodiment 1

A novel dermaceutical cream as disclosed in the preferred embodiment 1, said cream further incorporating any of any of a group comprising a buffering agent, an antioxidant, a chelating agent, and a humectant, or any combination thereof.

Embodiment no. 2

A novel dermaceutical cream as described in the preferred embodiment 1, wherein said corticosteroid is added in the form of Fluticasone propionate, added in an amount between 0.005% (w/w) and about 2.5% (w/w), preferably between 0.005% (w/w) and about 1.00% (w/w), and most preferably about 0.05%(w/w), and

said antifungal agent is added in the form if Clotrimazole, added in an amount between 0.5% (w/w) to about 5.0% (w/w), preferably from about 0.5% (w/w) to about 3.0% (w/w), and most preferably from about 1.0 % (w/w), and

said Fusidic acid is present 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 2.00 % (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) and about 25% (w/w), preferably between 0.5% (w/w) and about 5% (w/w) and more preferably about 2.08 % (w/w), and
said preservatives is 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),

said primary and secondary emulsifiers are selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Polysorbate-80, Span-80 and the like, either singly or any combination thereof, in an amount between 1% (w/w) and 25% (w/w), preferably 20% (w/w), more preferably 15% (w/w),

said waxy material is 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 preferably 12.5% (w/w),

said co-solvent is 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 35% (w/w), more preferably 30% (w/w),

said acid is selected from a group comprising acids such as HC1, H₂SO₄, HNO₃, Lactic acid and the like, either singly or any combination thereof, in an
amount between 0.005% (w/w) and 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.25% (w/w), and

water in the amount in the range of 5% (w/w) to 70% (w/w), preferably 10% (w/w) to 50% (w/w), more preferably 30% (w/w) to 40% (w/w), preferably purified water.

Embodiment no. 3

A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments no. 1 and 2, which further comprises a buffering agent, wherein said buffering agent is selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like, either singly or any combination thereof, in an amount between 0.01% (w/w) and 2.00% (w/w), preferably 1.5% (w/w), more preferably 1.0% (w/w).

Embodiment no. 4

A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments no. 1 to 3 which further comprises an anti-oxidant, wherein said anti-oxidant is selected from a group comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the like, either singly or any combination thereof, in an amount between 0.001% (w/w) and 5% (w/w), preferably 0.1% (w/w), more preferably 0.01% (w/w).
Embodiment no. 5

A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments nos. 1 to 4 which further comprises a chelating agent, wherein said chelating agent is selected from a group comprising Disodium EDTA and the like, either singly or any combination thereof, in an amount between 0.01% (w/w) and 1% (w/w), preferably 0.5% (w/w), more preferably 0.1% (w/w).

Embodiment no. 6

A novel dermaceutical cream as described in the preferred embodiment 1 and embodiments nos. 1 to 5 which further comprises a humectant, wherein said humectant is selected from a group comprising Glycerin, Sorbitol, Propylene glycol and the like, either singly or any combination thereof, in an amount between 5% (w/w) and 40% (w/w), preferably 35% (w/w), more preferably 30% (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

5 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

10 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 no. 2

A process to make a cream containing Fluticasone Propionate, Clotrimazole and fusidic acid, said cream being as disclosed in preferred embodiment 1 and embodiment 1, said process comprising 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, to which Fluticasone Propionate and Clotrimazole are added.
A process to make a cream containing Fluticasone Propionate, Clotrimazole and fusidic acid as described in the preferred embodiment nos. 1 and embodiment no. 1 wherein said 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, to which Fluticasone Propionate and Clotrimazole are added, further comprises the steps of:

a. heating purified water in the range from 5% (w/w) to 60% (w/w), preferably 10% (w/w) to 50% (w/w), more preferably 30% (w/w) to 45% (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 preferably 12.5% (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, Cetomacrogo 1-1000, 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 Cetomacrogo 1-1000 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 20%
(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,
H2SO4, HNO3, 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) and 20% (w/w), preferably 15% (w/w), more preferably 5% (w/w)
and purified water in an amount between 1% (w/w) and 20% (w/w),
preferably 15% (w/w), more preferably 5% (w/w), and dissolving
surfactant preferably Cetomacrogo1-1000 in an amount between 0.1%
(w/w) and 3% (w/w), preferably 1% (w/w), more preferably 0.5% (w/w)
and dispersing Fluticasone Propionate in it by continuous mixing to form a
dispersion, followed bypassing said dispersion through a colloid mill, said
Fluticasone Propionate being added in an amount between 0.005% (w/w)
and about 2.5% (w/w) , preferably between 0.005% (w/w) and about
1.00% (w/w), and more preferably between 0.005% (w/w) and
0.05%(w/w), and
k. adding in the third API - vessel propylene glycol in an amount 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 5% (w/w) and dispersing Clotrimazole in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill, and said Clotrimazole being added in an amount between 0.5% (w/w) and about 5.0% (w/w), preferably from about 0.5% (w/w) to about 3.0% (w/w), and most preferably 1.00% (w/w); and

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 of the colloid milled Fluticasone Propionate 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 Clotrimazole 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,
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,

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

Embodiment no. 11

In another embodiment of the present invention the process described in embodiment no. 10 further incorporates after the step of adding a preservative, a step of adding a chelating agent, selected from a group comprising Disodium EDTA and the like, either singly or any combination thereof, in an amount from about 0.01% (w/w) to 1% (w/w), preferably 0.5% (w/w), more preferably 0.1% (w/w).

Embodiment no. 12

In yet another embodiment of the present invention the process described in embodiments no. 10 and 11 further incorporates after the step of adding the chelating agent, a buffering 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. 13

In a further embodiment of the present invention the process described in embodiments no. 10, 11, and 12 further incorporate in the step h of embodiment 10, an anti oxidant 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. 14

In a further embodiment of the present invention the process described in embodiments no. 10, 11,12 and 13 further incorporate a humectant in the step a of embodiment 10, wherein said humectant is selected from a group comprising Glycerin, Sorbitol, Propylene glycol and the like, either singly or any combination thereof, in an amount between 5% (w/w) and 40% (w/w), preferably 35% (w/w), more preferably 30% (w/w).

Embodiment no. 15

A process to make a cream containing Fluticasone Propionate and fusidic acid as described in embodiment no 8 comprising the steps of:

a. heating purified water in the range from 5% (w/w) to 60% (w/w), preferably 10% (w/w) to 50% (w/w), more preferably 30% (w/w) to 45% (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% (w/w), more preferably 0.5% (w/w) and said humectant is preferably Propylene Glycol, added in an amount preferably 5% (w/w) to 40% (w/w), more preferably 25% (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 0.5% 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-400 adding propylene glycol, or any mixture thereof, in an amount preferably between 5% (w/w) and 30% (w/w), more preferably 20% (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 0.01% (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, H₂SO₄, HNO₃, 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. in a second API-vessel adding propylene glycol, in an amount preferably between 1% (w/w) and 20% (w/w), more preferably 5% (w/w) and purified water in an amount between 1% (w/w) and 20% (w/w), more preferably 5% (w/w), and dissolving Surfactant, preferably Cetomacrogol-1000 in an amount between 0.1% (w/w) and 3% (w/w), more preferably 0.5% (w/w) and dispersing Fluticasone Propionate in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill, said Fluticasone Propionate being added in an amount between 0.005% (w/w) and about 2.5% (w/w), preferably between 0.005% (w/w) and about 1.00% (w/w), and most preferably about 0.05% (w/w), and

m. adding in the third API-vessel propylene glycol in an amount 1% (w/w) to 20% (w/w), more preferably 5% (w/w), and dispersing Clotrimazole in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill, said Clotrimazole being added in an
amount between 0.5% (w/w) and about 5.0% (w/w), preferably from about 0.5% (w/w) to about 3.0% (w/w), and most preferably about 1.0% (w/w), and

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 colloid milled Fluticasone Propionate from 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 Clotrimazole 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. cooling the contents of said mixing vessel of step p to 30 °C to 37 °C using circulation of cooled water from 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. 16

A method of treating primary & secondary skin infections and inflammations said method comprising applying of a cream containing at least one corticosteroid 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 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.

It is thus clear that the process of the Invention uses a technology whereby Sodium Fusidate is precipitated as Fusidic acid as a result of a mixture of the water-based alkaline solution of SF and an acid. The precipitated fusidic acid, while still in the liquid (and thereby barred from exposure to atmospheric oxygen) is dissolved using a suitable solvent under the effect of inert gas.

Experimental Data

The stability of the product is confirmed by the stability studies performed for 3 or 6 months as per ICH guidelines.
APIs-stability experiments were carried out (see tables 4 - 6 ) using the product of the present invention. Tests were carried out to observe (or measure as appropriate) the physical appearance of the product, the pH value and assay of the APIs over a period of time. Each gram of product of the present invention used for the tests contained Sodium Fusidate in the amount required to produce 2% (w/w) Fusidic acid in the finished product and appropriate amount of steroids and antifungals as mentioned below.

Table 3 :
Composition : Sodium Fusidate + Fluticasone Propionate + Clotrimazole Cream

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ingredients</th>
<th>Specification</th>
<th>% (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sodium Fusidate</td>
<td>BP</td>
<td>2.08</td>
</tr>
<tr>
<td>2</td>
<td>Fluticasone Propionate</td>
<td>BP</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>Clotrimazole</td>
<td>IP</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>White soft Paraffin</td>
<td>IP</td>
<td>12.5</td>
</tr>
<tr>
<td>5</td>
<td>Cetostearyl Alcohol</td>
<td>IP</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>Polyoxyl 20 Cetostearyl ether (Cetomacrogol 1000)</td>
<td>USP</td>
<td>0.5</td>
</tr>
<tr>
<td>7</td>
<td>Polysorbate 80</td>
<td>IP</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Benzoic Acid</td>
<td>IP</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>Disodium Edetate</td>
<td>IP</td>
<td>0.1</td>
</tr>
<tr>
<td>10</td>
<td>Disodium Hydrogen Orthophosphate anhydrous</td>
<td>IP</td>
<td>1.0</td>
</tr>
<tr>
<td>11</td>
<td>Propylene Glycol</td>
<td>IP</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>Butylated Hydroxy Toluene</td>
<td>IP</td>
<td>0.01</td>
</tr>
<tr>
<td>13</td>
<td>1 M Nitric Acid Solution</td>
<td>IP</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>Purified water</td>
<td>IP</td>
<td>34.1</td>
</tr>
</tbody>
</table>
PRODUCT: SODIUM FUSIDATE + FLUTICASONE PROPIONATE + CLOTRIMAZOLE CREAM

PACK: Aluminum Collapsible tube

Composition

Each gm contains:

i) Sodium Fusidate BP equivalent to Fusidic Acid BP 2.0 %

ii) Fluticasone Propionate BP 0.05 %

iii) Clotrimazole IP 1.0 %

Table 4: Description Test, Batch No. SFF-02

Measured parameter: Physical appearance

Best value of measured parameter: Homogeneous White to off White Viscous cream

Method of measurement: Observation by naked eye

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Initial</th>
<th>1st Month</th>
<th>2nd Month</th>
<th>3rd Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>40°C 75% RH</td>
<td>Homogenous White to off White viscous cream</td>
<td>Homogenous White to off White viscous cream</td>
<td>Homogenous White to off White viscous cream</td>
<td>Homogenous White to off White viscous cream</td>
</tr>
<tr>
<td>30°C 65% RH</td>
<td>-</td>
<td>Do</td>
<td>Do</td>
<td>Do</td>
</tr>
<tr>
<td>25°C 60% RH</td>
<td>-</td>
<td>Do</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Temperature cycling</td>
<td>-</td>
<td>Do</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Freezthaw</td>
<td>-</td>
<td>Do</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5: pH Test, Batch No. SFF-02

Measured parameter: pH

Limits of measured parameter: 3-6

Method of measurement: Digital pH Meter

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Initial</th>
<th>1st Month</th>
<th>2nd Month</th>
<th>3rd Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>40°C 75% RH</td>
<td>5.54</td>
<td>5.54</td>
<td>5.52</td>
<td>5.53</td>
</tr>
<tr>
<td>30°C 65% RH</td>
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Table 6: Assay (%) Test, Batch No. SFF-02

**Measured parameter:** Assay (%)
**Limits of measured parameter:** 90-110
**Method of measurement:** HPLC Method

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The product used for the stability studies tests contained approximately 10% extra APIs (overages). 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). The % of sodium fusidate, antifungal and the corticosteroid used in all examples are measured w/w with respect to the final product.
It is evident from the foregoing description that the present invention has the following distinctions and advantages over the commercially available comparable products:

- It has been prepared using Sodium Fusidate which is more stable than Fusidic acid
- It has a more stable and quality enriched Fusidic acid as the final API
- The Fusidic acid in the present invention degrades more slowly than the conventional products
- The stability level of the Fusidic acid in the present invention remains within the acceptable limits throughout the shelf life of the product
- The particle size of the Fusidic acid is finer and overall particle distribution in the cream is better, thereby providing better dermatological efficacy

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 novel dermaceutical cream containing Fluticasone Propionate as a corticosteroid, Clotrimazole as a antifungal agent, Fusidic acid as an antibacterial agent and a cream base containing at least one of each of a preservative, a primary and secondary emulsifiers, a waxy material, a co-solvents, an acid, and water, preferably purified water, characterised in that said fusidic acid is manufactured in situ under oxygen-free environment from Sodium Fusidate so that the average particle size of said fusidic acid in said cream is less than 2µm.

2. A novel dermaceutical cream as claimed in claim 1, said cream further incorporating any of any of a group comprising a buffering agent, an antioxidant, a chelating agent, and a humectant, or any combination thereof.

3. A novel dermaceutical cream as claimed in claim 1, wherein said corticosteroid is added in the form of Fluticasone propionate, added in an amount between 0.005% (w/w) and about 2.5% (w/w), preferably between 0.005% (w/w) and about 1.00% (w/w), and most preferably about 0.05% (w/w), and said antifungal agent is added in the from if Clotrimazole, added in an amount between 0.5% (w/w) and about 5.0% (w/w), preferably from about 0.5% (w/w) to about 3.0% (w/w), and most preferably from about 1.0% (w/w), and
said Fusidic acid is present 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 2.00 % (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) and about 25% (w/w), preferably between 0.5% (w/w) and about 5% (w/w) and more preferably about 2.08 % (w/w), and

said preservatives is 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),

said primary and secondary emulsifiers are selected from a group comprising Cetostearyl alcohol, Cetomacrogol-1000, Polysorbate-80, Span-80 and the like, either singly or any combination thereof, in an amount between 1% (w/w) and 25% (w/w), preferably 20% (w/w), more preferably 15% (w/w),

said waxy material is 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 preferably 12.5% (w/w),
said co-solvent is 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 35% (w/w), more preferably 30% (w/w),

said acid is selected from a group comprising acids such as HCl, H$_2$SO$_4$, HNO$_3$, Lactic acid and the like, either singly or any combination thereof, in an amount between 0.005% (w/w) and 0.5% (w/w), preferably 0.3% (w/w), more preferably 0.25% (w/w), and

water in the amount in the range of 5% (w/w) to 70% (w/w), preferably 10% (w/w) to 50% (w/w), more preferably 30% (w/w) to 40% (w/w), preferably purified water.

4. A novel dermatological cream as claimed in claims 1 and 3 which further comprises a buffering agent, wherein said buffering agent is selected from a group comprising Di Sodium Hydrogen Ortho Phosphate, Sodium Hydrogen Ortho Phosphate and the like, either singly or any combination thereof, in an amount between 0.01% (w/w) and 2.00% (w/w), preferably 1.5% (w/w), more preferably 1% (w/w).

5. A novel dermatological cream as claimed in claims 1, 3, and 4 which further comprises an anti-oxidant, wherein said anti-oxidant is selected from a group
comprising Butylated Hydroxy Anisole, Butylated Hydroxy Toluene and the
like, either singly or any combination thereof, in an amount between 0.001% (w/w) and 5% (w/w), preferably 0.1% (w/w), more preferably 0.01% (w/w).

6. A novel dermaceutical cream as claimed in claims 1, and 3 to 5, which
further comprises a chelating agent, wherein said chelating agent is selected
from a group comprising Disodium EDTA and the like, either singly or any
combination thereof, in an amount between 0.01% (w/w) and 1% (w/w),
preferably 0.5% (w/w), more preferably 0.1% (w/w).

7. A novel dermaceutical cream as claimed in claims 1 and 3 to 6, which
further comprises a humectant, wherein said humectant is selected from a
group comprising Glycerin, Sorbitol, Propylene glycol and the like, either
singly or any combination thereof, in an amount between 5% (w/w) and 60%
(w/w), preferably 35% (w/w), more preferably 30% (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 take 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, preferably nitrogen.

11. A process to make a cream as claimed in claims 1 and 3 comprising the steps of:

   a. heating purified water in the range from 5% (w/w) to 60% (w/w), preferably 10% (w/w) to 50% (w/w), more preferably 30% (w/w) to 45% (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 preferably 12.5% (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 1-1000, 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 1-1000 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 20% (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, H₂SO₄, HNO₃, 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 5% (w/w) and purified water in an amount between 1% (w/w) and 20% (w/w), preferably 15% (w/w), more preferably 5% (w/w), and dissolving surfactant preferably Cetomacro go1-1000 in an amount between 0.1%
and dispersing Fluticasone Propionate in it by continuous mixing to form a dispersion, followed by bypassing said dispersion through a colloid mill, said Fluticasone Propionate being added in an amount between 0.005% (w/w) and about 2.5% (w/w), preferably between 0.005% (w/w) and about 1.00% (w/w), and more preferably between 0.005% (w/w) and 0.05% (w/w), and

k. adding in the third API-vessel propylene glycol in an amount 1% (w/w) to 20% (w/w), preferably 15% (w/w), more preferably 5% (w/w) and dispersing Clotrimazole in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill, and said Clotrimazole being added in an amount between 0.5% (w/w) and about 5.0% (w/w), preferably from about 0.5% (w/w) to about 3.0% (w/w), and most preferably 1.00% (w/w); and

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 of the colloid milled Fluticasone Propionate 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 Clotrimazole 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. 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,

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

12. 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 60% (w/w), preferably 10% (w/w) to 50% (w/w), more preferably 30% (w/w) to 45% (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% (w/w), more preferably 0.5% (w/w) and said humectant is preferably Propylene Glycol, added in an amount preferably 5% (w/w) to 40% (w/w), more preferably 25% (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 0.5% 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-400 adding
propylene glycol, or any mixture thereof, in an amount preferably between
5% (w/w) and 30% (w/w), more preferably 20% (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 0.01 %
(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$_2$SO$_4$, 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. in a second API-vessel adding propylene glycol, in an amount preferably between 1% (w/w) and 20% (w/w), more preferably 5% (w/w) and purified water in an amount between 1% (w/w) and 20% (w/w), more preferably 5% (w/w), and dissolving Surfactant, preferably Cetomacrogol-1000 in an amount between 0.1% (w/w) and 3% (w/w), more preferably 0.5% (w/w) and dispersing Fluticasone Propionate in it by continuous mixing to form a dispersion, followed bypassing said dispersion through a colloid mill, said Fluticasone Propionate being added in an amount between 0.005% (w/w) and about 2.5% (w/w), preferably between 0.005% (w/w) and about 1.00% (w/w), and most preferably about 0.05% (w/w), and

m. adding in the third API-vessel propylene glycol in an amount 1% (w/w) to 20% (w/w), more preferably 5% (w/w), and dispersing Clotrimazole in it by continuous mixing to form a dispersion, followed by passing said dispersion through a colloid mill, said Clotrimazole being added in an
amount between 0.5% (w/w) and about 5.0% (w/w), preferably from about 0.5% (w/w) to about 3.0% (w/w), and most preferably about 1.0% (w/w), and

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 colloid milled Fluticasone Propionate from said second API-vessel of step 1 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 Clotrimazole 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. cooling the contents of said mixing vessel of step p to 30 °C to 37 °C using circulation of cooled water from 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.
13. A method of treating primary & secondary skin infections and inflammations said method comprising applying any of the creams as claimed in claims 1 to 10.
### A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/415 A61K31/57 A61K31/575 A61P17/00

ADD.

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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, BIOSIS, EMBASE, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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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 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.
  * "Z" document member of the same patent family

Date of the actual completion of the international search

27 April 2011

Date of mailing of the international search report

03/05/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk

Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer

Young, Astrid
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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