FUSIDIC ACID – TOPICAL ANTIMICROBIAL IN THE MANAGEMENT OF STAPHYLOCOCCUS AUREUS

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ABSTRACT

Fusidic acid (FA) is derived from the fungus Fusidium coccineum which was originally isolated from monkey faeces and available in the market since 1962. FA inhibits bacterial protein synthesis by interference with elongation factor G (EF-G), which promotes translocation on the ribosome after peptide bond formation, preventing further elongation by inhibiting the GTPase function of the EF-G. The steroid like structure of FA confers good skin penetration and does not possess the unwanted side effects of steroids.

INTRODUCTION

FA is primarily active in vitro against various strains of staphylococci including Methicillin susceptible and resistant variety of S. aureus, heterogenous and non heterogenous vancomycin – intermediate S. aureus and most coagulase negative staphylococci, clostridia species, Peptococcus and Peptococcus are susceptible. Neisseria and Moraxella species, Legionella pneumophila are susceptible gram negative bacteria to FA. Alterations in EF-G structure, leading to FA binding or to acquisition of FA resistance gene, fusB. Mutations in fusA gene that lead into individual amino acid exchanges in EF-G leading to decreased affinity of the drug for the target.

Co-administration of a statin and fusidic acid may result in significant elevations of both agents, resulting in the severe rhabdomyolysis.

In view of newer technological advancements in the field of dermal delivery of fusidic acid is better option than the previous formulations. This is evidenced by recent patents with novel approaches such as use of biopolymers with reduction in particle size granted results in to longer shelf-life, greater stability and better penetrability.

Fusidic acid (FA) is derived from the fungus Fusidium coccineum which was initially isolated from monkey faeces[1] and available in the market since 1962. FA is weak acid with pKa of 5.7 and is available in ionized form in plasma and tissue at pH of 7.4. FA is highly (95-97%) protein bound, has similarity to bile salts and forms micelles at concentration of 1.44 to 4.56mM [2] and has a unique mode of action. FA is a tetracyclic triterpene, similar to cephalosporin P1 but differs by the addition of a few acetyl groups, which increases the activity. The nucleus has properties which is similar to adrenocorticoids and bile salts like cholate and taurocholate[3]. FA inhibits bacterial protein synthesis by interference with elongation factor G (EF-G), which promotes translocation on the ribosome after peptide bond formation, preventing further elongation by inhibiting the GTPase function of the EF-G[4]. The action of FA is mainly bacteriostatic but, at high concentrations, may be bactericidal. The steroid like structure of FA confers good skin penetration and does not possess the unwanted side effects of steroids [5]. The structure is shown in the figure 1.

Fig. 1: Structure of fusidic acid

FA is primarily active in vitro against various strains of staphylococci including Methicillin susceptible and resistant variety of S. aureus, heterogenous and non heterogenous vancomycin – intermediate S. aureus and most coagulase negative staphylococci, clostridia species, Peptococcus and Peptococcus are susceptible. Neisseria and Moraxella species, Legionella pneumophila are susceptible gram negative bacteria to FA. Whereas it has limited activity against streptococci and enterococci and most of the gram negative bacteria are resistant [6].

Susceptibility is generally defined as an MIC of ≤ 0.25 or ≤ 0.5 mg/L and resistance as an MIC of ≥ 2 mg/L. FA has MIC of 0.03 to 0.25 mg/L for S. aureus, 0.066 to 0.09 for MSSA and MRSA. A range of MIC between 0.12 and 0.25 is reported for Coagulase negative staphylococci. Marginal activity is seen against Streptococci at a concentration of 0.5 mg/L[7].

Mechanism of action

Two elongation factors, EF-Tu and EF-G are involved in the process of bacterial protein synthesis. FA blocks the bacterial protein synthesis by binding to EF-G on the ribosome, thereby preventing releasing of EF-G guanosine diphosphate complex and effectively stalling bacterial protein synthesis by inhibiting the translation, which is next step [8]. The action is mainly bacteriostatic but, at high concentrations, may be bactericidal. The gene encoding EF-G is fusA, which is chromosomally located.

Mechanism of resistance

Alterations in EF-G structure, leading to FA binding or to acquisition of FA resistance gene, fusB. Mutations in fusA gene that lead into individual amino acid exchanges in EF-G leading to decreased affinity of the drug for the target [9]. The mechanism of acquisition of plasmid mediated fusB resistant determinant which encodes modest levels FA resistance, leading to MIC of 16 mg/L[10]. The mechanism fusB mediated resistance is unclear.

Formulations

FA is available in the market in different formulations viz., oral tablets, which is film coated, oral suspension, intravenous formulation and most importantly, topical preparations. Topical preparations includes, a cream containing FA 2% in oil in water cream base, an ointment, and a gel. Sterile gauze squares impregnated with FA ointment is also available. Combination of FA with corticosteroid is also available in the market which has FA 2% along with either hydrocortisone or betamethasone in an ointment or cream base. It is also available as specially designed ophthalmic preparation for installing into conjunctival sac[11].

Absorption and penetration

A study has obtained 2.3% penetration is observed when sodium fusidate applied over excised skin of cadaver [12]. Levels above 1mg/L were achieved for longer than 12 hours, in the tear fluid of...
rabbits, dogs and humans after topical application of eye drops[13].

FA is highly bound to albumin, which ranges from 91 to 98% and it is potent displacer of bilirubin.

After the oral administration of FA 500 mg, peak concentrations (Cmax) range from 14.5 mg/L to 33.3 mg/L and time to Cmax is 2-3.2 hours. Level of FA is present even after 8 hours is 8-12.5 mg/L and at 12 hours is 7.5-10 mg/L, which exceeds the typical MIC of susceptible pathogens[11].

**Efficiency of FA**

Oral preparation of FA is available in the form of 250 mg film coated tablets, which is administered in twice daily regimen. Earlier evidences came from case series, where as randomized control trials are started at 1994, which has clearly stated that FA is as effective as other oral antibiotics in skin and soft tissue infections along with similar or greater tolerability[14]. These are tabulated in Table 1.

Bacteriological efficacy (BE), which is defined as eradication of the pre treatment pathogen or no swab being taken at the end of the treatment because no pathological material was present. The studies have demonstrated FA has similar or higher efficacy compared with other drugs[15-19]. Staphylococci were the predominant organism, and has efficacy of 92 to 100% compared with erythromycin and pristinamycin[20].

Various studies had shown that, both ointment and cream were effective in treating various SSTIs[21-39]. It was applied over skin, two or three times per day. FA has similar clinical and BE compared with other drugs. However, in some instances, advantages of FA were visible. In one study[30], FA ointment is as effective as mupirocin ointment and patients considered it is more acceptable because of greasiness of the mupirocin ointment. A Cochrane review revealed that, topical FA is equally, or more effective than oral antibiotics for impetigo patients[40]. A systematic review on Impetigo, concludes that, FA and mupirocin are equally effective and recommend the use for seven days and has better tolerability, hence better compliance compared to oral antibiotics[41]. A new drug retapamulin in impetigo condition had showed similar efficacy with fewer drug related adverse events for FA[34].

Atopic eczema is usually infected with *S. aureus*, and combination therapy of FA with steroid component are recommended as first line therapy. When the combination of FA/hydrocortisone was used, it is more effective than FA alone or hydrocortisone alone[42].

The studies have demonstrated the efficacy of Fusidic acid with infected eczema [35-39]. In all these studies, FA-stroid combination had shown similar or superior clinical or BE compared to other products.

### Epidemiology of FA resistance

A large, multicenter, study of staphylococcal resistance suggested that, the *S. aureus* resistance to FA was highly variable. The mean rate of FA resistance was 5% (median 1%, range 0-9%) with the highest rates were reported in Greece, Kuwait and newzeland with the rate of 49%, 20% and 13% respectively. MRSA was responsible organism in Greece and Kuwait, MSSA in Newzeland. Interestingly, low rates of resistance were observed in US and Australia[43].

When patients received the FA mono therapy for a shorter course (<2weeks) has reported resistance of around 5%, whereas, who received longer duration of therapy, reported 15% of resistance. When patients received the FA along with other drugs(pencillin,flucloxacillin,methicillin), the resistance rate is as low as 0.8% irrespective of shorter or longer duration of therapy[44].

Topical use of FA has increased in wide variety of SSTI. It also leads to increase in the resistance to FA. In a study conducted at UK, atopic eczema patients were most affected having 78% of isolates was resistant[45]. Retrospective study done by Mason et al., suggested that, exposure to FA during the previous six months were significantly associated (OR 2.77 and p=0.027) and leading to infection caused by FA resistant MSSA.

Incidences of MSSA and MRSA infections were on rise, which was showed in fig. 2, the data suggests that, MRSA isolates were low, before 1994 and percentage rates of resistance to FA is variable[46].

### Table 1: Clinical response of fusidic acid

<table>
<thead>
<tr>
<th>Reference</th>
<th>Fusidic acid Clinical response rate (Cure or improvement)</th>
<th>Comparator</th>
<th>Comparator clinical response rate (Cure or improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordin 1994 [20]</td>
<td>93.2%</td>
<td>Flucloxacillin</td>
<td>90.8%</td>
</tr>
<tr>
<td>Machet 1994 [15]</td>
<td>99%</td>
<td>Pristinamycin</td>
<td>96%</td>
</tr>
<tr>
<td>Newby [16]</td>
<td>86.6%</td>
<td>Ciprofloxacillin</td>
<td>91.5%</td>
</tr>
<tr>
<td>Morris 1990 [17]</td>
<td>75.8%</td>
<td>Flucloxacillin</td>
<td>81.1%</td>
</tr>
<tr>
<td>Wall 2000 [18]</td>
<td>85.3%</td>
<td>Erythromycin</td>
<td>87.3%</td>
</tr>
<tr>
<td>Claudy 2001 [19]</td>
<td>79.7%</td>
<td>Pristinamycin</td>
<td>76.1%</td>
</tr>
<tr>
<td>Macotela Ruiz 1988 [21]</td>
<td>95%</td>
<td>Dicloxacillin</td>
<td>89%</td>
</tr>
<tr>
<td>Langston 1990 [22]</td>
<td>95%</td>
<td>Mupirocin</td>
<td>98%</td>
</tr>
<tr>
<td>El Moty 1990 [23]</td>
<td>78%</td>
<td>Trimethoprin-polymixin</td>
<td>84%</td>
</tr>
<tr>
<td>Jafar 1991 [24]</td>
<td>47%</td>
<td>Trimethoprin-polymixin</td>
<td>73%</td>
</tr>
<tr>
<td>Hamann 1991 [25]</td>
<td>87%</td>
<td>Erythromycin</td>
<td>77%</td>
</tr>
<tr>
<td>Sutton 1992 [26]</td>
<td>97%</td>
<td>Mupirocin</td>
<td>98%</td>
</tr>
<tr>
<td>Christiansen 1994 [27]</td>
<td>82% (BE-93%)</td>
<td>Hydrogen peroxide</td>
<td>72% (BE-88%)</td>
</tr>
<tr>
<td>Koning 2002 [28]</td>
<td>95% (BE-89%)</td>
<td>Oxidine/floxine</td>
<td>86% (BE-74%)</td>
</tr>
<tr>
<td>Zelvedler 1984 [29]</td>
<td>99%</td>
<td>Mupirocin</td>
<td>86%</td>
</tr>
<tr>
<td>Morley 1988 [30]</td>
<td>86%</td>
<td>Mupirocin</td>
<td>97% (BE-93%)</td>
</tr>
<tr>
<td>White 1989 [31]</td>
<td>93% (BE-89%)</td>
<td>Mupirocin</td>
<td>94% (BE-97%)</td>
</tr>
<tr>
<td>Gilbert 1989 [32]</td>
<td>94% (BE-87%)</td>
<td>Mupirocin</td>
<td>90%</td>
</tr>
<tr>
<td>Jasuja 2001 [33]</td>
<td>84%</td>
<td>Retapamulin</td>
<td>95% (BE-98%)</td>
</tr>
<tr>
<td>Oranje 2001 [34]</td>
<td>90% (BE-94%)</td>
<td>Miconazole</td>
<td>68.6% (BE-83%)</td>
</tr>
<tr>
<td>Poyner 1996 [35]</td>
<td>69.5% (BE-97.9%)</td>
<td>/hydrocortisone</td>
<td>90% (BE-88%)</td>
</tr>
<tr>
<td>Wilkinson 1985 [36]</td>
<td>95% (BE-91%)</td>
<td>Neomycin/betamethasone</td>
<td>90% (BE-88%)</td>
</tr>
<tr>
<td>Javier 1986 [37]</td>
<td>75% (BE-78%)</td>
<td>Neomycin/betamethasone</td>
<td>81% (BE-72%)</td>
</tr>
<tr>
<td>Strategos 1986 [38]</td>
<td>98% (BE-86%)</td>
<td>Gentamicin/betamethasone</td>
<td>90% (BE-86%)</td>
</tr>
<tr>
<td>Hill 1998 [39]</td>
<td>57.9%</td>
<td>Cloquino/betamethasone</td>
<td>60.4%</td>
</tr>
</tbody>
</table>

BE- Bacteriological Efficacy
Drug Interactions

Co-administration of a statin and fusidic acid may result in significant elevations of both agents. In a recently published case series[47] had clearly demonstrated the fact, when a concomitant use of statin along with fusidic acid resulting the severe rhabdomyolysis. Convincing evidence exists for an interaction between these drugs.

Several other cases[47-57] which were reported, the statins were used for prolonged period, and when the fusidic acid was introduced, as it necessitates, causing the morbidity and mortality. Fusidic acid inhibits theCYP3A4 enzyme system and that this particular drug combination is likely to potentiate the toxicities of both drugs[48]. Hence, it is advised that, importance of close monitoring of patients on statins, when it is co prescribed with fusidic acid, by determining creatine kinase and liver function tests and by examining for new muscle weakness.

Pharmaceutical Technology relating to Formulation

Fusidic acid has a distinctive mechanism of action as an antimicrobial agent. It’s mainly active against staphylococci including multi-resistant strains. Fusidic acid is available in numerous formulations such as oral, intravenous and topical use.

Oral tablet/capsule

Fusidic acid was the first time used as the orally active antibiotics Leo Laboratories Limited USA based company launched the tablet formulation as Fucidin of 250 and 500mg[58].

The reports are available for conduct of the clinical studies of 250mg of the capsule for antiviral activity[59,60]. Sodium salt of fusidic acid was available as an enteric-coated which was available in the market for many years in several countries. In 1980, the enteric-coated form was reformulated as a film coated tablets for the fusidic acid which appears to be better tolerated and gives higher blood levels[61].

Oral suspension

Oral suspension of the fusidic acid has been available from launch of the product. Diethanolamine salt was formulated as oily suspension for intravenous use which showed the poor bioavailability parameters. Later it was formulated as an aqueous suspension containing fusidic acid hemihydrate. The hemihydrate was formulated in various flavors such as a chocolate and banana-flavored suspension[61].

Fig. 2: Trend showing the resistance of FA during 1990 to 2001. Adopted from Howden B and Garyson L[46]
the particle of the fusidic acid around 2-5μm compared with convention particle size of around 20 μm. The patent clearly evaluated for the comparative evaluation of the developed formulation to that of fusidin which was developed by Leo Pharmaceuticals Pvt Ltd. The Apex Laboratories claims that developed formulation is having longer shelf life, long term storage stability compared to the fusidin. The data here show that the developed formulation of fusidic acid diffusion rate is far higher than that of fusidin at all-time points measured and found that 74.20% of the drug release in 8hrs against 20.43%. The developed formulation uses the biopolymer as chitosan. Further Apex lab has developed pharmaceutical technology such as use of biofilms to have better penetration in the skin layer along with different therapeutic class such as steroids and antifungal agents with various pharmaceutical technology aspects. These formulations are having better penetrability across the skin layer and reduce the toxicity results in reduction in the microbial resistance.

Leo Pharmaceuticals Pvt Ltd also patented the technology for the preparation of the tablet dosage form by reducing the particle size which helps in better achievement of the plasma concentration in the body. Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim Sirketi filed the patent for the particle size distribution of the fusidic acid granules for the preparation of the tablet.

Table 2: Selected patents on fusidic acid

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Patent No.</th>
<th>Title of patent</th>
<th>Brief description</th>
<th>Inventor/Assignee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>US 6593 319 B1</td>
<td>Fusidic acid derivatives</td>
<td>The compound of present invention can be use both in the systemic treatment of infections and topical treatment of infections related to skin and eye.</td>
<td>Leo Pharmaceutical Products Ltd. Ballerup (DK)</td>
</tr>
<tr>
<td>2.</td>
<td>US 2011/0257144 A1</td>
<td>Novel dermaceutical cream made using sodium fusidate</td>
<td>A dermaceutical cream containing the fusidic acid which formed in situ from sodium fusidate. The developed cream has the greater shelf life stability and the finer particles size.</td>
<td>Apex Laboratories Private Ltd Chennai TN (IN)</td>
</tr>
<tr>
<td>3.</td>
<td>US 2011/281831 A1</td>
<td>Novel dermaceutical cream made using sodium fusidate, antifungals and steroids</td>
<td>A dermaceutical cream containing Betamethasone Valerate, Fluticasone Propionate, Mometasone Furoate, Dexamethasone Acetate, Hydrocortisone Acetate, Globetasol Propionate, Beclomethasone Dipropionate, Betamethasone Dipropionate and antifungal agents such as Miconazole Nitrate, Terbinafine Hydrochloride, Ketoconazole and an antibacterial agent in the form of fusidic acid is formed which formed in situ from sodium fusidate.</td>
<td>Apex Laboratories Private Ltd Chennai TN (IN)</td>
</tr>
<tr>
<td>4.</td>
<td>US 2011/301 137A1</td>
<td>Dermaceutical gel made using sodium fusidate and A process to make it</td>
<td>A dermaceutical gel containing the fusidic acid which formed in situ from sodium fusidate. The developed gel had the greater shelf life stability and the finer particles size. The gel base containing a natural, semi synthetic or synthetic polymers, a preservative an acid an alkali, a co-solvent with water.</td>
<td>Apex Laboratories Private Ltd Chennai TN (IN)</td>
</tr>
<tr>
<td>5.</td>
<td>US 2011/301 138A1</td>
<td>Process to make fusidic acid cream</td>
<td>A dermaceutical cream containing the fusidic acid which formed in situ from sodium fusidate. The developed cream has the greater shelf life stability and the finer particles size. The base comprises a preservative, an acid, a co-solvent, an emulsifier and wax material along with water.</td>
<td>Apex Laboratories Private Ltd Chennai TN (IN)</td>
</tr>
<tr>
<td>6.</td>
<td>US 2012/0035144 A1</td>
<td>Medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, a corticosteroid and an antifungal agent, and process to make it</td>
<td>The cream comprises of a biopolymer in the form of Chitosan, the fusidic acid which formed in situ from sodium fusidate, hydrocortisone and clotrimazole.</td>
<td>Apex Laboratories Private Ltd Chennai TN (IN)</td>
</tr>
<tr>
<td>7.</td>
<td>US 2012/0040946 A1</td>
<td>Medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, and process to make it</td>
<td>The cream comprises of a biopolymer in the form of Chitosan, the fusidic acid which formed in situ from sodium fusidate.</td>
<td>Apex Laboratories Private Ltd Chennai TN (IN)</td>
</tr>
<tr>
<td>8.</td>
<td>US 4025 620</td>
<td>Treatment of canine otitis and composition thereof</td>
<td>A liquid veterinary composition containing the diethanolamine fusidate and an antifungal antibiotic such as nystatin. The composition contain additionally a broad spectrum antibi-otics such as neomycin B</td>
<td>Leo Pharmaceutical Products Ltd A/S Ballerup, Denmark</td>
</tr>
<tr>
<td>9.</td>
<td>US 3287218</td>
<td>Antibacterial combination of fusidic acid or dihydrofusidic acid with novobiocin or dihydrofusidic acid with novobiocin</td>
<td>Antibacterial combination of fusidic acid or dihydrofusidic acid with novobiocin or dihydrofusidic acid</td>
<td>Lovens Kemiske, Fabrik Produktions-Aktieselskab Ballerup Denmark</td>
</tr>
</tbody>
</table>
A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, mometasone as a corticosteroid and clotrimazole as an antifungal agent, and a process to make it.

The cream comprises Chitosan as a biopolymer with fusidic acid that has been generated in situ from sodium fusidate, Mometasone furoate and clotrimazole.

13. WO2012049542

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

The cream comprises Chitosan as a biopolymer with fusidic acid that has been generated in situ from sodium fusidate, Mometasone furoate and clotrimazole.

14. WO2012049541

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

The cream comprises of a biopolymer in the form of Chitosan, fusidic acid that has been generated in situ from sodium fusidate and Hydrocortisone acetate.

15. WO2012049545

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer and a process to make it.

The cream comprises of a biopolymer in the form of Chitosan, fusidic acid that has been generated in situ from sodium fusidate which is having greater shelf life with finer particle size.

16. WO2012049544

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

The cream contains a biopolymer in the form of Chitosan, and active Pharmaceutical Ingredients (APIs), in the form of fusidic acid that has been generated in situ from sodium fusidate Hydrocortisone acetate & clotrimazole. The cream has greater shelf-life and the finer particle size of the API than the conventional creams containing Fusidic acid.

17. WO2012049543

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

A cream containing a biopolymer in the form of Chitosan, and active Pharmaceutical Ingredients (APIs), in the form of fusidic acid that has been generated in situ from sodium fusidate & Mometasone furoate. The cream has greater shelf-life and the finer particle size of the API than the conventional creams.

18. WO2012049540

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.

A cream containing a biopolymer in the form of Chitosan, and active pharmaceutical ingredients (APIs), in the form of fusidic acid that has been generated in situ from sodium fusidate, Hydrocortisone acetate and Miconazole nitrate. The cream has greater shelf-life and the finer particle size of the API than the conventional creams containing Fusidic acid.

19. WO2012049539

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.

A cream containing a biopolymer in the form of Chitosan, and active Pharmaceutical Ingredients (APIs), in the form of fusidic acid that has been generated in situ from sodium fusidate, Mometasone furoate and Miconazole nitrate.

20. WO2012030513

Methods for the treatment of bacterial infections in the respiratory system of a subject, such as the lungs of a subject, using fusidic acid alone or in combination with a second bacterial agent such as tobramycin, amikacin, fosfomycin or levofloxacin. The active ingredients, namely Chitosan, Betamethasone Dipropionate, Terbinafine Hydrochloride and Fusidic Acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic acid.

21. WO2012017370

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, betamethasone dipropionate, terbinafine hydrochloride and a process to make it.

Methods for the treatment of bacterial infections in the respiratory system of a subject, such as the lungs of a subject, using fusidic acid alone or in combination with a second bacterial agent such as tobramycin, amikacin, fosfomycin or levofloxacin. The active ingredients, namely Chitosan, Betamethasone Dipropionate, Terbinafine Hydrochloride and Fusidic Acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic acid.

22. WO2012017368

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, betamethasone dipropionate, and fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic acid.
A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, beclomethasone dipropionate, terbinafine hydrochloride and a process to make it

Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

23. WO2012017371

The cream comprises Chitosan. Globetasol Propionate, Terbinafine Hydrochloride and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, clobetasol propionate, oxiconazole nitrate, and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

24. WO2012017369

The active ingredients, namely Chitosan, Betamethasone Dipropionate, Clotrimazole and Fusidic Acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, beclomethasone dipropionate, clotrimazole and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

25. WO2012017383

The cream containing active ingredients, namely Chitosan, Betamethasone Dipropionate, Terbinafine Hydrochloride and Fusidic Acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, beclomethasone dipropionate, clotrimazole and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

26. WO2012017382

The cream containing active ingredients, namely Chitosan, Betamethasone Dipropionate, Miconazole Nitrate and Fusidic Acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, betamethasone dipropionate, clotrimazole and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

27. WO2012017381

The cream containing active ingredients, namely Chitosan, Betamethasone Dipropionate, Clotrimazole and Fusidic Acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, fluticasone propionate, oxiconazole nitrate, and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

28. WO2012023079

The cream comprises Chitosan. Fluticasone Propionate, Oxiconazole Nitrate and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, betamethasone dipropionate, oxiconazole nitrate, and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

29. WO2012023077

The cream comprises Chitosan. Globetasol Propionate, Oxiconazole Nitrate and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, clobetasol propionate, and an antifungal agent - oxiconazole nitrate, and a process to make it

Apex Laboratories Private Ltd Chennai TN (IN)

30. WO2012017372

The cream comprises Chitosan. Globetasol Propionate, Miconazole Nitrate and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.
and incorporating, a biopolymer, clobetasol propionate, miconazole nitrate and a process to make it acid. Sodium Fusidate is converted into Fusidic acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

31. WO2012023082 A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, a corticosteroid - hydrocortisone acetate, and an antifungal agent - terbinafine hydrochloride, and a process to make it The cream comprises Chitosan. Hydrocortisone acetate, Terbinafine Hydrochloride and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

32. WO2012023081 A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, a corticosteroid - hydrocortisone acetate, and an antifungal agent - oxiconazole nitrate, and a process to make it The cream comprises Chitosan. Dexamethasone Acetate, Oxiconazole Nitrate and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

33. WO2012023080 A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, a corticosteroid - fluticasone propionate, and an antifungal agent - terbinafine hydrochloride and a process to make it The cream comprises Chitosan. Fluticasone Propionate, Terbinafine Hydrochloride and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

34. WO2012023078 A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, a corticosteroid - dexamethasone acetate, and an antifungal agent - oxiconazole nitrate, and a process to make it The cream comprises Chitosan. Dexamethasone Acetate, Oxiconazole Nitrate and Fusidic acid. Sodium Fusidate is converted into Fusidic Acid under oxygen-free environment created using inert gas, preferably nitrogen, and Chitosan. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic Acid.

35. EP2419087 A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer and a process to make it The cream comprises a biopolymer in the form of Chitosan, with an Active Pharmaceutical Ingredient (API), in the form of fusidic acid which is formed in situ from Sodium Fusidate by converting it into Fusidic acid under oxygen-free environment created using inert gas, preferably nitrogen. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic acid and found to be surprisingly superior for use against skin infections with allergy & itching, & wounds on human skin than alternative creams currently available.

36. WO2011101830 A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer and clobetasone, and a process to make it The dermaceutical cream containing Clobetasone Butyrate and Fusidic acid, which is formed in situ from Sodium Fusidate converted into Fusidic acid under oxygen-free environment. The cream has greater shelf-life stability and the finer particle size of the API than the conventional creams containing Fusidic acid.

37. WO2011008193 (A1) Fusidic acid dosing regimens for treatment of bacterial infections Novel dosing regimens for the treatment and prevention of bacterial infections using fusidic acid salt for oral administration. The use of a high loading dose of fusidic acid, followed by moderate maintenance doses of the drug, have been used to prevent development of drug-resistant strains of bacteria, to increase the effective spectrum of the drug, and to avoid nausea and vomiting.
§P fusidic acid is better option.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Abstract</th>
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<tbody>
<tr>
<td>EP2382968 (A1)</td>
<td>Particle size distribution of fusidic acid granules</td>
<td>Associated with a prolonged course of therapy of high amounts of the drug.</td>
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<tr>
<td>WO2009063493</td>
<td>Topical pharmaceutical composition for the combination of fusidic acid and a corticosteroid</td>
<td>The present invention relates to topical compositions comprising combination of mometasone furoate and fusidic acid for prevention and treatment of dermal infections. The present invention also relates to topical compositions comprising Halobetasol propionate and fusidic acid and their use for prevention and treatment of dermal conditions.</td>
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<tr>
<td>EP1945654 (A2)</td>
<td>Preparation of an antibiotic crystalline fusidic acid</td>
<td>The present invention relates to processes for the crystallisation and for the preparation and isolation of a novel crystalline form of fusidic acid, to the use of said processes in the manufacture of pharmaceutical formulation or medicament.</td>
</tr>
<tr>
<td>EP0773783 (A1)</td>
<td>Preparation of fusidic acid tablets</td>
<td>The preparation of fusidic acid sodium salt tablets without an enteric coating in which the active ingredient in dry powdered form is compressed in a roller compactor, followed by size reduction to form a granulate for tabletting.</td>
</tr>
<tr>
<td>WO9301817 (A1)</td>
<td>Antiviral compositions comprising fusidic acid, L-ascorbic acid and salicylic acid and derivatives</td>
<td>A pharmaceutical composition for treating viral infections, notably the human immunodeficiency virus (HIV) comprises fusidic acid or a derivative or salt thereof such as sodium fusidate, L-ascorbic acid and salicylic acid or a pharmaceutically acceptable salt or derivative thereof such as acetyl salicylic acid.</td>
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CONCLUSION

Given the current scenario, emergence of fusidic acid resistance and increase in the hospital and community acquired Methicillin-resistant Staphylococcus aureus strains, restricting the use of fusidic acid as monotherapy for longer duration to treat chronic skin condition should be considered.

When we consider in medical practice suboptimal clinical outcomes will lead to longer therapy duration lesser adherence to therapy, possible adverse drug reactions and increase in the cost of therapy. Hence in view of newer technological advancements in the field of dermal delivery of fusidic acid is better option than the previous formulations. This is evidence by recent patents with novel approaches such as use of biopolymers with reduction in particle size granted by different authorities globally. Alternatively, pharmaceutical technology invention results in the modification of fusidic acid particle size results in to longer shelf-life, greater stability and better penetrability. Simultaneous it is also imperative to use with cautions on patients safety front. The extremely serious in-vivo interactions were observed between fusidic acid and statins when administered orally.

REFERENCES

15. Machet L, Puisant A, Vaillant L. Essai comparatif multicentrique de l'acide fusidique contre 's a deux posologies (500 mg et 1 g/jour) versus prestonamycine contre 's (2 g/jour) dans le traitement des infections cutanees. Nouv Dermatol 1994; 13: 520-524. [Treatment of skin infections with two dosages of fusidic acid.]

388
Comparison of fusidic acid and other treatments in the treatment of skin and soft tissue infection. (Clin Res 1999; 2:77-84).


Zelvedler WG. A double-blind comparative study of sodium fusidate (topical), amoxycillin (oral) and the combination of both drugs in skin infections. (Tijdshr Geneesmiddelen 1989; 48:87-92).


Januja K, Gupta SK, Arora DR, Gupta V. Bacteriology of primary pyoderma and comparative efficacy of topical application of mupirocin and sodium fusidate ointments in their treatment. (Indian J Dermatol Venereol Leprol 2001; 67:132-134).


Poeny TF, Dass BK. Comparative efficacy and tolerability of Fusidic acid/hydrocortisone cream (Fucidin H cream) and miconazole/hydrocortisone cream (Daktacort cream) in infected eczema. (Eur Acad Dermatol Venereol 1996; 2(Suppl. 1):S23-30).

Wilkinson JD, Leigh DA. Comparative efficacy of betamethasone and either fusidic acid or neomycin in infected or potentially infected eczema. (Curr Ther Res 1985; 38:177-182).


