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Research Article

FUSIDIC ACID – TOPICAL ANTIMICROBIAL IN THE MANAGEMENT OF STAPHYLOCOCCUS AUREUS

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ABSTRACT

Fusidic acid (FA) is derived from the fungus *Fusidiumcoccineum* 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 staphylocci, clostridia species, *Peptococcus* and *Peptrococcus* 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 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 triterpenoid, 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.

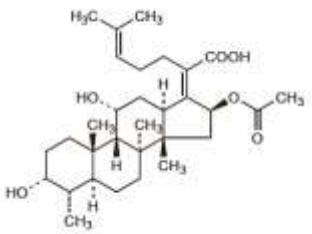

Fig. 1: Structure of fusidic acid

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 staphylocci, clostridia species, *Peptococcus* and *Peptrococcus* 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 concentaration 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 conjuctival 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 2-3.2hours. 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- steroid combination had shown similar or superior clinical or BE compared to other products.

Table 1: Clinical response of fusidic acid

Reference	Fusidic acid Clinical response rate (Cure or improvement)	Comparator	Comparator clinical response rate (Cure or improvement)
Nordin 1994 [20]	93.2%	Flucloxacillin	90.8%
Machet 1994 [15]	99%	Pristinamycin	96%
Newby [16]	86.6%	Ciprofloxacin	91.5%
Morris 1990 [17]	75.8%	Flucloxacillin	81.1%
Wall 2000 [18]	85.3%	Erythromycin	87.3%
Claudy 2001 [19]	79.7%	Pristinamycin	76.1%
Macotela Ruiz 1988 [21]	95%	Dicloxacillin	89%
Langdon 1990 [22]	95%	Mupirocin	98%
El Mofty 1990 [23]	78%	Trimethoprim-polymixin	84%
Jaafar 1991 [24]	47%	Trimethoprim-polymixin	73%
Hamann 1991 [25]	87%	Erythromycin	77%
Sutton 1992 [26]	97%	Mupirocin	98%
Christensen 1994 [27]	82% (BE-93%)	Hydrogen peroxide	72% (BE-88%)
Koning 2002 [28]	95% (BE-89%)	Povidine /Iodine	86% (BE-74%)
Zelvelder 1984 [29]	93%	Amoxycillin	97%
Morley 1988 [30]	86%	Mupirocin	86%
White 1989 [31]	93% (BE- 89%)	Mupirocin	97% (BE- 93%)
Gilbert 1989 [32]	94% (BE-87%)	Mupirocin	94% (BE-97%)
Jasuja 2001 [33]	84%	Mupirocin	90%
Oranje 2007 [34]	90% (BE- 94%)	Retapamulin	95% (BE- 98%)
Poyner 1996 [35]	69.5%(BE- 97.9%)	Micanozole /hydrocortisone	68.6% (BE-83%)
Wilkinson 1985 [36]	95% (BE- 91%)	Neomycin/betamethasone	90% (BE- 88%)
Javier 1986 [37]	75% (BE- 78%)	Neomycin/betamethasone	81% (BE- 72%)
Strategos 1986 [38]	98% (BE- 86%)	Gentamicin/betamethasone	90% (BE- 86%)
Hill 1998 [39]	57.9%	Clioquinol/betamethasone	60.4%

BE- Bacteriological Efficacy

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].

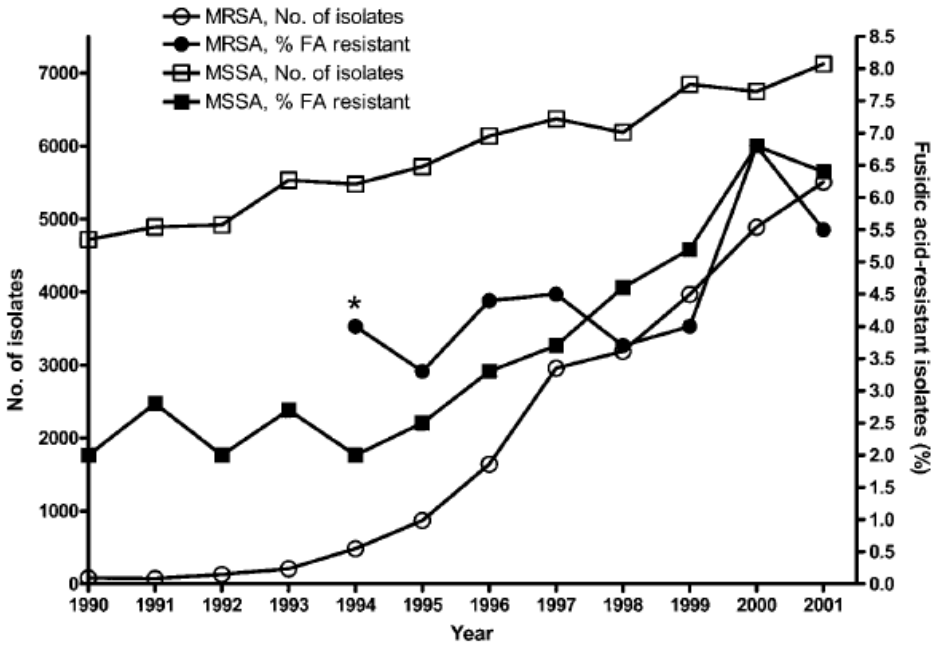

Fig. 2: Trend showing the resistance of FA during 1990 to 2001. Adopted from Howden B and Garyson L[46]

Drug Interactions

Co-administration of astatin 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'smainly active against staphylococci including multi-resistant strains. Fusidic acid is available in numerousformulations 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].

The pharmacokinetic of the developed pediatrics suspension was studied by Leo pharmaceutical in 1993[62].

Intravenous formulation

Various intravenous formulations were developed for fusidic acid salt. First developed formulation was using the diethanolamine salt which was replaced by sodium salt[63]. The original formulation contained the diethanolamine salt as suspension had higher molecular weight at 622 than the sodium salt currently in use at 539. Currently available intravenous formulation contains the sodium salt equivalent to 500 mg of fusidic acid per vial[60].

Topical preparations

Topic use of fusidic acid well established and consider being one of the best as a narrow-spectrum antibiotic. The fusidic acid is active against *staphylococcus aureus* used as topical antibacterial for managing skin and soft-tissue infections. The fusidic acid has shown good skin permeability and low allergenic potential [64].

Numbers of the topical formulation were developed such as ointment, cream, gel, lotions etc[65]. It is also available as a specially designed ophthalmic preparation (Fucithamic®) for instillation into the conjunctival sac by Leo Pharmaceutical.

Finn Schultz Larsen et al[66] reported the clinical efficacy of the newly developed Fucicort® Lipid cream contain the fusidic Acid and Betamethasone 17-Valerate (Fucicort® Lipid Cream) with Fucicort® cream for treatment of clinically infected atopic dermatitis which was developed by Leo Pharma, Ballerup, Denmark. The newer formulation contains mainly the lipid base. It was found that the Fucicort® Lipid Cream is very more efficacious.

The numbers of patents were filled on fusidic acid(Table 2).

Cempra Pharmaceuticals filled the patent for methods of treating bacterial infections through pulmonary delivery of fusidic acid. Numbers of patents are filled for the dermal application of the fusidic acid. More patents are filed by the Apex Laboratories, mainly based on topical preparation of the fusidic acid. The Apex laboratories prepared the fusidic acid cream along with various steroid combinations. The patent filled in European Patent register, 'A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer and a process to make it' (Patent No. EP2419087) is one of the major inventions in dermal application by Apex Laboratories. The invention was focused on the reduction of

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 the fucidin which was developed by Leo Pharmaceuticals Product Ltd. The Apex Laboratories claims that developed formulation is having longer shelf life, long term storage stability compared to the fucidin.The data here show that the developed formulation of fusidic acid diffusion rate is far higher than that ofFucidin at all-time points measured and found that 74.20% of the drug release in 8hrs against 20.43%. The developed formation 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 layers and reduce the toxicity results in reduction in the microbial resistance.

Leo pharmaceuticals Product 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

S. No.	Patent No.	Title of patent	Brief description	Inventor/Assignee
1.	US 6593 319 B1	Fusidic acid derivatives	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	Leo Pharmaceutical Products Ltd. Ballerup (DK)
2.	US 2011/0257144 A1	Novel dermaceutical cream made using sodium fusidate	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.	Apex Laboratories Private Ltd Chennai TN (IN)
3.	US 2011/281831 A1	Novel dermaceutical cream made using sodium fusidate, antifungals and steroids	A dermaceutical cream containing Betamethasone Valerate, Fluticasone Propionate, Mometasone Furoate, Dexamethasone Acetate, Hydrocortisone Acetate, Clobetasol 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.	Apex Laboratories Private Ltd Chennai TN (IN)
4.	US 2011/ 301 137A1	Dermaceutical gel made using sodium fusidate and A process to make it	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 of active pharmaceutical ingredient than the conventional creams. The gel base containing a natural, semi synthetic or synthetic polymers, a preservative an acid an alkali, a co-solvent with water.	Apex Laboratories Private Ltd Chennai TN (IN)
5.	US 2011/ 301 138A1	Process to make fusidic acid cream	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 cream base comprising a preservative, an acid, a co-solvent, an emulsifier and wax material along with water.	Apex Laboratories Private Ltd Chennai TN (IN)
6.	US 2012/0035144 A1	Medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, a corticosteroid and an antifungal agent, and process to make it	The cream comprises of a biopolymer in the form of Chitosan, the fusidic acid which formed in situ from sodium fusidate, hydrocortisone and clotrimazole.	Apex Laboratories Private Ltd Chennai TN (IN)
7.	US 2012/0040946 A1	Medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, and process to make it	The cream comprises of a biopolymer in the form of Chitosan, the fusidic acid which formed in situ from sodium fusidate.	Apex Laboratories Private Ltd Chennai TN (IN)
8.	US 4025 620	Treatment of canine otitis and composition thereof	A liquid veterinary composition containing the diethanolamine fusidate and an antifungal antibiotic such as nystatin. The composition contain additionally a broad spectrum antibiotics such as neomycin B	Leo Pharmaceutical Products Ltd A/S Ballerup, Denmark
9.	US 3287218	Antibacterial combination of fusidic acid or dihydrofusidic acid with novobiocin or dihydronovobiocin	Antibacterial combination of fusidic acid or dihydrofusidic acid with novobiocin or dihydronovobiocin	Lovens Kemiske, Fabrik Produktions-Aktieselskab Ballerup Denmark.
10. 1	US 2011/0009375 A1	Fusidic acid regimens for treatment of bacterial infections	Novel dosing regimen for the treatment and prevention of bacterial infections using the fusidic acid.	Cempra Pharmaceuticals Inc.

11.	WO2012162439 (A2)	Compositions comprising fusidic acid and packages therefor	Composition of the solid pharmaceutical dosage form as tablet of fusidic acid as sodium salt of fusidate along with packaging to enhance stability.	Cempra Pharmaceuticals Inc.
12.	WO2012127407 (A1)	Pharmaceutical composition for use in nasal administration containing corticoid, and a quinolone or fusidic acid	Used for the treatment of the sinusitis containing the corticoid, quinolone and fusidic acid	Dos Santos, Antonio
13.	WO2012049542 (A1)	A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, mometasone as a corticosteroid and clotrimazol as antifungal agent, and a process to make it	The cream comprises of Chitosan as biopolymer with fusidic acid that has been generated in situ from sodium fusidate, Mometasone furoate and clotrimazole	Apex Laboratories Private Ltd Chennai TN (IN)
14.	WO2012049541 (A1)	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,	Apex Laboratories Private Ltd Chennai TN (IN)
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.	Apex Laboratories Private Ltd Chennai TN (IN)
16.	WO2012049544	A medicinal fusidicacid 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.	Apex Laboratories Private Ltd Chennai TN (IN)
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 finer particle size of the API than the conventional creams.	Apex Laboratories Private Ltd Chennai TN (IN)
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.	Apex Laboratories Private Ltd Chennai TN (IN)
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	Apex Laboratories Private Ltd Chennai TN (IN)
20.	WO2012030513	Methods of treating bacterial infections through pulmonary delivery of fusidic acid	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.	Cempra Pharmaceuticals Inc [US]
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	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.	Apex Laboratories Private Ltd Chennai TN (IN)
22.	WO2012017368	A medicinal fusidic acid cream made using sodium fusidate and incorporating a	The cream comprises Chitosan, Beclomethasone Dipropionate and Fusidic acid. Sodium Fusidate is converted into	Apex Laboratories Private Ltd Chennai TN (IN)

		biopolymer, beclomethasone dipropionate 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	A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, clobetasole propionate, terbinafine hydrochloride and a process to make it	The cream comprises Chitosan. Clobetasol 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.	Apex Laboratories Private Ltd Chennai TN (IN)
24.	WO2012017369	A medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, betamethasone dipropionate, clotrimazole and a process to make it	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.	Apex Laboratories Private Ltd Chennai TN (IN)
25.	WO2012017383	A medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, beclomethasone dipropionate, terbinafine hydrochloride and a process to make it	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.	Apex Laboratories Private Ltd Chennai TN (IN)
26.	WO2012017382	A medicinal fusidic acid cream made using sodium fusidate and incorporating biopolymer, beclomethasone dipropionate, miconazole nitrate and a process make it	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.	Apex Laboratories Private Ltd Chennai TN (IN)
27.	WO2012017381	A medicinal fusidic acid cream made using sodium fusidate and incorporating, biopolymer, beclomethasone dipropionate, clotrimazole and a process to make it	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.	Apex Laboratories Private Ltd Chennai TN (IN)
28.	WO2012023079	A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, fluticasone propionate, oxiconazole nitrate and a process to make it	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.	Apex Laboratories Private Ltd Chennai TN (IN)
29.	WO2012023077	A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, a corticosteroid - clobetasol propionate, and an antifungal agent - oxiconazole nitrate, and a process to make it	The cream comprises Chitosan. Clobetasol 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.	Apex Laboratories Private Ltd Chennai TN (IN)
30.	WO2012017372	A medicinal fusidic acid cream made using sodium fusidate	The cream comprises Chitosan. Clobetasol Propionate, Miconazole Nitrate and Fusidic	Apex Laboratories Private Ltd Chennai TN (IN)

		and incorporating, 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.	Apex Laboratories Private Ltd Chennai TN (IN)
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. Hydrocortisone 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.	Apex Laboratories Private Ltd Chennai TN (IN)
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.	Apex Laboratories Private Ltd Chennai TN (IN)
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.	Apex Laboratories Private Ltd Chennai TN (IN)
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.	Apex Laboratories Private Ltd Chennai TN (IN)
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.	Apex Laboratories Private Ltd Chennai TN (IN)
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	Cempra Pharmaceuticals Inc. Building Four Quadrangle 6340 Quadrangle Drive Suite 100 Chapel Hill, NC 27517 / US.

			associated with a prolonged course of therapy of high amounts of the drug.	
38.	EP2382968 (A1)	Particle size distribution of fusidicacid granules	The present invention relates to a tablet of fusidic acid or a salt thereof characterized in that said tablets prepared form a mass of granules which have specific particle and granule size distribution.	Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim Sirketi Abdi Ibrahim Uretim TesisleriPatent DepartmaniSanayi MahallesiTunc Caddesi No. 3Esenyurt Istanbul / TR
39.	WO2009063493	Topical pharmaceutical composition for the combination of fusidicacid and a corticosteroid	The present invention relates to topical compositions comprising combination of mometasone furoate and fusidic aciduse 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.	Glenmark Pharmaceuticals Limited Glenmark House HDO-Corporate Bldg. Wing A, B.D. Sawant Marg Chakala, Andheri (East) Mumbai 400 099 / IN
40.	EP1945654 (A2)	Preparation of an antibiotic crystalline fusidic acid	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.	Leo Pharma A/S 55, Industriparken 2750 Ballerup / DK
41.	EP0773783 (A1)	Preparation of fusidic acid tablets	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 tableting.	LEO Pharmaceutical Products Ltd. A/S (Lovens Kemiske Fabrik Produktionsaktieselskab) Industriparken 55 2750 Ballerup / DK
42.	WO9301817 (A1)	Antiviral compositions comprising fusidic acid, l-ascorbic acid and salicylic acid and derivatives	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.	SSALI, Charles Lwanga 24 Kenton Road Harrow, Middlesex HA1 2BW / GB.

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 leads 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.

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