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Pharmaceutical Composition of Cefazolin Sodium Coupled Silver Nanoparticles Dermal Gel with Improved Antibacterial Activity

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Abstract---*In present invention, a novel gel was designed for enhancing the antibacterial activity of cefazolin sodium by using the nanoparticles synthesized by green chemistry approach against S. aureus, E.coli and methicilin resistant Staphylococcus aureus infected wounds and to provide faster healing of infected wounds. Skin damage is one of the most common lesions that people suffer from, and some injuries such as chronic wounds and deep burns are notoriously difficult to eliminate. The already existing therapies have been proved to be inadequate and unsatisfactory. An imminent global public health problem is the rapid development of antibiotic resistance to pathogeic microbes. Nanoparticles are the small-sized particles that exist on a nanometer scale. Modern nanotechnology offers an unprecedented ability to revolutionize and invent new medicines or treatments or to increase the efficacy of current treatments. Dermal gel or hydrogel is a promising anti-bacterial product. Dermal gel or hydrogel is a biomaterial synthesized with a water-soluble natural polymer, or a synthesized polymer, which transforms into gel by alteration of signals such as temperature, ionic force, pH, ultraviolet exposure, etc. Dermal gels is one of the ideal biomaterial for the supply of drugs in antimicrobial areas due to its high hydrophilicity, its special three-dimensional network, fine biocompatibility and cell adherence.*

Keywords--- *Antibacterial activity, cefazoiln sodium, nanoparticles, green chemistry, S. aureus, E. coli, chronic wounds, nanotechnology, dermal gel, hydrophilicity, biocompatibility, cell adherence*

I. INTRODUCTION

The recent emergence of infectious disease and antibiotic-resistant strains, especially inside gram negative micro organizations, has made nanotechnology more significant in the field of biomedical and pharmaceuticals as an alternative to antimicrobial strategy [1][2]. Green nanoparticles with the plant extracts is an interesting area of nanotech, which has economic and environmental advantages over chemical and physical methods of synthesis [3]. Nanoparticles (NP) are usually not more than 100 nm in length. Because of their small size and the high surface-to-volume ratio, their biocidal efficacy is suggested and permits intimate interactions with microbial membranes [4][5].

Skin, the human body's largest organ, acts as an immune, sensory and defensive key barrier. Due to its exposure to the outside environment, the skin has a range of external factors that lead to skin damage and injury of different kinds. In recent years, the prevalence of people with chronic injuries has risen sharply as obesity and chronic conditions such as diabetes, venous and arterial insufficiencies are dramatically increased [6]. According to a study, it has been demonstrated that the effect of chronic wounds is 1-2% on the population of European and United States

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[7]. Traditional therapies usually include costly and durable treatments with an ulcer recurrence rate of more than 70 percent[8]. The impressive number of patients who are keen for improved healing performance and the spectacular budget for wound care are still in the research work for wound healing and skin regeneration prominently.

Wounds if remained untreated or do not get healed on time leads to bacterial attack, following infection which can further cause sepsis and ultimately death. However, currently there are many products available to heal the wounds and to minimize bacterial bioburden on the wounds. But owing to continuous rise in resistant microorganism species particularly the methicilin resistant strain, the efficacy of different antibiotics has been decreased toward the harmful pathogen and healing pattern of wounds is also disturbed.

A new drug delivery system is required in these cases with the potential of absorption and delayed potential of release. The antibiotic can be transported and protected by either the nanocarrier system or the nano-drug delivery system (DDS). Nanomaterials which have the antimicrobial activity or which can improve the efficacy and safety of antimicrobial drugs are known as the nanoantimicrobials (NAMs). The improved bioavailability, protection, mucoadherence, absorption, controlled release or targeting for encapsulated medicines or surface-adsorbed medicines could be an effective alternative to conventional antibiotics [9]. The NAM family may classify a variety of organic, inorganic and hybrid materials [10]. Hydrogel or dermal gel is a three-dimensional cross-linked polymer network among all NAM's which, while maintaining its structure and regulating drug release, can dramatically swell into an aqueous medium such as body fluids [11]. Dermal gels can also be activated by stimulations including changes in pH, temperature, enzyme catalysis, ultraviolet gamma radiations and inflammation. Dermal gel may be filled with “urinary catheters, central venous catheters, contact lenses, joint and dental implants and local injection for drug release and wound healing injections”. In contrast, certain kinds of hydrogels have antimicrobial characteristics. The anti-bacterial agent, combined with the use of nanomaterials, such as dermal gel or hydrogel, can be used at lower dose than administering systemically to solve the resistance issue and to some degree diminishing the other undesirable secondary effect. In the pharmaceutical and medical fields, these characteristics have attracted particular attention, especially for antimicrobial use (figure 1).

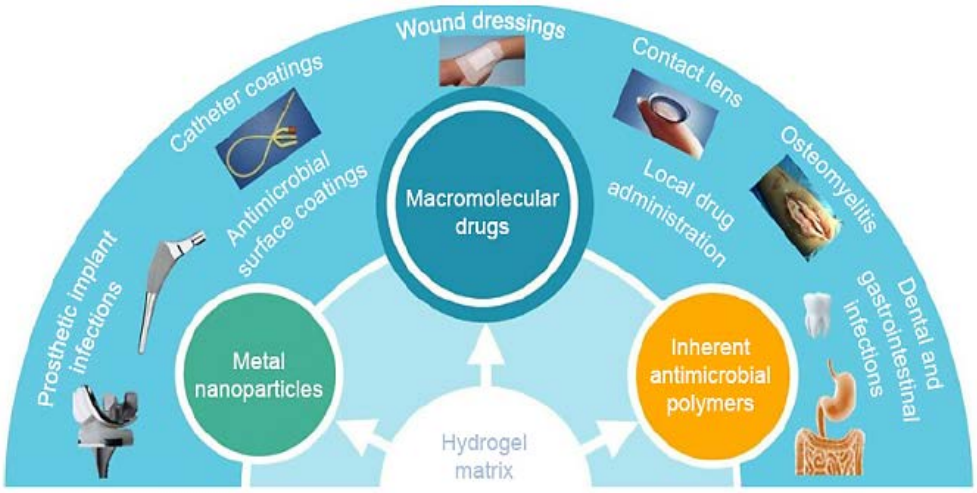

Fig.1. Different applications of hydrogels

Cefazolin Sodium is the sodium salt of cefazolin, a first generation cephalosporoin with bactericidal activity. It is widely used as broad spectrum antibiotic, administered parenterally for moderate to severe infection with susceptible organism. Cefazolin is used to treat infections that are strongly suspected to be caused by bacteria, it is still uniformly resistant to methicilin resistant staphylococci. To deal with the growing resistance among the microorganisms against antibiotics and decreasing efficiency, silver nanoparticles have been emerged as new generation bactericidal agents and are also believed to be effective in overcoming the microorganism resistance to certain antibiotics in conjugation with them. However, cefazolin has been used parenterally as prophylaxis to prevent surgical wound infections but its low molecular weight (476.5 g/mol) and broad spectrum antibacterial activity allow us to formulate a topical product of cefazolin in conjugation with silver nanoparticles which would not only efficiently release the drug for its desired antibacterial activity but will also lead to an improved wound healing pattern owing to wound healing properties of silver nanoparticles when used topically on infected wounds.

II. METHODS AND RESULT:

In present invention, a novel gel was designed for enhancing the antibacterial activity of cefazolin sodium against *S. aureus*, *E.coli* and *methicilin resistant staphylococcus aureus* infected wounds and to provide faster healing of infected wounds. Initially, identification of cefazolin sodium was carried out using FT-IR (PerkinElmer Spectrum Version 10.03.08, UK). The FT-IR spectrum showed specific peaks in the range of 3300-3500 cm^{-1}, 3100-3000 cm^{-1}, 3000-2850 cm^{-1}, 1760-1700 cm^{-1}, 1680-1630 cm^{-1}, 1600-1400 cm^{-1}, 1350-1000 cm^{-1} and 1640-1550 cm^{-1} which confer its identity. Subsequently, standard curve for cefazolin sodium was prepared in the concentration range of 5-50 µg/ml respectively at 254 nm that follow the linear regression equation (y=0.021x+0.010 R^2=0.998) (Figure 2).

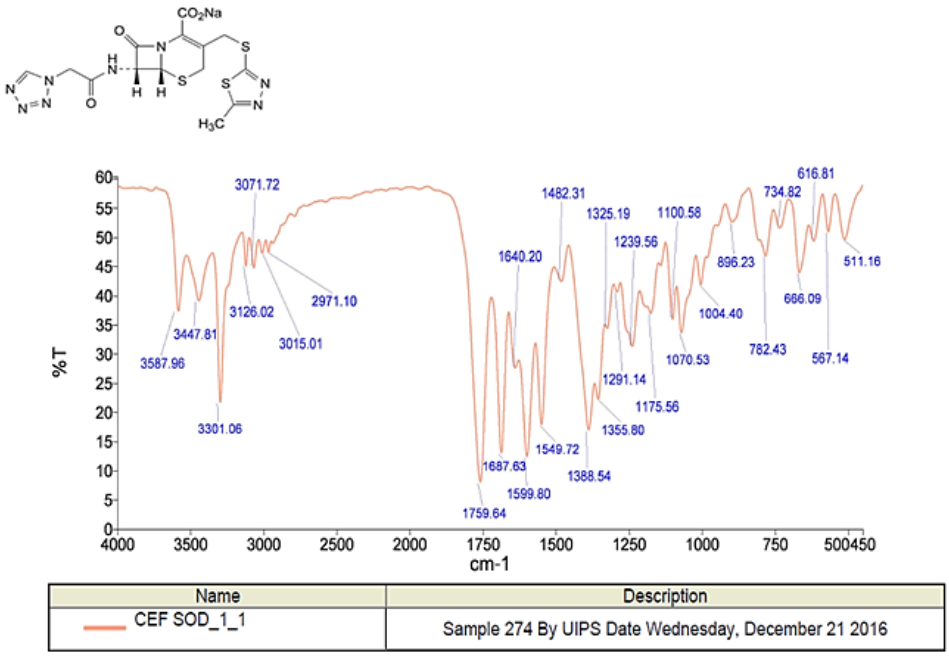

Fig.2. FT-IR spectrum and peak assignment of cefazolin sodium

Next, silver NPs were prepared by the reduction of $AgNO_3$ with tri-sodium citrate. For the preparation of AgNPs, 125 ml of silver nitrate solution 1 mM was heated and as soon as boiling commenced, 5 ml of 1% sodium citrate solution was added. Heating was continued until a color change from transparent to pale yellow was evident. Then the solution was removed from the heating element and stirred until it had cooled down to room temperature. The UV-visible spectrum of Ag-NPs suspension presented absorbance maxima at 421 nm which confirmed its synthesis. The TEM images of AgNPs at 50000x magnification showed spherical and somewhat irregular shape with a diameter of 20-40 nm (Figure 3). Further, AgNPs were analyzed for particle size distribution and zeta potential using zetasizer (Malvern Instruments, UK). The result showed an average particle size distribution of 107.46±25.3 nm with zeta potential of -36.93± 4.26 mV for AgNPs. Next, cefazolin sodium was coupled to AgNPs by dissolving specific amount of cefazolin sodium (0.8%) in AgNPs dispersion. The solution was kept undisturbed overnight to allow complete coupling between AgNPs and cefazolin sodium. A shift in zeta potential to -28.6±2.34 mV confirmed the coupling between cefazolin sodium and AgNPs. The average particle size distribution of cefazolin sodium coupled AgNPs was found to be 120.31±10.98 nm. Following this, novel cefazolin sodium coupled AgNPs dermal gel was prepared. Initially, AgNP dispersion was diluted with distilled water to attain specific concentration of AgNPs (0.03%). To this AgNP dispersion, an accurately weighed amount of cefazolin sodium (0.8%) was added and allowed to couple with AgNPs under mild stirring followed by 24 h incubation. After that carbapolultrez 10 NF (gelling agent) was dissolved in the AgNPs dispersion. Carbapol was dissolved by pouring it slowly into the dispersion under mild agitation to prevent air entrapment and lumps formation. Following a mixture of hydroxyl propyl methyl cellulose (HPMC) and poly ethylene glycol ($PEG_{1500)}$ was added to the carbapol containing dispersion. Subsequently, other ingredients were introduced into the dispersion under continuous stirring for 30 min. The pH was adjusted to 7 using triethanolamine (TEA) (Table 1). Next, dermal gel of cefazolin sodium coupled AgNPs was characterized and evaluated for its color, state, texture, homogeneity, pH, spreadability, viscosity, drug content, drug release, and antibacterial activity. The color, state, texture and homogeneity were recognized by visual appearance and observed to be pale yellowish, semisolid, smooth and uniform. The pH value of dermal gel was noticed to be 7.1±0.1154 by using calibrated pH meter. The spreadability of tailored gel was measured to be 2.56± 0.155 g cm/sec. In addition, the tailored gel followed Non-Newtonian curve. The drug content of the gel was determined using UV-Visible spectrophotometry and calculated to be 7.5 mg/gmof gel. The silver content of the dermal gel was determined using ICP-AES technique and found to be 28.06 µg/gmof the gel (Table 2). Next, the antibacterial study was conducted against *Methicillin resistant Staphylococcus aureus* (MRSA) by cup-plate method. The minimum inhibitory concentration (MIC) of cefazolin sodium was estimated to be 75µg/ml significantly (One-way ANOVA test, $P<0.001$) higher than 3 µg/ml of AgNPs and 0.56 µg/ml of cefazolin sodium coupled AgNPs. Hence, we predict that cefazolin sodium coupled AgNPs dermal gel would be potential candidate to inhibit the growth of microorganisms in MRSA oriented infections and wounds.

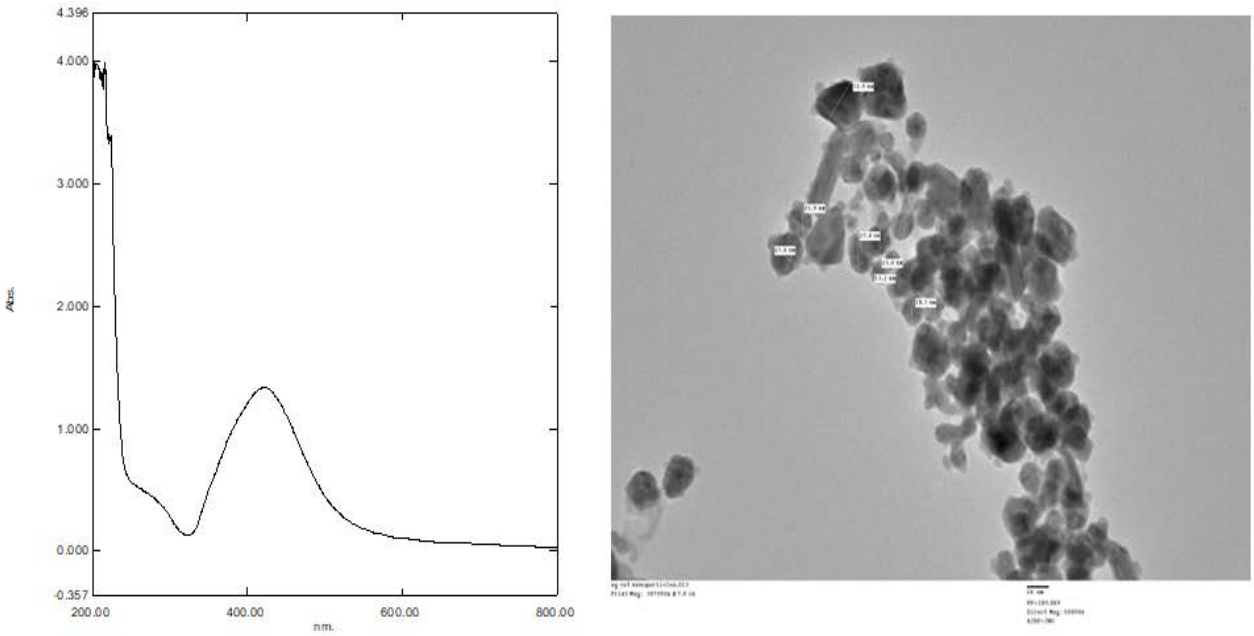

Fig.2. UV Visible spectrum and surface topography analysis of silver nanoparticles

Table 1: Pharmaceutical composition of dermal gel

Sr. No.	Ingredient	Concentration (%)	Use
1.	Carbapol ultrez 10 NF	1	Gel base
2.	Silver nanoparticles	0.003	Antimicrobial agent
3.	Cefazolin Sodium	0.8	Therapeutic agent
4.	Propylene glycol	30	Co-solvent
5.	Glycerine	0.1	Humectant
6.	Benzyl alcohol	1.26	Preservative
7.	HPMC E5	0.01	
8.	Polyethylene-glycol 1500	0.04	
9.	Purified water	q.s	

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Table 2: Characterization of cefazolin sodium coupled silver nanoparticle dermal gel

Sr. No.	Parameter	Observation
1.	Color	Pale yellowish
2.	State	Semisolid
3.	Texture	Smooth
4.	Homogeneity	Uniform
5.	pH	7.1±0.1154
6.	Spreadability	2.56± 0.155 g cm/sec
7.	Silver content	28.06 ppm/gm
8.	Drug content	99.9±0.02%

III. CONCLUSION:

In present invention, novel gel was formulated that contains active ingredient, cefazolin sodium coupled with silver nanoparticles and other components namely water, carbapolultrez 10 NF, propylene glycol, glycerine, benzyl alcohol, hydroxyl propyl methyl cellulose E5, polyethylene glycol1500. There is an amalgamation of cefazolin sodium coupled with silver nanoparticles into a pharmaceutical gel which possesses superior antibacterial activity against methicilin resistant staphylococcus aureus (MRSA) infected wounds. Moreover, cefazolin sodium coupled with silver nanoparticles in gel exerted synergistic action which provides faster wound healing and decreased microbial burden on burn wounds, surgical wounds and chronic wounds.

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