Original Article

Mupirocin Mounted Copper Nanoparticle Offered Augmented Drug Delivery against Resistant Bacteria

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ABSTRACT

Aim: In present investigation, mupirocin coupled copper nanoparticles were synthesized to overwhelm drug resistance in *Staphylococcus aureus*, responsible for dermal skin infections. **Materials and Methods:** Mupirocin (Anclaima Pvt. Ltd. India), copper sulphate (Thermo Fisher Scientific, India), Tri sodium citrate (Nice chemicals, India) Copper nanoparticles were produced by size reduction method by using Copper Sulphate and Tri sodium citrate. CuNPs were merged into gel base of carbopol which was formed by hot method. Carbapol gel shows no phase separation. **Results and Discussion:** The particle size of CuNPs was found to be 413.0 ± 30.2nm. The % EE was found to be 65.2%. On description unilamellar, sphere-shaped vesicles with soft surface were detected under transmission electron microscopy. XRD of CuNPs was found out crystalline in nature. The zeta potential of nanoparticle shows less aggregation of particle with - 15.1 ± 3.69 mV value. The amount of copper content was measured 5.9 microgram/10 mg of nanoparticles. *In vitro* release study of Cu NPs shows 96.5% release of drug and show effective antibacterial activity against *Staphylococcus aureus*. **Conclusion:** Mupirocin copper nanoparticles were produced and show excellent antibacterial activity upon *S. aureus*.

Keywords: Copper nanoparticle, Mupirocin, Carbopol gel, Antibacterial activity, Chemical reduction method, Copper sulphate.

INTRODUCTION

In the past decade, the cure of sickness has been consummate by administrating drugs to human body through different routes likes parental, oral, topical, sublingual, inhalation, rectal etc.[1] The delivery of drug through topical denotes the application of drug onto the body employing vaginal, rectal, ophthalmic and skin as the route of administration. On human body, skin is widely used and accepted route for local application and constitutes the principal administration for local application.

The term topical drug delivery means administration for medicament containing formulation to the skin to openly care for the cutaneous manifestations of a common illness (e.g. psoriasis) or cutaneous disorders with the purpose of confining the pharmacological or other effect of the medicament inside or surface of skin.[2]

During recent years, a report will show interest in the synthesis and applications of various metallic nanoparticles due to their outstanding optical and electronic properties, especially copper, gold and silver nanoparticles. Copper nanoparticles (CuNPs) have gradually become an active area of research because of unique chemical, physical, electrical and optical properties, low cost, ease availability and exhibit good antibacterial properties. The prime advantage of CuNPs is their low cost and its availability compared to gold and silver nanoparticles, resulting in the sample synthesis and various applications of CuNPs.[3,4]

Copper is easily available metal and one of the vital trace elements for mainly living

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creature. Copper was used as potential antimicrobial agent from ancient times.[5] Copper and its complexes used as an disinfectants, antiviral as well as antibacterial from centuries. It is said that the enhanced antimicrobial activity of Cu-NPs due to their crystallographic surface structure and large surface to volume ratio compared with copper salts. $Cu(OH)_2$ and $CuSO_4$ are used as the conventional inorganic antibacterial agents. Also, complex copper species, aqueous copper solutions or copper containing polymers are used as antifungal compounds as well as antibacterial. At current, advancement in new antibacterial agents is essential due to steady raise of new bacterial strains resistant to the potent antibiotics. Substances with low molecular weight like copper nanoparticles generally inhibit the growth or kill a wide range of bacterium bacteria. Copper ions shows antimicrobial activity across a wide range of microorganisms, such as *Salmonella enteric*, *Staphylococcus aureus, Campylobacter jejuni, Listeria monocytogenes* and *Escherichia coli*. The surfaces of copper can be used to kill viruses, yeasts and bacteria hence copper known as "contact killing".[6,7]

The Cu particles in nano range have been shown a antibacterial effect on the microbial cell functions in numerous ways, including electrostatic interaction between particles and gram negative bacteria cell wall, denaturation of the intracellular proteins and interaction with phosphorus- and sulfur containing compounds like DNA. The nanoparticles passed through bacteria cell membrane and then injurious for the vital enzymes of bacteria can be the primary mechanism of anti-microbial action in CuNPs.[8,9]

MATERIALS AND METHODS

Materials: The following chemicals were used: Mupirocin (Anclaima Pvt. Ltd. India), copper sulphate (Thermo Fisher Scientific, India), Tri sodium citrate (Nice chemicals, India.) Propylene glycol (S.D. Fine Chem. India), Methanol (Loba Chemie, India), Ethanol (Loba Chemie, India), Carbopol 940 (Lubrizol advanced material, Belgium), Methyl paraben (Lubrizol advanced material, Belgium), Propyl paraben (Lubrizol advanced material, Belgium), Triethanolamine (Nice chemicals, India).

Methods

Determination of melting point: In capillary tube, small amount of drug was added, and tube is sealed. The sealed tube was located in the melting point apparatus. The heat in the apparatus was slowly increased and the temperature at which whole drug gets melted was noted. DSC study of pure drug was conceded out on Shimadzu thermal analyzer DSC TA 60. The apparatus was calibrated using standard metal like high purity indium metal. The scans were conducted at heating rate of 10°C/min in nitrogen environment.

Solubility studies: The solubility study of Mupirocin was performed in methanol, ethanol, chloroform, acetone, distilled water, 0.1 N HCl, phosphate buffer solution pH 6.8, 7.4, individually by keeping the drug containing test tube on vortex mixture.

Preparation of standard curve in methanol: Accurately weighed 100 mg of mupirocin and transferred into 100 ml volumetric flask, make the volume up to 100 ml using methanol. From the above solution 10 ml was pipette out and transferred into 100 ml volumetric flask. The volume is made up with methanol in order to get standard stock solution containing 100 ppm. Form the above solution; a sequence of dilution (2, 4, 6, 8, 10 ppm) was diluted with the help of methanol. All dilutions were measured using UV spectrophotometrically against blank of methanol at 220 nm for mupirocin. Absorbance of drug at different concentrations was calculated and graph was plotted.[10]

Infrared spectroscopic analysis

The FTIR spectrums of mupirocin, carbopol and mixture of mupirocin, carbopol were recorded on IR spectrophotometer. All the samples are free from moisture. Infrared spectrum was recorded in the 4000-400 cm^{-1} regions (Bruker).

Copper nanoparticles synthesis

Cu nanoparticles were synthesized using size reducing agent like tri sodium citrate. Copper sulphate and trisodium citrate employed as initial substances in the development of copper NPs. All solutions were prepared in distilled water. Make 0.001 M $CuSO_4$ solution with distilled water, take 40 mL from this solution in beaker and heated the solution to boil. In above solution, 10mL of 1% trisodium citrate was mixed drop wise. The mixture was heated under continuous magnetic stirring for 30 minutes. The mix solution was them cooled near room temperature. The reaction was allowed to take place for 24 hr. Accurately weighed 2g mupirocin was dissolved in methanol and added to copper nanoparticles.[11]

Preparation of the carbopol gel

At low concentration, carbopol 940 forms very good flexible transparent gel. The gel base of 2% was prepared by scattering 2 g carbopol 940 in 86 ml warm distilled water. Accurately weighed 0.6 g propyl paraben and dissolved in ethanol. Accurately weighed 0.3 g methyl paraben and dissolved in 15 ml of propylene glycol. Stirred the mixture unless gelling occurred and then mixture was neutralized with the help of 50% (w/w) triethanolamine. Triethanolamine was added drop by drop to maintain the pH between 6-7.[12]

The nanoparticle formulation containing drug was slowly added in carbopol 940 gel base and mixed with the help of stirrer for 5 min continue stirring.

Evaluation of nanoparticles

Drug entrapment efficiency

Take 5 ml formulation and diluted the formulation up to 8 ml with distilled water and centrifuged the diluted formulation at 15,000 rpm at 4°C for 45 min using a cooling centrifuge. The sediment and supernatant were restored after centrifugation, their volume was calculated. Then sediment was break down through n-propanol and filtered using a 0.45 μm nylon filter. The concentration of mupirocin in the sediment and supernatant was examined by UV- spectrophotometer at 220 nm. The % entrapment efficiency was estimated:

% Entrapment efficiency:

$$\frac{\text{Amount of entrapped drug recovered}}{\text{Total amount of drug}} \times 100$$

Nanoparticle shape

Transmission electron microscopy (Philips Technai electron microscope, Netherlands) were used for the forecast of nanoparticle. At room temperature, sample was dried and vesicular were forecast under microscopy working at an acceleration voltage of 200 KV for 5 min.

Particle size estimation

Dynamic light scattering method was used for the determination of copper nanoparticles, using a computerized inspection system (Malvern Zetasizer Nano-ZS, Malvern, U.K.). For the measurement of size, copper nanoparticle solution was attenuated with distilled water and implement in cuvettes of zetasizer.[13]

Zeta potential measurement

Physical property like zeta potential which describe the net surface charge of copper nanoparticles. The stability criteria of CuNPs are measured when the zeta potential values ranges from higher than +30 mV to lower than −30 mV.[14]

X-ray diffraction

1 ml of the copper nanoparticle solution was extend on a glass slide and dried at 40°C in an oven. The Phillips Xpert Pro Diffractometer were recorded the spectra (Cu Kα radiation, λ = 1.54 Å) running at 40 kV and 30 mA. The diffracted intensities were recorded from 10 degrees to 80 degrees 2θ angles.[15]

Copper content determination

Determination the copper (II) ions, take 200 mL of tap water in the beaker. Water is evaporated upto 50 mL. Solution is transferred into a volumetric flask and the determination is performed. To different volumes of water, the solution containing copper is added and the solution is was brought up to the mark by mixture of acetate buffer. The absorbance is measured at a wavelength of 520 nm.[16]

Physical evaluation of nanoparticle gel

pH measurement of the nanoparticle gel

1 gm mupirocin coupled nanoparticle gel base was mixed in 100 ml beaker containing distilled water. After that pH electrode was deep in beaker and readings were reported from digital pH meter.

Viscosity study

The viscosity of copper nanoparticle was measured in Brookfield instrumentation by selecting appropriate spindle and rpm. In 50 ml beaker, 50 g of formulation was added which was set till spindle channel was drenched and set rpm. Reading pointed out over three minutes.

Spreadability

Spreadability term denote a area is required to which gel willingly fall on appliance to skin or affected part.[17,18] It was calculated through formulation:

$$S = M * L / T$$

Where T: time taken to separate the slides
L: length of slides
M: wt. tied to upper slide

Extrudability study

The extrudability of mupirocin coupled nanoparticle gel was considered by stuffing nanoparticle gel in the foldable tubes. Determination in words of weight in grams, 10 sec required to extrude a 0.5 cm ribbon of gel.

Percentage yield

Percentage yield was calculated by the formula.

Percentage yield:

$$\frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Grittiness and homogeneity

A tiny amount of nanoparticle gel was squeezed in the middle of index finger and the thumb. Uniformity of the nanoparticle gel is observed, any crude particles visible on fingers.[19,20]

In vitro release studies

Vertical Franz diffusion cell apparatus was employed for the *in vitro* absorption studies. It contain donor as well as receptor chamber that is filled with PBS. The donor chamber is filled and the permeation of solute through the membrane is monitored at different interval of time. Episodic sampling from the receptor chamber was collected and measured. The jacketed cell personified is stirred during experiment at 500 rpm using a magnetic agitator.[21]

Drug release kinetics

The kinetic of drug release was calculated by various kinetic models as zero order release kinetics plot, first order release kinetics plot, korsmeyer-peppas release kinetics plot and higuchi release kinetics plot. To study profile release kinetics of the copper nanoparticle figures obtained from *in-vitro* release profile were plotted for various kinetic models. The finest fit model was set by the value of R^2 close to 1.[22]

Antimicrobial activity studies

Antimicrobial activity has been assayed against bacteria by using agar diffusion method. The antibiotics action of drug is as oleic of its capability to growth inhibition of bacto nutrient agar or broth. Cup-plate method shall be used for the consideration of bacterial inhibition. In experiment, discs of average diameter were prepared in the bacto agar nutrient medium, containing standard bacterial inoculums. The test samples are injected in the disc and the diameter of the zone of inhibition was evaluated. All the test samples were evaluated for antibiotics activity against *Staphylococcus aureus* (gram positive).[23]

RESULTS AND DISCUSSION

Melting point determination: Melting point of pure mupirocin outcome at 78°C. Melting Point outcome three times and mean was noted.

DSC: The DSC thermograms showed quick endothermic peak equivalent to mupirocin melting point 77.31°C. The DSC thermogram of mupirocin is shown in Figure 1.

Solubility studies: Mupirocin was found to be soluble in acetone, methanol, 0.1 N HCL, distilled water, ethanol, chloroform, PBS of 6.8, 7.4

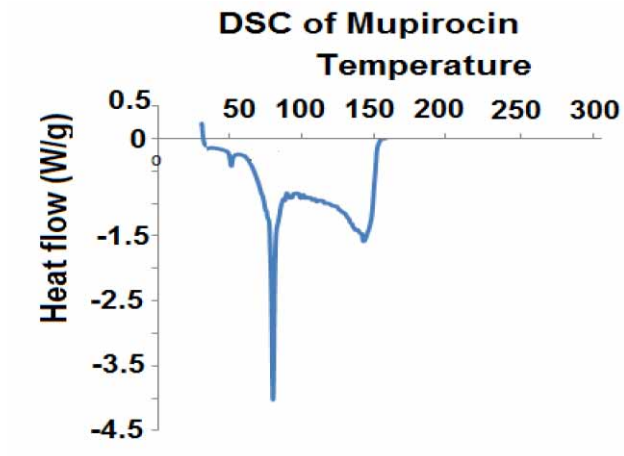

Figure 1: DSC thermogram of mupirocin.

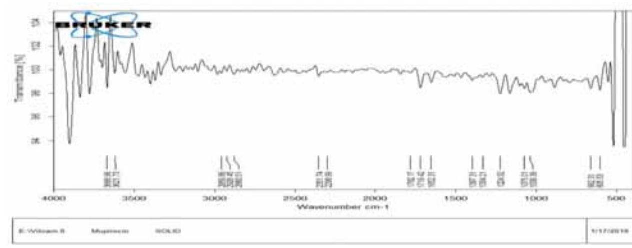

Figure 2: FTIR of Mupirocin

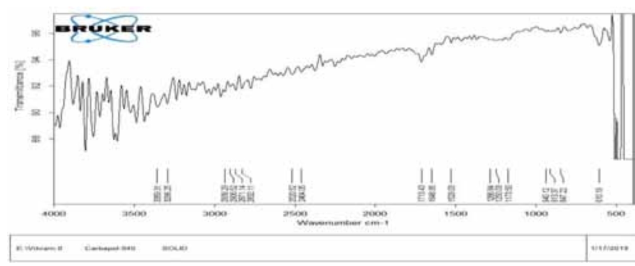

Figure 3: FTIR of Carbopol 940.

FTIR analysis: FT-IR analysis discovered that there was no interaction between the mupirocin and physical mixture as per given in pharmacopoeia. In the present investigation, it has been observed that there are no chemical and physical interactions because of some bond formation between mupirocin and physical mixture. Hence mupirocin drug was authentic and free from impurities. (comparison shown in Table 1) (Figure 2, 3 and 4 shown FTIR of Mupirocin, Carbapol and physical mixture of Mupirocin and Cabapol respectively).

Calibration curve of mupirocin

The graph obeyed beer lamberts law in this selected concentration range. The calibration equation for

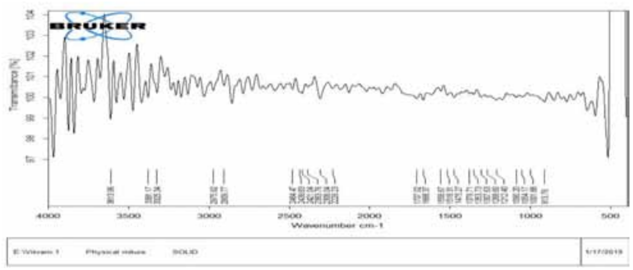

Figure 4: FTIR of Physical mixture.

Table 1: Comparison of observed peaks in drug and in physical mixture		
Observed peak in drug (frequency cm^{-1})	Group	Observed peak in physical mixture (frequency cm^{-1})
3621.73	OH group	3613.96
2959.86	C-H stretch of CH_3	2975.92
2351.74	C=O stretch of carboxylic acid	2383.76
1397.31, 1334.21	C-H bending of CH_3, CH_2	1379.71, 1307.63
1075.01	C=O stretch of ether	1090.20

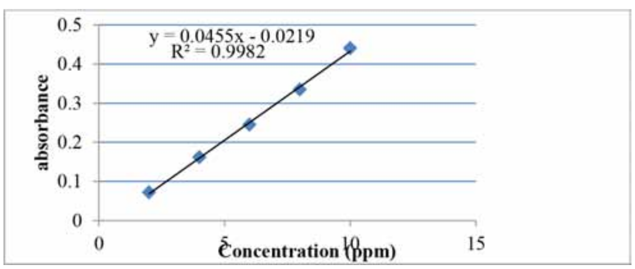

Figure 5: Standard calibration curve for different dilution of mupirocin at 220 nm.

straight line was observed to be y = 0.045x – 0.021 with correlation coefficient 0.998 shown in Figure 5.

Evaluation of nanoparticles

Drug entrapment efficiency

% E.E. of drug was found to be 65.2%

Transmission electron microscopy (TEM): Formulation was subjected for TEM to obtain, image of nanoparticles on scale bar of 200 nm with magnification 13.0x4000. On description unilamellar, spherical vesicles with smooth surface were noticed under transmission electron microscopy (TEM) shown in Figure 6.

Zeta potential

The zeta potential of copper nanoparticle shows in Figure 7, less aggregation of particle with –15.1 ± 3.69 mV value.

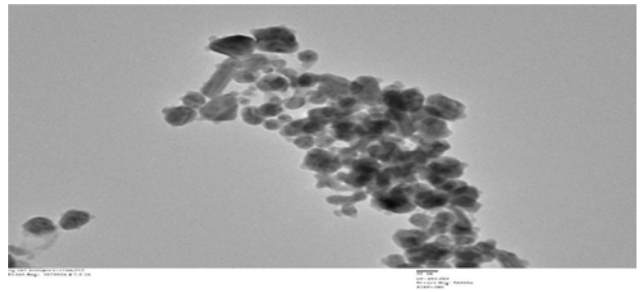

Figure 6: TEM of Copper nanoparticles.

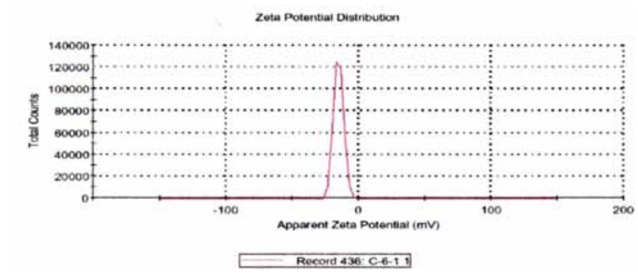

Figure 7: Zeta potential Copper nanoparticles.

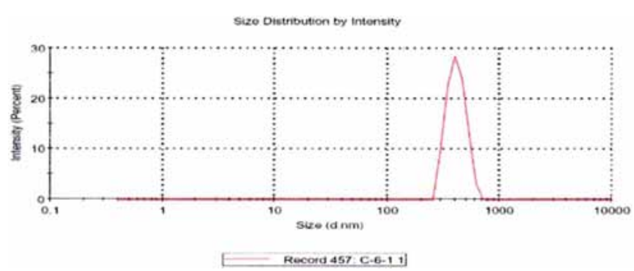

Figure 8: Particle size Copper nanoparticle.

Particle size measurement: Figure 8 shows the Dynamic Light Scattering of copper nanoparticles; the average size obtained was of 413.0 ± 30.2 nm with a narrow size distribution.

X-ray diffraction (XRD)

The crystal structure and phase composition of synthesized copper nanoparticles is analyzed by XRD, as shown in Figure 9. The diffraction data exhibits that the copper nanoparticles have crystalline structure.

Copper content determination

The amount of copper content was measured 5.9 microgram/10 mg of nanoparticles.

Physical Evaluations of Nanoparticle Gel

Organoleptic characteristics

Color = pale yellow
Odor = characteristic
Phase separation = no

Determination of pH of nanoparticle gel

The pH of nanoparticle gel was recognized as 7.1

Viscosity

The viscosity of carbopol 940 gel base and nanoparticle gel by Brookfield instrumentation was recognized 73,200 and 72,300 cP respectively.

Spreadability

The spreadability of mupirocin gel coupled copper nanoparticle was recognized 13.29 g.cm^2/sec. The results demonstrated that gel was effective.

Extrudability analyzed

The extrudability of mupirocin gel coupled copper nanoparticle was recognized positive. Positive extrudability showed the better application of gel.

Percentage yield

The % yield of mupirocin gel coupled copper nanoparticle was carried out 95.78%.

Homogeneity and grittiness

Mupirocin gel coupled copper nanoparticle was recognized homogeneous and no grittiness was indicated.

In vitro release profile

Franz diffusion cell apparatus was used for the *in vitro* release profile. The drug release profile of the mupirocin coupled copper nanoparticles is presented in Figure 10. *In vitro* release profile was performed[24-41] to determine amount of drug release at different interval of time. The cumulative drug releases from nanoparticle reach 96.5% in 48 hr.

Drug release kinetics

The kinetics for drug release of mupirocin coupled Cu NPs was carried out for different models. The release profile of various models was given in Table 2.

Zero Order release kinetics plot

Plot the graph % cdr Vs time (Graph shown in Figure 11)

First Order release kinetics Plot

Graph was prepared between log % cumulative drugs remaining Vs time (Graph shown in Figure 12)

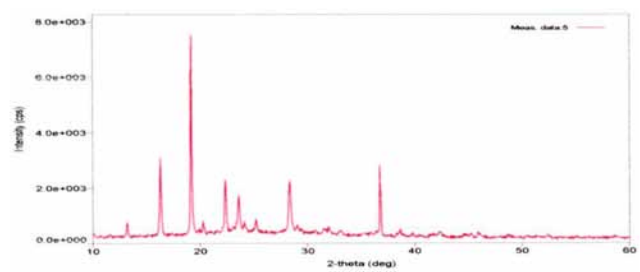

Figure 9: XRD spectra of Copper nanoparticles.

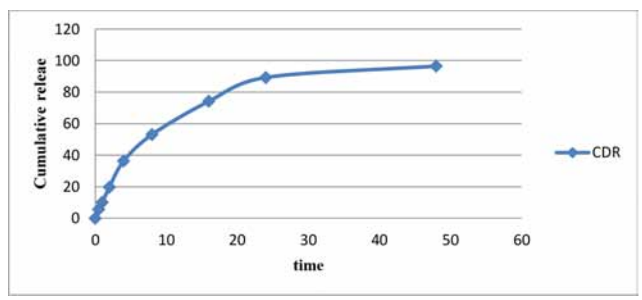

Figure 10: Release of drug from formulation in PBS at pH 7.4.

Table 2: Drug release kinetic of mupirocin coupled Cu NPs

Time (min.)	Log time	Square root of time	% cumulative drug release(CDR) of formulation	Log% cumulative drug release of formulation	% cumulative remaining	Log% cumulative remaining
0	0	0	0	0	100	2
30	1.48	5.48	5.7	0.76	94.3	1.97
60	1.75	7.75	10.1	1.00	89.9	1.94
120	2.08	10.95	19.8	1.29	80.2	1.90
240	2.38	15.49	36.3	1.56	63.7	1.80
480	2.68	21.91	53.1	1.73	46.9	1.66
960	2.98	30.98	74.2	1.86	25.8	1.40
1440	3.15	37.95	89.3	1.94	10.7	1.03
2880	3.46	53.67	96.5	1.97	3.5	0.58

Higuchi's Model release kinetics

Graph was prepared between % cdr Vs square root of time (Graph shown in Figure 13).

Korsmeyer-Peppas Model release kinetics

Graph was prepared between log % cdr Vs log time (Graph shown in Figure 14).

Some kinetic models describing drug release from modified released dosage forms. The model release data by correlation coefficient. The correlation coefficient value was used as criteria to choose the best model to explain the drug release. From these values, it was observed that the peppas model will be fitted best model with R^2 value of 0.980 shown in Table 3.

Antimicrobial activity

Antimicrobial activity was determined by cup plate method on *S. aureus*. Antimicrobial activity of pure drug shown in Figure 15 and Antimicrobial activity of copper nanoparticles gel containing mupirocin shown in

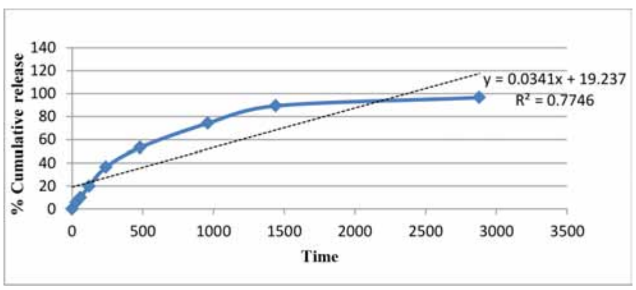

Figure 11: Zero Order release kinetics plot.

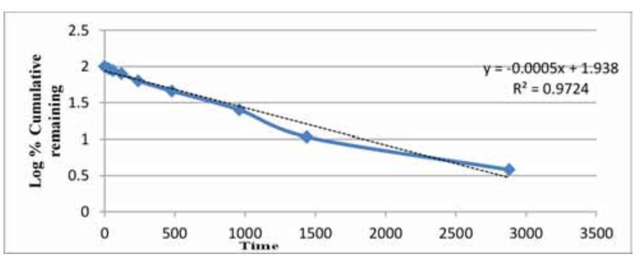

Figure 12: First Order release kinetics Plot.

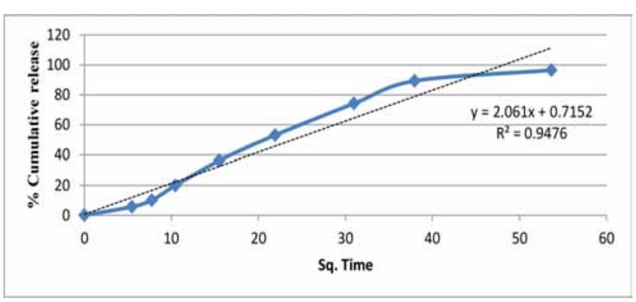

Figure 13: Higuchi plot for release kinetics plot.

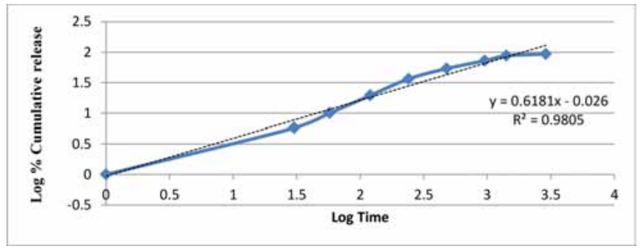

Figure 14: Peppas model release kinetics plot.

Table 3: Kinetics of drug release.

Plot	K_0	R^2
Zero order	0.077	0.774
First order	0.000	0.972
Higuchi	4.75	0.947
Peppas	1.41	0.980

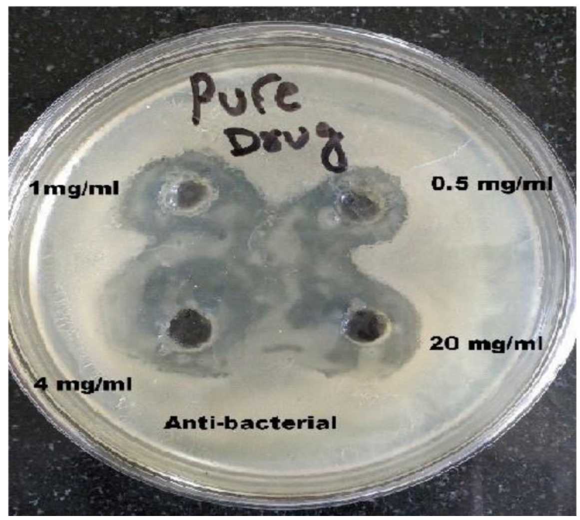

Figure 15: Antibacterial activity of pure drug mupirocin.

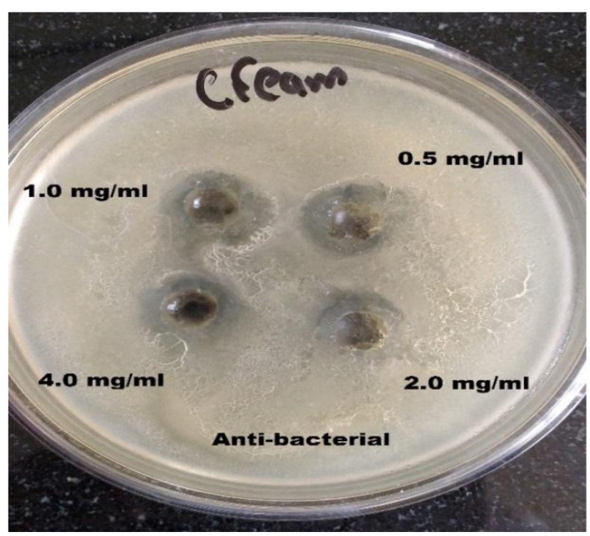

Figure 16: Antibacterial activity of copper Nanoparticle gel containing mupirocin.

Table 4: Antimicrobial activity by cup-plate method.		
Concentration (μg/ml)	Pure Mupirocin	Formulation
0.5	9 ± 1 mm	6± 2 mm
1	12 ± 2 mm	9± 2 mm
4	17 ± 1 mm	13 ± 3 mm
20	18± 3 mm	17 ± 1 mm
30	18± 2 mm	18 ± 2mm
40	19± 2 mm	18 ± 1 mm

MIC 20 μg 30 μg

Figure 16. Comparison of pure mupirocin and formulation of antibacterial activity shown in Table 4.

CONCLUSION

In present investigation, mupirocin coupled copper nanoparticles were synthesized to overwhelm drug resistance in *Staphylococcus aureus*, responsible for dermal skin infections. So, prepared and evaluate the mupirocin coupled Cu NPs to get the formulation with increased antibacterial activity and suit for topical application. The Cu NPs containing mupirocin were prepared by chemical reduction method and evaluated. Based on R^2 value the formulation followed the Pappas model. Mupirocin containing Cu NPs based gel displayed superior efficacy against *S. aureus* owning to prolonged release as compared to pure drug.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

Cu NPs: Copper Nanoparticle; **MIC:** Minimum inhibitory concentration; **Vs:** Versus; **PBS:** Phosphate buffer saline; **Pvt Ltd.**: Private limited**; TEM:** Transmission electron microscopy; **S:** *Staphylococcus.*

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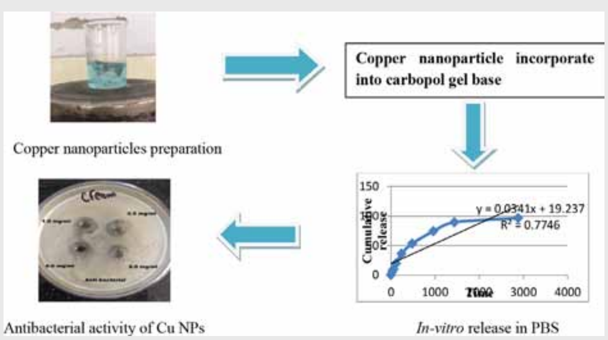
PICTORIAL ABSTRACT



SUMMARY

Topical route offers several potential advantages over conventional route. While optimizing topical drug delivery colloidal carrier system appears as upcoming development. Recently advancement in nanoparticle was done and obtained "copper nanoparticle" which has desirable advantages like alteration in properties of drug and antibacterial activity. Cu NPs potentiate the antibacterial action of drug. Copper nanoparticles were prepared by size reduction using chemical method. Gel was prepared by carbopol 940 as gelling agent, propyl paraben and methyl paraben added as preservatives. Cu NPs shows good antibacterial activity.

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