IJBPAS, January, 2023, 12(1): 455-474

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

# AN OVERVIEW ON ZINC-OXIDE NANOPARTICLES AS NOVEL DRUG DELIVERY SYSTEM

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Received 26th March 2022; Revised 25th April 2022; Accepted 10th July 2022; Available online 1st Jan. 2023

https://doi.org/10.31032/IJBPAS/2023/12.1.6794

## ABSTRACT

zinc oxide nanoparticles are highly effective against gram-positive bacteria. Zinc oxide is used as an antimicrobial substance that fulfills all the criteria required for an element to fit human consumption. They possess the ability to destroy microbes and safeguard the health of humans. Among all the metal oxide nanoparticles that have been analyzed, the nanoparticles of zinc oxide have been found to show very high toxicity against microbes. Their mechanism of action is degradation or breakdown of cell walls and accumulation in the cell membrane. Zinc oxide alters the metabolism of the bacterial cell, causing death of bacteria. The zinc oxide nanomaterial releases free reactive oxygen radical species, which are toxic to bacteria or microorganisms. Zinc oxide nanoparticles are site or target-specific so that unwanted toxicity to the host cell can be prevented. This causes the synergistic antimicrobial effect. Now antibiotics are used in combination with zinc oxide nanoparticles for high efficacy and bio-distribution, such as Azithromycin, Ciprofloxacin, Imipenem, Ceftriaxone, Gentamicin, Oxacillin, Ampicillin, Sulbactam, Oxytetracycline, and Chloramphenicol. From the literature study conducted, we infer that high efficiency is seen in combining antibiotic drugs with zinc oxide nanoparticles of various sizes and morphology. Furthermore, experiments on particle size, morphology, concentration, and surface modification can effectively control severe bacterial infection.

**Keywords: Zinc oxide, Nanoparticles, Sol-gel method; Drug delivery, Target-specific**

## INTRODUCTION

Nanoparticle's distinctive physicochemical properties that change the medical treatment to high potency and lesser toxicity perspective have gained exceptional attention in treatment and diagnosis **[1]**. Nanoparticles are most commonly employed as vehicles for drugs to enhance their specificity, delivery, and efficacy **[2]**. Nanoparticles are usually measured in nanometers. They often exist naturally but also occur due to the activities of humans. Nanoparticles are of extremely small sizes, due to which they tend to possess unique features that find their applications in various fields. For an element to be termed a nanoparticle, its dimensions must be within the range of 1-100nm. But it is clearly stated under its definition that it is enough if only one of its dimensions lies within the field. Not all the dimensions need to fit in the range of 1-100nm. Nanoparticles are usually classified on various basis. They are categorized as organic and inorganic nanoparticles by some classifications. Some polymers, dendrimers, and liposomes are organic nanoparticles, and gold, quantum dots, and fullerenes are inorganic nanoparticles **[3]**.

Another everyday basis of classification of nanoparticles includes their type like carbon-based, polymeric, semiconducting, or ceramic. Also, classification can be made as hard nanoparticles, silica nanoparticles, or soft nanoparticles. Primarily the classification of nanoparticles is based on the role played by the nanoparticle **[3]**.

Nanoparticles have three main physical properties which are correlated. The three properties are listed below:

- Nanoparticles show high mobility in their free state
- They have a large specific surface area
- Nanoparticles exhibit quantum effects

Nanoparticles have found their use in the field of medicine due to their very small size. With their unique design, they circulate throughout the body and also make entry into cells and could be designed to form bonds with cells. These properties possessed by nanoparticles have paved the way to developing new techniques of treatment like inducing hyperthermia locally or diseased tissue vasculature blockade.

By delineating nanoparticles, it is possible to improve fluorescent imaging, gain better images from PET (Positron emission tomography), or even enhance the ultrasound. These techniques require the nanoparticle to possess the ability to identify the cell that is in the diseased condition. Theoretically, the same logic is applied in drug delivery to specific sites.

The vehicles used for the delivery of a drug could be liposomes or a Nano capsule. It could also be packed in a nanostructure that is porous in nature which is bound at the targeted sites by which sustained release of the drug is ensured. Nanoparticles with all these properties assure a promise in the treatment of several neurological diseases.

They also have a significant role in producing and designing scaffold structures employed in bone and tissue repair. These materials are biocompatible. Many products like sunscreen have nanoparticles as their main constituent **[3]**.

**Nanoparticles in the environment**

Nanoparticles are present naturally in the ecosystem in more significant volumes. Aerosol emitted from the sea, volcanoes emitting smoke, dust from the fields and deserts, etc., produce nanoparticles in a huge variety. Even the trees have been found to release nanoparticles of hydrocarbons. Anthropogenic (human-made) nanoparticles are often released by industries and power stations, vehicles, and aircraft. These tend to cover up a large proportion of the nanoparticles that are emitted.

types of nanoparticles emitted:

- Hydrocarbons
- Cerium oxide
- Metallic dust
- Calcium carbonate

Other sources that emit nanoparticles include wastewater discharges that could be industrial or domestic, the health care industry, industries concerned with semiconductors, and the photography industry. The emission levels of these sources are much lower when compared to the level of emission done in the natural process **[3]**.

**Chemistry of zinc oxide**

one of the most common inorganic elements that possess a wide range of uses is zinc oxide.

- Molecular formula: ZnO or OZn
- Molecular weight: 81.4
- Solubility: Soluble in acids and bases that are dilute, Insoluble in water
- Melting point: very high (1975 ºC, also decomposes at the same point)
- Two crystalline forms: wurtzite and zincblende

Characteristics:

**Table 1: characteristics of zinc oxide**

| | |
|---|---|
| **Appearance** | **Yellow- gray granular solid** |
| **odor** | **No characteristic odor** |
| **solubility** | **Insoluble in water** |

Zinc oxide can be easily found in glass, ceramics, rubber, paints, plastics, lubricants, sealants, pigments, batteries, food, etc.

**Uses**

- Treatment of skin conditions
- Used in baby powders
- Treat diaper rashes
- Anti-dandruff shampoo
- Antiseptic ointments [4,5].a

**ZINC OXIDE NANOPARTICLES**

Based on the method of synthesis, they could be:

- Nanorods
- Nanospheres
- Nano boxes
- Nanoplates
- Hexagonal
- Tripods
- Tetrapods
- Nanowires
- Nanotubes
- Nanorings
- Nanocages
- Nanoflowers

Studies report that these zinc oxide nanoparticles are highly effective against gram-positive bacteria. Zinc oxide is used as an antimicrobial substance that fulfills all the criteria required for an element to fit human consumption. The properties for an antimicrobial substance to be ideal are enlisted below:

1. The element should be non-toxic
2. The antimicrobial substance should be inert. It should neither react with the food nor the container.
3. The taste of the substance should be agreeable.
4. It should have a pleasant odor or should be odorless **[6]**.

Zinc oxide can be used and is considered safe to be used in preservatives and medicine and can be employed as an antimicrobial agent **[7, 8]**. Zinc oxide nanoparticles can easily diffuse through food substances. They possess the ability to destroy microbes and safeguard the health of humans. Among all the metal oxide nanoparticles that have been analyzed as of now, the nanoparticles of zinc oxide have been found to show very high toxicity against microbes **[9]**. The zinc oxide nanoparticles have specific characteristics, all of which are dependent on physical properties like the shape and size of the particle, concentration of the nanoparticles, and the time of contact to the bacterial cell.

Zinc oxide nanoparticles must be non-toxic; they should not interfere with food or the storage container, should have a pleasant taste, or must be tasteless and also odorless. The zinc oxide particles morphology depends on the process of synthesis. Zinc oxide nanoparticles can be nanoplates, nanorods, nanoplates, nanospheres, nano boxes, hexagonal, tripods, nanotubes, nanorings, and nanoflowers. The synthesis of zinc oxide nanoparticles or microparticles is based on physical and chemical parameters like solvent type pH, precursors, and temperature.

There are physical and chemical techniques, but chemical technique like the thermal evaporation of zinc oxide powders, simple thermal sublimation, self-combustion, sol-gel technique, solution synthesis, vapor-liquid-solid technique, double gel precipitation, and polymerized complex method is the commonly used techniques.

The function or the characteristics of zinc oxide nanoparticles is based on the particle size, concentration, shape, and exposure time to the bacterial cell wall. An animal study conducted by Wang *et al*. shows that zinc oxide shows 50 to 500mg/kg of minimum toxicity in mice. The study shows sufficient distribution of zinc in the organ systems like the liver, pancreas, brain, kidney, and bones. The rate of absorption and distribution of zinc oxide is directly proportional to the size of the nanoparticles **[10]**.

Zinc oxide nanoparticles can also be used as drug delivery systems because they have a large surface area, phototoxic effect, and surface effect. In the treatment of cancer, zinc oxide nanoparticles with intrinsic blue fluorescence were loaded with doxorubicin. There was 75 percent efficacy observed. The zinc oxide nanoparticles have a coating of folate-conjugated chitosan, increasing the aqueous stability of zinc oxide nanoparticles. Electrostatic interaction between zinc oxide nanoparticles surface and folate via hydrogen bonding was used to trap the drug. The optimal Ph for release of doxorubicin was 7.4. Nanoparticles have a significant advantage of antigen delivery into the dendritic cell. Ferrosoferric oxide and zinc oxide core-shell nanoparticles were used to deliver carcinoembryonic antigen to the dendritic cells. The zinc oxide present in the nanomaterial aided in internalization and reduced the time needed for labeling dendritic cells **[11, 12]**.

Studies have related the exposure time of the zinc oxide nanoparticle and its effects. In a study conducted by Wang *et al*., the metabolism of zinc and the biodistribution of zinc oxide nanoparticles in mice for 3-35 weeks. The results of the study state that very minimal toxicity was observed in mice when exposed to zinc oxide nanoparticles (50 mg/kg, 500 mg/kg) via diet. When a larger dose was administered (5000mg/kg), the overall body weight of the mice was reduced by the zinc oxide nanoparticle. However, there was an increase in the weight of the mice's brain, lungs, and pancreas.

Elevation of SGPT activity was observed, and the expression of mRNA of the genes (metallothionein) related to the metabolism of zinc **[13]**.

## USES OF ZINC OXIDE NANOPARTICLES

Zinc oxide nanoparticles are increasingly used these days in various products ranging from the industrial sector to the field of medicine. In the last few decades, zinc oxide nanoparticles have been employed as biological agents in accordance with their high biocompatibility and lower toxicity. They are also found to be economical. Some of the uses are listed below:

- Fluorescence imaging
- Magnetic resonance imaging
- Positron emission tomography
- Dual modality imaging
- Drug delivery
- Gene delivery
- Biosensing molecules
- Anticancer activity
- Antibacterial activity
- Antioxidant
- Antidiabetic
- Anti-inflammatory activity
- Concrete production
- Photocatalysis
- Electronics
- Electrotechnology industries **[14]**.

**Advantages**

- High chemical stability
- Thermal resistance
- Robustness
- Longer shelf life
- Selective toxicity
- Bactericidal to gram-positive, gram-negative, and fungal spores
- Resistant to temperature
- Resistant to high pressure **[15]**.

## PREPARATION OF ZINC OXIDE NANOPARTICLES

The naturally occurring zinc oxide nanoparticles exist in various sizes and shapes and possess a wide range of features. Several methods have been developed in recent years for the preparation of zinc oxide nanoparticles. Preparation by chemical method, solution-free method, sol-gel method, biosynthesis method, pyrolytic method, etc.

**Chemical precipitation method**

This is the most commonly employed method for the preparation of zinc oxide nanoparticles. This method consists of two reagents: purified zinc forerunner (zinc acetate, zinc sulfate, or zinc nitrate) and a precipitation solution like ammonium hydroxide or sodium hydroxide **[16]**. The precipitation solution should be added drop by drop to ensure that the zinc is dissolved until the pH of the solution reaches 10. Now, these solutions are mixed thoroughly to yield an intermediate of zinc hydroxide. Later, the zinc hydroxide sample is converted into zinc oxide after frottage at elevated temperatures.

The controlled parameters are the concentration of the precipitator of solution and the zinc precursor, the molar proportions of the reagents, the temperature at which the reaction takes place, and the temperature at which calcination takes place.

In the method taken up by Bisht *et al*. to produce zinc oxide nanoparticles, zinc acetate and sodium hydroxide in the ratio of 1:5 were used. The intermediate products that were obtained were calcined for two hours at 200°C in a muffle furnace from which fine white powder of zinc oxide was produced **[17]**.

Another method introduced by Bettini *et al*. used zinc sulfate and sodium hydroxide in the ratio 1:2. The solution undergoes vigorous stirring for about 12 hours at room temperature. The resultant is a white residue that is thoroughly washed several times and then centrifuged for separation **[17- 19]**. The residue is dried in an oven for six hours at 100°C. The nanoparticles are flake-like structures with a size distribution of 100 nm.

This chemical precipitation method for the preparation of zinc oxide nanoparticles is simple but can also be controlled with ease and industrialized quickly **[14]**.

**sol-gel method for preparation of zinc oxide nanoparticles**

Anderson and Spaniel first proposed this method for the synthesis of zinc oxide nanoparticles **[20]**, and it is carried out in three steps:

1. *Zinc precursor preparation*

A small quantity of zinc acetate is taken and dissolved in ethanol. This preparation is set in a distillation apparatus. Then it is refluxed at atmospheric pressure for a few hours. The preparation is boiled at 80°C and is stirred, which yields a product and hygroscopic reaction mixture.

2. *Zinc oxide clusters preparation*

The concentration of the hygroscopic reaction mixture is reduced by diluting the mixture to an ethanolic solution by the addition of lithium hydroxide powder. The mixture under the influence of an ultrasonic bath turns transparent. This process speeds up the release of hydroxyl ions. When it takes place at lower temperatures and certain air conditions, this reaction could prevent the growth of rapid particles and yield zinc oxide sols.

3. *Growth of crystals*

This is a self-induced process that occurs at room temperature. The growth rate of crystals, the size, and the shape of the crystals produced are strongly influenced by the amount of lithium hydroxide used. The growth of zinc oxide induced by lithium hydroxide is given by:

$Zn(CH_3COO)_2.2H_2O + 2LiOH \rightarrow Zn(OH)_2 + 2CH3COOLi + 2H2O$

$ZN(OH)_2 + 2H2O \rightarrow Zn(OH)_4^{2-} + 2H^+$

$Zn(OH)_4^{2-} \rightarrow ZnO + H_2O + 2OH^-$

The use of other alkalis was also found to yield zinc oxide; one such study stated that the use of sodium hydroxide in place of lithium hydroxide successfully yielded zinc oxide nanoparticles with the crystalline size of 14nm at pH 9 **[21]**.

This method is of keen interest because of its mild synthesis conditions, simplicity, and low cost.

**Solid-state pyrolytic method**

wang *et al*. developed this method initially. It is highly advantageous due to its ease of operation and low cost. This also results in inefficient growth of zinc oxide nanoparticles of high grade **[22]**.

The synthesis procedure includes making a mixture of zinc acetate and sodium bicarbonate at room temperature. The resultant is pyrolyzed at the temperature of the reaction. As a result, zinc acetate is converted into zinc oxide, and sodium bicarbonate is converted into sodium acetate, which is cleared out with the aid of deionized water. The process of thermal decomposition obtains the yield of zinc oxide nanoparticles. The selection of pyrolytic temperature determines the particle size of the resultant. The resultants from this method range in sizes from 8-35nm.

**Solution-free mechanochemical method**

The preparation of zinc oxide nanoparticles via the solution-free mechanochemical method is a two-step process. In the first step, zinc acetate is ground along with oxalic acid powder for a definite time to produce nanoparticles of zinc oxalate **[23]**.

The second step involves zinc oxalate thermal decomposition at extremely high temperatures, yielding zinc oxide nanoparticles.

$$ZnC_2O_4 \cdot 2H_2O \rightarrow ZnC_2O_4 + 2H_2O\uparrow$$

$$ZnC_2O_4 \cdot 2H_2O \rightarrow ZnO + CO_2\uparrow + CO\uparrow + 2H_2O\uparrow$$

$$CO + O_2 \rightarrow CO_2\uparrow$$

$$2H_2C_2O_2 \cdot 2H_2O + O_2 \rightarrow 4CO_2\uparrow + 4H_2O\uparrow$$

$$CH_3COOH\text{ (liquid)} \rightarrow CH_3COOH\text{ (gas)}$$

The main advantages of this method include lower cost of production and high homogeneity of the crystalline morphology and structure. However, the morphology of the zinc oxide nanoparticles depends on the reaction mixture's milling time. A longer duration of milling yields smaller particles. The zinc oxide nanoparticles range in sizes from 24-40 nm.

In their study, Pardeshi and Patil reported that they synthesized zinc oxide nanoparticles of different crystalline sizes and varied morphologies by this method. However, the temperatures for calcination were varied from 400°C to 900°C. The observation made from the experiment was that calcination of zinc oxide took place between 400°C to 550°C and the crystalline growth was similar with the range of 38-55 nm **[24]**.

**Biological methods for the preparation of zinc oxide nanoparticles**

Although the chemical and physical methods for the preparation of zinc oxide have developed several folds, there is a greater focus on the growth and development of green chemistry as it is a convenient, eco-friendly option **[25]**. Several plant species and their extracts have been used for the preparation of zinc oxide nanoparticles. The species are listed below:

**Table 2: Plant species used for the preparation of zinc oxide nanoparticles**

| SPECIES | SOURCE |
|---|---|
| ***Azadirachta indica*** **[23]** | **Leaf** |
| ***Cochlospermum religiosum*** **[24]** | **Leaf** |
| ***Plectranthus amboinicus*** **[25]** | |
| ***Andrographis paniculata*** **[26]** | |
| ***Aloe barbadensis*** **[27, 28]** | |
| ***Nephelium lappaceum*** **[29]** | **Peel** |
| ***Polygala tenuifolia*** **[30]** | **Root** |
| ***Zingiber officinale*** **[31]** | **Rhizome** |
| ***Trifolium pratense*** **[32]** | **Flower** |
| ***Jacaranda mimosifolia*** **[33]** | |
| ***Physalis alkekengi*** **L [34]** | **Seeds** |

The biosynthesis of zinc oxide nanoparticles is found to be more economical, environmental friendly, biocompatible, and non-toxic than the earlier used physical and chemical methods. It was found that the zinc oxide nanoparticles produced from biological sources exhibited the essential potential to be applied medically as it tends to possess antibacterial and anticancer activity **[14]**.

**CHARACTERISATION OF ZINC OXIDE NANOPARTICLES**

The prepared zinc oxide nanoparticles were characterized by various techniques, some of which are listed below:

- X-ray diffraction
- Scanning electron microscopy (SEM)
- Transmission electron microscopy (TEM)
- Selected area electron diffraction
- UV absorption
- Photoluminescence spectroscopy **[35]**.

**X-ray diffraction**

The peak intensity, full-width at half-maximum [FWHM], and the position were determined from the x-ray diffraction pattern analysis. The zinc oxide nanoparticles were hexagonal. The diameter of the zinc oxide nanoparticle was calculated by the Debye-Scherrer formula **[36]**.

$$d=0.89\lambda/\beta\cos\theta$$

**Morphological Studies**

The obtained results convey that zinc oxide nanoparticles are mildly spherical with some faceting. They were indexed as hexagonal formations. SEM and TEM operations are performed to analyse the morphology and topography of the nanoparticles.

**UV absorption spectrum**

The characteristic features of the zinc oxide nanoparticles depend mainly on the size of the particles that are synthesized. Thus, the evolution of the size of the nanoparticles is essential for analyzing the properties that the nanoparticles can exhibit. It was found that zinc oxide nanoparticles showed maximum absorption at 355 nm. It was also found to be evident from the study that the sharp absorption stipulates the nature of mono dispersion of the nanoparticle.

**Cytotoxic effect of zinc oxide nanoparticles delivery system**

Zinc oxide nanomaterial loaded with aminopolysiloxane was used to treat leukemia K562/A02 resistant to Adriamycin. The Cytotoxic effect of the nanomaterial varies based on their size. Incubation with Zinc oxide nanoparticles suppressed the process of cell proliferation by treating it with UV radiation. Zinc oxide loaded with daunorubicin increased or enhanced the activity of the drug, whereas the nanoparticles enhanced the cellular uptake of DNR. They also inhibited cell proliferation of the two cell lines **[37, 38]**.

**Mechanism of zinc oxide nanoparticles in antibacterial action**

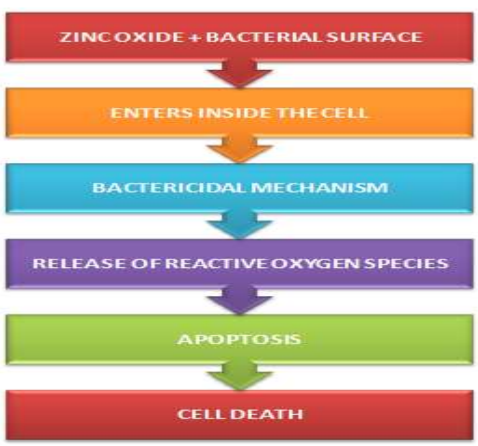


**Figure 1**


**Figure 2**

**Figure 1 & 2: Flowcharts showing the mechanism of zinc oxide nanoparticles in antibacterial action**

**Photodynamic therapy**

In cancer, non-invasive treatments using nanoparticles are a recent and the most promising advancement. Light of specific wavelength and prescribed dose will generate reactive oxygen species, which will induce apoptosis followed by cell death. After absorption of UV illumination in an aqueous solution, zinc oxide nanoparticles induce the release of reactive oxygen species like hydroxyl radical, hydrogen peroxide, and super oxides. Zinc oxide Nano rods trapped with daunorubicin by electrostatic interaction showed enhanced anticancer efficacy on SMMC-7721cells by photocatalysis **[37]**.

**Zinc oxide as preservatives**

Zinc oxide nanoparticles are used as preservatives, medicine. They are mainly used as antimicrobial agents. They are used as preservatives in packaging. Zinc oxide may affect the quality or the nature of the food packed while used as preservatives; therefore, it is only used in polymeric packaging material **[37, 38]**.

**Zinc oxide as an antibacterial agent**

Control of bacterial infections and diseases is becoming more complex day by day because of bacterial mutation, social complications, and economic factors. This resulted in antimicrobial resistance, the emergence of new bacterial strains, and the lack of vaccines in underdeveloped countries, most notably in children. Food-borne bacterial infections are causing approximately 1.5 million deaths every year due to contamination of food and water.

Zinc oxide is more effective against gram-positive bacteria. They are commonly used against *Salmonella typhi* and *Staphylococcus aureus*. Their mechanism of action is degradation or breakdown of cell walls and accumulation in the cell membrane. Zinc oxide alters the metabolism of the bacterial cell, causing death. The zinc oxide nanomaterial releases free reactive oxygen radical species, which is toxic to bacteria or microorganisms. Zinc oxide nanoparticles are site or target-specific so that unwanted toxicity to the host cell can be prevented. This causes a synergistic antimicrobial effect. Zinc oxide nanoparticles show increased membrane permeability and localization which leads to cell damage. The above action leads to dysfunction of mitochondria, intracellular outflow, and oxidative stress due to the toxicity caused by the zinc ions from the nanoparticles. The smaller the zinc oxide nanoparticles' size, the more is the physical transfer of zinc oxide nanoparticles into the inner cellular structure. The reactive oxygen species released are hydrogen peroxide, hydroxyl species which degrades the lipid, protein, and DNA.

A study Su-Eon Jin *et al*. in the year 2021 studied the relationship between physicochemical properties and the antibacterial activity in zinc oxide nanoparticles or micro-particles **[39]**.

The study reported that Zinc oxide nanorods of size ranging from 500nm to 1 µm showed antibacterial activity against *K. pneumoniae* at 88.7nm. These nanoparticles were synthesized by precipitation method using a capping agent. A study by Taghizdeh *et al*. zinc oxide nanorods of the size of 3.4nm shows antibacterial activity against *E.coli, P.aeruginosa, S.aureu*s, and *Enterococcus faecalis* at a MIC of 250µg/ml **[40]**. `

Zinc oxide of hexagonal hollow tube-like morphology with an approximate length of 500 nm length 278.6 nm pore size, and surface area of $17.8 m^2/g$ is effective against *E.coli, S.aureus, B.subtilis*. Zinc oxide nanoparticles obtained from citric acid monohydrate were also effective against the above-mentioned species **[41]**.

**Combination of zinc oxide nanoparticles with drugs**

The anti-inflammatory activity and antimicrobial activity can be enhanced by using the combination of zinc oxide nanoparticles with antimicrobial agents, anti-inflammatory agents, or natural agents. Previously zinc oxide nanoparticles were used in combination with Clindamycin and triamcinolone as endodontic dressing. ZnO NPs are used in combination with eugenol as dental cement. Now antibiotics are used in combination with zinc oxide nanoparticles for high efficacy and bio-distribution. For example, drugs like Azithromycin, ciprofloxacin, imipenem, ceftriaxone, gentamicin, oxacillin, ampicillin, and sulbactam, oxytetracycline, and chloramphenicol **[42]**.

**Antibacterial drugs loaded in zinc oxide nanoparticles**

In 2015 Rath *et al*. performed a study on the development and characterization of cefazolin-loaded zinc oxide nanoparticles composite gelatine fiber mats for postoperative surgical prophylaxis.1:1 ratio of zinc oxide and cefazolin with an average diameter of 200-900 nm has antibacterial activity. Cell lysis and cell disruption take place when observed under a transmission electron microscope. The nanofiber enhanced the wound healing rate post-surgery. Enhanced cell adhesion, epithelial migration is the key factors to prefer zinc oxide nanoparticles hybrid cefazolin nanofiber instead of plain cefazolin and zinc oxide NPs mat **[43]**.

In a study conducted in 2020, Curcumin-loaded zinc oxide nanoparticles were studied for activity-enhancing antibacterial and anticancer activity. Zinc oxide-Curcumin nanocomposites were synthesized. Their activity against gram-negative and gram-positive bacteria, where rod-shaped and spherical shaped nanoparticles of Curcumin loaded zinc oxide nanoparticles showed effective antimicrobial activity against the bacterial strains. Zinc oxide provided an additive effect **[44]**.

In a study conducted in the year 2019, titanium oxide-loaded zinc oxide nanoparticles supported into 4A zeolite were assessed. The antibacterial activity of titanium oxide loaded zinc oxide NPs against *staphylococcus aureus, pseudomonas fluorescens, listeria monocytogenes*, and *E.coli* was observed. The nanoparticles were synthesized using the hypodermal method. The size of the synthesized nanoparticles was 50nm; the 4A zeolite particle size synthesized was 400-600 nm. The study results gave us a clear insight into the antibacterial activity of the titanium oxide-loaded zinc oxide nanoparticles. The Ti-ZnO NPs has good antibacterial activity against both gram-positive and gram-negative microorganism. The NPs showed enhanced activity against pseudomonad fluorescence **[45]**. Noor Akbar *et al*. studied the potential antibacterial activity. Zinc acetate dihydrate and sodium hydroxide were used as precursors to synthesize zinc oxide nanoparticles. Beta cyclodextrin capped zinc oxide NPs, drug-loaded beta-cyclodextrin capped zinc oxide NPs containing *quercetin, naringin, ceftriaxone, ampicillin, and amphotericin B*. the prepared NPs were suspended in deionized water **[46]**.

The drug-loaded nanoparticles were tested against methicillin-resistant staphylococcus aureus, *E.coli, streptococcus pyrogens, S. pneumoniae, Serratia marceacens*. Conjugation of the five drugs with zinc oxide enhanced the antibacterial activity. This is because of the larger surface area discussed earlier. The ZnO NPs release reactive oxygen species, enhancing the antibacterial activity; the antibacterial spectrum was high against *S.aureus* and was poor against *E.coli* **[46]**. Antibacterial activity of hydroxyapatite and zinc oxide nanoparticles were studied by Grenho *et al*. suggests that the zinc oxide nanoparticles synthesized by the simple sponge replication method were found to be effective against *S.aureus* and *staphylococcus epidermidis* in vivo and in vitro. The study shows that nano-HA ZnO NPs are suitable for use in dental and orthopaedics to avoid biomaterial-associated infections and bone regeneration **[47]**. The hypodermal approach produced zinc oxide nanoparticles within the gum acacia polyhydrogel networking, and the antibacterial property was studied. The size of the zinc oxide nanoparticle ranges from 40-60 nm. The result suggests that the nanoparticle composite is effective against *E.coli* **[47]**.

Control of infection caused by a multi-drug-resistant microorganism can be achieved by using combination therapy. The study interprets the antimicrobial activity of the zinc nanoparticles against fungi, gram-negative bacteria, and gram-positive bacteria and the interaction between the ZnO NPs and the chosen antibiotics. The antimicrobial activity was tested using the microdilution method. Comparing the 10% doped zinc oxide nanoparticle and the 1 % loading and pure zinc oxide nanoparticles, the former shows enhanced antimicrobial activity in combination therapy. The combination therapy gave way to synergism and additive effect. The results rely on the MIC.

- Ciprofloxacin+ Zinc Oxide NPs → increased synergistic effect
- No antagonistic effect
- Ampicillin+ Zinc Oxide NPs →synergistic effect

A study by Usha Kadivala *et al*. in the year 2018 gives us a clear insight into the antibacterial activity of zinc oxide nanoparticles against methicillin-resistant staphylococcus aureus. The study evaluates the novel toxicity mechanism by using gene transcription microarray analysis increase in the generation of reactive oxygen species and lipid peroxidation. The ZnO NPs showed a notable (three log) reduction in the colonies of methicillin-resistant staphylococcus aureus. Up-regulation of pyrimidine biosynthesis and carbohydrate degradation was carried out by ZnO NPs **[48]**.

Hydroxyl radical generation property of zinc oxide was detected using ultraviolet photocatalysis. Bacterial broth testing, cytocompatibility via live/dead assay was used to study the antibacterial property of 3D printed zinc oxide- alginate nanoparticle. Decreased bacterial growth was more when nanoparticle was used instead of using alginate only gels.

Chronic wound healing is possible by using zinc oxide nanoparticles embedded with alginate gels because of mobility in the mobility of molecular exchange **[49- 51]**. A study on the use of ciprofloxacin conjugated zinc oxide nanoparticles to treat multidrug-resistant bacterial infection was conducted in the year 2014. Ciprofloxacin was loaded with amino-functionalized zinc oxide nanoparticles using EDC/NHS chemistry. FTIR spectra were used to confirm the conjugation of ciprofloxacin and zinc oxide nanoparticles. The conjugated nanoparticle showed very good antibacterial activity against multi-drug-resistant *E.coli, staphylococcus aureus, Klebsiella* species. The particle size, on average, was 18-20 nm. The size was obtained from a transmission electron microscope. The ciprofloxacin conjugated zinc oxide nanoparticles of 20μg/ml concentration were taken in a separate flask; a conical flask containing bacterial suspension was also prepared. The surface topology was studied using atomic force microscopic image, x-ray diffraction. The results from surface topology indicated that zinc oxide nanoparticle has a hexagonal crystal structure. Upon the introduction of the conjugated zinc oxide nanoparticle, bacterial cell damage can be identified. The degradation of bacterial cell membrane damage there will be the release of cytoplasmic constituents and DNA and RNA from the cytoplasm. This can be monitored by measuring the absorbance at

260 nm. To control a multi-drug-resistant bacterial infection, we have to target bacterial DNA's cell division process and destruction. The zinc oxide helped in the entry of ciprofloxacin following cell membrane destruction. This leads to inhibition of bacterial cell growth **[52]**.

**CONCLUSION**

This article focused on discussing the potential of zinc oxide nanoparticles to control the alarming antibiotic, specifically antibacterial resistance worldwide. From the literature study conducted, we infer that high efficiency is seen in the combination of antibiotic drugs with zinc oxide nanoparticles in various sizes and morphology. Furthermore, experiments on particle size, morphology, concentration, and surface modification can effectively control severe bacterial infection. The common mechanism of action of zinc oxide nanoparticles is the generation of reactive oxygen species, which leads to damage of bacterial cell membrane and cell lysis. An in-depth study on zinc oxide nanoparticles' antibacterial activity may lead to new findings of nanobiological toxicity to drug-resistant organisms and to treat infectious disease with less available treatment.

**ACKNOWLEDGEMENT**

The authors would like to express their admiration to the college of Pharmacy, SRMIST for providing them with tremendous opportunities to accomplish this work.

**DECLARATIONS**

*Conflict of interest:* The authors report no conflict of interest.

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