Review
Of
Literature
2. Nanomaterials

2.1 Metal-nanoparticles

Presently, bacterial infectious diseases and infections associated with medical implants are increased, which leads to the morbidity and mortality globally. In this context, metal-NPs as alternative to antimicrobial drugs due to emergence of bacterial resistance to these drugs resulted decrease their applicability [Morris, 2007; Montanaro et al., 2011]. Various types of metal and metal oxide NPs has antimicrobial activity due to its physiochemical properties and high surface area to volume that contributes to effective antimicrobial activities and do not develop bacterial resistance. Many studies reveal that metal-NPs inhibited or kill different bacterial species. The mode of action of metal-NPs against bacteria comprise as (1) inhibition of protein synthesis (2) bacterial cell wall disruption (3) generation of reactive oxygen species, which damage viral and cellular component (4) interruption of energy transduction. The metal NPs and their oxides generate reactive oxygen species (ROS) under UV light and enhance their applicability towards formulation and wound dressing [Huh and Kwon, 2011]. Fig. 2.1 describes the mechanism of the antimicrobial nanomaterials on bacterial cells.

![Fig. 2.1 A schematically representation of antimicrobial mechanism of nanomaterials](image-url)
Recent focus is to explore the antimicrobial nanomaterials that inhibit bacterial growth/resistant via drug delivery system. In this context, many recent studies focus on some metal nanoparticles (NPs) based drug delivery system. The metal NPs such as Ag, Cu, and Zn etc are known to have antibacterial properties which may be utilized to overcome the infectious diseases [Jing et al., 2008; Huh and Kwon., 2011; Ansari et al., 2012]. These NPs have several advantages, for example, insignificant toxicity, may not develop bacterial resistant and small cost in comparison with that of the conventional antibacterial agents. Metal NPs have retained much longer in the human body than small molecules of antibacterial agents, which could be effective for sustained therapeutics [Allaker and Ren, 2008; Weir et al., 2008]. The metal-NPs adhere to bacterial cells and inhibit synthesis of protein, thus prevent multiplication of bacteria. These metal-NPs are effective against various bacterial strains especially E.coli, S.aureus, and MRSA bacterial strains, which are inherently present in different burning and surgical wounds, and also, in diabetic foot-ulcer infections [Boateng et al., 2008].

Several metal NPs such as gold (Au), silver (Ag), Zinc (Zn), and Copper (Cu) and their oxides are well known antimicrobial agents, and effectively used against various microorganism. High reactivity of Ag, titanium and Zn oxide has been extensively utilized in water purification and surface coating on catheters. Among all of them, Cu and Zn have cheapest metals and lower toxicity towards mammalian cell lines [Shahverdi et al., 2007; Ruparelia et al., 2008; Huh and Kwon, 2011; Bindhu et al., 2014].

The Ag-NPs are well known antibacterial agents and has been used for dental works, catheter, and burn wound treatment and controlling of bacterial infections. Ag-NPs have proven to be the most effective against bacteria, viruses and other microorganisms. The Ag-NPs affect the cell division and respiratory chain that leads to death of cells. The Ag-NPs combined with different antibiotics such as amoxicillin, penicillin G, erythromycin, and vancomycin, resulted synergetic effects against both gram negative and gram positive bacterial strains [Gu et al., 2003; Shahverdi et al., 2007; Rai et al., 2009; Fayaz et al., 2010]. There are various studies carried out to investigate the Ag-NPs efficiently used as antibacterial agent against bacterial strains such as S. aureus, E. coli, Bacillus Calmette-Guérin (BCG) and MRSA [Zhou et al., Shahverdi et al., 2007; Rai et al., 2009; Fayaz et al., 2010].
The Cu-NPs and its oxide forms widely used as efficient materials for sterilizing liquids, textiles, various cells/tissues and antimicrobial agents. The combination of Copper sulphate, lime and water, and also with sodium carbonate were used as prospective fungicide and used in agricultural applications. Besides, act as antibacterial agents, Cu and its complexes also used for antiviral, molluscicidal and antifungal agents [Borkowand Gabbay, 2009; Ingle et al., 2014]. Several study reported on bactericidal effects of Cu-NPs mechanism action, suggested that releases of Cu ions from the Cu-NPs interact with the sulfur and phosphorus containing biological molecules such as proteins and DNA to alter their structure and also interrupt different biochemical processes. The mesoporous Cu-doped silica xerogels also used for antibacterial effects, where antibacterial activity increased with increasing concentration of Cu [Ruparelia et al., 2008; Wu et al., 2009; Raffi et al., 2010]. Several studies reported that the effective antibacterial activity of Cu against various bacterial strains such as S. aureus, E. coli, Bacillus subtilis and MRSA [Theron et al., 2008; Das et al., 2010; Schrand et al., 2010; Ramyadevi et al., 2012].

The Zn and its oxide are well known antimicrobial agents. The Zn is widely used in drugs carrier, cosmetics and medical implants. The Zn metals considered to be non-toxic, biocompatible and safer. Several studies reported, the efficient antibacterial activity of Zn-NPs against different pathogenic and non-pathogenic microorganism including E. coli and S. aureus. Some of them describes the size dependent antibacterial activity, which shows that the smaller particle size have larger antibacterial activity [Stoimenov et al., 2002; Brayner et al., 2006; Raghupathi et al., 2011; Azam et al., 2012; Cepin et al., 2015]. Zn is widely used in different applications such as agriculture, anti-oxidant, food industries (food additive), medical implants, wound dressing and skin products because of its biocompatibility, non-toxicity and environmentally friendly [Ramani et al., 2012; Ureña et al., 2015]. The non-toxicity of Zn has been making a good substitute for other toxic materials.

Various techniques have been developed to produces metal-NPs such as chemical reduction using different reducing agents such as trisodium citrate, hydrazine hydrate, sodium borohydrate, ascorbic acid and ammonium solution. However, metal-NPs synthesized using reducing agents cannot be directly applied in end applications [Lee et al., 2010; Quang et al., 2011; Zhang et al., 2013; Srinivasan et al., 2013].
2.2 Carbon based nanomaterials

Carbon based nanomaterials such as carbon nanotubes (CNTs), nanorods, and quantum dots were used in fluorescence imaging due to the formation of fluorescence in visible and IR regions. The carbon based nanomaterials potentially able for drug delivery system due to distinctive sp\(^2\) hybridization and hydrophobic nature. DNA/RNA and several types of drugs easily absorbed on the surface of carbon based nanomaterials due to hydrophobic interactions or π–π stacking. These drugs loaded nanomaterials can accumulate into specific site of infections and provide synergetic effects against diseases.

2.2.1 Carbon nanoparticles

Carbon is a well known adsorbent and widely used in different applications such as purifications, environmental remediation, delivery and storage of gases, recovery of metals, catalysis, treatments of gaseous effluents, and different biological applications including drug delivery system. The activated carbon has high surface area and adsorption capacity [Bystrzejewski et al., 2005; Kim et al., 2008; Mandal et al., 2013].

Carbon NPs have a potential ability towards drug delivery, imaging, and cellular labeling due to distinctive properties such as optical, high surface area, and excellent chemical and thermal stability. Mendes et al reported that insignificant toxicity of carbon based nanoparticles makes suitable for biomedical applications [Mendes et al., 2014]. The combination of carbon-iron based particles effectively used for treatment of tumors, and successfully trial on more than 150 patients [Kuznetsov et al., 1997]. Several studies reported that the carbon encapsulated metal NPs were used for different biomedical application including drug delivery system and biosensors [Bystrzejewski et al., 2005; Ramanujan et al., 2007; Bystrzejewski, et al., 2007; Kim et al., 2008; Mandal et al., 2013].

2.2.2. Activated carbon fibers

Presently, activated carbon fibers (ACFs) have been used as substitute of activated carbon due to their solid substrate support, which is related to physico-chemical properties of the fibers. ACFs have been used in purification, separation, and catalysis process due to enhanced surface area, highly porous structure, and
surface reactivity [Das et al., 2004; Dwivedi et al., 2004; Gaur et al., 2005; Adapa et al., 2006; Bikshapati et al., 2012]. Many efforts have been made of metal-based ACFs using various surface treatments processes to combat environmental issues. The transitional metals including Ag and Cu were used as antibacterial agents because of the bacteria adhere to solid support (ACFs) [Oya et al., 1996; Park and Jang, 2003; Pei et al., 2013]. [Oh et al., 2003] describes that the ACFs samples impregnated with herbs used for different biological activities. Some studies also carried out using ACFs impregnated with Ag and effectively used in chronic wounds [Lin et al., 2012; Tsaia et al., 2014].

2.2.3 Carbon nanotubes (CNTs)

CNTs were discovered by Iijima, is as an allotrope of carbon, which turn over into single walled cylindrical tubes. The nanotubes categorized basically two types based on the structure (1) single walled nanotubes (SWCNTs), containing single sheet of grapheme arranged into cylindrical structure, and (2) multi-walled carbon nanotubes (MWCNTs) consist of few layers of graphene. The multi walled CNTs (MW-CNTs) were made up from graphitic rods. CNTs made up pure carbon and correspond to fullerene family. The cylindrical structures of CNTs make novel nanomaterials for different biomedical applications including drug delivery applications. Recently, CNTs considered as potential candidate as a nanocarrier for drug delivery system. Several applications such as targeted drug delivery, controlled drug delivery, in cancer cells, delivery of bionanotechnology products, enzymes, improved solubility of poorly water soluble drugs, vaccine delivery, hormones, and nanofluidic device in drug delivery system. CNTs also been used in different biomedical applications including nanosensors, diagnostic tools, nanoprobes for reorganization of various diseases [Danailov et al., 2002; Flahaut et al., 2003; Dresselhaus et al., 2004; Joselevich, 2004; Foldavari and Bagonluri, 2008; Hilder and Hill, 2008].

Some studies reported that SWCNTs have antimicrobial activity however poor dispersion of CNTs destabilized the assurance as antimicrobial as well as antiviral agents [Jia et al., 2005; Li et al., 2008]. To overcome dispersion issues of CNTs different stabilizing agents such as surfactant (sodium decyl benzene sulphate, sodium dodecyl sulphate, triton-X-100) or polymers were used to enhance dispersity
of the CNTs [Hyung et al., 2007]. The antimicrobial mechanisms of CNTs involves few steps, (1) contact of bacteria with CNTs (2) membrane disruption (3) generation of reactive oxygen species [Li et al., 2008; Brady-Estévez et al., 2008 and 2010]. The chemically surface functionalization of CNTs is also enhances the antimicrobial activity [Aslan et al., 2010].

Several studies have been reported on various aspects such as synthesis, characterization, and antimicrobial activity of metal-CNTs [Mehra et al., 2015]. The bimetallic Ag-Fe-CNTs exhibited excellent antibacterial activity against E. coli [Liu et al., 2012; Kima et al., 2013]. Another study reported that Ag-CNTs have superior antibacterial activity and stable up-to six months [Li et al., 2011]. Moreover, the functionalization of CNTs widely used in different biomedical applications due to enhances biocompatibility, enhanced solubility, and dispersion in aqueous medium. Several CNTs based drug delivery system have been implemented, which enhances the bioavailability of ophthalmic drugs to combat conventionally drug delivery system. Very few reports are available in ocular drug delivery system. However, CNTs might be used as ocular targeting of therapeutic agents [Bega et al., 2012].

Several studies reported the biomedical application of CNTs, these studies reveals that CNTs cannot be directly use and further treatments are required for aforementioned applications. These treatment involves surface functionalization, hybrid CNTs using liposomes for antioxidants activity and, Cu and Ag-NPs binds on the carboxylic groups of CNTs, Which enhance applicability towards end applications [Misra et al., 2010; Li et al., 2011; Zardinia et al., 2012; Kazmia et al., 2014; Barbinta-Patrascu et al., 2014].

2.2.4 Carbon nanofibers (CNFs)

CNFs are carbonaceous nanomaterials used mainly in advanced composite materials to improve strength, stiffness, durability, electrical conductivity, or heat resistance [Darne et al., 2010]. The cost of production of CNF is significantly less than that of carbon nanotubes (CNTs), and therefore, the former offers significant advantages over the latter, providing a high performance to cost ratio.

For the surface-related applications of carbon nanomaterials, it is important to know how surface morphology, structure, and chemistry are effective and how many effective sites the materials possess on the surface. CNFs can have a high surface area
ranging between 50 to 800 m$^2$/g, if they are catalytically prepared or post-chemically activated [Bikshapati et al., 2012]. CNFs composites have been investigated for improving the adhesive properties at the interface between the fiber and the matrix of carbon-fiber reinforced composites and to yield a macroscopic frame or support to be anchored by CNFs to solve handling difficulty and the pressure drop problem [Bikshapati et al., 2012; Jahangiri et al., 2013].

The broad utility of nanomaterials results in increased levels of production, however, with increased human exposure and potential release of the materials into the environment. Therefore, much attention is also required for toxicological issues related to nanoparticles, including various fibrous nanomaterials [Shvedova et al., 2010]. CNFs have been widely used as adsorbents and/or metal supports for environmental remediation applications, antimicrobial agents and insignificant toxicity [Magrez et al., 2006; Bikshapati et al., 2012].

Recently, the transition metal NPs- (Fe, Cu, Ag, Ni) grown carbon nanofibers (CNFs) were used for a wide range of applications including environmental remediation, antibacterial activities, purification of bioactive agents, and drug delivery. In such materials, NPs were attached at the tips of the CNFs and were released under controlled conditions [Gupta et al., 2009; Bikshapati et al., 2012; Khare et al., 2013; Singh et al., 2013; Singh et al. 2014; Talreja et al., 2014].

2.3 Polymeric nanocomposite

The motivation of developing biocompatible materials having persistent antimicrobial activity emerged following a few recent research activities on the antibiotics drugs loaded with combinations of dental cements and resins. However, the interest in achieving carriers that could deliver active drugs directly at the site of infection was subsequently extended to soluble or pH sensitive polymers [Liu et al., 2009; Campoccia et al., 2010].

Polymers are increasingly being used in several pharmaceutical applications such as binder in drugs and controlled release drug delivery system [Uhrich, 1999; Shaik et al., 2012]. With regard to polymeric materials used as a carrier, several types of polymers such as poly vinyl alcohol (PVA), polylactic acid, poly lactide-co-glycolide (PLGA), and chitosan have been used as encapsulating agents for the controlled release of drugs [Schmaljohannet, 2006; Lin et al., 2012]. However, major
drawbacks exist in these materials, including weak interaction between the biopolymers and drugs and the rapid collapse of the polymeric encapsulating agents during drug release process. Various processes including blending, crosslinking of co-polymers have been shown to be useful for enhancing the performed of polymeric carriers [Kim et al., 2001; Kai et al., 2003; Bulmer et al., 2012].

Polyvinyl alcohol (PVA) and cellulose acetate phthalate (CAP) are well known biodegradable polymers and contain desirable property such as biocompatibility, and nontoxic. These polymers are widely used in the drug delivery system. PVA are also used in many biomedical applications in contact with tissues and blood such as soft contact lenses, implants of artificial organs, cartilage skin, dialysis membranes, lens, skin, cardiovascular devices, and invertebral discs, because of their excellent flexibility and swelling property in water [Seabra and oliveira, 2004.; Gann et al., 2009; Jannesari et al., 2011]. However, biological interaction of the biomaterials including platelet activations, cell adhesion, cell migration and bacteria adhesion consequently determine the biocompatibility of a material [Tsaia et al., 2011].

CAP is widely used as an enteric film coating of drugs, and has antimicrobial as well as antiviral activity against bacterial vaginiosis, hepatitis and HIV. CAP is not soluble at pH \( \leq 5.8 \) in water. Because of this unique property it is extensively used in the drugs coating. Blending of polymers is widely used in controlled drug delivery system [Neurath et al., 2003; Chen et al., 2013].

The proposed research work wills focus on the unique properties of the blended polymers with the combination of PVA and CAP as a carrier, with dispersed Carbon nanofibers (CNFs) as nano-antibiotics. CNFs have been extensively studied under recognition as a unique carbon material [Iijima, 1991; Rodriguez, 1993; Rodriguez et al., 1995].

### 2.4 Biocompatibility

Biocompatibility of the materials is the appropriate host response towards the specific applications. Advances in nanotechnology and nano-biotechnology have led to an increase in the production of nanomaterials and biomaterials. For blended polymers as a drug carrier, ascertaining the potential toxicity of the prepared polymeric matrices is necessary [Liu et al., 2011]. The properties of nanomaterials are
different from those of micron or larger size materials, allowing them to exert novel physical and chemical functional activities [Colvin, 2003; Oberdorster et al., 2004]. Nanoparticles can be translocated to the subepithelial space to a greater extent than larger particles [Clurg et al., 1998]. Several studies have reported that small-sized nanoparticles can be translocated from the lungs into the blood [Donaldson et al., 2001; Magrez et al., 2006] and can thereby move to other organs and tissues, raising concern that they may cause oxidative stress-mediated toxicity in biological systems [Akhtar et al., 2010]. The interactions of particles with cell membranes result in the generation of reactive oxygen species (ROS). The generated oxidative stress may cause a breakdown of membrane lipids, an imbalance of intracellular calcium homeostasis, and DNA breakage [Petruska et al., 1991; Clutton, 1997]. Genotoxic activities may result from direct interaction of particles with the genetic material or secondary damage resulting from particle-induced reactive oxygen species (ROS) production. Both pathways may relate to surface properties, the presence of transition metals, intracellular iron mobilization, or lipid peroxidation processes. Other aspects relevant to primary cytotoxicity are particle size, shape, and the presence of mutagens carried with the particles [Schins, 2002]. In this context, the synthesis of newer nanomaterials and its polymeric carrier for delivery system to combat this severe health problem mainly infectious disease including wound healing application.

2.5 Other’s applications

The metal and metal oxide based nanoparticles (NPs) such as Cu, Ag, Al, Fe, Mn, Zn, Au, ZnO, CeO, and TiO2 have been used in agricultural applications and enhances growth of the plant [Khot et al., 2012; Larue et al., 2012; Kumar et al., 2013; Liu and Lal, 2015]. Carbon-based materials also been used as the growth stimulants for the plants [Husen and Siddiqi, 2014; Sarlak et al., 2014].

On the otherhand, different nanomaterials including carbon based materials are used in energy and sensing applications. Recently, Ni metal-based CNF [Singh and Verma, 2015] and Al-Ni bimetals-based CNF [Singh and Verma, 2015] was used as electrode materials for the generation of electricirty in microbial fuel cells. The Cu-based CNFs was coated on a fluorine-doped tin oxide glass substrate and used as the electrode of a dye-sensitized solar cell [Gupta et al., 2015].