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Nanoparticles as Antimicrobial Agents and Drug Delivery Systems - A Review

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Abstract

The world is facing major issues related to antibiotic resistance, specific drugs targeting and its side effects. Such obstacles can be rectified by nanotechnology as they have essential characteristics with smaller size, target specificity, easy deliverable with lesser side effects. The prime nature of the nanoparticles are, it can probe into the cell wall of the pathogenic microbes and even have the capacity to intrude into cellular pathways. Nanoparticles themselves are capable of destroying unwanted foreign particles or toxic cells, which enter into our bodies. Nanoparticles can be treated as carriers, in which they combine with specific drugs and deliver to target specific cells with lesser side effects. Nanoparticles are used as a drug delivery agent for various kinds of diseases related to cancer. Nanoparticles with drugs increase the antibiotic release at the different target sites and these nanoparticles have a great tendency to deliver a large number of drugs to a cell. In this current review, we discuss the bright future of NPs as drug delivery agents as it can overcome all conventional problems.

Keywords: Nanoparticles, Drug delivery system, Antibiotics, Bacteria, Cancer

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INTRODUCTION

This recent point of concern in the medical field is microorganisms becoming resistant to drugs.[1] There is a rapid increase in bacteria becoming resistant, viruses becoming resistant[2] and protozoa.[3] Resistome is a serious global issue which is caused by continuous growth of population, increased global migration, high usage of antibiotics in clinics, animal production, wildlife spread , bad sanitation, pressure of selection and due to a bad sewage disposal system.[4] Antibiotics is a large chemical group produced by different types of microorganisms they contain a capability to inhibit growth of bacteria or destroy bacteria and many other microorganisms, antibiotic is a chemical which is produced by microorganisms which can inhibit the growth of other organisms.[5] Several groups of microorganisms were observed to produce antibiotics such as bacteria, fungi and actinomycetes but due to no proper usage of antibiotics several organisms have become resistant to antibiotics.[6]

Bacteria use special kind of mechanisms to overcome or escape from the effect of antibiotics. These mechanisms are used by bacteria to avoid the effect of antibiotics it acquires or increases the expression of drug efflux pumps, these pumps are used to expel drugs from cytoplasm and they decrease their ability to fulfill their target.[7] There are certain bacteria, which are naturally resistant like *mycobacterium;* glycopeptide antibiotics like vancomycin have large size hence most gram-negative bacteria are resistant to it as they have smaller pores at outer membrane of gram-negative bacteria. Some bacteria acquired resistance by mutation, gene transfer, vertical gene transfer, horizontal gene transfer, conjugation, transformation and transduction. Latest discoveries in nanotechnology to work on nanoparticles have properties of antibacterial, some nanoparticles showed antimicrobial properties against *Mycobacterium tuberculosis, Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae, methicillin-resistant Staphylococcus aureus,* vancomycin resistant enterococci.[8]

Silver nanoparticles (AgNp) have highly strong antimicrobial activity for gram positive microorganisms which involve those multidrug resistant, (AgNp) is tested for antimicrobial capacity against *Salmonella sp* and it was highly effective.[9] They have done investigation of antimicrobial activity of silver-coated gold nanoparticle (Au-AgNp) which showed immobilized on cellulose paper. This gave results showing high toxicity and strong antibacterial activity,[10] if the copper is soluble then it is toxic for bacteria but nanostructure copper is not much effective.[11] Platinum nanoparticles have antimicrobial activity against several microorganisms like *Proteus vulgaris* (17.66 ± 2.08), coagulase negative *Staphylococcus sp* (20.33 ± 1.52), *Staphylococcus aureus* (16.33 ± 1.52), *E.coli* (12.33 ± 1.52), *E. cloacae* (14.00 ± 2.64) and they showed poor antibacterial activity against *K. pneumoniae* (07.66 ± 1.52) and *P. aeruginosa.*[12]

ZnO-Nps are used as antibacterial agents against foodborne diseases, they are used in packaging of food where if any bacterial growth takes place ZnO-Nps kills the bacteria.[13] Antibacterial activity of nanoparticles are destroying and rupturing cell membrane by ZnO, TiO2, Ag, Au and chitosan. The nanoparticles which can cause disturbances in energy production, energy transport and these nanoparticles can produces reactive oxygen species (ROS) is (TiO2), chitosan can inactivate the functions of cell enzymes, Ag and chitosan can inhibit the replication of DNA.[14] AgNp have capability of inhibiting the formation of biofilm and have efficiency to kill bacteria, which already formed biofilm. AgNp is good agent for prevention and treatment for biofilm related infections caused by mainly MDR (multi drug resistant organisms) like MDR, *K. pneumoniae strains*.[15]

Cancer is still a dangerous killer throughout humans in the world, though there are continuous researches are going on continuously new drugs and new ideas of treating cancer is coming up still it is very difficult to kill cancer cells completely. Till 2050 the population of world is expected to reach 10 billion, from this big population 20 million new cases of cancer is expected to be diagnosed.[16] Health care expenditure on cancer is highly costly still there is no assurance of completely cured.[17] The exact data (death and survival rate), which cannot compared through different countries and it is difficult because proper and accurate data is not available. This affects the economy of a person as well as the entire country face the loss of the economy.[18]

Nanotechnology have capacity of selecting and targeting which increases the potency of physical, chemical, and biological reach of eliminating cancer cells and at the same time minimizes the cytotoxicity of nonmalignant cells, the nanomaterials can target the cancer cells with higher specificity by both the methods of passive and active targeting. Nanoparticles have all the essential properties such as ability to load drugs, large surface area, smaller size and have capability to enhance the absorption of conjugated. Thus, nanoparticles considered as good tumor-targeting agent. The nanoparticles are used, as a carrier are liposomes, polymeric nanoparticle, magnetic nanoparticles, and dendrimers nano shells. Lipid based nanoparticles have been used as conjugated there are many other conjugated anticancer drugs of different stages of clinical trial for treatment of different types of cancer.[19]

Nanoparticles used as drug delivery system for eye

For delivery, drugs to eye have several limitations that can be overcome by usage of nanoparticles, as a specialty of nanoparticle-based drug delivery system and active uptake by corneal, better precorneal retention by muco-adhesive characteristics, conjunctival epithelia lead to enhanced ocular permeation and bioavailability. Poly(alkyl cyanoacrylate) nanoparticle - PACA nanoparticles are considered as good drug delivery system to brain and eyes, the drugs are loaded PACA and delivered to cornea and PACA found to cause lysis in cells and also damaged cornea.[20] Flax seen gum (FX) was isolated from *Linum usitatissimum* and FX and CH nanoparticles were prepared and checked for drug delivery for glaucoma treatment they were highly biocompatible with cornea penetration and marketed eye drops.[21]

There is advancement in usage of mucoadhesive polymers chitosan and hyaluronic acid in drug delivery systems; the nanoparticles increase the biocompatibility and bioavailability. The mucoadhesiveness is essential (the interaction among the ocular delivery system and mucin present on the eye) they checked the nanoparticle and drugs in contact with mucin in various different ratios. Their results showed the ability to interact with the ocular surface and the time of residence of drugs in the eye is increased. There chitosan/ TPP-hyaluronic acid nanoparticle eye drop is one of the good options for drug delivery with better and increased mucoadhesive properties.[22]

Dendrimers are used in drug delivery in the ocular system in various ways, such as anti-neovascular, anti-apoptotic/ neuroprotective or anti-neuroinflammatory drugs are combined with dendrimers. Dendrimers are used in glaucoma treatment where encapsulation of antiglaucoma drugs. Acetazolamide into PPI dendrimers (generation) is prepared which showed good results and dendrimers were considered as good drug delivery systems. Dendrimers were also used as drug delivery agent for neuroinflammatory ocular diseases the photoreceptor cell death and neuroinflammatory that was conjugated with PAMAM dendrimer and released for more than 90 days this gave a hope treatment.[23]

Nanoparticles used as drug delivery system for antibacterial agents

Older drugs which were used for antibacterial treatment have several limitations which made scientists to focus on new methods to overcome the problems such as a antibiotics is not so ineffective , they have less bioavailability , limitations in sites of penetration and high rate increase in resistant bacteria.[24] The nanoparticles have the capability of promoting the exact targeting of the pathogen , enhancing interaction of drugs and pathogens particularly against those bacteria which are resistant to several drugs, enabling the anti - virulence approaches for drug - free antimicrobial activity.[25]

AgCl was combined with TiO2NPs (ATNPs) have showed quality of anti-quorum sensing against *Chromobacterium violaceum* it is a gram-negative bacterium with acyl homoserine lactone autoinducer. The capability of anti QS activity was observed at 20 times lower concentration then a bactericidal concentration, this was TiO2 was considered as good supporting matrix thus it is been used in food packaging purpose ZnO nanoparticles have shown activity of antibiofilm against *Pseudomonas aeruginosa* at lower concentration then bactericidal level.[26] Heavy metal nanoparticle are used drug carriers as well as they have antibacterial activity against several bacteria, they lead to cell death by destroying DNA

of bacteria .In bacteria the role of FoF1 ATPase in response against Ag nanoparticles is a latest topic of research.[27]

They investigated several paths of internalization of nanoparticle that they found out by forming intracellular vacuoles formation and the destruction of cellular membrane leads to bacterial cell death. Ferric oxide nanoparticle killed the bacteria and also inhibited the growth of bacteria and also inhibited the growth of bacteria in the culture media, the rifampicin conjugated with silver nanoparticle (Rif-AgNPs) with some modifications have an excellent capability of antimicrobial biofilm inhibition.[28] Magnetic nanoparticles enhance the antimicrobial activity of phosphoinositide binding domain of gelonin, modulate its mode of action and are strong then the idea of employment for developing new treatment methods.[29] Nanoparticles showed higher internalization uptake, accumulation and retention time of drug improving antibacterial activity drug decreasing antimicrobial resistance and also inhibit biofilm formation these benefits of nanoparticles can be used against *S. aureus* mastitis.[30]

Nanoparticles used for drug delivery for brain

The microenvironment of the central nervous system is the most delicate part of the body, which has a protection system called blood- brain barrier (BBB) which regulates the homoeostasis. The entrance of ions and small molecules going through blood - brain barrier (BBB) is very difficult as BBB provides protection to brain and structure of BBB is very complex which gives protection from injuries and diseases .This BBB turns a problem for drug delivery which affects the therapy of neural disorders.[31] The problems related to brain such brain cancer, Parkinson's disease, Alzheimer's disease, Multiple sclerosis and Stroke drug administration, development and targeting is the most difficult process treating the brain. There is a development of nanotechnology, which is helpful, is development, administration and targeting of drugs into brain the properties of nanoparticles is very much beneficial for overcoming the limitations faced in brain treatment. The properties such as reduced size, biocompatibility, non-toxicity, prolonged blood circulation is being used drug delivery and targeting to specific site of the brain.[32]

Nanoparticles which is coated with polysorbate 80 which was administered in outbred C57BL/6 mice an .The synthesized nanoparticles are combined with molecules which have therapeutic value both are properly encapsulated while targeting specific transport process in the vasculature this enhance drug transport through the BBB in neurodegenerative/ ischemic disorders and target particular region in the brain for regenerative process. For AD therapy the nanoparticles are helpful to permeable into the BBB where NGF adsorbed on PBCA and it reached the brain parenchyma in significantly higher amounts at 45mins after administration.[31]

There are almost all types of nanoparticles are permeable to BBB such as the first generation of nanoparticles drug delivery system is Liposomes. Generally liposomes and are formed of biocompatible and biodegradable lipid, which are present in biological membrane. The liposomes are the nanoparticles mostly used in large amount for brain drug delivery. Polymeric nanoparticles in which drugs can be embedded this enhance the drugs delivery to brain mediated by these devices, dendrimers are a type of branched nanoparticles looks like a branched tree etc. Various types of nanoparticles can used for drug delivery systems for brain related diseases with higher efficiency. These properties help in interacting BBB and enter the brain to a particular specific region.[33]

There are various types of reaching methods to overcome BBB using nanoparticles, such as the magnetic nanoparticle, which are based on the magnetic strength, which helps to reach to specific target. Nanogel approach works on the basis of colloidal carrier which was made of nanoscale polymeric network of crosslinked ionic polyethyleneimine (PEI) and non-ionic PEG chains.[33] Charged nanoparticles works based on charges man positive surface charges of nanoparticles to induce an adsorptive-mediated transcytosis. The surfactant based approach is based on the surfactant as a coating or encapsulated to nanoparticle and acts as targeting agent, there are Ligand based approach which binds based on ligands.[34]

There is a one big challenge faced when it comes to brain tumors, there is already present BBB which is compromised in surrounding area for instance erlotinib distribution in the U87

tumor core is 4.69-fold more than that in the brain around the tumor core hence drug delivery to brain tumor is more difficult to compared to another tumor. It is said that the BBTB (blood - brain tumor barrier restricts the entrance of drugs from blood to brain tumor, when it is compared with blood tumor barrier in peripheral tumor the BBTB exhibits a smaller pore size and expresses a more level of drugs efflux pumps. It has tried for drug delivery through the passage of nasal cavity but there are several obstacles between the absorption of drugs in both respiratory regions and olfactory region that decreases the volume of drugs in its pathway. These problems which come in the way of treatment of brain related diseases can be overcome by nanoparticles where nanoparticles are taken as a vehicle to deliver drugs its properties.[35]

Nanoparticles are used as drug delivery agent for cancer

Cancer is a threat to the human kind; millions of people die because of cancer each day in almost all over the world at the same rate. The treatment methods used are not so effective to overcome the cancer. Cancer is dangerous and increasing rapidly, but nanotechnology can help the treatment methods to overcome specific cancer deaths nanoparticles can be used and programmed for drug delivery, for recognizing cancerous cells which helps to give accurate drug delivery to selected cells. There are several methods by which cancerous cells are killed using nanotechnology by active targeting, specific receptor targeting, antibody mediated targeting, passive targeting.[36] There are heparin drug conjugates, which are considered as a sensitive best agent for drug delivery. For pH sensitive based drug there is preparation and characterization of dendronized heparin-doxorubicin which is a combination of dendrimer and heparin, where nanoparticles effectively kill cancerous cells. This combination of dendronized heparin-dox conjugate based nanoparticles have more higher capacity of antitumor with lesser side effects.[37]

Nanotechnology provides better ways for treating cancer, over the conventional drug delivery systems (DDS), nanoparticles used as a carrier or drugs delivery system they are called smart drug delivery systems, the smart drug delivery system consists of smart nanocarriers, targeting mechanisms and stimulus technique.[34] Peptide dendrimers have an excellent source for drug delivery the PEGylated peptide dendrimer-doxorubicin (dendrimer - Dox) conjugate-based nanoparticles is prepared and characterized as an enzyme-response drug delivery agent. The nanoparticles decreases the toxicity which is related to Dox and gives good biosafety and lesser side effects to various other normal organs of both tumor and healthy-organs. The PEGylated peptide dendrimer-Dox conjugate-based nanoparticles may a potential nanoscale drug delivery agent especially for breast cancer.[33]

In additional benefits, the formulations of these nanoparticles have imaging contrast agents, which provides efficient systems for cancer diagnosis. There are multi-functional nanoparticles whose multiple-qualities can help in treating the dangerous disease cancer. These multi-functional nanoparticles include which combines tumor targeting, tumor therapy and tumor imaging in an all in one system, which can be excellent systems useful for multi-model approach in the battle against cancer. The drug taxol, which is an antitumor alkaloid, have strong capability to fight against different types of tumor, but there are obstacles such as low aqueous solubility. Cremophor and ethanol has used as excipients in the pharmaceutical drug formulations. A particular type of nanoparticle which is polyvinylpyrrolidone nanoparticle which have taxol which was formed by micro emulsion method, the effect of antitumor in taxol encapsulated nanoparticle showed excellent results for cancer treatment.[35] Proteins are alternative of polymers which is various other ways for several kinds of drug formulations, proteins nanoparticles can be used for drug delivery which gives a better biocompatibility and biodegradability, it can be prepared under normal condition avoiding chemicals and toxic substances or organic solvent. As proteins have defined primary structure, the nanoparticle formed of proteins gives a better chance of surface modification including proper covalent of drugs and targeting ligands.[38]

CONCLUSION

There are several obstacles faced by medical field to reduce side effects of medicines, several problems are related to targeting of

pathogens or cancerous cells, which is one of the major reasons of not overcoming on diseases and it ends up leading to millions of deaths all over the world. Due to its resistance, it is very difficult to get rid of these microbes and pathogens. Cancer cells are cannot killed completely by drugs and all the available methods against cancer are not completely curing the cancer. There are areas, which are difficult to reach to do operations and it has difficult to identify that drug has been reached the infected organ or some other organ. For example, eyes, it is a highly sensitive area. For all such problems, nanotechnology gives options to overcome is nanotechnology and this have bright future in resolving issues in the medical field and in saving the lives of human kind. In this current review, we explained the importance of nano particles and how these nano particles will increase the quality of human life.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

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All the data sets analyzed or generated during this current study are included in this Manuscript.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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