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REVIEW ARTICLE

Polymeric nanoparticles as potential source to overcome antimicrobial resistance

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Abstract

Antimicrobial resistance is one of the top three health issues in the world as many of the existing antimicrobial therapies have become ineffective due to resistance produced by different organisms. The need is to develop more effective strategies to overcome this issue. Nanoparticles based therapy and drug delivery have made a breakthrough. Polymeric nanoparticles including PLGA, PLA, Chitosan etc. have an effective mechanism to combat this issue with their antimicrobial properties and they also make many drug therapies effective by efficient drug delivery system. They have many applications in medical field including cancer therapy and vaccine delivery but their role in antimicrobial therapy is of utmost importance as the antimicrobial resistance issue is critical and requires effective alternate therapies, so that resistance to sensitive bacteria can be prevented.

Keywords

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PGLA
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Introduction

At the time antibiotics were discovered, the thought provoked that antimicrobial infections will no longer remain a problem. But, this satisfaction was for time being, as resistance to antibiotics emerged soon after their discovery (Choudhury et al., 2012). World health organization (WHO) published a report in which they showed that resistance of common bacteria reached alarming situation in most parts of the world, such as that of Klebsiella and E.coli, to the third generation cephalosporin's and carpanems (Mouiche et al., 2019). Annual rise in deaths due to antimicrobial resistance has been estimated to increase from 70,000 to 10,000 yearly and that may cost around us$100 million up to 2050 (Jasovský et al., 2016).

Antimicrobial resistance is among the three major threats to public health, as declared by WHO. The factors that contribute towards antimicrobial resistance have been studied from many years. These mainly include availability of illegitimate antimicrobials, excessive and unnecessary use of newer and potential antibiotics, irrational use of antibiotics in food and poultry industry and some scientific reasons including existence of subsistome and resistome, intrinsic resistance and jugglery also play their part (Van Staden, 2020).

This situation generates a question mark on antibiotics that; either we are moving towards pre-antibiotic era? Antibiotics have served mankind well for around 70 years, but now the situation demands to look into alternate options (Ghosh et al., 2019). The alternative techniques may start from simpler ones such as synergistic and combinational use of antibiotics with each other or with other substances (Laws et al., 2019), to the complex ones including peptidomimetics, nanoparticles and their derivatives, quorum sensing inhibition molecules, fimh inhibitors, phage therapies and neo-glycosides (Tillotson & Theriault, 2013).

We may have many alterative options to combat antimicrobial drug resistance but the use of nanoparticles

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may be an ideal option (Vazquez-Muñoz et al., 2019). They may provide an effective substitution to bulk materials as because they not only act as antimicrobials but they have the ability to serve as drug carriers and deliver them effectively to the target sites with sustained release (Wang et al., 2017a). NPs have numerous characteristics that furnish them to be excellent carriers to combat disease producing pathogens that helps them to amplify the drug solubility (Huh & Kwon, 2011) and makes their synthesis convenient(Gholipourmalekabadi et al., 2017). These characteristics also enhance their biocompatibility to cope with the target agents and make them efficient carriers (Wang et al., 2017b).They possess extra small size and also have large surface to volume ratio that make them a better choice while considering penetration. These characteristics furnish them unique properties as compared to other antimicrobial agents and their bio functionalization is another weapon in their arsenal (Baptista et al., 2018).

Out of the available nanoparticles, polymeric NPs are one of the promising options available. The main advantage of these include their multivalency which provides them higher cell recognition and binding ability (Lam et al., 2018). They also allow efficient encapsulation of the molecules that need to be released at the specific target sites (Oh et al., 2008). Also the fabrication of inorganic- polymer hybrid NPs provide the option for new synergistic therapeutic options such as photodynamic therapy or diagnostic purposes (Lam et al., 2018). Many natural and synthetic nanoparticles show effective antimicrobial activity, these include chitosan, PLGA, PLA, gelatin, dextran etc. They have effective antimicrobial activity, as it can be seen in chitosan, a hydrophilic polysaccharide, having the affinity to attach with the cell wall of negatively charged bacteria and cause membrane disruption. It also alters the membrane permeability. It also inhibits the replication of DNA and ultimately cell death occurs (Jana et al., 2017).

In this article, we will discuss the emergence of antibiotic resistance, its mechanism of development and alternative therapies to combat this, specially we will look into the role of polymeric nanoparticles as antimicrobial agents.

Mechanism of antimicrobial resistance: Resistance is the capability of bacteria to counter the effect of an antibacterial agent that may act on its reproduction to work as bacteriostatic or may kill it being bactericidal. The resistance develops due to certain reasons but the main cause is irrational and ill-suited use of antibiotics (Cesur & Demiröz, 2013).

Types of resistance: The five major principal forms of antibiotic resistance include natural resistance, adaptive resistance, acquired resistance, cross-resistance and multidrug resistance (MDR) (Hasan & Al-Harmoosh, 2020).

Natural resistance: It is the natural ability of an organism to repel the attack or withstand attack by biotic and abiotic agents. Intrinsic resistance is a characteristic bestowed to bacterial genus and is based on two mechanisms. First is the lack or inaccessibility of the specific target structure in the concerned bacteria e.g. cell wall-free bacteria like *mycoplasma* spp. are resistant to glycopeptides and β-lactam antibiotics or gram-negative bacteria are vancomycin resistant due to its inability to penetrate their outer membrane. Secondly, production of inactivating enzymes that may be specific for certain species of bacteria, for example acrabitoic system or production of ampc β-lactamse in E.coli and presence of exports systems can be the reason (Schwarz et al., 2017).

Acquired resistance: It involves the genetic composition of bacteria, thus transforming an in vivo effective drug to be non-effective. Limiting intercellular concentration of the antimicrobial agent by diminishing the influx or elevating efflux, use of reversible or irreversible enzymes that inactivate the drug, preventing interference of antimicrobial agents by target alteration and creation of new metabolic pathways to eliminate the target are some of the key mechanisms used by bacteria to acquire resistance against antimicrobial agents (Adekunle, 2012).

It involves incorporation of genetic material or some mutations that provide the bacteria new potentiality to counter higher concentrations of antibiotics. It can involve several mechanisms that may include efflux pumps, high rates of mutation, epigenetic inheritance, gene amplification, population structure and heterogeneity, and biofilm formation. (Sandoval-Motta & Aldana, 2016).

Either by addition of new genetic material (Naked DNA, Plasmids, Transposons, etc) or due to mutations, the formerly sensitive microbes can become resistant to certain drug. They mostly induce low-level resistance which induces resistance in the clinically sensitive organisms (Fernández & Hancock, 2012).

Cross-resistance: The cross-resistance involves the antibiotics having same class and exhibiting single mechanism. The drugs that have similar class are related chemically and usually have same target site in the cell, thus they have to face cross-resistance. For instance, rifabutin and rifampin have shown cross resistance against tuberculosis (Perichon et al., 2009).

Multidrug resistance (MDR): It is defined as insensitivity of microbes to which they were sensitive earlier, even upon administration of antimicrobials that were structurally unrelated and had different target sites. According to world health organization (WHO), the microbes adopt to the conditions and by making alterations, they combat the antimicrobial attack. This leads to ineffective treatment even after use of more than one antimicrobial agents.(Tanwar et al., 2014).

The mechanism of MDR usually involves accumulation of multiple genes, in which each gene codes for the resistance to a single drug involving a

single cell, that usually occurs on resistance plasmids. It can also involve multi-drug efflux pumps due to increased gene expression that may result in extrusion of broad range of drugs. (Nikaido, 2009).

Mechanisms involved in antimicrobial resistance: Bacterial pathogens are becoming resistant to many antimicrobial agents due to widespread and irrational use of antibiotics either is it from human or veterinary origin. There are several mechanisms that may be involved in development of resistance by different types of bacteria (As seen in flowsheet 1). These may involve changes in the permeability of cell membrane , which restrict the access of drug to target sites, increased efflux of the antimicrobial agent from the cell , target site mutations/alterations, enzymatic degradation or modification, possession of alternate metabolic pathways to the ones already inhibited by the drug (Magiorakos et al., 2012), (Mc Dermott et al., 2003).

Enzyme inactivation: Production of inactivating enzymes is the defense mechanism by bacteria that degenerate or modifies the drug itself. This includes three distinct mechanism that are a) hydrolysis that can be seen in β-lactamases, b) group transfer such as transferases inactivates aminoglycosides and chloramphenicol and c) redox reaction that involves oxidation of tetracycline antibiotics by the TetX enzyme (Džidić et al., 2008). Some bacteria have the ability to produce modifying enzymes that inhibit within or near to the cell surface, thus target and inactivate the particular drug. Enzymatic inactivation through hydrolysis or by modification plays a vital role in resistance to natural antibiotic by pathogenic bacteria. The most diverse and vulnerable form of resistance enzymes is the group transferase. These covalently modify antibiotics causing structural alterations that alter target binding. (Bockstael & Aerschot, 2009).

Target alteration: Target alteration can be seen in resistance to trimethoprim and sulfonamides that inhibits di-hydrofolate reductase and dihydropteroate synthase respectively. Methicillin resistance in case of staphylococcus aureus also involves target alteration (Spratt, 1994).

rRNA methylases encoded by erm genes were the first acquired genes that were recognized to confer resistance to streptomycin b, macrolides and licosamide antibiotics, they also work on this mechanism. These genes can be present in aerobic, anaerobic, Gram positive and Gram negative genra (Van Duijkeren et al., 2018).

Changes in cell permeability (Efflux pumps): The membrane proteins that transport antibiotics out of the cell and retain their low-intracellular concentrations are known as efflux pumps. The speed at which these antimicrobials are penetrating the cell, efflux mechanism expels them out again thus hindering them to reach their target. As a result, low intracellular concentration of antibiotics is present that is insufficient to produce required antimicrobial effect. These efflux pumps exist in the cytoplasmic membranes. Antibiotics of all classes other than polymyxin are sensitive to the activation of efflux system. These pumps at times, become selectively specific to expel antibiotics like tetracyclines, lincosamides, streptogramins and macrolides. Most of them have capability to produce multi-drug resistance by pumping out wide range of independent antibiotics (Kapoor et al., 2017).

Decreasing antibiotic uptake: Antibiotics naturally bind to the specific binding proteins on the bacterial cell surface. Due to the resistance built when bacteria occupies the binding sites , the antibiotics are no longer able to bind proteins on bacterial cell surface due to their modification (Huh & Kwon, 2011). In pseudomonas aeruginosa, carbapenem uptake is reduced by mutants who lack outer membrane prion channel, oprd2. These also elevate the resistance due to low availability of penicillin binding proteins that are the target sites for the drug (Yoneyama & Katsumata, 2006).

Biofilms: Biofilms are complicated and communistic network of microorganisms hidden in an autogenic polymeric structure that is composed of polysaccharides, extracellular DNA and proteins (Bhando et al., 2019). The biofilm formation involves different stages. The earliest stage involves transient attachment, in which the planktonic bacteria attach acompact surface by characteristic adherence. The second stage involves formation and accumulation of micro colonies adjoined by extra polymeric substances matrix that is protective discharge molecule. Lastly, dissemination occurs that is having discharge as planktonic bacteria or as micro colonies coming from the mature biofilm. The colonization of the host with biofilms may occur during dispersal stage. This results in unlimited availability of nutrients as well as accumulation of waste(Chadha, 2014). Bacteria protect themselves from antibiotics, host defense and disinfectants by forming biofilm. Bacteria that are inside biofilm are lot more resistant as compared to planktonic forms. Therefore, bacteria that were non-resistant to any antimicrobial agent transform to resistant form after formation of biofilm. The antibiotic resistance through this mechanism makes the treatment difficult due to low penetration of antibiotics into the biofilms and existence of adaptive stress response develops multiphase defense of bacterium, and slows the reproduction (Dincer et al., 2020).

Antimicrobial resistance and need to develop more effective strategies: At the time antibiotics were discovered, the healthcare workers developed the notion that infectious diseases won't remain a problem anymore. However, with time, the bacteria developed resistanceto multiple antimicrobial agents and world became familiar with the term of Multi-drug resistance. Presently, many infectious diseases have become a major

cause of diseases and deaths, in both humans and animals, around the world (Reygaert, 2018). While biocides play their primary role in hindering potential sources of infection and many of them are still efficacious, the situation creates worries about the growing use of these in the community and the accompanying pressure due to resistance development as well as the possibilities for cross resistance against clinically important antibiotics (Poole, 2002). Prolonged and irrational therapy with antibiotics can lead to the emergence of resistance in a microorganism. Antimicrobials that previously respond to antibiotics later adjust themselves gradually and develop resistance (Giedraitienė et al., 2011). It has been roughly calculated that annual losses due to antimicrobial- resistant staphylococcus aureus infection cause about loss of $4.6 billion only in the United States (Cepas et al., 2019).

Antibiotics transformed medicine dramatically in many aspects and millions of lives had been saved due to them. Antimicrobial's discovery proved to be a wonder in human history but the use of these drugs has been followed by the emergence of strains that developed resistance against them. Medical pundits have blown the warning whistle about the return to the pre-antibiotic ages. A published data forecasted that around twenty thousand potential resistance genes (r genes) having around four hundred different types are present. But to our luck, the functional resistance determinants are much smaller in number(Davies & Davies, 2010).

The causes for the advent and dissemination of bacterial resistance are complicated and multifactorial. The major causes include a) overuse b) inadequate prescriptions and c)irrational use in agriculture and livestock (Rios et al., 2016). Bacterial strain resistant to penicillin appeared for the first time in 1947, when 4 penicillin resistant staphylococci strains were identified. 1n 1959, methicillin was developed by the pharmaceutical industry that has the capability to avoid penicilinase, the penicillin rings breaking enzyme. It was introduced in the market around 1960, while methicillin resistant staph. Aureus strains emerged just an year later (Monserrat-Martinez et al., 2019).

We need to have specific plan to reduce the further increase in antimicrobial resistance by taking certain important measure including, a) strengthening the knowledge and data base through research and surveillance, b) Efficient sanitation to reduce the production of infection , c) improved awareness as well as proper understanding of AMR through training, education and productive communication, d) regulating the use of antimicrobial medicines being used in human and veterinary health settings and e) sustainable investment to producesome new, effective, safe and economical medicines, vaccines, diagnostic tools and other interventions (Diaz et al., 2018).

A serious concern being discussed by public health experts worldwide is the emergence of antibiotic resistant pathogenic bacteria. There is an immediate need to understand the distribution of resistance determinants in bacterial populations and to explore resistance mechanisms and discover environmental factors that enhance their dissemination to find out the alternative options. World health organization has declared it as matter of concern and are regularly striving to find alternatives (Diaz et al., 2018; Pang et al., 2019).

We have limited options left in case of antibiotics choice, so we should use more accurate and appropriate ways of dosing and combining drugs to extend efficacy and diminish resistance. Sequential regimen can also be used to avoid separate and repeated use of antibiotics. Pair of synergistic antibiotics are more efficacious as compared to the sum of each antibiotic used alone as far as their efficacy is concerned (Richardson, 2017).

Some other available options include antibodies, host immune response modifiers, antibiotic-sequestering products, bacteriophages, lysins, microbiome and pro-biotics, metal chelation and nucleic acids (antibacterial and anti-resistance), vaccines and peptides (Rex et al., 2019). The recent advances made in biomedical fields have provided other therapeutic options in the form of novel drug delivery system that are equipped with the ability to target the infected site. The use of these Nano-sized materials is rapidly evolving to overcome and counter bacterial resistance.

WHO has been devising strategies from many decades but most of them haven't been implemented. In the last few years, the emergence of multidrug resistant organisms that have the capability of resisting the most efficacious latest generation of antimicrobial and chemotherapeutic agents has generated serious apprehension among clinicians and public health experts. Need of the hour is to devise and implement plans so that we could be able to check the further development of resistance (Raviglione et al., 2011).

Overcoming strategies for traditional antibiotic material: Traditional antibiotics are becoming less useful due to the antimicrobial resistance as described above. Now the situation demands to look for alternative techniques to cure the diseases caused by the resistant microbes. The available alternative options may include.

1) a microbial community approach to new antibacterial options including a) characterization of communities of micro biota, (Yasir, 2018; Sabino et al., 2019), b) manipulating bacterial signaling and communication (Hirakawa & Tomita, 2013), and c) pro-biotic therapies (Ouwehand et al., 2016; Lokesh et al., 2019), 2) understanding biological processes to devise new antibiotics including a) biological understanding required to intervene in microbial pathogenesis (Banin et al., 2017; Geddes-McAlister, 2020), b) alternatives to direct killing of microorganisms (Lillehoj et al., 2018;

Geddes-McAlister, 2020; Kundukad et al., 2020), and c) strategic outlook to discovery of anti-infective substances to be used in amalgam, 3) addressing antibiotic resistance including a) conventional medicines and plant-extracted antibiotic therapies (Cowan, 1999; Klugman & Black, 2018; Anand et al., 2019), b) antibiotics-conjugated vaccination (Klugman & Black, 2018; Buchy et al., 2020), c) bacteriophage therapy (Coates & Hu, 2007), d)combinational antimicrobial chemotherapies (Barber, 1965; Jackson et al., 2018) e) synergistic combinations of plant extract/compounds with conventional antibiotics (Cheesman et al., 2017) and f) new drugs like quorum sensing inhibitors and biologics (Bhardwaj et al., 2013), 4) Combinational dual-drug delivery approaches can be used that include combination approaches to target certain different pathways, combinations of antibiotics drugs with non-antibiotic adjuvants that may act as vehicle, combinational approaches that target the same pathway, combination approaches that have the mechanism to act on the same target, certain approaches used in combination to address poly-microbial type infections (Bhardwaj et al., 2013; Tyers & Wright, 2019), and novel antibiotics targets (Mantravadi et al., 2019), 5) antibiotic delivery, a) systemic versus local antibiotic delivery including antimicrobial polymers (Stebbins et al., 2014), b) a distinctive local delivery system-nanoparticles/liposome based delivery (Bamrungsap et al., 2012; Stebbins et al., 2014; Sercombe et al., 2015).

Nanoparticles use in antimicrobial therapy: The prefix "Nano" got famous for its increasing utilization in various fields of knowledge in the last decade, including Nanotechnology, Nano-materials, Nano-science or Nano-chemistry, these are the few brand-new terms relating to this field. It has got worldwide appreciation. The word "Nano" belongs to aantique Greek "*vavo"*which came through latin "*nanus"* that partcularly means "*dwarf"* and, in general means "*very small*". The International system of units (SI) uses this term to mention a factor that is reduced 109 times. So, the Nano-sized world is essentially measured nanometers (1nm corresponding to 10-9 m) and it comprises of systems in which size exceeds molecular dimensions but it is less than the size of macroscopic ones (generally > 1 nm to <100nm) (Pal et al., 2011).

Nanoparticles are the materials whose three-dimensional space is within the nanometer scale range (1-100nm) or essentially one dimension is within the said range. Nano-materials have the diverse activity and they can work against all major form of pathogens includingbacteria (gram positive and gram negative), fungi and mycobacteria (Fernando et al., 2018).

The physical activity differs among the different types of the nanoparticles. The physical structure of the nanoparticle itself may have innate antibacterial properties due to its membrane harming abrasiveness, as seen in graphite oxide nanoparticles. Amplified release of antibacterial metal ions from the surface of nanoparticles may also be involved. The low surface to volume ratio of the nanoparticles can expand the antimicrobial activity allowing more interaction of nanomaterial with the adjoining environment. Zeta potential, particle size , particle shape and chemistry are among the most pertinent variables influencing antibacterial activity (Wang et al., 2017a).

These NPs have long been documented to manifest microbial, micro-biostatic actions and act as potential antibiotic agents in medical and industrial applications. The nanoparticles have been actually known for targeted drug delivery; hence arrest microorganism growth. These properties have widened the scope of their applications (Qidwai et al., 2018). Nano-particles are complex molecules, and they a three layered structure i.e. a) first is the surface layer, which involves organization of a variety of many small molecules, surfactants, metal ions and polymers, b) second one is the shell surface, which doesn't, chemically, relate to core in any aspect, while the last one is called c) the core, which is the principal portion of the NPs and actually known to be the Nano-particle itself (Khan et al., 2019). The fundemental benefits of nanoparticles are i) they improve the bioavailability by amplifying aqueous solubility, ii) increase the resistance time in the body, thus, enhance the half-life for clearance/intensifying specificity for its cognate receptors and iii) NPs target drug to particular location in the body (its site of action) (Mudshinge et al., 2011).

Further, their advantages include elevated solubility, excessive carrying capacity, viability of consolidation of both the hydrophilic and hydrophobic substances, and access of variable routes of administration (Gelperina et al., 2005).

Properties of nanoparticles: The nanometer size of these nanoparticles furnishes them; i) large fraction of surface atoms, ii) reduced imperfections, iii) high surface energy, iv) spatial confinement which does not mostly exist in other bulk materials.

Nanoparticles are distinguished due to following properties

1. Size, 2. Protection, 3.Precision and security, 4.Contractibility, 5.Combination, 6.Roughness, 7.Zeta potential, 8. Doping modification (Alagarasi, 2011; Gatoo et al., 2014).

Mode of action of nanoparticles: Nano-particles may are blessed with some unique properties that include physical, chemical, mechanical, electric, electronic, dielectric, thermic, optical, and biologic in nature. Nanoparticles have great importance as potential antimicrobial agents because they have distinct characteristics (as described before) that furnish them as antimicrobial agents. Nano-particles are drawn to bacteria through the electro-static interaction between the

bacterial surfaces (negatively charged) and the particles having zeta potential (Strongly positive), this mechanism assists particles penetration into the membrane that leads to disruption of membrane, depletion in viability as well as bacterial flocculation. The antimicrobial activity of Nano-particles can also be enhanced by formation of reactive species (Nas et al., 2018).In addition to this, Nano-particles have the ability to damage the membrane integrity of bacteria through physical contact with the target microbial cell, thus, they can disrupt the DNA during the microorganism's replication and cell division. Nano-particles do possess abrasive properties which cause breakdown of bacterial cell, the property to release some toxic metal ions do support them in the said mechanism.(Kandi & Kandi, 2015).

Polymeric Nanoparticles: These have countless attributes that provide them special status as they are cheaper, non-toxic, non-immunogenic, they can be easily prepared, are water soluble and biodegradable. Due to these properties, they provide efficient drug delivery and hit the target efficiently. Polymeric Nano-particles equipped with these properties work as antimicrobials as well as anti-inflammatory and also have the ability to regress tumors.(Jasmine & Prabhu, 2013).

They also work as efficient drug carrying molecules due to which they can be effectively used to control the release of drugs, they also provide protection to the drug molecules against environment as they are encapsulated inside particles. PNPs also enhance the bio-availability and potentiate the therapeutic index.

Nano-particles include Nanocapsules and Nanospheres which have a special morphology that makes them distinct. The former are composed of an oily core which causes controlled release as the drug is dissolved in a polymeric shell. The later are incessant polymeric network-based molecules which allow the drug to be held internally and absorbed towards the surface. The Nano-sphere is known as matrix system while Nano-capsule is known as reservoir system (Zielińska et al., 2020).

List of polymers used in nanoparticle formation: Many biopolymers are used in nanopartciles formation including Natural polymers (Alginate, Albumin, Chitosan, Gelatin), Synthetic homo-polymers { poly(lactide), poly(isohexylcyanoacrylate), poly(lactide-co-glycolide), poly(isobutylcyanoacrylate)}, Co-polymers { poly(lactide)-poly(ethylene glycol), poly(epsilon-caprolactone)-poly(ethylene glycol)} and colloid stabilizers (Tween 20&80, Dextran) (KrishnaSailaja & Siddiqua).

Different techniques for preparation polymeric nanoparticles: In common technique used to prepare biodegradable Nano-particles, drug is dispersed in preformed polymers. Some others techniques include a) dialysis b)solvent evaporation, c) salting out d) Nano-precipitation, , e) emulsification/solvent diffusion, f) supercritical fluid technology ,g) interfacial polymerization (Nagavarma et al., 2012).

Polymeric nanoparticles-based drug delivery: Polymeric nanoparticles with biodegradable and biocompatible polymers are good contender as carrier for antimicrobial agents and drug delivery. Many studies that have been carried out to investigate this property have shown that it has the ability to potentiate the stability of therapeutic agents that are subjected to enzymatic degradation, but by harmonizing polymer characteristics, they can be used to attain required therapeutic levels of drugs in the target tissues for the desired time period required for optimum therapeutic efficiency (Patel et al., 2017).

The ultimate target in smart drug delivery is the ability to hold and release various active agents when required by using micro and Nano-fabricated therapeutic drug release devices. Now a days, this has become possible due to the distinguishing possibility provided by micro-electrical-mechanical system to prepare and manufacture fabricated (Micro or Nano) biomedical devices.s. These systems possess various crucial benefits such as many active ingredients could now be stored in Nano form easily within the system and then they can be released sustainably, as required. An electric or mechanical stimulus begins the drug release by the dissolution and dissipation of outer membrane barrier, that helps in promising sustained release of drug. It can be attained in any (high or low) dose of drugs at the specific targeted site and also helps to enhance the stability of drugs by developing a membrane barrier that prohibits the diffusion of water into the reservoirs (Kasagana & Karumuri, 2011).

Four main modes involved in the controlled drug delivery systems are roughly be categorized as, i) Rate-Controlled drug delivery, where drug diffuses into the system following a specific release rate, ii) Activation-modulated drug delivery, where various factors (physical, chemical etc) prompt the drug release, iii) feedback-based drug delivery, where biochemical substance concentrations estimates the rate of release of drug, it usually depends on the concentration exhibited in the target, iv) site-targeted delivery systems, that involves a complex process that includes multiple diffusion rate and the rate of drug release is adjusted by the specific targeting moiety (Bennet & Kim, 2014).

Mechanism of drug release: Maintaining the desired concentration of the drug in the blood is one of the chief goals of the controlled drug release to attain therapeutic efficacy. To serve the purpose, carriers that offer low dosing frequency and can provide controlled drug release are required. To attain this, Zero-order drug release profile delivery system are required, which allow the uniform release of drug. Nano-carrier based drug release depends upon several determinants including the type of composition being used either it be drug, polymer

Table 1: An overview of polymeric nanoparticles in antibacterial treatment

Polymeric NPs	Antimicrobial Agent	Size (nm)	E.E (%)	Susceptible Bacteria	Result	Reference
Chitosan	Gentamicin	100	72	*Brucella*	MIC 50% low (loaded drug	(Razei et al., 2019)
	Ciprofloxacin	72	23	*Staph.aureus E. coli*	MIC 50% low (loaded drug)	(Sobhani et al., 2017)
	Temporin B	185 + 10	75	*Staph. epidermidis*	4-log reduction in number of viable bacteria	(Piras et al., 2015)
	Clarithromycin	155-360	12.1 to 57.56	*S. pneumonia*	MIC lower around 1/4th to 1/2	(Ashvini et al., 2019)
Poly(lactide-co-glycolide) (PLGA)	Ciprofloxacin	190.4+ 28.6	79	*P.aeruginosa*	Significant antimicrobial activity at all concentrations	(Türeli et al., 2017)
	Minocycline	85-7070	29.95	*A. actinomycetemcomitans*	MIC 2 times lower (loaded) Zone of inhibition for loaded 9.2mm while for free was 3.5mm.	(Kashi et al., 2012)
PLA	Thymol	240-260	60.3 + 8	*E. coli*	At 0.5mg/ml conc., loaded thymol shown long term effects as compared to free drug	(Marcet et al., 2018)
	Minocycline	100	46.5	Many (periodontitis disease)	Effective drug conc. Maintained for long time	(Yao et al., 2014)
Polyethyleneimine (PEI)	d-mannose	-	-	*E. coli*	Loaded drug showed strong activity at 10µg/ml as compared to 220µg/ml free drug	(Liu et al., 2018b)
	Zinc oxide NPs	20	-	*H.pylori*	At 100µg/ml, ZnNP give 50% while PEI-ZnNps give 95% inhibition	(Chakraborti et al., 2013)

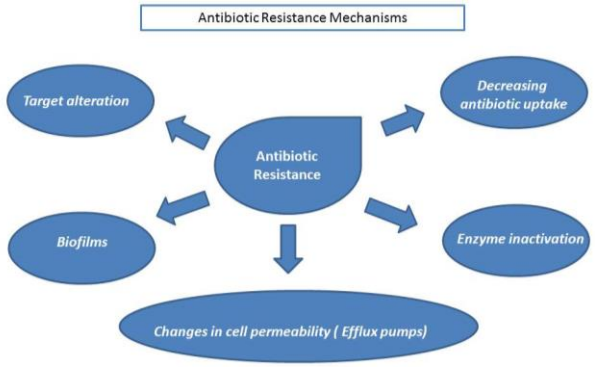

Figure 1: Mechanisms of antibiotic resistance

or excipient, also the ratio of composition as well as interaction (physical or chemical) among components and the methods used in manufacturing (Son et al., 2017). The drug-release rates from polymer nanoparticles rely on i) dissorption of the surface-bounded/adsorbed drug, ii) polymer nanoparticle erosion and a combined erosion diffusion process, iii) diffusion from the polymer nanoparticle. So the biodegradation and diffusion control the process of drug release (Lu et al., 2011).

Polymeric nanoparticles as potent new antibiotics to combat infectious diseases: The distinguished properties of Nano-materials make them best available option for antibacterial therapies as it also provides the sustained release that is absent in bulk materials. Use of nano-particles provides rapid, precise, efficacious and sensitive bacterial destruction (as in Table 1). These also possess distinct properties as antimicrobial drug delivery systems as they can be designed as environmentally responsive, targeted and combined drug delivery system (Karaman et al., 2017).

Chitosan: Chitosan, structurally known as poly-β(1→4)-2-amino-2-deoxy-d-glucose, a natural amino polysaccharide that is derived through the deacetylation of chitin (Pereira et al., 2019). It is a natural as well as nontoxic biopolymer which is used for its antimicrobial and antifungal properties. Factors that affect the antibacterial activity includes type of chitosan, Ph (inversely proportional), molecular weight, degree of chitosan polymerization and its physicochemical properties. It is highly effective against gram positive bacteria rather than gram negative. Deacetylated chitosan loaded nanoparticles can be used for the antimicrobial controlled release of amoxicillin and metronidazole. The rapid adherence of negatively charged bacterial surface with the polycationic chitosan with a higher charge density on the surface helps in its quick antibacterial activity. The higher affinity between both, aids in the adsorption of the chitosan nanoparticle on the surface of bacteria; disrupting its membrane and causing a leakage of intracellular components. Chelation of chitosan with the trace elements can enhance its effectiveness. For example the complex with copper can enhance the antibacterial effect to many folds as in the treatment of *S.choleraesuis (salmonella enterica)* (Qi et al., 2004). Zno-chitosan nanoparticles also shown greater antibacterial activity for *S.aureus (*gram positive)

than *E.coli*, which is gram negative (Hu et al., 2019). Chitosan nanoparticle is advantageous over other formulations because it is less toxic and have good biodegradability (Lee et al., 1995) with addition to showing an immune-stimulant effect (Nishimura et al., 1986) and greater muco-adhesive activity (Lehr et al., 1992; Rampino et al., 2013). E -polylysine-loaded chitosan-sodium alignate nanoparticles (pl-np) are effective against *E.coli, M.luteus, B.subtilis and S.aureus* (Liu et al., 2018a). Topical formulation of chitosan nanoparticles can be used for treatment of skin diseases as psoriasis and bacterial infection (Paliwal et al., 2020). Chitosan also has an application in wound healing because it is anti-inflammatory, biocompatible and antimicrobial in nature, as well as, easy processability into different forms (Moeini et al., 2020).

Poly(lactide-co-glycolide) (PLGA): PLGA poly(-lactide-co-glycolide) are safe, biocompatible, has a safe release and is biodegradable in nature. They are proposed for the treatment of intracellular infections (Panyam & Labhasetwar, 2003). Different antibiotics such as ciprofloxacin, azithromycin and rifampicin are incorporated in PLGA preparations for a better action against *Mycobacterium avium, Pseudomonas aeruginosa* and multidrug- resistant (MDR) salmonella typhi. It works by targeting phagocytes for the treatment of intracellular infections as it circulates in blood for a longer duration due to its negative charge (Soukos et al., 2003). PLGA hydrolyze in the body to biodegradable metabolites like lactic and glycolic acid (Rudramurthy et al., 2016).

Polyethylene glycol (PEG): PEG is a synthetic polymer (Keshavarz et al., 2020). Polymeric NPs have been often embellished with lectin that is a protein and ties to carbohydrates (simple or complex) on cell wall of bacteria. Lectin-conjugated gliadin nanoparticles are used for treatment of *H. pylori* related infections. It was discovered that lectin-conjugated NPs tie exponentially to carbohydrate-receptors present on cell wall of *H. pylori* and discharge various antimicrobial agents into the microbes. There are presently two distinct kinds of polymeric nanoparticles use for the antimicrobial delivery. One, out of these is framed by means of unconstrained self-assembled di-block copolymers comprising of hydrophilic as well as hydrophobic fragments. The hydrophobic fragment frames a polymeric center containing the medications while the hydrophilic portion shields the center from opsonization and breakdown. The pace at which drug is to be discharge can be altered by fluctuating the length of the hydrophobic chain. An assortment of biodegradable polymers has been utilized to frame the hydrophobic polymeric center, including poly (lactic acid) (PLA), poly (glycolic acid) (PGA) and poly(lactide-co-glycolide) (PLGA) while polyethylene glycol (PEG) has been normally utilized as a hydrophilic fragment. These are basically used to convey and deliver inadequate water soluble drugs in view of the hydrophobic nanoparticle center (Rudramurthy et al., 2016). Peglation is done to surface of NPs to interact with mononuclear phagocytes so that it can remain for a longer duration of action in the systemic circulation.

Polyethyleneimine (PEI): PEI is a cationic polymer having a definite charge density acting as a reductant and stabilizer in nanoparticle formulations. The positive charge is due to the amino group (Lee et al., 2011). They exhibit a strong antibacterial effect against bacteria such as *Streptococcus mutans*. They are effective against gram negative (Nombona et al., 2012), gram positive bacteria that include mainly *Staphylococcus aureus* ,*Pseudomonas aeruginosa*, , *Enterococcus faecalis*, *Staphylococcus epidermis and Escherichia coli* (Jeong et al., 2008; Gupta et al., 2019). The insoluble cross-linked quaternary ammonium compounds with octyl-groups is said to act by lysis of bacterial cell wall causing leakage of cytoplasmic components by displacement of divalent cations that binds with the surface of lipopolysaccharide that is negatively charged.

Hyaluronic acid (HA): Hyaluronic acid (HA), a biocompatible and biodegradable natural polymeric disaccharide containing n-acetyl glucosamine and glucuronic acid (Lee et al., 2011), showing antibacterial properties. They are modified with octenyl succinic anhydride posigamphiphilic properties to the formulations (nanogels) (Keshavarz et al., 2020). Ha nanoparticles are mostly loaded with antibiotics such as vancomycin and ciprofloxacin to exhibit its antibacterial effects.

Polylysine (PLL): Polylysine is a cationic homo-polymer occurring naturally which is non-toxic, biocompatible and antibacterial agent against both the gram-negative as well as gram- positive bacteria. PLL act on both kind of bacteria, by delivering a photosensitizer allowing a specific photo destruction protecting the host's cells. Additionally, it also act as an aid for an improved uptake into microbial cells exhibiting a photodynamic response as they attach themselves with the bacterial cellulose cell wall (Soukos et al., 2003; Liu et al., 2018c). For a sustained antibacterial action of copper nanoparticles (CuNPs), a carrier of pLL modified-reduced graphene oxide is used. (Chakraborti et al., 2014).

Polyamidoamine (PAMAM): Polyamidoamines are expressed as multifunctional nanoparticles formed by *prim*- and *sec*-amines by michael type polyaddtition with bisacrylamides. They are dendrimer for the modification of pet (Hu & Zhang, 2012). They act by forming new functional groups by nucleophilic attack on the ester groups. It shows a wide application as anti-parasitic, anticancerous and as antimicrobial agents (Ranucci & Manfredi, 2019).

Interaction of bacteria with Nano-materials: Nano-materials can overcome the antimicrobial resistance attributed to their special physiochemical properties, empowering Nano-materials with various novel bactericidal pathways to accomplish antimicrobial action. Nano-materials bind and disrupt the bacterial layers that cause spillage of cytoplasmic segments. Upon permeation of membrane, Nano-materials can likewise tie to the intracellular apparatus, such as, Deoxyribonucleic acid, ribosomes and catalysts that disturb the normal functioning of cell. Interruption in the cell apparatus can prompt oxidative pressure, imbalance of electrolytes and catalyst restraint, bringing about cell destruction or death.

Nanomaterial-microbial interaction rely on various factors, for example, van der waals forces, hydrophobic and receptor–ligand collaboration and electrostatic attraction. An investigation of the connection among nanomaterials and microbes gives vital understanding to structuring novel antimicrobials. The gram-positive cell wall has a structure that contains thick peptidoglycan layer (15–100 nm) and polymeric techoic acids with a cytoplasmic film residing under it. The phosphates present in the techoic-acid polymeric chains are liable for the negative charge present on bacteria and provide restricting locales for the solution divalent cations. Then again, gram-negative microbes comprise of a cytoplasmic film and have a thin peptidoglycan layer as compared to its counterpart which is additionally ensured by a hydrophobic lipid bilayer comprising of lipopolysaccharides. This extra lipid layer incredibly diminishes the entrance capacity of various hydrophobic antibacterial agents like detergents. The bacterial film have a negative charged principally because of phosphates and carboxylates as parts of lipopolysaccharides present on gram-negative microscopic organisms (Rudramurthy et al., 2016) (Gupta et al., 2019).

Advantages, drawbacks and limitations: Various sorts of nanomaterials have been accounted for to offer preferences in reduction of toxicity, overpowering resistance and decreasing the cost, when contrasted them with customary anti-infection agents.

Nanoparticles, for example, liposomes, have demonstrated invaluable at solubilizing therapeutic payloads, directed delivery of drug, significantly enhancing the circulation of drug. Enhanced penetrability and retention (epr) impact in pathologies, from infections to cardiovascular function failure, nanoparticle-based medication delivery is rising as an incredible system in a few particular malady conditions, as showed by clinical endorsement of nanoparticle details for parasitic contaminations, hepatitis a, and multiple sclerosis and end-stage renal illness. Their long lifetime of circulation and capacity to extravasate to disease location to a great extent improved their safety and tolerance of nanoparticle-defined medications, in contrast to conventional treatments (Şen Karaman et al., 2018).

They have potential for expanded medication half-lives and improving a medication's affinity to gather at injury site. Numerous drugs with poor oral bioavailability will have full utilization with the assistance of nanotechnology. Nanoformulations offer assurance against degradable and denaturatable drug products when presented to extreme ph, and furthermore prolong drug half-life by extending drug retention through bioadhesion(Panyam & Labhasetwar, 2003). Another expansive utilization of nanotechnology is antigen delivery for vaccination purposes. Late advances in animal modeling and encapsulation shows that nanoparticles are fit for enhancing immunization. The pathophysiological conditions and changes in anatomy of diseased or inflamed tissues can possibly trigger a lot of extensions for the improvements in nanotechnological field. (Şen Karaman et al., 2018).

Drawbacks: In spite of their increased half-life and improving a drug affinity to gather at locales of injury, this formulation face a mind-boggling arrangement of natural obstructions that seriously limit specific site bioavailability, forestalling accomplishment of appropriate therapeutic results. These hindrances incorporate opsonization and resulting sequestration by the mononuclear phagocyte system (mps), distribution that is nonspecific, hemorheological/flow of blood impediments, pressure slopes, and internalization of cell, endosomal escape and compartments of lysosomes and pump responsible for its efflux (Medina et al., 2007). Some non-functionalized nanomaterials may display a narrow spectrum against bacterial species. In addition, some of them exhibit low indices that has less therapeutic range (like selectivity) against some mammalian cells, restricting them across the board use in biomedical applications. Further they show toxic degradation, residual material associated with them, toxic monomers aggregation and toxic degradation process is involved with them. (Singh et al., 2017).

Limitations: NPs can be formulated by various distinct strategies and it do not surpass 100 nm in size. The significant challenge experienced is to control the size and state of ultrafine NPs with sufficient stability during its formulation.

NPs pose potential dangers to human health due to the critical accumulation of ultra-fine particles in various cells, tissues, and cellular components. Studies have shown the impact of NPs on human body and biological system. It has been reported that interaction between biological systems to NPs with a diameter under 100 nm may present known and unknown dangers to the human health. In addition, dangers related with nanoparticles fluctuate with NPs type (Medina et al., 2007).

Conclusion: The Nanoparticles are a solution to the various types of antibiotic resistance bacteria causing diseases in human. Multi-drug loaded nanoparticles present multifaceted drug deliverance to the site of action along with flexibility in dose unloading as well as reduced toxicity and longer circulation duration of the therapeutics. Variety of preparation methods are available that incorporate different Nano-materials. Nanoparticles have a versatile and all-purpose outlook along with a promising future in the field of antimicrobials. The nanoparticles have numerous advantages over conventional drug delivery as different mechanism can be combined precisely, thus reducing the drug resistance and increasing the drug therapeutic actions with a targeted delivery route. Though nanoparticles open a gate to a world with better treatment options through a controlled delivery of drug, but its unknown nature also poses some unseen risks to the human and its environment. It is still believed that the combinatorial nanoparticles drug therapies will do good than to harm humans. Advancement in the field of Nano-medicine will lead to an ideal therapy to combat infections cause by microbes and the multidrug resistance issue caused by these organisms can be solve by using Nano approach. At present nanoparticles are considered as an innovation in the field of medicine with much potential yet to be discovered entirely.

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