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Antibacterial Potential of Polymeric Nanoparticles Against Enterobacteriaceae: A Comprehensive Review

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ABSTRACT

The Enterobacteriaceae family encompasses a wide range of Gram-negative bacteria, including pathogenic species such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Salmonella enterica*. These pathogens are responsible for severe infections and exhibit significant resistance to conventional antibiotics, posing a major public health challenge. Polymeric nanoparticles have emerged as a promising solution to struggle these resistant strains due to their unique physicochemical properties, including high surface area, size, and the ability to encapsulate and release antimicrobial agents in a controlled manner.

This review focuses on the antimicrobial properties of polymeric nanoparticles directed against the Enterobacteriaceae family. We explore the various types of polymeric nanoparticles, including chitosan, PLGA (poly (lactic-co-glycolic acid)), dendrimers and their mechanisms of action, such as disruption of bacterial cell walls, inhibition of biofilm formation, and enhanced delivery of encapsulated antibiotics. The synthesis methods, characterization techniques, and in vitro and in vivo studies demonstrating their efficacy are discussed. Additionally, we address the challenges associated with the clinical translation of polymeric nanoparticles, such as biocompatibility, potential toxicity, and large-scale production. The review also highlights the potential for synergistic effects when polymeric nanoparticles are combined with traditional antibiotics, offering a multi-faceted approach to overcoming bacterial resistance.

In conclusion, polymeric nanoparticles represent a versatile and potent strategy for targeting the Enterobacteriaceae family, with the potential to revolutionize the treatment of bacterial infections. Further research and development are required to optimize their design and application, ensuring their safe and effective use in clinical studies.

Keywords: Enterobacteriaceae, polymeric nanoparticles, antimicrobial agents, chitosan, PLGA, dendrimers

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I. INTRODUCTION:

Enterobacteriaceae infections are treated with beta-lactam antibiotics; however, the bacteria have the ability to manufacture beta-lactamases, antibiotics ineffective. which render the Commercially marketed antibiotics may now have their activity increased or restored thanks to the exciting field of nanotechnology. The capacity of nanoparticles to transport medications into bacterial cells, lower the dosage of antibiotics, increase therapeutic efficacy, and lessen microbial resistance makes them useful for treating infections. There are two types of nanoparticles: nanoparticles polymeric (NPs) and lipid nanoparticles (NLS).^[1]

Polymeric nanoparticles are tiny particles, usually ranging from 10 to 1000 nm in size, composed of biodegradable and biocompatible polymers. Common polymers used in their production include poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polycaprolactone (PCL). These polymers are FDA-approved for clinical use due to their safety and ability to degrade into non-toxic byproducts.^[1]

1.1. Polymeric nanoparticles:

It is solid particles made from polymers, typically ranging in size from 1 to 1000 nanometers. They are increasingly utilized in drug delivery systems due to their unique properties and advantages. It have emerged as a promising tool in combating bacterial infections, including those caused by the *Enterobacteriaceae* family, a group of Gram-negative bacteria responsible for various infections like urinary tract infections, pneumonia, and bloodstream infections. This family includes clinically significant pathogens such as *Escherichia coli, Klebsiella pneumoniae, Salmonella, Shigella,*

and *Enterobacter* species, many of which have developed resistance to conventional antibiotics.^[2]

1.2. Characteristics of Polymeric Nanoparticles –

1.2.1. *Size:* The diameter of PNPs usually ranges from 10 to 1000 nm. The biodistribution, cellular absorption, and biological barrier-crossing capabilities of a nanoparticle, including the bloodbrain barrier, can all be influenced by its size.^[3]

1.2.2. *Shape:* PNPs can be designed in a variety of forms, including as spheres or rods. Their shape affects tissue penetration, circulation time, and their interaction with cells. Although spherical particles are more frequently encountered, alternative forms may have distinct benefits in particular contexts.^[3]

1.2.3. *Positive or Negative Charge:* PNPs' interactions with biological membranes and cells are influenced by their surface charge. The negatively charged bacterial cell membranes can interact with positively charged (cationic) nanoparticles more easily, increasing cellular absorption or membrane rupture. On the other hand, a high positive charge could be harmful to human cells.^[3]

1.2.4. *Biodegradable and biocompatible Polymers:*poly (lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and polycaprolactone (PCL) are examples of biodegradable polymers generally used to make PNPs. The body can readily eliminate these substances as non-toxic byproducts of their breakdown. ^[4]

1.2.5. *Colloidal & physicochemical Stability:* PNPs need to be able to withstand aggregation and premature release of their contents in biological fluids (blood, mucus, etc). To improve stability and lengthen the circulation period, stabilizers such as surfactants or coating agents (such polyethylene glycol or PEG) are frequently utilized. In hostile biological conditions, the polymer matrix should shield the medicine or therapeutic agent from premature breakdown or inactivation.^[4]

1.2.6. **Passive & active targeting:** PNPs can passively accumulate in tissues where blood arteries are leaky, such as tumors or infection sites, because of the enhanced permeability and retention (EPR) effect. To improve the precision of the therapy, PNPs can be functionalized with targeting ligands, such as peptides, antibodies, or small molecules, which bind to certain receptors on cancerous or bacterial cells.^[5]

1.2.7. *Improved Bioavailability& biodistribution:* PNPs increase the solubility and bioavailability of poorly soluble medications, facilitating the more efficient delivery of these substances to therapeutic concentrations in the

body. PNPs' size, charge, and surface changes can all be adjusted to affect how they distribute throughout the body, enabling targeted delivery to particular organs or tissues.^[5]

1.2.8. *Low Cytotoxicity& biocompatibility:* The polymers utilized to make PNPs should be as non-toxic to human cells as possible without sacrificing their antimicrobial or therapeutic properties. PNPs are made to be biocompatible, which means that when ingested by the body, they shouldn't have any negative impacts on the immune system or cause any problems.^[5]

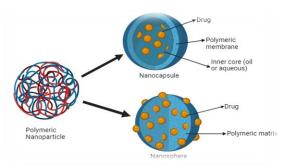


Fig 1: Structures of Polymeric Nanoparticle

1.3. Types of polymeric nanoparticles –

1.3.1. *Nanospheres*:Itis solid, matrix-type nanoparticles where the drug or therapeutic agent is either dispersed throughout the polymer matrix or adsorbed onto the surface. It used in controlled drug delivery systems, especially for poorly soluble drugs. They are also employed in the targeted delivery of anticancer agents or antibiotics.^[6]

1.3.2. *Nanocapsules:*Itis vesicular systems where the drug is confined to a core surrounded by a polymeric shell. The core can be either aqueous or oily. It is often used for targeted drug delivery, such as anticancer drugs, vaccines, or antimicrobial therapies.^[6]

1.3.3. *Polymeric Micelles:*Itis self-assembled nanoparticles formed from amphiphilic block copolymers. They have a hydrophobic core and a hydrophilic shell. It is frequently used in cancer therapy to deliver hydrophobic anticancer drugs, and they are also explored in antimicrobial therapies.^[6]

1.3.4. **Dendrimers:** It is highly branched, tree-like structures made from polymer chains. They have a central core and a series of branched layers known as generations. It is used in drug delivery, gene therapy, imaging, and antimicrobial applications. Their multi-functional surface also allows for targeted delivery by attaching ligands, antibodies, or peptides.^[7]

1.3.5. *Polysomes* (*Polymeric Vesicles*):Itare hollow, spherical structures formed by the self-assembly of amphiphilic polymers. They are similar to liposomes but made of polymeric materials. It is used for the delivery of both hydrophilic and hydrophobic drugs, as well as in gene therapy, imaging, and vaccine delivery.^[8]

1.3.6. **PEGylated** Nanoparticles: These are nanoparticles coated with polyethylene glycol (PEG), a hydrophilic polymer, to improve biocompatibility and extend circulation time in the bloodstream. It reduces the recognition and clearance of nanoparticles by the immune system (i.e., opsonization and phagocytosis), which prolongs their circulation in the bloodstream and increases the chance of reaching target tissues. It is commonly used in cancer therapy, where prolonged circulation is crucial, as well as in antimicrobial therapies and vaccines.^[8]

1.3.7. Hydrogel Nanoparticles: These nanoparticles are highly versatile and can swell in response to environmental conditions, allowing for controlled drug release. They can encapsulate both hydrophilic and hydrophobic drugs. Itis used in drug delivery systems for sustained release, gene delivery, and tissue engineering. They are also explored for use in wound healing and antimicrobial applications due to their biocompatibility.^[9]

1.3.8. *Crosslinked Nanoparticles:*Itis made from polymers that are chemically or physically crosslinked to create a stable, rigid structure.They are used in applications where stability is crucial, such as in drug delivery for chronic diseases, sustained-release formulations, and vaccine delivery.^[9]

1.4. Methods of Polymeric Nanoparticles –

Nanoparticle preparation can be done in a number of ways.Drugs, for instance, can be chemically conjugated to the polymer, enclosed in a nanoparticle core, wrapped in a shell-like polymer membrane, or adsorbently attached to the surface of the particle.

1.4.1. Solvent evaporation: Evaporation technique is one of the procedures used to prepare the solvent for emulsification nanoparticles. It is mostly employed to encapsulate hydrophobic medications, but it performs poorly when hydrophilic bioactive chemicals are added. The process of solvent evaporation involves dissolving the molecule and polymer in an organic solvent, such as methylene chloride, ethyl acetate, or chloroform, and then emulsifying the mixture in an aqueous phase with a stabilizer (like PVA). The solvent diffuses to the exterior phase until saturation shortly after the nanoemulsion forms.^[10] Nanospheres are formed at the same time as the polymer precipitates due to the solvent molecules continuing to diffuse from the inner droplets of the emulsion to the external phase as a result of the solvent molecules evaporating as they reach the water-air interphase. In numerous instances, homogenization or sonication can be used to induce nanoscale polymer droplets. After the organic evaporates. centrifugation solvent and lyophilization are often used to gather the nanoparticles. The double or multiple emulsion approach can be utilized to encapsulate hydrophilic substances and proteins with the little modifications made to this procedure. [10]

Stabilizer and a medication that is hydrophilic dissolve in water. The aqueous phase is dispersed into an organic solvent that has a dissolved polymer in order to create the primary emulsion. Then, in an outer aqueous phase that also contains stabilizer, this is emulsified. The solvent evaporation process can be used to create nanoparticles. Rapid molecule diffusion into the outer aqueous phase during emulsification is a major issue when encapsulating hydrophilic molecules such as proteins or peptidedrugs. Poor encapsulation efficiency, or drug loading, may arise from this.^[11]

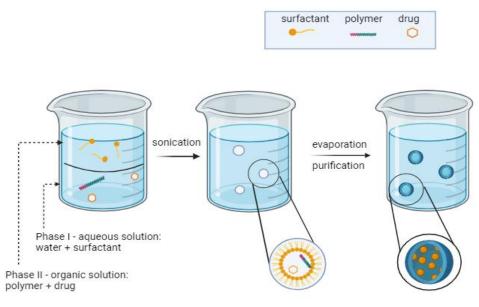


Fig 2: Solvent evaporation methods

1.4.2. **Emulsification diffusion:**It is another technique that can be applied to the creation of nanoparticles. Acetone or propylene carbonate, or any somewhat water-soluble solvent, is used in this procedure. After dissolving in the solvent, the medication and polymer are emulsified in the stabilizer-containing aqueous phase. By adsorbing on the droplets' surface, the stabilizer's function is to stop the emulsion droplets from aggregating. When water is added to the emulsion, the solvent is allowed to diffuse into the water. The stirring of the solution causes the particles to precipitate at the

nanoscale. Moreover, dialysis is an efficient way to remove the solvent, or it can be collected by centrifugation. ^[12]

This method's primary issue is that during the diffusion stages, the water soluble medications have a tendency to seep out of the polymer phase. Therefore, to circumvent this issue, the dispersion media was modified from an aqueous one to one that contained medium chain triglycerides along with a minor quantity of surfactant. Centrifugation is used to remove the nanoparticles from the oily suspension.^[12]

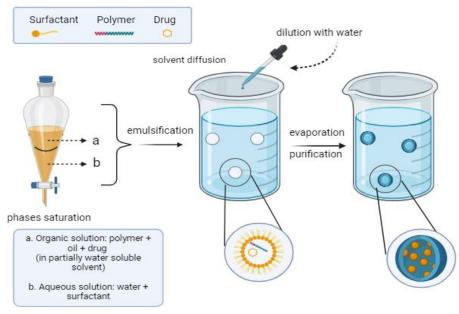


Fig 3: Emulsification diffusion method

1.4.3. Nanoprecipitation: The process of nanoprecipitation can be used to create nanoparticles. In this procedure, the medication and polymer are dissolved in acetone, ethanol, or methanol and added to an aqueous surfactant while being stirred magnetically. solution Instantaneous diffusion of the organic solvent to

the external aqueous phase is followed by the polymer and drug precipitating. The solvent is removed and the suspension is concentrated at low pressure once the nanoparticles have formed. This method's benefit is that it doesn't use surfactants, but it can only be used with medications that are very soluble in polar solvents.^[13]

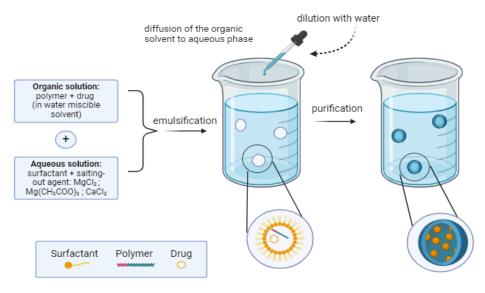


Fig 4: Nanoprecipitation method

1.4.4. **Salting-out method:**Another technique for creating nanoparticles is the salting-out procedure. This method, which is based on the precipitation of a hydrophobic polymer, can be used to encapsulate hydrophilic or hydrophobic

drugs because it allows for the choice of solvents for the drug's dissolution, including polar ones like methanol or acetone as well as non-polar ones like methylene chloride or chloroform.^[14]

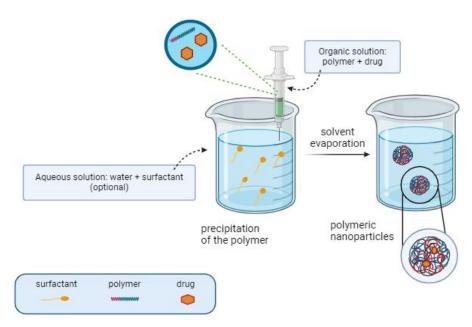


Fig 5: Salting-out method

Sl. No.	Types of Polymeric Nanoparticle	Polymer(s) used	Targeted bacteria	Mechanism of action	Antimicrobial effectiveness	Reference
1	Nanocapsules	Poly(lactic-co- glycolic acid) (PLGA)	E.coli, Klebsiella pneumoniae	Controlled release of antibiotics directly at infection site, reducing bacterial growth	Reduces bacterial load significantly; prevents resistance development	[15]
2	Nanospheres	Polyethylene glycol PEG), Chitosan	Klebsiella pneumoniae, E.coli	Increases permeability of bacterial cell membrane, enhances antibiotic uptake	Enhanced killing of drug-resistant strains, reduced MIC (Minimum Inhibitory Concentration)	[15]
3	Dendrimers	Poly(amidoamine)	E.coli, Enterobacter spp.	Electrostatic interaction with bacterial membrane causes disruption and cell death	Highly effective in both plaktonic and biofilm forms of bacteria	[16]
4	Hydrogels	Chitosan, PLGA	E.coli, Klebsiella pneumoniae	Forms a bioadhesive layer, releasing antibiotics slowly at wound sites	Promotes healing while providing long-term antimicrobial action	[16]
5	Biodegradable nanoparticles	PLGA, Polylactic acid (PLA), Chitosan	E.coli, Salmonella spp.	Degradable polymer releases encapsulated drugs over time; biofilm disruption	Enhanced antibiotic penetration into biofilms; long-lasting effects	[16, 17]
6	Stimuli- responsive nanoparticles	PLGA, Chitosan	Klebsiella pneumoniae, E.coli	pH-responsive release of antibiotics in acidic infection environments	Localized antimicrobial action in infection sites (e.g., wounds, biofilms)	[17]

Table 01:Antimicrobial activity of polymeric nanoparticles against *Enterobacteriaceae* family

The Enterobacteriaceae family of bacteria, which includes important pathogens like *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter species*, has been the target of polymeric nanoparticles encouraging antibacterial action.

2.1. Mechanism of action of polymeric nanoparticles against *E. coli*:

An effective method of treating Escherichia coli (E. coli) infections, particularly those caused by antibiotic-resistant strains, is the use of polymeric nanoparticles (PNPs). Because they can bypass resistance mechanisms, increase cellular penetration, and improve drug delivery, they have antibacterial action.

2.1.1. *Targeted Drug Delivery:* antimicrobial medicines, such as antibiotics, can be more effectively delivered straight to E.coli cells by encasing them in polymeric nanoparticles. Antibiotic concentration at the infection site rises as a result of reducing antibiotic degradation.^[18]

2.1.2. *Membrane disruption:* Certain polymeric nanoparticles, especially those with surfaces that are cationic (positively charged), have the ability to

interact with the negatively charged bacterial cell membrane, causing membrane disruption and possibly even bacterial death.^[19]

2.1.3. *Biofilm Penetration:* It is well known that pathogenic strains of E.coli, in particular, can develop biofilms on surfaces such as urinary tracts or catheters. Because nanoparticles are small enough to get past these biofilms and into the biofilm structure, where conventional antibiotics might not work, and treatment can be more effectively administered. ^[19]

2.1.4. Sustained Release: A number of polymeric nanoparticles offer an extended period of time for the antibacterial action of encapsulated medications to take effect, thus lowering the frequency of doses that may be necessary.^[20]

2.1.5. *Intrinsic Antimicrobial Properties:* Certain polymers, including chitosan, have inherent antibacterial qualities that work in concert with encapsulated antibiotics.^[20]

2.2. Mechanism of action of polymeric nanoparticles against *Klebsiella pneumoniae*:

The potential of polymeric nanoparticles (PNPs) to treat *Klebsiella pneumoniae* infections is receiving attention. This is especially true for infections brought on by multidrug-resistant (MDR) strains of

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the bacteria, like carbapenem-resistant *K. pneumoniae* (CRKP). Urinary tract infections (UTIs), bloodstream infections, pneumonia, and other severe diseases are caused by the opportunistic bacterium *K. pneumoniae*. Alternative strategies like medication delivery systems based on nanoparticles are essential because traditional antibiotics frequently fail to combat resistant bacteria.

2.2.1. *Improved Drug Delivery:* The solubility, stability, and bioavailability of encapsulated medications are all improved by polymeric nanoparticles. Through targeted delivery, the local concentration of antibiotics at the infection site is increased, improving efficacy and reducing systemic toxicity.^[21]

2.2.2. Antibiotic Resistance: Using the nanoparticles, *K. pneumoniae* can inactivate antibiotics by blocking resistance mechanisms including efflux pumps and the synthesis of enzymes (like beta-lactamases). Nanoparticles shield the antibiotic payload from some bacterial defences, enabling the medications to reach their intended target. ^[22]

2.2.3. *Membrane Disruption:* When negatively charged bacterial membranes contact with certain polymeric nanoparticles with modified surfaces (such as cationic charges), the result is membrane destabilization, permeability, and bacterial cell death. ^[22]

2.2.4. *Biofilm Penetration:* It is well known that *K. pneumoniae* can develop biofilms, particularly on medical equipment and in hospital environments. Polymeric nanoparticles have the ability to pierce biofilms and introduce medications into these antibiotic-resistant, protective bacterial colonies.^[22]

2.2.5. *Controlled Drug Release:* By providing sustained drug release, nanoparticles can lower the frequency of dosing by extending the duration of antibacterial activity at the site of infection.^[23]

2.3. Mechanism of action of polymeric nanoparticles against *Enterobacter species*:

Polymeric nanoparticles (PNPs) have demonstrated a great deal of promise in treating Enterobacterrelated infections. Bloodstream infections, urinary tract infections, pneumonia, and other hospitalacquired infections (HAIs) are frequently linked to Enterobacter species, such as *Enterobacter aerogenes* and *Enterobacter cloacae*, which are opportunistic pathogens. Interest in nanoparticlebased drug delivery methods has increased as a result of the emergence of multidrug-resistant (MDR) Enterobacter strains, especially those resistant to carbapenems, which have made treatment more challenging. **2.3.1.** *Targeted Drug Delivery:* antimicrobial drugs, such as antibiotics, can be better dissolved and stabilized by encapsulating them in polymeric nanoparticles. Nanoparticles can strengthen the drug's concentration at the infection site by delivering these medications straight to the bacterial cells, evading certain of Enterobacter's resistance mechanisms.^[24]

2.3.2. Overcoming Drug Resistance: Betalactamase and efflux pump synthesis are two major resistance mechanisms used by MDR Enterobacter strains that nanoparticles can assist in evading. Nanoparticles can improve intracellular delivery and delay antibiotic degradation by encasing the antibiotic within a polymeric carrier. ^[24]

2.3.3. *Disruption of Biofilms:* Enterobacter species, like other members of the Enterobacteriaceae family, have the ability to build highly resistant biofilms against antibiotics. Where conventional antibiotics frequently fail, polymeric nanoparticles can directly administer antibiotics into the biofilm matrix by penetrating these biofilms.^[25]

2.3.4. *Membrane disruption:* As a result of interactions with the negatively charged bacterial membranes, some polymeric nanoparticles, particularly those with cationic (positively charged) surfaces, can destabilize the membrane and ultimately kill the cell. When it comes to MDR strains, this technique can be especially useful. ^[25]

2.3.5. Sustained Release of Antimicrobials: A lot of polymeric nanoparticles are made to allow for the sustained release of the medications they contain, extending their antibacterial action and lowering the need for frequent dosage.^[26]

3. APPLICATIONS

3.1. Medicine and Clinical Practice

3.1.1. *Targeted Drug Delivery:* PNPs have the ability to deliver antimicrobial medicines to bacterial cells directly, increasing their effectiveness and minimizing their negative effects. Treatments for infections brought on by bacteria belonging to the *Enterobacteriaceae* family that are resistant to drugs, like *Klebsiella pneumoniae* and *Escherichia coli*, can benefit greatly from this.^[27]

3.1.2. *Wound Healing:* PNPs can be used to wound dressings to offer a prolonged antibacterial effect against infections brought on by *Enterobacteriaceae species*, accelerating healing and averting long-term infections. ^[27]

3.1.3. Urinary tract infections (UTIs:Itis commonly caused by Enterobacteriaceae, which includes Proteus mirabilis and Escherichia coli. Long-acting medication formulations based on

PNP may improve local UTI treatment while reducing systemic exposure. ^[27, 28]

3.1.4. *Biofilm Disruption:* A large number of Enterobacteriaceae produce biofilms, which are more resistant to traditional antibiotics. By breaking through the biofilm matrix and directly administering antimicrobials, polymeric nanoparticles can improve treatment outcomes by penetrating biofilms. ^[28]

3.2. Food Safety

3.2.1. *Food packaging:* By adding polymeric nanoparticles with antimicrobial activity to food packaging materials, food safety can be improved and shelf life extended by preventing the growth of pathogenic Enterobacteriaceae (such as *Salmonellasp.*and*E.coli*) on food surfaces. ^[29]

3.2.2. Surface Coatings in Food Processing: To lessen contamination by bacteria belonging to the *Enterobacteriaceae* family, surfaces in food processing facilities might be coated with antimicrobial PNPs.^[29]

3.3. Agriculture

3.3.1. *Livestock Protection:* To improve animal health and lessen the need for conventional antibiotics, polymeric nanoparticles can be applied topically or included in feed to prevent bacterial infections brought on by *Enterobacteriaceae species*.^[30]

3.3.2. *Plant Protection:* Plant pathogens include several *Enterobacteriaceae species*, such as *Erwinia species*. In agricultural sprays or coatings, antimicrobial PNPs can be employed to stave against diseases and encourage higher crop yields.^[30]

3.4. Research on Pharmaceuticals

3.4.1 New antibacterial Agent Formulation: PNPs can improve the effectiveness and stability of recently created antibacterial agents. They offer a controlled release mechanism that may lower dosage frequency and increase patient compliance, particularly for types of *Enterobacteriaceae* that are resistant. ^[31]

3.4.2 Synergistic Effects: PNPs have the potential to work in concert with other antimicrobial agents to produce a synergistic impact that improves the efficiency of both of their capacity to kill or inhibit bacteria. ^[31]

3.5. Environmental and Public Health Applications

3.5.1. *Water Treatment:* To stop the spread of *Enterobacteriaceae* family waterborne pathogens, polymeric nanoparticles with antimicrobial activity can be incorporated into water filtering systems. ^[32]

3.5.2. *Sanitizing Agents:* To stop Enterobacteriaceae-related infection outbreaks, these nanoparticles can be added to surface sanitizers or disinfectants that are utilized in public areas, schools, and hospitals.^[32]

IV. DISCUSSIONS & CONCLUSIONS

Antibiotic-resistant Enterobacteriaceae strains can be effectively combated by polymeric nanoparticles, among other strains. Their capacity to directly interact with bacterial membranes or to transport medicines in a regulated manner is frequently cited as the reason for their antibacterial efficacy. Polymeric nanoparticles have an antibacterial impact that is usually attributed to mechanisms including rupturing bacterial cell membranes, producing reactive oxygen species, or releasing antimicrobial chemicals at the infection Compared to traditional antibacterial site. treatments, polymeric nanoparticles have a number of benefits. These consist of improved stability, extended release, decreased toxicity, and improved targeting of particular bacterial strains.

V. FUTURE ASPECTS

In the future, studies may concentrate on shape, and the size, surface improving modifications of polymeric nanoparticles in order to enhance their capacity to target and eliminate a wider variety of Enterobacteriaceae species. The safety of polymeric nanoparticles for human usage must be guaranteed. Their antibacterial efficacy must be maximized while minimizing potential toxicity and addressing biocompatibility in future research. To treat illnesses generated by the Enterobacteriaceae family, these factors are essential to the advancement of polymeric nanoparticle application. The ability of polymeric nanoparticles to target а variety of Enterobacteriaceae species, including strains that are resistant to multiple drugs, may be investigated in further research. One possible approach to this would be to create nanoparticles that can get past the defences put up by bacteria. Polymeric nanoparticles may work in concert with other antimicrobial treatments or agents to produce synergistic effects that will make it easier to fight resistant forms of bacteria. All things considered, polymeric nanoparticles appear to have a bright future in the fight against Enterobacteriaceae infections; further study in this area is likely to reveal new uses and advancements.

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