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POLYMERIC NANOPARTICLES – A REVIEW

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Abstract

Polymeric nanoparticles have emerged as versatile and promising platforms in the field of nanotechnology, offering unique properties and functionalities for various applications. These nanoparticles, typically ranging from 1 to 1000 nanometers in size, are composed of biocompatible or biodegradable polymers, offering controlled drug delivery, imaging capabilities, and targeted therapy. This abstract provides an overview of the synthesis methods, characterization techniques, and applications of polymeric nanoparticles in drug delivery, gene therapy, diagnostics, and imaging. Various polymeric materials, including synthetic and natural polymers, are explored for their suitability in nanoparticle formulations. The choice of polymers influences crucial properties such as biocompatibility, biodegradability, and controlled drug release kinetics, enhancing the therapeutic efficacy and reducing side effects. The ability to encapsulate a diverse range of payloads, including hydrophobic and hydrophilic compounds, makes polymeric nanoparticles highly adaptable for different applications.

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Introduction

Nanoparticles are the fundamental component of nanotechnology. Nanoparticles size ranges from 1 to 100nm and made up of metal, metal oxides, organic matterand carbon.Nanoparticles differ from various dimensions, to shapes,sizes and structures. They can be spherical, cylindrical, conical, tubular, hollow core, spiral or irregular etc.The surface of nanoparticles can either be uniform or irregular. They also exist in crystalline and amorphous forms which can be either single crystal solid or multi-crystal solid. They are divided into different classes based on their properties, sizes or shapes. The different groups include fullerenes, metal nanoparticles, ceramic nanoparticles and polymeric nanoparticles [1].

Polymeric nanoparticles are tiny, solid and colloidal particles within the size range from 1to 1000 nm. It is an innovate form of materials derived through nanotechnology for technological improvement in drug delivery and other biomedical applications. Polymeric nanoparticles could be optimized to improve drug bioavailability or specific delivery at the site of action. Polymeric nanoparticle is commonly used as a drug carrier, they have good biodegradability, biocompatibility and high drug-loading capacity. These nanoparticles also show low toxicity, increased therapeutic effectiveness, improved drug penetration, controlled drug release and enhanced physical and chemical stability [2]. Polymeric nanoparticles are widely used as a delivery system, subsequently they are able to load natural and synthetic agents including protein, peptides, growth factors, DNAs, mRNA and drugs. Nanospheres and nanocapsules are two forms of the nanoparticles, which differ with respect to their morphology. Nanospheres are formed by dense polymeric matrix in which drug can be retained inside or adsorbed on to their surface.Nanocapsules contain a liquid/solid core in which the drug, geneand other substances are incorporated into the interior cavity that is surrounded by a distinctive polymeric membrane. These two types of polymeric nanoparticles recognized as a reservoir system (nanocapsule) and matrix system (nanosphere) [3].

Types of polymeric nanoparticles

Polymeric materials used to prepare nanoparticles are commonly categorized into two types which are natural and synthetic.

Natural polymers

Natural polymers are derived from a wide range of plant or animal-based sources. Natural polymers are often highly biocompatible and nontoxic at wide range of concentrations and also inexpensive. These may be extracted from raw materials through complicated separation processes or reproduced synthetically through often complicated multi step

path ways. These natural polymers do have the inherent advantages, such as biocompatibility, specific interactions with some biomolecules and easy surface modification furnish them with greater versatility in drug delivery [4].

Examples: Cellulose, chitosan, alginates, starch, albumin, gelatin, xantham gum, dextran, agarose, pectin.

Chitosan nanoparticles

Chitosan is a natural cationic biopolymer composed of N-acetyl-D-glucosamine and D-glucosamine units connected by β-1,4-glycosidic linkages. Chitosan is a linear polysaccharide which is obtained from demineralization and deproteinization of chitin. It is obtained from various natural sources such as marines, insects, fungi, or animals. Chitosan is a biodegradable, biocompatible, nontoxic and has notable antimicrobial properties. They also shows improve drug release, permeability, stability and the ability to be functionalized with specific markers which may allow for targeted delivery with a range of therapeutics [5].

Preparation of chitosan nanoparticles

The most common methods used to prepare chitosan nanoparticles include ionic gelation, microemulsion, emulsion-based solvent evaporation and emulsification solvent diffusion.

Ionic gelation method

Materials

Low molecular weight chitosan (MW 50-190 kDa), sodium tripolyphosphate (TPP) and acetic acid.

Synthesis of chitosan nanoparticles

Ionic gelation involves dissolving chitosan (which is positively charged) in 1% acetic acid to a concentration of 1mg/mL at room temperature. The chitosan solution (21 mL) was set on magnetic stir plate (1000 rpm) for an hour. A second solution is prepared using tripolyphosphate (polyanion and also act as an ionic cross linker) dissolved in deionized water. 9 mL of 1 mg/mL aqueous tripolyphosphate solution was added drop wise at a rate of 1 mL/min thus resulting in a complex coacervate aqueous phase. The mixture needs to be magnetically stirred at room temperature. The solution results in three individual phases depending upon the stage of the procedure, starting with clear (chitosan solution), followed by opalescent or milky (after adding tripolyphosphate to chitosan solution) and finally aggregated (after adding more tripolyphosphate to a milky solution), whereby the milky appearance is the sign of the formation of chitosan nanoparticles prior to purification and collection [6].

Applications of chitosan nanoparticles

Table1: Potential applications of chitosan nanoparticles [7].

No	Area of application	Used as
1	Antioxidant	Antioxidant activities against hydroxyl, superoxide free radicals.
2	Antimicrobial	The positively charged molecules of the chitosan interact with the negatively charged microbial cell membrane and tend to pull apart the cell membrane, thus show its effects.
3	Agriculture	Due to the presence of antimicrobial activity it is useful for inhibiting various plant pathogens. It is also able to increase the auxin concentration and urea release in the soil, germination capacity, root length, root activity and seedling height.
4	Drug delivery	Delivery of various drugs through various routes inside body like oral, nasal, ocular and vaginal etc. Due to presence of an amine group (positively charged), it can adhere to negatively charged biological surfaces (mucosal glycoproteins) as a bioadhesive material, due to this it is considered as a favorable material for drug delivery processes.
5	Gene therapy	Delivering of various genes which are used in gene therapy, cancer therapy and siRNA (small interfering RNA)technology.
6	Obesity treatment	Chitosan has the capability of lowering cholesterol and low-density lipoprotein thus aids in obesity treatment. Chitosan also mediates the anti-obesity activities by interfering with the adipocyte differentiation and inhibits the adipogenic transcription factors and genes.
8	Wastewater treatment	Chitosan includes functional amino and hydroxyl groups, which makes nanoparticles interesting for the removal of a range of pollutants such as heavy metals, pesticides and dyes.
9	Regenerative technology	Used in bone regeneration, neural regeneration technology, cornea and cardiac regeneration technologies.
10	Environmental protection	Used in removal of organic and inorganic pollutants, heavy metals and harmful pesticides from the environment.

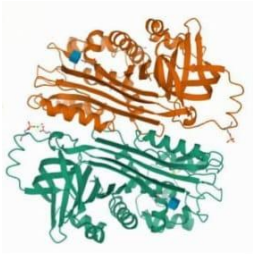
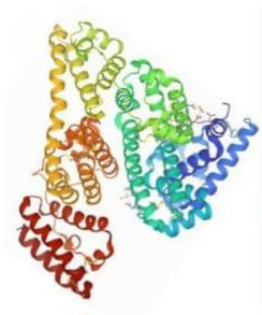
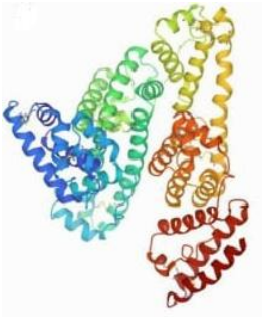
Albumin nanoparticles

Albumin-based nanoparticles have received considerable interest due to their biological origin, biodegradability, non-toxicity, non-immunogenicity, water solubility, easy availability and more importantly their ability to accumulate in the tumor sites. Albumin is a natural protein present in the human body so albumin nanoparticles have high biocompatibility. They reduce the possibility of immune reactions and toxicity, which is an important factor in the development of drug nanoparticles. Albumin possesses functional groups, such as amino and carboxylic groups, which can be employed for functionalization of albumin nanoparticles with targeting igands [8].

Types of albumin

Albumin can be obtained from various sources including vegetables, animals and human sources. The most commonly used albumin includes egg white (called ovalbumin), bovine serum albumin (BSA) and human serum albumin (HSA). Among them BSA is widely used and applied in research because of its low cost, easy availability and purification.

Table 2: Basic information of types of albumin [9]

Types of albumin	Structure	Length (aminoacid)	Molecular weight	Half life	Organism	Uses
Ovalbumin		385	45kDa	19 days	Egg white	Ovalbumin nanoparticles are used to enhance efficiency of antigen uptake. Self-assembled ovalbumin nanoparticles can deliver polyunsaturated fatty acids. Ovalbumin complex nanoparticles exhibits good encapsulation efficiency.
Bovine serum albumin		583	66.43kDa	19 days	Bovine serum	BSA complex nanoparticles shows high stability, good cell penetrating ability and potential anticancer activity. Cu2+ BSA complex nanoparticles can be used as biocompatible nanoparticles robes for super resolution imaging. BSA nanoparticles are often used as drug carriers to control the drug release.
Human serum albumin		585	67kDa	14 days	Human serum	HSA nanoparticles have good biocompatibility, good biodegradability, high biological stability, and noncytotoxicityso it is widely used in the development and application of albumin drugs-carriers. HSA-functionalized nanoparticles can deliver antitumor drug to HER-2-positive breast cancer cells.

Preparation of albumin nanoparticles

For the synthesis of albumin-based nanoparticles the desolvation method is the most commonly used method. Other methods for synthesis of albumin nanoparticles are thermal gelation, emulsification, double emulsification, self-assembly and spray-drying.

Desolvation method

It is the most common technique used for fabrication of albumin nanoparticles. The process of desolvation is done by a dehydration process of albumin.

Materials

Albumin, desolvation agent like ethanol (or) acetone and gluaraldehyde (cross-linking agent).

Synthesis of albumin nanoparticles

The preparation of albumin nanoparticles takes place with a continuous mixing at a certain speed by adding a desolvating agent (ethanol or acetone) to a well-dissolved albumin solution in water. During the addition of desolvating agent, conformational change in albumin structure occurs gradually from a stretched to a coiled conformation and the water solubility of albumin decreases; hence the formation of nanoparticles takes place. Then they formed nanoparticles are stabilized by cross-linking agents (gluaraldehyde) cause particles cross-linking. The concentration of gluaraldehyde needed for the stabilization of nanoparticles is 40%, allowing the reaction to proceed for 24 hours, ensuring the sufficient cross-linking of albumin amino groups. Finally, the residual cross-linking agent and organic solvent were removed to obtain purified albumin nanoparticles [10].

Applications of albumin nanoparticles

Albumin based nanoparticles can be used in the diagnosis and therapy of various diseases, such as various kinds of cancer, diabetes, kidney inflammation, liver diseases and so on.

- Cancer therapy

Table 3: Albumin nanoparticles used for different types of cancer [9]

Type of albumin-based nanoparticleused	Type of cancer
Cabazitaxel loaded bovine serum albumin nanoparticles	Prostate cancer
Bevacizumab loaded albumin nanoparticles	Colorectal cancer
Paclitaxel loaded albumin nanoparticles	Breast cancer
Paclitaxel and carboplatin loaded albumin nanoparticles	Lung cancer
Enzyme-sensitive Gemcitabine conjugated albumin nanoparticles	Pancreatic cancer
Doxorubicin loaded bovine serum nanoparticles	Lymphoblastic leukemia
Albumin and micellar nanoparticles of Itraconazole	Lung cancer
Human serum albumin co-modified Erlotinib loaded albumin nanoparticles	Lung cancer

- Kidney disease-Medial arterial calcification is a common cause of chronic kidney disease (CKD) and it occurs as linear mineral deposits along the degraded elastin lamellae. To treat calcification particularly in CKD, are predominantly focused on regulating the mineral disturbance and other risk factors. Ethylene diamine tetraacetic acid (EDTA) is a chelating agent can resorb mineral deposits, but the systemic delivery of EDTA may causesevere side effects such as hypocalcemia and bone resorption. So EDTA-loaded albumin nanoparticles conjugated with an anti-elastin antibody were developed, these targeted nanoparticles deliver EDTA at the site of vascular calcification and reverse mineral deposits without any side effects [11].
- Rheumatoid arthritis-Albumin is considered as an attractive drug carrier for hydrophobic drugs to target inflamed joints of rheumatoid arthritis. Albumin-based nanoparticles on delivery of Tacrolimus to enhance target ability and anti-arthritic efficacy.

Synthetic polymers

Synthetic polymers are not generally found in nature and are synthesized through polymerization reactions starting from a wide range of monomeric units. They are often created from petroleum-derived raw materials through precision growth methods; because of their defined chemical structure, their physical and chemical properties can be more easily tuned than natural polymer. Synthetic polymers are highly tunable, easily controllable materials that offer advantages over natural polymer. Due to tenability they can allows the precise control of API release. They can be designed to possess mechanical properties similar to those of biological tissue [12].

Examples: Poly (glycolic acid), poly (lactic acid), poly (caprolactone), poly(lactic-co-glycolic acid), poly(acrylic acid), poly(vinyl alcohol), poly(cyanoacrylates).

Poly (lactic-co-glycolic acid) nanoparticles

Poly (lactic-co-glycolic acid) (PLGA) is a biodegradable polymer; it is obtained by various combinations of lactic acid and glycolic acid during polymerization. PLGA is the best candidate as biomaterials for drug deliverydue to its design and performance. It has several interesting properties such as controlled and sustained release, low cytotoxicity, long-standing biomedical applications, biocompatibility with tissues and cells and targeted delivery. The use of PLGA for the delivery of drugs and biomedical applications is associated with minimal systemic toxicity. PLGA based nanomedicines helps in multipurpose carrier for designing novel drug delivery systems for widespread pharmaceutical applications including targeting cancer, infectious diseases, delivery of pharmaceuticals and biopharmaceuticals etc [13].

Preparation of poly (lactic-co-glycolic acid) nanoparticles

Methods used for the synthesis of poly (lactic-co-glycolic acid) nanoparticles are emulsification-diffusion, emulsification-evaporation, nanoprecipitation or solvent displacement, solvent diffusion and phase inversion.

Emulsion-solvent evaporation

Materials

PLGA (50:50 acid terminated, Mw 40000-75000 Da), polyvinyl alcohol (PVA), 88% hydrolyzed dichloromethane (DCM) and ultrapure water

Synthesis of PLGA nanoparticles

Specific amount of PLGA was dissolved in 4ml DCM, resulting as organic phase. Now, this phase was added dropwise to 20% aqueous solution of PVA with 10mL/h dropping speed, under ultrasonication in an ice bath. The obtained mixture was homogenized by using sonication for 15 min on ice. Then, solvent evaporation was done by magnetic stirring at 1000 rpm for 3 hours at 35^0C. These leads to the formation of nanoparticles and they are recovered by centrifugation at 9000 rpm for 15 min, washed three times with distilled water at 35^0C-38^0C to remove all residual surfactants. The obtained nanoparticles were either used freshly or dried in oven for further use [14].

Applications of PLGA nanoparticles

- Cancer therapy by photodynamic and photothermal therapy- Reactive oxygen species can be generated by the process of photoexcitation of photosensitizing agents which is used in this therapy. Most of the photosensitizing agents are water repellent. Under laser irradiation, the photosensitizing agents give rapid decomposition; due to this the agents are not accumulated well in the tumor. This can be improved, when they are formulated by using PLGA nanoparticles [15].
- Gene therapy-In gene therapy affected genes can be replaced with a complete double-standard DNA or gene silencing in response to small interfering RNA. The delivery of the negatively charged large nucleic acid is problematic in gene therapy. This can be minimized with the help of PLGA-based nanoparticles which protect and deliver nucleic acid at the desired target [16].
- Tissue engineering-PLGA application in tissue engineering is through the development of the PLGA scaffolds that are capable of including bone tissue regeneration, treat bone neoplasia and pseudoarthrosis. Since PLGA boasts a tunable degradation rate it is possible to avoid further

surgery to remove the implants, due to PLGA implants are growing rapidly in many orthopedic applications [17].

- Inflammatory diseases-The topical preparations to treat inflammatory conditions shows some side effects while treatment. Topical preparations like in-situ gel, inserts, vesicular systems, nanocarriers have been used ocular drug delivery and exhibits some limitations in considerations with bioavailability, to improve the bioavailability PLGA and chitosan-based carrier system has been used for mucoadhesive ocular controlled drug delivery. Chitosan-coated PLGA nanoparticles entrapping Atorvastatin have been synthesized and used as thermosensitive gel against ocular inflammation [18].
- Theranostics-It is an emerging field that combines diagnostics and therapeutics into multifunction nanoparticles systems. PLGA based luminescent hybrid nanocomposite modified with the mixture of polyethylene glycol and folic acid segments to co-deliver Doxorubicin and vascular endothelial growth factor (VEGF) small hairpin RNA (shRNA) [19].

Polycaprolactone nanoparticles

Polycaprolactone (PCL) is Food and Drug Administration approved biodegradable semi-crystalline polyester and also it is hydrophobic non-toxic and biocompatible. When compared to other polymers, PLC shows slow biodegradation hence, it can be highly suitable for the design of controlled release delivery systems and also used as an implantable biomaterial in various biomedical applications. PCL has been used as carrier for sustained delivery of several therapeutic molecules. It is produced by ring-opening polymerization of ε-caprolactone [20]. Several studies have reported that the PLC based nanoparticles for the delivery of various drugs, including anticancer agents, antibiotics, and anti-inflammatory agents.

Preparation of polycaprolactone nanoparticles

PCL-based nanoparticles are generally prepared by using several methods such as solvent evaporation-emulsification, nanoprecipitation and solvent displacement methods.

Solvent evaporation emulsification

Materials

PCL (Mw = 45,000 Da), Tween 80, acetone and liquid CO_2 at 99.9%

Synthesis of PCL nanoparticles

The organic phase consists of a homogenous solution of PCL in acetone and Tween 80, and deionized water made up the aqueous phase. At first, appropriate quantity of PCL was dissolved in acetone (0.6-10% w/w) in a thermostatic water bath at 40^0C, before addition of surfactant in a centrifuge tube to obtain required concentrations (0.07 and 0.14%) or ratios (1:1-16:1 w/w). The contents in the tube were mixed by using a vortex mixer for 1 min. After complete mixing, 35.8g of warm deionized water (40^0C) was added, and the tube is placed back on the vortex mixer for 5 min to get a homogenous emulsion [21].

Applications of PCL nanoparticles

PCL based nanoparticles are widely used in implants in various tissues, extensively 3D scaffolds to promote repair and regeneration in bone, skin or other tissues.

- Drug delivery-PCL nanoparticle based drug delivery systems has shown efficiency of controlled and targeted drug delivery, high capability to cross various physiological barriers and reduced systemic side effects and it also shows excellent therapeutic potential due to high permeability, good biocompatibility and also it has ability to be excreted totally from the body once bioresorbed [22].
- Bone tissue regeneration-PCL is most common material in fabricating scaffolds. The slow degradation of PCL allows tie for bone remodeling and can also be manipulated to adjust the polymers biodegradation rates and also it is one of the most preferred polymers for extrusion-based 3D printing due to its melting temperature of 55-60^0C [23].
- Wound healing-PCL is widely used in the biomedical applications mainly in wound healing and tissue engineering. Due to its biodegradability, it is used in the preparation of scaffolds for wound repair and bone tissue regeneration and it has excellent viscoelastic and rheological properties in comparison to its resorbable-polymer

Characterization of polymeric nanoparticles

Characterization of nanoparticles is a branch of nanometrology which deals with the measurement of physical and chemical properties of the nanoparticles. There are various types of characterization techniques used for polymeric nanoparticle characterization.

1. Fourier transformed infrared spectroscopy (FTIR): It is a spectroscopic technique which is based on the measurement of vibrational transitions between different excitation states of molecules and it can be also used as a quantitative tool in some specific conditions. It is widely used in the nanomedicine field but also in a variety of scientific field. FTIR is used to confirm the attachment of biomolecules onto nanoparticles surface, and it results in a band pattern as a function of the chemical groups [25].
2. Differential scanning calorimetry (DSC): It is a technique that continuously measures the apparent specific heat of a system as a function of the temperature. It is used to determine the stability and structure of nanoparticles and it is also used to determine the conformation, since material transition will change depending upon the nanoparticle composition [26].
3. High-performance liquid chromatography (HPLC): It is the most used type of chromatography for colloidal nanosystem studies and also for other type of materials (e.g., proteins). It is used for the fine quantification and separation of drugs. The advantages of HPLC are the high resolution, the low volumes required and an easy, rapid and economic manipulation [27].
4. UV-Visible spectroscopy: It is a spectroscopy type that emits radiation of wavelength between 190 and 800 nm, widely used for the quantification of compounds concentration and also size and shape in some cases. It has been used to determine the conjugation and ratio of conjugation of biomolecules to nanomedicines. It is the simple, fast and cost effective technique that can be applied for variety of nanomaterials [27, 28].

5. Thermo gravimetric assay (TGA): It is a type calorimetric technique which measures the weight loss of the sample. It is useful to determine the amount of nanoconjugation, since the change in the nanoparticle composition produces changes in the temperature weight loss [27, 28]
6. X-ray diffraction (XRD): It is a non-destructive testing technique, which helps in examining wide variety of materials including minerals, polymers, metals, semiconductors, plastics and ceramics. XRD is used for examining and characterizing the position of atoms, arrangement of atoms in each unit cell and spacing between the atomic planes [29, 30].

Discussion

In discussion, the field of nanotechnology has covered the way for the development and application of polymeric nanoparticles, which play a crucial role in various biomedical and technological advancements. Nanoparticles, with sizes ranging from 1 to 100 nm, exhibit diverse shapes, sizes, and structures, making them versatile for different applications. They can be categorized into different classes, including fullerenes, metal nanoparticles, ceramic nanoparticles and polymeric nanoparticles.

Polymeric nanoparticles, specifically, have gained significant attention for their use in drug delivery and various biomedical applications. They offer advantages such as good biodegradability, biocompatibility, high drug-loading capacity, low toxicity, controlled drug release and improved therapeutic effectiveness. Two main forms of polymeric nanoparticles are nanospheres and nanocapsules, acting as reservoir and matrix systems respectively.

Polymeric materials used for nanoparticle preparation can be classified into natural and synthetic polymers. Natural polymers, derived from plant or animal sources, are often biocompatible and cost-effective. Examples include cellulose, chitosan, alginates, and gelatin. Chitosan, in particular, has notable properties like biodegradability, biocompatibility, and antimicrobial activity, making it suitable for drug delivery applications The preparation method used for chitosan nanoparticles is ionic gelation method. Albumin nanoparticles, a type of natural polymeric nanoparticle, have gained attention due to their biological origin, biodegradability, and biocompatibility. Albumin, a natural protein, is sourced from various origins such as egg white, bovine serum, and human serum. These nanoparticles are prepared by using desolvation method. Albumin nanoparticles find applications in cancer therapy, kidney disease treatment, rheumatoid arthritis, and more.

Synthetic polymers, on the other hand, are created through polymerization reactions and offer tunability and controlled properties. Examples include : Poly(glycolic acid), poly(lactic acid), poly(caprolactone), poly(lactic-co-glycolic acid), poly(acrylic acid), poly(vinyl alcohol), poly(cyanoacrylates). Poly (lactic-co-glycolic acid) (PLGA) nanoparticles, a widely used synthetic polymer, have advantages such as controlled and sustained release, low cytotoxicity, and biocompatibility. These nanoparticles are prepared by emulsion-solvent evaporation method. PLGA nanoparticles find applications in cancer therapy, gene therapy, tissue engineering, and inflammatory diseases. Polycaprolactone (PCL) nanoparticles, another synthetic polymer, are biodegradable and biocompatible, making them suitable for controlled release delivery systems and implantable biomaterials. For the preparation of PCL nanoparticles solvent evaporation emulsification method is used. PCL nanoparticles are used in drug delivery, bone tissue regeneration, wound healing, and more.

Characterization of polymeric nanoparticles is crucial for understanding their properties and ensuring their effectiveness. Various techniques such as Fourier-transformed infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), high-performance liquid chromatography (HPLC), UV-Visible spectroscopy, thermogravimetric assay (TGA), and X-ray diffraction (XRD) are employed for nanoparticle characterization.

In summary, polymeric nanoparticles, whether natural or synthetic, offer a wide range of applications in drug delivery, disease treatment, diagnostics, tissue engineering, environmental protection and various biomedical applications. As research in this field advances, further innovations and applications are expected to emerge, contributing to the ongoing progress in nanomedicine.

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