

Drug Polymer Nanoparticles: An Advancement in Biomedical Solutions and Targeted Drug Delivery

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Abstract: Polymer nanoparticles (PNPs) are compact particulate systems typically ranging from 10 to 1000 nm in size and have emerged as versatile platforms in modern biomedical research. Their growing importance stems from a unique combination of physicochemical properties, including tunable size, surface functionality, high drug loading capacity, and favourable biocompatibility. These features enable PNPs to act as efficient matrix carriers capable of encapsulating, protecting, and co-delivering a wide variety of therapeutic agents, including small molecules, proteins, and nucleic acids, within a single targeted delivery system. One of the key advantages of PNPs lies in their ability to improve both pharmacokinetic and pharmacodynamic profiles of drugs. By controlling drug release, enhancing solubility of poorly water soluble compounds, and reducing premature degradation or clearance, PNP-based systems can increase therapeutic efficacy while minimizing systemic toxicity. Targeting ligands can be incorporated on the nanoparticle surface to promote site-specific drug delivery, further improving treatment outcomes. A range of preparation techniques has been developed for the fabrication of advanced PNPs. These methods are generally classified according to the underlying particle formation mechanism, including polymerization-based approaches that generate nanoparticles directly and techniques that utilize preformed polymers. Advances in nanotechnology and polymer chemistry have enabled precise control over nanoparticle composition, morphology, and surface characteristics, leading to the development of sophisticated colloidal drug delivery systems. The integration of diverse nanomaterials into PNP formulations has further expanded their functional scope, significantly influencing the pharmacological and biopharmaceutical behavior of encapsulated drugs. Owing to their biocompatibility and design flexibility, PNPs have found broad applications in the treatment of cancer, neurodegenerative diseases, central nervous system disorders, and other complex medical conditions. This review elaborates on these aspects, highlighting the potential of PNPs as adaptable and powerful tools in next-generation therapeutic strategies.

Keywords: polymer nanoparticles, liposomes, drug delivery, targeted therapy, disease cure

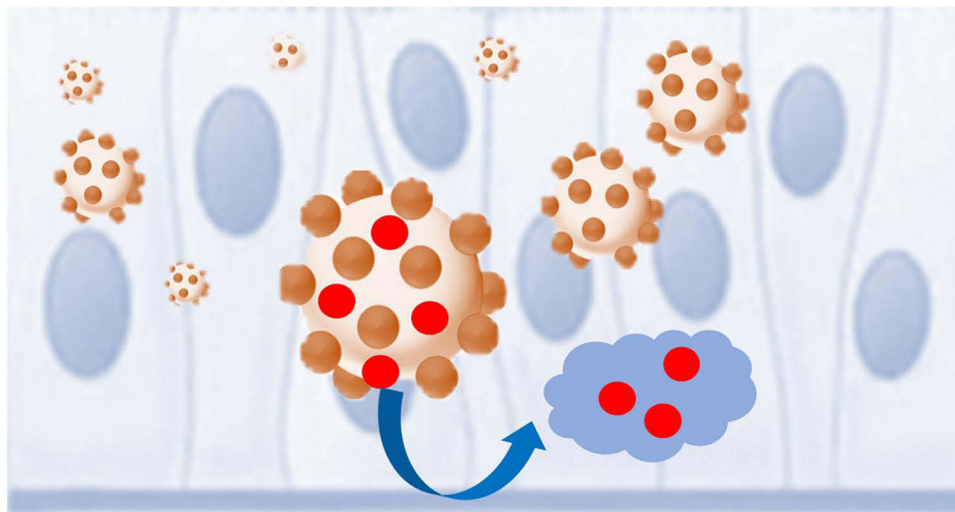
Introduction

The class of natural or artificial materials known as polymers is made up of large molecules known as macromolecules. The size of polymer nanoparticles (PNPs) ranges from 1 to 1000 nm. Active chemicals trapped at the surface are adsorbed onto the polymeric core. Polymers possess advantageous characteristics when used as carriers in targeted medication delivery systems, making them a suitable choice of material in such systems. Polymer nanoparticles have different shapes, are easy to produce and engineer, and show interesting biomedical properties.¹ These macromolecular materials dissolve, entrap, encapsulate, adsorb, or chemically attach therapeutically active ingredients.²

Polymers are light materials with several very interesting and versatile properties and can be used in a vast number of various applications. PNPs are formed variously by molding to construct diverse structures like monolayers, bilayers, thin films, and a nano-coated film that is synthesized by different methods such as film casting, spin-coating, dip-coating, and printing.³ Conducting polymers are a key element in various sectors, eg, electronics, sensors, photonics, pollution control, environment, and biotechnology.^{4,5} Due to their nanosize, these polymer-based nanoparticles possess superlative



Graphical Abstract



traits. Without changing the nature of the materials, the bulk polymer is converted into a nano-sized polymer that provides tantalizing new features. By transforming polymers into polymer nanoparticles, physicochemical property modifications will ultimately introduce the functions of nanoscience and nanotechnology.^{6,7}

PNPs are efficient tools in terms of transportation and targeting of drugs, proteins, and genes to a specific cell that is needed. Their minute size not only allows them to remain stable during blood circulation but also facilitates their penetration through cell membranes. Polymers are essentially perfect materials to fabricate various molecular designs, which can be further combined with special properties for more efficient medicinal applications.⁸ Nanomedicines were created based on PNPS across various types of nanoparticles,⁹ hydrogel nanoparticles,¹⁰ metal-organic frameworks (MOFs),¹¹ liposomes,¹² drug nanoparticles,^{13–15} etc as well as different sizes and shapes.

As depicted in Figure 1, the PNPs can be developed and synthesized in many different forms such as spherical polymer micelles, dendrimers, nanodiscs, nanospheres, nanoring polymersomes, and nanorods. These figures are what mainly cause the remarkable difference of their functions.

Improved drug pharmacokinetics and bioavailability, less toxicity, and the potential to increase therapeutic dosage are all benefits of PNP-based drug delivery systems converted into nanomedicines.¹⁶

PNPs' enhanced stability and simplicity of manufacture position them as a substantial advance over conventional oral and intravenous administration techniques. With reduced toxicity and adverse drug reactions, they can be utilised in drug delivery processes, including for tissue engineering and organ distribution.

Functionalization of PNPs can occur using drugs, biomolecules, targeting agents, and other nanoparticles as shown in Figure 2. Their large surface area and small size aggregation, however, make physical handling difficult in both liquid and dry powder form. The main disadvantage is the preparation process's usage of organic solvents, which can damage physiological systems and the environment, and ruin some pharmaceutical drug molecules.^{2,17,18}

Polymer-based nanoparticles are a colloidal system made from natural or synthetic polymers. They retain significant advantages over other nanocarriers like micelles, liposomes, and inorganic nanosystems. The polymer has two types of nanoparticles, viz., natural and synthetic PNPs, which differ based on the preparation of nanoparticles. The natural polymer which has been produced naturally from plant origin or animal origin that dissolves in water is named natural hydrophilic polymer. For examples- starch,¹⁹ algin,²⁰ pectin,²¹ xanthan gum,²² insulin, agarose etc. are natural hydrophilic polymers. The choice of polymer in polymeric nanoparticle (PNP) synthesis is a critical factor that directly influences the physicochemical properties, stability, and biological performance of the nanoparticles. Biodegradable

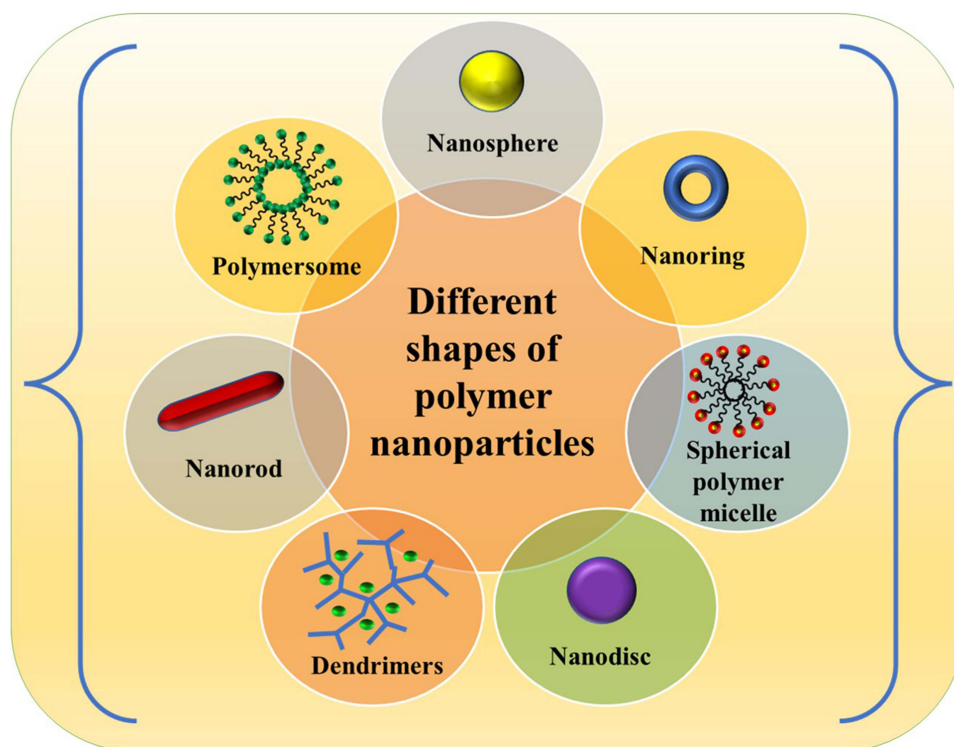


Figure 1 Different shapes of polymeric nanoparticles.

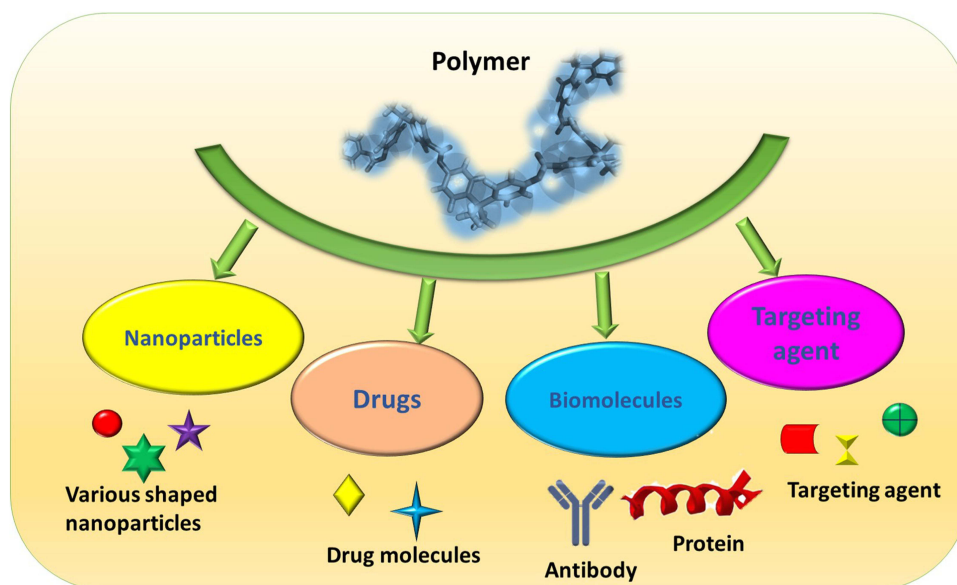


Figure 2 Possible conjugations of polymer nanoparticles with nanoparticles, drug molecules, and targeting agents.

polymers, such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and natural polymers like chitosan and alginate, are commonly selected due to their biocompatibility and safe degradation products. The polymer's molecular weight, hydrophilicity or hydrophobicity, and functional groups determine drug loading efficiency, release kinetics, and surface characteristics, which in turn affect cellular uptake and biodistribution. Additionally, polymers can be tailored or functionalized to provide stimuli-responsiveness, targeting capabilities, or prolonged circulation times. Therefore,

polymer selection is guided by the intended therapeutic application, the nature of the encapsulated drug, and the desired pharmacokinetic and pharmacodynamic profile, ensuring optimal efficacy and safety of the PNP formulation.

Synthetic polymers, including Polyacrylic acid (PAA), Polyethylene glycol (PEG), Polyvinyl pyrrolidone (PVP), and Polylactic acid (PLA), are chemically synthesized and utilized in biotechnology, pharmacology, and chemistry. These polymers, extracted from regenerative sources, have been approved by the FDA as drug conjugated carriers for clinical use.²³

- a. Polyacrylic acid (PAA) is a homopolymer of acrylic acid which is cross-linked with allyl ether propylene. It has the potential of absorbing and retaining water and also swells many times to its original volume so it is used in disposable diapers.²⁴
- b. Polyvinyl pyrrolidone (PVP) is a binder used in tablet formation, synthesized by polymerizing vinylpyrrolidone in water or isopropanol. Its molecular weight ranges from 40,000 to 360,000, and it is widely available in different grades.²⁵
- c. Polyethylene glycol (PEG) is a promising material for drug delivery due to its high drug loading ability, biocompatibility, biodegradability, extended circulation half-life, and simple functionalization.²⁶
- d. Polylactic acid (PLA) is a significant polymer suitable for synthesizing polymeric nanoparticles due to its biodegradability and biocompatibility properties. Due to its low molecular weight, PLA is chosen as a drug carrier due to its shorter degradation time, accelerating the formation of a required drug delivery system in multiple formulations.²⁴
- e. Polycaprolactone (PCL) - PCL is biodegradable polyester. PCL is formed by ring-opening polymerization of ϵ -caprolactone by using a catalyst like stannous octanoate. Various drugs can be encapsulated within PCL used for targeted drug delivery. PCL is conjugated with starch to obtain a good biodegradable material.²⁷
- f. Poly(lactic-co-glycolic acid) (PLGA)- PLGA, a biocompatible and biodegradable polymer, is under study as a delivery vehicle for proteins, drugs, and macromolecules like peptides, RNA, DNA, and RNA due to its tunable mechanical properties and its long-term stability.^{28,29} Drugs were released at specific doses without surgery, allowing active PLGA degradation. The physical properties of the polymer-drug matrix were adjusted to achieve the desired dosage and release intervals, based on factors such as polymer molecular weight, lactide-glycolide ratio, and drug concentration, depending on the type of drug.^{30,31}
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the desired dosage and release intervals, based on factors such as polymer molecular weight, lactide-glycolide ratio, and drug concentration, depending on the type of drug.^{30,31}

Synthetic hydrophobic polymers are those which are not soluble in water or other polar solvents such as epoxides, polystyrene, polyvinylchloride (PVC), polystyrene, polyisobutylcyanoacrylates, polymethyl (meth)cyanoacrylates, poly (butylcyanoacrylates), and poly (alkyl cyanoacrylates).^{32,33}

Drug therapies have long been a cornerstone of medicine, yet more than half of the currently approved medications suffer from low solubility and weak permeability, limiting their clinical utility.³⁴ Polymer-drug conjugates, particularly those utilizing drug-loaded polymeric nanoparticles, present a highly promising therapeutic strategy. This method involves the attachment of sensitive bioactive molecules—including proteins, peptides, hormones, enzymes, and growth factors—to a hydrophilic polymer backbone through reversible, physiologically degradable linkers. These linkages protect encapsulated and potentially fragile therapeutic agents from premature enzymatic degradation and significantly prolong their circulation half-life, thereby enhancing the potential for intestinal absorption and systemic bioavailability. It is to be noted that a sustained presence in the bloodstream increases the likelihood that the conjugate will interact with its intended molecular target, establishing a controlled delivery system that enhances therapeutic efficacy while also narrowing the therapeutic window. By meticulously adjusting essential physicochemical properties such as surface charge, hydrodynamic diameter, and biocompatibility, these polymer-drug conjugates can achieve targeted and effective delivery to the specific site of action.^{35,36}

Given their unique pharmacokinetic behavior, these entities are regarded as novel chemical entities distinct from the parent compound, and they are incorporated into standard pharmaceutical formulations by being physically entrapped within the carrier matrix.^{13,37} Ongoing investigation is directed at enhancing the absorption of the drug, achieving disease-targeted delivery, improving solubility, minimizing toxicity, and amplifying the therapeutic efficacy of bioactive agents by surmounting biological barriers.^{38–40} The employment of nanoparticles in biomedicine is underpinned by their size-dependent physical and chemical characteristics, which modify their biological behavior in ways not observed with bulk materials.⁴¹

Polymer is a macromolecule that is composed of repeating units that are organized in a chain-like structure exhibiting multiple compositions and properties. Polymeric nanoparticles (PNPs) represent a significant advancement in the field of drug delivery and are also utilized in biosensing and bioimaging applications.⁴² Their growing importance in targeted therapies is attributed to their ability to accumulate in specific tissues, exhibit low toxicity, and retain drugs effectively. The method of production typically corresponds to the chemical characteristics of the therapeutic compound, allowing for the use of either natural or fully synthetic polymers to achieve targeted delivery. Techniques such as surface modification and drug encapsulation enhance the therapeutic capacity of these nanoparticles while optimizing their distribution and retention in diseased tissues.⁴³

This review highlights the potential of PNPs for the delivery of poorly soluble, hydrophobic compounds. Although such drugs often suffer from limited bioavailability, their integration with nanoparticles can markedly improve solubilization, stability, and therapeutic indices. We focus on synthetic and loading techniques that facilitate a smooth transition of these compounds from the formulation stage to clinical impact, ensuring efficient delivery to the intended site of action while minimizing off-target effects.

Synthesis Strategies of Polymer Nanoparticles

Because of their high molecular weight and inability to pass across lipid membranes, water-soluble phytochemicals with poor absorption qualities are frequently found in drugs. Over 40% of newly developed molecules suffer from slow uptake and low water solubility, resulting in suboptimal exposure and drug delivery. To enhance the clinical usefulness of these compounds, the formulation of drug-polymer nanoparticles has become indispensable.^{44–47} These carriers stand out due to their elevated surface-to-volume ratio, their capacity to entrap active agents, and the modulation of quantum confinement effects. By shielding the drug from harsh conditions—such as extreme pH, enzymatic cleavage, and systemic degradation—they facilitate transport to the target site after administration. Achieving nanoparticles with the desired stability, release profile, and tissue targeting mandates careful selection of

fabrication techniques. Mastery of these parameters is key to transforming pharmacologically promising molecules into effective therapeutics.^{48–50}

Dispersion of Preformed Polymers

This synthesis method enhances various factors such as ligand density, biodistribution, pharmacokinetics, structural integrity, chemical uniformity, and regulated biodegradability, all of which offer significant benefits for pharmaceutical applications.⁵¹ In this technique, five various methods are prevalent.

Solvent Evaporation Method

To create emulsions, the polymer solution is prepared in volatile solvents. To create an oil-in-water or water-in-oil emulsion, emulsions are specifically prepared in aqueous solutions using emulsifying agents or surfactants such as poly (vinyl alcohol), gelatin, or polysorbate-80.⁵² Following the solvent's evaporation from the polymer, these emulsions are transformed into nanoparticle suspensions, which are subsequently permitted to diffuse through the continuous emulsion phase.^{53,54} The water-oil-water method was used to produce water-soluble drug-loaded nanoparticles.⁵⁵

Spontaneous Emulsification

This technique is an advanced solvent evaporation process referred to as solvent diffusion. It involves the creation of polymer nanoparticles within the oil phase by combining water with a water-miscible solvent, such as methanol or acetone, alongside inorganic solvents like dichloromethane or chloroform.⁵⁶ When the saturated polymer is emulsified in aqueous solutions containing stabilizers, the solvent migrates to the external phase, leading to the formation of nanocapsules or nanospheres, which is influenced by the ratio of oil to polymer. In the end, the removal of the solvent occurs via either evaporation or filtration, which is contingent upon its boiling point.

Salting Out

In this methodology, both emulsification and solvent diffusion techniques are utilized. An aqueous gel is created by dissolving the polymer alongside the active pharmaceutical ingredient in a solvent such as acetone. This process is then augmented by the addition of salting-out agents, which may be classified as either electrolytes or non-electrolytes. The inclusion of a colloidal stabilizer promotes the diffusion of acetone. To further enhance acetone diffusion and facilitate the formation of nanospheres, the oil-water emulsion is subsequently diluted with water. The extraction of the solvent and salting-out agents is performed via cross-flow filtration, highlighting the importance of selecting an appropriate salting-out agent to ensure the drug's effectiveness.⁵⁷

Nano-Precipitation

This method, commonly known as solvent displacement, is utilized in the production of polymeric nanoparticles (PNPs).⁵⁸ The underlying principle resides in the interfacial deposition of a semi-polar solvent that is compatible with water, originating from a lipophilic solution. PNP synthesis requires solvent and non-solvent phases, with polymers like polylactide being commonly used,^{59,60} biodegradable polyesters,^{61,62} poly(lactide-co-glycolide),^{63,64} polyalkyl-cyanoacrylate^{65,66} and eudragit.⁶⁷ In certain cases, polymers are copolymerized to reduce the recognition of nanoparticles by a reticular endothelial system to avoid drug clearance out of the body.⁶⁸ This method is a straightforward, reproducible, and efficient method for creating nanospheres and nanocapsules.⁵⁰

Dialysis

By dissolving the polymer in an organic solvent, the dialysis technique distributes small, thin polymeric nanoparticles. Solvents such as dimethyl sulfoxide, dimethylformamide, and dimethylacetamide are utilised to create poly (lactide)-b-poly (ethylene oxide) and poly (γ -glutamic acid) nanoparticles. Nevertheless, this method presents considerable drawbacks, including limited capacity for drug loading and the instability of nanoparticles.^{69–71}

Desolvation Method

A widely utilized approach for producing polymeric nanoparticles is the desolvation method. This technique involves the addition of a desolvating agent, such as ethanol or a concentrated solution of organic salts, to alter the charge and pH of

the system. In practice, a solution containing the protein and the drug is gradually combined with ethanol until turbidity occurs, signaling a shift in the concentration of hydrogen ions. To ensure the stability of the resulting coacervates, glutaraldehyde is employed, with a required minimum concentration of 40%. The nanoparticles must then undergo a reaction time of 24 hours to achieve adequate stability. Subsequently, any surplus cross-linking agent and unbound drug are eliminated from the nanoparticles via centrifugation.^{57,72} The nanoparticle powder is obtained by freeze-drying the nanosuspension, with the inclusion of 5% mannitol serving as a cryoprotectant during this process.

Supercritical Fluid Technology

Since polymer dispersion necessitates the use of hazardous organic solvents, environmentally safe, supercritical fluid technology was developed for PNP synthesis. This process creates extremely pure PNPs without the need for organic solvents by using environmentally benign solvents.⁷³ Rapid expansion of supercritical solution (RESS) and rapid expansion of supercritical solution into a liquid solvent (RESOLV) are the two principles that underpin the production of PNPs using supercritical fluid technology. A solution that extends into the surrounding air is created when the solute dissolves in a supercritical fluid. Rapid pressure decrease, homogenous nucleation, and high supersaturation all aid in the creation of well-dispersed nanoparticles.⁷⁴

Poly (perfluoropolyether diamide) droplets were created using RESS.⁷⁵ The RESOLV technique, which expands the supercritical solution into a liquid solvent rather than ambient air, has been developed as a modification of the RESS method, which generates micro-scaled products, to address its primary shortcomings.⁵⁶ Despite being widely used in tissue engineering and drug administration, high molecular weight polymers are difficult to use because of their poor solubility in supercritical fluids, as explained by the RESOLV technique. Among the medications developed in PNPS using supercritical technology were indomethacin,⁷⁶ growth factors,^{77,78} griseofulvin,⁷⁹ ibuprofen,⁸⁰ dexamethasone,⁸¹ and amoxicillin.^{82,83} These medications showed encouraging outcomes in terms of drug delivery.

Ionotropic Gelatin Technique

Polymers play a primary role in designing an oral delivery system. In this context, the use of natural polymers like chitosan and alginates instead of toxic chemical polymers in the oral delivery system enhances the permeation effect, enzyme inhibitory ability, and mucoadhesive property of the drug. Briefly, based on the solubility of the drug and polymer, they are dissolved in a weakly acidic medium or water, and the resultant solution is added to the solution containing counter ions and stabilizer dropwise under constant stirring. Spherical-shaped particles are formed due to the complexation of oppositely charged species, which results in gelation and precipitation. The particle size is reduced to the nanometric range by sonicating the resultant solution. The nanosuspension produced is freeze-dried using 5% mannitol as a cryoprotectant to obtain a fine powder of Nanoparticles.⁸⁴

Production of Various PNPs by Natural Polymers

Albumin nanoparticles are formed in an external-oil suspension using one of two procedures viz., chemical treatment in vegetable oil or thermal treatment at high temperatures (958°C–1708°C), stabilization, aqueous medium, or iso-octane emulsions. The nanospheres are produced by homogenizing the oil phase containing albumin droplets and thermally stabilizing them by heating at 1758°C to 1808°C for 10 minutes.⁸⁵ The mixture is cooled, diluted with ethyl ether, and separated by centrifugation. The drug molecules, which are not sensitive to heat, are treated with heat, resulting in the preparation of nanoparticles by emulsifying the serum albumin aqueous solution in cottonseed oil at 258°C.⁸⁶ The cross-linking agent's formaldehyde or 2,3-butadiene was used to denature albumin, resulting in particles that were stirred, isolated, and dried by lyophilization. These particles were not as fast as those releasing the drug doxorubicin,⁸⁶ hence, the purification step is the major difficulty in the removal of the cottonseed oil.⁸⁷ A technique was identified based on the isolation of natural macromolecules, in which the step of purification was simplified.⁸⁸ The procedure involves an aqueous solution of albumin, emulsified in chloroform with stabilizers and hydroxypropyl cellulose, and then cross-linked with glutaraldehyde, but lacks advantages over other techniques due to the need for chlorinated solvents.⁸⁹

Sodium alginate, a water-soluble polymer, can form gels when mixed with multivalent cations.⁹⁰ To prepare alginate nanoparticles, sodium alginate solution is added to calcium chloride solution, resulting in particles ranging from 1 to 5

nm in size.⁹¹ Gelatine is induced in a low calcium concentration, creating invisible calcium alginate gels. The internal gelation method or emulsification is used to prepare alginate particles, which can be achieved at room temperature without specific equipment.⁹² However, washing the nanoparticles is a major problem, and new approaches have been developed to address this issue.⁵⁷

Chitosan nanoparticles have been developed to encapsulate proteins like bovine serum albumin, tetanus, diphtheria toxoid,⁹³ insulin,⁹⁴ anticancer agents,⁹⁵ vaccines,⁹⁶ and nucleic acids.⁹⁷ They are enhanced by the absorption of peptides like insulin and calcitonin across the nasal epithelium.⁷² Chitosan nanoparticles are prepared by spontaneously forming complexes between chitosan and polyanions.⁹⁸ The gelation of a chitosan solution is dispersed in an oil emulsion,⁹⁹ resulting in small, spherical chitosan nanoparticles like tripolyphosphate. However, the method's drawback is the difficulty in eradicating organic solvents during particle separation, which can cause toxicity.¹⁰⁰

High Drug Loading Strategies

Post-Loading

Drug-loading nanocarriers can be created using porous-structured materials like carbon nanoparticles, MOF, hydrogel nanoparticles, and silica nanoparticles as shown in Figure 3.^{101,102} These materials offer high surface area, straightforward functionalization chemistry, and adjustable pore size and volume.^{103,104} Other non-porous materials, like proteins and polypeptides have also been studied for post-loading procedures.^{105,106}

Doxorubicin, commonly administered in a PEGylated liposomal formulation, plays a significant role in the treatment of various cancers, including leukemia.^{107,108} However, the drug's high hydrophilicity complicates its encapsulation within hydrophobic polymer matrices. Research indicates that micelles formed by the coprecipitation of Doxorubicin with PLGA-PEG can have loading capacities as low as 0.51% and loading efficiencies near 23%.¹⁰⁹ Despite these challenges, recent advancements in drug delivery techniques have improved the loading capacity of Doxorubicin, and several nanoparticle systems have shown a rapid release profile for the drug. Additionally, the conjugation of Doxorubicin to polymers is further complicated by the drug's complex structure, which features three hydroxyl groups, two phenolic hydroxyls, one ketone, and one amine group. Furthermore, its susceptibility to pH variations, heat, metal ions, and light adds complexity to its conjugation chemistry. One conjugation strategy is to couple the terminal carboxylate of PLA with Doxo by creating an amide linkage through the $-NH_2$ of Doxo.¹¹⁰

Co-Loading

Figure 3 illustrates various drug loading strategies developed during nanoparticle formation, including various systems. Formation of nanoparticles with a co-loading strategy includes proteins,⁷⁹ drug-polymer conjugate,¹¹¹ solid-lipids,¹¹²

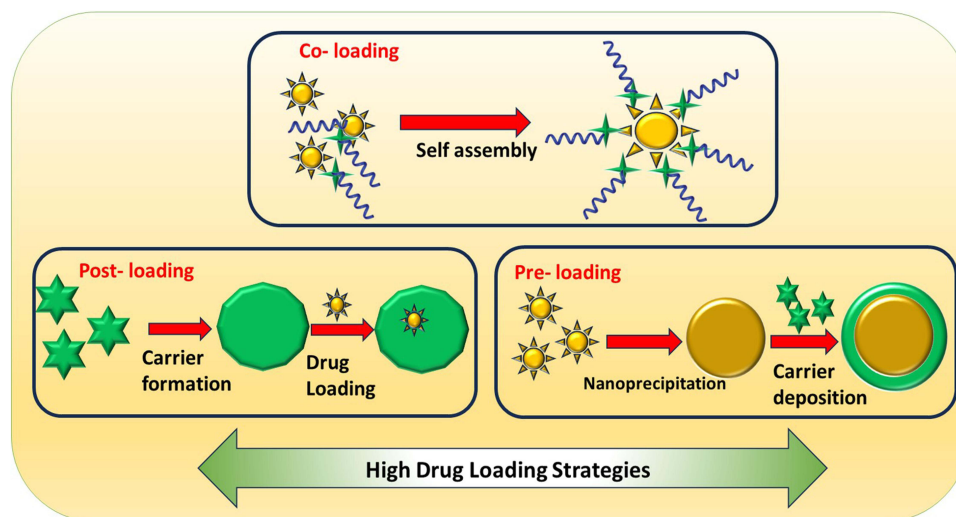


Figure 3 High drug loading strategies for polymeric nanoparticles.

proteins,⁷⁹ pure drugs,¹¹³ drug-silsesquioxane conjugate,¹¹⁴ and polymers.^{115,116} Covalent binding and electrostatic co-loading strategies have successfully achieved 18.5 to 100.0% drug loadings with nanoparticle sizes ranging from 29 to 400 nm.

Drug-polymer nanoparticles self-assemble amphiphilic drug-polymer molecules by taking use of the characteristics of hydrophilic polymers and hydrophobic medicines. DOX, 7-ethyl-10-hydroxycamptothecin, and camptothecin are a few examples.¹¹¹ A low molecular weight oligoethylene glycol chain and SN38 were used to create a drug-polymer conjugate, which resulted in nanoparticles with 36% drug loading.¹¹⁷ Using flash nanoprecipitation, carboxymethyl cellulose-based nanoparticles demonstrated a 29.5% drug loading.¹¹¹ For self-assembly, carboxymethyl cellulose was coupled to the hydrophobic anticancer medication cabazitaxel. For cisplatin-loaded silica nanoparticles with a drug loading between 35–47%, a drug-silsesquioxane conjugate was created.¹¹⁴

Drugs can be encapsulated in polymers using nanoprecipitation, which uses non-covalent hydrophobic interactions.¹¹⁸ Nonetheless, the majority of systems have low drug loadings—typically less than 10%. Improving medication loading requires careful control of mixing time. The non-ionic surfactant D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) is frequently utilised to enhance drug loading in PNPS. Nanoparticles with drug loadings ranging from 20 to 80% have been created using a variety of medications and polymers.^{115,116} A quick, scalable, and continuous bottom-up method for creating monodispersed nanoparticles with adjustable particle sizes and high drug loading is flash nanoprecipitation.^{111,119} For flash nanoprecipitation, two mixing devices—a multi-inlet vortex mixer and a restricted impinging jet mixer—have been widely utilised. λ -cyhalothrin loaded poly(ethylene glycol)-poly(D,L-lactide) (PEG-PDLLA) nanoparticles were produced using a multi-inlet vortex mixer, achieving 49.7% drug loading and 99% encapsulation efficiency.¹²⁰

Pre-Loading

One technique for creating drug nanoparticles and stabilising and protecting them is the core-shell strategy.¹²¹ Benefits of this structure include protection against degradation and regulated medication release.^{122,123} Drug delivery, biosensing, imaging, and diagnostics can all benefit from the use of polymers as the shell material because of their biocompatibility, biodegradability, and ease of production.²⁹

Camptothecin (Cpt), a topoisomerase I inhibitor from *Camptotheca acuminata*, has shown anticancer activity in animal models.¹²⁴ However, it has low aqueous solubility in its active lactone form and is rapidly converted to its carboxylate form, producing toxic and inactive molecules.^{125,126} While Cpt-polymer nanoparticles have been prepared to overcome the solubility limit of the drug, nanoparticles prepared with conventional coupling chemistry are plagued by various heterogeneities. To achieve a better-controlled polymerization, Beta-diiminate Zinc [(BDI-II) ZnN] Transcranial Magnetic Stimulation (TMS) was tested. However, the (BDI-II) ZnN (TMS)/Cpt-mediated resulted in only 61% Cpt incorporation, indicating the inefficient formation of Cpt-Zn complexes during the initiation step.¹²⁷

The drug-loaded nanospheres or nanocapsules can be produced by simple, safe, and reproducible techniques. The selection of PNPs depends on the drug's physicochemical properties, yield and entrapment potential, the use of less toxic reagents, and simplification methods. These techniques are now available for drug-loaded PNPs, showing great promise for drug delivery systems. Nanoparticles have shown promise in improving drug delivery systems, as demonstrated in the results discussed in [Table 1](#).

Formulation optimization is a critical step in developing effective polymer nanoparticle (PNP) drug delivery systems, as it directly influences stability, drug loading, release behavior, and in vivo performance. Polymer-to-drug ratio is one of the primary parameters optimized during formulation. Lower polymer-to-drug ratios may increase drug loading but often lead to particle aggregation, burst release, or poor encapsulation. Conversely, very high polymer content improves nanoparticle stability and encapsulation efficiency but can dilute the drug payload and require higher dosing volumes. Most reported PLGA- or PEG-PLGA-based systems achieve optimal performance at polymer-to-drug ratios ranging from 5:1 to 20:1, depending on drug hydrophobicity and molecular weight. The goal is to identify a ratio that balances high encapsulation with acceptable particle size and reproducible batch-to-batch characteristics. Drug loading efficiency (DLE) and encapsulation efficiency (EE) are key quantitative metrics. EE reflects how much of the initially added drug is retained within the nanoparticles, while DLE indicates the drug content relative to the total nanoparticle mass. Hydrophobic drugs generally show higher EE in polymeric matrices due to favorable polymer-drug interactions, whereas hydrophilic drugs often require strategies such as polymer modification, double emulsion techniques, or ionic

Table 1 Different Synthesis Methods of PNPs

Polymer Nanoparticle	Conjugation with	Type of Nanoparticle	Synthesis Method	References
Polyvinyl pyrrolidone (PVP) NPs	Ferric oxide (Magnetite nanoparticle)	Nanocapsules	Nanoprecipitation method	[128]
Poly(lactic-co-glycolic acid) NPs (PLGA)	Rampamycin	Nanospheres	Co-loading	[129]
Poly(lactide) NPs (PLA) Nanoparticle	Coumarin-6 (C-6)	Nanospheres	Spontaneous emulsification	[130]
Biopolymer of Poly(caprolactone) NPs (PCL)	Amphotericin B (Amp B)	Nanocapsules	Nano-precipitation	[131]
Poly(ethylene glycolic) nanoparticles PEG	Pegademase bovine	Colloidal-nanocapsules	Nanoprecipitation/Co-loading	[132]
Ovomucin NPs	Ciprofloxacin Riboflavin	Nanocapsules	Nano-precipitation	[133]
PLGA 50:50	Paclitaxel		Solvent diffusion	[134]
Alginate NPs	Silver saccharinate (AgS)	Nanospheres	Reverse emulsification	[135]
Poly(caprolactone) NPs (PCL)	Dapivirine	Nanospheres	Solvent displacement method	[136]
Poly(methylmethacrylate) copolymers NPs	Doxorubicin	Nanospheres	Emulsification	[137]
Poly(lactic acid)–poly(glycolic acid) copolymer NPs	DNA	Nanospheres	Solvent evaporation	[138]
Poly(lactic acid) NPs	Savoxepin	Nanospheres	Salting-out	[53]
Poly (lactic acid)–poly (glycolic acid) copolymer NPs	p-THPP		Solvent diffusion	[139]
Poly(methylcyanoacrylat) NPs	Triamcinolone	Nanospheres	Spontaneous emulsification	[140]
Chitosan NPs	Ascorbic acid	Gel	Ionotropic gelation	[141]
Poly(caprolactone) NPs	Cyclosporin A	Nanospheres	Solvent displacement/ Nanoprecipitation	[142]
Polyacrylamide NPs	Enzymes	Nanospheres	Spontaneous emulsification	[143]
Poly (lactic acid) NPs	DNA	Nanospheres	Solvent diffusion	[144]
Acetalated Dextran (AcDex) NPs	Hyperforin	Nanospheres	Solvent evaporation	[145]

complexation to improve retention. Optimization typically involves adjusting solvent systems, polymer molecular weight, and preparation method (eg, nanoprecipitation vs emulsion evaporation) to minimize drug loss during fabrication.

Selection criteria for final polymeric nanoparticles go beyond loading metrics. Particle size (typically 80–250 nm for systemic delivery), narrow size distribution (low PDI), surface charge, and colloidal stability in physiological media are essential. Release kinetics must align with the therapeutic goal, whether sustained release, stimuli responsiveness, or rapid payload availability. Biocompatibility, biodegradability, and use of polymers with regulatory acceptance (such as PLGA, chitosan, or PEGylated systems) are crucial for translational relevance. Ultimately, the optimized formulation is selected based on a combined assessment of physicochemical stability, drug loading performance, reproducibility, and in vitro and in vivo efficacy, ensuring both scientific robustness and clinical feasibility.

To strengthen reproducibility and translational relevance, formulation optimization of PNPs should systematically include polydispersity index (PDI), stability assessments under different conditions, and complementary physicochemical and biological parameters, alongside polymer/drug ratio and drug loading metrics.

Polydispersity index (PDI) is a critical indicator of size uniformity and formulation quality. For drug delivery applications, a $PDI \leq 0.20$ is generally considered acceptable, while values ≤ 0.10 indicate highly monodisperse systems. Low PDI is essential for predictable biodistribution, reproducible cellular uptake, and consistent drug release. During optimization, PDI is strongly influenced by polymer molecular weight, solvent–antisolvent ratio, stirring or sonication energy, and surfactant concentration. Formulations with high drug loading but elevated PDI are often deprioritized in favor of slightly lower loading but better size uniformity.

Stability under different conditions is equally important. Colloidal stability is typically evaluated in aqueous buffers (PBS, pH 7.4), cell culture media containing serum proteins, and across physiologically relevant pH values (pH 5.0–6.8 for endosomal or tumor microenvironments). Stable PNPs show minimal changes in particle size, PDI, and zeta potential over time (24–72 h short-term; weeks to months for storage studies). Temperature stability at 4 °C, 25 °C, and 37 °C is also assessed to simulate storage, handling, and in vivo conditions. PEGylation or surface charge optimization is often used to suppress aggregation and protein corona–induced instability.

Additional parameters enhancing reproducibility include zeta potential (typically ± 20 – 30 mV for electrostatic stability), drug release kinetics under sink conditions, and batch to batch consistency. Encapsulation efficiency (EE), drug loading efficiency (DLE), and polymer/drug ratio must be reported together with preparation method details to allow meaningful comparison across studies. Morphological confirmation by TEM or SEM further validates size measurements obtained from DLS.

For final formulation selection, researchers prioritize nanoparticles that combine low PDI, high colloidal stability, reproducible drug loading, controlled release, and compatibility with biologically relevant environments. Reporting these parameters in a standardized manner not only improves experimental reproducibility but also facilitates regulatory evaluation and clinical translation of polymeric nanoparticle-based drug delivery systems.

Application of Polymeric Nanoparticles

In inflammation, the immune system will be activated for abnormally long periods (months, years), which produce different proinflammatory cytokines that will induce damages to healthy tissue.¹⁴⁶ Growing evidence reveals that inflammation is the underlying cause of most chronic diseases.^{147,148} PNPs are used in the treatment of inflammation, targeted drug delivery, neurodegenerative disease, tissue engineering, infectious disease, and cancer as represented in Figure 4. Most of the therapeutic strategies were managing inflammation work by neutralizing the activity of cytokines,

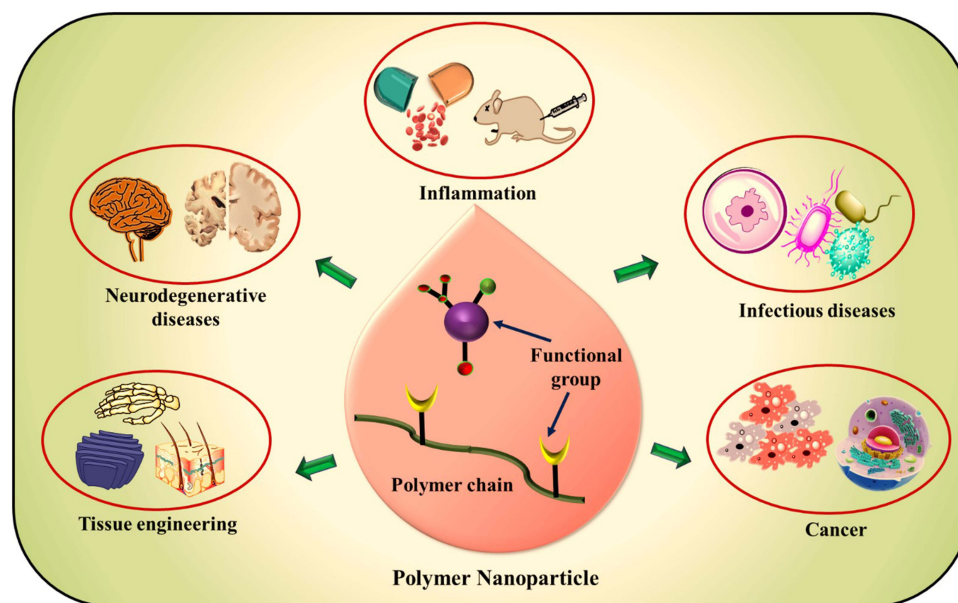


Figure 4 Contribution of drug–polymer nanoparticles to managing diseases.

downregulating cellular pathways that produce proinflammatory cytokines, or upregulating cellular pathways for the biosynthesis of anti-inflammatory cytokines.^{149,150} Due to the lack of specificity, conventional therapies (non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids) present numerous adverse effects, many novel anti-inflammatory molecules suffer from low bioavailability. Nanocarriers offer possibilities of overcoming these challenges by optimizing site-specific delivery and improving drug solubility.^{151,152} The design of such nanocarriers are often adapted from the microenvironment of the inflamed tissue, which is characterized by acidic pH value, increasing permeability, and high presence of reactive oxygen species (ROS).¹⁵² Here, naproxen was primarily modified with phenylboronic acid (a ROS-sensitive ligand) and then conjugated to activated dextran (a pH-sensitive polymer) to form dual-stimuli responsive NPs.¹⁵³ Similarly, dual-responsive smart particles were encapsulated indomethacin as an adjunct anti-inflammatory therapy to doxorubicin-loaded NPs.¹⁵⁴ Pioglitazone-loaded Poly(lactic-co-glycolic acid) Nanoparticle (PLGA NPs) were significantly more effective than oral pioglitazone to decrease the number of atherosclerotic plaques. Pioglitazone represents an antidiabetic drug that has been shown to stabilize atherosclerotic plaque and prevent ruptures.¹⁵⁵ Pioglitazone-NPs regulated the inflammation response in vivo by decreasing the number of pro-inflammatory monocytes and slightly increasing the anti-inflammatory monocytes.¹⁵⁶

PNPs have gained attention in the treatment of pain. Pain is often a lifelong disease, which drastically worsens the quality of life of its sufferers.¹⁵⁷ Numerous anti-inflammatory drugs (including Non-steroidal anti-inflammatory drugs (NSAIDs), steroids, opioids) have been formulated into biodegradable PNPs [PLGA, PLA, chitosan, Poly(N-isopropyl acrylamide (PNIPAm))] to regulate administered doses through the controlled release mechanism.¹⁵⁸

PNPs for Infectious Diseases

Antibiotic multidrug resistance (AMR) is a significant global health threat due to uncontrolled antibiotic use.¹⁵⁹ Some bacterial species have evolved into “superbugs” that can resist any available antibiotics.¹⁶⁰ Mechanisms for AMR include enzyme production, efflux protein overexpression, gene mutations, and microbial biofilm formation.¹⁶¹ Nanobiotechnology offers potential for designing formulations with physicochemical properties that facilitate drug penetration, protect against enzymes, and prolong antibiotic circulation time.¹⁶² Encapsulation of vancomycin into gelatin nanocarriers improved the survival rate of *S. aureus*-infected zebra fish. These mechanisms are being explored as potential targeting strategies for developing new antimicrobial therapies.¹⁶³

Moreover, several bacteria and fungi are known to form biofilms around their cell structures to protect themselves from the immune cells of the host. The microbial biofilm consists of polysaccharides, DNA, and proteins, which form the so-called extracellular polymeric substances (EPS) matrix.¹⁶⁴ Biofilm-targeting described it was exploited in nanobiotechnology to develop novel antimicrobials with better therapeutic efficacies.¹⁶⁴ Nanotechnological principles are applied to circumvent obstacles in the treatment of viral infections. Ritonavir and Efavirenz were incorporated into pH-sensitive polysaccharide-based nanoparticles (NPs) to enhance the solubility of these drugs.¹⁰³ In this study, various derivatives of cellulose acetate, modified with differing quantities of substituents such as carboxylic, acetate, and/or butyrate groups, were evaluated for particle formation. The findings indicated that an increase in the polymer's hydrophobic characteristics leads to heightened crystallinity, which subsequently reduces the solubility of the antiviral-loaded NPs.¹⁶⁵ Another research team developed acyclovir-loaded PLGA NPs integrated into biocompatible buccal films made from polymer-based nanoparticles aimed at biomedical applications, utilizing cellulose derivatives, PEG 200, or Carbopol 974P to enhance the bioavailability of acyclovir. In vitro, ex vivo, and in vivo studies consistently demonstrated a controlled release of the drug from the buccal films, resulting in a threefold increase in plasma concentration in vivo when compared to free acyclovir.¹⁶⁶ Similar strategies are being explored in antiviral treatments for HIV/AIDS. To have prepared stealth NPs loaded with, lamivudine, raltegravir, nevirapine, and zidovudine using Poly(ethylene glycol)/poly(methyl-methacrylate) (PEG-PMMA) and poly(ethylene-glycol)-polycaprolactone (PEG-PCL) polymers, it was shown that the antiviral NPs effectively inhibited HIV-1 infections in vitro.¹⁶⁷

PNPs for Neurodegenerative Disease

Neurological disorders, including neuroinflammatory, neurodegenerative, and neoplastic diseases, affect the central nervous system and brain. As the population ages, the incidence of these disorders increases, making them the most

expensive medical conditions globally. Neurodegenerative diseases, such as Alzheimer's¹⁶⁸ and Parkinson's,¹⁶⁹ result from progressive neuronal cell loss and have significant social and economic impacts. Current treatments only improve symptoms but do not cure these diseases due to impaired functioning of proteins and enzymes. Drugs encountering the blood-brain barrier (BBB) have limited beneficial substances, making further efforts to develop systems to enable drug passage through the BBB.¹⁷⁰

In order to increase bioavailability, decrease adverse effects, and lower medicine dosage, nanoparticles such Poly (glycolic acid) (PGA), PLA, and PLGA nanoparticles are being created to deliver therapeutic agents at precise places. These nanoparticles can deliver medications to treat neurological diseases by passing across the blood-brain barrier (BBB).¹⁷¹ Drug absorption that is size-dependent is made possible by the interactions that functionalised NPs can have with different BBB components. Because PLA-NPs have trans-activating transcriptor peptide on their surface, they improve the transport of neurotrophic peptides across the blood-brain barrier (BBB), which in turn improves BBB permeability and penetration of the central nervous system (CNS).¹⁷² In the brain, loperamide and rhodamine-123 are efficiently transported by PEGylated PLA-NPs coupled with a glyco-heptapeptide. Functionalised PLA-NPs with two targeting peptides—one specific to the blood-brain barrier and the other having a high affinity for the amyloid beta peptide 1–42—are used to treat Alzheimer's disease (AD).^{173,174} Their potential as a targeted treatment is supported by their efficacy in both in vitro and in vivo studies.¹⁷⁵ Because of its focused distribution, biomedical applications, minimal cytotoxicity, controlled release, and biocompatibility, PLGA-NPs are frequently used.¹⁷⁶ Memantine (MEM) was employed in PEG-PLGA-NPs to treat AD; it reduced beta-amyloid plaques both in vitro and in vivo and had a slower release profile than free drug solutions.¹⁷⁷

A new drug delivery system for treating Parkinson's disease (PD) has been developed using PLGA-NPs loaded with ropinirole.¹⁷⁸ This system can revert PD-like symptoms in an animal model assay. Functionalizing PLGA-NPs can also restore their function through lysosomes.¹⁷⁹ These new drugs are being developed to provide early diagnosis and regress Alzheimer's disease (AD). Curcumin-PLGA-NPs can pass through the BBB, interrupting A-beta aggregates.^{180,181} Quercetin, functionalized with PLGA-NPs or rosmarinic acid, could be a potential candidate for AD treatment.^{182,183}

Lysosomal storage disorders (LSDs) are a group of around 50 pathologies caused by inherited gene mutations in genes that normally codify lysosomal enzymes. Most LSD outbreaks occur during childhood and 75% of them have serious neurological consequences, leading to progressive neurodegeneration, physical deterioration, potential death, and functional impairment.¹⁸⁴ This highlights the need for more research into developing efficient ERT systems. Nanoparticles (NPs) can efficiently deliver drug molecules, diagnostic agents, enzymes, proteins, and nucleic acids to the CNS, making them more stable and safer than other nanocarrier systems like quantum dots.¹⁸⁵

PNPs for Cancer Treatment

One of the major drawbacks of conventional radio- and chemotherapy is the difficulty of discriminating cancer cells from healthy cells. There are other characteristics of cancer cells that can be used as targeting strategies, such as the acidic extracellular environment of cancer cells, their higher temperature than normal cells, the enzymes associated with cancer, the surface molecules expressed on cancer cells, hypoxic conditions, and reductive oxygen species (ROS). The effect of enhanced permeability and retention (EPR) alone does not appear to be as effective in humans.¹⁸⁶ PNPs are highly modified systems that can be manipulated into a certain size and surface architecture to suit the cancer microenvironment.¹⁸⁷ Polymer-based nanoparticles for biomedical applications uptake is to design delivery systems with cancer-recognizing molecules for active targeting. Several polymeric NP delivery systems of anticancer drugs (doxorubicin, paclitaxel, camptothecin) have been investigated for targeting the various type of cancers.¹⁸⁸ Furthermore, the well-known anticancer drug curcumin has been formulated into cancer-targeting delivery systems using different biocompatible polymers (PLGA, lecithin, fibroin). Encapsulating curcumin loaded into PLGA NPs and functionalizing their surface with a target ligand to block the P-glycoprotein efflux mechanism increased the cellular uptake and effectiveness of curcumin when compared to the nontarget curcumin-NPs.¹⁸⁹ Functionalized curcumin-loaded PEG-lecithin-PLGA NPs with an aptamer, which has a high affinity to adhere to epithelial cells. Compared to free curcumin, the curcumin nanoformulation with the targeting ligand showed a sixfold increase in bioavailability because of better mucoadhesion to cancer cells in the colon.¹⁹⁰ NPs for the treatment of breast cancer are found by combining three

targeting approaches. NPs targeting liver cancer were prepared by reversibly crosslinked polymer and folic acid NPs loaded with paclitaxel, which would de-crosslink under the reductive condition of the intracellular medium of cancer. PNPs provide a broad platform for the design of drug-delivery vehicles based on the pathophysiology of cancer cells.^{188,191}

PNPs for Tissue Engineering

Chitosan, a natural biodegradable polymer, has been approved by the FDA for use in various pharmaceutical formulations.¹⁹² The advancement of bone tissue engineering significantly relies on innovative scaffold designs, including a newly developed scaffold utilizing nanospheres aimed at facilitating the regeneration of bone tissue lost due to injury or disease. This composite scaffold not only promotes the formation of new bone tissue but also enhances the process of bone conduction. Additionally, bioactive glass-ceramic nanoparticles (nBGC) play a crucial role in this field, as they more closely mimic the natural composition of bone compared to metal nanoparticles. A double-layered scaffold composed of bioactive glass combined with polyvinyl alcohol and silk fibroin has shown promise in enhancing the proliferation and differentiation of bone marrow cells.¹⁹³

Moreover, both bone marrow and umbilical cord tissue have been identified as effective stimulants for bone formation and angiogenesis. Various materials, including alginate, cross-linked dextran, polycaprolactone (PCL), chitosan (PCL-CHI), poly(lactic-co-glycolic acid) (PLGA), collagen, and fibrin, have been integrated with bioactive glass to develop scaffolds for bone-tissue engineering. In vivo studies show that nanocellulose composite systems can inhibit Multiple Drug Resistance (MDR) bacteria-derived wound infections and improve skin regeneration. These nanocomposite materials demonstrate significant capabilities in promoting skin tissue repair. Polymer micelles, generated through self-assembly and emulsion evaporation techniques, are advantageous for the efficient delivery of therapeutics in disease management. The critical micelle concentration (CMC) is a vital factor in drug administration, as lower CMC values correlate with improved pharmacokinetic stability.^{192,194} A specialized group was established utilizing adjustable drug delivery micelles, which improved tumor endocytosis and penetration, surmounted biological barriers, boosted immune responses, and effectively inhibited tumor growth, metastasis, and recurrence in both in vivo and in vitro settings.¹⁹⁵ Additionally, a micelle-based drug delivery system with dual-targeting capabilities—aiming at both mitochondria and cellular structures—has been developed for the treatment of pancreatic ductal adenocarcinoma. The Dendrimer–camptothecin (CPT) conjugate, which combines camptothecin with polyamidoamine dendrimers, has demonstrated enhanced drug penetration characteristics and increased antitumor efficacy. This system has been shown to improve drug distribution at both cellular and subcellular levels, thereby augmenting its therapeutic effectiveness against PDA.¹⁹⁶

Elsewhere, modified cisplatin and dendrimers were chemically linked to create stimulating responsive clustered nanoparticles (NPs) for antitumor use, primarily concentrating in tumor sites and releasing drugs to inhibit tumor growth.¹⁹²

PNPs are crucial to contemporary drug and gene delivery systems because they increase drug accumulation in particular organs and tissues, which reduces adverse effects, improves bioavailability, and minimizes drug breakdown. With a variety of preparation techniques and biomedical uses, they are synthesised utilising both natural and synthetic polymers as shown in Figure 5. While functionalised PNPs provide precise drug release by targeting particular cellular receptors, especially in neurological diseases and cancer disorders, irregular PNPs have characteristics including slow degradation and reactivity to stimuli. Functionalised PNPs have enormous potential, especially when it comes to treating various ailments as shown in Table 2.

Comparison Between PNPs and Other Nanocarrier Systems

PNP based drug delivery systems differ from other established nanocarriers such as liposomes, micelles, and dendrimers in ways that highlight both their novelty and their translational relevance as summarized in Table 3. PNPs offer high structural stability due to their solid polymeric matrix, which allows sustained and controlled drug release over extended periods. In contrast, liposomes, while clinically successful, are relatively fragile systems. They are prone to leakage, fusion, and oxidation, especially during storage and circulation. PNPs therefore provide better control over drug retention and release kinetics, which is critical for chronic therapies and precision dosing. Compared to polymeric micelles, PNPs

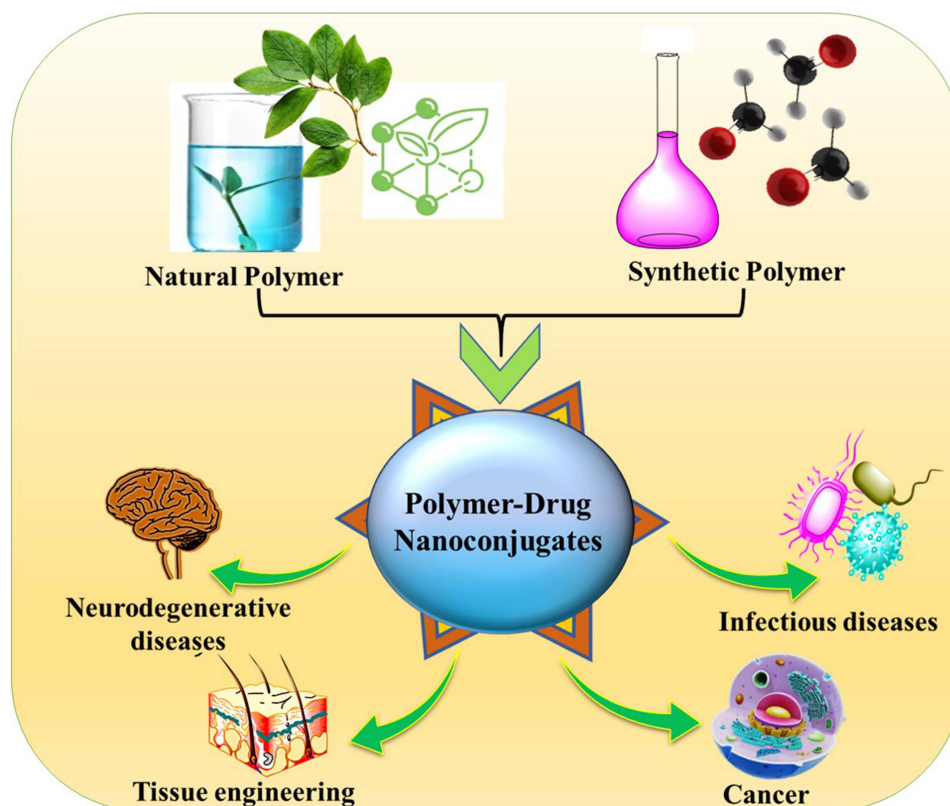


Figure 5 Drug-polymer nanoparticle systems employed in diverse biomedical applications.

exhibit superior stability *in vivo*. Micelles rely on non-covalent self-assembly and can dissociate upon dilution below their critical micelle concentration, leading to premature drug release. PNPs, formed from preassembled polymers or polymerization processes, remain intact under physiological conditions, enabling more predictable pharmacokinetics and reduced off-target toxicity.

Dendrimers offer precise molecular architecture and multivalent surface functionality, but their synthesis is complex, costly, and difficult to scale. Additionally, cationic dendrimers often raise concerns related to cytotoxicity and hemolysis. PNPs, by comparison, can be produced using scalable and industry-compatible methods such as nanoprecipitation or emulsion techniques, using FDA-approved biodegradable polymers like PLGA, chitosan, or PEGylated systems. This makes PNPs more attractive for clinical translation. From a translational perspective, PNPs stand out due to their formulation flexibility. They can encapsulate hydrophobic and hydrophilic drugs, support co-delivery of multiple therapeutics, and allow surface modification for active targeting or stealth behavior. Their compatibility with regulatory expectations, established manufacturing pipelines, and long-term safety data further strengthens their clinical potential. Overall, while liposomes, micelles, and dendrimers each address specific therapeutic needs, PNPs uniquely balance stability, versatility, scalability, and safety. This combination positions polymer nanoparticles as a robust and clinically relevant nanocarrier platform, bridging the gap between advanced nanomedicine design and real-world therapeutic application.

In vivo Investigations on Drug Polymeric Nanoparticles

Biological evaluation should include comparative studies to clearly support cytotoxicity and safety claims. Blank PNPs must be tested alongside drug-loaded PNPs and free drug to confirm that observed effects arise from the therapeutic agent and not the polymer carrier. Blank PNPs generally serve as biocompatibility controls and should show minimal cytotoxicity across relevant concentration ranges. Drug-loaded PNPs should be compared with free drug at equivalent doses to demonstrate improved efficacy, controlled release, or enhanced cellular uptake. Inclusion of uptake, apoptosis,

Table 2 Conjugation of PNPs for Biomedical Applications

Polymer Nanoparticle	Conjugation with	Application	Important Results	References
PLGA-lecithin-curcumin-PEG nanoparticles	Ribonucleic acid (RNA) Aptamers (Apts)	Targeted drug delivery to human colorectal adenocarcinoma cells	Enhance the targeting and drug delivery of CUR by enhancing the binding to HT29 colon cancer cells and improvement in cellular uptake.	[197]
Diisopropylamino ethylmethacrylate (PDPA)-amphiphilic lipid polyethylene glycol (lipid-PEG)-RGD (iRGD) nanoparticles	RGD (iRGD) peptide	Breast cancer therapy	The quick endosomal pH response of the PDPA polymer produces fast intracellular drug release and thus effective inhibition of tumor growth.	[198]
Acyclovir loaded PLGA nanospheres	Acyclovir	Buccal oral drug delivery	Buccal film permeated with acyclovir-loaded nanospheres expresses a significant approach for drug delivery of acyclovir by increased T_{max} value (6h) indicates the prolonged acyclovir delivery.	[199]
PLGA nanoparticles	Indomethacin and coumarin-6	Transdermal drug delivery and iontophoresis	Conjugation of charged nanoparticles with iontophoresis is efficient transdermal systemic delivery of therapeutic agents with high drug loading and release.	[200]
PEGylated poly (lactic-co-glycolic acid) (PLGA) nanoparticles	Doxorubicin (DOX)	Drug delivery	DOX loaded nanoparticles were found to be effective as free DOX against A20 murine B-cell lymphoma cells in culture and efficacy against subcutaneously implanted tumors.	[201]
Poly(lactide-co-glycolide)-d- α -tocopheryl Polyethylene Glycol 1000 Succinate Nanoparticles	Doxorubicin (DOX) and metformin (Met)	Breast cancer chemotherapy	The cytotoxicity of dual drug-loaded NPs was increased intracellular drug accumulation due to improved cellular uptake and reduced drug efflux which was achieved by Met and TPGS in reducing cellular ATP content and inhibiting P-gp.	[202]
Polymeric EGCG-encapsulated nanoparticles (NPs)	L-Aspartyl-L-Glutamate (AG) dipeptide	Prostate cancer prevention and therapy	EGCG encapsulating NPs led to improved anti-proliferative activity in PCa cell lines equaled to the free EGCG.	[203]
Polydopamine-Functionalized CA-(PCL-ran-PLA) Nanoparticles	Docetaxel	Target Delivery and Chemo-photothermal Therapy of Breast Cancer	Effectively enhanced drug concentration in tumor sites, reduced side effects and eliminated tumor.	[204]
Poly(lactide-co-glycolide) (PLGA) nanoparticles	Cytotoxic T lymphocytes (CTLs)	Cancer immunotherapy	Increased CTL response, which developed in important prophylactic and therapeutic ability in melanoma, bladder, and renal cell carcinoma tumor models.	[205]
Poly(lactic-co-glycolic acid) (PLGA) based PTX and SP-LPS containing nanoparticles (TLNP)	Paclitaxel (PTX) and SP-LPS (a nontoxic derivative of lipopolysaccharide)	Chemo-immunotherapy	Anticancer activity of TLNP was found to be higher as compared to PTX when analyzed in a tumor cell-splenocyte coculture system.	[206]

(Continued)

Table 2 (Continued).

Polymer Nanoparticle	Conjugation with	Application	Important Results	References
BVP-loaded poly (D, L-lactic acid) nanoparticles (BVP-PLA-NPs)	Breviscapine (BVP)	Drug delivery	BVP-PLA-NPs could prevent the capture by the reticuloendothelial system and prolong the half-life of BVP and NPs could penetrate BBB to enhance the accumulation of BVP in the brain.	[171]
³ H-ritonavir-loaded nanoparticles [Poly (L-lactide) (PLA)]	Ritonavir and trans-activating transcription (TAT) peptide	Drug delivery	Improved the CNS bioavailability and sustained drug levels for a time period that was efficient in decreasing the viral load in the CNS.	[173]
Coumarin-6- and docetaxel-encapsulated poly(D,L-lactide-co-glycolide) nanoparticles	Coumarin-6- and docetaxel	Drug delivery	The maximum cellular uptake and got maximum fluorescence concentration in the brain tissues with surface modification.	[207]
Glutathione-coated poly-(lactide-co-glycolide) (PLGA) nanoparticles	Paclitaxel	Brain cancer	The NP was not substrate for P-gp and would not be effluxed by P-gp present in the BBB.	[176]
Poly(lactic-co-glycolic) (PLGA) nanoparticles	Memantine	Alzheimer's disease	Improve the benefit of decreasing memory impairment when using MEM-PEG-PLGA NPs in comparison to the free drug.	[208]
Poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles	Ropinirole	Parkinson's disease	Brain histology and immunochemistry and behavioral testing exhibited that RP-loaded PLGA NPs can revert PD-like symptoms of neurodegeneration.	[178]
Poly (lactide-co-glycolic acid) (PLGA) nanoparticles	Brain targeting peptide [CRT (cyclic CRTIGPSVC peptide)] and curcumin	Alzheimer's disease	Reduced levels of A β , reactive oxygen species (ROS), and improved the activities of superoxide dismutase (SOD) and synapse numbers in the AD mouse brains.	[181]
Polyacrylamide-cardiolipin-poly (lactide-co-glycolide) nanoparticles	Rosmarinic acid, curcumin, and 83-14 monoclonal antibody	Alzheimer's disease	83-14 MAb improved the permeability coefficient of RA and CUR using the nanocarriers with permeate the BBB and reduce the fibrillar A β -induced neurotoxicity.	[209]

and time-dependent assays further strengthens interpretation. Such comparative biological assessments are essential for reproducibility and translational relevance. The Table 4 summarizes recent in-vivo studies on polymeric nanoparticles, highlighting animal models, dosing routes, and therapeutic outcomes. Across cancer and metabolic disease models, polymeric nanoparticles consistently improve drug efficacy, bioavailability, and safety compared with free drugs, supporting their strong translational potential. While a few polymeric nanoparticle formulations have reached late stage clinical evaluation, broad clinical translation remains limited compared with lipid nanoparticles. Regulatory challenges include ensuring large scale reproducible manufacturing, comprehensive safety profiling, and clear demonstration of benefit over existing therapies. However, advances in both patented designs and ongoing trials indicate a growing trajectory for PNPs in precision medicine and diversified therapeutic areas.[ref]

Table 3 Comparison of PNPS with Other Nanocarrier Systems Like Liposomes, Micelles, Dendrimers

Nanocarrier Type	Model Drug/Payload	Size (nm)	Encapsulation/Loading (%)	Release/Functional Outcome	Reference
Polymer Nanoparticles (PNPs)	Curcumin	Loaded 200nm spheres	Encapsulation Efficiency ~80%	Controlled drug release at various pH range	[210]
Polymer Nanoparticles (PNPs)	Quercetin	Loaded 300–400 nm, rod shaped	Encapsulation Efficiency ~94%	Sustained drug release at pH 7.4	[211]
Polymer Nanoparticles (PNPs)	5-Flourouracil	Loaded 200–400 nm, nano discs	Encapsulation Efficiency ~90%	Prolonged and controlled drug release at various pH range	[212]
Polymer Nanoparticles (PNPs)	Curcumin	~NPs: 2.6% loading measured; EE data reported	Encapsulation Efficiency ~77.3%	pH-responsive release with sustained profile; aggregation at high load noted in study system.	[213]
PNPs (PLGA – curcumin)	Curcumin	168.5 ± 2.5 (blank); ~281.6 ± 17.2 (loaded)	EE ~28.23 ± 2.49%	Improved bioefficacy and reduced toxicity in zebrafish model.	[214]
Liposomes	<i>General formulations</i>	Typically, 50–500	Variable encapsulation (dependent on cargo type)	Widely used in vaccines and therapeutics; superior biocompatibility, accommodates hydrophilic/hydrophobic drugs alike.	[215]
Polymeric Micelles	<i>General literature on micelles</i>	~10–100 (typical)	Drug loading varies (often >10% depending on system)	Enhanced solubility and circulation; often improves pharmacokinetics relative to free drug.	[216]
Stimuli-Responsive Micelles	DOX (model)	Size increases with polymer length	Qualitative <i>high drug retention</i>	Thermo-responsive assembly and controlled DOX retention in micelle shell adaptable through polymer design.	[217]
Dendrimers	Cisplatin / DOX in PAMAM dendrimers (reported in comparative datasets)	<100 (typical)	Encapsulation often >40–60% depending on generation and surface groups	High surface functionalization allows targeting but synthesis complexity and scale-up remain challenges.	[218]

Table 4 In-vivo Studies on Polymeric Nanoparticles

Polymer System	Drug/Payload	Animal Model	Dose & Route	Design	Key in vivo Outcomes	Reference
PLGA NPs (single)	Doxorubicin + Paclitaxel	Rat glioblastoma model	Not stated (IV)	Tumor-bearing rats	Combination therapy reduced tumor size, increased survival compared with free drugs	[219]
CS/ALG core-shell NPs	Insulin	Diabetic rats	Oral (dose not specified)	Diabetic rats	Substantial hypoglycemic effect, ↑insulin bioavailability; no systemic toxicity	[220]
PEG-PLGA NPs	Paclitaxel	Cancer model (reviewed)	IV (typical doses)	Mice	Enhanced antitumor effect, improved circulation vs free drug	[221]
PLGA-TPGS hybrid NP	Doxorubicin	4T1 breast tumor-bearing mice	IV	4T1 mice	Greater tumor control vs free DOX; pH-triggered release	[222]
PEG-Chitosan NPs	Betaine + Nedaplatin	Breast cancer model	IV	Tumor-bearing mice	Significant tumor inhibition in vivo	[223]
PLGA NPs	Oral polymeric nanoparticle skin penetration	Skin cancer model	Topical/skin	Murine model	Enhanced skin penetration and controlled drug release	[224]

Conclusion

Polymeric nanoparticles (PNPs) have emerged as versatile and effective platforms for targeted drug delivery, offering clear advantages in improving drug stability, bioavailability, and site-specific therapeutic action. Their performance is strongly governed by particle size, surface functionalization, polymer chemistry, and synthesis route, all of which determine biological interactions and therapeutic outcomes. This review highlights the diversity of polymer systems and nanoconjugates currently explored for biomedical applications, emphasizing how rational design enables precise control over drug loading and release at disease-specific sites.

From a clinical translation perspective, the use of biodegradable and regulatory-accepted polymers such as PLGA, PEG, and chitosan has accelerated progress toward human applications. However, large scale manufacturing, batch reproducibility, long term stability, and standardized characterization remain key regulatory challenges. Comprehensive toxicity evaluation, including chronic exposure and immunogenicity studies, is essential to meet safety requirements set by regulatory agencies.

Beyond oncology, PNPs show strong potential in treating neurodegenerative disorders, infectious diseases, inflammatory conditions, metabolic disorders, and gene-based therapies. Their ability to integrate electrical, optical, and magnetic functionalities further expands their applicability in diagnostics, imaging, and theranostics. Future research should focus on clinically relevant disease models, harmonized regulatory frameworks, and environmentally safe manufacturing processes. Despite existing challenges, continued interdisciplinary efforts will position PNP based nanomedicines as integral components of next generation, precision driven healthcare.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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