

Polymer-Based Nanomaterials for Controlled Drug Delivery: Synthesis, Characterization, and Release Studies

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ABSTRACT

Polymer-based nanomaterials have become one of the most extensively investigated platforms for controlled drug delivery because of their excellent biocompatibility, biodegradability, tunable physicochemical properties, and capacity to regulate drug release with high precision. Unlike conventional drug administration, which often produces fluctuating plasma drug concentrations and systemic toxicity, polymeric nanocarriers can improve therapeutic efficacy through sustained, targeted, and stimuli-responsive drug release. Recent advances in polymer chemistry, controlled polymerization techniques, and nanofabrication technologies have enabled the development of diverse nanostructures, including polymeric nanoparticles, micelles, dendrimers, polymersomes, and nanogels for the delivery of small molecules, proteins, nucleic acids, and gene-editing therapeutics. This review critically examines the current state of polymer-based nanomaterials with particular emphasis on synthesis strategies, physicochemical characterization, drug-loading mechanisms, and controlled release behavior. Conventional fabrication techniques such as nanoprecipitation, emulsification-solvent evaporation, ionic gelation, and microfluidic synthesis are discussed alongside advanced controlled polymerization methods, including reversible addition-fragmentation chain transfer polymerization, atom transfer radical polymerization, and ring-opening polymerization. The review further summarizes modern characterization techniques, including dynamic light scattering, transmission electron microscopy, scanning electron microscopy, Fourier-transform infrared spectroscopy, X-ray diffraction, differential scanning calorimetry, and thermogravimetric analysis, highlighting their importance in nanoparticle quality assessment. Drug release mechanisms and mathematical kinetic models are comprehensively discussed together with recent biomedical applications in cancer therapy, antimicrobial treatment, vaccine delivery, and gene therapy. Finally, the article examines current challenges related to large-scale manufacturing, regulatory approval, toxicity evaluation, and clinical translation. Collectively, polymer-based nanomaterials represent a versatile and rapidly evolving platform for next-generation precision medicine, although improvements in reproducibility, safety evaluation, and scalable manufacturing remain essential for broader clinical implementation.

Keywords: polymeric nanoparticles, controlled drug delivery, PLGA, chitosan, nanomaterials, release kinetics, characterization, biodegradable polymers

1. Introduction

Controlled drug delivery has become a major objective in pharmaceutical science because conventional dosage forms frequently suffer from poor bioavailability, rapid drug clearance, repeated dosing requirements, and undesirable systemic side effects. Traditional drug administration often results in fluctuating therapeutic concentrations that reduce treatment efficacy while increasing toxicity to healthy tissues. The emergence of nanotechnology has fundamentally transformed drug delivery by enabling nanoscale carriers capable of protecting therapeutic molecules, enhancing tissue penetration, prolonging circulation time, and releasing drugs in a controlled and programmable manner (Peer et al., 2007; Zhang et al., 2008).

Among the numerous nanocarrier systems investigated during the past two decades, polymer-based nanomaterials have received exceptional attention because of their remarkable versatility and excellent biological performance. These materials can be engineered using both synthetic polymers, such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), polycaprolactone (PCL), and polylactic acid (PLA), and naturally derived polymers, including chitosan, alginate, gelatin, and hyaluronic acid. Their physicochemical properties can be precisely tailored through molecular engineering, enabling improvements in drug encapsulation efficiency, circulation stability, cellular uptake, and targeted delivery (Makadia & Siegel, 2011; Geszke-Moritz & Moritz, 2024).

Recent advances in controlled polymerization techniques, including reversible addition-fragmentation chain transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP), and ring-opening polymerization (ROP), have further expanded the capabilities of polymeric nanocarriers. These techniques allow precise control over molecular weight, polymer architecture, and functional group distribution, facilitating the development of multifunctional drug delivery systems with stimuli-responsive behavior (Kamaly et al., 2016; Lu et al., 2024).

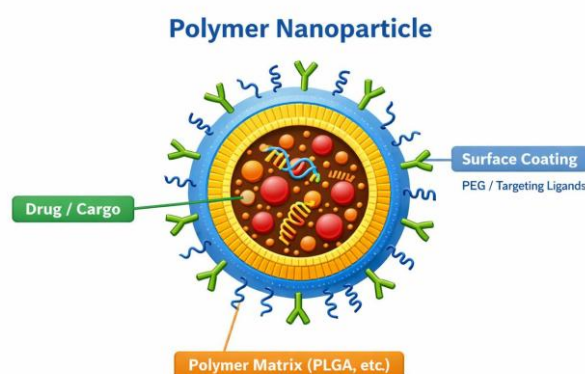
This review provides a comprehensive evaluation of polymer-based nanomaterials for controlled drug delivery by examining their synthesis methodologies, characterization techniques, drug release mechanisms, biomedical applications, and current translational challenges.

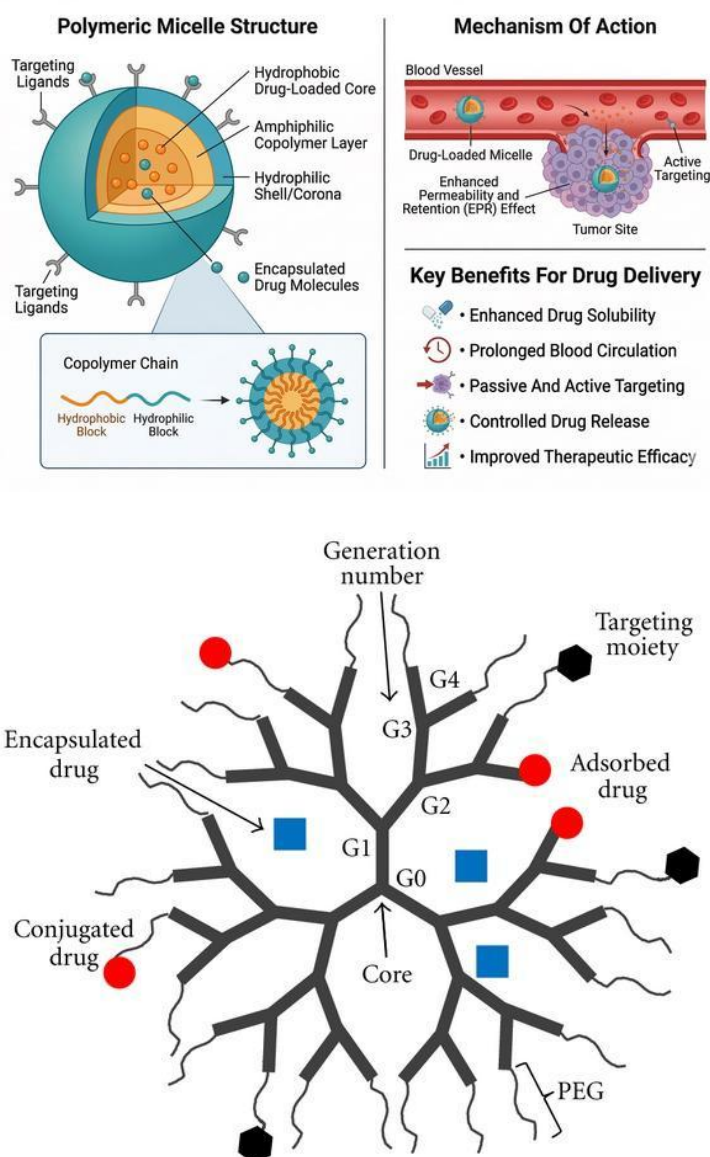
2. Literature Search Strategy

The literature included in this review was systematically identified through searches of Scopus, Web of Science, PubMed, and Google Scholar. Peer-reviewed articles published between 2007 and December 2024 were considered, while earlier landmark publications were included when necessary to establish the historical development of polymeric drug delivery systems. Search terms included polymeric nanoparticles, controlled drug delivery, PLGA nanoparticles, polymeric micelles, chitosan drug delivery, stimuli-responsive polymers, and drug release kinetics. Priority was given to highly cited original articles, comprehensive review papers, and publications from leading journals in biomaterials, pharmaceutical sciences, and nanomedicine (Geszke-Moritz & Moritz, 2024; Lu et al., 2024).

3. Polymer-Based Nanomaterials for Drug Delivery

Polymeric nanomaterials encompass a diverse family of nanoscale drug carriers whose therapeutic performance depends largely on their structural organization, polymer composition, and drug-loading mechanism. Unlike lipid-based systems, polymeric nanocarriers offer greater flexibility for molecular engineering because their architecture can be customized to regulate degradation rates, drug release profiles, surface functionality, and biological interactions (Torchilin, 2014; Kamaly et al., 2016).





Polymeric nanoparticles generally range from 10 to 500 nm in diameter and may exist as nanospheres, where drugs are uniformly dispersed throughout the polymer matrix, or nanocapsules, where therapeutic molecules are enclosed within a polymer shell. These systems exhibit high drug encapsulation efficiency, improved protection against premature degradation, and controlled release behavior. PLGA remains one of the most extensively studied biodegradable polymers because its degradation products—lactic acid and glycolic acid—are naturally metabolized through the Krebs cycle, making it particularly suitable for clinical applications (Makadia & Siegel, 2011).

Polymeric micelles are formed through the spontaneous self-assembly of amphiphilic block copolymers in aqueous environments. Their hydrophobic core efficiently encapsulates poorly water-soluble drugs, while the hydrophilic shell, frequently composed of PEG, reduces opsonization and reticuloendothelial clearance, thereby extending systemic circulation time (Torchilin, 2014). Dendrimers represent another important class of polymeric nanocarriers characterized by highly branched three-dimensional architectures containing numerous terminal functional groups that facilitate simultaneous drug loading, imaging agent conjugation, and ligand-mediated targeting (Kamaly et al., 2016).

Polymersomes possess vesicular structures similar to liposomes but exhibit greater membrane stability because of their polymeric composition. Their bilayer architecture enables simultaneous encapsulation of both hydrophilic and hydrophobic therapeutic agents, making them attractive candidates for combination therapy (Goel et al., 2024). Nanogels constitute cross-linked polymer networks capable of absorbing substantial quantities of water while maintaining structural integrity. Their swelling behavior enables environmentally responsive drug release, particularly in response to pH, temperature, and enzymatic stimuli (Singh et al., 2024).

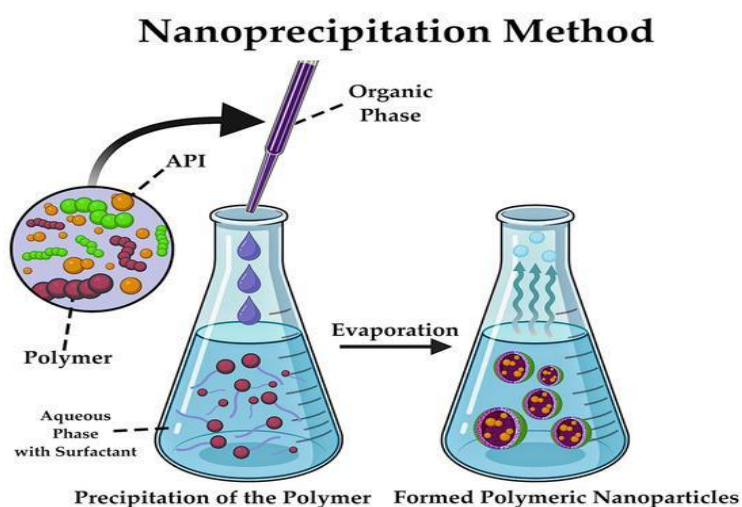
4. Polymers Used in Controlled Drug Delivery

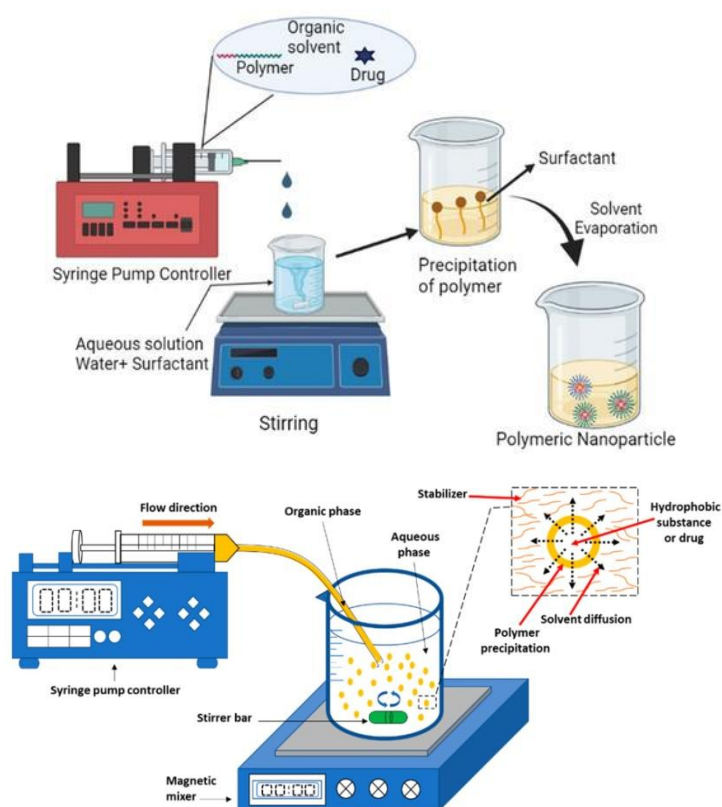
The selection of polymer materials fundamentally determines nanoparticle stability, degradation behavior, drug release kinetics, and biological compatibility. Synthetic polymers such as PLGA, PEG, PCL, and PLA provide excellent reproducibility and precisely controllable degradation profiles. PLGA has become the benchmark biodegradable polymer because its degradation rate can be systematically adjusted by modifying the lactide-to-glycolide ratio, molecular weight, and crystallinity. A 50:50 PLGA composition generally exhibits faster degradation than formulations containing higher lactide content, allowing researchers to customize sustained release durations according to therapeutic requirements (Makadia & Siegel, 2011).

Natural polymers, including chitosan, alginate, gelatin, and hyaluronic acid, offer exceptional biological compatibility because of their structural similarity to naturally occurring biomolecules. Chitosan exhibits strong mucoadhesive properties and positive surface charge, facilitating enhanced cellular uptake and gene delivery, although its limited solubility under neutral and alkaline conditions often necessitates chemical modification (Kumari et al., 2010). Hyaluronic acid has attracted considerable interest because of its ability to target CD44 receptors overexpressed in many tumor cells, thereby enhancing selective drug delivery (Gulati et al., 2024).

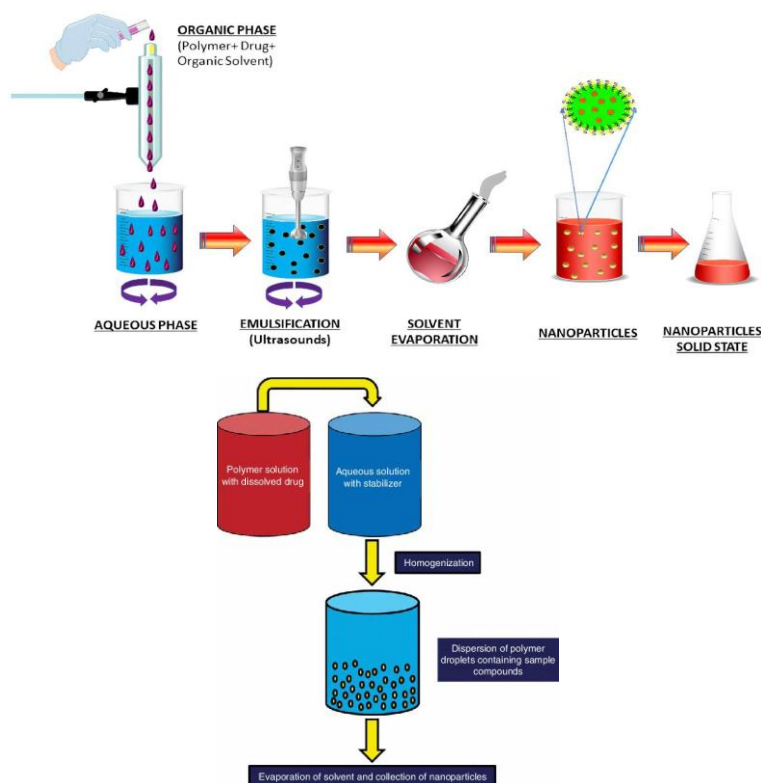
5. Synthesis Strategies

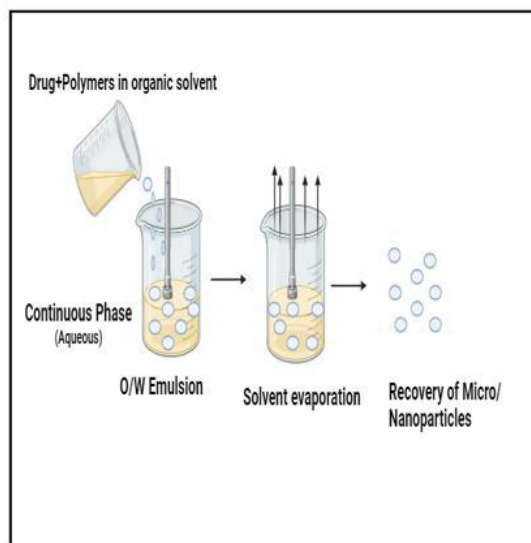
The synthesis method plays a decisive role in determining nanoparticle size, morphology, encapsulation efficiency, and reproducibility. Nanoprecipitation, also known as solvent displacement, represents one of the simplest and most widely used methods for preparing polymeric nanoparticles. In this approach, the polymer and drug are dissolved in a water-miscible organic solvent before being introduced into an aqueous phase under continuous stirring, where rapid solvent diffusion induces polymer precipitation (Mora-Huertas et al., 2010).





Emulsification-solvent evaporation remains the preferred technique for encapsulating hydrophobic drugs within PLGA nanoparticles. Single oil-in-water emulsions are commonly employed for hydrophobic compounds, whereas double water-in-oil-in-water emulsions are particularly suitable for proteins, peptides, and nucleic acids (Kumari et al., 2010).



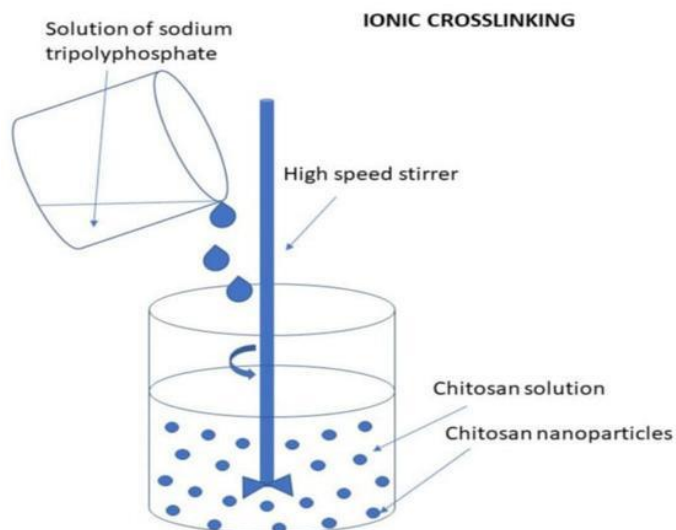
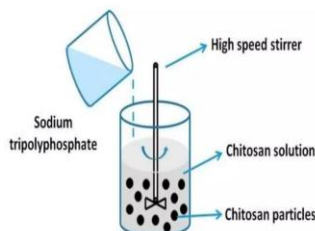


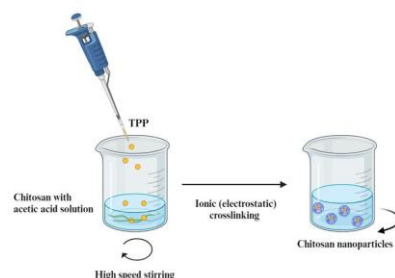
Ionic gelation has become especially important for natural polymers such as chitosan. This method relies on electrostatic interactions between positively charged chitosan molecules and negatively charged crosslinking agents, particularly sodium tripolyphosphate, allowing nanoparticle formation without harsh organic solvents (Kumari et al., 2010).

Ionic Gelation Method

- Complexation between **Positively** charged amine group of **Chitosan** and **Negatively** charged **Tripolyphosphate**.

- The process is simple, and rapid





More recently, microfluidic synthesis has emerged as a highly reproducible manufacturing platform capable of producing nanoparticles with exceptional size control through precisely regulated mixing conditions. Continuous-flow microfluidic systems offer promising opportunities for industrial-scale production while improving batch-to-batch consistency, an important requirement for clinical translation (Beach et al., 2024; Lu et al., 2024).

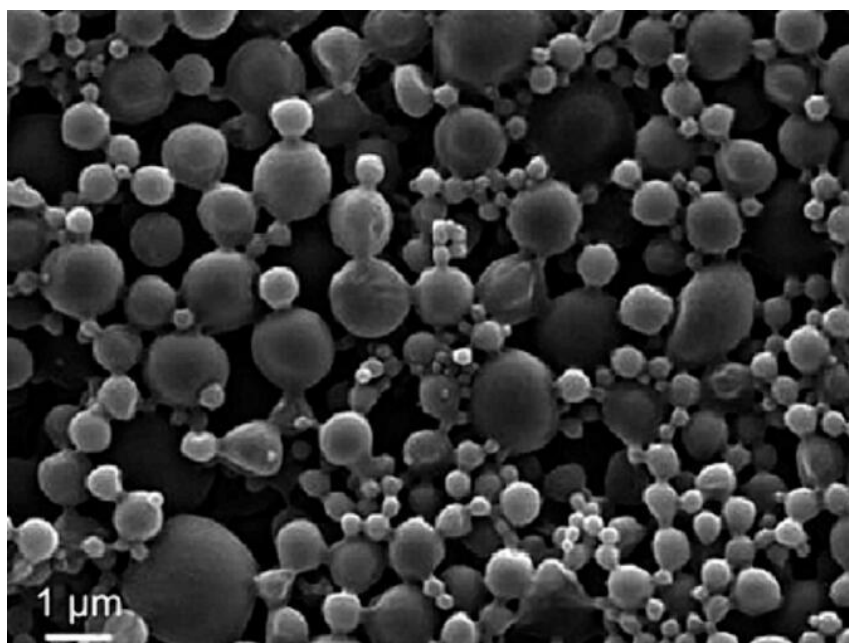
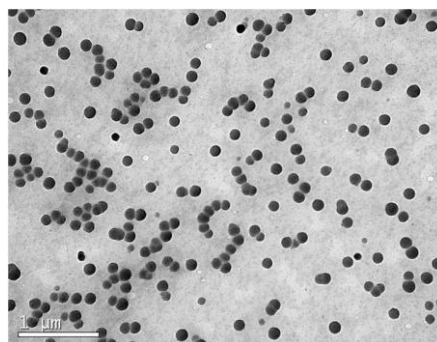
6. Physicochemical Characterization

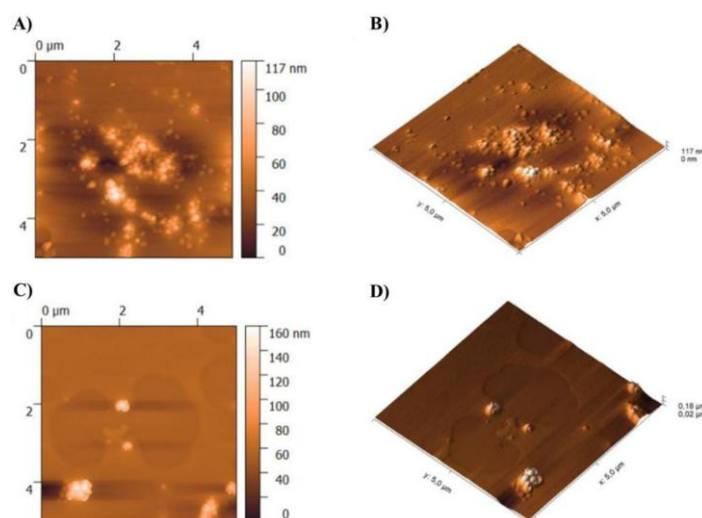
Comprehensive characterization is essential for understanding nanoparticle performance because physicochemical properties directly influence biological interactions, therapeutic efficacy, and formulation stability. Dynamic light scattering (DLS) remains the standard technique for determining hydrodynamic particle diameter, size distribution, and polydispersity index. Nanoparticles exhibiting PDI values below approximately 0.20 are generally considered relatively uniform, whereas larger values indicate broader size distributions that may compromise reproducibility (Danaei et al., 2018).





Surface charge is commonly evaluated through zeta potential measurements because electrostatic stability significantly influences nanoparticle aggregation. Absolute zeta potential values exceeding approximately ± 30 mV generally indicate improved colloidal stability through enhanced electrostatic repulsion (Danaei et al., 2018).





Morphological characterization is primarily performed using transmission electron microscopy, scanning electron microscopy, and atomic force microscopy, each providing complementary information regarding internal structure, surface morphology, and nanoscale topography (Mora-Huertas et al., 2010). Chemical characterization techniques such as Fourier-transform infrared spectroscopy and Raman spectroscopy identify functional groups and evaluate drug-polymer interactions, while X-ray diffraction determines crystalline organization and drug dispersion within polymer matrices. Differential scanning calorimetry and thermogravimetric analysis further assess thermal stability, glass transition behavior, and decomposition characteristics, thereby ensuring formulation quality and reproducibility (Makadia & Siegel, 2011).

7. Drug Loading and Encapsulation

Efficient drug loading represents one of the most important determinants of therapeutic performance because insufficient loading increases carrier burden while reducing delivery efficiency. Drug loading percentage and encapsulation efficiency are commonly calculated using standardized equations:

$$DL(\%) = \frac{W_d}{W_n} \times 100 \quad DL(\%) = \frac{W_d}{W_n} \times 100$$

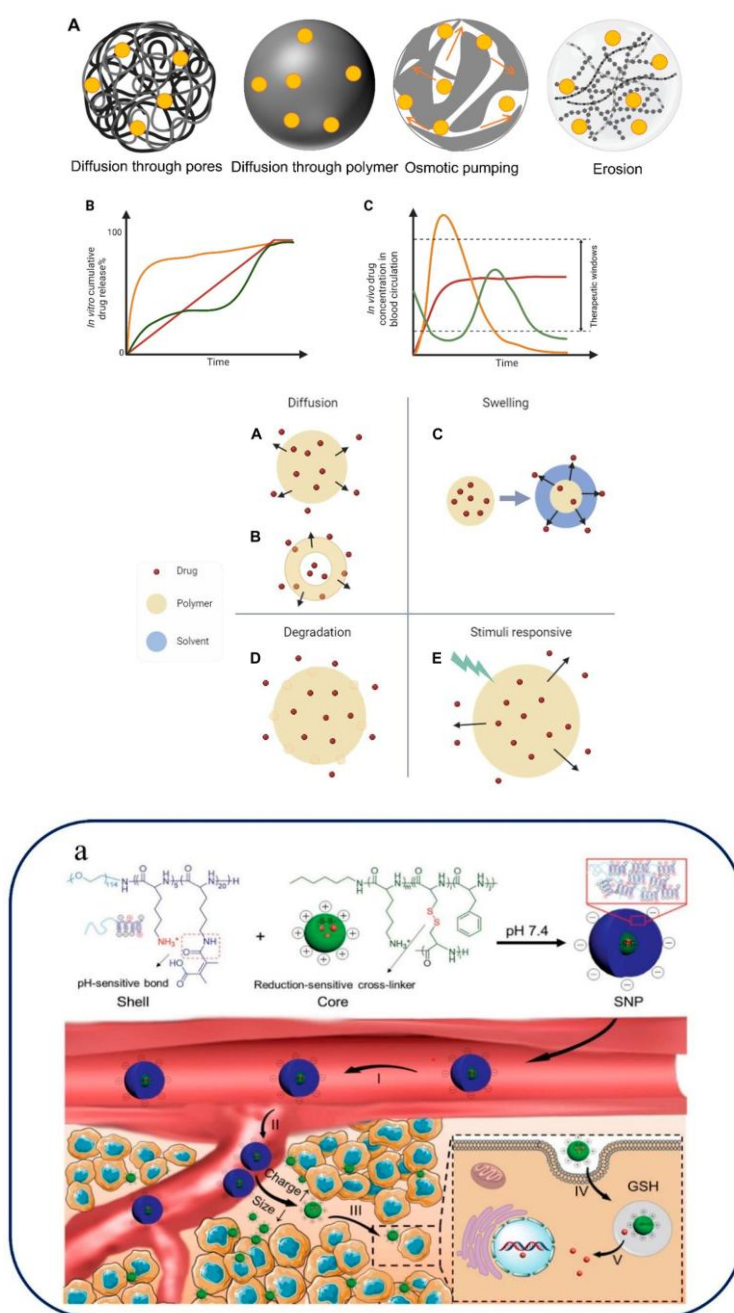
$$EE(\%) = \frac{W_e}{W_i} \times 100 \quad EE(\%) = \frac{W_e}{W_i} \times 100$$

where W_d represents drug mass, W_n denotes total nanoparticle mass, W_e indicates encapsulated drug mass, and W_i represents the initial drug quantity.

Encapsulation efficiency depends on multiple variables, including polymer composition, drug solubility, preparation method, and polymer-drug interactions. Hydrophobic drugs generally exhibit higher encapsulation efficiencies in PLGA formulations, whereas ionic interactions substantially improve loading performance in chitosan-based systems (Makadia & Siegel, 2011; Kumari et al., 2010).

8. Controlled Drug Release Mechanisms

Controlled drug release from polymeric nanomaterials is governed by multiple overlapping mechanisms whose relative contributions depend on polymer properties, environmental conditions, and drug characteristics. Most polymeric nanoparticles exhibit a characteristic three-stage release profile consisting of an initial burst release, sustained diffusion-controlled release, and a final degradation-dominated release phase (Kamaly et al., 2016).



The initial burst release commonly occurs because drug molecules located near the nanoparticle surface rapidly diffuse into the surrounding environment immediately after administration. This phase is subsequently followed by sustained diffusion through the polymer matrix, which provides prolonged therapeutic exposure. Finally, biodegradable polymers undergo hydrolytic degradation, gradually releasing the remaining encapsulated drug as the polymer structure disintegrates (Makadia & Siegel, 2011).

Hydrophilic polymers such as chitosan and gelatin additionally exhibit swelling-controlled release, in which water absorption enlarges polymer networks and facilitates molecular diffusion. Stimuli-responsive polymers further enhance therapeutic precision by responding to pH, temperature, redox conditions, or enzymatic activity. Such smart systems are particularly valuable in cancer therapy

because tumor microenvironments frequently exhibit acidic conditions and elevated enzymatic activity that selectively trigger drug release within diseased tissues (Singh et al., 2024).

9. Mathematical Models for Drug Release Studies

Mathematical modeling provides valuable insight into the mechanisms governing drug release behavior and enables quantitative comparison between different formulations. Zero-order kinetics describes systems that release drugs at a constant rate independent of concentration, whereas first-order kinetics assumes concentration-dependent release. The Higuchi model explains diffusion-controlled release from polymer matrices, while the Korsmeyer-Peppas equation serves as a widely used empirical model for identifying release mechanisms (Higuchi, 1963; Korsmeyer et al., 1983).

$$M_t/M_\infty = k t^n \quad \frac{M_t}{M_\infty} = k t^n \quad M_t/M_\infty = k t^n$$

The release exponent n provides important mechanistic information. Values below approximately 0.45 generally indicate Fickian diffusion, values between approximately 0.45 and 0.89 suggest anomalous transport involving both diffusion and polymer relaxation, and values approaching 0.89 indicate Case II transport dominated by polymer relaxation processes (Korsmeyer et al., 1983).

The Hixson-Crowell model describes systems undergoing erosion-controlled release through progressive changes in particle dimensions.

$$W_0^{1/3} - W_t^{1/3} = k t \quad W_0^{1/3} - W_t^{1/3} = k t \quad W_0^{1/3} - W_t^{1/3} = k t$$

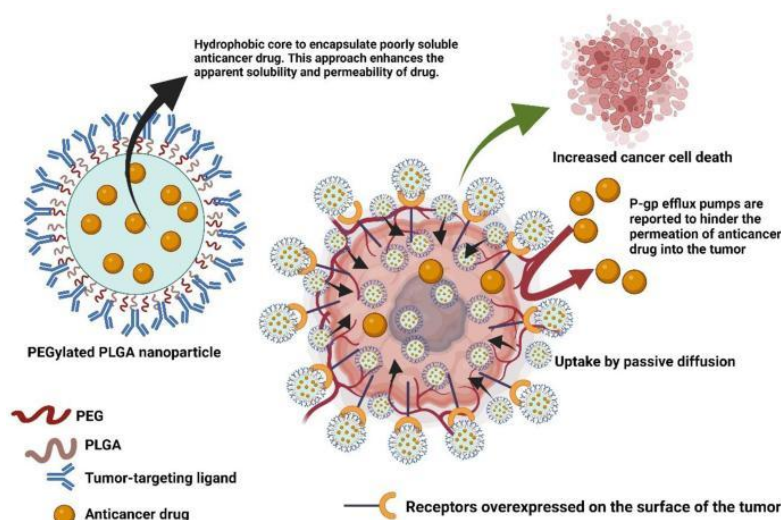
Collectively, these mathematical models provide essential tools for interpreting experimental release data and optimizing formulation design.

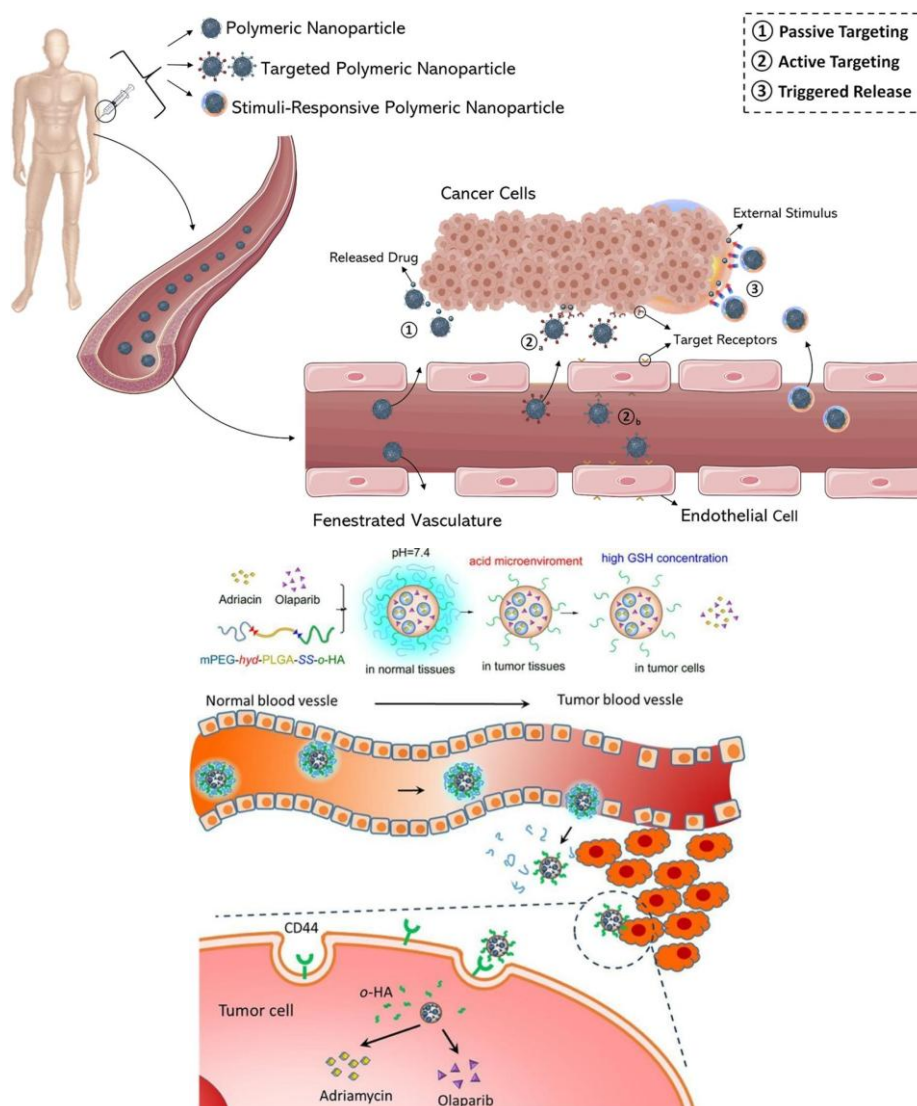
10. Biomedical Applications

Polymer-based nanomaterials have demonstrated remarkable versatility across numerous biomedical applications because their physicochemical properties can be tailored to accommodate diverse therapeutic molecules. Cancer therapy remains the most extensively investigated application, where polymeric nanoparticles improve tumor accumulation through both passive enhanced permeability and retention effects and active targeting strategies involving antibodies, peptides, folic acid, and hyaluronic acid. Controlled drug release significantly reduces systemic toxicity while maintaining prolonged therapeutic concentrations within tumors (Peer et al., 2007; Gulati et al., 2024).



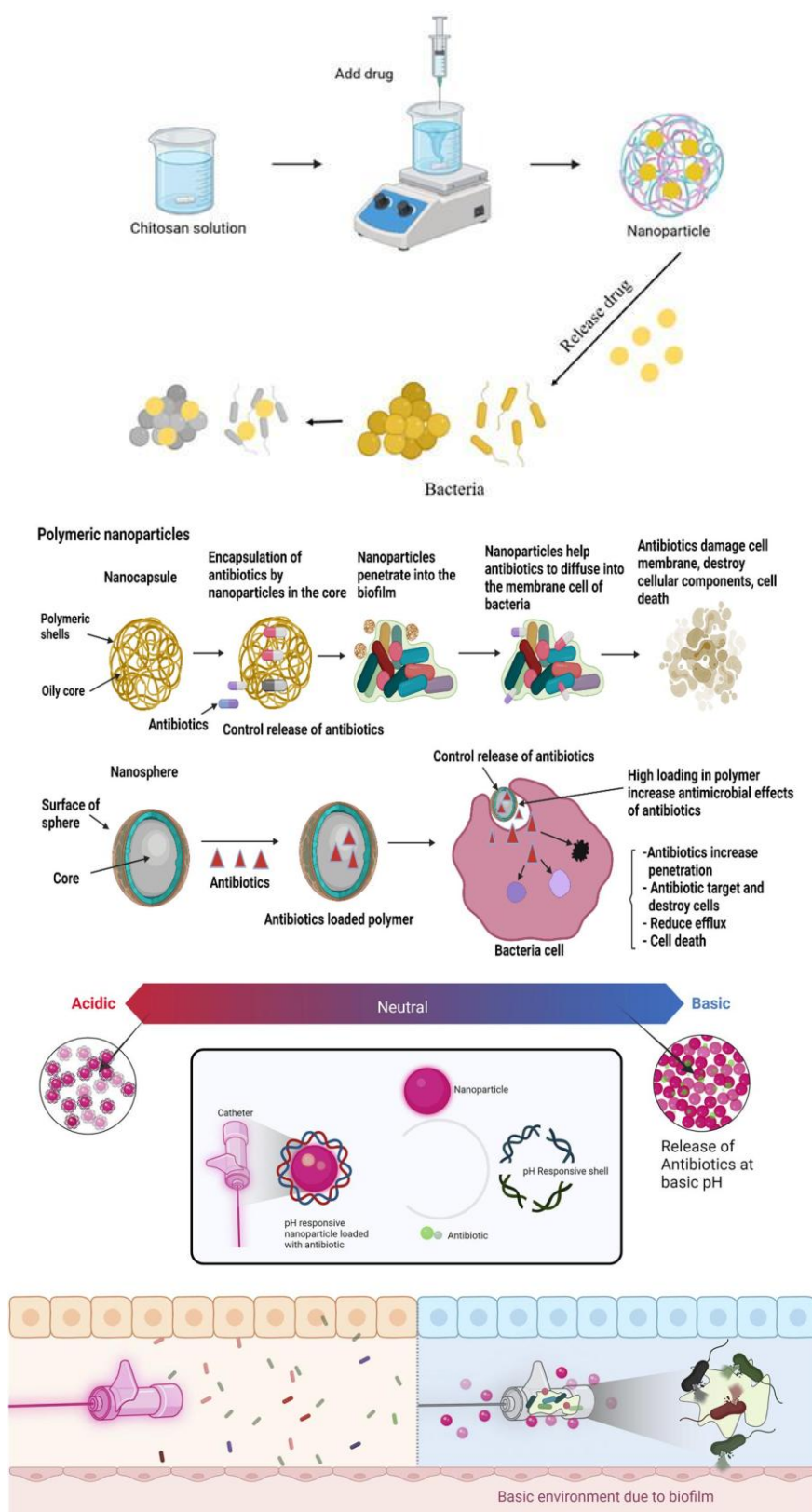
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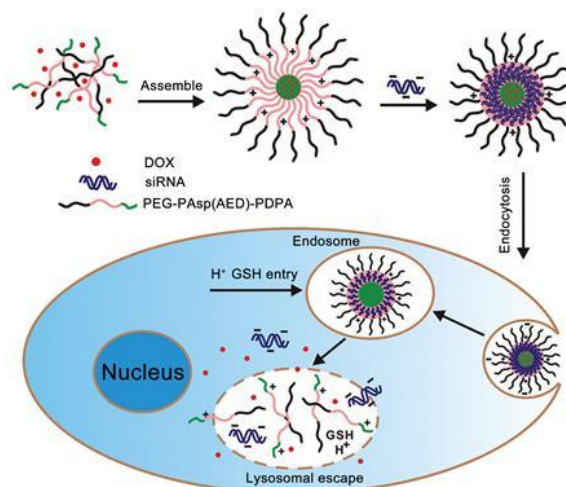
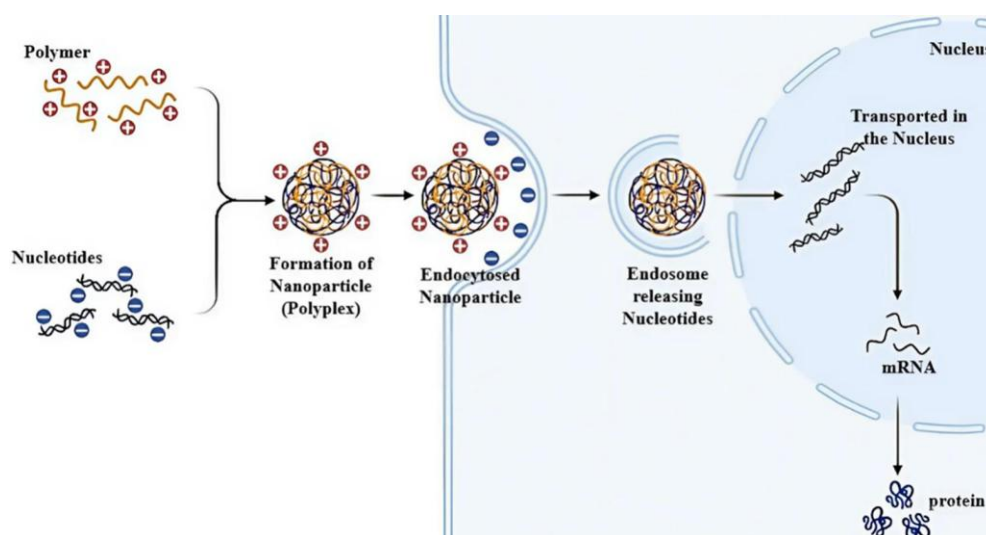
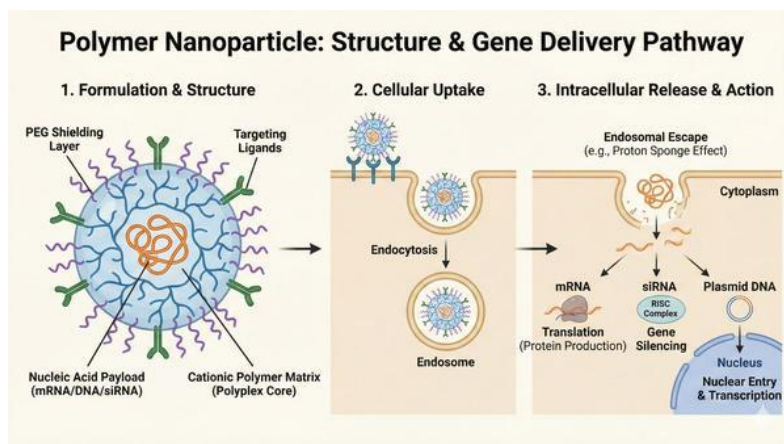


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Antimicrobial therapy represents another rapidly expanding application because chitosan-based nanoparticles exhibit intrinsic antimicrobial properties while simultaneously improving antibiotic penetration into bacterial biofilms. Controlled release formulations also reduce dosing frequency and may help mitigate antimicrobial resistance development (Kumari et al., 2010).



immunogenicity associated with viral vectors. Following the success of nucleic acid therapeutics, polymer-lipid hybrid systems have emerged as particularly promising platforms for mRNA delivery because they combine polymer stability with efficient intracellular delivery (Beach et al., 2024).



Polymeric nanoparticles have also enhanced vaccine delivery by protecting antigens against degradation, promoting controlled antigen presentation, and stimulating stronger immune responses (Lu et al., 2024).

11. Clinical Translation, Toxicity, and Regulatory Considerations

Despite remarkable laboratory success, relatively few polymeric nanomedicines have successfully reached clinical practice because translational barriers remain substantial. Manufacturing reproducibility, large-scale production, long-term safety evaluation, and regulatory standardization continue to represent major challenges for commercialization. Continuous-flow microfluidic manufacturing offers promising opportunities for improving batch consistency and industrial scalability, while quality-by-design approaches increasingly support robust pharmaceutical development (Lu et al., 2024; Beach et al., 2024).

Several PLGA-based formulations have already received regulatory approval, including Lupron Depot, Risperdal Consta, and Bydureon, demonstrating the clinical feasibility of biodegradable polymer platforms (Makadia & Siegel, 2011). Nevertheless, each new nanocarrier requires extensive evaluation regarding pharmacokinetics, biodistribution, immunogenicity, degradation products, and long-term toxicity. Although biodegradable polymers generally exhibit favorable safety profiles, nanoparticle characteristics such as particle size, surface charge, and chemical composition can influence oxidative stress, inflammatory responses, and cellular uptake. Surface modification through PEGylation and biodegradable polymer selection has reduced many safety concerns, yet comprehensive long-term toxicity studies remain necessary before widespread clinical adoption (Kamaly et al., 2016).

12. Future Perspectives

Future research is expected to increasingly integrate advanced polymer chemistry, artificial intelligence, precision medicine, and sustainable biomaterials to develop next-generation nanocarriers. Artificial intelligence-assisted formulation optimization may substantially accelerate nanoparticle design by predicting encapsulation efficiency, stability, and release behavior before experimental validation. Multi-responsive polymeric systems capable of simultaneously responding to pH, temperature, enzymes, and redox signals may further improve disease-specific drug delivery. Additionally, biodegradable polymers derived from renewable resources offer promising opportunities for environmentally sustainable nanomedicine while maintaining high therapeutic performance (Beach et al., 2024; Geszke-Moritz & Moritz, 2024).

13. Conclusion

Polymer-based nanomaterials have fundamentally transformed controlled drug delivery by providing highly adaptable platforms capable of improving therapeutic efficacy while reducing systemic toxicity. Advances in polymer synthesis, controlled polymerization, and nanofabrication technologies have enabled the precise engineering of nanoparticles with customizable degradation rates, drug-loading capacities, and release profiles (Makadia & Siegel, 2011; Lu et al., 2024). Comprehensive physicochemical characterization ensures formulation quality, while mathematical modeling provides valuable insight into release mechanisms. The expanding applications of polymeric nanocarriers in cancer therapy, antimicrobial treatment, vaccine delivery, and gene therapy underscore their growing importance in precision medicine. Although challenges related to manufacturing scalability, regulatory approval, and long-term safety remain significant, continued innovation in polymer science and pharmaceutical engineering strongly suggests that polymer-based nanomaterials will play an increasingly central role in future therapeutic technologies (Beach et al., 2024; Geszke-Moritz & Moritz, 2024).

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