

Nanostructured Polymeric Carriers for Efficient Drug Encapsulation and sustained release

Shital A. Kakade*, Komal V. Mankar, Madhavi S. Jadhav

Gouvernement Polytechnic,Awasari(Kh) Pin Code 412405,

Government Polytechnic,Karad,Pin Code 415124,

Rajashri Shahu Commerce and Science college,Wagholi,Pin Code 412207

ARTICLE INFO

Received: 02 April 2026

Revised 17 May 2026

Accepted: 28 May 2026

ABSTRACT

Nanostructured polymeric carriers have emerged as versatile platforms for overcoming important limitations of conventional pharmaceutical formulations, including poor aqueous solubility, physicochemical instability, rapid elimination, low bioavailability, nonspecific biodistribution, and dose-dependent toxicity. Polymeric nanospheres, nanocapsules, micelles, dendrimers, and nanogels provide structurally diverse environments in which small-molecule drugs, proteins, peptides, and nucleic acids can be physically entrapped, adsorbed, ionically complexed, or chemically conjugated. Their pharmaceutical performance can be modulated through polymer chemistry, molecular weight, crystallinity, hydrophilic–hydrophobic balance, particle size, surface characteristics, crosslinking density, drug–polymer affinity, and manufacturing conditions. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), polycaprolactone (PCL), chitosan, and alginate have received considerable attention, whereas amphiphilic and stimuli-responsive polymers have expanded opportunities for spatially and temporally controlled delivery. Drug release from polymeric nanocarriers generally results from interacting processes involving surface desorption, diffusion, swelling, polymer relaxation, hydrolytic degradation, erosion, and carrier disassembly. Despite substantial preclinical progress, translation remains constrained by burst release, inadequate drug loading, colloidal instability, biological barriers, scale-up difficulties, sterilization requirements, batch variability, insufficiently predictive in vitro release models, and regulatory complexity. This review critically examines nanostructured polymeric carrier architecture, polymer selection, mechanisms of drug encapsulation, fabrication strategies, characterization, sustained-release mechanisms, stimuli-responsive delivery, biomedical applications, manufacturing limitations, and future research priorities. Particular attention is directed toward relationships among material structure, encapsulation efficiency, drug loading, and release kinetics. The available literature indicates that future clinical progress will depend on establishing reproducible structure–property–performance relationships integrating therapeutic efficacy with manufacturability, stability, safety, and clinically meaningful release profiles.

Keywords: polymeric nanoparticles; nanostructured carriers; drug encapsulation; sustained release; controlled drug delivery; PLGA; polymeric micelles; nanogels; dendrimers; nanomedicine.

1. Introduction

The therapeutic effectiveness of a pharmacologically active compound depends not only on its intrinsic biological activity but also on whether an adequate concentration reaches the intended biological site and remains there for an appropriate duration. Conventional pharmaceutical formulations frequently provide

insufficient control over these processes. Poor aqueous solubility, chemical instability, enzymatic degradation, rapid metabolism, short circulation half-life, limited membrane permeability, and nonspecific biodistribution can substantially reduce therapeutic exposure. Increasing the administered dose or dosing frequency may partially compensate for inadequate exposure but can simultaneously increase systemic toxicity, produce undesirable fluctuations in plasma drug concentrations, and reduce patient adherence. Consequently, pharmaceutical research has progressively shifted toward engineered delivery systems capable of controlling the spatial and temporal disposition of therapeutic molecules (Patra et al., 2018; Mitchell et al., 2021).

Nanotechnology has contributed substantially to this transition by enabling pharmaceutical carriers whose dimensions and physicochemical characteristics can be systematically engineered. Polymeric nanoparticles are particularly attractive because polymer chemistry provides extensive control over size, shape, architecture, surface charge, functionality, degradation behavior, and responsiveness to environmental conditions. Such properties enable polymeric nanocarriers to encapsulate chemically diverse therapeutic molecules while providing opportunities to navigate biological barriers and control drug release (Mitchell et al., 2021; Beach et al., 2024).

Polymeric nanocarriers comprise several structurally distinct systems rather than a single class of nanoparticles. These include matrix-type nanospheres, reservoir-type nanocapsules, self-assembled polymeric micelles, hyperbranched dendrimers, hydrated nanogels, polymersomes, polymer–drug conjugates, and polymer-containing hybrid systems. The spatial location and molecular state of the therapeutic agent vary among these architectures. Drugs can be distributed throughout a polymer matrix, retained within an internal reservoir, partitioned into the hydrophobic core of a micelle, incorporated within a crosslinked nanogel network, associated with dendritic cavities, adsorbed onto the nanoparticle surface, or covalently attached through biodegradable or stimuli-responsive linkages (Kotta et al., 2022; Apartsin, 2023; Beach et al., 2024).

The ability to coordinate drug encapsulation with controlled release represents one of the principal advantages of polymeric nanocarriers. Encapsulation can protect unstable therapeutic molecules against premature chemical or enzymatic degradation, improve the apparent aqueous dispersibility of poorly soluble compounds, modify pharmacokinetic behavior, and potentially decrease exposure of healthy tissues. Sustained release can subsequently maintain therapeutically relevant concentrations for longer periods and potentially reduce dosing frequency. These advantages, however, are not automatic consequences of nanoscale dimensions. Efficient encapsulation requires favorable relationships among the drug, polymer, solvent system, stabilizer, and fabrication process, while sustained release depends on diffusion pathways, hydration, polymer mobility, drug distribution, degradation, erosion, and drug–polymer affinity (Mitchell et al., 2021; Beach et al., 2024).

PLGA represents one of the most extensively investigated biodegradable polymers for drug-delivery applications. Its physicochemical and degradation characteristics can be modified through lactide-to-glycolide composition, molecular weight, terminal chemistry, particle architecture, and processing conditions. PLGA nanoparticles have consequently been investigated for numerous therapeutic applications, including cancer treatment and transdermal delivery (Kumar et al., 2023; Narmani et al., 2023). However, PLGA systems can exhibit burst release, variable drug loading, complex degradation behavior, and substantial manufacturing challenges, demonstrating that the selection of an established biodegradable polymer does not eliminate formulation complexity (Operti et al., 2021).

Natural polymers provide a complementary range of characteristics. Chitosan is a cationic polysaccharide possessing functional amino groups that enable ionic interactions, chemical modification, and mucoadhesive behavior. Drug transport and release from chitosan-based nanoparticles are influenced by

crosslinking, particle morphology, dimensions, matrix density, and the physicochemical characteristics of the therapeutic molecule (Herdiana et al., 2021). Alginate is an anionic polysaccharide capable of ionic gelation, and combinations of chitosan and alginate can form polyelectrolyte complexes suitable for drug-delivery applications (Niculescu & Grumezescu, 2022).

The development of polymeric nanocarriers should nevertheless distinguish between prolonged release observed under simplified laboratory conditions and therapeutically useful controlled release in vivo. A formulation releasing a drug slowly in buffer may behave differently in physiological environments containing proteins, enzymes, electrolytes, lipids, and cells. Nanoparticles must additionally encounter route-specific biological barriers, immune recognition, tissue transport limitations, and clearance mechanisms (Mitchell et al., 2021). Clinically relevant nanocarrier development therefore requires the integration of material properties, formulation science, release kinetics, pharmacokinetics, biological interactions, toxicology, manufacturing, and regulatory considerations.

This review evaluates nanostructured polymeric carriers with particular emphasis on relationships among carrier architecture, efficient drug encapsulation, and sustained release. Polymer selection, fabrication strategies, encapsulation mechanisms, physicochemical characterization, release processes, responsive designs, biomedical applications, translational limitations, and future research priorities are critically discussed.

2. Literature Review Methodology

The literature considered in this review focused on polymeric nanoparticles, nanospheres, nanocapsules, polymeric micelles, dendrimers, nanogels, biodegradable polymers, drug encapsulation, controlled release, sustained release, stimuli-responsive delivery, nanoparticle manufacturing, and pharmaceutical translation. Particular emphasis was placed on peer-reviewed literature published between 2020 and 2024, while established earlier studies and reviews were retained when necessary to explain fundamental concepts.

The literature was organized around three interconnected scientific questions: how polymeric architecture and material characteristics determine drug incorporation; how formulation and processing variables influence sustained release; and why apparently successful laboratory formulations frequently encounter difficulties during biological evaluation, manufacturing, and clinical translation. Encapsulation and release were therefore treated as interdependent formulation outcomes rather than isolated characteristics. Manufacturing conditions that improve drug retention can simultaneously alter particle morphology, surface drug distribution, porosity, and release behavior, whereas modifications introduced to prolong release can influence biological interactions, degradation, stability, and manufacturability (Operti et al., 2021; Beach et al., 2024).

3. Polymeric Carrier Architecture, Drug Encapsulation and Formulation

Nanostructured polymeric carriers can be classified according to their architecture and the spatial relationship between polymer and therapeutic cargo. In matrix-type nanospheres, therapeutic molecules are dispersed throughout or associated with a polymeric matrix. Nanocapsules contain a distinct internal reservoir surrounded by a polymeric shell. Polymeric micelles are typically generated through self-assembly of amphiphilic polymers and contain a hydrophobic domain surrounded by a hydrophilic corona. Dendrimers possess highly branched architectures with internal domains and numerous terminal functional groups, whereas nanogels are nanoscale crosslinked networks capable of absorbing

considerable quantities of water (Kotta et al., 2022; Apartsin, 2023; Rajput et al., 2023; Beach et al., 2024).

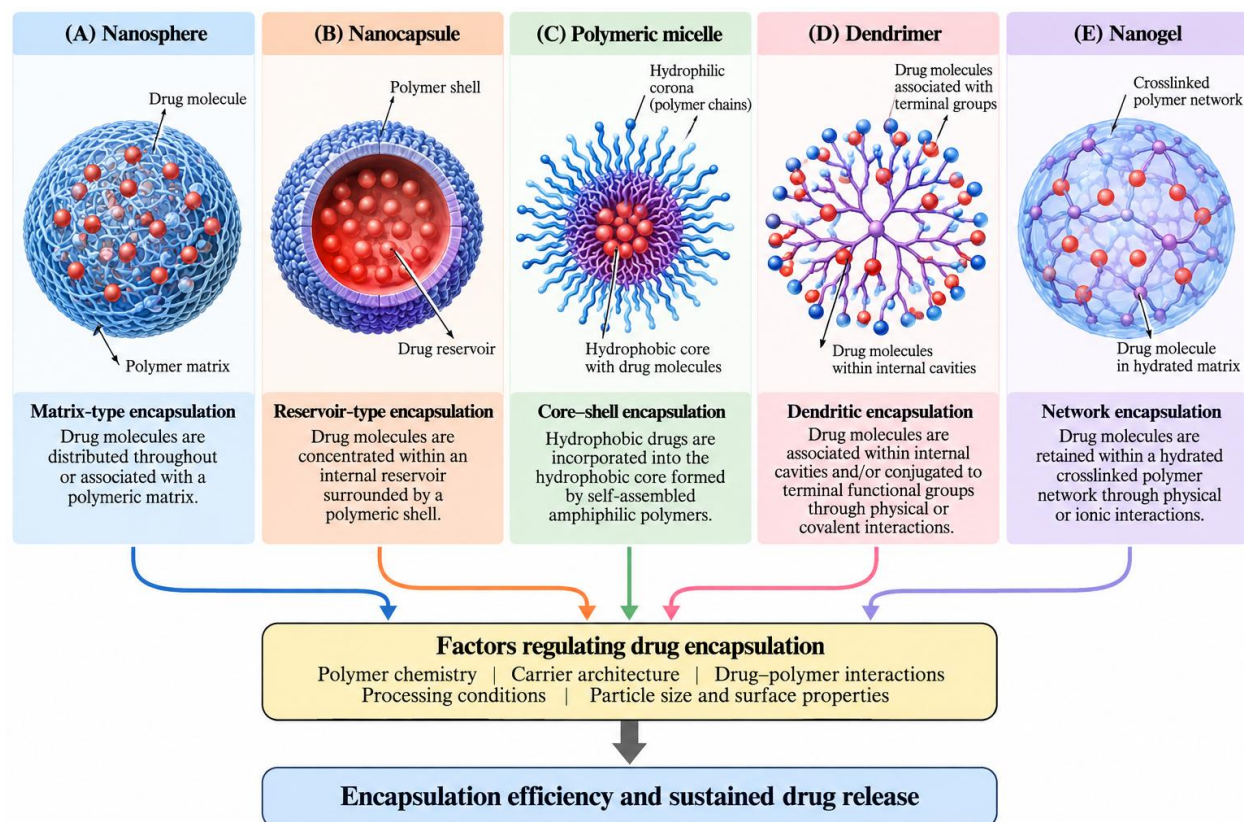


Figure 1. Major nanostructured polymeric carriers and mechanisms of drug encapsulation

Figure concept: A schematic representation containing five carrier architectures: (A) nanosphere showing drug distributed throughout a polymer matrix; (B) nanocapsule showing drug concentrated in an internal reservoir surrounded by a polymer shell; (C) polymeric micelle showing hydrophobic drug within the core and a hydrophilic corona; (D) dendrimer showing therapeutic molecules associated with internal cavities and terminal groups; and (E) nanogel showing drug molecules retained within a hydrated crosslinked polymer network. Arrows should illustrate that polymer chemistry, carrier architecture, drug-polymer interactions, and processing conditions jointly regulate encapsulation efficiency and subsequent release.

The polymer selected for carrier construction determines much of the physicochemical environment experienced by the therapeutic molecule. Synthetic biodegradable polyesters such as PLGA, PLA, and PCL have been widely investigated because their degradation, mechanical characteristics, hydrophobicity, and drug-release behavior can be modified through polymer composition and molecular architecture. PLGA is particularly prominent because variations in molecular weight, lactide-to-glycolide ratio, and terminal groups can alter hydration, degradation, and drug-release behavior (Operti et al., 2021; Kumar et al., 2023; Narmani et al., 2023).

Natural polymers such as chitosan and alginate provide distinct formulation opportunities. Chitosan contains protonatable amino groups that facilitate electrostatic complexation and chemical functionalization. Its cationic character under appropriate conditions also enables interactions with

negatively charged biological surfaces, contributing to its widespread investigation for mucosal drug delivery (Herdiana et al., 2021). Alginate contains carboxylate groups and can form ionically crosslinked structures. Chitosan–alginate combinations exploit interactions between oppositely charged polysaccharides to produce nanoscale delivery systems with potential applications in pharmaceutical and biomedical fields (Niculescu & Grumezescu, 2022).

Polymeric micelles provide a different strategy for drug incorporation. Amphiphilic polymers can self-assemble in aqueous environments so that hydrophobic segments form an internal core while hydrophilic segments form an external corona. Poorly water-soluble therapeutic molecules can partition into the hydrophobic core, thereby increasing their apparent dispersibility in aqueous media. Polymeric micelles have consequently been investigated for oral, parenteral, transdermal, intranasal, and tumor-directed drug delivery (Kotta et al., 2022). Their dynamic nature, however, means that dilution and interactions with biological components can affect stability and drug retention.

Dendrimers provide a highly branched macromolecular architecture containing numerous terminal functional groups. Therapeutic compounds can associate with dendrimers through electrostatic interactions, hydrogen bonding, hydrophobic interactions, physical entrapment, or covalent attachment. The high density of surface groups also facilitates functionalization with targeting or responsive components, although the resulting structural complexity and potential surface-related toxicity require careful control (Apartsin, 2023).

Nanogels are particularly attractive for hydrophilic therapeutic compounds and biological macromolecules because their crosslinked networks can absorb substantial amounts of aqueous fluid while maintaining nanoscale dimensions. Drug retention and release can be regulated through polymer composition, electrostatic interactions, crosslink density, swelling, and environmental responsiveness. These systems have been extensively investigated for drug and gene delivery and particularly for cancer therapeutics (Rajput et al., 2023).

Table 1. Major polymeric carrier systems for drug encapsulation and sustained release

Carrier system	Structural characteristics	Principal loading mechanism	Major advantages	Principal limitations
PLGA/PLA nanoparticles	Biodegradable polyester matrix	Matrix entrapment, adsorption	Tunable degradation, broad drug applicability	Burst release, degradation-related complexity
PCL nanoparticles	Slowly degrading hydrophobic matrix	Hydrophobic partitioning	Potentially prolonged release	Slow degradation may be unsuitable for some applications
Polymeric micelles	Amphiphilic core–shell structure	Hydrophobic-core incorporation	Improved apparent solubility of poorly soluble drugs	Dilution-induced instability and premature leakage
Chitosan nanoparticles	Cationic polysaccharide network	Ionic complexation, adsorption, entrapment	Mucoadhesion, mild fabrication	pH-sensitive behavior and formulation variability

Chitosan–alginate carriers	Polyelectrolyte network	Ionic entrapment	Mild processing and potential pH responsiveness	Stability depends strongly on ionic environment
Dendrimers	Hyperbranched macromolecule	Internal association and surface conjugation	High functionalization capacity	Synthetic complexity and potential toxicity
Nanogels	Hydrated crosslinked network	Physical and ionic entrapment	High water content and responsive behavior	Crosslinking and storage stability require optimization

Efficient encapsulation is governed by both thermodynamic compatibility and kinetic retention during particle formation. Encapsulation efficiency describes the fraction of initially added therapeutic agent retained in the final carrier and can be represented as:

$$\text{Encapsulation efficiency (\%)} = (\text{mass of encapsulated drug} / \text{mass of drug initially added}) \times 100$$

Drug loading describes the proportion of the final drug-loaded nanocarrier represented by the therapeutic molecule:

$$\text{Drug loading (\%)} = (\text{mass of encapsulated drug} / \text{total mass of drug-loaded nanoparticles}) \times 100$$

The distinction is important because high encapsulation efficiency does not necessarily imply high drug loading. A formulation may retain almost all of a small quantity of added drug and therefore show high encapsulation efficiency while containing only a small drug fraction relative to polymer mass. Low drug loading becomes particularly problematic during translation because administering a therapeutic dose may require an impractically high quantity of carrier material (Beach et al., 2024).

Drug–polymer compatibility is a major determinant of encapsulation. Hydrophobic compounds generally partition more favorably into hydrophobic polymer matrices or micellar cores than into external aqueous phases. Conversely, highly water-soluble compounds can escape from hydrophobic matrices during fabrication. Ionic interactions may improve retention of charged therapeutic molecules, whereas hydrogen bonding, hydrophobic association, van der Waals interactions, and covalent conjugation can further influence drug incorporation and stability (Beach et al., 2024).

Importantly, maximizing drug–polymer affinity is not necessarily desirable. Very weak interactions may produce premature leakage, whereas excessively strong interactions can prevent therapeutically useful release. The desired formulation therefore requires sufficient affinity to maintain drug association during manufacturing, storage, and biological transport while still permitting release at the required site and timescale.

Nanoprecipitation is one of the most widely used approaches for producing polymeric nanoparticles. Polymer and therapeutic cargo are commonly dissolved in a water-miscible organic solvent and subsequently mixed with an aqueous nonsolvent. Changes in solvent quality induce polymer precipitation and particle formation. Particle characteristics are influenced by polymer concentration, solvent composition, mixing conditions, phase ratio, temperature, and molecular interactions. Traditional bulk

nanoprecipitation, flash nanoprecipitation, and microfluidic nanoprecipitation provide different levels of control over mixing and particle formation (Liu et al., 2020).

Emulsion–solvent evaporation is another established approach. Polymer and drug are dissolved or dispersed in an organic phase that is emulsified into an aqueous phase containing a stabilizer. Subsequent solvent removal results in polymer solidification and nanoparticle formation. The process is versatile but strongly influenced by solvent selection, emulsifier concentration, phase ratio, mixing energy, and evaporation conditions (Beach et al., 2024).

Water-in-oil-in-water double emulsions are particularly useful for hydrophilic molecules. The therapeutic compound is first dissolved in an internal aqueous phase and emulsified within a polymer-containing organic phase. This primary emulsion is then dispersed within a second aqueous phase. The method can facilitate encapsulation of proteins, peptides, and other hydrophilic molecules but may expose sensitive biological therapeutics to organic interfaces and mechanical stress.

Ionic gelation is widely associated with polysaccharides such as chitosan and alginate. Particle formation occurs through electrostatic interactions between charged polymers and suitable counterions or oppositely charged macromolecules. Mild processing and reduced dependence on organic solvents are important advantages, although particle characteristics can be strongly influenced by pH, ionic strength, polymer molecular weight, and crosslinking conditions (Herdiana et al., 2021; Niculescu & Grumezescu, 2022).

Table 2. Major fabrication approaches for nanostructured polymeric carriers

Fabrication method	Principle	Particularly suitable for	Advantages	Major limitations
Nanoprecipitation	Solvent displacement induces polymer precipitation	Hydrophobic drugs	Simple, rapid, controllable	Poor retention of some hydrophilic drugs
Emulsion–solvent evaporation	Emulsification followed by solvent removal	Polyester nanoparticles and hydrophobic drugs	Established and versatile	Residual solvent and scale-up challenges
Double emulsion	Internal aqueous phase entrapped through W/O/W emulsification	Proteins, peptides, hydrophilic drugs	Improved hydrophilic cargo loading	Leakage and biomolecule destabilization
Ionic gelation	Electrostatic crosslinking	Chitosan/alginate systems	Mild conditions	Sensitive to pH and ionic environment
Self-assembly	Organization of amphiphilic polymers	Polymeric micelles	Efficient hydrophobic-domain formation	Dilution stability can be problematic
Microfluidic/controlled mixing	Rapid, controlled microscale mixing	Reproducible nanoparticles	Narrower size distribution and process control	Throughput and scale-up require engineering

Physicochemical characterization must extend beyond reporting mean particle diameter. Particle-size distribution and polydispersity provide information regarding formulation uniformity, while zeta potential can provide information about surface charge and colloidal interactions. Electron microscopy and related imaging techniques can characterize morphology, whereas chromatography is commonly used to quantify drug content, impurities, and degradation products. Spectroscopy, differential scanning calorimetry, and X-ray diffraction can provide information about molecular interactions and the physical state of incorporated therapeutic compounds (Beach et al., 2024).

Release testing must similarly be interpreted carefully. Apparent sustained release can sometimes result from inadequate drug solubility, poor sink conditions, membrane limitations, or analytical artifacts rather than genuine carrier-controlled behavior. Release medium composition, temperature, agitation, sampling, sink conditions, and analytical methodology therefore require careful standardization.

4. Sustained Release, Stimuli-Responsive Delivery and Biomedical Applications

Sustained release from polymeric nanocarriers generally results from several overlapping processes rather than a single mechanism. Water penetrates or hydrates the carrier, drug molecules become dissolved or mobilized, and transport subsequently occurs through polymeric domains, water-filled pores, or swollen networks. Polymer chains may relax, biodegradable bonds may undergo hydrolysis, and the carrier can progressively erode or disintegrate. The relative contribution of these processes depends on polymer chemistry, carrier architecture, therapeutic cargo, and environmental conditions (Beach et al., 2024).

Diffusion is particularly important when aqueous fluid penetrates the carrier and mobilizes drug before substantial polymer degradation occurs. Diffusion rates depend on molecular size, drug solubility, polymer free volume, porosity, tortuosity, polymer mobility, and drug–polymer interactions. Nanogels can exhibit substantial swelling that increases network mesh size and facilitates diffusion, whereas polymeric micelles can release drugs through diffusion from their hydrophobic cores and through partial or complete carrier disassembly (Kotta et al., 2022; Rajput et al., 2023).

Biodegradable polyesters add a degradation-dependent component to release. Hydrolysis progressively decreases polymer molecular weight and modifies matrix permeability. PLGA particles can therefore exhibit multiphasic release, with surface-associated drug contributing to an early phase, diffusion dominating intermediate release, and polymer degradation or erosion becoming increasingly important at later stages (Operti et al., 2021; Narmani et al., 2023).

Initial burst release remains a major limitation of sustained-release nanoparticles. Burst release commonly occurs when a substantial fraction of the therapeutic molecule is located close to the particle surface or within highly accessible pores. Rapid hydration, weak drug–polymer interactions, porous morphology, and redistribution of drug during particle formation can further increase early release. Although a moderate initial release may be therapeutically useful when a loading dose is required, excessive burst can increase toxicity and reduce the quantity of drug available for prolonged delivery.

Strategies to reduce burst release include improving drug–polymer compatibility, modifying solvent-removal conditions, decreasing surface migration during particle formation, controlling porosity, increasing polymer molecular weight, introducing secondary coatings, and using reversible drug–polymer conjugation. Crosslink density can similarly be increased in nanogels to restrict rapid diffusion.

Figure 2. Integrated mechanisms of sustained and stimuli-responsive release from polymeric nanocarriers

Figure concept: The left side should show a drug-loaded polymeric nanoparticle immediately after administration. The center should illustrate hydration followed by three major pathways: diffusion through the polymer matrix, polymer swelling/relaxation, and degradation/erosion. Surface-associated drug should be shown producing an initial burst, while matrix-associated drug produces prolonged release. The right side should illustrate internal stimuli—pH, redox conditions, and enzymes—and external stimuli—temperature, light, ultrasound, and magnetic fields—triggering changes in permeability, bond cleavage, swelling, or carrier disassembly.

Mathematical models are commonly used to describe drug-release profiles. The Higuchi equation is frequently applied to diffusion-associated release:

$$Q = kH t^{1/2}$$

where Q represents cumulative drug release, kH is the Higuchi release constant, and t represents time.

The Korsmeyer–Peppas equation can be expressed as:

$$Mt/M_{\infty} = kt^n$$

where Mt/M_{∞} represents the fraction of drug released at time t , k is a kinetic constant, and n is the release exponent.

However, mathematical fitting alone does not establish a molecular release mechanism. Different kinetic equations may provide acceptable fits to the same experimental data, particularly when the sampling period is limited. Mechanistic interpretation should therefore be supported by measurements of polymer degradation, morphology, swelling, molecular weight, porosity, and drug distribution.

Stimuli-responsive carriers attempt to combine sustained release with environmental sensitivity. pH-responsive polymers contain ionizable groups or cleavable linkages capable of changing charge, swelling, solubility, or structural integrity in response to local acidity. Redox-responsive systems can contain linkages that undergo cleavage under reducing conditions, while enzyme-responsive carriers contain components susceptible to specific biological enzymes. Thermoresponsive polymers undergo changes in conformation, hydration, or solubility with temperature. These mechanisms can potentially improve temporal or spatial control of therapeutic release (Beach et al., 2024).

External stimuli provide additional possibilities. Light-responsive systems can incorporate photolabile or photothermal elements, ultrasound can modify carrier permeability or induce disruption, and magnetically responsive polymer-containing systems can enable externally influenced localization or release. Although such systems can increase control, additional structural components can also increase manufacturing complexity and regulatory burden.

Table 3. Major formulation variables governing encapsulation and sustained release

Formulation variable	Effect on encapsulation	Effect on release	Development consideration
Drug–polymer affinity	Compatible interactions generally improve retention	Excessively strong affinity can delay release	Optimize rather than maximize
Polymer molecular	Can improve matrix	Often decreases	Match to therapeutic

weight	integrity	diffusion and slows degradation	duration
Polymer composition	Alters hydrophobicity and compatibility	Influences hydration and degradation	Particularly important for copolymers
Particle size	Changes surface area and drug distribution	Smaller particles can show faster release	Balance release with biological fate
Drug loading	Can alter internal morphology	High loading may increase burst release	Evaluate together with EE
Crosslink density	Improves network retention	Higher density generally slows diffusion	Critical for nanogels
Surface-associated drug	Can increase measured drug association	Major contributor to burst release	Distinguish surface and matrix drug
Porosity	Influences internal drug accommodation	Increases fluid and penetration diffusion	Control during fabrication
Environmental pH	Alters ionization and interactions	Influences swelling, solubility and degradation	Use biorelevant release conditions
Proteins and enzymes	Can alter colloidal behavior	Can change degradation and release	Complement buffer studies with biological media

Cancer therapy remains one of the most extensively investigated applications of polymeric nanocarriers. Many anticancer compounds exhibit poor aqueous solubility, narrow therapeutic indices, systemic toxicity, or unfavorable pharmacokinetics. Polymeric nanoparticles can improve the apparent dispersibility of hydrophobic drugs, protect unstable molecules, modify exposure, and enable sustained or stimuli-responsive release. PLGA nanoparticles, polymeric micelles, dendrimers, and nanogels have therefore been extensively explored for cancer treatment (Narmani et al., 2023; Rajput et al., 2023).

Targeted nanocarriers can be functionalized with antibodies, peptides, aptamers, sugars, and small molecules designed to interact with selected biological receptors. However, ligand functionalization does not guarantee selective delivery. Before receptor binding can occur, nanoparticles must remain sufficiently stable in biological fluids, avoid excessive clearance, reach the relevant tissue, and encounter the intended cell population. Biological adsorption at nanoparticle surfaces can additionally alter their effective biological identity (Mitchell et al., 2021).

Oral administration creates a different set of challenges. Polymeric carriers may protect unstable compounds, improve apparent solubility, interact with mucus, and modify gastrointestinal residence. Chitosan-based nanoparticles are particularly attractive because of their mucoadhesive characteristics, whereas chitosan–alginate systems can provide polyelectrolyte structures with potentially useful pH-dependent behavior (Herdiana et al., 2021; Niculescu & Grumezescu, 2022). Nevertheless, gastrointestinal pH, enzymes, food components, mucus turnover, intestinal permeability, and transit time can substantially alter nanoparticle performance.

Proteins, peptides, and nucleic acids present additional challenges because they are susceptible to degradation and can lose biological activity during formulation. Their hydrophilic character can also produce poor incorporation into conventional hydrophobic matrices. Double emulsions, nanogels, dendrimers, ionic complexes, and polymer conjugation provide potential solutions. For biological therapeutics, however, encapsulation efficiency alone is insufficient; structural integrity and biological potency must also be confirmed after release.

5. Translational Challenges and Future Perspectives

Despite extensive academic development, the clinical translation of sophisticated polymeric nanocarriers remains limited relative to the enormous volume of preclinical research. Historical evaluations of nanoparticle medicines have demonstrated the importance of considering regulatory approval and clinical development separately from promising laboratory performance (Bobo et al., 2016). More recent analyses similarly emphasize that sophisticated control over polymeric nanoparticle properties has not yet translated into widespread clinical application (Beach et al., 2024).

A major reason for this translational gap is that formulation optimization frequently emphasizes particle size, encapsulation efficiency, and in vitro release while underemphasizing manufacturability. A clinically viable formulation must be produced reproducibly, purified, sterilized or manufactured aseptically, stored for an acceptable period, characterized through validated analytical procedures, and administered at a practical dose.

Scale-up represents a particularly important challenge. A preparation process optimized at laboratory scale may not behave identically when transferred to larger equipment because mixing time, shear, mass transfer, solvent-removal kinetics, and temperature gradients can change with process scale. These differences can alter particle size, polydispersity, morphology, drug loading, and release kinetics. PLGA nanomedicine manufacturing illustrates how nanoparticle production, purification, sterilization, and scale-up are interconnected rather than independent development stages (Operti et al., 2021).

Continuous and controlled-mixing approaches offer potential solutions. Nanoprecipitation is highly dependent on mixing conditions, and microfluidic or rapid-mixing technologies can improve control over particle nucleation and growth (Liu et al., 2020). Integration of nanoparticle formation with continuous purification and process analytical technologies could eventually reduce batch-to-batch variability.

Downstream processing deserves equal attention. Nanoparticle production does not end when particles form. Formulations may require purification, removal of free drug and residual solvent, concentration, sterile processing, drying, reconstitution, packaging, and long-term storage. Each operation can change particle characteristics. Lyophilization may improve storage stability but can cause aggregation if appropriate cryoprotective conditions are not identified.

Quality-by-design strategies provide a rational framework for addressing these issues. Critical material attributes can include polymer molecular weight, copolymer composition, terminal chemistry, drug purity, stabilizer properties, and solvent characteristics. Critical process parameters can include phase ratio, flow rate, mixing intensity, temperature, homogenization energy, solvent-removal conditions, and purification procedures. These variables should be linked systematically to critical quality attributes such as particle size, PDI, morphology, surface charge, encapsulation efficiency, drug loading, residual solvent, release profile, sterility, and storage stability.

Biological characterization must also become more predictive. Nanoparticles entering physiological fluids interact with proteins and other biomolecules, potentially altering colloidal stability, immune recognition,

cellular uptake, and biodistribution. Consequently, physicochemical characterization performed only in water immediately after preparation provides an incomplete representation of in vivo behavior (Mitchell et al., 2021).

Safety evaluation should consider the complete nanocarrier rather than assuming safety from historical use of the parent polymer. Nanostructuring changes surface area, degradation behavior, biodistribution, cellular interactions, and exposure to functional groups. Residual solvents, stabilizers, crosslinking agents, targeting ligands, degradation products, and impurities can also influence toxicity. This is particularly relevant to sustained-release formulations because carrier materials may remain within biological tissues longer than rapidly eliminated soluble drugs.

Structural complexity represents another important translational issue. Academic nanocarriers frequently combine biodegradable matrices, hydrophilic coatings, targeting ligands, imaging components, stimuli-sensitive linkages, and therapeutic payloads. Each component can improve functionality, but every additional element creates manufacturing, analytical, toxicological, stability, and regulatory requirements. Consequently, the most structurally sophisticated nanocarrier may not necessarily provide the most practical therapeutic product (Beach et al., 2024).

Future formulation studies should move beyond reporting encapsulation efficiency as the primary indicator of success. Encapsulation efficiency, drug loading, manufacturing yield, nanoparticle concentration, release completeness, colloidal stability, storage stability, and clinically required dose should be evaluated together. A formulation with very high encapsulation efficiency can remain impractical when drug loading is too low to deliver the required dose without excessive carrier administration.

Release testing should likewise become more biologically meaningful. Simple buffer studies remain useful for screening formulations but cannot fully reproduce physiological environments. Protein-containing media, relevant ionic compositions, appropriate pH conditions, enzymes, and route-specific simulated fluids should increasingly complement conventional release testing. Establishing robust in vitro–in vivo relationships will be particularly important for sustained-release formulations.

Computational modeling and machine-learning approaches may eventually assist formulation development by identifying relationships among polymer chemistry, drug descriptors, processing conditions, nanoparticle characteristics, encapsulation, and release. Their effectiveness will depend strongly on access to standardized and sufficiently large experimental datasets. Poorly standardized literature data cannot reliably support predictive formulation models.

Future research should therefore focus on quantitative structure–property–performance relationships integrating polymer composition, molecular architecture, manufacturing process, encapsulation, release, biological fate, therapeutic response, and product quality. Such integration can reduce empirical trial-and-error development and help identify the simplest carrier architecture capable of meeting the therapeutic requirement.

6. Conclusion

Nanostructured polymeric carriers constitute highly adaptable platforms for improving drug encapsulation and regulating therapeutic release. Nanospheres, nanocapsules, polymeric micelles, dendrimers, and nanogels provide structurally distinct environments capable of incorporating hydrophobic and hydrophilic small molecules as well as proteins, peptides, and nucleic acids. Synthetic biodegradable polymers such as PLGA, PLA, and PCL provide tunable matrix properties, whereas natural

polymers such as chitosan and alginate provide ionic functionality, mucoadhesion, mild processing opportunities, and versatile carrier construction (Herdiana et al., 2021; Niculescu & Grumezescu, 2022; Beach et al., 2024).

Efficient encapsulation and sustained release are fundamentally interconnected. Drug–polymer affinity affects loading but simultaneously determines the ease with which a therapeutic molecule can escape from the carrier. Manufacturing conditions determine encapsulation while also establishing particle morphology, porosity, surface-associated drug, and internal drug distribution. Polymer molecular weight, composition, crystallinity, particle dimensions, crosslink density, hydration, and environmental conditions subsequently influence release behavior (Operti et al., 2021; Beach et al., 2024).

Sustained release should therefore be understood as a composite process involving surface desorption, diffusion, swelling, polymer relaxation, degradation, erosion, and carrier disassembly rather than as a single phenomenon. Stimuli-responsive systems can introduce additional control through pH, redox conditions, enzymes, temperature, light, ultrasound, or magnetic fields. Nevertheless, increasing functional complexity also introduces manufacturing, analytical, safety, stability, and regulatory challenges (Apartsin, 2023; Beach et al., 2024).

The future clinical success of polymeric nanocarriers will depend on integrating pharmaceutical performance with translational requirements from the earliest stages of development. Reproducible manufacturing, purification, sterilization, storage stability, validated characterization, biologically relevant release testing, toxicological assessment, and quality control should be considered fundamental aspects of nanocarrier design rather than downstream requirements (Operti et al., 2021).

Overall, polymeric nanocarriers have considerable potential to improve the therapeutic use of compounds limited by poor solubility, instability, rapid elimination, inadequate localization, or undesirable systemic exposure. Their ultimate clinical value will depend not on nanoscale dimensions alone but on the successful integration of efficient drug encapsulation, predictable sustained release, biological compatibility, scalable manufacturing, product stability, and demonstrable therapeutic benefit.

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