

FORMULATION AND CHARACTERIZATION OF POLYMERIC NANOPARTICLES FOR SITE-SPECIFIC DRUG DELIVERY AND IMPROVEMENT OF ORAL BIOAVAILABILITY OF POORLY ABSORBED DRUGS

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Abstract

Oral drug delivery remains the most preferred route of administration owing to its convenience, patient compliance, and cost-effectiveness; however, a substantial proportion of new chemical entities emerging from modern drug discovery programs exhibit poor aqueous solubility, limited intestinal permeability, extensive first-pass metabolism, or susceptibility to enzymatic and chemical degradation within the gastrointestinal (GI) tract. These physicochemical and biopharmaceutical limitations translate into low and erratic oral bioavailability, restricting the clinical utility of otherwise promising therapeutic molecules. Polymeric nanoparticles (PNPs), colloidal carriers fabricated from biodegradable and biocompatible natural or synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, polycaprolactone (PCL), and albumin, have emerged as a versatile nanocarrier platform capable of addressing these challenges simultaneously. By encapsulating or adsorbing drug molecules within a submicron polymeric matrix, PNPs can protect labile drugs from gastric and enzymatic degradation, enhance mucoadhesion and epithelial residence time, promote paracellular and transcellular transport, circumvent P-glycoprotein (P-gp)-mediated efflux, and enable controlled or site-specific release through stimuli-responsive surface engineering. This review provides a comprehensive account of the formulation strategies employed for polymeric nanoparticle fabrication, including nanoprecipitation, emulsification-solvent evaporation, ionic gelation, salting-out, and supercritical fluid technology, along with the physicochemical, morphological, and biopharmaceutical characterization techniques used to evaluate them. Furthermore, the review examines the mechanistic basis of site-specific targeting achieved through ligand conjugation, pH-responsive and enzyme-responsive polymer design, and mucoadhesive engineering, as well as the mechanisms by which PNPs enhance oral bioavailability. Representative case studies, in vivo pharmacokinetic evidence, regulatory and translational challenges, and future directions including artificial intelligence-assisted formulation design are also discussed. Collectively, the evidence indicates that rationally engineered polymeric nanoparticles represent a clinically promising strategy for overcoming the oral bioavailability barrier of poorly absorbed drugs.

Keywords: Polymeric nanoparticles; oral bioavailability; site-specific drug delivery; PLGA; chitosan; mucoadhesion; nanoprecipitation; P-glycoprotein efflux; controlled release; nanomedicine

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1. Introduction

The oral route continues to be regarded as the gold standard for drug administration due to its non-invasive nature, ease of self-administration, high patient acceptability, and lower cost of manufacturing and distribution compared with parenteral formulations. Despite these advantages, an estimated 40% or more of drugs currently in development pipelines, and a comparable fraction of marketed drugs, fall under Biopharmaceutics Classification System (BCS) Class II and Class IV, characterized by poor aqueous solubility and, in the case of Class IV, additionally poor intestinal permeability. Even for drugs with favorable solubility and permeability profiles, oral bioavailability can be severely compromised by pre-systemic metabolism in the intestinal wall and liver, chemical instability in the acidic gastric environment, enzymatic degradation by luminal and brush-border peptidases, and active efflux via transporters such as P-glycoprotein (P-gp).

Conventional formulation approaches, including salt formation, particle size reduction by micronization, solid dispersions, cyclodextrin complexation, and lipid-based systems, have achieved partial success but often fail to address the multifactorial nature of the oral absorption barrier simultaneously. Nanotechnology-based drug delivery systems, and polymeric nanoparticles in particular, have attracted considerable research interest because of their unique ability to combine solubility enhancement, mucosal protection, controlled release, and targeting functionality within a single, tunable carrier platform. Polymeric nanoparticles are solid colloidal particles typically ranging from 10 to 1000 nm in diameter, in which the drug is dissolved, entrapped, encapsulated, or adsorbed onto the polymeric matrix or surface, existing either as nanospheres (matrix systems) or nanocapsules (reservoir systems with a polymeric shell surrounding a core).

The rationale for employing polymeric nanoparticles in oral delivery rests on several interconnected mechanisms: (i) the high surface-area-to-volume ratio of nanoparticles increases the dissolution rate of poorly soluble drugs in accordance with the Noyes-Whitney equation; (ii) the polymeric matrix can shield encapsulated drugs from gastric acid and proteolytic enzymes; (iii) surface modification with mucoadhesive or cell-penetrating moieties prolongs GI residence time and enhances intimate contact with the absorptive epithelium; (iv) nanoparticles can be internalized by enterocytes via endocytic pathways or sampled by M-cells of the Peyer's patches, bypassing some components of the P-gp efflux and first-pass

metabolism; and (v) surface functionalization with targeting ligands enables site-specific delivery to particular regions of the gut, to inflamed tissue, or to specific cell populations such as tumor cells or antigen-presenting cells. This review consolidates current knowledge on the formulation, characterization, and performance evaluation of polymeric nanoparticles designed for site-specific oral drug delivery, with an emphasis on the translational challenges that must be resolved for clinical and commercial success.

2. Polymeric Nanoparticles: An Overview

2.1 Structural Classification

Polymeric nanoparticles are broadly classified into two structural types. Nanospheres are matrix-type systems in which the drug is uniformly dispersed or dissolved throughout a continuous polymeric network, offering sustained and diffusion-controlled release kinetics. Nanocapsules, in contrast, are vesicular reservoir-type systems consisting of an oily or aqueous core surrounded by a thin polymeric membrane, in which the drug is typically confined to the core and released following membrane permeation or erosion. The choice between these architectures depends on the physicochemical properties of the drug, the intended release profile, and the fabrication method employed.

2.2 Polymers Used in Nanoparticle Fabrication

The selection of polymer is a critical determinant of nanoparticle stability, drug loading capacity, release kinetics, biocompatibility, and mucoadhesive or targeting functionality. Polymers used in oral nanoparticle fabrication are broadly categorized as natural or synthetic.

2.2.1 Natural Polymers

- Chitosan – a cationic polysaccharide derived from chitin; valued for its mucoadhesive property arising from electrostatic interaction with the negatively charged mucus layer, and its capacity to transiently open tight junctions, thereby enhancing paracellular drug transport.
- Sodium alginate – an anionic polysaccharide capable of ionic gelation with divalent cations such as calcium, widely used for its biocompatibility and gel-forming ability.
- Albumin and gelatin – protein-based carriers offering high drug-binding capacity and biodegradability, with albumin nanoparticles additionally exploiting receptor-mediated transport (e.g., gp60/SPARC pathways).
- Gum-based and cellulose derivatives – including guar gum, pectin, and hydroxypropyl

methylcellulose, used for their pH-dependent solubility and colon-targeting potential.

2.2.2 Synthetic Polymers

- Poly(lactic-co-glycolic acid) (PLGA) – the most extensively studied synthetic polymer, approved by the US FDA and EMA for parenteral and other uses, biodegradable via hydrolysis into lactic and glycolic acid monomers, with tunable degradation rates based on the lactide:glycolide ratio.
- Polylactic acid (PLA) and polycaprolactone (PCL) – biodegradable polyesters offering slower degradation and prolonged release compared with PLGA.
- Polyalkyl cyanoacrylates (PACA) – rapidly biodegradable polymers historically used for nanoparticle formulation with high drug encapsulation efficiency.
- Eudragit polymers – pH-sensitive methacrylate copolymers (e.g., Eudragit L100, S100, RS/RL) widely employed for enteric protection and colon-specific release.

2.3 Advantages of Polymeric Nanoparticles over Conventional Oral Formulations

Compared with conventional tablets, capsules, or simple suspensions, polymeric nanoparticles offer several distinct advantages, including enhanced saturation solubility and dissolution velocity of poorly soluble drugs, protection of acid- or enzyme-labile molecules (proteins, peptides, and nucleic acids) during GI transit, prolongation of mucosal residence time through bioadhesion, the possibility of achieving sustained or triggered release profiles, reduction of dosing frequency and associated GI side effects, and the capacity for active or passive targeting to specific gut regions, diseased tissue, or intracellular compartments.

3. Formulation Methods for Polymeric Nanoparticles

The selection of a fabrication technique depends primarily on the physicochemical characteristics of the drug (hydrophilic versus lipophilic), the polymer type, the desired particle size and release profile, and considerations of scalability and residual solvent toxicity. The principal methods are summarized below.

3.1 Nanoprecipitation (Solvent Displacement Method)

In this technique, the polymer and drug are dissolved in a water-miscible organic solvent (e.g., acetone or ethanol) and the resulting solution is added dropwise, under moderate stirring, into an aqueous phase containing a stabilizer such as poloxamer or polyvinyl alcohol (PVA). The rapid diffusion of the organic solvent into the aqueous phase, described by the Marangoni effect, causes instantaneous polymer

precipitation as nanoparticles. This method is simple, reproducible, and avoids high-energy homogenization, but is best suited to lipophilic drugs and polymers soluble in water-miscible solvents.

3.2 Emulsification-Solvent Evaporation

The polymer and drug are dissolved in a volatile, water-immiscible organic solvent (e.g., dichloromethane or ethyl acetate) to form the dispersed phase, which is emulsified into an aqueous continuous phase containing a surfactant using high-shear homogenization or ultrasonication to generate an oil-in-water emulsion. Subsequent evaporation of the organic solvent, either at ambient pressure or under vacuum, causes polymer precipitation and nanoparticle hardening. A double emulsion (water-in-oil-in-water) variant is employed for hydrophilic drugs, including peptides and proteins, to improve encapsulation efficiency.

3.3 Ionic Gelation (Ionotropic Gelation)

This aqueous, organic-solvent-free method is particularly suited to natural polyelectrolytes such as chitosan and alginate. Nanoparticle formation occurs through electrostatic crosslinking between the oppositely charged polymer and a multivalent counterion, such as tripolyphosphate (TPP) for chitosan, under mild stirring at room temperature. The mild processing conditions make this method attractive for the encapsulation of biomacromolecules that are sensitive to heat, shear, and organic solvents.

3.4 Salting-Out Technique

A water-miscible solvent such as acetone containing the dissolved polymer and drug is emulsified into an aqueous gel containing a high concentration of an electrolyte (e.g., magnesium chloride) or a non-electrolyte (e.g., sucrose), which prevents the solvent from mixing with water. Subsequent dilution with water reduces the salting-out effect, allowing the solvent to diffuse into the aqueous phase and induce nanoparticle formation. This method avoids the use of chlorinated solvents and surfactants but requires extensive purification to remove the salting-out agent.

3.5 Supercritical Fluid Technology

Supercritical carbon dioxide (scCO₂)-based techniques, such as Rapid Expansion of Supercritical Solutions (RESS) and Supercritical Anti-Solvent (SAS) precipitation, offer an environmentally friendly, organic-solvent-minimizing alternative for nanoparticle production. These methods exploit the tunable solvating power of supercritical fluids to precipitate polymer and drug as fine nanoparticles upon rapid depressurization or anti-solvent addition, yielding products with low residual solvent content, though the technique requires specialized high-pressure equipment.

3.6 Emerging and Scalable Techniques

Microfluidic nanoprecipitation, using staggered herringbone or flow-focusing microchannel devices, has gained prominence for producing polymeric nanoparticles with narrow size distribution and high batch-to-batch reproducibility by enabling precise control over mixing time at the microscale. Spray-drying and electrospraying are also employed for solvent-free, single-step conversion of nanoparticle suspensions into dry powders suitable for encapsulation into oral dosage forms such as capsules or enteric-coated tablets.

3.7 Comparative Summary of Formulation Techniques

Technique	Solvent System	Suitable Drug Type	Typical Size Range	Key Limitation
Nanoprecipitation	Water-miscible organic solvent	Lipophilic drugs	100 – 300 nm	Limited to water-miscible solvent-soluble polymers
Emulsification-solvent evaporation	Water-immiscible organic solvent	Lipophilic & hydrophilic (double emulsion)	200 – 600 nm	High shear may denature proteins
Ionic gelation	Aqueous, no organic solvent	Hydrophilic drugs, peptides	150 – 400 nm	Limited to polyelectrolyte polymers
Salting-out	Water-miscible solvent + electrolyte	Lipophilic drugs	200 – 500 nm	Extensive purification needed
Supercritical fluid (SAS/RESS)	Minimal/no organic solvent	Thermolabile, solvent-sensitive drugs	100 – 500 nm	High capital equipment cost

Technique	Solvent System	Suitable Drug Type	Typical Size Range	Key Limitation
Microfluidic nanoprecipitation	Water-miscible organic solvent	Broad applicability	50–200 nm	Lower throughput at lab scale

Table 1. Comparative overview of common polymeric nanoparticle fabrication techniques.

4. Characterization of Polymeric Nanoparticles

Comprehensive physicochemical, morphological, and biopharmaceutical characterization is essential to establish the critical quality attributes (CQAs) of polymeric nanoparticles, ensure batch-to-batch reproducibility, and predict in vivo performance.

4.1 Particle Size, Polydispersity Index, and Zeta Potential

Particle size and size distribution, typically expressed as the polydispersity index (PDI), are most commonly measured by dynamic light scattering (DLS), which correlates the fluctuation in scattered light intensity caused by Brownian motion with the hydrodynamic diameter of the particles. A PDI below 0.3 is generally considered indicative of a monodisperse, homogeneous suspension suitable for reproducible biological performance. Zeta potential, measured via electrophoretic light scattering, reflects the surface charge of the nanoparticles and serves as an indirect indicator of colloidal stability; values exceeding ± 30 mV are generally regarded as conferring adequate electrostatic stabilization against aggregation, while mucoadhesive cationic systems (e.g., chitosan nanoparticles) intentionally carry a positive zeta potential to promote electrostatic interaction with the negatively charged mucosal surface.

4.2 Morphological Analysis

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide direct visualization of nanoparticle shape, surface texture, and structural integrity, complementing the hydrodynamic size data obtained from DLS. Atomic force microscopy (AFM) additionally offers three-dimensional surface topography and can be used to probe nanomechanical properties such as surface roughness and rigidity.

4.3 Drug Loading and Encapsulation Efficiency

Encapsulation efficiency (EE%) and drug loading capacity (DL%) are determined by separating free (unencapsulated) drug from the nanoparticle suspension, commonly via ultracentrifugation,

ultrafiltration, or dialysis, followed by quantification of drug content using UV-visible spectrophotometry or high-performance liquid chromatography (HPLC). EE% is calculated as the ratio of the amount of drug entrapped to the total amount of drug used in formulation, while DL% expresses the entrapped drug as a percentage of the total nanoparticle mass.

4.4 Solid-State and Chemical Characterization

- Fourier-transform infrared spectroscopy (FTIR) – used to confirm the absence of chemical incompatibility between drug and polymer by comparing characteristic functional group absorption bands.
- Differential scanning calorimetry (DSC) – detects changes in melting endotherms indicative of drug encapsulation, amorphization, or polymorphic transitions within the polymeric matrix.
- Powder X-ray diffraction (PXRD) – confirms the crystalline or amorphous state of the drug within the nanoparticle, with the disappearance of characteristic drug diffraction peaks suggesting molecular dispersion or amorphization, which often correlates with enhanced dissolution.

4.5 In Vitro Drug Release Studies

In vitro release is typically evaluated using dialysis bag diffusion, the reverse dialysis technique, or USP dissolution apparatus (Type I/II) under biorelevant media simulating gastric (pH 1.2) and intestinal (pH 6.8) fluids, sometimes supplemented with simulated gastric or intestinal fluids containing digestive enzymes (SGF/SIF). Release data are commonly fitted to mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations, to elucidate the underlying release mechanism, whether diffusion-controlled, erosion-controlled, or a combination thereof.

4.6 Mucoadhesion and Permeability Studies

Mucoadhesive strength is assessed using texture analyzers measuring detachment force from mucin discs or excised intestinal mucosa, while ex vivo permeability is commonly evaluated using the everted gut sac technique or Ussing chamber diffusion studies with excised rat or porcine intestinal segments. In vitro cell-based models, particularly Caco-2 monolayers (and Caco-2/HT29-MTX co-culture models to include a mucus-producing component), are widely used to predict apparent permeability coefficients (Papp) and to investigate transport mechanisms and P-gp interaction.

4.7 Stability Studies

Physical and chemical stability of nanoparticle suspensions or lyophilized powders are evaluated under ICH-recommended storage conditions (e.g., 25°C/60% RH and 40°C/75% RH) over defined time

intervals, monitoring changes in particle size, PDI, zeta potential, drug content, and appearance. Lyophilization with cryoprotectants such as trehalose or sucrose is frequently employed to improve long-term storage stability of aqueous nanoparticle dispersions.

5. Strategies for Site-Specific Oral Drug Delivery

Site-specific delivery within the GI tract aims to release the drug at a predetermined location, such as the stomach, small intestine, or colon, or to target specific cell populations, thereby maximizing local or systemic therapeutic effect while minimizing degradation, systemic exposure, or off-target effects.

5.1 pH-Responsive Polymeric Systems

The GI tract exhibits a distinct pH gradient, ranging from highly acidic conditions in the stomach (pH 1.2–3.5) to near-neutral conditions in the small intestine (pH 6.5–7.5) and colon (pH 6.5–7.5, with regional variation). Enteric polymers such as Eudragit L100 and S100, and cellulose acetate phthalate, remain intact in acidic gastric conditions but dissolve at higher pH, enabling drug release to be delayed until the nanoparticles reach the small intestine or colon, thereby protecting acid-labile drugs and reducing gastric irritation.

5.2 Mucoadhesive and Mucus-Penetrating Systems

Mucoadhesive nanoparticles, typically formulated with cationic polymers such as chitosan or thiolated polymers (thiomers), adhere to the mucus layer overlying the intestinal epithelium, prolonging residence time and increasing the concentration gradient driving drug absorption. Conversely, mucus-penetrating particles, engineered with dense PEGylated coatings to minimize mucoadhesive interactions, are designed to rapidly traverse the mucus mesh and reach the underlying epithelium before mucus clearance can remove them, an approach that can be advantageous when epithelial contact rather than mucosal retention is the primary goal.

5.3 Enzyme-Responsive and Colon-Targeted Systems

Polysaccharide-based polymers such as pectin, guar gum, and chondroitin sulfate remain largely undigested in the stomach and small intestine but are selectively degraded by the dense microbial enzymes (e.g., bacterial polysaccharidases) present in the colon, enabling colon-specific release. This strategy is particularly valuable for the local treatment of inflammatory bowel disease and colorectal cancer, as well as for the delivery of drugs that are absorbed more efficiently in the colon or that require protection from upper GI degradation.

5.4 Ligand-Mediated Active Targeting

Surface functionalization of nanoparticles with targeting ligands, including lectins, folate, transferrin, RGD peptides, and vitamin B12, enables receptor-

mediated active targeting to specific epithelial or immune cell populations. For example, lectin-conjugated nanoparticles bind specifically to glycoprotein and glycolipid receptors on the enterocyte brush border, promoting receptor-mediated endocytosis and enhanced transcytosis, while M-cell-targeting ligands (e.g., RGD peptides, Aal lectin) exploit the enhanced transcytotic capacity of M-cells overlying Peyer's patches, an approach of particular interest for oral vaccine and biologic delivery.

5.5 Stimuli-Responsive Smart Systems

Beyond pH and enzyme responsiveness, redox-responsive polymers containing disulfide linkages, and temperature-responsive polymers such as poly(N-isopropylacrylamide) (PNIPAM), have been explored to achieve triggered release in response to the specific biochemical microenvironment of the target tissue, such as the elevated glutathione concentration within inflamed or tumor tissue.

6. Mechanisms of Oral Bioavailability Enhancement

6.1 Enhanced Solubility and Dissolution Rate

Encapsulation within a nanoparticulate carrier dramatically increases the effective surface area available for dissolution and can convert crystalline drug into an amorphous or molecularly dispersed state within the polymer matrix, both of which, per the Noyes-Whitney and Ostwald-Freundlich relationships, substantially increase the apparent saturation solubility and dissolution rate of poorly water-soluble (BCS Class II) drugs.

6.2 Protection from Gastrointestinal Degradation

The polymeric matrix acts as a physical barrier, shielding acid-labile and enzyme-labile drugs, particularly peptides, proteins, and nucleic acid-based therapeutics, from degradation by gastric acid, pepsin, and pancreatic and brush-border peptidases, thereby preserving the pharmacologically active form of the drug until it reaches the absorptive site.

6.3 Enhanced Epithelial Permeability

Certain polymers, most notably chitosan, transiently and reversibly open the tight junctions between adjacent enterocytes by interacting with junctional proteins such as ZO-1 and occludin, facilitating paracellular transport of otherwise poorly permeable hydrophilic macromolecules. Nanoparticles can additionally be internalized via clathrin-mediated or caveolae-mediated endocytosis, enabling transcellular transport across the epithelial barrier.

6.4 Circumvention of P-glycoprotein Efflux

P-glycoprotein, an ATP-binding cassette efflux transporter highly expressed on the apical membrane of enterocytes, actively extrudes a broad range of substrate drugs back into the intestinal lumen, substantially limiting their net absorption. Several polymers commonly used in nanoparticle fabrication,

including certain grades of Pluronic (poloxamer), TPGS (D-alpha-tocopheryl polyethylene glycol succinate), and chitosan derivatives, have demonstrated intrinsic P-gp inhibitory activity, while nanoparticle encapsulation itself can mask the drug from transporter recognition until intracellular release occurs, collectively reducing efflux-mediated loss of absorbed drug.

6.5 Avoidance of Pre-Systemic (First-Pass) Metabolism

Nanoparticles taken up via the lymphatic route, particularly through M-cells of the Peyer's patches or via chylomicron-associated lymphatic transport for lipophilic drugs, can bypass hepatic first-pass metabolism, since intestinal lymph drains into the systemic circulation via the thoracic duct rather than passing through the portal vein and liver.

6.6 Sustained and Controlled Systemic Exposure

The sustained-release characteristics of polymeric nanoparticles reduce fluctuations in plasma drug concentration, prolong the time above the minimum effective concentration, and can reduce dosing frequency, collectively contributing to a more favorable and reproducible pharmacokinetic profile compared with immediate-release conventional dosage forms.

7. In Vivo and Pharmacokinetic Evaluation

Ultimately, the translational value of any polymeric nanoparticle formulation must be confirmed through in vivo pharmacokinetic and pharmacodynamic evaluation, most commonly conducted in rodent models (rats or mice), with comparison to a reference oral suspension or solution and, where feasible, an intravenous reference formulation to establish absolute bioavailability. Key pharmacokinetic parameters assessed include the maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve (AUC_{0-t} and $AUC_{0-\infty}$), elimination half-life ($t_{1/2}$), and relative oral bioavailability (F_{rel}), calculated as the dose-normalized AUC ratio between the nanoparticle formulation and the reference formulation.

Across numerous published studies, polymeric nanoparticle formulations of poorly absorbed drugs, including insulin, cyclosporine A, paclitaxel, curcumin, and various antihypertensive and antidiabetic agents, have consistently demonstrated several-fold increases in relative oral bioavailability compared with conventional suspensions, along with prolonged T_{max} values reflective of sustained absorption and reduced C_{max} -associated toxicity risk. Biodistribution studies using radiolabeled or fluorescently tagged nanoparticles further confirm preferential accumulation in target GI segments or lymphoid tissue when appropriately surface-

engineered, supporting the mechanistic basis for site-specific enhancement of absorption.

7.1 Illustrative Pharmacokinetic Comparison

Parameter	Conventional Oral Suspension	Polymeric Nanoparticle Formulation
C _{max}	Baseline (1×)	2–5× increase (typical range)
T _{max}	Short (rapid absorption/degradation)	Delayed/prolonged, reflecting sustained release
AUC _{0–∞}	Baseline (1×)	3–8× increase (drug- and carrier-dependent)
Relative bioavailability (F _{rel})	10–20% (representative poorly absorbed drug)	40–70% (representative optimized nanoparticle)

Table 2. Representative, literature-informed comparison of pharmacokinetic outcomes for conventional versus nanoparticle oral formulations (values are illustrative ranges; actual results are drug- and formulation-specific).

8. Representative Applications and Case Studies

8.1 Insulin and Peptide/Protein Delivery

Oral insulin delivery represents one of the most extensively pursued applications of polymeric nanoparticles, given the severe degradation and permeability barriers faced by peptide therapeutics in the GI tract. Chitosan- and alginate-based nanoparticles, often further coated with enteric polymers, have demonstrated measurable hypoglycemic effect following oral administration in animal models, attributed to combined enzymatic protection, mucoadhesion, and transient tight-junction modulation, although absolute bioavailability achieved to date generally remains modest and a significant translational gap to clinical use persists.

8.2 Anticancer Agents

PLGA and albumin-based nanoparticles have been widely investigated for oral delivery of poorly soluble anticancer agents such as paclitaxel and docetaxel, aiming to improve patient convenience relative to intravenous infusion while co-administering P-gp inhibitors or employing P-gp-inhibitory excipients (e.g., TPGS) within the formulation to counteract the high intestinal efflux that limits oral absorption of these substrates.

8.3 Poorly Soluble Nutraceuticals and Phytoconstituents

Natural compounds with recognized pharmacological activity but poor oral bioavailability, such as curcumin, resveratrol, and quercetin, have been extensively formulated as polymeric nanoparticles (e.g., PLGA-, chitosan-, or zein-based) to overcome their inherently low aqueous solubility and extensive first-pass glucuronidation/sulfation metabolism, with reported bioavailability enhancements ranging from several-fold to over an order of magnitude relative to the free compound.

8.4 Antihypertensive, Antidiabetic, and Antimicrobial Agents

BCS Class II/IV drugs such as glibenclamide, repaglinide, and certain antihypertensive and antitubercular agents have similarly been formulated as polymeric nanoparticles to improve dissolution and permeability, with several studies reporting reduced dosing frequency and improved therapeutic consistency as additional clinical benefits.

9. Challenges and Limitations

Despite considerable preclinical promise, the clinical and commercial translation of polymeric nanoparticles for oral delivery faces several significant challenges.

- Scale-up and manufacturing reproducibility: Laboratory-scale fabrication methods, particularly emulsification and nanoprecipitation, often face difficulty in reproducing critical quality attributes (particle size, PDI, EE%) at pilot and commercial manufacturing scale, necessitating process analytical technology (PAT) and quality-by-design (QbD) approaches.
- Residual solvent and excipient toxicity: Organic solvents and stabilizers used during fabrication must be reduced to levels compliant with ICH Q3C guidelines, and the long-term safety of chronic oral exposure to nanoparticulate polymers and novel excipients requires further investigation.
- Stability during storage and GI transit: Aqueous nanoparticle suspensions are prone to aggregation, drug leakage, and polymer degradation during storage, often necessitating lyophilization, while the formulation must additionally retain structural and functional integrity as it transits the harsh pH and enzymatic environment of the GI tract.
- Limited and variable absorption enhancement: Despite mechanistic promise, the absolute magnitude of oral bioavailability enhancement achieved for many biologics (e.g., insulin) remains insufficient for clinical dosing practicality, and inter-individual variability in GI physiology (pH, motility, microbiota composition, food effects) can further affect reproducibility of absorption.

- Regulatory complexity: Nanomedicines face an evolving and, in many jurisdictions, still-developing regulatory framework, requiring extensive characterization data, particle-specific toxicology and immunogenicity assessment, and well-validated analytical methods to support regulatory submission.
- Cost of goods and manufacturing infrastructure: Specialized equipment (e.g., microfluidic or supercritical fluid systems) and the need for stringent process control can substantially increase manufacturing cost relative to conventional oral dosage forms, posing a barrier to commercial viability, particularly for lower-cost generic markets.

10. Future Perspectives

Future research efforts are likely to focus on several converging directions to address the translational challenges outlined above. Advances in microfluidic and continuous-flow manufacturing platforms promise improved reproducibility and direct scalability from laboratory to commercial production. The application of artificial intelligence and machine learning to formulation design, including predictive modeling of polymer-drug compatibility, optimal process parameters, and in vitro-in vivo correlation (IVIVC), is expected to accelerate rational formulation development and reduce reliance on empirical trial-and-error approaches. Increasing sophistication in multi-functional and stimuli-responsive nanoparticle design, combining pH-responsiveness, enzyme-responsiveness, and active targeting within a single platform, may enable more precise spatiotemporal control over drug release. Additionally, greater emphasis on biomimetic and cell-membrane-coated nanoparticles, as well as hybrid lipid-polymer nanoparticles combining the advantages of both carrier classes, represents an active area of investigation. Finally, continued harmonization of regulatory guidance specific to oral nanomedicines, alongside robust long-term safety and immunogenicity data, will be essential to support the clinical translation and commercial adoption of these promising delivery systems.

11. Conclusion

Polymeric nanoparticles represent a versatile and mechanistically well-justified platform for addressing the multifactorial challenges limiting the oral bioavailability of poorly absorbed drugs. Through a combination of enhanced dissolution, protection from gastrointestinal degradation, mucoadhesive and permeation-enhancing properties, P-glycoprotein efflux circumvention, and the capacity for site-specific and stimuli-responsive targeting, these carriers offer a rational and adaptable approach to overcoming the biopharmaceutical limitations of BCS Class II and IV

drugs, as well as peptide, protein, and nucleic acid therapeutics. While substantial preclinical evidence supports the efficacy of polymeric nanoparticles in enhancing oral drug absorption, successful clinical translation will require continued progress in scalable and reproducible manufacturing, comprehensive long-term safety evaluation, and evolving regulatory clarity. With continued interdisciplinary research spanning materials science, pharmaceuticals, and computational formulation design, polymeric nanoparticle-based oral delivery systems hold considerable promise for improving the therapeutic outcomes of an important class of currently underutilized drug candidates.

References

1. Danhier, F., Ansorena, E., Silva, J. M., Coco, R., Le Breton, A., & Préat, V. (2012). PLGA-based nanoparticles: an overview of biomedical applications. *Journal of Controlled Release*, 161(2), 505–522.
2. Des Rieux, A., Fievez, V., Garinot, M., Schneider, Y. J., & Préat, V. (2006). Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. *Journal of Controlled Release*, 116(1), 1–27.
3. Rescignano, N., Tarpani, L., Romani, A., Bicchi, I., Mattioli, S., Emiliani, C., ... & Kenny, J. M. (2015). Protein encapsulation in biodegradable polymeric nanoparticles: morphology, fluorescence behaviour and stem cell uptake. *Macromolecular Bioscience*, 15(9), 1303–1311.
4. Bhattacharjee, S. (2016). DLS and zeta potential – what they are and what they are not. *Journal of Controlled Release*, 235, 337–351.
5. Yun, Y., Cho, Y. W., & Park, K. (2013). Nanoparticles for oral delivery: targeted nanoparticles with peptidic ligands for oral protein delivery. *Advanced Drug Delivery Reviews*, 65(6), 822–832.
6. Agrawal, U., Sharma, R., Gupta, M., & Vyas, S. P. (2014). Is nanotechnology a boon for oral drug delivery? *Drug Discovery Today*, 19(10), 1530–1546.
7. Reis, C. P., Neufeld, R. J., Ribeiro, A. J., & Veiga, F. (2006). Nanoencapsulation I: methods for preparation of drug-loaded polymeric nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, 2(1), 8–21.
8. Chan, J. M., Valencia, P. M., Zhang, L., Langer, R., & Farokhzad, O. C. (2010). Polymeric nanoparticles for drug delivery. *Cancer Nanotechnology: Methods and Protocols*, 163–175.
9. Mudie, D. M., Amidon, G. L., & Amidon, G. E. (2010). Physiological parameters for oral delivery and in vitro testing. *Molecular Pharmaceutics*, 7(5), 1388–1405.

10. Ensign, L. M., Cone, R., & Hanes, J. (2012). Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. *Advanced Drug Delivery Reviews*, 64(6), 557–570.
11. Sosnik, A., das Neves, J., & Sarmiento, B. (2014). Mucoadhesive polymers in the design of nano-drug delivery systems for oral cancer treatment. *Progress in Polymer Science*, 39(12), 2030–2075.
12. Bansil, R., & Turner, B. S. (2018). The biology of mucus: composition, synthesis and organization. *Advanced Drug Delivery Reviews*, 124, 3–15.
13. Gao, W., Chan, J. M., & Farokhzad, O. C. (2010). pH-responsive nanoparticles for drug delivery. *Molecular Pharmaceutics*, 7(6), 1913–1920.
14. Bansal, T., Akhtar, N., Jaggi, M., Khar, R. K., & Talegaonkar, S. (2009). Novel formulation approaches for optimising delivery of anticancer drugs based on P-glycoprotein modulation. *Drug Discovery Today*, 14(21–22), 1067–1074.
15. des Rieux, A., Ragnarsson, E. G. E., Gullberg, E., Pr  at, V., Schneider, Y. J., & Artursson, P. (2005). Transport of nanoparticles across an in vitro model of the human intestinal follicle associated epithelium. *European Journal of Pharmaceutical Sciences*, 25(4–5), 455–465.
16. Damg  , C., Michel, C., Aprahamian, M., & Couvreur, P. (1988). New approach for oral administration of insulin with polyalkylcyanoacrylate nanocapsules as drug carrier. *Diabetes*, 37(2), 246–251.
17. Onoue, S., Yamada, S., & Chan, H. K. (2014). Nanodrugs: pharmacokinetics and safety. *International Journal of Nanomedicine*, 9, 1025–1037.
18. Belouqui, A., Coco, R., Memvanga, P. B., Ucakar, B., des Rieux, A., & Pr  at, V. (2014). pH-sensitive nanoparticles for colonic delivery of curcumin in inflammatory bowel disease. *International Journal of Pharmaceutics*, 473(1–2), 203–212.
19. Zhang, Y., Wang, X., Li, S., Liu, X., & Zhang, X. (2013). Nanoparticles containing insulin or insulin-like growth factor for oral delivery. *Frontiers in Pharmacology*, 4, 91.
20. Woodruff, M. A., & Hutmacher, D. W. (2010). The return of a forgotten polymer—polycaprolactone in the 21st century. *Progress in Polymer Science*, 35(10), 1217–1256.