POLYMERIC NANOSPHERES FOR ORAL DRUG DELIVERY: EMERGING FORMULATION TECHNOLOGIES, TRANSLATIONAL CHALLENGES, AND FUTURE CLINICAL PERSPECTIVES

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ABSTRACT:
Oral drug delivery remains the most widely preferred route of drug administration owing to its convenience, patient compliance, cost-effectiveness, and suitability for long-term therapy. However, the oral delivery of many therapeutic agents is significantly limited by poor aqueous solubility, low intestinal permeability, gastrointestinal degradation, extensive first-pass metabolism, and efflux transporter activity, resulting in inadequate bioavailability and inconsistent therapeutic outcomes. Polymeric nanospheres have emerged as a promising nanotechnology-based platform capable of overcoming these physiological and biopharmaceutical barriers through enhanced drug protection, controlled release, improved mucosal interaction, and targeted intestinal absorption. The selection of appropriate biodegradable polymers, together with advances in formulation technologies such as nanoprecipitation, solvent evaporation, microfluidics, and continuous manufacturing, has considerably improved the physicochemical properties and therapeutic performance of oral nanosphere formulations. Furthermore, recent developments in surface engineering, stimuli-responsive polymers, artificial intelligence (AI)-assisted formulation design, machine learning (ML), and Quality by Design (QbD) have accelerated the optimization and translation of polymeric nanospheres from laboratory research toward industrial manufacturing. This review comprehensively summarizes the fundamental principles, classification, formulation strategies, characterization techniques, drug release mechanisms, surface functionalization approaches, and smart polymeric nanosphere systems developed for oral drug delivery. In addition, recent therapeutic applications in cancer, diabetes, infectious diseases, inflammatory disorders, neurological diseases, and biological therapeutics are critically discussed. The review also highlights current translational challenges, regulatory considerations, clinical perspectives, and future research directions with particular emphasis on intelligent nanomedicine, precision drug delivery, and sustainable pharmaceutical manufacturing. Overall, polymeric nanospheres represent a versatile and rapidly evolving oral drug delivery platform with significant potential to improve drug bioavailability, therapeutic efficacy, and patient outcomes while facilitating the development of next-generation oral nanomedicines.

Keywords: Polymeric nanospheres; Oral drug delivery; Biodegradable polymers; Nanotechnology; Drug delivery systems; Controlled drug release; Surface engineering; Artificial intelligence; Machine learning; Therapeutic applications; Clinical translation; Precision medicine.

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INTRODUCTION:

Oral drug delivery remains the most preferred and widely employed route for drug administration because of its convenience, cost-effectiveness, patient acceptance, and suitability for both acute and chronic therapies.[1-2] Compared with parenteral, transdermal, pulmonary, and other alternative delivery routes, oral administration is non-invasive, does not require specialized medical personnel, and facilitates self-medication, thereby improving treatment adherence. These advantages have established oral dosage forms as the cornerstone of modern pharmacotherapy, accounting for a substantial proportion of commercially available

pharmaceutical products. Conventional oral formulations such as tablets, capsules, powders, and suspensions are extensively used for the management of cardiovascular disorders, diabetes, infectious diseases, neurological conditions, gastrointestinal disorders, and various chronic illnesses.[3-5]

Despite these advantages, oral drug delivery continues to encounter significant physiological, biochemical, and pharmaceutical challenges that limit the therapeutic performance of many active pharmaceutical ingredients (APIs). The increasing number of newly discovered drug molecules with poor aqueous solubility and limited intestinal permeability has become a major obstacle in pharmaceutical development. A considerable proportion of compounds identified through modern drug discovery pipelines exhibit unfavorable biopharmaceutical properties, including low dissolution rates, inadequate gastrointestinal absorption, chemical instability,[6] enzymatic degradation, and extensive first-pass metabolism. These limitations frequently result in low and highly variable oral bioavailability, necessitating higher doses or repeated administration to achieve therapeutic plasma concentrations. Consequently, formulation scientists are increasingly focused on developing advanced drug delivery systems capable of overcoming these biological barriers while enhancing drug absorption and therapeutic efficacy.[7-10]

The gastrointestinal tract presents a complex and dynamic environment that profoundly influences the fate of orally administered drugs. Following ingestion, drug molecules encounter acidic gastric conditions, digestive enzymes, variable gastrointestinal transit times, mucus layers, epithelial tight junctions, intestinal efflux transporters, metabolic enzymes, and hepatic first-pass metabolism before reaching systemic circulation. Each of these physiological barriers can significantly reduce the fraction of drug absorbed, particularly for poorly soluble compounds, macromolecules, peptides, proteins, and drugs susceptible to enzymatic degradation. In addition, interindividual variability in gastrointestinal physiology, age, disease state, diet, and gut microbiota further contributes to inconsistent drug absorption and therapeutic response.[8-12]

Nanotechnology has emerged as one of the most promising strategies for addressing these limitations by enabling precise control over drug solubility, stability, permeability, release kinetics, and tissue distribution. Among the diverse nanocarrier systems investigated over the past two decades, polymeric nanospheres have attracted considerable attention because of their structural stability, high drug-loading capacity, tunable physicochemical properties, and ability to provide controlled and targeted drug release. Polymeric nanospheres are matrix-type nanoparticles in which drug molecules are uniformly dispersed, dissolved, or entrapped throughout a biodegradable or biocompatible polymer network. Their small particle size, high surface-area-to-volume ratio, and adaptable surface chemistry facilitate intimate interaction with the intestinal mucosa, thereby improving dissolution, prolonging gastrointestinal residence time, enhancing epithelial transport, and reducing premature drug degradation.

The selection of appropriate polymeric materials is a critical determinant of nanosphere performance. Both natural polymers, including chitosan, alginate, gelatin, dextran, and hyaluronic acid, and synthetic polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), polycaprolactone (PCL), polyethylene glycol (PEG), and Eudragit derivatives have been extensively investigated for oral drug delivery applications. These polymers provide distinct advantages in terms of biodegradability, mechanical strength, mucoadhesive behavior, surface functionalization, and controlled drug release. Recent advances in polymer chemistry have further enabled the development of stimuli-responsive, pH-sensitive, enzyme-responsive, and ligand-functionalized nanospheres capable of site-specific drug delivery within the gastrointestinal tract.[13-17]

The rapid evolution of formulation technologies has substantially expanded the therapeutic potential of polymeric nanospheres. Conventional preparation techniques such as solvent evaporation, nanoprecipitation, ionic gelation, and double-emulsion methods have been complemented by advanced manufacturing approaches, including microfluidic synthesis, flash nanoprecipitation, continuous manufacturing, and green fabrication techniques. Furthermore, the integration of Quality by Design (QbD), process analytical technology, computational modelling, and artificial intelligence has facilitated systematic formulation optimization, improved manufacturing reproducibility, and accelerated the translation of laboratory-scale formulations toward industrial production.[18-20]

Beyond formulation advances, polymeric nanospheres are increasingly being investigated for a broad spectrum of therapeutic applications. They have demonstrated significant potential for improving the oral delivery of anticancer agents, antidiabetic drugs, anti-inflammatory agents, antimicrobial compounds, cardiovascular medications, central nervous system therapeutics, herbal bioactives, peptides, proteins, nucleic acids, and other biologically active molecules that are otherwise limited by poor oral absorption. Surface engineering strategies involving polyethylene glycol coating, receptor-specific ligands, cell-penetrating peptides, and biomimetic functionalization have further enhanced intestinal

transport, prolonged systemic circulation, and improved tissue-specific targeting. These developments have expanded the applicability of polymeric nanospheres beyond conventional drug delivery, supporting emerging fields such as precision medicine, personalized therapeutics, and advanced nanomedicine.[16-22]

Despite the remarkable progress achieved during the past decade, several challenges continue to impede the widespread clinical translation of polymeric nanosphere-based oral drug delivery systems. Large-scale manufacturing, batch-to-batch reproducibility, long-term stability, sterilization, regulatory compliance, cost-effectiveness, and comprehensive safety evaluation remain major concerns that must be addressed before successful commercialization. In addition, harmonized regulatory guidelines for nanomedicines are still evolving, emphasizing the need for standardized characterization methods, robust quality control strategies, and well-designed clinical investigations.[21-23]

In view of these developments, a comprehensive and critical assessment of recent advances in polymeric nanospheres for oral drug delivery is both timely and necessary. Unlike earlier reviews that primarily focused on conventional formulation approaches, the present review aims to integrate emerging formulation technologies, polymer engineering strategies, advanced characterization techniques, biological performance, therapeutic applications, translational barriers, regulatory considerations, and future clinical perspectives. Special emphasis is placed on innovations such as microfluidic manufacturing, Quality by Design, artificial intelligence-assisted formulation development, surface functionalization, stimuli-responsive polymeric systems, and current challenges associated with the clinical translation of polymeric nanospheres. By critically evaluating recent scientific progress and identifying remaining knowledge gaps, this review seeks to provide researchers, formulation scientists, clinicians, and pharmaceutical industries with an updated framework for the rational design and successful development of next-generation oral polymeric nanosphere delivery systems.[24-27]

Table 1: comparison between the Conventional Oral Dosage and Polymeric Nanospheres

Aspect	**Conventional Oral Dosage Forms**	**Polymeric Nanospheres**
Drug solubility	Limited improvement	Markedly enhanced
Protection from GI degradation	Minimal	High
Controlled drug release	Limited	Excellent
Mucoadhesion	Poor	Good to excellent
Drug targeting	Not feasible	Surface-functionalization possible
Oral bioavailability	Often low	Improved
Patient compliance	High	High
Suitability for poorly soluble drugs	Limited	Highly suitable

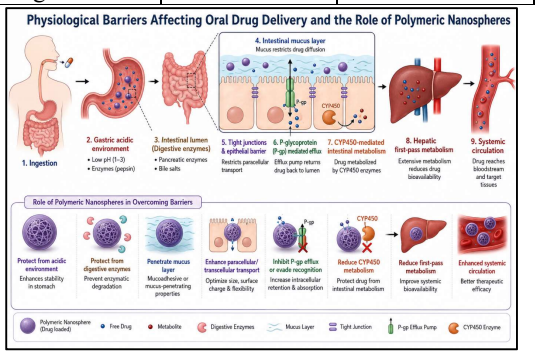

Figure 1: Physiological Barriers Affecting Oral Drug Delivery and the Role of Polymeric Nanospheres

ORAL DRUG DELIVERY: CURRENT CHALLENGES

Oral administration remains the most preferred route for drug delivery owing to its convenience, safety, cost-effectiveness, and high patient acceptance. Despite these advantages, the oral route presents several physiological and biochemical barriers that significantly limit the absorption and therapeutic performance of many drug molecules. Modern drug discovery has produced a growing number of active pharmaceutical ingredients (APIs) with poor physicochemical properties, particularly low aqueous solubility and limited intestinal permeability, resulting in suboptimal oral bioavailability. Furthermore, harsh gastrointestinal conditions, enzymatic degradation, efflux transporters, and extensive first-pass metabolism collectively reduce the fraction of drug reaching systemic circulation. Consequently, overcoming these barriers has become a major objective in the development of advanced oral drug delivery systems, particularly polymeric nanospheres, which offer improved drug protection, enhanced intestinal absorption, and controlled drug release.[28-40]

Poor Aqueous Solubility

Poor aqueous solubility is one of the most significant challenges limiting the oral delivery of pharmaceutical compounds. Approximately 40–70% of newly developed drug candidates exhibit low water solubility, leading to inadequate dissolution within gastrointestinal fluids and

consequently reduced absorption across the intestinal epithelium. According to the Biopharmaceutics Classification System (BCS), Class II and Class IV drugs are particularly affected because dissolution becomes the rate-limiting step for systemic absorption. Insufficient dissolution not only delays therapeutic onset but also results in variable plasma drug concentrations and reduced clinical efficacy.

Several conventional approaches, including salt formation, particle size reduction, solid dispersions, cyclodextrin complexation, and lipid-based formulations, have been employed to improve drug solubility. However, these strategies often provide limited enhancement for highly hydrophobic compounds. Polymeric nanospheres address this limitation by reducing particle size to the nanometer range, increasing surface area, enhancing wettability, and maintaining drug molecules in a dispersed state, thereby significantly improving dissolution rate and oral absorption.

Low Intestinal Permeability

Following dissolution, drug molecules must permeate the intestinal epithelial membrane to enter systemic circulation. Drugs with poor membrane permeability exhibit limited absorption despite adequate solubility. Hydrophilic compounds, macromolecules, peptides, proteins, and nucleic acid-based therapeutics are particularly affected because they cannot readily diffuse through the lipid-rich epithelial membrane. In addition, tight junctions restrict paracellular transport, further limiting the uptake of large or highly polar molecules.

Polymeric nanospheres improve intestinal permeability through multiple mechanisms, including prolonged mucosal residence, enhanced epithelial interaction, cellular uptake via endocytosis, and transient modulation of tight junctions when appropriate polymers such as chitosan are used. Surface-functionalized nanospheres can further facilitate receptor-mediated transport, thereby increasing drug permeation while minimizing systemic toxicity.

Gastrointestinal Degradation

The gastrointestinal tract presents a chemically and enzymatically hostile environment that can significantly degrade susceptible drug molecules before absorption. Gastric hydrochloric acid, digestive enzymes such as pepsin, trypsin, chymotrypsin, lipases, and intestinal esterases contribute to the degradation of peptides, proteins, nucleic acids, and acid-sensitive drugs. Consequently, many therapeutics lose biological activity before reaching the absorption site.

Polymeric nanospheres provide a protective polymeric matrix that shields encapsulated drugs from acidic pH and enzymatic degradation during gastrointestinal transit. Controlled drug release within the intestine further enhances drug stability and improves the amount of active drug available for absorption. This protective effect is particularly beneficial for biological therapeutics and chemically unstable compounds.

First-Pass Metabolism

After intestinal absorption, orally administered drugs are transported through the portal circulation to the liver, where extensive metabolism may occur before the drug reaches systemic circulation. This phenomenon, known as hepatic first-pass metabolism, substantially decreases the bioavailability of numerous therapeutic agents. In addition to hepatic metabolism, metabolic enzymes expressed within the intestinal mucosa, particularly cytochrome P450 isoenzymes, contribute to presystemic drug elimination.

Advanced polymeric nanospheres can partially overcome first-pass metabolism by promoting lymphatic uptake, sustaining drug release, and improving intracellular transport pathways. These mechanisms reduce premature metabolic degradation and increase systemic drug exposure, thereby enhancing therapeutic efficacy and reducing dose variability.

P-Glycoprotein Efflux

P-glycoprotein (P-gp), an ATP-dependent efflux transporter located on the apical membrane of intestinal epithelial cells, plays a major role in limiting oral drug absorption. After passive diffusion into epithelial cells, many drugs are actively transported back into the intestinal lumen by P-gp, thereby reducing intracellular drug concentration and systemic absorption. This transporter contributes significantly to the poor oral bioavailability of numerous anticancer agents, antiviral drugs, antibiotics, and immunosuppressive medications.

Polymeric nanospheres have demonstrated the ability to minimize P-gp-mediated drug efflux by facilitating intracellular nanoparticle uptake through endocytic pathways and by incorporating polymers or excipients capable of modulating transporter activity. Surface engineering strategies may further enhance drug retention within epithelial cells, leading to improved intestinal absorption.

Poor Oral Bioavailability

Oral bioavailability represents the proportion of an administered dose that reaches systemic circulation in an unchanged form. It is influenced by multiple interconnected factors, including poor solubility, inadequate permeability, gastrointestinal degradation, transporter-mediated efflux, presystemic metabolism, and rapid gastrointestinal transit. These limitations frequently result in inconsistent therapeutic outcomes and increased interpatient variability.

Polymeric nanospheres simultaneously address several of these barriers by enhancing dissolution, protecting drugs from degradation, improving

epithelial transport, prolonging gastrointestinal residence time, and enabling sustained drug release. The synergistic improvement of these parameters contributes to significantly higher oral bioavailability compared with conventional formulations.

Patient Compliance

Patient compliance is a critical determinant of therapeutic success, particularly in chronic diseases requiring prolonged treatment. Conventional oral dosage forms often require frequent dosing because of poor drug absorption, short biological half-life, or inadequate therapeutic exposure. Repeated administration may reduce patient adherence and compromise treatment outcomes.

Controlled-release polymeric nanospheres can reduce dosing frequency by maintaining therapeutic drug concentrations for extended periods. Improved drug stability, enhanced bioavailability, and reduced adverse effects further contribute to better patient acceptance and overall treatment compliance. These advantages make polymeric nanospheres particularly attractive for the long-term management of chronic conditions such as diabetes, cardiovascular disorders, cancer, and inflammatory diseases.

Table 2. Major Challenges in Oral Drug Delivery and the Potential Role of Polymeric Nanospheres

Challenge	Impact on Oral Drug Delivery	Strategy Offered by Polymeric Nanospheres
Poor aqueous solubility	Slow dissolution and limited absorption	Increased surface area and improved dissolution
Low intestinal permeability	Reduced epithelial transport	Mucoadhesion, endocytosis, enhanced permeation
Gastrointestinal degradation	Drug degradation in acidic and enzymatic environments	Protection through polymeric encapsulation
First-pass metabolism	Reduced systemic drug availability	Sustained release and partial lymphatic transport
P-glycoprotein efflux	Active drug transport back into the intestinal lumen	Reduced efflux through intracellular nanoparticle uptake
Poor oral bioavailability	Variable therapeutic response	Simultaneous enhancement of solubility, stability, and permeability
Poor patient compliance	Frequent dosing and reduced adherence	Controlled release and reduced dosing frequency

POLYMERIC NANOSPHERES: FUNDAMENTALS, CLASSIFICATION, AND EMERGING FORMULATION TECHNOLOGIES[41-58]

Polymeric Nanospheres: Fundamentals

Polymeric nanospheres are matrix-type colloidal drug delivery systems with particle sizes generally ranging from 10 to 1000 nm, in which the drug is uniformly dispersed, dissolved, or entrapped throughout a continuous polymeric matrix. Unlike polymeric nanocapsules, which possess a core-shell structure, nanospheres consist of a homogeneous polymer network that enables sustained and controlled drug release. Their nanoscale dimensions provide a high surface area-to-volume ratio, facilitating enhanced dissolution, improved interaction with the gastrointestinal mucosa, and increased oral drug absorption.

The growing interest in polymeric nanospheres is primarily attributed to their ability to overcome the limitations of conventional oral dosage forms. These nanocarriers protect encapsulated drugs from acidic gastric conditions, enzymatic degradation, and premature metabolism while simultaneously improving aqueous solubility, intestinal permeability, and systemic bioavailability. In addition, polymeric nanospheres can be engineered to achieve controlled, targeted, and stimuli-responsive drug release, making them suitable for delivering poorly soluble drugs, peptides, proteins, herbal phytoconstituents, and other bioactive molecules.

The physicochemical properties of polymeric nanospheres, including particle size, surface charge, morphology, polymer composition, and drug-loading efficiency, significantly influence their biological performance. These characteristics determine their stability, mucoadhesion, cellular uptake, biodistribution, and drug release kinetics. Consequently, careful polymer selection and formulation optimization are essential for developing safe, effective, and clinically translatable oral nanomedicines.

Classification of Polymeric Nanospheres

Polymeric nanospheres are commonly classified according to the origin of the polymer, biodegradability, and functional properties. The most widely used classification categorizes polymers into natural**,** synthetic biodegradable, and synthetic non-biodegradable polymers.

Natural polymers are derived from biological sources and possess excellent biocompatibility, biodegradability, and mucoadhesive properties. Chitosan, alginate, gelatin, dextran, hyaluronic acid, pullulan, and starch derivatives are frequently

employed because they improve intestinal residence time and enhance epithelial drug transport. Their ability to transiently open tight junctions further supports the oral delivery of hydrophilic drugs and macromolecules.

Synthetic biodegradable polymers are extensively investigated because of their predictable degradation profiles and controlled drug-release characteristics. Polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), polycaprolactone (PCL), and polyethylene glycol (PEG)-based copolymers have received considerable attention owing to their excellent safety profiles and regulatory acceptance. These materials allow precise control over particle size, drug release, and degradation kinetics, making them suitable for long-term therapeutic applications.

Synthetic non-biodegradable polymers, including polymethyl methacrylate (PMMA) and selected acrylic polymers, provide superior mechanical stability and prolonged drug retention. Although their application in oral drug delivery is relatively limited because of concerns regarding long-term accumulation, they remain useful for specific controlled-release formulations and experimental drug delivery systems.

Table 3. Classification of Polymers Commonly Used for Oral Polymeric Nanospheres

Polymer Class	Representative Polymers	Major Characteristics	Pharmaceutical Applications
Natural polymers	Chitosan, Alginate, Gelatin, Dextran, Pullulan, Hyaluronic acid	Biocompatible, biodegradable, mucoadhesive	Oral protein delivery, herbal formulations, controlled release
Synthetic biodegradable polymers	PLGA, PLA, PCL, PEG copolymers	Controlled degradation, sustained release, high stability	Oral delivery of poorly soluble drugs, anticancer and antidiabetic agents
Synthetic non-biodegradable polymers	PMMA, Acrylic polymers	High mechanical stability, prolonged release	Experimental controlled-release formulations

POLYMERS USED IN ORAL NANOSPHERES[51-67]

The selection of an appropriate polymer is a critical factor influencing the performance of polymeric nanospheres. An ideal polymer should exhibit excellent biocompatibility, biodegradability, low toxicity, high drug-loading capacity, adequate mechanical strength, and compatibility with large-scale pharmaceutical manufacturing. The physicochemical properties of the polymer also determine encapsulation efficiency, particle stability, drug release behavior, and biological interaction within the gastrointestinal tract.

Among natural polymers, chitosan is the most extensively investigated owing to its mucoadhesive nature, positive surface charge, and ability to transiently enhance intestinal permeability by modulating epithelial tight junctions. Alginate offers excellent pH-responsive behavior and protects acid-sensitive drugs from gastric degradation. Gelatin provides high drug encapsulation efficiency and biocompatibility, whereas dextran and hyaluronic acid facilitate targeted delivery and prolonged circulation through surface functionalization.

Synthetic polymers provide greater flexibility in formulation design and process reproducibility. PLGA remains the gold standard because of its excellent biodegradability, predictable degradation profile, and regulatory acceptance. PLA offers prolonged drug release due to its slower degradation, while PCL is particularly useful for sustained delivery of highly lipophilic drugs. Polyethylene glycol (PEG) is frequently incorporated to improve nanoparticle stability, reduce protein adsorption, and enhance mucus penetration.

Table 4. Frequently Used Polymers for Oral Polymeric Nanospheres

Polymer	Type	Major Advantages	Typical Applications
Chitosan	Natural	Mucoadhesive, permeation enhancer	Peptides, proteins, antidiabetic drugs
Alginate	Natural	pH-responsive, biodegradable	Colon-targeted delivery
Gelatin	Natural	High encapsulation efficiency	Protein and herbal drug delivery
Hyaluronic acid	Natural	Biocompatible, targeting ability	Targeted oral nanomedicine
PLGA	Synthetic biodegradable	Controlled release, FDA-approved	Anticancer, anti-inflammatory and antidiabetic drugs

PLA	Synthetic biodegradable	Slow degradation, sustained release	Long-acting oral formulations
PCL	Synthetic biodegradable	Excellent stability, prolonged release	Lipophilic drug delivery
PEG	Synthetic polymer	Enhanced stability and mucus penetration	Surface modification and stealth nanoparticles

EMERGING FORMULATION TECHNOLOGIES[68-75]

Recent advances in pharmaceutical nanotechnology have led to the development of highly efficient techniques for the preparation of polymeric nanospheres with improved reproducibility, scalability, and product quality. Conventional methods such as solvent evaporation, nanoprecipitation, ionic gelation, emulsification, and double-emulsion techniques remain widely employed because of their simplicity and versatility. However, these methods often exhibit limitations related to solvent consumption, particle-size variability, and scale-up.

Emerging formulation technologies are increasingly addressing these challenges. Microfluidic-assisted nanoparticle synthesis enables precise control over mixing conditions, resulting in uniform particle size distribution and excellent batch-to-batch reproducibility. Flash nanoprecipitation provides rapid nanoparticle formation with high encapsulation efficiency and is particularly suitable for poorly water-soluble drugs. Continuous manufacturing has gained considerable attention because it improves production efficiency, minimizes process variability, and facilitates industrial-scale manufacturing. Furthermore, green formulation technologies, employing environmentally friendly solvents and sustainable processing methods, are becoming increasingly important in response to global regulatory and environmental requirements.

The integration of Quality by Design (QbD) principles, advanced process analytical technologies (PAT), computational modelling, and artificial intelligence has further transformed formulation development. These approaches enable systematic optimization of critical material attributes and process parameters, leading to robust formulations with improved quality, reproducibility, and clinical translation potential.

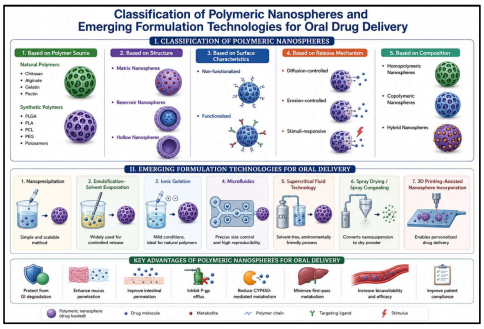

Figure 2: Classification of Polymeric Nanospheres and Emerging Formulation Technologies for Oral Drug Delivery

CHARACTERIZATION TECHNIQUES, DRUG RELEASE MECHANISMS, SURFACE ENGINEERING, AND SMART POLYMERIC NANOSPHERES[76-88]

Characterization Techniques

The successful development of polymeric nanospheres largely depends on comprehensive physicochemical characterization, which ensures product quality, stability, reproducibility, and therapeutic performance. Various analytical techniques are employed to evaluate particle size, morphology, surface properties, drug encapsulation, crystallinity, thermal behavior, and in vitro drug release. These characterization parameters significantly influence the biological fate, intestinal absorption, and overall oral bioavailability of nanosphere formulations.

Particle Size and Polydispersity Index (PDI)

Particle size is one of the most important characteristics influencing dissolution rate, cellular uptake, mucosal penetration, and drug absorption. Generally, polymeric nanospheres with particle sizes between 100 and 300 nm exhibit improved intestinal permeation and prolonged systemic circulation. The polydispersity index (PDI) reflects particle size distribution, where values below 0.30 indicate a homogeneous nanoparticle population. Dynamic Light Scattering (DLS) is the most commonly employed technique for simultaneous measurement of particle size and PDI.

Zeta Potential

Zeta potential represents the electrical charge present on the nanoparticle surface and serves as an important indicator of colloidal stability. Nanospheres with zeta potential values greater than ±30 mV generally exhibit sufficient electrostatic repulsion to prevent particle aggregation. Surface charge also influences mucoadhesion, cellular interaction, and gastrointestinal residence time, particularly for positively charged polymers such as chitosan.

Morphological Analysis

The morphology and surface architecture of polymeric nanospheres are examined using high-resolution microscopic techniques. Scanning Electron Microscopy (SEM) provides information

regarding particle shape and surface texture, whereas Transmission Electron Microscopy (TEM) offers detailed visualization of internal structure and particle dimensions. Atomic Force Microscopy (AFM) further enables three-dimensional surface profiling and roughness analysis.

Drug Encapsulation and Loading Capacity

Drug encapsulation efficiency (EE%) and drug loading (DL%) are critical quality attributes that determine formulation efficiency and therapeutic performance. High encapsulation efficiency minimizes drug loss during formulation, while optimal drug loading reduces the amount of carrier material required for effective therapy. These parameters are generally determined using validated UV-Visible spectrophotometric or chromatographic techniques such as HPLC.

Solid-State Characterization

Solid-state analytical techniques are employed to evaluate the physical state and compatibility of drug and polymer within the nanosphere matrix. Fourier Transform Infrared Spectroscopy (FTIR) identifies chemical interactions and functional groups, Differential Scanning Calorimetry (DSC) evaluates thermal transitions and compatibility, while X-ray Diffraction (XRD) determines crystalline or amorphous characteristics. Conversion of crystalline drugs into an amorphous form frequently enhances dissolution and oral bioavailability.

***In Vitro* Drug Release and Stability**

In vitro release studies provide valuable information regarding drug release kinetics under simulated gastrointestinal conditions. These investigations help predict in vivo performance and optimize sustained or controlled drug release profiles. In addition, accelerated and long-term stability studies evaluate changes in particle size, zeta potential, drug content, and encapsulation efficiency during storage, ensuring product quality throughout its shelf life.

Table 5. Common Characterization Techniques for Polymeric Nanospheres

Parameter	Analytical Technique	Pharmaceutical Significance
Particle size	Dynamic Light Scattering (DLS)	Influences dissolution, absorption, and cellular uptake
Polydispersity Index	DLS	Indicates particle size uniformity
Zeta potential	Electrophoretic Light Scattering	Determines colloidal stability and surface charge
Morphology	SEM, TEM, AFM	Evaluates particle shape and surface characteristics
Drug loading & Encapsulation efficiency	UV-Visible Spectroscopy, HPLC	Measures formulation efficiency
Chemical compatibility	FTIR	Detects drug–polymer interactions
Thermal behavior	DSC	Evaluates compatibility and thermal stability
Crystallinity	XRD	Determines crystalline or amorphous nature
Drug release	Dissolution apparatus	Assesses release kinetics and formulation performance
Stability	ICH stability studies	Evaluates long-term product stability

Drug Release Mechanisms

Drug release from polymeric nanospheres is governed by the physicochemical properties of both the drug and polymer, as well as environmental conditions within the gastrointestinal tract. Controlled release enhances therapeutic efficacy by maintaining drug concentrations within the desired therapeutic window while reducing dosing frequency and minimizing adverse effects.

Diffusion-Controlled Release

Diffusion is the most common mechanism of drug release, whereby dissolved drug molecules gradually migrate through the hydrated polymer matrix into the surrounding dissolution medium. The diffusion rate depends on polymer porosity, molecular weight, particle size, and drug solubility.

Polymer Degradation

Biodegradable polymers such as PLGA, PLA, and PCL gradually undergo hydrolytic or enzymatic degradation following oral administration. As the polymer matrix degrades, entrapped drug molecules are progressively released, providing prolonged therapeutic action over an extended period.

Swelling-Controlled Release

Hydrophilic polymers absorb gastrointestinal fluids and undergo swelling, resulting in increased pore size within the polymer matrix. Drug diffusion subsequently occurs through the swollen network, enabling sustained and predictable drug release.

Erosion-Controlled Release

Certain biodegradable polymers gradually erode following hydration, leading to continuous exposure and release of encapsulated drug molecules. Polymer erosion is particularly useful for developing long-acting oral formulations requiring extended therapeutic effects.

Stimuli-Responsive Drug Release

Modern polymeric nanospheres can be engineered to release drugs selectively in response to physiological stimuli such as changes in pH, enzymes, temperature, reactive oxygen species (ROS), or redox conditions. These intelligent systems improve site-specific drug delivery while minimizing systemic exposure and adverse effects.

Table 6. Major Drug Release Mechanisms in Polymeric Nanospheres

Release Mechanism	Principle	Major Advantage
Diffusion	Drug diffusion through polymer matrix	Sustained release
Polymer degradation	Polymer hydrolysis or biodegradation	Controlled long-term delivery
Swelling	Hydration-induced polymer expansion	Predictable release profile
Erosion	Gradual polymer erosion	Extended therapeutic effect
Stimuli-responsive release	Triggered by physiological conditions	Site-specific drug delivery

Surface Engineering and Functionalization

Surface engineering has emerged as an effective strategy for improving the biological performance of polymeric nanospheres. Modification of nanoparticle surfaces enhances gastrointestinal stability, prolongs circulation time, improves mucus penetration, facilitates receptor-mediated uptake, and enables targeted drug delivery.

PEGylation

Polyethylene glycol (PEG) coating reduces protein adsorption, improves nanoparticle stability, and facilitates penetration through the intestinal mucus barrier. PEGylation also prolongs systemic circulation by reducing recognition by the mononuclear phagocyte system.

Mucoadhesive Surface Modification

Polymers such as chitosan and carbopol enhance adhesion to the intestinal mucosa, thereby increasing gastrointestinal residence time and improving drug absorption. Mucoadhesive nanospheres are particularly advantageous for poorly permeable drugs.

Ligand-Mediated Targeting

Surface conjugation with ligands including folic acid, vitamin B12, transferrin, lectins, antibodies, and peptides enables receptor-specific drug delivery. These ligands promote receptor-mediated endocytosis, improving drug uptake by target tissues while minimizing off-target effects.

Biomimetic Functionalization

Recent advances include coating polymeric nanospheres with cell membranes, extracellular vesicles, or biomimetic materials to enhance immune evasion and biological compatibility. Such strategies improve circulation time and increase therapeutic efficiency.

Table 7. Surface Functionalization Strategies for Polymeric Nanospheres

Surface Modification	Purpose	Therapeutic Benefit
PEGylation	Improved stability	Enhanced circulation and mucus penetration
Chitosan coating	Mucoadhesion	Increased intestinal absorption
Folic acid conjugation	Receptor targeting	Improved cancer therapy
Vitamin B12 conjugation	Intestinal targeting	Enhanced oral uptake
Peptide or antibody conjugation	Active targeting	Increased cellular internalization
Biomimetic coating	Immune evasion	Improved therapeutic efficiency

Smart and Stimuli-Responsive Polymeric Nanospheres

Smart polymeric nanospheres represent an advanced generation of oral nanocarriers capable of responding to specific physiological or pathological stimuli. These intelligent systems release encapsulated drugs only when exposed to predetermined biological triggers, thereby improving therapeutic precision while reducing systemic toxicity.

pH-Responsive Systems

pH-sensitive polymers remain stable in the acidic gastric environment but undergo dissolution or swelling within the neutral to slightly alkaline intestinal pH. These systems effectively protect acid-sensitive drugs and promote site-specific intestinal drug release.

Enzyme-Responsive Systems

Enzyme-responsive polymers are specifically degraded by gastrointestinal or disease-associated enzymes, allowing localized drug release at the desired target site. Such systems are particularly useful for colon-targeted therapy.

Temperature-Responsive Systems

Temperature-sensitive polymers undergo reversible physicochemical changes in response to temperature variations, facilitating controlled drug release under physiological or pathological conditions.

Redox- and ROS-Responsive Systems

Redox-responsive and reactive oxygen species (ROS)-responsive nanospheres exploit differences in intracellular oxidative environments to trigger selective drug release. These systems have shown considerable promise for cancer and inflammatory disease management.

Multi-Stimuli-Responsive Systems

The latest generation of polymeric nanospheres integrates multiple stimuli-responsive mechanisms, such as pH, enzyme, and redox sensitivity, within a single delivery platform. These multifunctional nanocarriers provide highly controlled drug release, improved targeting efficiency, and superior therapeutic outcomes, making them promising candidates for precision medicine and next-generation oral drug delivery.

Table 8. Smart Polymeric Nanospheres and Their Biological Triggers

Smart System	Biological Trigger	Major Applications
pH-responsive	Gastrointestinal pH	Intestinal and colon-targeted delivery
Enzyme-responsive	Digestive or microbial enzymes	Colon-specific drug delivery
Temperature-responsive	Physiological temperature	Controlled release formulations
Redox-responsive	Intracellular glutathione	Cancer therapy
ROS-responsive	Oxidative stress	Inflammatory and malignant diseases
Multi-stimuli-responsive	Multiple physiological signals	Precision oral drug delivery

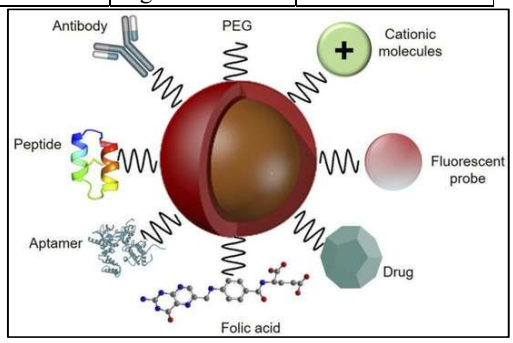

Figure 3: Surface engineering strategies for polymeric nanospheres

Artificial Intelligence and Machine Learning in Polymeric Nanosphere Development, Therapeutic Applications, Translational Challenges, and Clinical Perspectives[89-101]

The rapid advancement of artificial intelligence (AI) and machine learning (ML) has significantly transformed pharmaceutical formulation research by enabling data-driven design, optimization, and prediction of nanoparticle characteristics. Conventional formulation development often relies on extensive trial-and-error experimentation, which is time-consuming, labor-intensive, and resource intensive. AI-assisted computational approaches provide an efficient alternative by analyzing large experimental datasets, identifying complex relationships among formulation variables, and predicting optimal process conditions with improved accuracy.

Machine learning algorithms can accurately predict critical quality attributes such as particle size, polydispersity index, zeta potential, encapsulation efficiency, drug loading, and release kinetics based on polymer composition, formulation variables, and processing parameters. These predictive models reduce the number of experimental trials while improving formulation reproducibility and manufacturing efficiency.

Machine Learning Algorithms

Several machine learning techniques have been successfully applied in nanoparticle formulation. Artificial Neural Networks (ANN), Random Forest (RF), Support Vector Machine (SVM), Decision Trees, Gradient Boosting, and Deep Learning algorithms are increasingly employed for optimization of polymer selection, formulation composition, and process parameters. These algorithms continuously improve prediction accuracy by learning from previously generated experimental data.

Quality by Design and AI Integration

The integration of AI with the Quality by Design (QbD) framework enables systematic optimization of Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and Critical Quality Attributes (CQAs). AI-assisted Design of Experiments (DoE) accelerates formulation optimization, minimizes experimental variability, and enhances process robustness. Such integrated approaches are expected to facilitate regulatory compliance and improve industrial scalability.

Future Digital Technologies

Emerging digital technologies including digital twins, cloud-based pharmaceutical modelling, big-data analytics, and autonomous formulation platforms are expected to revolutionize nanosphere development. These technologies support real-time process monitoring, predictive quality control, and continuous manufacturing, ultimately accelerating the translation of laboratory-scale formulations into commercial pharmaceutical products.

Table 9. Applications of Artificial Intelligence in Polymeric Nanosphere Development

AI Technique	Primary Application	Major Advantages
Artificial Neural Network (ANN)	Formulation optimization	High prediction accuracy
Random Forest	Particle size prediction	Handles complex datasets
Support Vector Machine	Drug release prediction	Robust statistical modelling
Deep Learning	Image and morphology	Automated characterization

	analysis	
Bayesian Optimization	Process optimization	Reduced experimental workload
Digital Twin	Manufacturing simulation	Real-time process control

THERAPEUTIC APPLICATIONS OF POLYMERIC NANOSPHERES[102-114]

Polymeric nanospheres have demonstrated remarkable potential for improving oral drug delivery across a wide range of therapeutic areas. Their ability to enhance drug solubility, protect sensitive molecules, improve intestinal permeability, and provide controlled drug release has expanded their application beyond conventional pharmaceutical formulations.

Cancer Therapy

Polymeric nanospheres significantly improve the oral delivery of anticancer drugs by enhancing solubility, reducing systemic toxicity, prolonging circulation time, and increasing drug accumulation within tumor tissues. Surface-functionalized nanospheres further facilitate receptor-mediated targeting, improving therapeutic efficacy while minimizing adverse effects.

Diabetes Management

Numerous antidiabetic drugs exhibit poor aqueous solubility and variable gastrointestinal absorption. Polymeric nanospheres improve oral bioavailability through sustained drug release, enhanced intestinal permeability, and prolonged therapeutic action, resulting in improved glycemic control and reduced dosing frequency.

Infectious Diseases

Polymeric nanospheres enhance the therapeutic performance of antibiotics, antiviral agents, and antiparasitic drugs by improving drug stability, maintaining sustained drug concentrations, and reducing antimicrobial resistance associated with subtherapeutic exposure.

Neurological Disorders

The oral delivery of neuroprotective drugs remains challenging because of poor absorption and limited blood-brain barrier permeability. Polymeric nanospheres improve drug stability and systemic bioavailability, thereby increasing the potential for effective treatment of neurodegenerative diseases.

Inflammatory and Cardiovascular Diseases

Controlled-release polymeric nanospheres have been successfully investigated for anti-inflammatory and cardiovascular therapies. These systems improve therapeutic efficacy by maintaining prolonged plasma drug concentrations while reducing adverse effects associated with repeated dosing.

Delivery of Biological Therapeutics

Recent advances have expanded the application of polymeric nanospheres for oral delivery of peptides, proteins, nucleic acids, vaccines, probiotics, and herbal phytoconstituents. Polymeric encapsulation protects these sensitive biomolecules from enzymatic degradation and improves their intestinal absorption.

Table 10. Therapeutic Applications of Polymeric Nanospheres

Therapeutic Area	Major Advantages	Representative Drug Categories
Cancer	Targeted delivery, reduced toxicity	Anticancer drugs
Diabetes	Sustained release, improved bioavailability	Antidiabetic drugs
Infectious diseases	Enhanced stability	Antibiotics, antivirals
Neurological disorders	Improved absorption	Neuroprotective agents
Cardiovascular diseases	Controlled release	Antihypertensive and lipid-lowering agents
Inflammatory diseases	Reduced dosing frequency	NSAIDs, corticosteroids
Biological therapeutics	Protection from degradation	Peptides, proteins, vaccines

Translational Challenges

Despite substantial progress in laboratory research, only a limited number of polymeric nanosphere formulations have successfully advanced toward clinical application. The transition from experimental development to commercial pharmaceutical products remains challenging because of scientific, manufacturing, regulatory, and economic limitations.

Manufacturing and Scale-Up

Most polymeric nanospheres are developed under laboratory conditions using small-scale preparation techniques. Scaling these processes to industrial production while maintaining particle size, drug loading, and batch reproducibility remains a significant challenge.

Stability and Storage

Long-term physical and chemical stability is essential for commercial pharmaceutical products. Aggregation, polymer degradation, drug leakage, and changes in particle size during storage may negatively influence therapeutic performance and product shelf life.

Regulatory Challenges

The absence of universally harmonized regulatory guidelines for nanomedicines complicates product

approval. Regulatory agencies require comprehensive characterization, safety assessment, manufacturing validation, and quality assurance before commercialization.

Toxicity and Safety

Although many pharmaceutical polymers exhibit excellent biocompatibility, comprehensive evaluation of chronic toxicity, biodistribution, immunogenicity, and environmental safety remains necessary before widespread clinical application.

Economic Considerations

Advanced formulation technologies, sophisticated analytical instrumentation, and stringent manufacturing requirements increase production costs. Development of cost-effective, scalable, and sustainable manufacturing processes remains a major objective for future commercialization.

Table 11. Major Translational Challenges in Polymeric Nanosphere Development

Challenge	Impact	Possible Solution
Scale-up	Batch variability	Continuous manufacturing
Stability	Drug leakage and aggregation	Optimized formulation and packaging
Regulatory approval	Delayed commercialization	Standardized regulatory guidelines
Toxicity evaluation	Clinical uncertainty	Comprehensive preclinical studies
Manufacturing cost	Limited industrial adoption	Green and cost-effective technologies

CLINICAL PERSPECTIVES[115-118]

Recent progress in polymer chemistry, nanotechnology, computational modelling, and pharmaceutical manufacturing has accelerated the clinical translation of polymeric nanospheres. Several biodegradable polymers, particularly PLGA and PLA, have demonstrated excellent clinical safety profiles, encouraging further development of orally administered nanomedicines. The future clinical success of polymeric nanospheres will largely depend on the integration of advanced formulation technologies, artificial intelligence, Quality by Design, and precision medicine. Personalized oral nanomedicine based on patient-specific physiological characteristics, disease biomarkers, and pharmacogenomic information is expected to significantly improve therapeutic outcomes.

Furthermore, emerging technologies such as microfluidic manufacturing, continuous pharmaceutical processing, digital twins, organ-on-chip models, and biomimetic nanocarriers are likely to improve formulation reproducibility, regulatory acceptance, and industrial scalability. Collaborative efforts among academic researchers, pharmaceutical industries, clinicians, and regulatory authorities will be essential for translating promising laboratory findings into safe, effective, and commercially viable oral nanomedicine products.

Overall, polymeric nanospheres represent one of the most promising platforms for next-generation oral drug delivery. Continued interdisciplinary research integrating pharmaceutical sciences, biomaterials engineering, computational intelligence, and clinical medicine will facilitate the development of innovative nanotherapeutics capable of addressing unmet medical needs and improving patient care.

Table 12. Future Research Directions in Polymeric Nanospheres

Emerging Area	Expected Impact
Artificial intelligence-assisted formulation	Faster formulation optimization
Machine learning-based prediction	Improved product quality
Digital twins	Real-time manufacturing control
Continuous manufacturing	Industrial scalability
Biomimetic nanospheres	Enhanced biological performance
Precision medicine	Personalized oral therapy
Organ-on-chip models	Improved preclinical evaluation
Green nanotechnology	Sustainable pharmaceutical manufacturing
Smart multifunctional polymers	Targeted and controlled drug delivery
Clinical translation	Improved commercialization of nanomedicines

REGULATORY CONSIDERATIONS[114-121]

The successful clinical translation and commercialization of polymeric nanosphere-based oral drug delivery systems require compliance with stringent regulatory standards to ensure product quality, safety, efficacy, and manufacturing consistency. Unlike conventional pharmaceutical formulations, nanomedicines possess unique physicochemical characteristics, including particle size, surface charge, morphology, and drug release behavior, which necessitate specialized evaluation throughout product development. Consequently, regulatory agencies have emphasized the need for

comprehensive characterization and risk-based assessment during the approval process.

Regulatory framework

Several international regulatory authorities, including the United States Food and Drug Administration (FDA), the European Medicines Agency (EMA), the International Council for Harmonisation (ICH), and the World Health Organization (WHO), have published recommendations relevant to the development and evaluation of nanomedicines. Although no universally harmonized regulatory framework currently exists specifically for polymeric nanospheres, existing pharmaceutical guidelines are increasingly being adapted to accommodate nanoparticle-based drug delivery systems.

Quality and Safety Assessment

Regulatory approval requires comprehensive evaluation of critical quality attributes (CQAs), including particle size distribution, zeta potential, encapsulation efficiency, drug loading, stability, residual solvent levels, impurity profiling, sterility (where applicable), and in vitro drug release. In addition, extensive preclinical studies are necessary to evaluate acute and chronic toxicity, immunogenicity, biodistribution, pharmacokinetics, and biodegradation before initiation of clinical trials.

Good Manufacturing Practice (GMP)

Large-scale manufacturing of polymeric nanospheres must comply with Good Manufacturing Practice (GMP) requirements to ensure batch-to-batch reproducibility, process robustness, and product consistency. The implementation of Quality by Design (QbD) principles, Process Analytical Technology (PAT), and continuous manufacturing strategies has improved process control and reduced variability, facilitating industrial production of nanomedicines.

Regulatory Challenges

Despite considerable scientific progress, regulatory approval of polymeric nanospheres remains challenging because of the lack of standardized characterization protocols, validated analytical methods, and globally harmonized guidelines. Establishing internationally accepted standards for nanoparticle evaluation, toxicity assessment, and quality control will play a crucial role in accelerating the commercialization of polymeric nanosphere-based oral drug delivery systems.

Table 13. Regulatory Requirements for Polymeric Nanosphere-Based Oral Drug Delivery Systems

Regulatory Aspect	Major Requirement	Importance
Product quality	Particle size, PDI, zeta potential, drug loading	Ensures formulation consistency
Safety evaluation	Toxicity, immunogenicity, biodegradation	Confirms patient safety
Efficacy	Pharmacokinetic and pharmacodynamic studies	Demonstrates therapeutic effectiveness
Manufacturing	GMP compliance and process validation	Ensures reproducible production
Stability	ICH stability studies	Establishes product shelf life
Clinical evaluation	Phase I–III clinical studies	Confirms clinical safety and efficacy

FUTURE PERSPECTIVES:

The field of polymeric nanospheres is evolving rapidly with continuous advancements in biomaterials, pharmaceutical engineering, computational modelling, and precision medicine. Future research is expected to focus on the development of multifunctional nanocarriers capable of simultaneously improving oral bioavailability, disease-specific targeting, controlled drug release, and patient-specific therapy. The integration of biodegradable polymers with advanced surface engineering strategies will further enhance therapeutic performance while minimizing systemic toxicity.

Artificial intelligence, machine learning, and digital pharmaceutical technologies are anticipated to revolutionize formulation development by enabling predictive modelling, autonomous optimization, and real-time quality monitoring. Digital twins, cloud-based pharmaceutical manufacturing, and data-driven process optimization will facilitate continuous manufacturing, improve product reproducibility, and shorten development timelines.

Another important research direction involves the development of smart polymeric nanospheres capable of responding to multiple physiological stimuli, including pH, enzymes, oxidative stress, temperature, and inflammatory biomarkers. Such intelligent delivery systems are expected to provide highly selective drug release, reduce off-target effects, and improve therapeutic precision. In addition, biomimetic nanospheres coated with cell membranes or extracellular vesicles represent promising platforms for enhancing gastrointestinal transport and immune compatibility.

Personalized medicine is also expected to influence the future design of oral nanomedicines. The combination of pharmacogenomics, disease biomarkers, and patient-specific physiological characteristics may enable individualized drug delivery strategies with improved therapeutic efficacy and reduced adverse reactions. Furthermore, organ-on-chip technologies, three-dimensional (3D) bioprinting, and advanced in vitro intestinal models are likely to improve

preclinical evaluation and reduce dependence on animal experimentation.

Although significant progress has been achieved, successful clinical translation will require stronger collaboration among pharmaceutical scientists, clinicians, engineers, regulatory agencies, and industrial partners. Continued innovation in sustainable manufacturing, regulatory harmonization, and cost-effective production technologies will be essential for expanding the commercial availability of polymeric nanosphere-based oral drug delivery systems.

Table 14. Emerging Trends and Future Research Directions

Emerging Research Area	Potential Impact
Artificial intelligence and machine learning	Predictive formulation design and optimization
Smart multifunctional nanospheres	Controlled and site-specific drug delivery
Biomimetic nanocarriers	Improved intestinal transport and biocompatibility
Precision medicine	Patient-specific oral drug delivery
Continuous manufacturing	Industrial-scale production
Digital twins and PAT	Real-time process monitoring
Organ-on-chip technology	Improved preclinical evaluation
Green nanotechnology	Sustainable pharmaceutical manufacturing
Gene and nucleic acid delivery	Advanced therapeutic applications
Clinical translation	Commercialization of oral nanomedicines

CONCLUSION:

Polymeric nanospheres have emerged as one of the most promising nanotechnology-based platforms for improving oral drug delivery by addressing the major limitations associated with conventional dosage forms, including poor aqueous solubility, limited intestinal permeability, gastrointestinal degradation, and extensive first-pass metabolism. Their unique structural characteristics, versatile polymer composition, and capacity for controlled and targeted drug release have enabled significant improvements in drug stability, bioavailability, therapeutic efficacy, and patient compliance. Recent advances in formulation technologies, surface engineering, smart stimuli-responsive polymers, artificial intelligence-assisted optimization, and continuous manufacturing have substantially expanded the capabilities of polymeric nanospheres. These innovations have facilitated the development of more efficient, reproducible, and clinically relevant oral nanocarrier systems for a broad spectrum of therapeutic applications, including cancer, diabetes, infectious diseases, inflammatory disorders, and biological therapeutics. Despite encouraging progress, several challenges remain before polymeric nanospheres can achieve widespread clinical adoption. Large-scale manufacturing, long-term stability, standardized characterization, comprehensive safety evaluation, regulatory harmonization, and economic feasibility continue to represent major obstacles to commercialization. Addressing these issues through multidisciplinary research and close collaboration among academia, industry, clinicians, and regulatory authorities will be essential for accelerating clinical translation.

Overall, polymeric nanospheres represent a highly versatile and rapidly evolving oral drug delivery platform with considerable potential to transform future pharmaceutical therapy. Continued advances in biomaterials science, pharmaceutical nanotechnology, computational intelligence, and precision medicine are expected to drive the development of safer, smarter, and more effective nanomedicines, ultimately improving patient outcomes and expanding the clinical application of oral drug delivery systems.

CONFLICT OF INTEREST:

The authors declare that they have no competing financial interests.

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