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NOVEL MICROSPHERE FORMULATIONS: RECENT ADVANCES, PREPARATION STRATEGIES, CHARACTERIZATION, AND THERAPEUTIC APPLICATIONS

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ABSTRACT

Microspheres are effective drug delivery systems that offer controlled, sustained, and targeted drug release, enhancing therapeutic efficacy and patient compliance. This review discusses advancements in microsphere formulations, focusing on their structure, classification, materials, and fabrication techniques. It compares traditional methods, like solvent evaporation and spray drying, to innovative ones such as microfluidics and AI-assisted design. Recent developments include stimuli-responsive and multifunctional microspheres that improve site-specific drug delivery and precision therapeutics. The review highlights characterization techniques for evaluating microspheres in drug delivery, including aspects like particle size and release profiles. It explores their therapeutic potential in various applications, but notes challenges such as burst release and regulatory approval. Future research directions emphasize personalized medicine, AI-driven optimization, and sustainable manufacturing for clinical translation.

KEYWORDS: Microspheres, Crystallinity, Nanocomposite, Microencapsulation, Microfluidics, Controlled drug delivery, Targeted drug delivery, Polymeric microspheres, Stimuli-responsive microspheres.

1. INTRODUCTION

Drug delivery systems have evolved from conventional dosage forms, such as tablets, capsules, and injections, to advanced controlled and targeted delivery platforms that improve therapeutic efficacy while minimizing adverse effects. Among these, microspheres have emerged as promising carriers for site-specific and sustained drug delivery.

Microspheres are free-flowing spherical particles (1–1000 μm) composed of natural or synthetic polymers, in which the drug is uniformly dispersed throughout a polymeric matrix. Unlike microcapsules, they lack a distinct core–shell structure. Microsphere formulations enhance bioavailability, provide controlled drug release, reduce dosing frequency, improve patient compliance, and enable targeted delivery, making them valuable for delivering anticancer drugs, peptides, proteins, vaccines, and other sensitive therapeutics.[1,2,3,4]

2. DISTINCTIONBETWEEN MICROSPHERES AND MICROCAPSULES

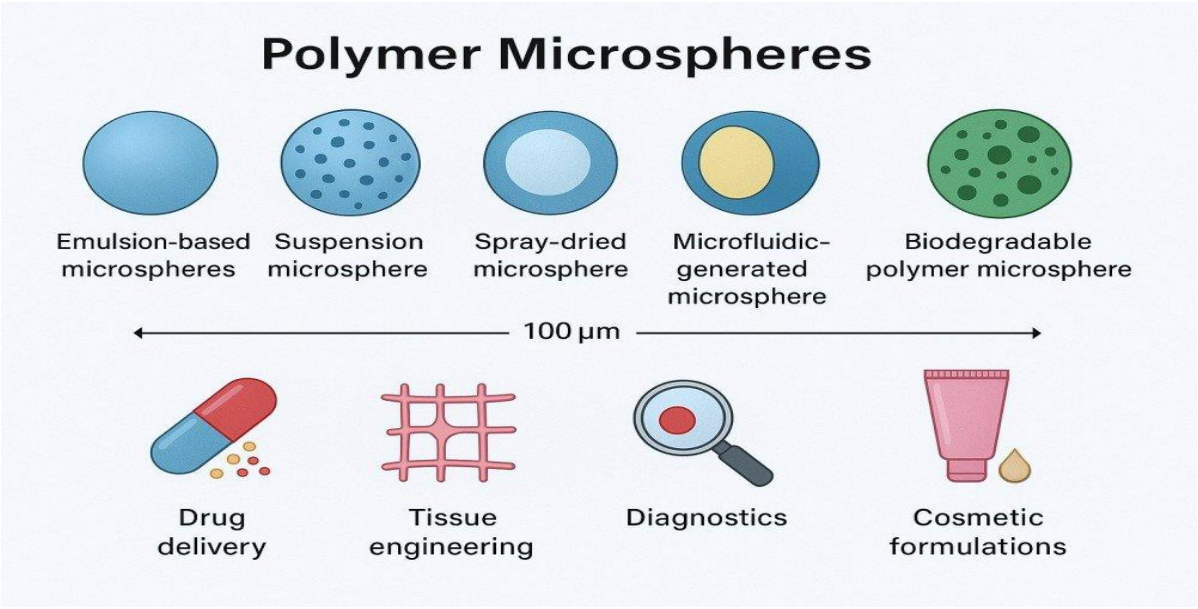
Microspheres and microcapsules are multiparticulate drug delivery systems that differ in structure and drug distribution. Microspheres are matrix systems with the drug uniformly dispersed throughout the polymer, whereas microcapsules possess a distinct core–shell structure enclosing the drug within a polymeric membrane. Microspheres release drugs through diffusion or matrix degradation, while microcapsules rely on membrane permeability or rupture.

Consequently, microcapsules provide superior drug protection, whereas microspheres offer simpler fabrication and sustained drug release.[5,6]

3. STRUCTURAL FEATURES OF MICROSPHERES

The structure of microspheres plays a critical role in determining their drug-loading capacity, release behavior, and biological performance. A typical microsphere consists of three major components:

1. **Polymeric Matrix:** Forms the structural framework of the microsphere and controls drug release.
2. **Active Pharmaceutical Ingredient (API):** Distributed uniformly or partially within the matrix.
3. **Surface Layer:** Determines particle interaction with biological tissues and influences mucoadhesion, cellular uptake, and targeting efficiency.



Microspheres may exhibit different internal architectures, including dense, porous, hollow, or multi-layered structures. Porous microspheres possess interconnected pores that enhance drug loading and facilitate rapid diffusion, whereas hollow microspheres are characterized by a central cavity that imparts buoyancy and gastro-retentive properties (Dastidar et al., 2018). Surface modifications such as PEGylation, ligand conjugation, and antibody attachment can further improve targeting specificity and circulation time.[7,8]

4. CLASSIFICATION OF MICROSPHERES

4.1 Classification of Microspheres Based on Composition

Microspheres are classified based on their composition into polymeric, protein-based, lipid, and ceramic/inorganic types. Polymeric microspheres may be biodegradable or non-biodegradable. Protein-based microspheres, such as albumin and gelatin, provide excellent biocompatibility. Lipid microspheres improve drug stability and bioavailability, while ceramic and inorganic microspheres, including silica, hydroxyapatite, and magnetic microspheres, are widely used for targeted drug delivery, imaging, and tissue engineering.[9]

4.2 Classification of Microspheres Based on Functional Properties

Based on functional properties, microspheres are classified as bioadhesive, floating, radioactive, magnetic, mucoadhesive, stimuli-responsive, and targeted microspheres. Bioadhesive and mucoadhesive systems enhance residence time and absorption, while floating microspheres prolong gastric retention. Radioactive and magnetic microspheres enable localized and targeted therapy. Stimuli-responsive microspheres release drugs in response to specific triggers, and targeted microspheres improve therapeutic efficacy by delivering drugs directly to diseased tissues.[10]

5. MATERIALS USED IN NOVEL MICROSPHERE FORMULATIONS

Novel microsphere formulations employ natural, synthetic, and smart polymers. Natural polymers such as chitosan, alginate, gelatin, and collagen provide biocompatibility and biodegradability. Synthetic polymers, including PLGA, PLA, PCL, PMMA, ethyl cellulose, and Eudragit, offer controlled drug release and stability. Smart materials, including thermoresponsive, pH-sensitive, redox-sensitive, enzyme-responsive, and self-healing polymers, enable stimuli-responsive, targeted, and precision drug delivery.[11]

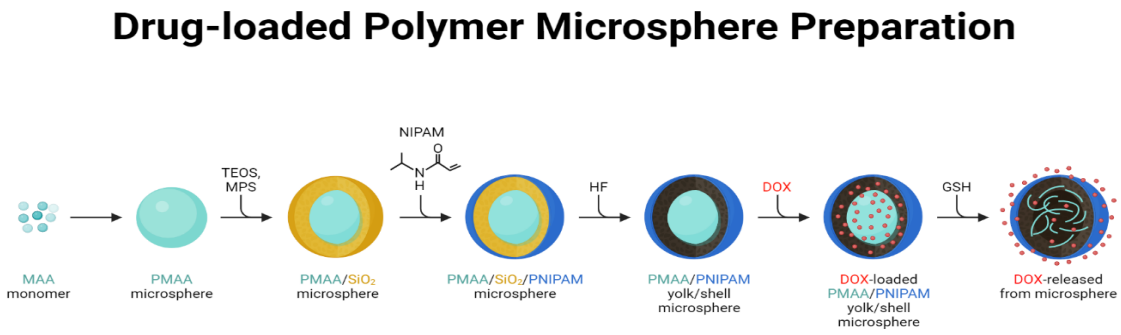
6. PREPARATION METHODS OF NOVEL MICROSPHERES

6.1 Conventional Techniques for Microsphere Preparation

Conventional methods include solvent evaporation, solvent extraction, phase separation/coacervation, spray drying, spray congealing, and emulsion crosslinking. Solvent evaporation and extraction are widely used for drug encapsulation and sustained release. Phase separation provides high drug loading but requires careful optimization.

Spray drying enables rapid, large-scale production, whereas spray congealing eliminates the need for organic solvents.

Emulsion crosslinking is commonly employed for natural polymers such as gelatin and chitosan. Although these techniques are economical and scalable, they may result in solvent residues, particle aggregation, and variable encapsulation efficiency.[12]



6.2 Advanced and Novel Fabrication Techniques

Advanced fabrication methods improve particle uniformity and formulation performance. Microfluidics produces monodisperse microspheres with precise size control, while electrospraying offers high encapsulation efficiency.

Supercritical fluid technology provides a green manufacturing approach with minimal solvent use. Membrane emulsification generates uniform particles, whereas 3D printing supports personalized drug delivery. AI-assisted formulation development integrates machine learning and Quality-by-Design (QbD) to optimize formulation parameters and predict product performance.[13]

6.3 Comparative Evaluation of Preparation Methods

Preparation methods differ in particle size control, scalability, encapsulation efficiency, and cost. Microfluidics provides excellent size control but is expensive. Spray drying is highly scalable and economical. Solvent evaporation offers good encapsulation efficiency but requires solvent handling. Electrospraying ensures precise particle formation with limited scalability, while supercritical fluid technology requires specialized equipment despite its environmental advantages.[14]

Method	Particle Size Control	Scalability	Encapsulation Efficiency	Cost
Solvent Evaporation	Moderate	Moderate	High	Moderate
Spray Drying	Moderate	High	Moderate	Low
Microfluidics	Excellent	Low–Moderate	High	High
Electrospraying	Excellent	Moderate	High	Moderate–High
Membrane Emulsification	High	Moderate	High	Moderate
Supercritical Fluid Technology	High	Moderate	High	High

7. CHARACTERIZATION OF MICROSPHERES

7.1 Particle Size Analysis

Particle size is a critical parameter affecting drug loading, release behavior, stability, and therapeutic performance.

Optical microscopy is a simple and economical method for measuring particle size and morphology. Laser diffraction determines particle size distribution based on light scattering and is suitable for a broad size range. Dynamic Light Scattering (DLS) measures particle size by analyzing Brownian motion and is particularly useful for small particles.

These techniques ensure formulation consistency and quality control.[15]

7.2 Morphological Evaluation

Morphological evaluation assesses the shape, surface characteristics, and internal structure of microspheres. Scanning Electron Microscopy (SEM) provides high-resolution images of surface morphology, porosity, and particle integrity.

Transmission Electron Microscopy (TEM) reveals the internal architecture at the nanometer scale, while Atomic Force Microscopy (AFM) generates three-dimensional surface images and measures surface roughness. These techniques help correlate morphology with drug loading, release behavior, and formulation stability.[16]

7.3 Surface Characterization

Surface characterization is important for evaluating microsphere stability and biological performance. Zeta potential measures surface charge and predicts colloidal stability, with higher absolute values indicating lower aggregation.

Surface roughness, commonly analyzed by AFM, influences drug release, mucoadhesion, cellular uptake, and protein adsorption. Together, these parameters provide valuable information on formulation stability and targeting efficiency.[17]

7.4 Drug Loading Parameters

Drug loading parameters determine the efficiency of microsphere formulations. Drug Loading Capacity (DLC) represents the amount of drug incorporated relative to the total microsphere weight, whereas Encapsulation Efficiency (EE) indicates the percentage of drug successfully entrapped during formulation. High DLC and EE improve therapeutic efficacy, minimize drug wastage, and support sustained drug release.[18]

7.5 Thermal Analysis

Thermal analysis evaluates the physicochemical properties and stability of microspheres. Differential Scanning Calorimetry (DSC) measures thermal transitions such as melting point and glass transition temperature, providing information on drug–polymer compatibility and crystallinity. Thermogravimetric Analysis (TGA) monitors weight changes with temperature to assess thermal stability, moisture content, and decomposition behavior. These techniques are essential for formulation optimization and storage stability.[19]

7.6 Crystallinity Studies

X-ray Diffraction (XRD) is widely used to determine the crystalline or amorphous nature of drugs and polymers in microspheres. Changes in diffraction peaks indicate drug encapsulation, drug–polymer interactions, or conversion to an amorphous state. Since crystallinity influences solubility, dissolution, stability, and drug release, XRD is an important tool for formulation development and quality assessment.[20]

7.7 Chemical Interaction Studies

Chemical interaction studies evaluate compatibility between drugs and excipients. Fourier Transform Infrared Spectroscopy (FTIR) identifies functional groups and detects drug–polymer interactions through characteristic absorption peaks. Raman spectroscopy complements FTIR by providing information on molecular structure, crystallinity, and chemical composition. These techniques confirm successful drug encapsulation and ensure formulation stability.[21]

7.8 In Vitro Drug Release Studies

Chemical interaction studies evaluate compatibility between drugs and excipients. Fourier Transform Infrared Spectroscopy (FTIR) identifies functional groups and detects drug–polymer interactions through characteristic absorption peaks. Raman spectroscopy complements FTIR by providing information on molecular structure, crystallinity, and chemical composition. These techniques confirm successful drug encapsulation and ensure formulation stability.[22]

7.9 Stability Studies

Stability studies assess the quality, safety, and efficacy of microsphere formulations during storage. Following ICH guidelines, formulations are evaluated under normal and accelerated conditions to determine the effects of temperature, humidity, and light. Parameters including particle size, drug content, encapsulation efficiency, morphology, and release profile are monitored. Accelerated stability testing helps predict shelf life, establish storage conditions, and ensure consistent product quality.[23]

8. NOVEL MICROSPHERE FORMULATIONS AND RECENT ADVANCES

8.1 Stimuli-Responsive Microspheres

Stimuli-responsive microspheres are advanced drug delivery systems that release drugs in response to specific internal or external stimuli. pH-sensitive microspheres target regions with different pH, such as the gastrointestinal tract and tumors. Thermo-responsive microspheres release drugs upon temperature changes, while magnetic-responsive microspheres are guided by external magnetic fields for site-specific delivery. Ultrasound-responsive and light-triggered microspheres enable controlled, non-invasive, and precise drug release, improving therapeutic efficacy and minimizing side effects.[24]

8.2 Multifunctional Microspheres

Multifunctional microspheres combine therapeutic and diagnostic functions in a single platform. Theranostic microspheres integrate drug delivery with disease monitoring. Drug-imaging systems incorporate imaging agents such as fluorescent dyes or magnetic nanoparticles to visualize drug distribution. Dual-drug loaded microspheres deliver two therapeutic agents simultaneously or sequentially, producing synergistic therapeutic effects. These systems enhance precision medicine, improve treatment outcomes, and reduce systemic toxicity.[25]

8.3 Nanocomposite Microspheres

Nanocomposite microspheres combine polymeric matrices with nanomaterials to improve drug delivery. Polymer–nanoparticle hybrids enhance drug loading, stability, and targeting efficiency. Graphene-containing microspheres provide high surface area, improved mechanical strength, and controlled drug release. Carbon nanotube-integrated microspheres offer enhanced drug adsorption, cellular uptake, and stimuli-responsive behavior. These systems have promising applications in cancer therapy, tissue engineering, and regenerative medicine.[26]

8.4 Surface-Modified Microspheres

Surface modification enhances the biological performance of microspheres. PEGylated microspheres prolong circulation time by reducing protein adsorption and immune recognition. Ligand-conjugated microspheres target specific receptors using molecules such as folic acid or peptides, while antibody-targeted microspheres improve

selective binding to diseased cells. These modifications increase drug accumulation at target sites, improve therapeutic efficacy, and reduce systemic toxicity.[27]

8.5 Injectable Depot Microspheres

Injectable depot microspheres are long-acting formulations that provide sustained drug release after a single administration. Typically prepared using biodegradable polymers such as PLGA, they maintain therapeutic drug concentrations over extended periods. Monthly and quarterly injectable formulations are widely used for hormones, antipsychotics, and peptide drugs. These systems reduce dosing frequency, improve patient adherence, ensure consistent drug release, and enhance the management of chronic diseases.[28]

9. THERAPEUTIC APPLICATIONS

9.1 Cancer Therapy

Microspheres have become important carriers in cancer therapy due to their ability to provide controlled drug release and reduce systemic toxicity. They encapsulate chemotherapeutic agents, maintaining therapeutic drug concentrations for prolonged periods. Tumor-targeting microspheres, functionalized with ligands, antibodies, or magnetic materials, selectively accumulate at tumor sites. Radioembolization microspheres, such as yttrium-90-loaded systems, deliver localized radiation directly to liver tumors. These approaches enhance therapeutic efficacy, minimize damage to healthy tissues, and improve treatment outcomes.[29]

9.2 Oral Drug Delivery

Microspheres enhance oral drug delivery by improving bioavailability and prolonging gastrointestinal residence time. Gastroretentive (floating) microspheres remain buoyant in gastric fluids, providing sustained drug release and improved absorption. Colon-targeted microspheres release drugs specifically in the colon using pH-sensitive or enzyme-responsive mechanisms. These systems are beneficial for treating inflammatory bowel disease, colorectal disorders, and delivering sensitive biomolecules such as proteins and peptides while reducing systemic side effects.[30]

9.3 Ocular Drug Delivery

Microsphere-based ocular formulations overcome rapid drug elimination associated with conventional eye drops. They provide sustained drug release, reducing dosing frequency and improving patient compliance. Microspheres can also be designed for retinal targeting, enabling efficient delivery to the posterior segment of the eye for diseases such as age-related macular degeneration and diabetic retinopathy. These systems improve ocular bioavailability and therapeutic effectiveness.[31]

9.4 Pulmonary Drug Delivery

Microspheres are increasingly used for pulmonary drug delivery because their particle size (1–5 μm) allows efficient deposition in the lungs. They provide sustained drug release and enhance absorption through the alveolar surface.

Pulmonary microspheres are useful for treating asthma, chronic obstructive pulmonary disease (COPD), pulmonary infections, and lung cancer. They also protect sensitive biomolecules from degradation, improving therapeutic efficacy.[32]

9.5 Nasal Drug Delivery

Microsphere-based nasal systems offer a non-invasive route for local and systemic drug delivery. Their mucoadhesive properties prolong residence time in the nasal cavity and enhance drug absorption. They protect drugs from enzymatic degradation and improve the bioavailability of peptides and proteins. Nasal microspheres are particularly promising for nose-to-brain delivery, enabling direct transport of drugs to the central nervous system while bypassing the blood–brain barrier.[33]

9.6 Transdermal Applications

Microspheres have significant potential in transdermal drug delivery by providing controlled and sustained drug release across the skin. Drug encapsulation improves stability and allows gradual release, maintaining therapeutic concentrations over extended periods. These systems enhance skin permeation, reduce dosing frequency, and improve patient compliance. Microspheres are incorporated into patches, gels, and creams for the delivery of analgesics, anti-inflammatory drugs, hormones, and cardiovascular medications while minimizing first-pass metabolism.[34]

9.7 Vaccine Delivery

Microsphere-based vaccine delivery systems protect antigens from degradation and enhance immune responses. Biodegradable polymers such as PLGA provide sustained antigen release, reducing the need for multiple vaccine doses. Microspheres also act as adjuvants by improving antigen uptake by immune cells and promoting stronger humoral and cellular immunity. These systems have shown promise in infectious disease vaccines, cancer immunotherapy, and next-generation vaccine development.[35]

9.8 Protein and Peptide Delivery

Microspheres are effective carriers for proteins and peptides because they protect these molecules from enzymatic degradation and improve their stability. Biodegradable polymeric microspheres enable sustained and controlled drug release, reducing injection frequency and improving patient compliance. They have been successfully used for the delivery of insulin, hormones, growth factors, and therapeutic peptides, resulting in enhanced bioavailability and prolonged therapeutic effects.[36]

9.9 Gene Delivery

Microspheres are promising non-viral vectors for gene delivery because they protect nucleic acids such as DNA, mRNA, siRNA, and plasmids from degradation. Biodegradable polymeric microspheres provide controlled release and improve cellular uptake. Surface modification with targeting ligands further enhances tissue-specific delivery. These systems have potential applications in gene therapy, cancer treatment, vaccine development, and the management of inherited diseases.[37]

9.10 Tissue Engineering and Regenerative Medicine

Microspheres play a vital role in tissue engineering by serving as carriers for cells, growth factors, and bioactive molecules that promote tissue regeneration. Biodegradable microspheres incorporated into scaffolds provide sustained release of signaling molecules, supporting cell proliferation and differentiation. They have been widely investigated for bone, cartilage, skin, vascular, and nerve tissue engineering. Microsphere-based systems improve scaffold properties, mimic the extracellular matrix, and facilitate the development of advanced regenerative therapies.[38,39,40,41]

10. CHALLENGES AND LIMITATIONS

- Burst Release Phenomenon: Rapid initial drug release may cause dose dumping.
- Low Encapsulation Efficiency: Reduced drug loading and increased formulation costs.
- Reproducibility Concerns: Batch-to-batch variations in particle size and drug release.
- Sterilization Challenges: Sterility maintenance may affect drug and polymer stability.
- Regulatory Barriers: Stringent FDA, EMA, and ICH requirements delay approval.[42,43, 44,45]

11. FUTURE PERSPECTIVES

The future of microsphere technology is driven by advances in precision medicine and intelligent drug delivery.

Personalized microsphere therapy aims to tailor drug release profiles to individual patient needs. AI-driven formulation design and predictive modeling can accelerate optimization, improve quality, and reduce development costs.

Microfluidics and continuous manufacturing offer precise particle control and scalable production. Smart responsive delivery systems capable of reacting to pH, temperature, enzymes, or external stimuli will enhance targeted therapy.

Additionally, combination therapies, gene and mRNA delivery applications, and sustainable green manufacturing approaches are expected to expand the clinical utility, safety, and commercial viability of microsphere-based drug delivery systems.[46]

12. CONCLUSION

Novel microsphere formulations have significantly advanced drug delivery by enabling controlled release, targeted delivery, enhanced bioavailability, and improved patient compliance. Recent developments in smart polymers, microfluidics, nanocomposite systems, and stimuli-responsive technologies have expanded their applications across cancer therapy, vaccine delivery, regenerative medicine, and gene therapy. These innovations highlight the growing importance of microspheres in modern therapeutics and precision medicine. Despite successful clinical products, challenges related to scale-up, reproducibility, regulatory approval, and long-term stability remain. Future research should focus on personalized therapies, AI-assisted formulation design, sustainable manufacturing, and improved translational strategies to accelerate clinical adoption and maximize therapeutic benefits.

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