

## Microsphere Technology in Pharmaceuticals: Principles, Preparation Methods, and Applications in Targeted Diabetes Drug Delivery

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### Abstract

Microsphere technology has emerged as a promising drug delivery strategy in modern pharmaceuticals, offering controlled release, improved bioavailability, and targeted therapeutic action. These spherical particulate systems, typically ranging from 1–1000  $\mu\text{m}$ , are prepared using natural or synthetic polymers and can encapsulate a wide range of therapeutic agents. In diabetes management, microspheres have gained significant attention for delivering antidiabetic drugs, insulin, and novel biologics in a sustained and site-specific manner, thereby improving patient compliance and therapeutic outcomes. Advances in polymer science, nanotechnology integration, and smart drug delivery approaches have further enhanced their potential in targeted diabetes therapy. This review discusses the fundamental principles of microsphere technology, preparation methods, characterization techniques, recent innovations, and their applications in targeted diabetes drug delivery.

**Keywords:** Microspheres, Targeted Drug Delivery, Diabetes Mellitus, Controlled Release, Polymeric Carriers, Insulin Delivery, Advanced Pharmaceuticals.

### Introduction

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide, characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The condition is broadly classified into type 1 diabetes, caused primarily by autoimmune destruction of pancreatic  $\beta$ -cells leading to insulin deficiency, and type 2 diabetes, which involves insulin resistance combined with inadequate compensatory insulin secretion. The increasing global burden of diabetes has become a major public health concern due to its association with severe complications such as cardiovascular disease, neuropathy, nephropathy, retinopathy, and impaired wound healing. Effective long-term pharmacotherapy and consistent glycemic control are essential to prevent these complications and improve patient quality of life.

Conventional antidiabetic drug delivery systems, including oral tablets, capsules, and injectable formulations, have been widely used for decades. However, these traditional dosage forms often present several limitations. Frequent dosing requirements can lead to poor patient adherence, especially in chronic diseases requiring lifelong therapy. Additionally, conventional formulations may produce fluctuating plasma drug concentrations, resulting in suboptimal therapeutic outcomes and increased risk of side effects. Drugs such as insulin and certain peptide-based therapies are particularly susceptible to enzymatic degradation, poor absorption, and instability, which further complicates their effective delivery. These challenges highlight the need for advanced drug delivery strategies capable of improving therapeutic efficacy while minimizing adverse effects.

In recent years, microsphere-based drug delivery systems have emerged as a promising approach to overcome the limitations of conventional formulations. Microspheres are small spherical particles, typically ranging from 1 to 1000 micrometers in diameter, composed of biodegradable or non-biodegradable polymers that encapsulate therapeutic agents. These systems offer controlled and sustained drug release, allowing maintenance of optimal drug concentrations over extended periods. This controlled release profile not only enhances therapeutic efficacy but also reduces dosing frequency, thereby improving patient compliance. Such advantages are particularly beneficial in diabetes management, where consistent glycemic control is critical.

Another significant advantage of microsphere technology is its ability to protect sensitive drugs from degradation. Many antidiabetic drugs, especially proteins and peptides like insulin, are prone to degradation by gastrointestinal enzymes or environmental factors such as pH and temperature. Encapsulation within microspheres provides a protective barrier that enhances drug stability and bioavailability. This protection facilitates the development of alternative delivery routes, including oral, pulmonary, and transdermal administration, which are less invasive compared to traditional injections and thus more acceptable to patients.

Targeted drug delivery represents another key benefit of microsphere systems. Through surface modification, ligand attachment, or magnetic guidance, microspheres can be engineered to deliver drugs selectively to specific tissues or organs. Targeted delivery improves therapeutic outcomes by concentrating the drug at the site of action while reducing systemic exposure and associated side effects. In diabetes therapy, targeted approaches can enhance insulin delivery, improve glucose regulation, and reduce complications associated with long-term drug use. Furthermore, advances in polymer science have enabled the development of smart or stimuli-responsive microspheres that release drugs in response to physiological triggers such as glucose concentration, pH, or temperature, offering a more precise and personalized therapeutic approach.

Microsphere systems also provide versatility in terms of administration routes. Oral microspheres are designed to enhance drug absorption and prolong gastrointestinal residence time, making them suitable for drugs with narrow absorption windows. Injectable microspheres can act as depot formulations, providing sustained drug release over weeks or months. Pulmonary microsphere formulations allow non-invasive insulin delivery through inhalation, while transdermal microspheres facilitate controlled drug diffusion across the skin. Such diverse delivery options expand therapeutic possibilities and improve patient comfort and adherence.

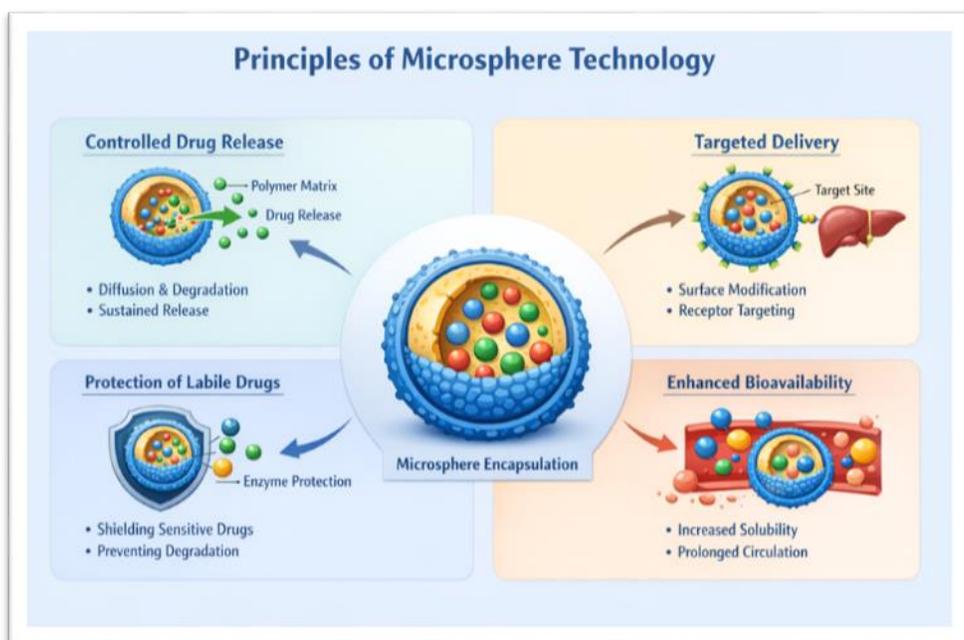
Despite their promising advantages, the development of microsphere-based drug delivery systems presents certain challenges. These include complexities in formulation design, scale-up difficulties during manufacturing, potential stability issues, and regulatory considerations. Ensuring reproducibility, biocompatibility, and consistent drug release profiles remains a critical focus in research. Nevertheless, ongoing advancements in material science, nanotechnology integration, and pharmaceutical engineering continue to address these challenges, enhancing the feasibility of microsphere systems for clinical use.

Overall, microsphere technology represents a significant advancement in pharmaceutical drug delivery, particularly for chronic conditions such as diabetes mellitus. By providing controlled release, enhanced stability, targeted delivery, and

improved patient compliance, microspheres have the potential to transform diabetes management. Continued research and technological innovation are expected to further optimize these systems, paving the way for more effective, safe, and patient-friendly therapeutic solutions in the future.

### Principles of Microsphere Technology

Microsphere technology represents an advanced pharmaceutical drug delivery approach in which therapeutic agents are encapsulated within polymeric matrices to achieve controlled, targeted, and efficient drug delivery. Microspheres are typically spherical particles ranging from 1 to 1000  $\mu\text{m}$  in size and are prepared using biodegradable or non-biodegradable polymers depending on the intended therapeutic application. These carriers are designed to encapsulate active pharmaceutical ingredients within a protective polymer shell or matrix, enabling improved drug stability, controlled release, and enhanced therapeutic performance. The fundamental principles underlying microsphere technology involve mechanisms of drug release control, site-specific targeting, protection of sensitive drug molecules, and enhancement of drug bioavailability.



**Controlled drug release** is one of the most important principles of microsphere-based delivery systems. Drugs incorporated into microspheres can be released in a sustained or controlled manner through diffusion, polymer degradation, erosion, or osmotic pressure mechanisms. Diffusion-controlled release occurs when the drug gradually diffuses through the polymer matrix, while degradation-controlled release involves gradual breakdown of biodegradable polymers such as polylactic acid or chitosan. This sustained release helps maintain consistent plasma drug levels, minimizes dosing frequency, reduces peak-trough fluctuations, and improves patient adherence to therapy. Such controlled release is particularly beneficial in chronic diseases like diabetes, where long-term and stable drug delivery is essential for effective glycemic control.

**Targeted drug delivery** is another key principle of microsphere technology. Surface modification of microspheres using ligands, antibodies, polymers, or magnetic materials enables site-specific drug delivery to targeted tissues or cells. This targeting can be passive, based on particle size and physiological characteristics, or active, involving receptor-mediated interactions. Targeted delivery enhances therapeutic efficacy by concentrating the drug at the desired site of action while minimizing systemic exposure and adverse effects. Advances in surface engineering and functional polymer design have significantly improved the precision of targeted drug delivery using microspheres.

**Protection of labile** or sensitive drugs represents another major advantage of microsphere systems. Many therapeutic agents, particularly proteins, peptides, and certain small molecules, are prone to degradation due to environmental conditions such as pH changes, enzymatic activity, temperature fluctuations, or oxidation. Encapsulation within polymeric microspheres forms a protective barrier that shields the drug from these destabilizing factors. This protective effect enhances drug stability during storage and after administration, improving therapeutic efficacy. It also facilitates the development of non-invasive delivery routes such as oral or pulmonary administration for drugs that would otherwise require injection.

**Enhanced bioavailability** is an additional important principle associated with microsphere technology. Encapsulation can improve drug solubility, prolong circulation time, and enhance absorption across biological membranes. Microspheres may also increase residence time at the absorption site, improving drug uptake. By maintaining sustained drug concentrations and reducing rapid clearance, microspheres contribute to improved pharmacokinetic profiles and better therapeutic outcomes. These advantages are particularly valuable for drugs with poor water solubility, short biological half-life, or limited absorption.

### **Types of Microspheres Used in Diabetes Therapy**

Microsphere-based drug delivery systems have gained considerable importance in diabetes management due to their ability to provide controlled release, targeted delivery, and enhanced drug stability. Various types of microspheres are designed using different polymers and technologies to address specific therapeutic needs in diabetes treatment. These systems help improve drug bioavailability, reduce dosing frequency, and enhance patient compliance.

#### **Polymeric Microspheres**

- Polymeric microspheres are the most widely used drug delivery carriers in diabetes therapy.
- They are prepared using biodegradable polymers such as polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), chitosan, alginate, and gelatin.
- These polymers allow controlled and sustained drug release through gradual degradation or diffusion mechanisms.
- Particularly useful for insulin delivery and oral antidiabetic drugs to maintain stable plasma drug levels.
- They enhance drug stability, reduce dosing frequency, and minimize side effects.
- Biodegradable polymers ensure safety by breaking down into non-toxic metabolites in the body.

#### **Mucoadhesive Microspheres**

- Mucoadhesive microspheres adhere to mucosal surfaces such as the gastrointestinal tract.
- This adhesion prolongs residence time at the absorption site, improving drug bioavailability.

- Especially beneficial for drugs with poor absorption or short biological half-life.
- Common mucoadhesive polymers include chitosan, carbopol, and sodium alginate.
- These systems protect drugs from enzymatic degradation in the GI tract.
- They are particularly useful for oral insulin delivery and other peptide-based therapies.

### **Magnetic Microspheres**

- Magnetic microspheres contain magnetic materials such as iron oxide embedded within polymer matrices.
- External magnetic fields guide these microspheres to specific target sites in the body.
- This targeted delivery reduces systemic side effects and enhances therapeutic efficiency.
- Magnetic targeting is beneficial for localized drug delivery in diabetes-related complications.
- They also facilitate controlled release and improved drug localization.
- Research is ongoing to improve their biocompatibility and clinical applicability.

### **Floating Microspheres**

- Floating microspheres, also known as gastro-retentive microspheres, are designed to remain buoyant in gastric fluids.
- They prolong gastric residence time, allowing sustained drug release in the stomach.
- Particularly useful for drugs absorbed primarily in the upper gastrointestinal tract.
- These systems improve drug bioavailability and reduce dosing frequency.
- Commonly prepared using low-density polymers and gas-forming agents.
- Floating microspheres enhance therapeutic effectiveness of certain oral antidiabetic drugs.

### **Stimuli-Responsive (Smart) Microspheres**

- Stimuli-responsive microspheres release drugs in response to physiological triggers such as glucose concentration, pH, temperature, or enzymes.
- Glucose-responsive systems are especially important in diabetes therapy for controlled insulin release.
- These smart systems help maintain optimal blood glucose levels automatically.
- They improve therapeutic precision and reduce risk of hypoglycemia.
- Advanced polymers and nanotechnology integration enhance responsiveness and stability.
- Such systems represent a promising future direction for personalized diabetes treatment.

### **Preparation Methods of Microspheres**

The preparation method of microspheres significantly influences their particle size, drug encapsulation efficiency, stability, release kinetics, and therapeutic effectiveness. Selection of a suitable preparation technique depends on the physicochemical properties of the drug, polymer characteristics, desired release profile, and intended route of administration. Various conventional and advanced methods have been developed to fabricate microspheres for pharmaceutical applications, especially for controlled and targeted drug delivery in diabetes therapy.

### **Solvent Evaporation Method**

The solvent evaporation method is one of the most commonly used techniques for preparing polymeric microspheres. In this process, the polymer is first dissolved in a volatile organic solvent such as dichloromethane, chloroform, or ethyl

acetate, and the drug is either dissolved or dispersed within this polymer solution. The resulting mixture is emulsified into an aqueous phase containing surfactants or stabilizers to form an oil-in-water emulsion. Continuous stirring facilitates evaporation of the organic solvent, causing precipitation of the polymer and formation of solid microspheres encapsulating the drug. Particle size and morphology can be controlled by factors such as stirring speed, surfactant concentration, and viscosity of the phases. This method provides good encapsulation efficiency and sustained drug release characteristics, although careful solvent removal is necessary to avoid toxicity issues.

### **Emulsion Cross-Linking Method**

The emulsion cross-linking method is widely used for preparing microspheres from natural polymers such as chitosan, gelatin, albumin, and alginate. In this technique, a polymer solution containing the drug is emulsified into an immiscible continuous phase, usually oil, to form droplets. These droplets are stabilized through chemical or ionic cross-linking using agents such as glutaraldehyde or calcium ions, which form a rigid three-dimensional network that entraps the drug within the microspheres. This process enhances mechanical strength, stability, and controlled drug release properties. It is particularly suitable for encapsulating proteins, peptides, and insulin due to relatively mild preparation conditions. However, residual cross-linking agents must be carefully removed to prevent toxicity.

### **Spray Drying Technique**

Spray drying is a rapid, single-step, and scalable technique commonly employed in pharmaceutical industries for microsphere preparation. It involves atomizing a polymer-drug solution or suspension into a heated drying chamber, where rapid solvent evaporation produces dry, spherical microspheres. Particle size, morphology, and drug loading depend on operational parameters such as feed concentration, atomization rate, inlet temperature, and airflow conditions. This method produces uniform microspheres with relatively narrow size distribution and high production efficiency. Spray drying is particularly useful for heat-stable drugs and polymers and has applications in pulmonary insulin delivery systems and oral sustained-release antidiabetic formulations.

### **Phase Separation Coacervation Method**

The phase separation coacervation technique involves separation of a polymer-rich phase from a polymer solution to encapsulate drugs effectively. Coacervation can be induced by adding a non-solvent, changing temperature, or adjusting pH, resulting in deposition of the polymer around drug particles. Subsequent stabilization, usually by cross-linking or solvent removal, leads to formation of stable microspheres. This method offers high encapsulation efficiency and allows precise control over particle size and coating thickness. It is particularly suitable for encapsulating proteins, peptides, and other sensitive biomolecules such as insulin, as relatively mild processing conditions help preserve drug stability. However, the process may require careful optimization to ensure reproducibility.

### **Microfluidic and Advanced Fabrication Techniques**

Modern microfluidic and advanced fabrication techniques represent innovative approaches to microsphere preparation. Microfluidic systems utilize microscale channels to precisely control fluid flow, droplet formation, and particle size distribution. These techniques produce highly uniform microspheres with consistent drug loading and improved reproducibility. Advanced fabrication approaches such as electrospraying, supercritical fluid processing, and emerging

3D printing methods further enhance encapsulation efficiency and enable development of multifunctional and stimuli-responsive microspheres. These technologies show great potential for personalized drug delivery systems, particularly in diabetes management, although large-scale industrial application is still evolving.

### **Characterization of Microspheres**

Characterization of microspheres is a critical step in the development of effective drug delivery systems, as it determines their physicochemical properties, drug release behavior, stability, and therapeutic performance. Proper evaluation ensures quality, safety, and reproducibility of microsphere formulations, particularly for applications in controlled and targeted drug delivery such as diabetes therapy. Various analytical techniques are employed to assess particle size, morphology, drug loading, surface characteristics, release kinetics, and biocompatibility.

### **Particle Size and Morphology**

Particle size and morphology are essential parameters influencing drug release rate, biodistribution, cellular uptake, and overall therapeutic effectiveness of microspheres. Particle size is commonly measured using techniques such as optical microscopy, scanning electron microscopy, transmission electron microscopy, and laser diffraction analysis. Morphological evaluation provides information about shape, surface smoothness, and structural integrity. Uniform particle size distribution ensures consistent drug release profiles and improved stability, while irregular or aggregated particles may negatively affect drug delivery efficiency.

### **Drug Loading and Entrapment Efficiency**

Drug loading capacity and entrapment efficiency determine how much active pharmaceutical ingredient is successfully incorporated into the microspheres. These parameters are typically evaluated by dissolving microspheres and quantifying drug content using spectroscopic or chromatographic techniques. High entrapment efficiency indicates effective encapsulation and contributes to sustained drug release and therapeutic efficacy. Poor drug loading may lead to inconsistent dosing, reduced effectiveness, and increased production costs, making optimization of this parameter essential during formulation development.

### **Surface Properties**

Surface characteristics of microspheres, including surface charge, porosity, hydrophobicity, and functional group composition, significantly influence drug release behavior, stability, and targeting potential. Surface charge affects interactions with biological membranes and circulation time in the body, while porosity determines diffusion rate of the encapsulated drug. Hydrophilic or hydrophobic surface properties also influence adsorption, cellular uptake, and compatibility with biological environments. These characteristics are commonly assessed using techniques such as zeta potential measurement, porosimetry, and surface spectroscopy.

### **In Vitro Release Studies**

In vitro drug release studies are performed to evaluate the release kinetics and mechanism of drug delivery from microspheres. These studies simulate physiological conditions using dissolution media and controlled temperature settings. The release profile helps determine whether drug release occurs through diffusion, polymer degradation, erosion, or a combination of mechanisms. Controlled release patterns are particularly important for chronic diseases such as

diabetes, where maintaining consistent therapeutic drug levels is essential. Such studies also assist in predicting in vivo performance and optimizing formulation parameters.

**Stability and Biocompatibility Testing**

Stability and biocompatibility testing are essential to ensure safety, efficacy, and shelf life of microsphere formulations. Stability studies evaluate physical, chemical, and biological stability under various environmental conditions such as temperature, humidity, and light exposure. Biocompatibility testing assesses potential toxicity, immunogenicity, and compatibility with biological tissues. These evaluations are critical for regulatory approval and clinical application, ensuring that microspheres remain safe and effective throughout storage and therapeutic use.

Table 1: Applications in Targeted Diabetes Drug Delivery

Application Area	Description	Therapeutic Advantages in Diabetes
Oral Insulin Delivery	Microspheres protect insulin from enzymatic degradation and harsh gastrointestinal conditions while improving intestinal absorption.	Enables non-invasive insulin administration, improves patient compliance, and enhances bioavailability.
Controlled Release of Antidiabetic Drugs	Sustained release microsphere formulations deliver antidiabetic drugs over extended periods.	Maintains stable plasma drug levels, reduces dosing frequency, minimizes side effects, and improves glycemic control.
Pulmonary Insulin Delivery	Microsphere formulations designed for inhalation allow insulin absorption through lung alveoli.	Provides painless, rapid absorption, improved convenience, and better patient acceptance compared to injections.
Transdermal and Implantable Systems	Microspheres incorporated into patches or implantable depots provide long-term drug release.	Reduces dosing frequency, ensures prolonged therapeutic effect, and enhances adherence to diabetes therapy.
Combination Therapy Delivery	Microspheres encapsulate multiple drugs or therapeutic agents simultaneously.	Enables synergistic action, improved therapeutic effectiveness, reduced pill burden, and optimized diabetes management.

**Future Perspectives**

Future research in microsphere technology is expected to focus on the development of multifunctional and highly sophisticated drug delivery systems aimed at improving diabetes management. Advances in polymer science are leading to the design of more biocompatible, biodegradable, and non-toxic polymers that enhance drug stability, reduce adverse reactions, and improve patient safety. A major area of innovation is the development of glucose-responsive or “smart” microspheres capable of releasing insulin automatically in response to fluctuations in blood glucose levels. Such systems have the potential to mimic physiological insulin secretion, thereby improving glycemic control and reducing the risk of hypoglycemia.

Additionally, integration of microsphere drug delivery with digital health technologies such as biosensors, wearable monitoring devices, and personalized medicine platforms is gaining increasing attention. These technologies may allow

real-time monitoring of glucose levels and controlled drug release, leading to more precise and individualized treatment approaches. Research is also exploring combination therapy delivery using microspheres, enabling simultaneous administration of multiple therapeutic agents for enhanced efficacy. Overall, continued advancements in materials science, pharmaceutical engineering, and biomedical technology are expected to significantly improve therapeutic outcomes, patient compliance, and quality of life for individuals living with diabetes.

### **Conclusion**

Microsphere technology has emerged as an important advancement in modern pharmaceutical drug delivery, particularly for the management of diabetes mellitus. These systems provide controlled and sustained drug release, helping to maintain stable therapeutic drug levels and improve glycemic control. Their ability to protect sensitive drugs such as insulin from degradation enhances drug stability and bioavailability. Targeted delivery potential further improves therapeutic effectiveness while minimizing systemic side effects. Microspheres also support multiple administration routes, including oral, pulmonary, injectable, and transdermal delivery. This versatility contributes to better patient compliance and reduced dosing frequency. Advances in polymer science and formulation techniques continue to optimize microsphere performance. Integration with nanotechnology and smart drug delivery approaches is expanding their clinical relevance. Personalized and glucose-responsive delivery systems represent promising future developments. Despite some formulation and regulatory challenges, ongoing research is addressing these limitations. Overall, microsphere technology offers a promising strategy for improving diabetes therapy. Continued interdisciplinary innovation will further enhance therapeutic outcomes and patient quality of life.

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