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Review Article

Polymeric Microsphere-Based Systems for Controlled Topical Drug Delivery: A Comprehensive Review

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ABSTRACT

Topical drug delivery systems offer a strategic approach for administering therapeutic agents directly to the skin, bypassing hepatic first-pass metabolism and reducing systemic adverse effects. However, conventional formulations such as gels and creams often face challenges, including poor skin penetration, short residence time, and the necessity for frequent dosing. Polymeric microspheres spherical particles typically ranging from 1–1000 μm have emerged as a versatile solution to these limitations. By encapsulating active pharmaceutical ingredients within natural or synthetic polymeric matrices, these systems enable controlled, sustained drug release and improved site-specific delivery. This review examines the classification, preparation techniques (such as solvent evaporation and spray drying), and characterization methods of microspheres. Furthermore, it highlights their significant role in dermatological applications, including acne, anti-inflammatory, and antifungal therapies. Despite challenges related to manufacturing complexity and production costs, ongoing advancements in polymer science and nanotechnology continue to enhance the therapeutic efficacy and patient compliance of these advanced delivery systems, positioning them as a promising frontier in modern pharmaceutical sciences.

INTRODUCTION

Topical drug delivery systems are designed to administer therapeutic agents directly onto the skin for local or systemic action. These systems provide several advantages over conventional dosage forms, including avoidance of first-pass

metabolism, improved patient compliance, reduced systemic adverse effects, and targeted drug delivery at the site of action (1). However, conventional topical formulations such as creams, gels, ointments, and lotions often exhibit limitations including poor skin penetration, short

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residence time, rapid drug loss from the application site, and frequent dosing requirements (2).

To overcome these challenges, controlled drug delivery systems have gained considerable attention in pharmaceutical research. Controlled delivery aims to maintain drug concentration within the therapeutic window for prolonged periods while minimizing fluctuations in drug levels and reducing adverse effects (3). Among various carrier systems developed for controlled release applications, polymeric microspheres have emerged as promising drug delivery vehicles because of their ability to encapsulate active pharmaceutical ingredients and release them in a sustained and controlled manner (4).

Polymeric microspheres are small spherical particles ranging from approximately 1 μm to 1000 μm in diameter, composed of natural or synthetic polymers that encapsulate or disperse drug molecules within a polymeric matrix (5). Depending on their structural characteristics, microspheres may exist as microcapsules, where the drug is enclosed within a polymer shell, or as micromatrices, where the drug is uniformly distributed throughout the polymer network (6). Their unique properties, including controlled release capability, enhanced drug stability, improved bioavailability, and site-specific delivery, make them attractive carriers for topical formulations (7).

In topical drug delivery applications, polymeric microspheres can improve skin retention of drugs, reduce dosing frequency, enhance therapeutic efficacy, and minimize systemic absorption and irritation. Various natural polymers such as chitosan, gelatin, and alginate, as well as synthetic polymers including poly(lactic-co-glycolic acid) (PLGA), ethyl cellulose, and Eudragit, have been widely investigated for microsphere preparation

(8). Advances in microsphere technology continue to provide innovative opportunities for designing novel controlled topical drug delivery systems with improved clinical outcomes (9).

Thus, polymeric microspheres represent an effective and versatile approach in modern topical drug delivery, offering significant potential to overcome limitations associated with conventional formulations and improve patient treatment outcomes (10).

2. Topical Drug Delivery Systems

Topical drug delivery systems (TDDS) are formulations intended for application onto the skin or mucosal surfaces to deliver therapeutic agents either locally or systemically. The skin serves as a protective barrier and also acts as an attractive route for drug administration due to its large surface area and easy accessibility. Topical administration enables the drug to reach the site of action directly while minimizing systemic exposure and reducing adverse effects (11).

The primary objective of topical drug delivery systems is to achieve an adequate concentration of the drug at the target site for a prolonged period while maintaining therapeutic efficacy. Topical formulations provide several advantages over oral and parenteral routes, including avoidance of hepatic first-pass metabolism, painless administration, improved patient compliance, and ease of termination of therapy whenever required (12).

Drug penetration through the skin mainly occurs via three pathways: the transcellular pathway (through cells), intercellular pathway (between cells), and appendageal pathway (through hair follicles and sweat glands). Among these, the stratum corneum acts as the major barrier to drug



penetration because of its highly organized lipid structure (13).

Various conventional topical dosage forms include creams, ointments, gels, lotions, pastes, powders, and transdermal patches. However, these conventional systems often suffer from limitations such as poor skin permeation, low drug retention at the application site, short duration of action, and the need for repeated application (14).

Recent advancements in topical drug delivery have led to the development of novel carrier systems such as liposomes, niosomes, nanoparticles, microsponges, microspheres, nanoemulsions, and nanogels. These advanced systems improve drug penetration, enhance stability, provide controlled release characteristics, and increase therapeutic effectiveness (15).

Thus, topical drug delivery systems represent an important and continuously evolving field in pharmaceutical sciences, offering a promising approach for improving therapeutic outcomes and patient acceptability (16).

3. Polymeric Microspheres

Definition

Polymeric microspheres are free-flowing spherical particles composed of biodegradable or non-biodegradable polymers with sizes generally ranging from 1–1000 μm . These systems are designed to encapsulate active pharmaceutical ingredients within a polymer matrix or membrane structure for controlled and targeted drug delivery. Microspheres can protect drugs from environmental degradation, enhance stability, improve therapeutic efficacy, and provide sustained drug release characteristics (17).

Microspheres function as effective carrier systems because they can deliver drugs at a predetermined

rate over an extended period while reducing fluctuations in plasma drug concentration. Due to these properties, polymeric microspheres have gained considerable attention in pharmaceutical formulations, particularly in topical drug delivery applications where prolonged retention and controlled release are required (18).

Types of Polymeric Microspheres

Polymeric microspheres can be classified based on structure, polymer type, and mechanism of drug entrapment. The major types include:

1. Bioadhesive Microspheres:

Bioadhesive microspheres possess adhesive properties that enable attachment to biological surfaces such as skin and mucosal membranes. These systems prolong residence time at the site of application and improve drug absorption and therapeutic efficacy (19).

2. Magnetic Microspheres:

Magnetic microspheres contain magnetic materials and can be directed toward a specific target site using an external magnetic field. These systems are mainly used for site-specific delivery and diagnostic applications (20).

3. Floating Microspheres:

Floating microspheres have lower density than gastrointestinal fluids and are designed to float over biological fluids for prolonged retention. Though primarily intended for oral delivery, the concept has been adapted for controlled delivery applications (21).

4. Radioactive Microspheres:

These microspheres incorporate radioactive substances and are commonly utilized in cancer therapy for targeted radiation delivery (22).

5. Microcapsules:

In microcapsules, the drug is enclosed within a distinct polymer membrane surrounding the core material. Drug release occurs through



diffusion or degradation of the surrounding polymer shell (23).

6. Micromatrices (Matrix Microspheres):

In matrix microspheres, the drug is uniformly dispersed throughout the polymer matrix. Drug release occurs gradually through diffusion and matrix erosion mechanisms (24).

Advantages and Limitations

Advantages

- Provide controlled and sustained drug release.
- Enhance drug stability by protecting drugs from environmental degradation.
- Reduce dosing frequency and improve patient compliance.
- Minimize systemic side effects and toxicity.
- Improve drug bioavailability.
- Enable targeted and site-specific drug delivery.
- Improve therapeutic effectiveness and reduce drug fluctuations (25).

Limitations

- Preparation methods can be complex and expensive.
- Drug loading efficiency may be variable.
- Possible burst release of entrapped drug may occur.
- Polymer toxicity or incompatibility may affect formulation stability.
- Scale-up and industrial manufacturing can be difficult.
- Drug leakage during preparation and storage may occur (26).

Overall, polymeric microspheres have emerged as highly effective drug carrier systems due to their controlled release properties and ability to improve therapeutic outcomes. Despite certain limitations, continuous advancements in polymer science and formulation technologies are expanding their applications in topical and controlled drug delivery systems (27).

4. Polymers Used in Microspheres

Table 1: Natural and Synthetic Polymers Used in Microsphere Formulation

Category	Polymer	Source	Properties	Applications in Microspheres
Natural Polymers	Chitosan	Chitin obtained from crustacean shells	Biodegradable, biocompatible, bioadhesive	Controlled release, mucoadhesive and topical formulations
	Gelatin	Animal collagen	Biodegradable, non-toxic, film-forming property	Drug encapsulation and sustained release
	Alginate	Brown seaweed	Hydrophilic, biocompatible, gel-forming ability	Controlled drug release and wound healing systems
	Starch	Plant source	Biodegradable, inexpensive, non-toxic	Microsphere matrix and drug carrier

	Albumin	Protein from animal source	Biocompatible, biodegradable	Targeted and controlled drug delivery
	Dextran	Microbial polysaccharide	Water soluble, stable	Sustained release systems
Synthetic Polymers	Poly(lactic-co-glycolic acid) (PLGA)	Synthetic copolymer	Biodegradable, controlled degradation rate	Sustained and targeted drug delivery
	Poly(lactic acid) (PLA)	Synthetic polymer	Biocompatible, biodegradable	Controlled release formulations
	Polycaprolactone (PCL)	Synthetic polyester	Slow degradation, high stability	Long-term controlled release
	Ethyl cellulose	Cellulose derivative	Hydrophobic, film-forming	Sustained release microspheres
	Eudragit	Methacrylate polymer	pH-dependent release characteristics	Modified and controlled release systems
	Polyvinyl alcohol (PVA)	Synthetic polymer	Water soluble, stabilizing property	Emulsification and microsphere preparation

Natural polymers are widely used because of their biodegradability, low toxicity, and biocompatibility. However, variability in composition and lower mechanical strength may limit their use in certain formulations. Synthetic polymers provide better reproducibility, controlled degradation rates, and enhanced mechanical properties, making them suitable for advanced microsphere systems (28,29). Selection of polymers mainly depends on drug properties, route of administration, release characteristics, and therapeutic requirements (30).

5. Methods of Preparation of Polymeric Microspheres

Various techniques are employed for the preparation of polymeric microspheres depending on the physicochemical properties of the drug, polymer characteristics, desired particle size,

encapsulation efficiency, and release profile. Selection of an appropriate preparation method significantly influences the quality and performance of microspheres (31).

a. Solvent Evaporation Method

The solvent evaporation method is one of the most commonly used techniques for preparing polymeric microspheres. In this method, the drug and polymer are dissolved in a volatile organic solvent such as dichloromethane, chloroform, or ethanol. The resulting solution is dispersed into an external aqueous phase containing a stabilizing agent under continuous stirring to form an emulsion. Subsequently, the organic solvent evaporates, leading to polymer precipitation and formation of microspheres (32).



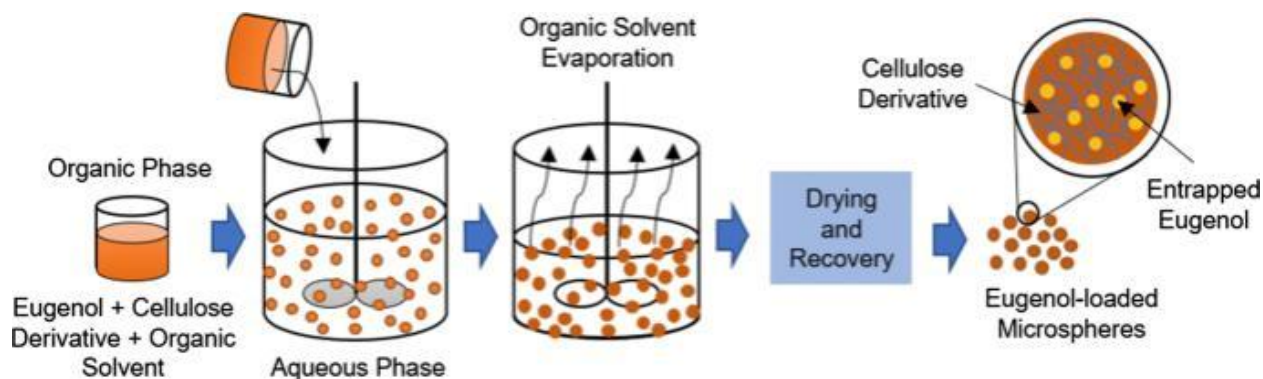


Figure 1: Solvent Evaporation Method

Advantages:

- Simple and reproducible method
- Suitable for heat-sensitive drugs
- High encapsulation efficiency
- Produces uniform particle size distribution

Limitations:

- Residual solvent may remain
- Requires large quantities of organic solvents

Emulsion methods involve the formation of single or multiple emulsions depending on drug characteristics. Single emulsion (oil-in-water, O/W) techniques are generally used for hydrophobic drugs, whereas multiple emulsion systems (water-in-oil-in-water, W/O/W) are suitable for hydrophilic drugs and proteins (33). The prepared emulsion is stabilized using surfactants and subjected to solvent removal processes, leading to microsphere formation.

b. Emulsion Techniques

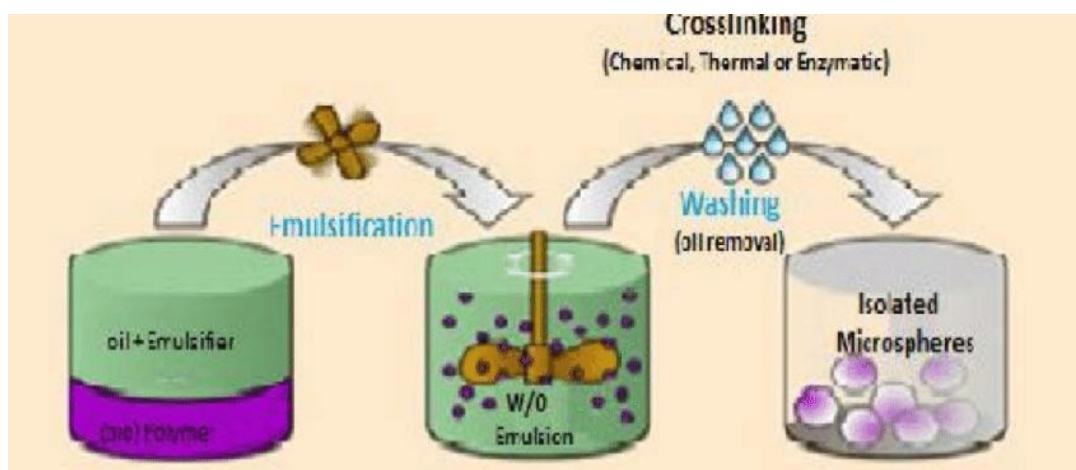


Figure 2: Emulsion technique

Advantages:

- Suitable for both hydrophilic and hydrophobic drugs
- Improved encapsulation of proteins and peptides
- Provides controlled particle size

Limitations:

- Complex procedure
- Possible drug leakage during preparation

c. Spray Drying Method

Spray drying is a rapid and widely used one-step process for preparing microspheres. In this method, the drug and polymer solution is atomized into fine droplets and introduced into a stream of heated air. Rapid solvent evaporation results in the

formation of dry microspheres that are collected through cyclone separators (34). This method is particularly suitable for large-scale industrial production due to its simplicity and rapid processing.

Advantages:

- Fast and economical process
- Suitable for industrial scale-up
- Produces dry and free-flowing particles

Limitations:

- Exposure to heat may affect thermolabile drugs
- Lower encapsulation efficiency for some formulations.

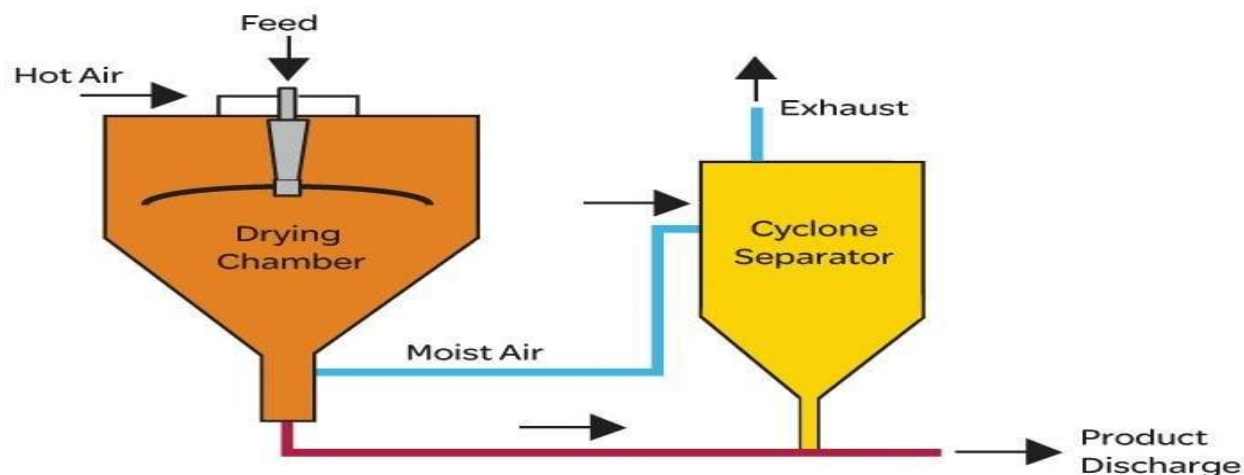


Figure 3: Spray drying technique

d. Coacervation Method

Coacervation or phase separation is a process involving separation of a polymer-rich phase from a polymer-poor phase under controlled conditions. Drug particles are dispersed within the polymer solution, and phase separation is induced by changing pH, temperature, or adding nonsolvents.

The polymer-rich phase deposits around drug particles and forms microspheres (35).

Coacervation can be categorized as simple coacervation and complex coacervation depending on the number of polymers involved.

Advantages:

- High drug loading capacity
- Suitable for sensitive compounds
- Provides sustained drug release

Limitations:

- Process parameters require careful control
- Difficult scale-up and higher production cost

Different preparation methods influence particle size, surface morphology, drug loading, encapsulation efficiency, and release characteristics of polymeric microspheres. Therefore, selecting a suitable method is essential for obtaining desired formulation characteristics and therapeutic performance (36).

6. Characterization of Microspheres

Characterization of microspheres is essential for determining their quality, stability, and performance in drug delivery systems. Various

parameters such as particle size, surface morphology, entrapment efficiency, drug loading, and in-vitro drug release are evaluated to ensure desired formulation properties. These parameters directly affect therapeutic efficacy, release behavior, and stability of microsphere formulations (37).

Particle Size and Morphology

Particle size and morphology significantly influence drug release characteristics, encapsulation efficiency, bioavailability, and stability of microspheres. Particle size analysis is commonly performed using optical microscopy, laser diffraction, dynamic light scattering (DLS), and scanning electron microscopy (SEM). Surface morphology and shape are usually analyzed by SEM, transmission electron microscopy (TEM), or optical microscopy (38).

Table 2: Methods for Particle Size and Morphology Analysis

Parameter	Method Used	Principle	Significance
Particle size	Optical microscopy	Direct measurement of particles	Determines size distribution
Particle size	Laser diffraction	Measures light scattering pattern	Rapid and accurate particle analysis
Particle size	Dynamic light scattering (DLS)	Measures Brownian movement	Suitable for small particles
Morphology	SEM	Surface imaging using electron beam	Determines shape and surface texture
Morphology	TEM	Internal structure visualization	Provides detailed particle structure

Smaller microspheres generally provide a larger surface area, leading to faster drug release, while larger particles may prolong drug release (39).

Entrapment Efficiency

Entrapment efficiency refers to the percentage of drug successfully encapsulated within

microspheres relative to the total amount of drug used during formulation. It indicates the effectiveness of the preparation method and drug incorporation process (40).

The entrapment efficiency can be calculated using the following equation:

Entrapment Efficiency (%) = $\frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$ Higher entrapment efficiency indicates effective incorporation of drug into the polymer matrix and better formulation performance.

Table 3: Factors Affecting Entrapment Efficiency

Factors	Effect
Polymer concentration	Increased concentration may increase entrapment
Drug-polymer interaction	Strong interaction improves encapsulation
Solvent type	Influences drug diffusion and polymer precipitation
Stirring speed	Affects particle formation and drug loss
Drug solubility	Highly water-soluble drugs may exhibit leakage

Drug Loading

Drug loading represents the amount of drug incorporated into microspheres relative to total microsphere weight. Drug loading determines the quantity of drug available for therapeutic action and influences release characteristics (41).

The percentage drug loading is calculated as:

Drug Loading (%) = $\frac{\text{Amount of drug in microsphere}}{\text{Total weight of microspheres}} \times 100$

Higher drug loading reduces the amount of carrier material required and improves formulation efficiency.

In-vitro Drug Release

In-vitro drug release studies are performed to determine the release profile of the drug from microspheres under simulated physiological conditions. Common methods include dissolution studies using paddle apparatus, basket apparatus, dialysis membrane methods, and diffusion cell techniques (42).

Drug release from microspheres generally occurs through diffusion, polymer swelling, erosion, or degradation mechanisms.

Table 4: Methods Used for In-vitro Drug Release Studies

Method	Principle	Applications
USP Paddle apparatus	Rotation of paddle in dissolution medium	Controlled release studies
USP Basket apparatus	Drug release from basket-containing samples	Solid dosage formulations
Dialysis membrane method	Drug diffusion through membrane	Sustained release studies
Franz diffusion cell	Drug diffusion across membrane/skin	Topical drug delivery studies



The in-vitro release profile provides information regarding release kinetics and helps predict in-vivo drug behavior. Sustained and controlled release patterns indicate successful microsphere formulation development (43).

7. Mechanism of Controlled Drug Release

Controlled drug release from polymeric microspheres occurs through several mechanisms that regulate the rate and duration of drug release from the polymeric matrix. The release behavior

depends on factors such as polymer characteristics, drug properties, particle size, degradation rate, and environmental conditions. Controlled release systems maintain drug concentrations within the therapeutic range for extended periods and reduce fluctuations in drug levels (44).

The major mechanisms involved in controlled drug release are diffusion, erosion, swelling, and degradation-controlled release.

Table 5: Mechanisms of Controlled Drug Release from Polymeric Microspheres

Mechanism	Description	Characteristics
Diffusion-controlled release	Drug molecules diffuse through pores or polymer matrix into the surrounding medium	Provides gradual and sustained drug release
Erosion-controlled release	Polymer matrix undergoes erosion leading to drug liberation	Release rate depends on polymer erosion
Swelling-controlled release	Polymer absorbs surrounding fluid and swells, allowing drug diffusion	Common in hydrophilic polymers
Degradation-controlled release	Polymer degradation gradually releases entrapped drug	Suitable for biodegradable polymers
Osmotically controlled release	Drug release occurs due to osmotic pressure differences	Produces predictable release patterns

Among these mechanisms, diffusion-controlled release is the most common process in polymeric microsphere systems. Biodegradable polymers such as PLGA and chitosan generally follow degradation-mediated release mechanisms, while hydrophilic polymers frequently exhibit swelling-controlled release behavior (45).

The mechanism of drug release significantly influences therapeutic efficacy and is important for designing effective topical formulations with

prolonged action and reduced dosing frequency (46).

8. Applications in Topical Drug Delivery

Polymeric microspheres have gained considerable importance in topical drug delivery because of their ability to provide controlled release, improve skin retention, increase drug stability, and minimize systemic side effects. Microsphere-based formulations can enhance drug penetration



through the skin and improve therapeutic effectiveness (47).

These systems are applied in various dermatological and pharmaceutical conditions.

Table 6: Applications of Polymeric Microspheres in Topical Drug Delivery

Application	Role of Microspheres	Examples
Acne treatment	Sustained release and reduced irritation	Benzoyl peroxide, Clindamycin
Antifungal therapy	Improved skin penetration and prolonged action	Ketoconazole, Fluconazole
Anti-inflammatory therapy	Localized delivery with reduced systemic effects	Diclofenac, Ibuprofen
Wound healing	Enhanced tissue repair and prolonged drug action	Silver sulfadiazine
Antibacterial therapy	Increased drug retention at infection site	Mupirocin
Cosmetic formulations	Controlled release of active ingredients	Vitamins, antioxidants
Psoriasis treatment	Reduced dosing frequency and improved efficacy	Methotrexate

Microsphere-based topical systems also improve patient compliance by decreasing application frequency and minimizing local irritation. In recent years, researchers have focused on integrating polymeric microspheres into creams, gels, ointments, and transdermal systems to improve therapeutic outcomes (48).

The application of polymeric microspheres in topical drug delivery continues to expand because of advancements in polymer technology and novel drug delivery approaches, offering promising potential for future pharmaceutical developments (49).

9.Recent Advances in Polymeric Microspheres

Recent advancements in polymeric microsphere technology have significantly improved the efficiency of controlled drug delivery systems. Continuous developments in polymer science, nanotechnology, and formulation strategies have enabled the design of microspheres with enhanced drug loading capacity, targeted delivery, and controlled release characteristics. These advancements have increased the application of polymeric microspheres in topical and other novel drug delivery systems (50).

Several innovative approaches have been introduced to improve microsphere performance, including the use of biodegradable polymers, stimuli-responsive materials, nanotechnology integration, and surface modification techniques.

Table 7: Recent Advances in Polymeric Microspheres

Recent advancement	Description	Benefits
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Biodegradable polymer-based microspheres	Use of biodegradable polymers such as PLGA, PLA, and chitosan	Reduced toxicity and improved safety
Stimuli-responsive microspheres	Drug release triggered by pH, temperature, enzymes, or light	Site-specific and controlled release
Nano-integrated microspheres	Combination of nanoparticles and microspheres	Enhanced penetration and bioavailability
Surface-modified microspheres	Surface functionalization with ligands or polymers	Improved targeting efficiency
Microsphere-loaded gels and creams	Incorporation into topical formulations	Improved patient compliance and prolonged action
Smart drug delivery systems	Systems responding to physiological changes	Better therapeutic outcomes

Nanotechnology-based microspheres have emerged as an important area of research because they enhance skin permeation and improve drug localization at the target site. Surface engineering techniques have also improved bioadhesion and controlled drug release properties of microspheres (51).

Despite considerable advancements, polymeric microspheres still face several limitations that affect their large-scale application and commercial development. Factors such as manufacturing complexity, high production cost, stability issues, and reproducibility remain important concerns in formulation development (52).

10. Challenges and Future Perspectives

Table 8: Challenges Associated with Polymeric Microspheres

Challenges	Impact on formulation
Complex manufacturing process	Difficulty in process optimization
High production cost	Limits commercial applicability
Low drug loading efficiency	Reduced therapeutic effectiveness
Initial burst drug release	May cause dose-related adverse effects
Stability issues	Reduced shelf life
Scale-up difficulties	Challenges in industrial production
Residual solvent toxicity	Safety concerns

Future research is expected to focus on developing safer and more efficient microsphere systems with improved targeting capability and personalized therapeutic approaches. Advanced techniques such as artificial intelligence-assisted formulation

design, 3D printing technologies, and multifunctional smart polymers may provide opportunities for overcoming current limitations (53).



The future of polymeric microspheres is directed toward personalized medicine, targeted delivery systems, and environmentally sustainable manufacturing processes. Continued research and technological advancements are expected to expand their role in controlled topical drug delivery and improve patient outcomes (54).

CONCLUSION

Polymeric microspheres represent a highly effective and versatile platform for modern topical drug delivery. By providing controlled, sustained release, they successfully overcome the inherent limitations of conventional topical formulations—such as rapid drug loss and the need for frequent

application—thereby enhancing therapeutic outcomes and patient compliance. While the field faces ongoing challenges concerning manufacturing complexity, scale-up difficulties, and production costs, continuous innovation in polymer science, nanotechnology, and smart delivery systems is actively addressing these barriers. As research progresses toward more efficient, targeted, and personalized therapeutic approaches, polymeric microspheres are poised to play an increasingly critical role in the future of dermatological treatments and controlled pharmaceutical delivery.

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