

**Natural Gum-Based Microballoons in Drug Delivery: A Systematic Review**

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Abstract

Natural gum-based microballoons represent a promising advancement in gastroretentive and colon-targeted drug delivery systems, leveraging the biocompatibility, biodegradability, and functional versatility of plant- and microbial-derived polysaccharides. This systematic review explores the formulation, characterization, and therapeutic applications of microballoons fabricated using natural gums such as guar, xanthan, gellan, and gum arabic. These hollow microspheres exhibit low density and prolonged gastric residence, enabling sustained drug release and improved bioavailability for drugs with narrow absorption windows or local gastrointestinal targets. Preparation techniques—including solvent evaporation, spray drying, and ionotropic gelation—are critically evaluated for their impact on particle morphology, buoyancy, encapsulation efficiency, and release kinetics. The review highlights the physicochemical properties of individual gums, their modification strategies, and their role in modulating drug diffusion and matrix erosion. Applications span across gastroretentive delivery of antibiotics, colon-specific release of anti-inflammatory agents, and localized chemotherapy. Despite formulation challenges such as gum variability and scalability, natural gum-based microballoons offer a sustainable and adaptable platform for controlled oral drug delivery. Future prospects include integration with smart polymers and nanotechnology to enhance site-specificity and clinical translation.

Keywords: Natural gums, Microballoons, Gastroretentive drug delivery, Colon-targeted therapy, Controlled release systems

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1. Introduction

Natural gums, polysaccharide polymers extracted from plant exudates or microbial fermentation, have garnered increasing attention as excipients and carriers in controlled drug delivery due to their biodegradability, biocompatibility, and versatility. Incorporating these gums into microballoon formulations enhances the stability and performance of drug delivery systems, particularly in achieving site-specific or sustained release in the gastrointestinal tract. Natural gum-based microballoons represent a critical intersection between green polymer technology and advanced drug delivery science, offering the potential to improve pharmacokinetics and therapeutic efficiency.¹

Microballoons, also referred to as hollow microspheres, are low-density, spherical particles capable of remaining buoyant in gastric fluids. The incorporation of natural gums such as guar, xanthan, gellan, and gum arabic into microballoons has demonstrated remarkable improvements in gastric retention, bioadhesion, and controlled drug release. This systematic review critically examines recent advancements in the use of natural gums for microballoon fabrication, focusing on preparation methods, physicochemical characterization, pharmacological performance, and clinical implications.²

2. Natural Gums as Pharmaceutical Polymers

Natural gums encompass various hydrophilic polysaccharides such as guar, xanthan, locust bean, tragacanth, gum arabic, and gellan gum, each with distinct rheological and gelling properties. These compounds swell in water and form viscous gels that are instrumental in modulating drug diffusion and providing mucoadhesion. Plant- and microbial-derived gums are particularly valued for their safety profile and responsiveness to physiological conditions in the gastrointestinal tract.³

Their physicochemical diversity—ionic charge, molecular weight, and branching—dictates the drug release mechanisms in microballoon systems. Gums like gellan and alginate form ionotropically crosslinked networks, while neutral gums such as guar and xanthan rely primarily on hydrogen bonding and physical entanglement. The structural modifications of these gums by grafting, thiolation, or esterification further enhance stability and target specificity.⁴

3. Significance of Microballoon Technology

Microballoon or hollow microsphere technology is an advanced gastroretentive drug delivery approach designed to overcome limitations of conventional oral administration, including rapid gastric emptying and poor bioavailability. These systems exhibit low density due to their hollow

core, enabling them to float on gastric fluids and extend gastric residence time. Upon contact with gastric acid, the gum-based hydrophilic polymer matrix swells, forming a gel layer that controls both buoyancy and drug release rate.²

The prolonged gastric residence allows for improved absorption of drugs that are preferentially absorbed in the stomach or upper intestine, such as metformin, ciprofloxacin, and verapamil. This method also mitigates local gastric irritation by modulating release rates and reducing drug exposure in the intestinal mucosa.²

3.1 Preparation Methods for Natural Gum-Based Microballoons

Microballoons can be prepared via several established methods—solvent evaporation, emulsion diffusion, spray drying, and thermal-induced phase separation—selectable based on polymer solubility and desired release profile.²

1. Solvent Evaporation Method

This is the most widely used technique for preparing natural gum-based hollow microspheres. The polymer and drug are dissolved in a volatile organic solvent (like ethanol or chloroform) and emulsified into an external aqueous phase containing a surfactant. Controlled evaporation of solvent leads to gas entrapment within the polymer matrix, forming spherical, hollow structures.

2. Spray Drying

In this approach, a gum-drug solution is atomized into a hot chamber, leading to rapid solvent evaporation and microballoon formation. This method allows precise control over particle size and high encapsulation efficiency, making it particularly suitable for temperature-stable natural gum formulations.

3. Thermal-Induced Phase Separation

Here, gum polymers dissolved at high temperatures precipitate upon cooling, entrapping the drug during phase separation. The resultant microparticles exhibit uniform porosity and structural integrity, ideal for thermo-stable actives.²

4. Freeze Drying (Lyophilization)

This method enhances floatability by dehydrating preformed microspheres at low pressure. It stabilizes the hollow structure and improves storage stability by preventing moisture-induced collapse.

3.2 Natural Gums in Microballoon Formulations

Gum Arabic

Gum Arabic, a complex branched polysaccharide from *Acacia* species, exhibits amphiphilic properties that make it ideal for microgel and microballoon formulations. Farooq et al. reported chemically crosslinked gum Arabic microgels with high yield and stability in acidic pH, showing hemocompatibility and antimicrobial activity against *E. coli* and *S. aureus*. Modified gum Arabic (GA-DETA, GA-TA) displayed tunable surface charge and improved biomedical potential.⁵

Zhou et al. prepared curcumin-loaded gum Arabic nanogels exhibiting sustained release in simulated gastrointestinal fluids, indicating strong potential for delivering hydrophobic bioactives. These systems showed small particle sizes (<85 nm) and high encapsulation efficiency. Similarly, Han et al. developed gum Arabic–chitosan complex nanoparticles to stabilize Pickering emulsions for controlled curcumin release and protection against degradation.⁵

Guar Gum

Guar gum, a non-ionic galactomannan derived from *Cyamopsis tetragonolobus*, forms highly viscous dispersions upon hydration and demonstrates mucoadhesive properties ideal for sustained drug release. Guar microballoons prepared via water-in-oil emulsion crosslinking have shown promise in colon-targeted delivery. Sharma et al. successfully utilized guar gum to deliver embelin for ulcerative colitis therapy, achieving selective release in the colon and effective anti-inflammatory response in rat models. Other formulations incorporating doxorubicin and metformin indicated strong colon-specific release and enhanced therapeutic outcomes in colorectal cancer treatment.⁵

Gellan Gum

Gellan gum, a microbial polysaccharide with the unique capacity for ionotropic gelation, forms robust gels in the presence of divalent cations. The egg-box model explains its crosslinking behavior. Gellan-based microballoons have been widely used for gastroretentive delivery of unstable drugs, providing prolonged floatation and controlled dissolution. Ionic crosslinking using calcium ions yields stable systems that resist gastric acidity and release drugs predictably.⁵

Xanthan and Karaya Gums

Modified xanthan gum microballoons exhibit swelling-controlled release, particularly advantageous for hydrophilic drugs. Karaya gum, due to its negatively charged residues and strong mucoadhesion, supports slow drug release through hydrogen bonding. These gums can be used singly or as blended systems to fine-tune mechanical strength and erosion rates.

3.3 Characterization Parameters

The performance of natural gum-based microballoons is assessed through physical, morphological, and functional parameters⁶:

- **Particle size and morphology:** Analyzed by Scanning Electron Microscopy (SEM) to confirm spherical morphology and uniform pores.
- **Buoyancy test:** Determines floating lag time and total floating duration in simulated gastric fluid.
- **Drug loading efficiency:** Assesses encapsulation capacity, generally above 70% for optimized systems.
- **In vitro drug release:** Follows sustained kinetics governed by Fickian diffusion and swelling-controlled mechanisms.
- **Density measurement:** Ensures the particles remain below gastric fluid density ($<1 \text{ g/cm}^3$) for buoyancy.
- **Stability studies:** Evaluate resistance to humidity and thermal degradation, crucial for storage stability.

3.4 Mechanism of Drug Release

Drug release from natural gum-based microballoons typically follows a dual mechanism of diffusion and matrix erosion. Initially, water penetrates the polymer shell, causing gum swelling and controlled diffusion of the encapsulated drug. Over time, matrix disintegration due to biodegradation or ionic disruption governs the final release phase. In polysaccharide systems susceptible to colonic microflora, degradation by bacterial enzymes further facilitates targeted release in the colon, making these systems particularly suitable for the treatment of inflammatory bowel diseases and colorectal cancer.⁷

3.5 Pharmacokinetic and Therapeutic Applications

Natural gum-based microballoons have demonstrated enhanced pharmacokinetics through controlled and site-specific drug release, improving bioavailability and reducing dosage frequency. These systems offer benefits across diverse therapeutic areas:

- **Gastro-retentive delivery:** Drugs like ciprofloxacin and amoxicillin show improved absorption in the stomach when delivered via gum microballoons.⁸

- **Colon-targeted therapy:** Guar and gellan gum systems effectively deliver anti-inflammatory drugs (e.g., mesalamine, curcumin) for ulcerative colitis.
- **Oral insulin delivery:** Gum-based microballoons protect peptide drugs from enzymatic degradation in the stomach.⁶
- **Cancer therapy:** Microballoons facilitate localized delivery of chemotherapeutic agents such as doxorubicin and 5-fluorouracil.

Overall, these systems enhance therapeutic index and minimize systemic toxicity compared to conventional oral formulations.

3.6 Advantages and Limitations

Natural gum-based microballoons combine the benefits of polymeric biocompatibility with formulation flexibility. Key advantages include sustained release, improved patient compliance, protection of acid-labile drugs, and reduced frequency of administration. The biopolymer nature ensures environmental safety and cost-effectiveness.⁸

However, several limitations persist. Batch-to-batch variability in gum purity and structure can affect reproducibility. Sensitivity to storage humidity and microbial contamination remains a challenge. Moreover, the scalability of gum-based microballoon production for industrial applications requires further optimization.⁷

4. Future Prospects

Emerging innovations in polymer science and nanofabrication provide exciting prospects for natural gum-based microballoons. The integration of **nanotechnology**, **magnetically guided floatation**, and **smart hydrogels** responsive to pH or temperature can dramatically enhance the specificity and performance of these systems. The development of **hybrid microballoons** combining gums with synthetic polymers like polyacrylates or Eudragit could yield formulations with superior mechanical strength and adjustable degradation rates.⁸

Clinical translation will depend on standardized purification of natural gums, improved reproducibility, and regulatory validation of biopolymer safety. With their eco-friendly origin and biological adaptability, natural gum-based microballoons have the potential to redefine oral controlled-release drug delivery systems.

5. Conclusion

Natural gum-based microballoons represent a revolutionary advance in oral drug delivery, merging the benefits of biopolymer science with microengineering. These systems exhibit extended gastric retention, sustained release profiles, and targeted drug disposition, making them suitable for a wide variety of therapeutic agents. Despite existing formulation challenges, continued innovation in polymer modification, fabrication methods, and nanotechnological integration promises robust progress toward clinical application and commercialization.

The systematic evidence underscores that natural gums like guar, gellan, xanthan, and gum arabic serve as versatile and safe excipients in designing efficient gastroretentive and colon-targeted microballoon systems. As research advances toward precision medicine, such bio-based delivery platforms may provide the next major leap in pharmaceutical biotechnology.

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