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Mucoadhesive microspheres by ionic gelation method: An approach to sustained drug delivery; A review

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Abstract
Microspheres have emerged as a versatile drug delivery system due to their ability to provide targeted, controlled, and sustained drug release. Among these, mucoadhesive microspheres hold significant potential owing to their prolonged residence time at the site of action or absorption. Mucoadhesion enhances the bioavailability of drugs, especially those with a narrow absorption window. In This review we are able to highlights the principles, evaluation techniques, and applications of microspheres, with a special emphasis on mucoadhesive microspheres prepared using the ionic gelation technique.

Keywords: Microspheres, mucoadhesion, natural, synthetic and semi synthetic polymers, chitosan

Introduction
The oral route is widely regarded as the most popular method for drug administration, primarily due to its ease of use and the flexibility offered by gastrointestinal physiology in designing dosage forms. [1] Sustained release, prolonged release, modified release, extended release, or depot formulations are terms used to describe drug delivery systems that are engineered to extend therapeutic effects by continuously releasing medication over a prolonged period after a single dose administration. [2]
These dosage forms are particularly attractive for several reasons. They enhance the bioavailability of the drug product, reduce the frequency of administration by maintaining effective blood levels for a longer duration, and minimize fluctuations in peak and trough concentrations.[2] Additionally, they lower the risk of side effects and potentially improve the targeted distribution of the drug within the body, contributing to a more efficient and patient-friendly therapeutic regimen. [3]

Microspheres
Microspheres are spherical, free-flowing particles ranging in size from 1 to 1000 micrometers, designed to encapsulate therapeutic agents. They offer advantages such as prolonged release, protection of unstable drugs, and site-specific delivery.[3]Mucoadhesive microspheres further enhance these benefits by adhering to mucosal tissues, ensuring localized delivery and increased drug absorption. This review explores the role of mucoadhesive microspheres in advanced drug delivery, focusing on the ionic gelation method as a key preparation technique. [4]

Advantages of Microspheres
1. Microspheres enable precise delivery of small quantities of potent drugs, minimizing drug concentration at non-target sites and reducing systemic side effects.
2. They offer protection to unstable drugs, both before and after administration, ensuring the drug remains effective until it reaches the intended site of action. [5]
3. Microspheres allow modulation of the drug's *in vivo* performance, including its pharmacokinetic profile, tissue distribution, and cellular interactions, thereby enhancing therapeutic efficacy.
4. They support controlled drug release, improving patient compliance and treatment outcomes.

Examples: Narcotics, antagonists, and steroid hormones. [6]

Types of Microspheres
Bioadhesive Microspheres
Bioadhesive microspheres prolong residence time at the application site, promoting intimate contact with the absorption site and enhancing therapeutic efficacy. [7]

Magnetic Microspheres
Magnetic microspheres are supramolecular particles small enough (<4 μm) to circulate through capillaries without causing embolic occlusion. They are ferromagnetic and can be captured in micro vessels and directed into adjacent tissues using a magnetic field of 0.5-0.8 tesla. [8]

Floating Microspheres
Gastro-retentive floating microspheres are low-density systems that float over gastric contents and remain in the stomach for prolonged periods without affecting gastric emptying. The drug is released at a controlled rate for enhanced therapeutic action. [8]

Radioactive Microspheres
Radioactive microspheres deliver a high radiation dose specifically to targeted areas, minimizing damage to surrounding healthy tissues. These microspheres are administered into arteries supplying the tumor. Types include α emitters, β emitters, and γ emitters. [9]

Polymeric Microspheres
- **Biodegradable Polymeric Microspheres:** These microspheres contain biodegradable polymers that prolong residence time on mucous membranes due to their high swelling capacity in aqueous media, forming a gel. Drug release is controlled in a sustained manner by polymer concentration.[7]
- **Synthetic Polymeric Microspheres:** Composed of synthetic polymers, these microspheres serve as bulking agents, fillers, embolic particles, and drug delivery vehicles, offering versatile applications in pharmaceutical formulations. [11]

Mucoadhesive drug delivery system

Mucoadhesive drug delivery refers to the technique in which a drug is delivered to specific sites in the body by adhering to mucosal surfaces, such as those in the mouth, nose, eyes, gastrointestinal tract, or vaginal and nasal cavities. This system is designed to improve the bioavailability of drugs, enhance their residence time at the site of action, and offer controlled and sustained release of the drug. [11-12]

Principles of Mucoadhesion

Mucoadhesion involves the interaction of a delivery system with the mucus layer covering mucosal tissues. The process occurs in two stages:

- **Contact Stage:** The delivery system comes into contact with the mucosal surface.
- **Consolidation Stage:** Chemical and physical interactions, such as hydrogen bonding and van der Waals forces, strengthen adhesion. [12]

Factors Influencing Mucoadhesion

- **Polymer Properties:** Molecular weight, chain flexibility, and functional groups.[13]
- **Mucosal Characteristics:** pH, turnover rate of mucus, and composition.
- **Environmental Conditions:** Presence of moisture and shear forces. [13]

Formulation of Mucoadhesive Microspheres

Polymers Used in Mucoadhesion

Mucoadhesive polymers are materials used in drug delivery systems that facilitate the attachment of the dosage form to the mucosal surfaces of the body.[8] These polymers interact with the mucus layer or the epithelial cells lining the mucosal tissues, allowing prolonged retention and controlled drug release at the site of action. The selection of mucoadhesive polymers is crucial for the effectiveness of the delivery system. [14]

Types of Mucoadhesive Polymers

1. Natural Polymers

- **Chitosan:** A biopolymer derived from chitin, commonly used due to its biodegradability, non-toxicity, and ability to form gel-like structures. Chitosan can interact with mucin, a glycoprotein in the mucus layer, through electrostatic and hydrogen bonding.
- **Alginate:** A polysaccharide extracted from seaweed, alginate is commonly used in mucoadhesive drug delivery because of its gel-forming ability and biocompatibility. It can form cross-linked networks that enhance retention on mucosal surfaces.[13]
- **Gelatin:** A natural protein derived from collagen. Gelatin has good mucoadhesive properties and is often used in oral drug delivery systems.
- **Acacia (Gum Arabic):** A natural gum that can form strong adhesive bonds with mucosal tissues. It is used in both oral and topical drug delivery systems.
- **Carrageenan:** A natural polysaccharide obtained from red seaweed, carrageenan is used for its gel-forming ability and interaction with mucosal surfaces. [14-15]

2. Synthetic Polymers

- **Polycarbophil:** A cross-linked acrylic acid polymer that exhibits strong Mucoadhesion due to its ability to form hydrogen bonds with mucin. It is widely used in the formulation of controlled-release systems. [14]
- **Polyvinyl Alcohol (PVA):** A synthetic polymer with good mucoadhesive properties, especially in ocular and nasal drug delivery. It can form stable films that adhere well to mucosal membranes. [15]
- **Polyacrylic Acid (Carbopol):** A synthetic polymer commonly used in gel formulations, Carbopol has excellent mucoadhesive properties due to its high degree of ionization and ability to form a network structure that adheres to mucosal surfaces.
- **Polyethylene Glycol (PEG):** A synthetic polymer often used in combination with other mucoadhesive agents to improve drug stability and release rates. [16]

3. Semi-Synthetic Polymers

- **Hydroxypropyl Methylcellulose (HPMC):** A modified cellulose derivative, HPMC is widely used for oral and topical mucoadhesive formulations due to its biocompatibility, safety, and ability to form viscous solutions. [15]
- **Carboxymethylcellulose (CMC):** A water-soluble cellulose derivative, CMC is used for its adhesive properties and ability to form hydrogels. It is frequently employed in oral drug delivery and ocular systems.
- **Methylcellulose:** Another cellulose derivative that is used as a binder and film-forming agent in mucoadhesive systems. It is often used in oral and ophthalmic formulations. [16]

4. Other Notable Mucoadhesive Polymers

- **Xanthan Gum:** A polysaccharide produced by bacterial fermentation, used in mucoadhesive drug delivery for its ability to form gels and interact with mucosal surfaces.
- **Sodium Alginate:** A salt of alginic acid that is used in formulations for its ability to form gel-like substances upon contact with water, improving its mucoadhesive properties. [17]

Characteristics of Mucoadhesive Polymers

- **Bioadhesion:** Ability to interact and adhere to the mucus layer or epithelial cells.
- **Biocompatibility:** Must be safe for use in the body and cause minimal irritation or allergic reactions.
- **Viscosity:** Higher viscosity often results in stronger adhesion. [14]
- **Swelling and Gel Formation:** Polymers that swell or form gels on contact with water enhance retention on mucosal surfaces.
- **Biodegradability:** Ideally, mucoadhesive polymers should degrade into non-toxic metabolites after drug release.
- **Release Profile:** Good mucoadhesive polymers facilitate the controlled and sustained release of the drug. [18]

Preparation Methods of Microspheres

- **Ionic Gelation:** Utilizes electrostatic interactions between a polymer (e.g., chitosan) and a crosslinking agent (e.g., sodium tripolyphosphate). [17]
- **Emulsion Solvent Evaporation:** Produces uniform microspheres with high encapsulation efficiency.
- **Spray Drying:** Rapid and scalable but may require optimization for heat-sensitive drugs.
- **Coacervation:** Separates the polymer phase from a solution to form microspheres. [19]

Ionic Gelation Method

The ionic gelation technique is a widely used and environmentally friendly method for the preparation of mucoadhesive microspheres. The process involves the following steps:

1. **Polymer Solution Preparation:**

- Chitosan is dissolved in a dilute acidic solution, commonly acetic acid, to protonate its amino groups and make it soluble.
- The concentration of chitosan is optimized to achieve the desired viscosity and gel strength.

2. **Drug Incorporation**

The therapeutic agent is dissolved or dispersed in the chitosan solution to ensure uniform encapsulation. [18]

3. **Crosslinking Agent Addition:**

- Sodium tripolyphosphate (TPP) is added dropwise to the chitosan solution under constant stirring.
- The electrostatic interaction between the positively charged amino groups of chitosan and the negatively charged phosphate groups of TPP leads to the formation of a gel matrix. [19]

4. **Microsphere Formation**

- The gel matrix forms microspheres, which can be further hardened by optimizing stirring speed, crosslinker concentration, and reaction time.

5. **Separation and Drying**

- The formed microspheres are separated by centrifugation or filtration, washed with deionized water to remove excess TPP, and dried using air drying or lyophilization. [20]

Advantages of Ionic Gelation

- **Mild Conditions:** Avoids the use of organic solvents and high temperatures, preserving drug stability.
- **Eco-Friendly:** Utilizes water-based systems, making the process environmentally safe.
- **Scalability:** Simple and cost-effective, suitable for large-scale production. [20]

Factors Affecting Ionic Gelation

- **Polymer Concentration:** Influences viscosity, particle size, and encapsulation efficiency.
- **Crosslinker Ratio:** Determines the degree of crosslinking and mechanical strength.
- **Stirring Speed:** Affects particle size and distribution.
- **pH and Ionic Strength:** Modulate the electrostatic interactions between chitosan and TPP. [21]

Evaluation Parameters

Microsphere Characterization

- **Particle Size and Distribution:** Measured by optical microscopy or SEM.
- **Encapsulation Efficiency:** Percentage of drug encapsulated relative to the initial amount.
- **Swelling and Degradation:** Assesses stability in physiological conditions.
- **Mucoadhesion Strength:** Tested using mucosal models in vitro. [10, 14]

Drug Release Studies

- Performed in simulated biological fluids.
- Data analyzed using mathematical models to determine release kinetics. [22]

Applications of mucoadhesive polymer in sustained release drug delivery

1. **Oral Drug Delivery**

- **Controlled Release in the Gastrointestinal Tract (GIT):**Mucoadhesive microspheres are commonly used in oral drug delivery systems to provide sustained release of drugs over a prolonged period. [2] By adhering to the mucosal lining of the stomach or intestines, they can help achieve targeted delivery and prolonged release of the drug, reducing fluctuations in plasma drug concentration and improving therapeutic outcomes.
- **Example:** Mucoadhesive microspheres containing anti-inflammatory drugs can help treat conditions like peptic ulcers or inflammatory bowel disease (IBD) by releasing the drug slowly at the site of action. [7]

2. **Buccal and Sublingual Drug Delivery**

- **Faster Absorption and Bypassing First-Pass Metabolism:** In buccal and sublingual drug delivery systems, mucoadhesive microspheres can adhere to the oral mucosa, facilitating direct absorption of the drug into the bloodstream, bypassing the first-pass metabolism in the liver. This provides a faster onset of action and higher bioavailability. [21]
- **Example:** Mucoadhesive microspheres containing pain relievers or antiemetic can be used for rapid relief by sticking to the mucosal surface in the mouth or under the tongue. [23]

3. **Nasal Drug Delivery**

- **Sustained Release for Systemic and Local Therapy:** Mucoadhesive microspheres are used in nasal drug delivery systems to prolong the residence time of the drug in the nasal cavity, allowing for more efficient systemic absorption or localized drug delivery to the nasal mucosa. [11]
- **Example:** Mucoadhesive microspheres containing vaccines or hormone therapies can provide sustained release for enhanced therapeutic effects and better patient compliance.

4. **Ocular Drug Delivery**

- **Prolonged Drug Release in the Eye:** Mucoadhesive microspheres are particularly useful for ocular drug delivery, where the drug needs to be released slowly over time to treat chronic conditions like glaucoma, conjunctivitis, or dry eye disease. By adhering to the

ocular mucosa, they ensure that the drug remains in contact with the eye's surface for a longer duration, improving therapeutic efficacy. [24]

- **Example:** Mucoadhesive microspheres containing anti-glaucoma drugs or antibiotics for eye infections can provide sustained release, reducing the need for frequent dosing.

5. Vaginal Drug Delivery

- **Sustained Localized Drug Release:** In vaginal drug delivery, mucoadhesive microspheres are employed for the sustained release of drugs directly at the site of action. This method is commonly used for treating vaginal infections, hormonal therapies, and contraception. The microspheres adhere to the vaginal mucosa, ensuring that the drug is released steadily over a prolonged period. [15]
- **Example:** Mucoadhesive microspheres containing antifungal agents for treating vaginal infections or progesterone for contraception can provide localized, sustained action with reduced side effects.

6. Targeted Drug Delivery in the GIT

- **Specific Site of Action:** Mucoadhesive microspheres can be used for targeted drug delivery to specific areas in the gastrointestinal tract, such as the stomach or intestines. By utilizing pH-sensitive or enzyme-sensitive polymers in conjunction with mucoadhesive materials, the microspheres can release the drug only at the desired site, improving the efficacy and reducing systemic side effects. [24]
- **Example:** Drugs for the treatment of ulcerative colitis or Crohn's disease can be delivered directly to the affected areas in the colon using mucoadhesive microspheres.

Advantages of Mucoadhesive Microspheres in Sustained Release

1. Prolonged Residence Time

Mucoadhesive microspheres enhance the retention time of the drug at the site of administration, allowing for sustained release over hours or even days. This reduces the frequency of dosing and improves patient compliance. [24]

2. Targeted Drug Delivery

By adhering to specific mucosal sites, mucoadhesive microspheres can deliver drugs directly to the site of action, increasing therapeutic efficacy and minimizing systemic side effects. [25]

3. Improved Bioavailability

Mucoadhesive microspheres can enhance the absorption of drugs that may have poor bioavailability or undergo extensive first-pass metabolism by ensuring prolonged contact with the mucosal surfaces for enhanced absorption. [26]

4. Reduced Side Effects

By delivering the drug locally at the site of action, the risk of systemic side effects is reduced. This is particularly important for drugs with a narrow therapeutic window or those that require local effects (e.g., antibiotics or anti-inflammatory drugs). [18]

5. Biocompatibility and Safety

Mucoadhesive microspheres are often made from biocompatible and biodegradable materials, reducing the risk of adverse reactions. [27]

Challenges and Future Perspectives

Challenges in the development of mucoadhesive microspheres include polymer variability, achieving optimal drug release profiles, and large-scale manufacturing. Future research should focus on advanced polymers, combination delivery systems, and *in vivo* studies to validate in vitro findings.

Conclusion

From the study we found that, Mucoadhesive microspheres represent a promising advancement in the field of sustained drug delivery systems. By combining the advantages of microsphere technology with the enhanced bioadhesive properties of mucoadhesive materials, these systems offer significant improvements in the targeted delivery, bioavailability, and therapeutic efficacy of drugs. The study has made us to believe that ionic gelation method stands out as an efficient and environmentally friendly approach to prepare mucoadhesive microspheres, utilizing readily available natural and synthetic polymers to achieve optimal drug encapsulation and controlled release.

Seeing utilization part we came across the applications of mucoadhesive microspheres span a wide range of delivery routes, including oral, buccal, nasal, ocular, vaginal, and targeted gastrointestinal delivery. It was noticed that each of these applications benefits from the prolonged residence time of the microspheres, resulting in sustained drug release and enhanced therapeutic outcomes. Moreover, we built an opinion that the ability to target specific sites of action reduces the potential for systemic side effects, further improving patient safety and compliance.

Despite the numerous advantages, challenges such as polymer variability, formulation optimization, and large-scale manufacturing remain. Future research in mucoadhesive microspheres should focus on developing more advanced and versatile polymers, refining drug release profiles, and validating the effectiveness of these systems in clinical settings. Additionally, exploring combination therapies and multi-functional delivery systems may open new avenues for more personalized and effective treatments.

In conclusion, mucoadhesive microspheres have the potential to revolutionize drug delivery by offering precise, sustained, and targeted release, ultimately leading to improved patient outcomes and compliance in the treatment of various chronic and localized diseases.

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