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# Development and characterization of gastroretentive mucoadhesive tablet as controlled release system: A review

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**Abstract**
Gastroretentive mucoadhesive tablets are a promising controlled drug delivery system designed to enhance the retention time of medications in the stomach. This approach helps improve the effectiveness of drugs that are intended to act locally in the gastric region or are absorbed primarily in the upper gastrointestinal tract. This thesis explores the various polymers used in the formulation of mucoadhesive tablets, examining their role in promoting adhesion to the gastric mucosa. Additionally, it discusses the key factors influencing mucoadhesion, such as the properties of the polymers, the pH of the gastric environment, and the composition of the dosage form. The thesis also reviews recent advancements in techniques for evaluating and characterizing mucoadhesive tablets, including *in vitro* methods that assess their performance and stability.

**Keywords:** Evaluation, gastric retention time, mucoadhesive tablets, polymers

## Introduction

Oral controlled release (CR) dosage forms have been developed over the past few decades to improve therapeutic outcomes. However, these systems are often ineffective for drugs with a narrow absorption window in the upper gastrointestinal tract due to short transit times, leading to suboptimal absorption and bioavailability. [1-2] Drugs in this category typically have enhanced absorption in the jejunum and ileum or better solubility in the stomach, and formulating them into gastroretentive systems like mucoadhesive tablets can extend their absorption phase. These tablets remain in the stomach, releasing the drug in a controlled manner, which improves absorption in the upper gastrointestinal tract. [3-4]

Prolonged gastric retention is beneficial for drugs absorbed in the proximal gastrointestinal tract or those less soluble in alkaline environments. Mucoadhesive tablets offer advantages such as efficient drug absorption due to intimate contact with the mucus layer of the stomach. These tablets provide controlled and sustained release, improving patient compliance by reducing the frequency of administration. [5-6]

In recent years, there has been significant progress in controlled release drug delivery systems, such as self-regulating insulin and oral osmotic systems. However, limitations due to gastrointestinal transit times still exist. Strategies to increase gastric retention, such as mucoadhesion, flotation, and modified shape systems, are being explored to extend drug residence time in the stomach. [6]

Mucoadhesive polymers, which adhere to mucosal surfaces, have shown promise in improving gastric retention and enabling localized drug delivery in the gastrointestinal tract. These polymers can also be used in other mucosal membranes, offering a broad range of applications. [7] By addressing issues like poor patient compliance and fluctuating drug concentrations, controlled and targeted drug delivery systems can enhance therapeutic efficacy and reduce side effects. Gastroretentive systems, which aim to prolong gastric residence time, provide new opportunities for more predictable and effective drug delivery. [8]

## Overview of the Stomach

The stomach is located in the upper-left part of the abdomen, just beneath the diaphragm, and occupies the epigastric and left hypochondriac regions. Its primary functions include temporarily storing food, grinding it, and gradually releasing it into the duodenum for further digestion. [9] Due to its relatively small surface area, the stomach's role in absorption is minimal. It acts as a barrier, limiting the direct delivery of drugs to the small intestine, where most absorption occurs. [10]

## Stomach Anatomy

The stomach consists of four main regions:(Fig.No.1)

- **Cardia**: Where the esophagus meets the stomach, preventing acid reflux.
- **Fundus**: The upper dome-shaped area that stores gases during digestion.
- **Body (Corpus)**: The largest section, responsible for mixing food with gastric juices.
- **Pylorus**: The lower part that regulates the passage of food into the duodenum.(11-12)

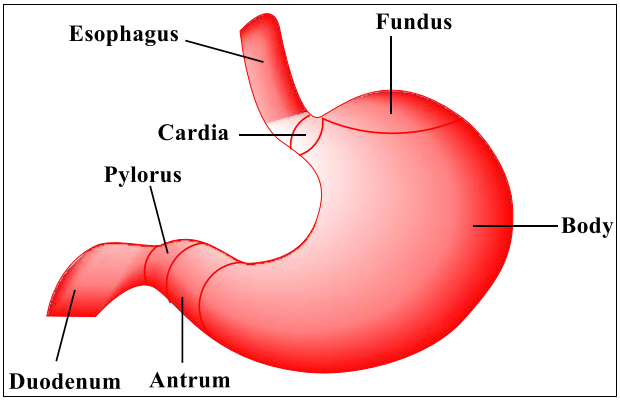


**Fig 1:** A CHEM DRAW sketch, Anatomy of stomach [11]

Themain function offundus and body mainly store food, while the cardia mixes and grinds it. The fundus adapts to increased food volume by relaxing its muscles and pushing

contents toward the lower stomach. The antrum grinds food into 1-2 mm particles, allowing it to pass through the pyloric valve into the small intestine. [12]

**Bioadhesion and Mucoadhesion**

Adhesion is the bond formed when an adhesive contacts a surface. In biological systems, bioadhesion includes four types: between normal cells, between a cell and a foreign substance, between a normal and pathological cell, and between an adhesive and a biological surface. [13] For drug delivery, bioadhesion refers to the attachment of a drug carrier to a biological site, often epithelial tissue. When the adhesive binds to a mucus layer, it is called mucoadhesion, similar to how mucus adheres to epithelial surfaces. [14]

**The Mucus Layer**

Mucus is a thick, translucent gel-like secretion, 50-450 μm thick in humans, produced by goblet cells or specialized glands. Its composition mainly consists of 95% water, 0.5-5.0% glycoproteins and lipids, 1% mineral salts, and 0.5-1.0% free proteins, varying with species, location, and health conditions. [15-16]

The mucus layerkey functions are to protects tissues with its hydrophobic properties, acts as a barrier that affects drug absorption and bioavailability, and adheres firmly to epithelial surfaces. It also keeps mucosal membranes moist through continuous secretion from goblet cells. The negative charge from sialic acid and sulfate residues enhances its bioadhesion. [16-17]

**Mucoadhesive polymers**

Mucoadhesive polymers are of two types: hydrophilic polymers and hydrogels. Hydrophilic polymers with carboxylic groups, like PVP, methyl cellulose, and hydroxypropyl cellulose, offer strong mucoadhesion. Hydrogels, which absorb water and adhere to mucus, include anionic polymers (e.g., Carbopol), cationic polymers (e.g., chitosan), and neutral polymers (e.g., Eudragit NE30D). [18-20]

**Characteristics of an Ideal Mucoadhesive Polymer**

An ideal mucoadhesive polymer should be non-toxic and non-absorbable in the GI tract, with non-irritating effects on the mucous membrane. It should form strong, non-covalent bonds with mucin and epithelial surfaces, ensuring quick adhesion and site specificity. The polymer must allow easy drug incorporation and controlled release without hindering its effectiveness. Additionally, it should remain stable throughout its shelf life and be cost-effective for widespread use. [21]

Robinson and his team, using fluorescence techniques, found that cationic and anionic polymers bind more effectively than neutral ones. They also noted that polyanions are superior to polycations in binding efficiency and that water-insoluble polymers provide more flexibility in dosage form design. [22] Anionic polymers with sulfate groups bind better than those with carboxylic groups, and the binding strength increases with charge density. Highly effective mucoadhesive polymers include carboxymethyl cellulose, gelatin, hyaluronic acid, carbopol, and polycarbophil. [23]

**Molecular Characteristics of Mucoadhesive Polymers**

Effective mucoadhesive polymers possess several key molecular characteristics: they feature strong hydrogen-bonding groups (e.g., –OH, –COOH), anionic charges, and sufficient flexibility to penetrate mucus networks or tissue crevices. Additionally, they should have suitable surface tension for proper wetting of mucus or mucosal tissues and a high molecular weight to enhance adhesive strength. [23]

**Examples of Mucoadhesive Polymers**

- **Natural**: Na alginate, Pectin, Tragacanth, Gelatin, Carrageenan
- **Synthetic**: Polyvinyl alcohol, Polyamides, Polycarbonates, Polyalkylene glycols
- **Biocompatible**: Esters of hyaluronic acid, Polyvinyl acetate
- **Biodegradable**: Poly(lactides), Poly(glycolides), Polycaprolactones, Chitosan [20, 24]

**Factors Affecting Mucoadhesion**

- **Polymer Factors**: Molecular weight, concentration, chain flexibility, conformation, swelling.
- **Environmental Factors**: pH, applied force, contact time.
- **Physiological Factors**: Mucin turnover, disease state. [16, 25]

**a) Polymer-Related Factors**

- **Molecular Weight**: Mucoadhesion improves with higher molecular weight (≥100,000 g/mol). Linear polymers like PEG show increased adhesion with higher weight, while dextran's helical structure may reduce adhesion despite a high molecular weight.
- **Concentration of Active Polymer**: The adhesive strength peaks at an optimal concentration. Too high a concentration reduces adhesion due to limited polymer chain interpenetration.
- **Flexibility of Polymer Chains**: Flexible polymers penetrate the mucus layer better. Crosslinking decreases flexibility, reducing adhesive strength.
- **Spatial Conformation**: The polymer's shape impacts adhesion. Linear polymers like PEG offer better adhesion than helical ones like dextran.
- **Swelling**: Proper hydration is crucial. Excessive swelling leads to a slippery mucilage that reduces adhesion. [16]

**b) Environment-Related Factors**

- **pH**: pH affects mucus charge and polymer interactions. For example, polycarbophil shows weak adhesion above pH 5.
- **Applied Strength**: Increased pressure and contact time enhance polymer-mucin interaction and adhesion.
- **Initial Contact Time**: Longer contact time improves mucoadhesive strength by allowing more swelling and interpenetration. [25]

**c) Physiological Factors:**

- **Mucin Turnover**: Rapid mucin turnover limits mucoadhesive residence time.
- **Disease State**: Mucus properties change during diseases, which may affect mucoadhesion, requiring testing under specific conditions. [16]

**Formulation of Mucoadhesive Tablets**

Gastroretentivemucoadhesive tablets are designed for controlled drug release in the gastrointestinal tract, utilizing polymers like Hydroxypropyl Methylcellulose (HPMC), Sodium Carboxymethylcellulose (SCMC), and Carbopol. These polymers ensure mucoadhesion, controlled drug release, and extended residence time in the stomach**.** [22]

**a) Ingredients**

- **HPMC**: For controlled release.
- **SCMC**: Enhances mucoadhesion and swelling.
- **Carbopol**: Increases bioadhesive strength.
- **Plasticizer** (e.g., glycerin): For flexibility.
- **Binder** (e.g., PVP): To bind ingredients together.
- **Filler** (e.g., MCC): To bulk the formulation.
- **Lubricant** (e.g., magnesium stearate): For smooth tablet compression. [20]

**b) Method**

1. **Polymer blending** for mucoadhesion and controlled release.
2. **Drug incorporation** for uniform distribution.
3. **Granulation** using a binder.
4. **Compression** into tablets.
5. **Coating** (optional) for protection or delayed release. [26]

**c) Evaluation**

- **Mucoadhesive Strength**: Tested using an *in vitro* method (e.g., physical balance).
- **Drug Release**: Assessed using USP Type II dissolution apparatus.
- **Tablet Hardness, Friability, and Weight Variation**: Ensures uniformity and durability.

This formulation provides sustained drug release with improved bioavailability and targeted delivery to the stomach. [27]

**Evaluation of Mucoadhesive Tablets**

The prepared mucoadhesive tablets were evaluated for various parameters to assess their quality and performance.

1. **Hardness**: Hardness was determined using a Monsanto hardness tester. Three tablets from each batch were tested to ensure consistency. [28]

2. **Friability**: The friability of twenty tablets was measured using a Roche friabilator at 25 rpm for 4 minutes. The percentage friability was calculated using the formula:

   % Friability=Initial wt. of tablets – Final wt. of tablets / Initial wt. of tablets ×100 [29]

3. **Weight Variation**: Twenty tablets from each batch were weighed individually. The average weight and standard deviation were calculated, and the batch passed the test if no more than two tablets deviated by more than the permissible percentage from the average weight. [30]

Weight variation =(IW-AW)/AW×100%

**Table 1:** Weight variation limits for tablets

| IP/BP | Limit | USP |
|---|---|---|
| 80 mg or less | 10% | 130mg or less |
| More than 80mg or less than 250 mg | 7.5% | 130 mg to 324 mg |
| 250 mg or more | 5% | 324 mg or more |

4. **Thickness**: The thickness of three randomly selected tablets was measured using a vernier caliper to ensure uniformity. [30]

5. **Mucoadhesive Strength**: Mucoadhesive strength was measured using a modified physical balance. The test involved attaching the tablet to a glass slide and establishing adhesion to goat or rat stomach mucosa. The mucosa was placed in a beaker with buffer solution (0.1N HCl, pH 1.2). A preload of 10 mg was applied for 5 minutes to ensure bonding. After preload removal, water was added to the left side of the balance until the tablet detached from the mucosa. The weight of water needed to detach the tablet was noted as the mucoadhesive strength in grams. From this, the force of adhesion and bond strength were calculated: [31-32]

Force of adhesion (N) = Mucoadhesive strength × 9.81 / 1000

Bond strength (N/m²) = Force of adhesion (N) / Surface area of tablet (m²)

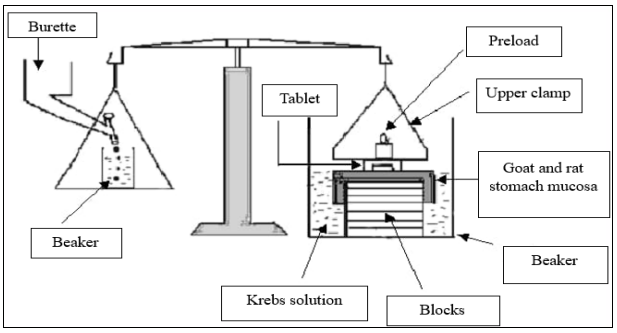


**Fig 2:** Mucoadhesive Test Apparatus [16]

**6. *In Vitro* Drug Release Dissolution Testing**

The *in vitro* drug release profile of Atorvastatin mucoadhesive tablets (formulations F1–F9) was evaluated using a USP Type II dissolution apparatus. The test was conducted in 900 mL of 6.8 pH phosphate buffer at 37 ± 0.5°C with a stirring rate of 50 rpm. At predetermined intervals, 5 mL samples were withdrawn from the dissolution medium, and an equal volume of fresh dissolution medium was added to maintain sink conditions. Each sample was filtered, and the absorbance was measured at 246 nm using a double-beam UV spectrophotometer, with the 6.8 pH phosphate buffer as the blank.

The percentage of drug released was calculated based on the absorbance using the following formula:

% Drug Release = K ×Absorbance

where the constant K is determined using the following equation:

K = Std. conc. × vol. of dissolution media × dilution factor × 100/std. abs. × dose × 1000

This method allowed the monitoring of the release kinetics and the evaluation of each formulation's performance. [30, 33]

### 7. Kinetic Analysis of Dissolution Studies

The dissolution data for the mucoadhesive tablets were analyzed using four kinetic models: Zero-order, First-order, Higuchi's, and Korsmeyer-Peppas. The goal was to identify the model that best describes the drug release behavior.

### Methodology

- **Zero-order Kinetics:** Cumulative percentage of drug released vs. time, assuming constant release rate.
- **First-order Kinetics:** Log of percentage of drug remaining vs. time, assuming release rate depends on remaining drug.
- **Higuchi's Model:** Cumulative percentage of drug released vs. square root of time, describing diffusion-based release.
- **Korsmeyer-Peppas Model:** Log of percentage of drug released vs. log of time, accounting for diffusion and erosion. [33-34]

### Conclusion

From a vast study of literature on Gastroretentive mucoadhesive controlled drug delivery system, we are of the view that mucoadhesive tablets provide an innovative drug delivery system, offering controlled release to specific site/s in the human body, including the oral cavity and gastrointestinal tract. These systems can be customized to target different mucosal tissues, making them useful for a variety of therapeutic applications. The advancements in medicine, particularly in protein/peptide drug delivery and gene therapy, are well supported by mucoadhesive polymers like HPMC, SCMC, carbopol, and its derivatives. Research into their potential for localized action in the stomach has shown promise.

However, we noticed challenges remain, particularly in the standardization of evaluation methods and the development of site-directed polymers. Present era research is focused on creating mucoadhesive polymers that are biodegradable, biocompatible, and capable of targeting specific cell types. We are of the opinion that a multidisciplinary approach will be essential to overcome these challenges and make mucoadhesive tablets a leading technology for controlled release drug delivery in both new and existing drug therapies.

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