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MUCOADHESIVE GASTRORETENTIVE SYSTEMS: A SITE SPECIFIC ORAL DELIVERY APPROACH

Nidhi Patel[1] , Dr. Shweta Paroha[2*] , Dr. Pragnesh Patni[3]

[1*,2,3]Khyati College of Pharmacy, palodia, Ahmedabad

***Corresponding Author**: Dr. Shweta Paroha
*Khyati College of Pharmacy, Palodia, Ahmedabad, Email: shwetatechno86@gmail.com

Abstract:
Due to its ease of administration, patient compliance, and formulation flexibility, the oral route of medication administration is the most preferred method. However, this method has some limitations, such as a short gastric residence time (GRT) for long-term drug delivery systems and for medications that are absorbed from particular gastrointestinal tract (GIT) sites. Numerous gastroretentive techniques, such as floating, bioadhesion, swelling, etc., are available for delivery. Several strategies have been put out to increase the gastric retention period of the delivery system in the upper gastrointestinal tract in order to get around these restrictions. By concentrating on site-specific drug release in the upper portion of the GIT, the gastroretentive dosage form (GRDF) extends the GRT. By improving the bioavailability of medications with a limited therapeutic window and enabling continuous and prolonged drug release, GRDFs help patients comply with their treatment regimens. The Gastrointestinal Mucoadhesive drug delivery system helps the drug perform better therapeutically by extending the dosage form's residence time at the site of absorption and facilitating close contact between the dosage form and the underline absorption surface. Wetting, adsorption, and interaction of polymer chains are only a few of the complex processes involved in the mucoadhesion process when using a polymeric drug delivery platform. Mucoadhesion and gastrointestinal retention are influenced by a number of factors.

Keywords: Mucoadhesive Drug Delivery System, Intestinal transit time, Gastro retentive system.

1. Introduction:

The most common method of medicine delivery in the past has been oral administration. Many oral delivery systems have been created during the last 20 years to serve as drug reservoirs from which the active ingredient can be delivered at a predetermined and regulated rate over a predetermined amount of time. An intravenous infusion, which constantly delivers the dosage required to maintain consistent plasma levels once the steady state is attained, should be comparable to the ideal sustained and controlled release dosage form from a pharmacokinetic perspective.[1] Formulation scientists have faced difficulties in developing oral controlled release systems due to their incapacity to confine and localise the system in the intended gastrointestinal tract region. The oral route is still preferred for any drug delivery to the systemic circulation due to its ease of dosage administration, patient compliance, and formulation flexibility, even though controlled release preparations employing alternate routes have been developed[2,3] In some cases, extending a delivery system's stomach retention is preferable in order to increase the medicinal substance's therapeutic value. For instance, longer gastric retention may be advantageous for medications that are absorbed in the proximal

portion of the gastrointestinal system and medications that are less soluble in or broken down by the alkaline pH.[4]

1.1 GASTRORETENTIVE DRUG DELIVERY SYSTEM:

Humans typically have a gastric emptying time of two to three hours through the primary absorption zone, which is the stomach or upper section of the intestine. This short period can cause inadequate drug release from the drug delivery system, which reduces the effectiveness of the amount that is provided. Therefore, there are many benefits to placing a drug delivery system in a particular area of the GIT, particularly for medications with a limited window for absorption. In addition to potentially increasing medication absorption, close contact between the dosage form and the absorbing membrane may also affect the rate of drug absorption. Oral sustained release dose formulations with the potential for intestinal or stomach retention have been developed as a result of these factors. Local drug release in gastro-intestinal dosage forms will significantly improve GIT pharmacotherapy by producing high drug concentrations at the intestinal or gastric mucosa that last for a long time. improve the GIT's pharmacotherapy, resulting in high drug concentrations in the intestinal or stomach mucosa that last for a long time.[5-7]

Current sustained release dosage forms still include a significant amount of the medication, which is subsequently lost and not available for absorption, even though they pass the absorption window. On the other hand, a suitable gastrointestinal dosage form that uses local drug release will significantly improve pharmacotherapy by delivering the entire dose over its specified GRT and ensuring that it is always accessible at the absorption site.

1.1.1 Different possibilities for a gastroprotective drug delivery system :

1. Medication that is mostly absorbed in the stomach, such as amoxicillin.
2. Medication that is poorly soluble in alkaline pH, such as diazepam and furosemide.
3. Medication with a limited window of absorption, such as methotrexate and levodopa.
4. Medication that breaks down in the intestines, such as metformin HCL and ranitidine.
5. Medicines that interfere with the typical microorganisms in the colon, such as antibiotics that fight Helicobacter pylori.
6. Drugs that are quickly absorbed from the gastrointestinal tract, including tetracycline.
7. Medication that acts locally in the stomach.[8]

The stomach's anatomy:

There are three primary regions that make up the gastrointestinal tract.

a) The stomach

b) The ileum, jejunum, and duodenum of the small intestine

d) The large intestine

The GIT is a muscular tube that runs from the mouth to the anus and is around 9 meters long. Through physiological processes like digestion, absorption, secretion, motility, and excretion, it absorbs nutrients and gets rid of waste. The proximal portion of the stomach has three layers of muscles known as oblique muscles, which extend out over the fundus and higher areas of the gastric body. The stomach is separated into the pylorus, body, and fundus.[9] The upper, left part of the abdomen contains the stomach, a shaped organ. The stomach's primary job is to briefly hold food, grind it, and then release it gradually into the duodenum.

Figure 1: General Gastrointestinal tract[10]

1.1.2 Factors affecting drug delivery system:

1) Dosage form density: To ensure effective stomach retention, high-density systems need a density of about 2.7g/ml.[11,12,13]
2) The dosage form's size: A dosage form with a diameter bigger than 7.5 mm has a longer gastric retention time because to the larger particle size. It cannot pass via the pyloric sinus and swiftly enter the bowel.[14]
3) Shape of the dose form: Tetrahedral and ring-shaped devices exhibit superior stomach retention as compared to other shapes.
4) Eating or not eating state: In the fasting state, the gastrointestinal motility is defined by the periods of intense motor activity that occur every 1.5-2 hours. Food intake, food viscosity and volume, caloric value and eating frequency have an intellectual impact on the gastric retention of the dosage form. The presence of the food in the gastrointestinal tract affects the gastric retention time of the dosage form.[15]
5) Meal composition: Giving indigestible polymers or fatty acid salts (cellulose, starch) can alter the pattern of stomach motility, delaying MMC and decreasing the pace of gastric emptying. This will also result un a prolonged duration of medication release.
6) Age: The GRT is longer in people over 70.
7) Gender: Women of the same age and race had a higher average GRT (4.6h) than men (3.4h).[16]

1.1.3 POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS:

1) medications with a short duration for absorption in the gastrointestinal tract (e.g., L-DOPA, p-aminobenzoic acid, furosemide, riboflavin)[17,3]
2) medications that operate locally in the stomach, such as antacids and misroprostol.[3]
3) medications that cause instability in the intestinal or colonic environment (such as metronidazole, captopril, and ranitidine HCl)[3,18]
4) medications that disrupt the normal microbiota in the colon (such as antibiotics like tetracycline, clarithromycin, and amoxicillin used to eradicate Helicobacter pylori).[19-21]
5) medications that are poorly soluble at high pH levels (such as verapamil, diazepam, and chlordiazepoxide)[22]

1.1.4 Advantages of gastroretentive drug delivery system:

- medication administration in the small intestine region with limited absorption windows.
- For a local effect in the upper portion of the small intestine, a prolonged residence period in the stomach would be advantageous. To treat peptic ulcer disease, for instance.
- It is expected that medications like cyclosporine, captopril, ranitidine, amoxicillin, ciprofloxacin, and others that are readily absorbed in the gastrointestinal system after release will have higher bioavailability.
- reduces the need for frequent administration.
- targeted therapy for upper digestive tract diseases that are localised
- Increase the dose form's retention period at the absorption location.
- Excellent accessibility.[23,24]

1.1.5 Disadvantages of gastro retentive drug delivery system:

- The amount of gastric juice must be raised.
- medications designed for the colon's selective release.
- Unpredictable compliance results from the stomach mucus wall's continuously changing condition.[25]
- The larger size of the drug delivery systems after several administrations presents a risk to life because of the possibility of long-term stomach retention.
- Super porous systems have disadvantages such as problematic storage of easily hydrolyzed, biodegradable polymers.

1.1.6 Need gastric retention drug delivery system:

- medications that are absorbed through the gastrointestinal tract's proximal end (GIT).
- For example, a medication that degrades or has poor solubility under alkaline pH.
- Short stomach emptying time that is unpredictable.
- To treat specific illnesses, a medication is released gradually into the stomach and proximal small intestine.[26]
- It works particularly well to treat peptic ulcers brought on by Helicobacter pylori infections.

1.2 MUCOADHESIVE SYSTEMS:

Attractive interactions between a pharmacological dosage form and a mucosal membrane at their interface are known as mucoadhesion. Mucoadhesive drug delivery systems are appealing and versatile in dosage form development because to their several administration routes, which include ocular, nasal, buccal and gingival, gastrointestinal (oral), vaginal, and rectal. Increased dosage form residence time, enhanced drug bioavailability, decreased administration frequency, ease of dosage form administration and therapy termination, and the ability to target specific body sites and tissues are some benefits linked to the use of mucoadhesives in drug delivery. Good described bioadhesion as the condition in which interfacial forces hold two materials together for a long time, at least one of which is biological in nature. It can also refer to a material's (biological or synthetic) capacity to stick to biological tissue for a long time.[27]

1.2.1 Mucoadhesion stages :

1) A close interaction between a membrane and a bioadhesive.
2) The bioadhesive's penetration into the tissue's surface fissures.
3) The polymer and mucin mechanically interlock.[28]

1.2.3 Types of Mucoadhesion:

There are 4 different kinds of mucoadhesion in biological systems:
1) A normal cell adhering to another normal cell.
2) A foreign material adhering to a cell.
3) A normal cell adhering to a diseased cell.

4) An adhesive's ability to stick to a biological surface.

1.2.4 Gastrointestinal Motility and Transit Time:

Two different types of gastrointestinal motility and secretions have been established based on the stomach's fed and fasting states. The stomach typically contains cellular waste, mucus, and saliva when fasting. The migrating myoelectric complex (MMC), a term used to describe some cyclic contractile processes, is linked to the fasting state. The sphincter's partial constriction facilitates the easy passage of liquid substances.Conversely, a "antral-sieveing" mechanism retains the big undigested items, which are then retropulsed into the stomach's main body and remain in the fed condition. The contents are moved towards the antrum and the pyloric sphincter by gastric contractions when the stomach is fed. In the stomach, a number of interdigestive processes often occur. However, this cycle is upset by feeding, which results in an uneven contractile pattern for a while. It has been said that the MMC, which controls the pattern of gastrointestinal motility, alternates between periods of activity and quiescence. It appears that the MMC experiences four distinct stages of activation.[29,4]

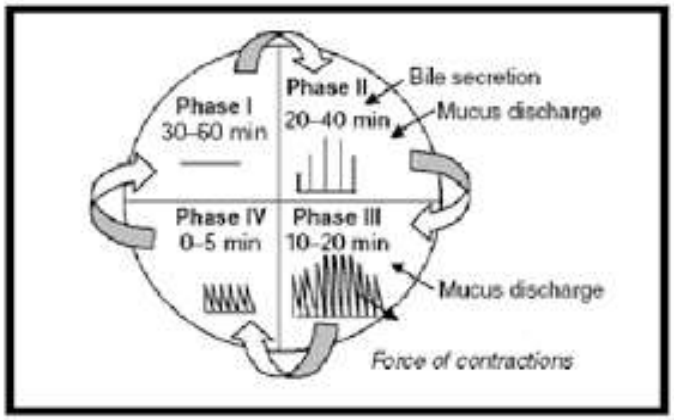

Figure 2 : GI motility phases[30]

Phase I: There are no contractions during this 30 to 60-minute time of calm.
Phase II: It lasts about 20 to 40 minutes and is characterised by sporadic contractions that progressively get stronger as the phase goes on. Later at this stage, the stomach starts to release liquids and tiny particles.
Phase III: This brief episode of strong proximal and distal gastric contractions (4–5 contractions per minute) lasts roughly 10–20 minutes. Known as the "house-keeper wave," these contractions force the contents of the stomach down the small intestine.
Phase IV: The contractions stop between the final section of phase III and phase quiescence, and this brief transitory period lasts roughly 0 to 5 minutes.

1.2.5 Mechanism of mucoadhesion:

The two stages of contact and consolidation are often when mucoadhesion develops from interactions between medication and carrier molecules with various mucus membranes (Fig. 3).[31] However, the mucoadhesion mechanism is extremely intricate and yet poorly understood. The mucoad hesion mechanism, which enables drug molecule interactions across the interface, involves a variety of chemical interactions, including ionic bonds, covalent bonds, hydrogen bonds, Van der Waals forces, and hydrophobic contacts.[32]

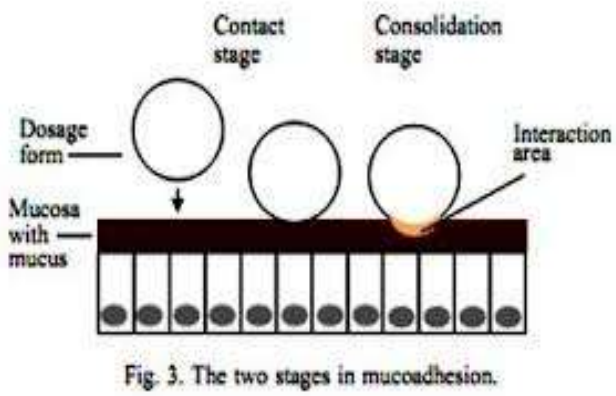

Fig 3: the two stages in mucoadhesion[33]

1) Contact stage:[34]
The mucous adhesion and mucosa are tightly moist at this point when the mucoadhesive material comes into contact with the mucosa. It is the mucus found in the mucosa that does this wetting of the mucoadhesives.

2) Consolidation stage:
The mucoadhesive substance adheres to the mucous membrane by a variety of physical and chemical attractive forces, resulting in persistent mucous membrane adhesion.This stage is referred to as the consolidation or merging phase. The mucous membrane adhesion process is finished after these two steps.

1.2.6 FACTOR AFFECTING MUCOADHESION:

- Molecular weight: Low molecular weight polymers benefit from interpenetration since greater molecular weight polymers may entangle and not moisten or diffuse as rapidly.
- Polymer concentration: A high mucoadhesive concentration might increase mucoadhesiveness because it contains a lot of functional groups that can establish molecular connections. Because there are fewer polymer chains per unit volume of mucus that penetrate, there is less interaction between polymers when the concentration of the polymer is too low.[35,36,37]
- The adaptability of polymer chains is thought to be a crucial factor in entanglement and penetration. Effective diffusion of the polymer chain into the mucous layer is necessary for bioadhesions to work.
- Swelling: The adhesion time increases as the polymeric matrix swells more. The concentration of the polymer, the strength of the ions, and the presence of water all affect it. By exposing the bioadhesion sites, this method creates mechanical entanglement and electrostatic or hydrogen bonding between the mucus network and the polymer.
- Hydrogen Bonding Capacity: Another crucial element in the polymer mucosa's ability to adhere is hydrogen bonding. The polymer needs a functional group that can create hydrogen bonds in order for the mucous membrane to stick to it.

1.2.7 Environmental – Related Factors:

- pH: The charge on the surface of polymers and mucus is influenced by pH. Because the functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone dissociate differently depending on pH, mucus will have a varied charge density, which could have an impact on adherence.
- Applied strength: A specific strength must be applied in order to install a solid bioadhesive system. Regardless of the type of polymer, the adhesion strength of such polymers rises as the applied strength does.

- Initial contact time: The degree of swelling and the interpenetration of polymer chains are determined by the initial contact time between the mucoadhesive and the mucus layer. As the initial contact time grows, so does the mucoadhesive strength.
- Physiological factors: Bioadhesion may be impacted by physiological factors such as mucin turnover and mucus layer illness.[38-41]

The mucoadhesive polymers carbopol, chitosan, sodium alginate, HPMC, polyethylene glycol, and polyacrylic acid are frequently utilised.[42,43] Mucoadhesive polymers help bind medications to mucosal surfaces and extend the duration of the medication's residency at the application site. An ideal mucoadhesive polymer interacts with the mucin by electrostatic, disulphide, hydrogen, and hydrophobic bonding; it is inert, non-irritating, nontoxic, clings to the mucosal surface, and has site specificity. The polymer's molecular weight, shape, flexibility of the polymeric chains, hydrogen bonding ability, cross-linking density, charge, concentration, or degree of hydration all affect its mucoadhesive qualities and contact strength.[44] The mucoadhesive qualities of the dosage form (total work of mucoadhesion, force of system detachment, and percentage of mucoadhesion) are often assessed using several ex vivo mucosal tissue types.[45-47] However, it might be challenging to collect mucosal tissues from laboratory animals, and from an ethical perspective, they are not good. In these situations, artificial hydrogels that resemble biological mucosa might be a useful synthetic alternative to animal tissues. Because of their hydrophilic structure, the hydrogels can absorb a lot of water into their three-dimensional networks, mimicking the characteristics of real tissues.[48] Because the mucus composition varies depending on the area of the mucous membrane, targeted targeting may be difficult in this system. Furthermore, high stomach moisture and the mucus's continuous turnover may reduce the bioadhesion of polymers. Additionally, there is a significant chance of adhesion to the oesophagus, which could result in collateral lesions.[49,50]

2. Conclusion:

Mucoadhesive gastroretentive drug delivery systems (MGDDS) provide an advanced and efficient method for improving oral drug administration performance, especially for medications with a limited window for absorption, those that are unstable in the intestinal or colonic environment, or those that are meant to act locally in the stomach. The bioavailability and therapeutic results of many medications are enhanced by these systems' ability to stay in the stomach area for prolonged periods of time. MGDDS's primary benefit is its capacity to stick to the stomach mucosa using mucoadhesive polymers, like chitosan, carbopol, and HPMC, which interact with the mucus layer to guarantee extended retention at the absorption site. The formulation remains in the stomach despite normal gastric motility and emptying thanks to this mucoadhesion and other gastroretentive mechanisms including floating, swelling, or high-density systems. mucoadhesive gastroretentive systems are a powerful tool in the advancement of oral drug delivery. Their ability to provide site-specific, prolonged drug release in the stomach aligns well with the goals of modern pharmacotherapy — maximizing therapeutic benefits while minimizing risks and inconvenience to the patient. With ongoing advancements in polymer science, nanotechnology, and personalized medicine, the future holds significant potential for the broader application and refinement of these systems in both commercial and clinical settings.

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