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Review on Floating and Mucoadhesive systems: A Smart Platforms for Sustained Drug Release

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A B S T R A C T

Drug delivery systems aim to maintain a constant, therapeutic, and non-toxic concentration of medication in your bloodstream and fluids over time. By interacting directly with the body's biological pathways, delivery systems like floating and mucoadhesive formulations typically achieve better outcomes than conventional methods. Recent advances in mucoadhesive and floating drug delivery systems examine the biological and technical factors that determine intestinal residence time, outline mucosal interactions and formulation structures, compare single-unit versus multi-unit designs, and detail their classification, advantages, and key characterization tests such as thickness and diameter measurements, bio-adhesion assessment, and drug content uniformity evaluations. Furthermore, this study details the experimental methods used to evaluate the deployment characteristics and performance efficacy of floating and mucoadhesive delivery systems.

Keywords: Floating Drug Delivery System (FDDS), Mucoadhesive drug delivery system, Gastric residence time, GRDDS, Mucoadhesion, Absorption, Characterization, Evaluation etc.

1. Introduction

Patients often prefer oral medications due to their low cost and easy to consume. This ease of administration makes them a leading option for delivering drugs, with oral methods accounting for most of the delivery systems currently in use.. [1] Floating systems, often referred to as hydrodynamic systems, are designed to be light and buoyant enough to rest on top of the stomach's contents. This allows them to remain in the stomach for an extended time without disrupting the normal gastric empting rate. [2] These systems are designed to slowly release the medication at a steady rate while floating on top of the stomach's contents. Once the drug has been delivered, the remaining system is naturally cleared from the stomach. This approach helps extend the gastric retention time (GRT) and provides more stable control over changes in drug levels within the bloodstream. For the system to stay afloat effectively, it's essential that both the stomach content and the upward floating force remain low. Various forms—like granules, powders, capsules, tablets, layered films, and hollow microspheres—have been developed to support this floating mechanism.

2. FLOATING DRUG DELIVERY SYSTEMS

Floating drug delivery systems—lightweight and buoyant by design—are able to rest on the stomach's contents for extended periods without disrupting the natural emptying process. This prolonged presence allows for better control over how the medication is absorbed into the bloodstream, helping maintain more consistent plasma levels. For these systems to be effective, the drug must be formulated to remain in the stomach long enough to be absorbed, ideally within the stomach or the upper part of the small intestine. These medications typically don't dissolve well in areas like the colon or duodenum, especially where the pH is higher. To support this approach, various formats have been developed, including tablets, capsules, powders, granules, layered films, and hollow microspheres. Examples for the same are mentioned in Table 1.

Table 1. List of Drugs Formulated as Floating Drug Delivery Systems

Dosage Form	Drugs
Tablets	Cholrpheniramine maleate, Theopsshylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCl, Isosorbide dinitrate, Sotalol, Isosorbide mononitrate, Aceraminophen, Ampicillin, Cinnarazine, Dilitiazem, Florouracil, Piretanide, Prednisolone, Riboflavin-5`Phosphate
Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-Dopa and benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic ac-id, Nicardipine

Dosage Form	Drugs
Microspheres	Verapamil, Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Tranilast, Iboprufen, Terfenadine
Films	P-Aminobenzoic acid, Cinnarizine, Pireta-nide, Prednisolone, Quinidine gluconate.
Powders	Riboflavin,phosphate, Sotalol, Theophyl-line.
Granules	Diclofenac sodium, Diltia-zem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mononitrate, Isosorbide dinitrate.

2.1 Fundamental Function of Gastrointestinal Tract [3-5]

Structurally, the stomach is made up of three main parts.

1. The fundus

The fundus refers to the upper section of the stomach, located near where the esophagus connects. This dome-shaped area serves as a reservoir for gases released during the chemical breakdown of food.

2. The body i.e., central region of the stomach, called the corpus, functions primarily as a reservoir where ingested food and liquids are temporarily held before further digestion.

3. The antrum (pylorus)

Located at the lower end of the stomach, the antrum acts like a muscular pump that helps propel stomach contents into the small intestine. It also plays a key role in churning and mixing food with digestive juices.

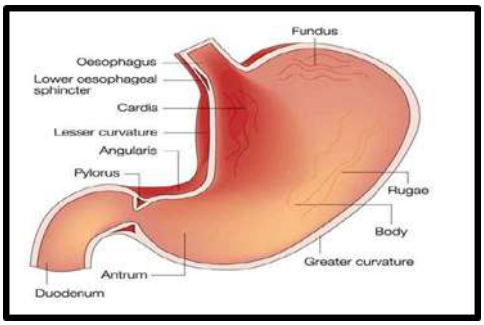

Fig. 1: Anatomy of Stomach

2.2 Pattern of intestinal motility

The stomach continues to release its contents regardless of whether food has been consumed or not, although the patterns of movement vary between fed and fasting states. In the absence of food, at every two to three hours, the stomach and intestines experience a wave of coordinated electrical activity known as the inter-digestive phase. This process is part of the migrating myoelectric complex (MMC), a cycle outlined by Wilson and Washington, which is divided into four distinct stages. These stages are shown in Fig. 2

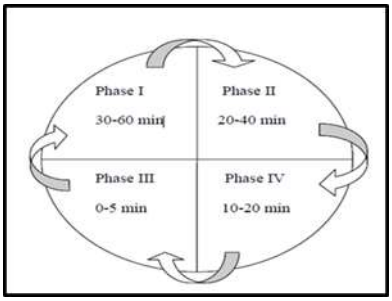

Fig. 2: Gastrointestinal Motility Pattern

Phase I:

The initial phase during initial phase, infrequent muscular contractions take place over a span of approximately 40 to 60 minutes.

Preburst phase, or phase II:

This phase typically spans 40 to 60 minutes and is characterized by occasional muscle contractions and bursts of electrical activity. As it progresses, there is a gradual increase in both the intensity and frequency of these physiological activities.

Phase III:

Commonly referred to as the burst phase, this stage lasts about four to six minutes and is marked by rapid, forceful contractions. These movements help clear the stomach by pushing any remaining undigested material into the small intestine. Because of this cleansing action, it's also known as the housekeeping wave.

Phase IV:

This brief transitional phase, lasting up to five minutes, occurs between phases I and III of two consecutive cycles. After consuming a mixed meal, the stomach's activity shifts from the fasting pattern to one typical of digestion. During this phase—known as the digestive motility pattern—the stomach undergoes continuous contractions resembling those seen in phase II of the fasting state. These muscular movements help grind food particles down to less than 1 millimeter in size and move them, suspended in fluid, toward the pylorus. When food is present in the stomach, the onset of the migrating motor complex (MMC) is postponed, which slows down the process of gastric emptying. Orally delivered, according to scientific research measuring gastric emptying rates. A brief stomach residency period and an erratic gastric emptying rate are the two primary issues with floating medication delivery devices.

2.3 Mechanism of floating systems [6]

To extend the time a drug remains in the stomach, various strategies have been explored. Examples of these attempts include gastric-emptying delaying devices, mucoadhesive systems, high-density systems, modified shape systems, co-administration of gastric-emptying delaying pharmaceuticals, and floating dosage forms (gas-generating systems and swelling or expanding systems Among these, floating drug delivery systems (FDDS) are the most widely used. Because their density is lower than that of gastric fluids, they can stay buoyant in the stomach for extended periods without interfering with its natural emptying rhythm. This prolonged gastric residence time (GRT) helps stabilize drug levels in the bloodstream. For FDDS to work effectively, the stomach must contain a minimal amount of content, and the dosage form must exert a sufficient upward force—known as floating force (F)—to remain afloat on the meal's surface. A newly introduced technique has been documented in scientific literature to evaluate the behavior of floating force over time. This method employs an apparatus that continuously records the equivalent force (denoted as F) required to maintain a submerged object in a fixed position. As demonstrated in Fig. 3, optimal buoyancy is achieved when the measured force remains predominantly in the positive range.

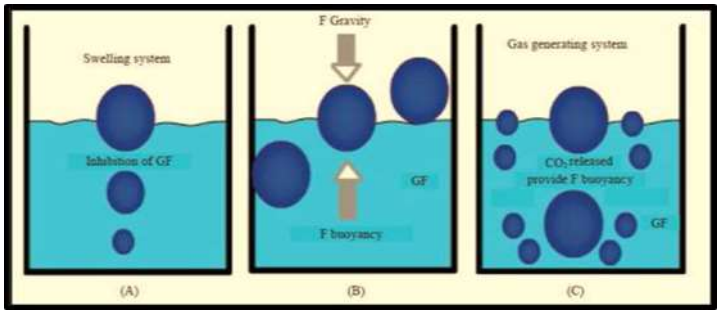

Fig. 3: Mechanism of Floating System (GF=Gastric fluid)

This device is designed to enhance the stability and persistence of the buoyant forces generated by floating drug delivery systems (FDDS), thereby minimizing the negative impact of inconsistent buoyancy behavior within the stomach.

$F = F_{buoyancy} + F_{gravity} = (Df - Ds)\, gv$---------- (1)

Where,

F= total vertical force,

Df = fluid density

Ds = object density,

v = volume

g = acceleration due to gravity.

2.4 Classification of floating drug delivery systems [7-11]

Floating drug delivery systems (FDDS), which works on principle of buoyancy to enhance gastric retention, have been developed through two primary technological strategies: effervescent-based formulations and non-effervescent mechanisms.

2.4.1 Effervescent System

Effervescent formulations typically incorporate carbonates like sodium bicarbonate, along with gas-generating compounds and organic acids such as citric and tartaric acid. These ingredients react to release carbon dioxide (CO_2), which facilitates buoyancy in the system. As a result, the system floats on top of the gastric fluid since its density is reduced. Alternatively, a matrix can be formulated with a volatile liquid component that vaporizes at body temperature, generating gas.

There are two types of these effervescent systems:

- Gas generating systems
- Volatile liquid/vacuum systems

2.4.2 Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)

These floating drug delivery systems are formulated by blending the active pharmaceutical ingredient with carbon dioxide-generating excipients. Due to their lower density compared to gastric fluids, they remain buoyant in the stomach for extended periods, thereby delaying gastric emptying. This prolonged retention allows the drug to be released gradually at a controlled rate. Eventually, the residual components are expelled naturally. As a result, the system enhances gastric residence time (GRT) and provides more consistent plasma drug concentrations" paraphrase this in scientific manner.

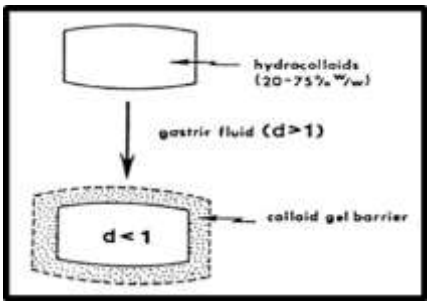

Fig. 4: Intragastric floating tablet

2.4.3 Intra Gastric Bilayer Floating Tablets

As illustrated in the fig.5, these are bilayer compressed tablets composed of two distinct layers.

(1) Immediate release layer (2) Sustained release layer

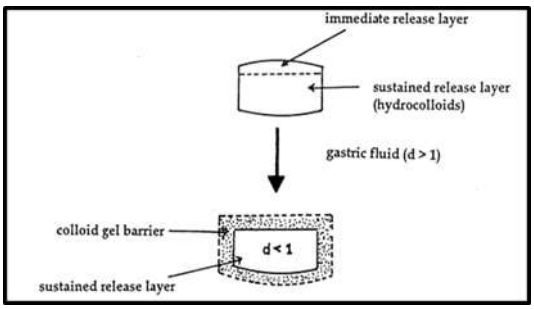

Fig. 5: Intra-gasrtric Floating Bilayer Tablet

2.4.4 Multiple Unit Type Floating Pills

These drug delivery systems are designed as dual-layered, extended-release capsules with a morphology reminiscent of small seeds. The inner core contains effervescent compounds, while the outer shell is composed of swellable polymers. Upon immersion in a medium at physiological temperature, the capsule initially sinks. However, as the outer layer hydrates and expands, carbon dioxide generated from the inner layer becomes entrapped, reducing the overall density. This transformation results in a swollen, buoyant structure with a balloon-like appearance, enabling the system to float and prolong its gastric retention.

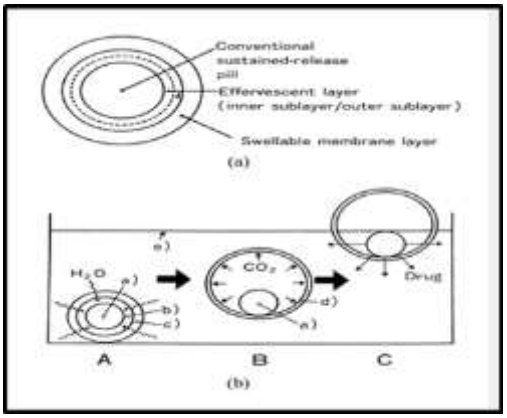

Fig. 6: (a) Multiple-unit Oral Floating Dosage System (b) Stage of floating Mechanism

2.4.5 Volatile liquid / vacuum containing systems

2.4.5.1 Intragastric Floating Gastrointestinal Drug Delivery System

These formulations achieve gastric buoyancy through a specialized chamber that can either be emptied or filled with air or an inert gas. The drug itself is encapsulated within a microporous structure that regulates its release.

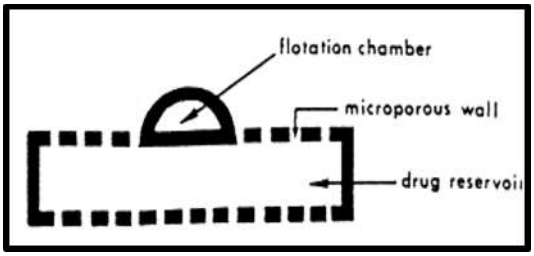

Fig. 7: Intragastric Floating Drug Delivery System

2.4.5.2 Inflatable Gastrointestinal Delivery Systems

These systems incorporate an inflatable chamber that expands within the stomach as liquid ether inside it vaporizes at body temperature. The design involves enclosing a drug reservoir—either a pure pharmaceutical compound or a polymer matrix infused with the drug—within this expandable chamber, which is then sealed inside a gelatin capsule. Upon ingestion, the capsule dissolves, allowing the chamber to inflate and release the drug reservoir. The inflated structure remains suspended in gastric fluid, ensuring the medication stays in the stomach for an extended duration.

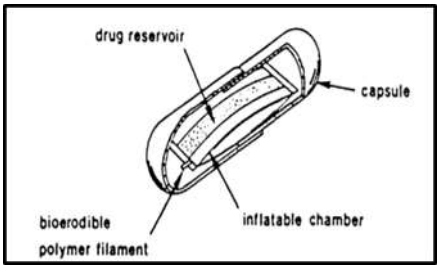

Fig. 8: Gastro-Inflatable Drug Delivery Device

2.4.5.3 Intragastric Osmotically Controlled Drug Delivery System

This drug delivery system consists of a biodegradable capsule that includes a buoyant support structure and an osmotic-controlled release mechanism. Once the capsule reaches the stomach, it quickly disintegrates, triggering the system. A temperature-sensitive liquid inside the support vaporizes at body temperature, inflating a flexible polymer bag that helps the device float in gastric fluid. The drug release mechanism is divided into two main sections: one holds the active drug, and the other contains an osmotic agent. The drug compartment is enclosed within a collapsible bag that features a delivery port and is protected by a barrier that prevents the entry of liquids and vapors. Meanwhile, the osmotic compartment is housed within a semi-permeable membrane and contains a salt that draws water from the stomach. As water enters, the salt dissolves, generating osmotic pressure. This pressure causes

the collapsible drug reservoir to contract, pushing the medication out through the delivery port in a controlled manner. After a predetermined period, a biodegradable plug within the floating support dissolves, deflating the system and allowing it to exit the stomach naturally.

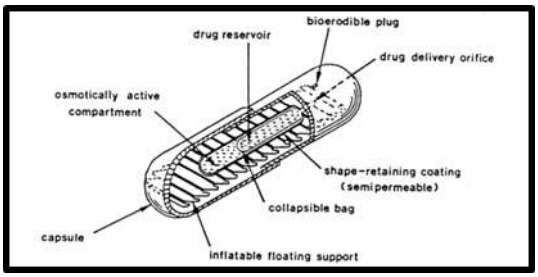

Fig. 9: Intra Gastric Osmotic Controlled System

2.4.5.4 Non Effervescent Systems

Non-effervescent floating drug delivery platforms prolong gastric residence by either swelling upon contact with gastric fluids or by adhering to the mucosal lining of the stomach.

Formulations typically include:

- Gel-forming hydrogels or highly swellable polysaccharide-based excipients
- Matrix polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene
- Mucoadhesive agents like chitosan and carbopol

The following types of these systems are available:

2.4.5.5 Single layer floating tablets

Formulation of these floating dosage forms involves blending the active drug with a gel-forming hydrocolloid whose bulk density very low, such that upon contact with gastric fluid, the hydrocolloid hydrates and swells into a porous polymer network that entraps air pockets. The resulting air-filled structure lowers the overall density of the tablet or capsule, allowing it to remain buoyant in the stomach.

2.4.5.6 Bilayer floating tablets

These dual-layer tablets combine an immediate-release portion for the initial dose with a sustained-release segment that takes up gastric fluid. The sustained-release layer contains a gel-forming polymer that hydrates and swells, creating an impermeable colloidal gel sheath. By keeping its overall density below one and trapping air within this gel network, the tablet remains buoyant in the stomach.

a. Alginate beads

Multiunit floating dosage forms are fabricated as freeze-dried calcium alginate beads. By dripping an aqueous sodium alginate solution into a calcium chloride bath, roughly 2.5 mm spheres form through instantaneous calcium alginate gelation. Freeze-drying these beads creates a highly porous network that traps gas and sustains buoyancy in gastric fluid for over 12 hours. In contrast, nonporous beads remained in the stomach for only about one hour, while the floating alginate beads achieved a residence time exceeding 5.5 hours.

b. Hollow Microsphere

Hollow polymer microspheres, often called microballoons, were produced using an emulsion-solvent dispersion approach. An enteric acrylic polymer and the active drug were co-dissolved in an ethanol/dichloromethane blend, then emulsified into a 40 °C aqueous PVA solution under controlled stirring. As dichloromethane volatilized from each dispersed droplet, the escaping gas formed an internal cavity within the solidifying polymer shell. The drug-loaded microballoons sustained buoyancy on acidic, surfactant-containing dissolving media for more than 12 hours in vitro.

2.5 Strategies for developing floating drug delivery system [12,13]

Various techniques have been documented to extend the duration that drugs remain in the stomach.

2.5.1 High Density Systems

Dosage forms with densities near 3 g/cm³ lodge securely within the gastric rugae and resist peristaltic clearance. [14,15] The principal drawback lies in combining a drug loading above 50 percent with a final product density of 2.4–2.8 g/cm³. Achieving these weights typically requires heavy diluents such as iron powder, zinc oxide, titanium dioxide, or high-density barium sulfate (4.9 g/cm³).

2.5.2 Swelling and Expanding Systems

Often called plug-type systems because they lodge at the pyloric sphincter, these hydrophilic polymer matrices can remain in the stomach for several hours after a meal. [16] Often called plug-type systems because they lodge at the pyloric sphincter, these hydrophilic polymer matrices can remain in the stomach for several hours after a meal. Selecting a polymer with the right molecular weight and swelling characteristics allows precise control over how long and how quickly the drug is released. Physicochemical crosslinks within the polymer network drive rapid water uptake and extensive swelling in gastric fluid, anchoring the matrix and sustaining drug diffusion.[14]

2.5.3 Incorporating Delaying Excipients

Administering digestible polymers or fatty acid salts can induce a fed-state motility pattern in the stomach, slowing gastric emptying and thereby extending the duration of drug release. For instance, incorporating triethanolamine myristate as a delaying excipient can further enhance gastric residence time. Triethanolamine myristate can be incorporated into a drug delivery formulation as a release-retarding excipient, effectively extending its gastric residence time. [15]

2.5.4 Modified Systems

By fabricating drug delivery devices in stable geometric configurations—either through extrusion of polyethylene blends or molding with silastic elastomers—and tuning their size, shape, and flexural modulus, the gastric residence time can be significantly prolonged..[16]

2.5.5. Mucoadhesive & Bioadhesive Systems

Bioadhesive platforms anchor a dosage form to the gastrointestinal mucosa, concentrating drug release at a targeted site and improving local absorption. They depend on mucoadhesive polymers that bind to the stomach's epithelial lining. Among the most widely studied excipients for this purpose are gliadin, polycarbophil, carbopol, lectins, chitosan, and carboxymethyl cellulose.[17]

2.5.6 Floating Systems

Floating drug delivery systems stay buoyant in the stomach because their overall density is lower than that of gastric fluids, letting them remain in place without altering the natural pace of gastric emptying. While they float on the stomach contents, they steadily release the active drug at a controlled rate. After the drug has been fully dispensed, the empty carrier is swept away by normal gastric motility. This sustained buoyancy is achieved by building a hollow compartment into the dosage form—filled with air, a vacuum, or an inert gas—to ensure the system floats throughout its gastric residence..[18]

2.5.6.1Factors Affecting Floating Drug Delivery System

- ***Shape and size of dosage form***

Dosage form geometry and size have a marked impact on how long they stay in the stomach. Units exceeding 7.5 mm in diameter exhibit longer gastric residence than those around 9.9 mm. Moreover, tetrahedral and ring-shaped devices engineered with flexural moduli of approximately 48 and 22.5 kg/sq in (KSI) respectively, achieve 90–100 percent retention after 24 hours.[19]

- **Density of dosage form**

The ability of a dosage form to float hinges on its buoyancy, which is directly tied to its density relative to gastric fluids. To achieve buoyancy, the formulation must have a density below that of stomach contents—ideally under 1.0 g/cm³. When the density falls beneath this threshold, the system remains atop the gastric medium; if it exceeds it, the dosage form will sink to the bottom.[20]

- **Caloric content**

Ingesting a meal rich in fats and proteins can delay gastric emptying by roughly 4 to 10 hours. When food is delivered in several smaller portions instead of a single feed, the reduced frequency of migrating myoelectric complexes further prolongs the floating system's residence in the stomach by over 400 minutes.[21]

- **Fed or Fasted State**

Under fasting conditions, the stomach cycles through strong contraction phases known as migrating myoelectric complexes about every 1.5 to 2 hours. If a dosage form reaches the stomach just as one of these MMC waves passes, it's rapidly expelled, giving it a very short gastric residence time. In contrast, after eating, these MMC cycles are postponed, and the formulation remains in the stomach for a significantly longer period.[22]

- **Formulation of single or multiple units**

Dividing the medication into multiple discrete units allows the inclusion of ingredients with distinct release profiles or chemical incompatibilities. This strategy also creates a safety buffer against total dosage failure and delivers more reliable performance if individual units underperform, compared to a single-unit formulation.[23]

- **Concomitant drug administration**

Concomitant administration of certain drugs—prokinetic agents such as metoclopramide and cisapride, opioid analgesics like codeine, and anticholinergics such as atropine or propantheline—can modify the buoyancy duration of floating dosage forms.[23]

2.5.6.2 Evaluation of Floating Dosage Forms

- **Size and Shape Evaluation**

Particle size and morphology play a critical role in influencing a drug's dissolution rate and, in turn, its potential bioavailability. To accurately characterize particle dimensions within a formulation, a range of analytical techniques may be employed. These include sieve fractionation, air elutriation, photographic imaging, optical microscopy, Coulter counter-based electrical resistance methods, sedimentation analysis, laser diffraction, ultrasound attenuation spectroscopy, and even environmental particle measurement tools used in air quality assessments.[24]

- **Floating Properties**

Using a continuous floating tracking system and statistical experimental methodology, the impact of formulation factors on the floating properties of FDDS was ascertained. [24]

- **Determination of Moisture Content**

Karl Fischer titration was utilized to accurately determine the moisture levels present in the developed formulations. In addition to this method, other analytical approaches such as thermogravimetric analysis, vacuum drying, conventional hot air oven drying, freeze-drying, and the use of moisture analyzers were also applied to assess water content. [24]

- **Surface Topography**

Surface topography and structural characteristics are analyzed using a range of advanced techniques, including atomic force microscopy (AFM), contact angle measurement, contact profiliometer, and scanning electron microscopy (SEM) operated at an accelerating voltage of 10 kV. These methods collectively provide detailed insights into surface texture, wettability, and microstructural features.[25]

- **Percentage Entrapment Efficiency**

Entrapment efficiency is commonly assessed using techniques such as microdialysis, ultracentrifugation, and pressure-driven ultrafiltration. The percentage of drug entrapped within the formulation serves as a precise indicator of how the active compound is distributed across different phases of the delivery system.[25]

- **Determination of the Drug Content**

The concentration of a drug within a formulation reflects the actual amount incorporated during its preparation and must remain within the limits defined by established pharmacopeial guidelines. To accurately assess this, researchers rely on a variety of analytical tools, including near-infrared spectroscopy (NIRS), microtitration methods, high-performance liquid chromatography (HPLC), high-performance thin-layer chromatography (HPTLC), and other spectroscopic techniques. These methods ensure the formulation meets both quality standards and regulatory expectations.[25]

- **Swelling Studies**

Swelling studies are conducted to explore the molecular behavior and structural properties of polymers when they absorb fluid and expand. These investigations utilize a range of analytical tools, starting from standard dissolution apparatus and optical microscopy, to more sophisticated techniques like proton nuclear magnetic resonance (^{1}H NMR) imaging, confocal laser scanning microscopy (CLSM), cryogenic scanning electron microscopy (Cryo-SEM), and light scattering imaging (LSI). For quantitative analysis, swelling measurements are often calculated using specific formulas outlined in pharmacopeial standards, such as those provided in USP-24. [26]

$$Swelling\ ratio\ =\ Weight\ of\ wet\ formulation\ /Weight\ of\ formulation$$

- **In-vitro Release Studies**

To determine the amount of drug released over a defined time period, in vitro release studies are performed using standardized dissolution apparatus, such as those described in USP-24. These evaluations often involve tools like the Franz diffusion cell system, synthetic membranes, and other dissolution testing setups, which collectively help simulate drug release under controlled laboratory conditions.[26]

- **Fourier Transforms Infrared Analysis**

Fourier Transform Infrared Spectroscopy (FT-IR), such as the Shimadzu RT-IR-8300 model, is widely employed to characterize both organic and inorganic compounds, including polymers and their functional groups. For spectral analysis, sample pellets are prepared using a potassium bromide (KBr) press under a hydraulic force of 150 kg/cm² at ambient temperature. The resulting spectra are recorded across a wave number range spanning from 3600 to 400 cm^{-1}, allowing detailed molecular fingerprinting of the materials.[26]

- **Powder X-ray Diffraction**

Powder X-ray diffraction is widely recognized as the standard technique for analyzing polycrystalline substances. In this method, samples are exposed to alpha radiation and examined across a temperature range of 2°C to 60°C to assess their structural properties. The instrumentation typically operates at a voltage of 30KV and a current of 30 mA, ensuring optimal conditions for precise diffraction pattern acquisition [27]

- **Differential Scanning Calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) is a widely used technique for analyzing the water of hydration in pharmaceutical substances. The instrument, equipped with an intercooler, records thermograms that reveal thermal transitions in the sample. Calibration of both temperature and enthalpy is performed using certified Indium and Zinc standards to ensure accuracy. For analysis, the sample is sealed in an aluminum pan and subjected to controlled heating from 25°C to 65°C at a constant rate of 10°C per minute. Throughout the process, a nitrogen purge at 50 mL per minute is maintained to create an inert environment and prevent oxidative interference.[27]

2.5.6.3 Advantages of FDDS [28,29]

- Enables targeted drug delivery to specific regions within the gastrointestinal tract
- Effective in managing GI disorders such as gastroesophageal reflux disease (GERD)
- Beneficial during episodes of diarrhea or rapid intestinal transit by maintaining gastric retention for improved drug action.
- Requires simple, cost-efficient equipment for formulation and design
- Provides sustained drug release, minimizing adverse interactions and enhancing therapeutic performance.
- Stabilizes drug concentration within therapeutic limits, improving pharmacodynamic and clinical outcomes.
- Enhances efficacy of drugs with short biological half-lives by prolonging their activity.
- Improves bioavailability and therapeutic effect while supporting economical dosing strategies.
- Floating dosage forms remain longer in the stomach and at the absorption site, even under alkaline intestinal conditions, promoting better absorption.
- Reduces dosing frequency and simplifies administration, contributing to improved patient adherence.
- Offers controlled drug release, minimizing irritation to the gastric and intestinal mucosa.

2.5.6.4 Disadvantages of FDDS [30,31]

- The formulation must swell rapidly to ensure full expansion before the stomach begins emptying.
- The buoyancy of the dosage form is directly influenced by hydration rate;
- Continuous renewal of gastric mucus can lead to inconsistent adhesion of the dosage form to the stomach lining.
- Adequate gastric fluid volume is essential for the system to float and perform effectively.
- Floating systems are unsuitable for drugs that are unstable or poorly soluble in the gastrointestinal environment.
- Drugs that undergo extensive first-pass metabolism and are efficiently absorbed throughout the GI tract—such as nifedipine and propranolol—are not ideal candidates for this delivery method.
- Medications known to irritate or harm the gastric mucosa, like certain NSAIDs, should not be formulated as floating dosage systems.

2.5.6.5 Applications of Floating Drug Delivery Systems

Floating drug delivery systems are particularly useful for improving the absorption of drugs with low bioavailability, as they help retain the medication in the upper GI tract where absorption is limited to a short timeframe. Below is a brief overview of their key applications:

- ***Enhanced Bioavailability***

The CR-GRDF of riboflavin significantly improves its bioavailability compared to conventional controlled-release polymeric systems. This enhancement is influenced by multiple physiological and pharmacokinetic factors that govern the drug's absorption and transit through the gastrointestinal tract. [32]

- ***Sustained Drug Delivery***

One of the challenges with oral controlled-release formulations is their limited residence time in the stomach. Floating drug delivery systems (FDDS) address this by allowing the drug to remain buoyant on gastric fluids, thereby prolonging its retention. These systems are designed with a bulk density lower than that of gastric contents (i.e., less than 1 g/cm³), enabling them to float. Due to their relatively larger size, they are prevented from passing through the pyloric sphincter, which helps maintain their position in the stomach for extended periods. [32]

- ***Absorption Enhancement***

Drugs with limited bioavailability can benefit from floating delivery systems, which improve absorption by prolonging the drug's presence in the upper gastrointestinal tract—where absorption is most favorable due to localized uptake mechanisms. [33]

- ***Site Specific Drug Delivery Systems***

Floating drug delivery systems are especially useful for drugs that are absorbed mainly in the stomach or the upper small intestine. These systems allow for gradual and controlled release of the medication within the stomach, helping to maintain therapeutic levels locally while limiting its spread into the bloodstream, which can reduce unwanted side effects. Moreover, extended gastric retention through targeted delivery may allow for less frequent dosing of drugs such as riboflavin and furosemide. [34]

- ***Minimized adverse activity at the colon***

Floating drug delivery systems help keep medications in the stomach, preventing them from reaching the colon, where they could cause undesirable effects. This targeted retention is especially beneficial for antibiotics like beta-lactams, which are absorbed mainly in the small intestine. Limiting their presence in the colon can help reduce the risk of promoting microbial resistance.[35]

- ***Reduced Fluctuations of Drug Concentration***

CR-GRDF systems provide a more consistent drug concentration in the bloodstream than immediate-release formulations by delivering the medication gradually over time. This controlled release helps minimize fluctuations in drug effects and lowers the risk of side effects caused by sudden spikes in concentration, which is particularly important for drugs with a narrow therapeutic window.[35]

3. MUCOADHESIVE DRUG DELIVERY SYSTEMS

The mucoadhesion drug delivery system has garnered a lot of interest lately because of its wide surface area and high blood flow rate, which help to speed up intimate contact between the dosage form and the underlying mucosa and increase the residence time at the application site. The main goals of this are to promote absorption and increase the drug's bioavailability %. Mucosal pharmaceutical delivery avoids the hepatic first-pass and keeps the gastrointestinal tract's enzymes from breaking down the medication. Thus, it is possible to assess this system's capacity to deliver an increasing number of high molecular weight substances, including proteins and peptides. Mucoadhesive controlled-release systems not only allow for prolonged and targeted drug release but also support site-specific delivery to mucosal surfaces, increasing their clinical usefulness. In addition to their systemic effects, these materials are being studied for local therapeutic roles, such as protecting and calming irritated tissues—like those found in gastric ulcers or oral injuries—and serving as lubricants in regions such as the mouth, eyes, and vaginal area. [36,37]

3.1 Bioadhesion and Mucoadhesion

Bioadhesion is a broad term describing the attachment of materials—whether naturally derived or synthetic—to biological surfaces. In drug delivery, it specifically refers to how polymers bind to mucosal tissues. When this interaction occurs at mucosal sites, it is termed mucoadhesion. Mucoadhesion involves the prolonged adherence of a biological surface and another material, facilitated by interfacial forces that maintain the bond over time. [42]

Bioadhesion can be classified into 3 types: [43,44]

- The bonding of two distinct biological stages.
- A biological phase adhering to a synthetic substrate.
- An artificial material's ability to stick to a biological substrate.

3.2 Mucous Membrane

It is the main location for administering bioadhesive systems. Mucosal tissues are organized into three distinct layers: a surface epithelium, a supportive connective tissue layer called the lamina propria, and an underlying smooth muscle layer referred to as the muscularis. A defining feature of these membranes is the presence of a mucus layer that overlays the epithelial surface. This mucus is rich in mucin, a glycoprotein that plays a pivotal role in maintaining the structural integrity and functional dynamics of the mucosal barrier. In the oral cavity, mucus thickness is less than 1 μm, but in the stomach, it ranges from 50 to 500 μm.[45,46]

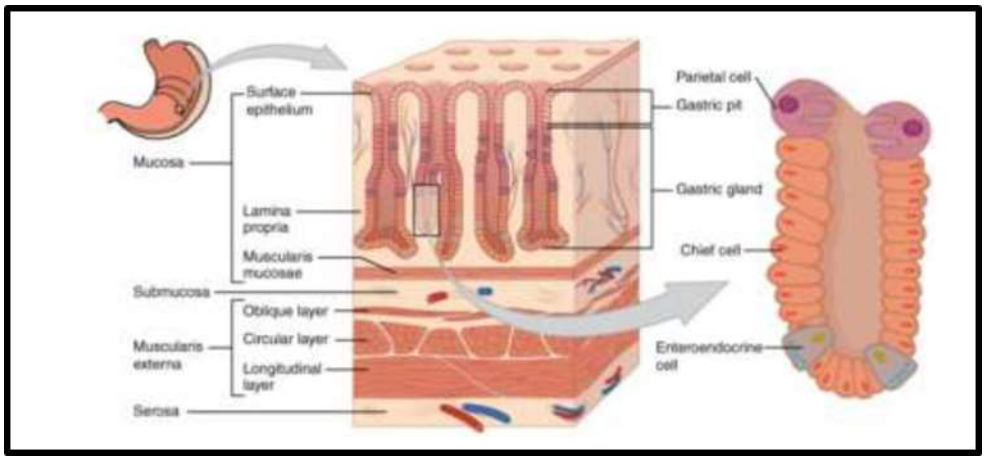

Fig. 10: Composition of mucous membrane

3.3 Composition of mucus layer

Because the mucus is made up of lipids, salts, glycoproteins, and around 95% water by mass, it is a very hydrophilic system. Oligosaccharide units including L-fucose, D-galactose, N-acetyl-Dglucosamine, Sialic acid, and N-acetyl-D-galactosamine are connected to high molecular weight proteins known as mucus glycoproteins. [47,48]

3.4 Functions of mucus layer [49]

- It affects the bioavailability of medications by impeding their and other substrates' absorption into tissues; it binds firmly to the surface of epithelial cells as a continuous gel layer, promoting adhesion; and it is essential for lubricating and preserving the moisture of the mucosal membrane.
- Mucus released by multicellular mucous glands, goblet cells, or both is commonly found covering these surfaces. Mucus functions as a frontline defense by sequestering microorganisms and airborne particles, effectively shielding epithelial surfaces from direct exposure. This barrier not only impedes pathogen infiltration but also promotes their removal, thereby supporting the preservation of mucosal structure and contributing to the body's innate immune protection.

3.5. Routes of mucoadhesive drug delivery systems

3.5.1 Buccal and sublingual delivery system

The buccal cavity presents a favorable route for administering therapeutic agents, despite its relatively modest surface area of approximately 45 cm^3. This route provides notable benefits, such as bypassing hepatic first-pass metabolism and enabling localized therapy for oral conditions. The enzymatic activity in this region is relatively low, which contributes to maintaining the chemical integrity of administered compounds. Additionally, if toxicity or adverse effects occur, the dosage form can be easily withdrawn, allowing for rapid discontinuation. For formulations requiring swift absorption, the sublingual mucosa is often selected, given its superior permeability compared to the buccal surface. [50,51,52]

3.5.2 Nasal drug delivery system

Despite the nasal mucosa covering an area of approximately 150–200 cm^2, drug formulations administered via this route typically remain in contact with the mucosal surface for only 10 to 30 minutes. This limited residence time is primarily due to enhanced mucociliary clearance, which is activated in response to inhaled foreign particles. The nasal route offers a pharmacokinetic advantage by bypassing hepatic first-pass metabolism, facilitated by its dense vascular network and direct access to systemic circulation. Among intranasal delivery systems, solution-based formulations—particularly those containing sympathomimetic vasoconstrictors—are highly effective, offering rapid relief from nasal congestion through swift absorption and localized action.[53,54]

3.5.3 Ophthalmic drug delivery systems

The ocular cavity presents unique challenges for drug delivery due to rapid clearance mechanisms such as tear secretion, blinking, and drainage through the lacrimal system, all of which contribute to reduced bioavailability of active pharmaceutical agents. To mitigate these limitations, specialized delivery platforms like ocular inserts and patches have been designed to prolong drug residence and enhance therapeutic outcomes. Considering the eye's limited volume capacity of roughly 30 µl, formulation approaches must be carefully tailored to maximize retention time. A variety of dosage forms—including solutions, gels, ointments, and solid inserts—have been explored to address this constraint. Among innovative strategies, in situ gelling systems show promise by transitioning from liquid to gel upon exposure to physiological stimuli such as changes in ion concentration, pH, or temperature. Additionally, mucoadhesive polymers offer improved localization by adhering specifically to the conjunctival mucosa under in vivo conditions. [55,56]

3.5.4 Vaginal and rectal drug delivery

Both vaginal and rectal routes have been widely investigated for delivering drugs locally and systemically. These administration pathways offer several pharmacokinetic benefits, including extensive surface area for absorption, robust blood flow, and high permeability to various active compounds. Their suitability for self-administration also supports better patient adherence. Crucially, these routes circumvent hepatic first-pass metabolism, which helps reduce liver-associated adverse effects and lowers the risk of mucosal irritation, tissue damage, or infection. Among these, the vaginal route is particularly advantageous due to its prolonged drug retention time compared to other mucosal sites like the intestinal or rectal epithelium, thereby enhancing therapeutic outcomes. [56]

3.5.5 Gastrointestinal drug delivery

Mucoadhesive drug delivery systems are frequently designed for application within the gastrointestinal tract to enhance bioavailability and extend the residence time of therapeutic agents. However, the sustained contact between the dosage form and the GI mucosa necessitates careful evaluation of potential adverse effects, such as the development of localized ulceration. Additionally, the dynamic nature of mucus turnover—driven by continuous secretion from gastric glands and its removal through peristaltic movement and dilution by gastric contents—poses a significant limitation to the effectiveness of mucoadhesion as a strategy for gastroretention [57]

3.6 Mechanism of Mucoadhesion

The mucoadhesive dosage form must disperse across the substrate to aid in the diffusion of mucus chains, encourage intimate contact, and increase surface contact. Attraction forces must be greater than repulsion forces for mucoadhesion to be effective. [58,59]

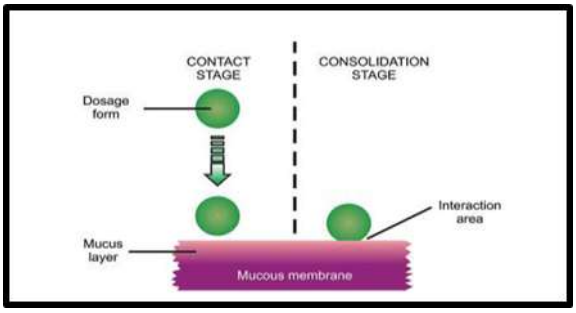

Fig.11: The two steps of the mucoadhesion process.

Step 1: Contact Stage

The process of wetting and swelling begins when a polymeric system traverses the mucosal barrier and establishes intimate contact with the underlying tissue. Upon exposure to moisture, hydrophilic components within the polymer absorb water, leading to expansion and increased surface interaction. In drug delivery systems designed for ophthalmic, buccal, or vaginal application, the formulation is typically anchored directly to the mucosal surface to ensure localized retention. In contrast, deposition in regions such as the nasal cavity is influenced by the organ's airflow dynamics. Within the gastrointestinal tract, peristaltic movements assist in promoting contact between the dosage form and the mucosa. As particles approach the mucosal interface, they encounter both attractive and repulsive forces; successful adhesion requires overcoming these repulsive interactions to enable effective binding. [60-62]

Step 2: Interpenetration Stage

Mucosal surfaces are rich in glycoproteins—large, complex polymers that play a key role in bioadhesion. During the second phase of adhesive interaction, polymer chains from both the bioadhesive material and the mucosal layer become physically intertwined, forming stable adhesive bonds. The extent of this interpenetration directly influences the strength of adhesion. Notably, when both polymers exhibit hydrophilic properties or share similar chemical structures, the likelihood of forming robust intermolecular interactions is significantly enhanced. [63]

Step 3: Consolidation Stage

During the consolidation phase of mucoadhesion, polymeric materials undergo structural rearrangement in the presence of moisture, forming weak hydrogen and Van der Waals bonds that enable reversible interactions. Two primary mechanisms—diffusion theory and dehydration theory—are commonly used to explain this process. According to the diffusion theory, mucoadhesive polymers establish adhesion by interpenetrating and forming secondary bonds with mucosal glycoproteins. In contrast, the dehydration theory suggests that polymers capable of rapid gelation in aqueous environments may draw water from the mucus layer due to osmotic gradients, leading to localized dehydration and enhanced adhesive contact. The accompanying fig.12 provides an illustration of this phenomena. The concentration gradient prolongs the time of contact by facilitating the passage of water into the formulation until osmotic equilibrium is established. [64-66]

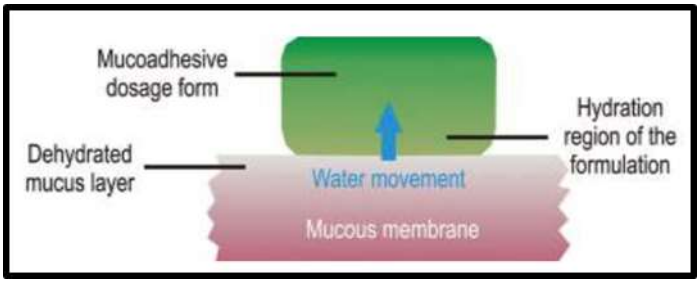

Fig.12: Regions of mucoadhesive bond rupture can occur

3.7 Advantages of mucoadhesive drug delivery systems [67,68]

- Boosts the formulation's residence time at the absorption site, increasing its bioavailability. Great accessibility, quick initiation of effect due to high perfusion rates and a massive blood supply.
- Increased patient adherence.
- Quick local site healing and cellular recovery
- A brief course of treatment.
- Greater safety margin for extremely powerful medications as a result of better plasma control high level of focus
- Maximum drug intake, which permits a decrease in the overall amount of medication given.

3.8 Disadvantages of mucoadhesive drug delivery systems [67,68]

- Only medications with lower dosage requirements can be given.
- Drugs that are absorbed by passive diffusion can only be delivered via this route; medications that are taken with saliva lose the benefits of the buccal route.
- The medication must be stable in the acidic vaginal pH when administered vaginally. It's possible for the vaginal formulation to leak and create mess. Pregnancy may make the vaginal formulation unsuitable.
- Ocular preparations have the potential to induce discomfort and blurring.
- The dosage form may become displaced from its location when administered via any method.
- When it comes to nasal formulations, the formulation's presence may cause sneezing, which could cause the formulation to come loose. The nasal mucosa, being highly sensitive, may react adversely to certain formulations, potentially leading to irritation. Moreover, when bioadhesive polymers absorb excessive moisture, they tend to swell significantly, which can compromise the structural integrity of the formulation or result in an overly lubricated surface, thereby affecting its intended performance.

3.9 Theories of Mucoadhesion / Bonding Mechanism

Investigations into the adhesive behavior of different materials and the interactions between polymers have contributed to the establishment of six foundational theories. These theoretical frameworks are systematically classified, as depicted in Fig. 13.

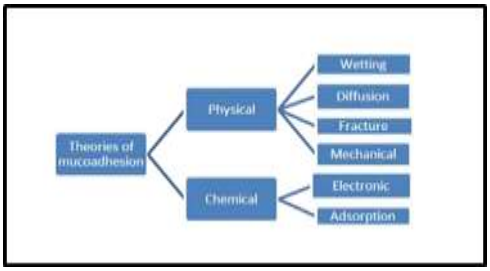

Fig. 13: Classification of theories of Mucoadhesion.

3.9.1 Wetting theory [69-71]

Measurement of the contact angle provides insight into the degree of interaction between liquid formulations and the mucosal surface. A lower contact angle typically indicates stronger wettability and enhanced affinity of the liquid system toward the mucus layer. In order to ensure adequate spreadability, the contact angle needs to be close to zero. illustration of the impact of the contact angle between the mucosal membrane and the dose form.

The spreadability coefficient (SAB) is determined by evaluating the difference between the surface energies of components A and B (γA and γB), along with their interfacial energy (γAB). This relationship is expressed mathematically in the following equation,

$$SAB = \gamma A - \gamma AB - \gamma AB$$

The work of adhesion, or WA, increases with the individual surface energy of the mucus and device relative to the interfacial energy,

$WA = \gamma A + \gamma B - \gamma AB.$

3.9.2 Diffusion theory [70,71]

According to the diffusion theory, bioadhesive polymers adhere to mucus by infiltrating and becoming entangled with its molecular structure. The strength of this interaction intensifies as the adhesive forces grow, leading to deeper and more extensive molecular integration. Inter-diffusion-induced secondary interactions is seen. The degree of penetration is dependent on a number of variables, including the diffusion coefficient, polymer chain flexibility, mucoadhesive chain type, motility, and contact time. To achieve effective bioadhesion, the polymer chains must penetrate the mucus layer to a depth of approximately 0.2 to 0.5 micrometers. This depth of interpenetration can be estimated using the equation $I = (t \cdot Db)^{1/2}$, where I represents the penetration depth, Db is the diffusion coefficient of the bioadhesive polymer within the mucus, and t is the duration of contact. For this diffusion process to occur efficiently, the bioadhesive and mucus must exhibit compatible chemical characteristics, ensuring mutual solubility and facilitating molecular interaction.

3.9.3 Fracture theory [70,71]

This theory focuses on evaluating the amount of force needed to detach two surfaces after an adhesive bond has been established between them. It has been discovered that longer polymer network fibers or a lower degree of cross-linking within such a system increase the work of fracture.The following equation helps estimate the fracture strength (σ) following the separation of two surfaces by relating it to the Young's modulus of elasticity (E), fracture energy (ε), and critical crack length (L),

$\sigma = E\,(\varepsilon/L).$

In tests of resistance to rupture, the force, Sm, is commonly determined by dividing the total surface area, A_o, engaged in the adhesive contact by the maximum detachment force,

$$Sm = Fm/Ao$$

3.9.4 Mechanical theory [72]

The mechanical theory of mucoadhesion suggests that adhesive bonding is enhanced when a bioadhesive liquid penetrates and fills the microscopic irregularities of a surface. These surface imperfections increase the available contact area, thereby facilitating greater energy dissipation and strengthening adhesion. The effectiveness of mucoadhesion is also governed by the inherent characteristics of the formulation and the conditions under which it is applied. Key intrinsic factors include polymer molecular weight, concentration, and chain flexibility. For polymers with linear structures, mucoadhesive strength tends to increase proportionally with molecular weight, whereas this relationship does not consistently apply to polymers with non-linear configurations.

3.9.5 Electronic theory [72]

The electronic theory proposes that bioadhesion arises because the adhesive polymer and the mucosal surface carry different electronic surface characteristics. Therefore, when the surfaces come into touch with each other, an electron transfer takes place to balance the Fermi levels. This happens as a result of the formation of an electrical double layer at the mucous membrane-bioadhesive interface. The origin of bioadhesive forces is proposed to be due presene of attractive force in second layer.

3.9.6 Adsorption theory [72]

This theory proposes that bioadhesion between a polymeric substrate and biological tissue is primarily driven by weak intermolecular forces, such as Van der Waals interactions and hydrogen bonding. Mucoadhesive behavior can also involve a range of other molecular interactions, including ionic and covalent bonds, as well as hydrophobic associations. Notably, in polymers that possess carboxyl functional groups, hydrogen bonding plays a dominant role in establishing interfacial adhesion with mucosal surfaces. In the phenomenon of sticky contact, several elements are essential. Many interactions can result in a high global adhesion despite their possible fragility.

3.10 Factors Affecting Mucoadhesive Drug Delivery Systems

3.10.1 Polymer related factors

3.10.1.1 Molecular weight-

In linear polymers, there is a well-established relationship between molecular weight and bioadhesive strength, with higher molecular weights generally enhancing adhesion. In contrast, for polymers with non-linear architectures, this correlation is less predictable and may not consistently influence adhesive performance. For effective bioadhesion, a minimum molecular weight of approximately 100,000 is typically required.[73]

3.10.1.2 Concentration of active polymer-

Achieving effective bioadhesion requires the active polymer to be present at an optimal concentration. When the concentration becomes too high, polymer chains tend to coil and disengage from the surrounding medium, which restricts their ability to penetrate the mucus layer and leads to a marked decline in adhesive strength. Conversely, at very low concentrations, the number of polymer chains available to interact with mucus is insufficient, resulting in inconsistent and unpredictable adhesive behavior.[74]

3.10.1.3 Swelling-

For mucoadhesive polymers to function effectively, they must absorb water, which allows them to swell and form a network structure large enough to interact with mucin. The degree to which these polymers swell—and thus how well they adhere—is influenced by factors like the ionic environment, the volume of water present, and how concentrated the polymer is. Maintaining the right level of hydration is key to achieving strong adhesion in laboratory settings, as the mucoadhesive process is both dynamic and sensitive to its surroundings. [75]

3.10.1.4 Spatial conformation–

Dextran, despite having a very high molecular weight—approximately 20 million—exhibits mucoadhesive properties similar to polyethylene glycol (PEG), which is significantly smaller in size. This surprising equivalence in adhesion may stem from dextran's helical configuration, which can conceal key functional groups involved in binding. On the other hand, polymers with a more linear arrangement are more likely to present these active sites openly, resulting in stronger mucoadhesive interactions.[76]

3.10.1.5 Flexibility of polymer chain-

When water-soluble polymers undergo cross-linking, the movement of their individual chains becomes restricted. This reduction in chain mobility limits the extent to which the polymer strands can infiltrate the mucus layer, thereby diminishing their mucoadhesive effectiveness. The flexibility of these polymers—largely influenced by their viscosity and diffusion characteristics—plays a crucial role in this process. Polymers with greater flexibility tend to diffuse more readily into the mucosal network, enhancing their adhesive interaction.[76]

3.10.1.6 Hydrogen bonding capacity-

For effective hydrogen bonding, polymers must contain functional groups such as hydroxyl and carboxyl moieties, which readily participate in intermolecular interactions. Co-polymers like polyvinyl alcohol, polymethacrylic acid, and hydroxylated methacrylate are particularly proficient in establishing these bonds due to their chemical structures, making them well-suited for applications requiring strong adhesive properties.[77]

3.10.1.7 Charge-

Polymers that contain ionic functional groups generally show greater bioadhesive performance than those lacking charge. In particular, cationic polymers like chitosan tend to adhere more effectively to mucosal tissues when the surrounding environment is neutral or slightly alkaline. [78]

3.10.1.8 Cross linking density-

he structural characteristics of a polymer network—namely, pore size, molecular weight distribution, and degree of cross-linking—are closely interrelated and play a critical role in its functional behavior. A higher degree of cross-linking typically results in smaller pores, which impedes the movement of water into the polymer structure. This reduced water uptake limits the polymer's swelling capacity and restricts its ability to interact effectively with the mucin layer, thereby diminishing its mucoadhesive efficiency.[79]

3.10.2 Environmental related [80,81]

3.10.2.1 pH of polymer substrate interface-

The pH of the environment plays a crucial role in determining the surface charge of both mucus and polymer systems. Shifts in pH influence the degree of ionization of functional groups found in the amino acids of the mucin protein backbone and in its carbohydrate side chains. These variations in charge density directly impact how effectively polymers can adhere to mucosal tissues, as electrostatic interactions are sensitive to such changes.

3.10.2.2 Moistening

Hydration of mucoadhesive polymers make them more capable of spreading across the mucosal surface. This promotes the development of a broad macromolecular structure that allows mucin and polymer chains to interweave. Such interpenetration improves the movement of polymer chains, which in turn strengthens the adhesive interaction with the mucus layer.

3.10.2.3 Initial contact time

Bioadhesive strength is closely linked to the duration of initial contact between the polymer and the mucosal surface. This contact time plays a pivotal role in governing how deeply the polymer interpenetrates the mucus layer and how extensively it swells. However, in gastric environments, this parameter is difficult to regulate due to the dynamic and uncontrollable nature of physiological conditions.

3.10.2.4 Applied strength

The depth of polymer penetration into the mucosal layer can be influenced by the initial force applied at the point of contact. When adequate pressure is maintained for a prolonged period, even polymers that do not naturally exhibit strong interactions with mucin may develop mucoadhesive properties. This effect is likely due to the increased closeness between the polymer and mucosal surface, which facilitates physical interaction at the interface.

3.10.2.5 Presence of metal ions –

Combining with mucous groups and/or charged polymers can reduce the number of interaction sites and the strength of mucoadhesive bonding.

3.10.2. Physiological factors [82]

3.10.2.1. <u>Disease state-</u>

Various pathological conditions—including respiratory infections like the common cold, gastrointestinal disorders such as peptic ulcers and ulcerative colitis, as well as microbial infections—can alter the physicochemical characteristics of mucus. These changes may affect its composition, viscosity, and overall behavior, potentially influencing its interaction with therapeutic agents or bioadhesive systems.

3.10.2.2. <u>Renewal rate of mucosal cells</u>

The specific type of mucosal tissue plays a crucial role in determining the rate of cellular turnover. Rapid renewal of mucosal cells can limit the residence time of bioadhesive formulations, thereby reducing their effectiveness on the mucosal surface.

3.10.2.3. <u>Mucin turnover</u>

Frequent mucin turnover can negatively impact the performance of bioadhesive systems. Firstly, rapid renewal of the mucin layer shortens the time that bioadhesive polymers remain attached, even when those polymers possess strong adhesive properties. Secondly, elevated mucin turnover may lead to the release of soluble mucin fragments that interact with the polymer before it reaches the structured mucin layer, thereby weakening the overall mucoadhesive effect.

3.11 Polymers Used In Mucoadhesive Drug Delivery System [83-87]

3.11.1. Gelatin

Gelatin, obtained from collagen, is a biodegradable and biocompatible protein with low immunogenicity. Its adaptable nature makes it useful in biomedical fields like gene delivery, cell culture, and tissue engineering. Gelatin-based systems can steadily release therapeutic agents, and when combined with pegylated liposomes, they effectively retain bioactive molecules.

3.11.2. Albumin

Mono-PEGylated albumin hydrogels were developed by chemically linking serum albumin with polyethylene glycol. These engineered hydrogels hold potential as structural matrices for controlled drug release in tissue engineering applications.

3.11.3. Dextran

Dextran is a glucose-based natural polymer with a predominantly linear structure formed by 1,6-glucopyranosidic linkages, along with some branches connected through 1,3 bonds. Its high water solubility, biological compatibility, and safe biodegradability have made it an increasingly valuable component in drug formulations and medical therapies.

3.11.4. Chitosan

Chitosan, a positively charged semi-synthetic polymer, is obtained through the deacetylation of chitin. It has demonstrated the ability to improve the uptake of water-soluble compounds by modifying proteins associated with cell junctions. Its adhesive properties to mucosal surfaces arise from ionic interactions between its amino groups and sialic acid residues. Additionally, the linear configuration of chitosan contributes to the flexibility of its polymer chains, enhancing its functional versatility in biomedical applications.

3.11.5. PAA derivatives

Derivatives of polyacrylic acid (PAA) are typically produced by cross-linking acrylic acid monomers using compounds such as divinyl glycol or polyalkenyl ethers. These materials are composed of primary polymer particles ranging from 1 to 5 micrometers in diameter, each forming a highly cross-linked, three-dimensional network of polymer chains. In aqueous media, one widely utilized PAA derivative—Carbopol—demonstrates exceptional swelling capacity, expanding up to 1000 times its original volume. This swelling and subsequent gelation occur within a pH window of 4.0 to 6.0, primarily due to electrostatic repulsion among negatively charged carboxylate groups. The resulting expansion of polymer chains significantly enhances the compound's mucoadhesive characteristics.

3.11.6. Collagen

Collagen is an endogenous structural protein characterized by its unique triple-helical configuration. Nineteen different collagen types have been identified, each contributing to specific physiological roles across various tissues. Its high biocompatibility, minimal antigenic response, and resistance to enzymatic breakdown post-implantation make collagen an ideal candidate for applications in tissue engineering and regenerative therapies.

3.11.7. Alginate

Alginate is a naturally occurring linear polysaccharide that has gained prominence in biomedical research due to its adaptable properties. Its derivatives are commonly applied in areas such as tissue engineering and drug delivery, supported by their strong biocompatibility, biodegradability, low toxicity, and minimal immune response. The material's solubility in water, affordability, efficient gelation and stabilization behavior, along with its high viscosity in aqueous systems, make alginate a valuable component in formulation.

3.11.8. Newer second generation polymers [87-89]

Recent advancements have led to the development of more advanced polymer systems exhibiting enhanced mucoadhesive characteristics. As illustrated in Fig. 14, the adhesion mechanisms of these innovative materials—such as lectins, thiolated polymers (thiomers), and alginate-polyethylene glycol acrylate conjugates—demonstrate improved interaction with mucosal surfaces, offering promising potential for targeted drug delivery and mucosal retention.

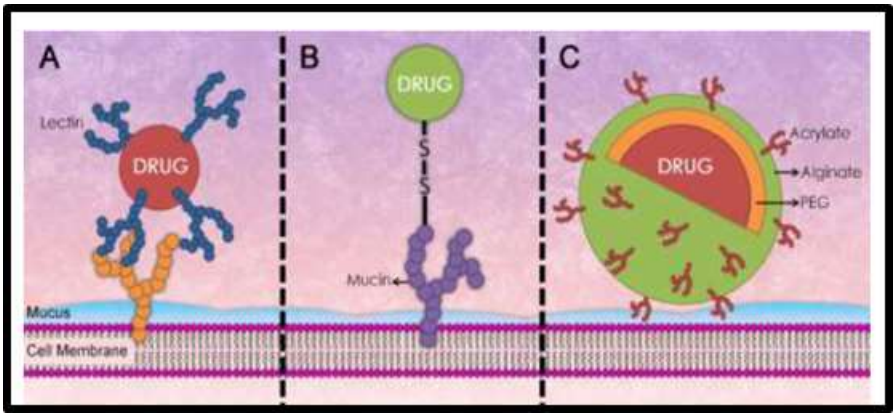

Fig.14: Mechanisms of mucoadhesion by (A) Lectins, (B) Thiomers, (C) Water Soluble Resins (WSR)

Alginate Polyethylene glycol acrylate

1. *Lectins*

Lectins are naturally occurring proteins that facilitate cellular recognition by selectively interacting with specific carbohydrate structures. These structurally diverse proteins and glycoproteins bind reversibly to sugar residues on cell surfaces, enabling targeted interactions. Upon binding, lectins may be internalized via endocytosis or remain anchored to the membrane, thereby supporting localized and controlled drug delivery. However, their clinical utility is limited by the potential to provoke immune responses.

2. *Thiolated Polymers*

Water-soluble polymers such as polyacrylates, chitosan, and deacetylated galactan gum can be chemically modified to form thiolated polymers, commonly referred to as thiomers. These thiomers interact with cysteine-rich domains of mucosal glycoproteins, forming disulfide bonds through thiol–disulfide exchange or direct oxidation. This mimics the natural covalent bonding seen in mucus glycoproteins, which are stabilized by disulfide linkages within the mucus layer. The presence of thiol groups enhances the polymer's mucoadhesive properties by prolonging its residence time and facilitating covalent attachment to mucosal surfaces. Moreover, the increased rigidity and cross-linking introduced by disulfide bonds may influence the drug release profile from the delivery system, offering potential for controlled therapeutic delivery.

3. *Water Soluble Resins (WSR)*

POLYOX™ polymers are high molecular weight polyethylene oxide homopolymers known for their quick hydration when used in pharmaceutical applications. They are safe, biocompatible, and easily soluble in water. Thanks to their adaptable physical and chemical characteristics, these polymers can be formulated into various dosage forms such as tablets, gels, films, microcapsules, and syrups.

3.12. Properties of an ideal mucoadhesive polymer [90,91]

- It must not break down throughout the course of the dosage form's shelf life.
- The polymer should have a high molecular weight and strong anionic charges.
- It must be sufficiently pliable to pass through tissue fissures or the mucous membrane.
- The polymer must have a high viscosity, balanced cross-linking, and a well-defined spatial configuration.
- The polymer and the by products of its breakdown should not be harmful, irritating, or able to be absorbed from the gastrointestinal tract.
- For a polymer to connect with a mucous membrane, it must contain strong H-bonding groups (-OH, -COOH)

3.13 Evaluation Studies of Mucoadhesive Drug Delivery System [92-94}

Ex vivo and in vitro tests:

1. Techniques for measuring mucoadhesive strength

A) Tensile strength measurement techniques

B) The process of falling liquid film

C) The use of fluorescent probes

D) The conjugate technique of colloidal gold mucus

2. The Thumb Approach

3. Index of Swelling

4. Conductivity of Electricity

5. Research on Stability

6. Residence Time Measurement and In-Vivo Methods

A) GI Transit with Tablets That Are Radio-Opaque

B) The Technique of Gamma Scintigraphy

3.13.1. Method of Mucoadhesive Strength Measurements

3.13.1.1. Methods for determining tensile strength

In tensile and shear tests, stress is distributed uniformly across the adhesive interface, whereas peel testing concentrates stress along the bond's edge. Tensile and shear assays therefore characterize the adhesive's bulk mechanical properties, while peel strength specifically measures the force needed to initiate and propagate detachment. A texture analyzer can be used in vitro to quantify the force required to remove bio-adhesive films from biological substrates. In a typical setup, a mucin-disc model or excised animal mucosal membrane is secured to a low-friction, movable stage. The bio-adhesive film is applied atop the tissue, and the analyzer—operating in tensile mode—peels the film away vertically at a controlled rate. This approach yields key metrics such as rupture tensile strength, shear strength, and detachment (peel) strength (see Fig. 15).

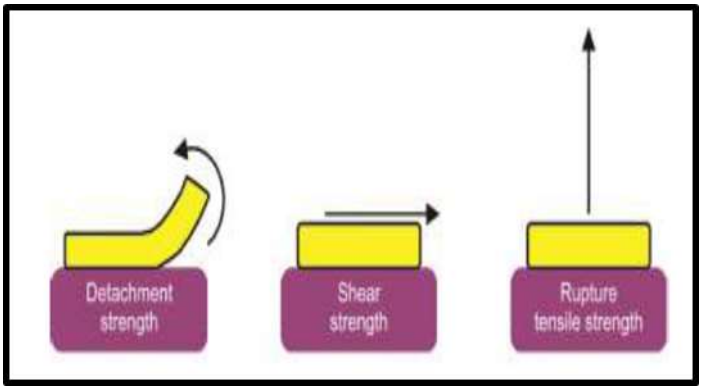

Fig.15: Different forces evaluated in mucoadhesion test.

Fig 16, illustrates a modified twin-beam balance setup for measuring mucoadhesive strength. The twin-beam balance was modified to balance weight on both pans during testing. The right pan is used in place of a glass slide with copper wire and an additional weight.

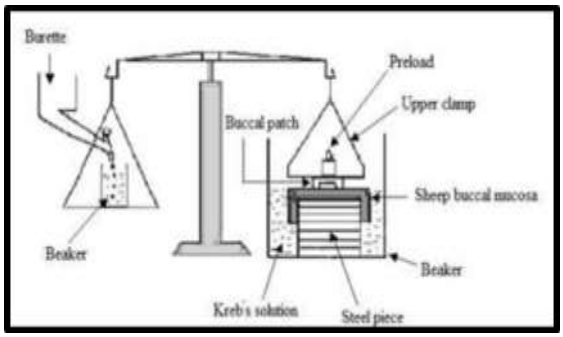

Fig.16: Measure of mucoadhesive strength.

The balance is used in such manner that its right-hand pan holds a beaker of 0.1 N HCl buffer (pH 1.2) fitted with a precisely machined Teflon block. Fresh goat or rat gastric mucosa—prehydrated with the same buffer—serves as the model membrane. One end of the mucoadhesive formulation is affixed to a glass slide on that arm, and the beaker is raised until the slide just contacts the tissue.

3.13.1.2. Falling liquid film method

Using this method, as shown in Fig. 17, a strip of mucosal tissue (5) is clamped inside a longitudinally split stainless-steel cylinder (4) and mounted at an incline within a 37 °C thermostatted chamber (1). An isotonic buffer (2) is driven across the tissue by a peristaltic pump (3), and the outflow is collected in a vessel (6). Retained particulate material on the mucosa is quantified with a Coulter counter, while any non-adhered fraction from semi-solid

formulations is determined by high-performance liquid chromatography. This dynamic system also allows polarized light microscopy to directly observe the development of a liquid-crystalline mesophase on the mucosal surface during fluid flow.

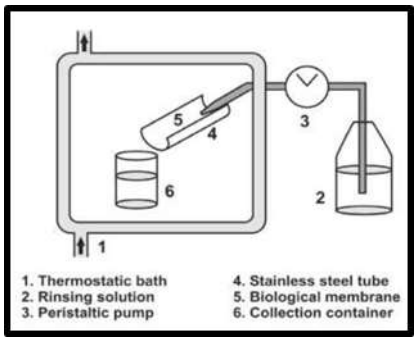

Fig. 17: Falling liquid film method.

3.13.1.3. Fluorescent probe Method

In this method, membrane proteins are labelled with fluorescein isothiocyanate and the lipid bilayer is tagged with pyrene. Upon introducing mucoadhesive polymers to the labelled cells, shifts in their fluorescence emission spectra has been monitored. These spectral changes reveal how the polymers engage with the membrane and clarify the underlying adhesion mechanism.

3.13.1.4. Colloidal gold mucin conjugate method

Colloidal gold staining provides a straightforward, sensitive assay for bioadhesion. In this method, red gold nanoparticles are conjugated to mucin, forming mucin–gold complexes that develop a vivid crimson color upon contact with a bioadhesive hydrogel. The adhesive strength is then quantified either by:

- Measuring the intensity of the red coloration bound to the hydrogel surface.
- Monitoring the decrease in mucin–gold conjugate concentration in solution via absorbance at 525 nm.

3.13.2. Thumb Method

This method supports the design of buccal adhesive delivery devices and provides a qualitative measure of a polymer's peel strength. Under controlled preload pressure and contact time, the strain required to pull a thumb away from the adhesive surface is recorded as the adhesiveness metric.

3.13.3. Swelling Index

The degree of swelling is determined by calculating the percentage increase in the formulation's weight following exposure to the swelling medium. This formula is used to calculate it:

$$(Wt - Wo/Wo) = Swelling\ Index\ (S.I.)$$

Here, Wt represents the weight of the tablet at a specific time point t, while Wo denotes its initial weight prior to immersion in the swelling medium. S.I. is the swelling index.

3.13.4. Electrical conductance

Electrical conductivity of various semisolid mucoadhesive ointments was assessed employing a modified rotating viscometer. The findings revealed that formulations exhibiting lower conductivity were consistently associated with the presence of adhesive components.

3.13.5. Stability Studies

A pharmaceutical formulation can only be considered successful if it demonstrates consistent stability over time. Stability studies play a critical role in confirming that the product remains effective and safe when stored under specified conditions throughout its intended shelf life. To ensure reliability and uniformity in these assessments, the testing process typically follows the standards outlined by the International Council for Harmonisation (ICH), which offer a globally accepted framework for evaluating product durability and quality.

3.13.6. Measurement of the Residence Time/ In-Vivo Techniques

Assessing how long a mucoadhesive formulation remains at its targeted site provides a quantitative measure of its adhesive performance. Gastrointestinal transit times for a variety of mucoadhesive systems have been determined by employing radioisotope tracing and fluorescence labelling techniques.

3.13.6.1. GI Transit using Radio-Opaque Tablets

This straightforward method evaluates the effect of mucoadhesive polymers on GI transit time using radio-opaque markers, such as barium sulphate, that are contained in mucoadhesive tablets.

3.13.6.2. Gamma Scintigraphy Technique

The amounts and distribution of radioactivity in the vaginal tract after using technetium-labeled hyaluronic-based biomaterial (HYAFF) tablets have been reported in a study. After 12 hours of delivery to the stomach epithelium, it was found that the dry powder formulation of mucoadhesive radio-labelled tablets manufactured from HYAFF polymer retained more of the tablets than the pessary formulation.

4. CONCLUSION

The bioavailability of several drug candidates has been improved and controlled drug administration has been accomplished through the use of various floating drug delivery system (FDDS) techniques. One promising technique for gastric retention is the controlled release floating medication delivery device. Developing an effective floating drug delivery system is inherently challenging, as the formulation must maintain gastric residence long enough to ensure optimal drug release. For drugs that are mostly absorbed in the upper gastrointestinal system, FDDS offers an additional advantage. In order to provide prolonged release and restrict the drug's distribution to the stomach, many drugs have been created as floating drug delivery systems. The buoyant preparation idea provides a simple and practical way to achieve.

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