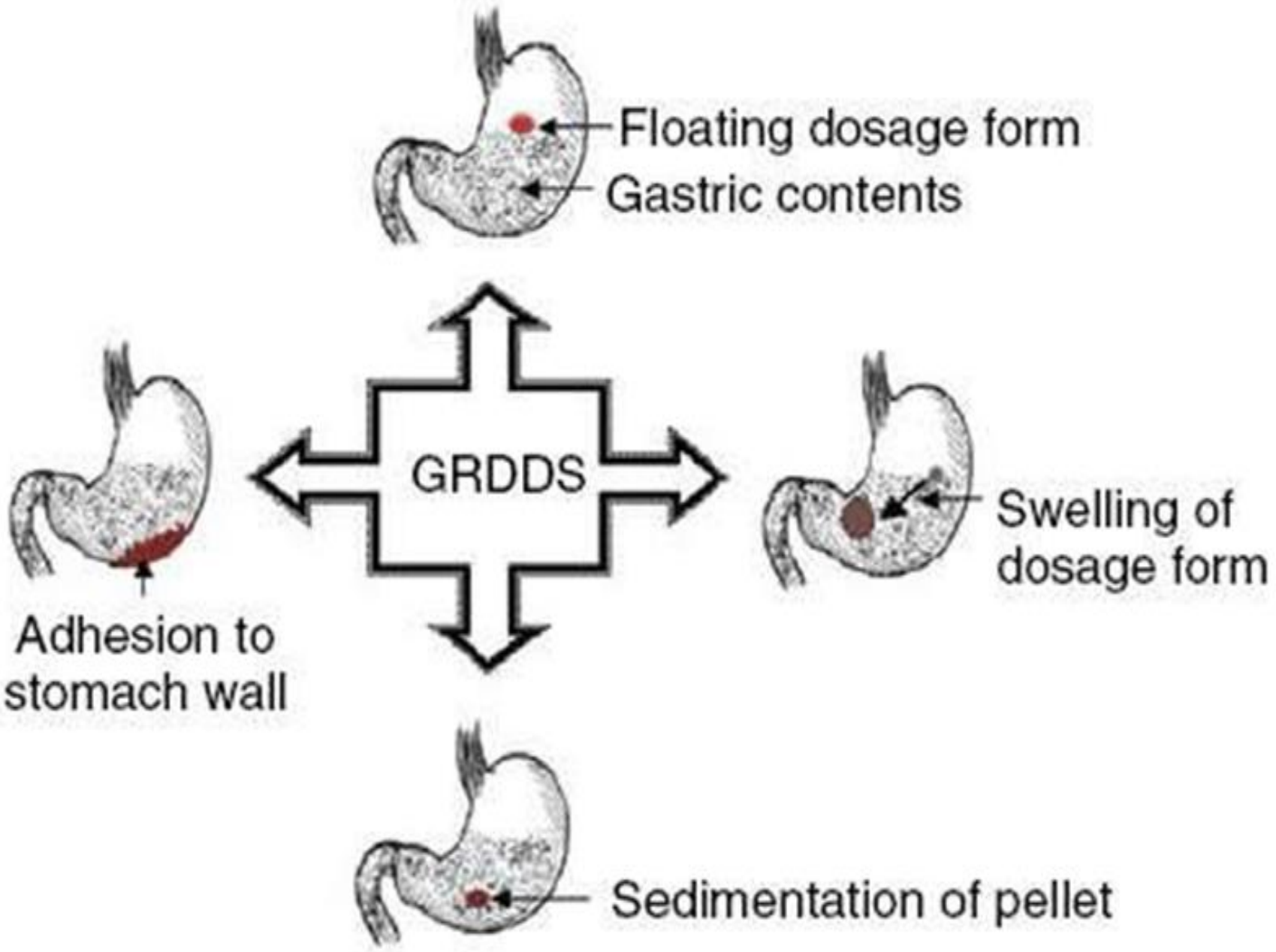
Gastro Retentive Drug Delivery System (GRDDS)


Floating dosage form
Gastric contents
GRDDS
Swelling of dosage form
Adhesion to stomach wall
Sedimentation of pellet

Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables.

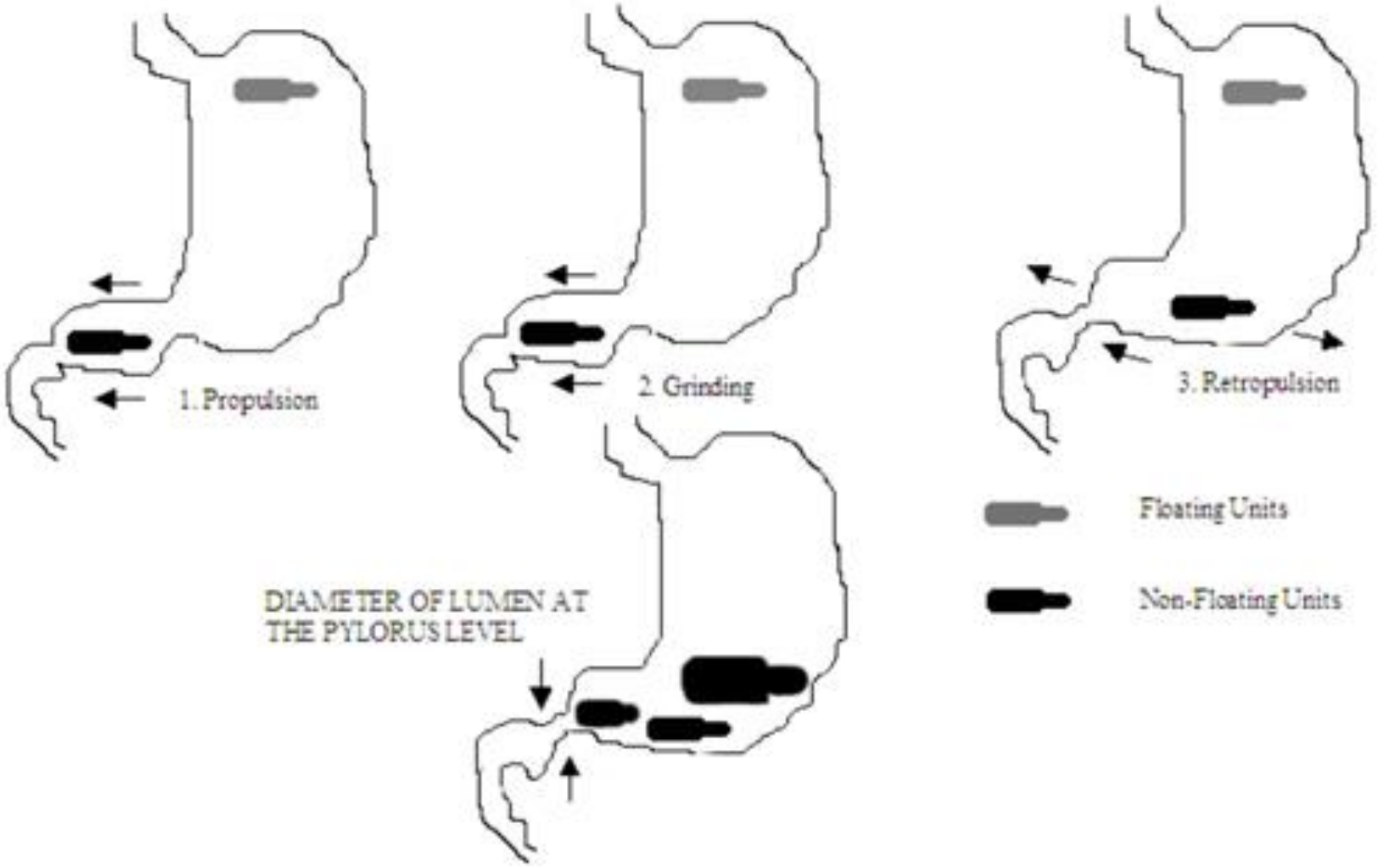
- **the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.**
- **Small intestinal transit time is an important parameter for drugs that are incompletely absorbed.**
- **Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.**
- **Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment.**
- **The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying.**

Factors Affecting Gastric Retention

The rate of gastric emptying depends mainly on viscosity, volume, and caloric content of meals.

- Increase in acidity and caloric value slows down gastric emptying time.
- Biological factors such as age, body mass index (BMI), gender, posture, and diseased states (diabetes, Chron's disease) influence gastric emptying.
- In the case of elderly persons, gastric emptying is slowed down.
- Generally females have slower gastric emptying rates than males.
- Stress increases gastric emptying rates while depression slows it down.

- The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster.
- Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.
- Gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.
- The density of a dosage form also affects the gastric emptying rate.
- A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.



Intragastric residence positions of floating and non-floating units.

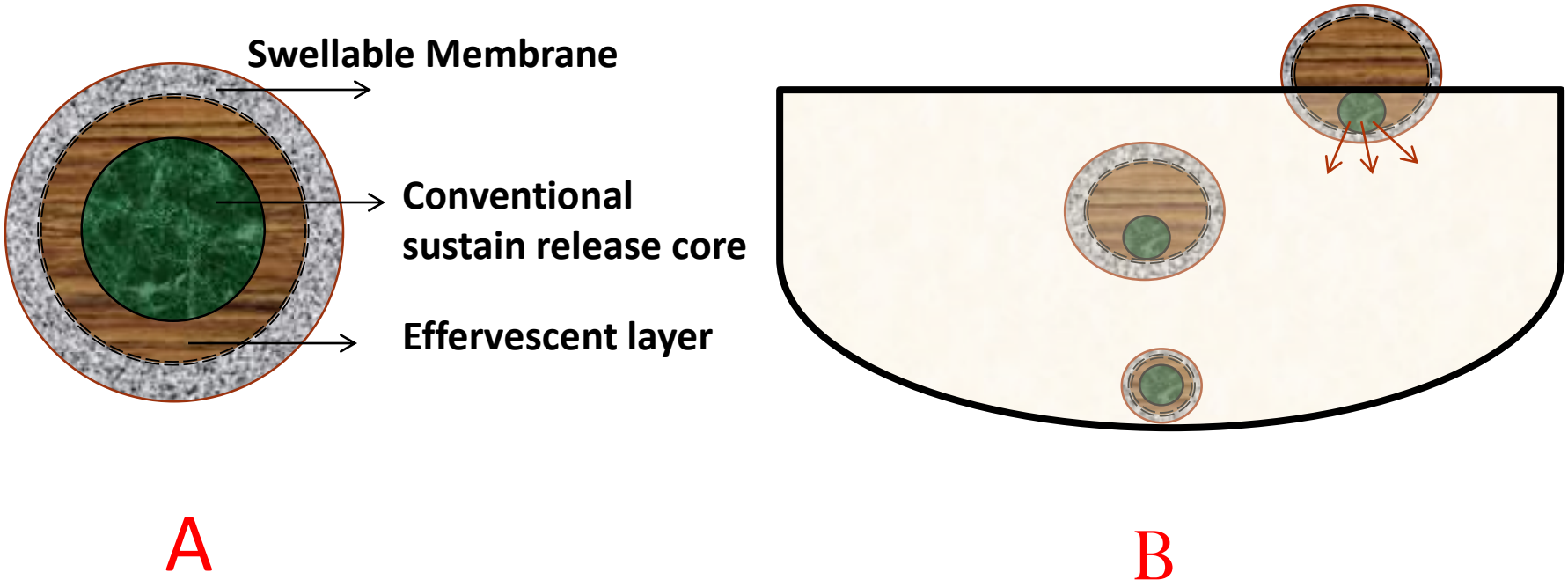
Classification:

Floating drug delivery systems are classified depending on the use of 2 formulation variables;

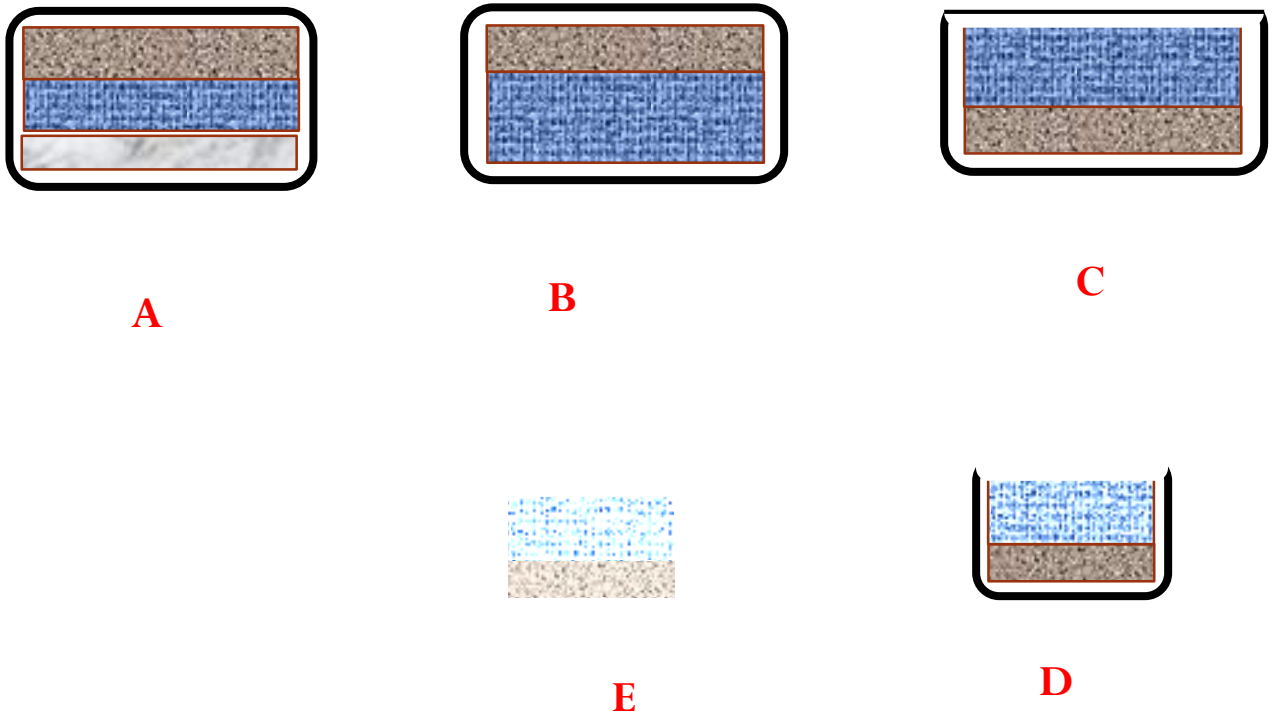
1. *Effervescent Floating Dosage Forms*
2. *Non-Effervescent Floating Dosage Forms*

Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.



(A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.



Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) and (E) Tablet erodes completely.

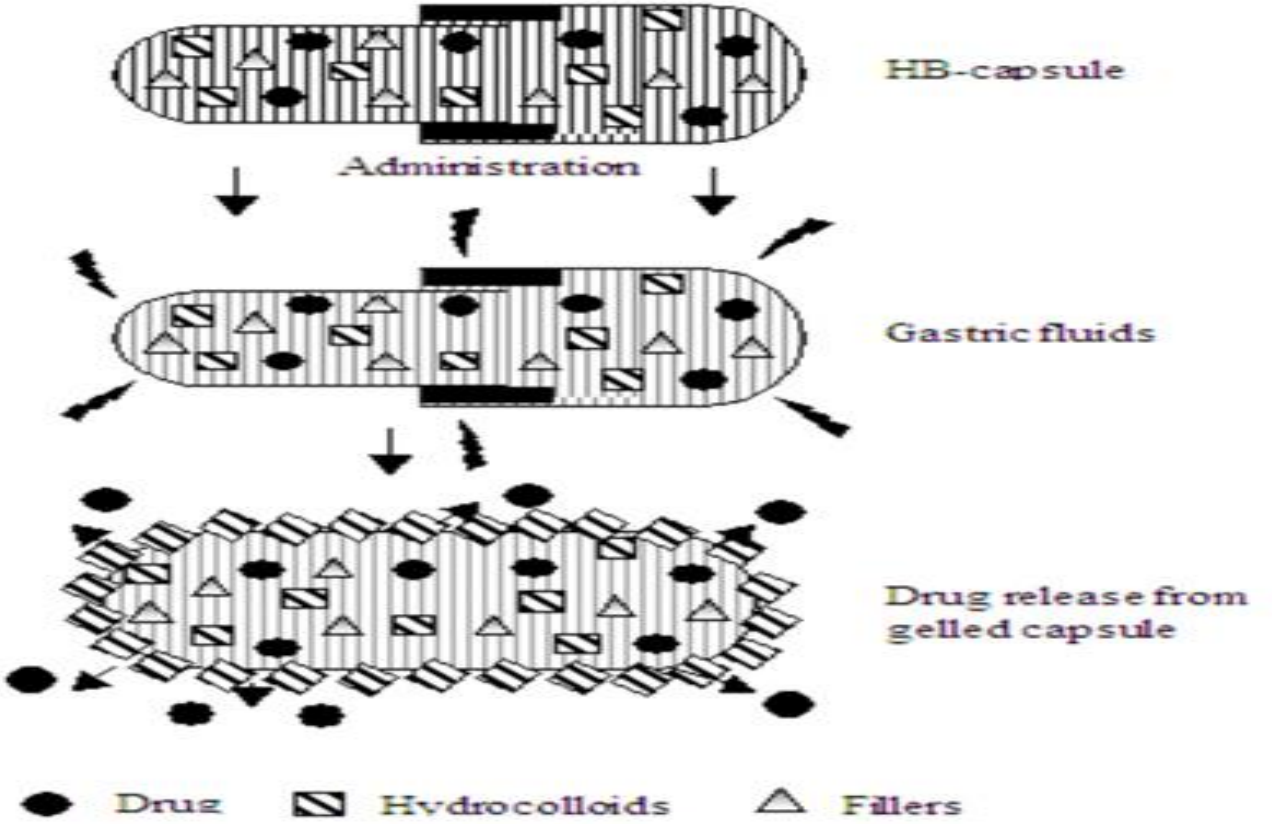
Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene.

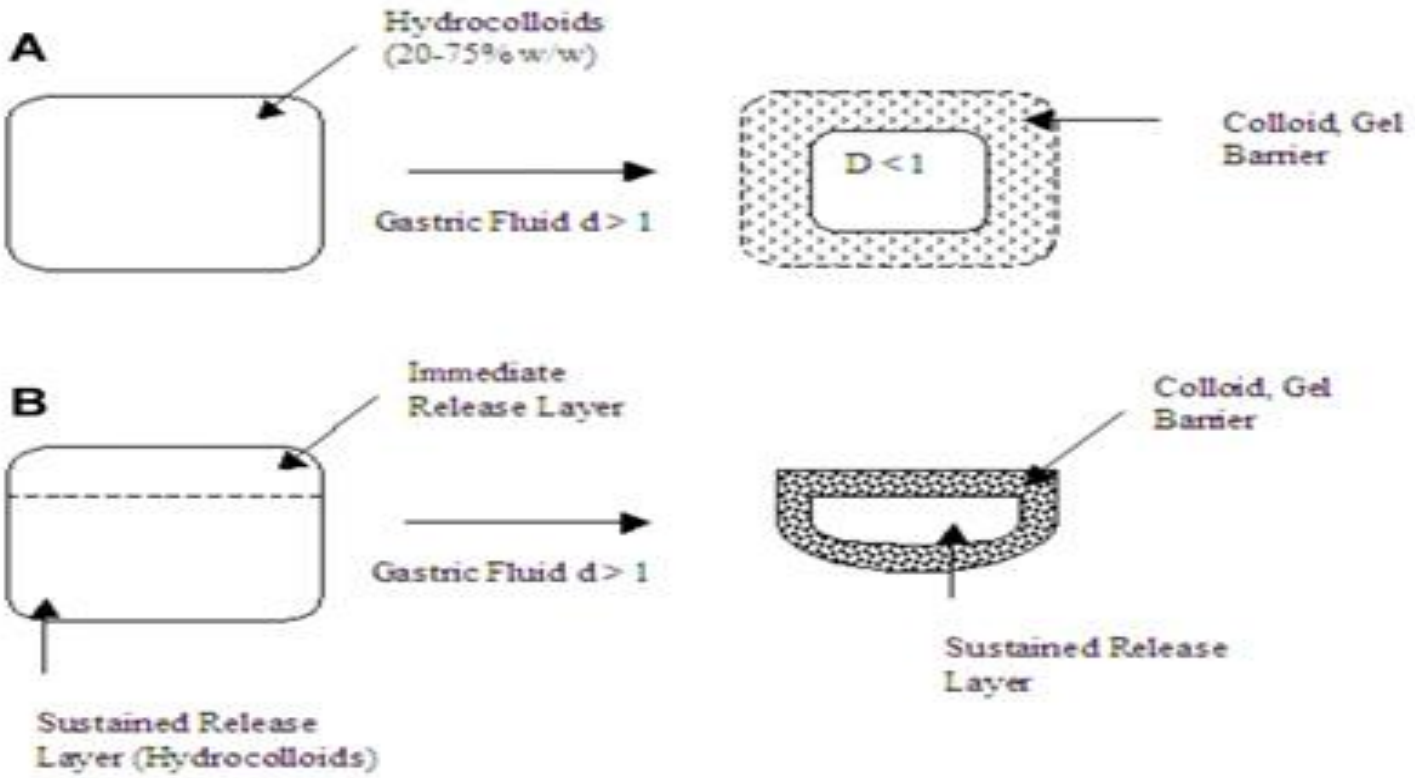
The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid.

After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1.

The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.



Working principle of Hydrodynamically balanced system.



Intragastric floating tablets. (A) United States patent 4 167 558, September 11, 1979. (B) United States patent 4 140 755, February 20, 1979.

Marketed Preparations of Floating Drug Delivery Systems

S. No	Product	Active Ingredient
1	Madopar	Levodopa and benserzide
2	Valrelease	Diazepam
3	Topalkan	Aluminum magnesium antacid
4	Almagate flatcoat	Antacid
5	Liquid gavison	Alginic acid and sodium bicarbonate
4	Almagate flatcoat	Antacid
5	Liquid gavison	Alginic acid and sodium bicarbonate

Evaluation of floating drug delivery systems

Various parameters that need to be evaluated in gastro-retentive formulations include;

1. Floating duration,
2. Dissolution profiles,
3. Specific gravity,
4. Content uniformity,
5. Hardness, and
6. Friability.

The tests for floating ability and drug release are generally performed in simulated gastric fluids at 37ºC.

Applications of Floating Drug Delivery Systems

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery

Site-Specific Drug Delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide.

Absorption Enhancement

- Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

Limitations of FDDS

Drugs that irritate the mucosa, those that have multiple absorption sites in the gastrointestinal tract, and those that are not stable at gastric pH are not suitable candidates to be formulated as floating dosage forms.

The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm).

Floating dosage form should not be given to a patient just before going to bed as the gastric emptying of such a dosage form occurs randomly when the subject is in supine posture.

Bio / Mucoadhesive Drug Delivery Systems

Involves the use of bio-adhesive polymers, which can adhere to the epithelial surface in the stomach.

Dosage form can stick to mucosal surface by following mechanisms;

- The electron theory
- The wetting theory
- The diffusion theory
- The absorption theory
- The mechanical theory
- The fracture theory

The electronic theory suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent results adhesion due to these attractive forces.

The wetting theory is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid.

The adsorption theory describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemi-sorptions theory, assumes an interaction across the interface occurs as a result of strong covalent bonding.

The diffusion theory describes interdiffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobilities. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond.

The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

The fracture theory differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion.

MECHANISMS OF MUCOADHESION

The mechanism of muco-adhesion is generally divided in two steps,

Contact stage

It is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over in other cases, the deposition is promoted by the aerodynamics of the organ to the membrane, the system is administered, such as for the nasal route.

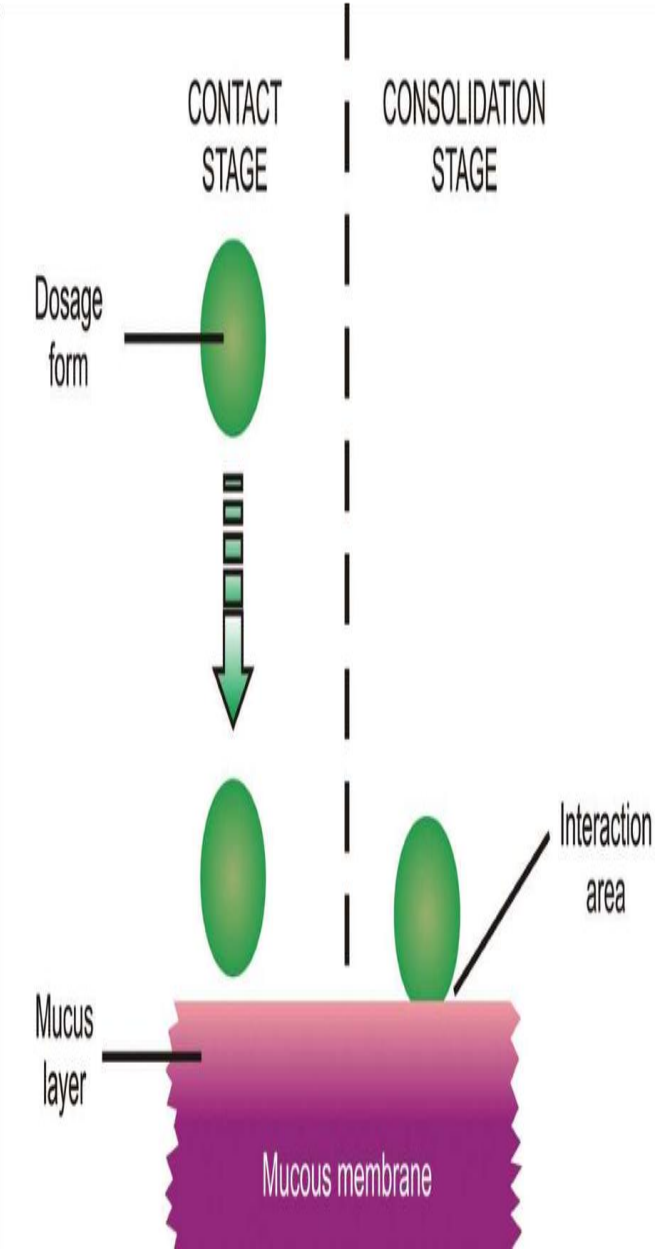
Consolidation stage

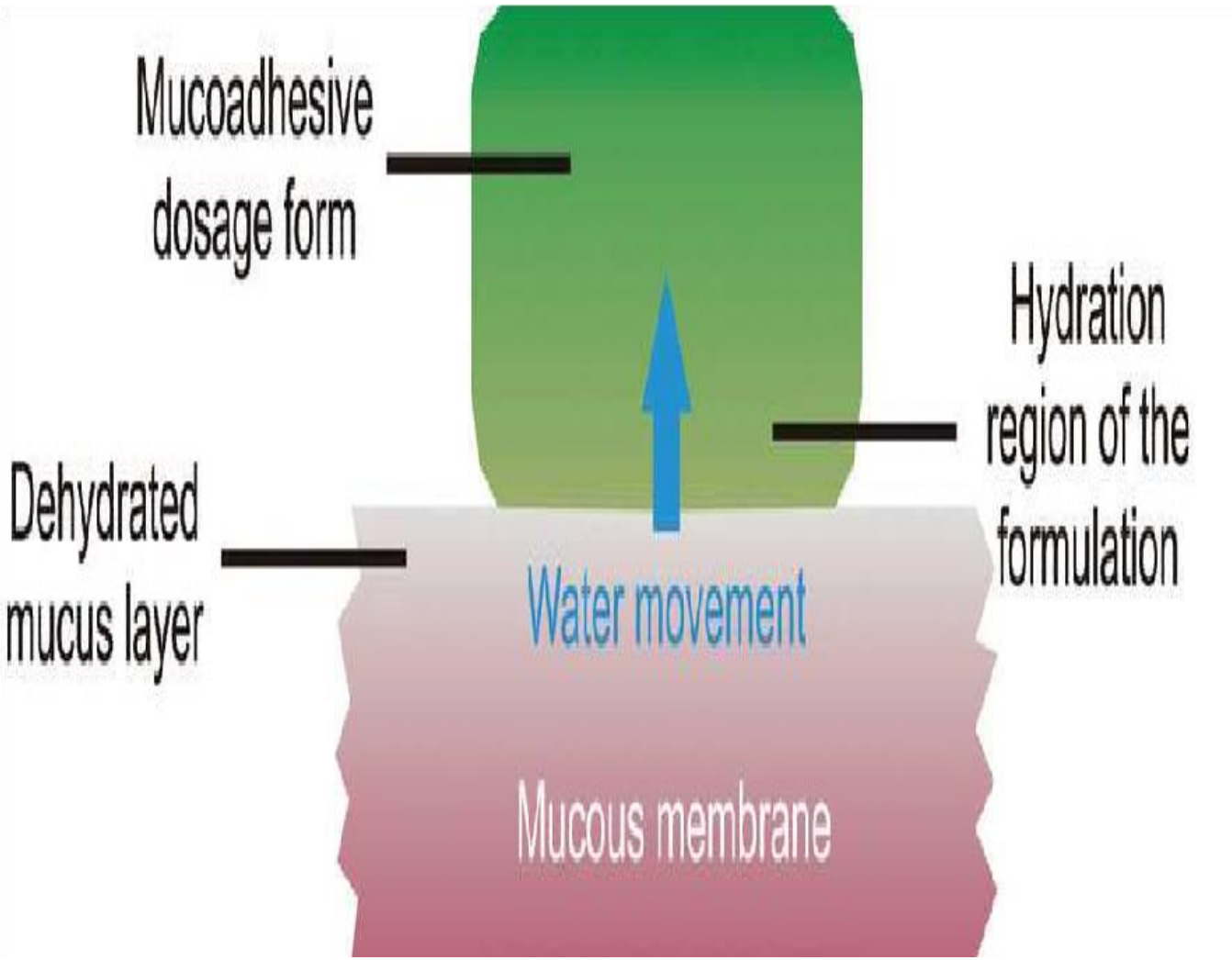
In the consolidation step, the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds.

There are two theories explaining the consolidation step:

- ❑ The Diffusion theory
- ❑ The Dehydration theory.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds. For this to take place the mucoadhesive device has features favoring both chemical and mechanical interactions. According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure.




Mucoadhesive
dosage form
Hydration
region of the
formulation
Dehydrated
mucus layer
Water movement
Mucous membrane

MUCOADHESIVE POLYMERS

Mucoadhesive drug delivery systems are based on the adhesion of a drug/ carrier to the mucous membrane. To promote this adherence a suitable carrier is required.

Synthetic polymers:

1. Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxyl ethyl cellulose, Hydroxyl propyl cellulose,

Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).

2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).

3. Poly hydroxyl ethyl methyl-acrylate.

4. Poly ethylene oxide.

5. Poly vinyl pyrrolidone.

Natural polymers:
Tragacanth, Sodium alginate, Guar gum, Xanthum, gum, soluble, starch, Gelatin, Chitosan

Mucoadhesive polymers can also classify into following categories:

Traditional non-specific first-generation mucoadhesive polymers;

It may be divided into three main subsets, namely:

1) Anionic polymers,

2) Cationic polymers,

3) Non-ionic polymers.

Of these, anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength.

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Typical examples include poly (acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin.

Polycarbophil (Noveon) and Carbomers (Carbopol), PAA derivatives have been studied extensively as mucoadhesive platforms for drug delivery to the GI tract.

Cationic Polymers

Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose. The intriguing properties of chitosan have been known for many years with many

Novel second-generation mucoadhesive

The major disadvantage in using traditional nonspecific mucoadhesive systems (first generation) is

that adhesion may occur at sites other than those intended. Unlike first-generation non-specific

platforms, certain second-generation polymer platforms are less susceptible to mucus turnover

rates, with some species binding directly to mucosal surfaces; more accurately termed“Cyto-adhesives”.

Lectins

The most widely investigated of such systems in this respect are lectins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues.

After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptormediated adhesion possibly become internalised via a process of endocytosis.

Thiolated polymers:

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan).Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly (acrylic acid)–homocysteine, chitosan–thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly (methacrylic acid)–cysteine and sodium carboxymethylcellulose–cysteine.

Polyox WSR

A class of high molecular weight polyethylene molecular weight polyethylene oxide homopolymers having the following properties,

- - Water soluble hydrophilic nature
- - Functional group for hydrogen bonding
- - Biocompatible and non toxic
- - High molecular weight

Novel polymers

- Tomato lectin showed that it has binding selectivity to the small intestine epithelium.
- A new class of hydrophilic pressure sensitive adhesives (PSA) have been developed by corium technologies. Complex have been prepared by non covalent hydrogen bonding crosslinking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends.

Ideal Characteristics of Mucoadhesive Polymers:

A mucoadhesion promotoing agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the mucosa. The agent can have such additional mucoadhesive strength can be attributed asp; anion>cation>non-ionic.

Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage.

Optimum pH – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit properties like swelling so as to promote the strong mucoadhesive forces.

FACTORS AFFECTING MUCOADHESION

FACTORS	PROPERTIES	COMMENTS
a. Polymer related factors	1. Molecular weight	The mucoadhesive force increases with molecular weight of polymer, up to 1,0000 and beyond this level there is no much effect.
	2. Concentration of active polymers	For solid dosage forms such as tablets showed that the higher the polymer concentration the stronger the muco-adhesion. There is an optimum concentration of polymer corresponding to the best muco-adhesion.
	3. Flexibility of polymer chain	Flexibility is an important factor for interpenetration and enlargement.
b. Environment related factors	1.pH	pH influences the charge on the surface of both mucus and the polymers.
	2.Applied strength	To place a solid mucoadhesive system, it is necessary to apply a defined strength.
	3. Initial contact time	The mucoadhesive strength increases as the initial contact time increases.
	4. Swelling	Swelling depends on both polymers concentration and on presence of water.
c. Physiological Variables	1.Mucin turn over	a. The mucin turnover is expected to limit the residence time of the mucoadhesive on the mucus layers.
	2.Diseased state	b. Mucin turnover results in substantial amounts of soluble mucin molecules. Physicochemical properties of mucus are known to change during diseased states, such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract and inflammatory conditions of the eye.