A COMPREHENSIVE REVIEW OF MICROBALLONS - A NOVEL APPROACH ON FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT:

The creation of gastro-retentive floating microballoon is a result of recent advancements in floating drug delivery systems, which included the even dispersion of multiparticulate dosage forms along the gastrointestinal tract. The floating microballoons show gastro-retentive controlled release distribution with efficient methods to enhance the bioavailability, making them a promising treatment option for stomach retention. Drug loaded microballoons in their outer polymer shells were described in detail, along with the preparation techniques. Microballoons float above the rate of gastric contents, increasing gastro-retention time and decreasing variations in plasma drug concentration. It is in safe and effective way.

KEY WORDS:

Microballoons, Gastro-retention, Floating drug delivery system (FDDS).

INTRODUCTION:

Gastro-retentive drug delivery systems (GRDDS) is a advanced approach to drug administration aimed at increasing the time a drug remains in the stomach. By prolonging gastric residence, these systems enable controlled and site-specific release of the drug in the upper gastrointestinal tract, enhancing both local and systemic therapeutic effects. The gastric retention time (GRT) of such formulations is significantly improved due to their extended stay in the stomach. Over the years, several strategies have been developed to achieve effective gastro-retention. Among these, oral administration remains the most convenient and efficient method for ensuring optimal drug absorption into systemic circulation(1)

In recent years, oral controlled-release drug delivery systems have gained significant attention in the pharmaceutical industry for their ability to enhance therapeutic effectiveness. These systems provide several benefits, such as reducing dosing frequency, improving patient adherence, and offering flexibility in formulation design. Drugs that have short half-lives and are

rapidly absorbed in the gastrointestinal tract are eliminated from the body quickly, requiring multiple doses to maintain effective therapeutic levels. To overcome this challenge, oral sustained-release formulations have been developed to release the drug gradually into the gastrointestinal tract, thereby maintaining consistent and prolonged drug concentrations in the bloodstream(2)

These delivery systems are specifically designed to remain in the stomach after oral intake, allowing the drug to be released gradually and continuously delivered to the absorption sites in the gastrointestinal tract (GIT). However, a short gastric retention time (GRT) and unpredictable gastric emptying time (GET) can limit their effectiveness, as they may result in incomplete drug release within the targeted absorption region (stomach or upper small intestine), thereby reducing the drug's therapeutic efficiency. (3)

A longer residence time of the drug in the stomach is beneficial for site-specific controlled-release formulations. It helps improve drug solubility, minimize drug loss, prolong drug release, and enhance the bioavailability of drugs that have low solubility in high-pH environments. Additionally, maintaining the drug in the stomach for an extended period can support localized treatments in the upper small intestine, such as therapy for peptic ulcers. (4)

APPROCHES ON FLOATING MICROBALLOONS:

Various approaches have been designed to increase the duration that dosage forms remain in the stomach. One effective method is developing a system with a density lower than gastric fluids, allowing it to float on the stomach contents. This floating system extends the gastric residence time (GRT), enhancing drug absorption in the stomach and upper part of the small intestine. Prolonging gastric resideence time also helps maintain a sustained and consistent therapeutic effect.(5)

These approaches have led to a detailed classification of floating drug delivery systems (FDDS) as shown in Fig 1. Scientists have explored in-vivo/in-vitro examination of floating drug delivery systems to determine their efficiency and usefulness. (34)

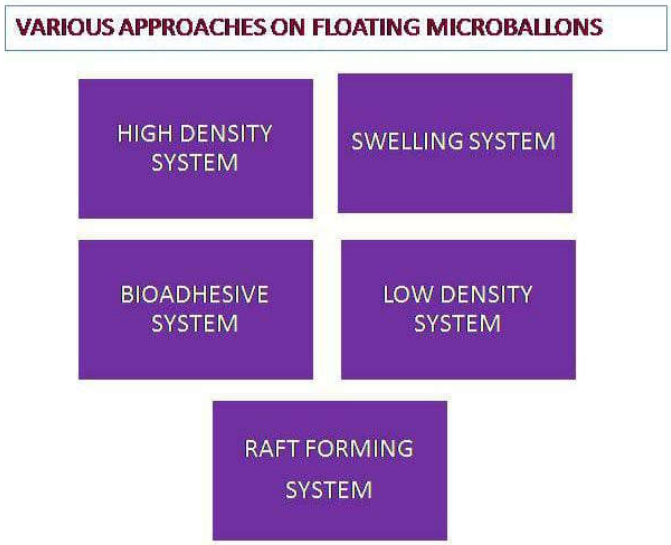

Fig 1. Various approaches on floating micro balloons.

- HIGH DENSITY SYSTEM:

The gastric contents have a density nearly equal to that of water (about 1.004 g/cm³). When a person is in an upright position, small, high-density pellets tend to settle at the bottom of the stomach. To achieve this higher density, drug formulations are often coated with heavy, inert substances such as barium sulfate, zinc oxide, titanium dioxide, or iron powder, allowing them to have a density greater than that of the gastric contents.(6,7)

- SWELLING SYSTEM:

This system is designed to swell upon contact with gastric fluids, increasing in size to a point where it cannot pass through the pylorus. As a result, the dosage form remains in the stomach for a prolonged period. The swelling occurs primarily due to osmotic absorption of water. Initially, the dosage form is small enough to be swallowed easily but expands significantly once it reaches the stomach.(8,9)Medicated polymer sheets and balloon hydrogels are examples of such delivery systems. To maximize benefits and avoid negative effects, it's important to strike a balance between swelling and erosion rates of the polymer. (126)

In the 1980s, Mamajek and Moyer developed and patented a drug reservoir system enclosed by a swellable expanding agent. The entire device was coated with an elastic polymeric membrane that allowed both the drug and body fluids to pass through, thereby controlling the drug release. As the drug and expanding agent were gradually depleted, or as the polymer

coating underwent bioerosion, the system slowly reduced in size and rigidity, allowing it to be safely eliminated from the body.(10)

- BIOADHESIVE SYSTEM:

Bioadhesive or mucoadhesive systems adhere to the gastric epithelial cells or the mucin layer, which helps to prolong the gastric residence time (GRT). This occurs by increasing the contact and interaction between the dosage form and the stomach lining. The natural adhesive properties of mucin are utilized in developing gastro retentive drug delivery systems to improve drug retention and absorption in the stomach.(11,12)

According to the wetting theory, bioadhesion occurs when bioadhesive polymers spread over the mucus layer and form close contact with it. The diffusion theory, on the other hand, explains that adhesion results from the intermingling or entanglement of mucin strands with the polymer chains, or by the penetration of mucin strands into the porous structure of the polymer surface. (13,14)

- LOW DENSITY:

The most practical and thoroughly researched gastro retentive dose forms are low-density/floating systems [15,16,17]. Davis first proposed the floating method in 1968. The dose form's bulk density in this system is less than the stomach fluid's (1.004 g/cm3). This characteristic enables the drug to be released from the system at the intended pace during the gastric residence time while the system stays buoyant in the stomach for an extended amount of time. (18,19)

- RAFT FORMING SYSTEM:

Another kind of GRDDS is raft-forming systems, which are made with gel-forming polymers and effervescent excipients to provide prolonged drug delivery. The idea behind these systems, which primarily concentrate on producing limited effects since floating rafts function as blockades between the esophagus and stomach. As a result, gastric esophageal reflux disease can be effectively managed with them. Raft-forming systems swell and create a viscous cohesive gel when they come into touch with stomach fluid, creating a continuous layer known as rafts.

The authors employed acid neutralizer and sodium bicarbonate as gas-generating agents and sodium alginate as a gel-forming polymer. The raft floats on the gastric fluid as a result of the generation of CO2 gas, which lowers the system's bulk density. (20) When carbonates and stomach juice react, it swells and retains CO2 bubbles, forming a thick and cohesive gel.(21)

PHYSIOLOGY OF STOMACH:

In gastro retentive drug delivery systems (GRDDS), the stomach plays a key role; hence, understanding its anatomy and physiology is essential for the effective design of these formulations. Structurally, the stomach is divided into two main regions: the **proximal part** which includes the *fundus* and *body*, and the **distal part**, comprising the *antrum* and *pylorus*. The stomach's primary functions are to **store food temporarily**, **grind it into smaller particles**, and **gradually release it into the duodenum**.(18)

The **fundus** and **body** of the stomach primarily serve as storage sites for undigested food, whereas the **antrum** functions as a muscular pump that facilitates **gastric emptying** by propelling the stomach contents into the small intestine.

The movement of the stomach, known as the migrating myoelectric complex (MMC), occurs in distinct phases. Although gastric emptying happens in both fed and fasted states, its pattern differs. During the fasted state, rhythmic electrical activity known as the inter digestive motility cycle takes place in the stomach and small intestine every 90–120 minutes in a repeating sequence.(22)

PARTS OF STOMACH:

This section discusses the structure and function of the gastrointestinal (GI) system. It includes an explanation of the main digestive organs the mouth, tongue, salivary glands, pharynx, esophagus, stomach, small intestine, and large intestine along with the accessory organs such as the liver, pancreas, and gallbladder.(23)

- STOMACH:

The stomach is a muscular, sac like organ that mixes food with gastric juices to begin digestion. It is divided into four main parts: the cardia, fundus, body, and pylorus as shown in Fig 2. The pylorus, which is funnel shaped, connects the stomach to the duodenum the first section of the small intestine. At this junction, the pyloric sphincter acts as a valve to control the release of stomach contents into the small intestine.(24)

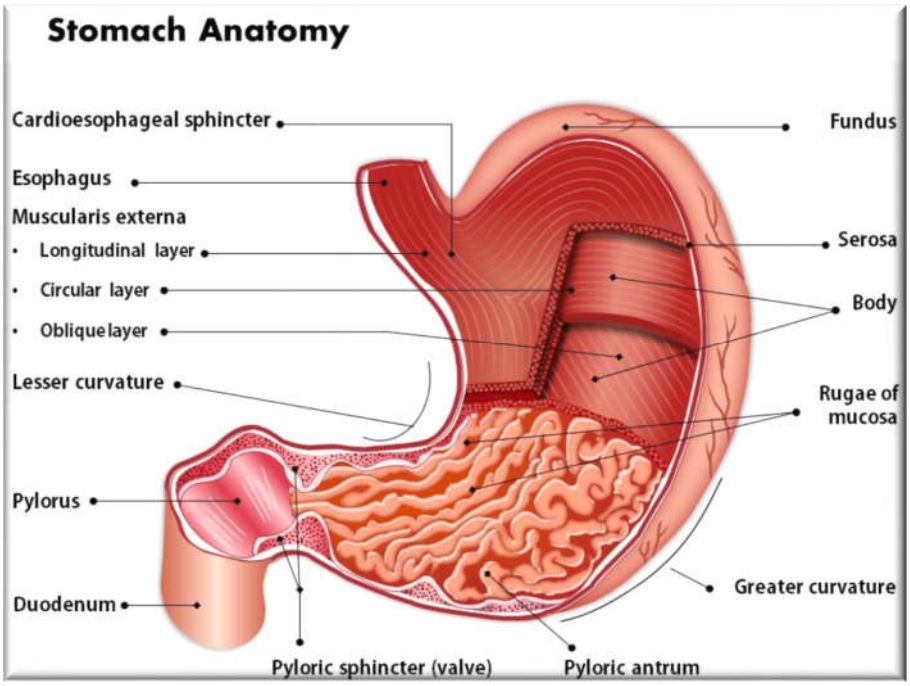

Fig 2. Anatomy of stomach (25)

The stomach's inner lining is made up of a mucous membrane that secretes alkaline mucus, forming a protective barrier against the strong stomach acid. Beneath this lining are gastric glands that produce gastric juice a digestive fluid containing water, mucus, hydrochloric acid, pepsin, and intrinsic factor. This gastric juice not only helps break down food but also protects the body from harmful microorganisms by creating an acidic environment. The main components of gastric juice are described in detail below.(24)

- SMALL INTESTINE:

Partially digested food, known as chyme, passes from the stomach into the small intestine through the pyloric sphincter. The small intestine is the primary site for digestion and nutrient absorption, where about 90% of the nutrients are absorbed into the bloodstream through tiny, finger like projections called villi that line its inner surface. Measuring about ten feet in length, the small intestine is named for its relatively small diameter of around one inch, in contrast to the large intestine, which has a diameter of about three inches.

The small intestine, a long coiled tube is divided into three parts: the duodenum, jejunum, and ileum. The ileum connects to the cecum, the first part of the large intestine, through the ileocecal sphincter. The ileocecal valve regulates the movement of chyme from the small intestine into the large intestine, ensuring proper flow and preventing backflow(26).

- LARGE INTESTINE:

The large intestine stretches from the cecum to the anus. Its main roles are to absorb the remaining nutrients and water, produce certain vitamins and form and remove feces (stool). Although it is only about half as long as the small intestine, it is called “large” because its diameter is about three inches nearly three times wider than that of the small intestine. It is divided into four major parts: the cecum, colon, rectum, and anal canal as shown in Fig 3. The colon is further divided into four sections ascending, transverse, descending, and sigmoid colon.(24).

Columnar epithelial cells and mucus-secreting goblet cells make up the large intestine’s mucosa, which facilitates fluid and electrolyte absorption and lubricates the mucosa.(26)

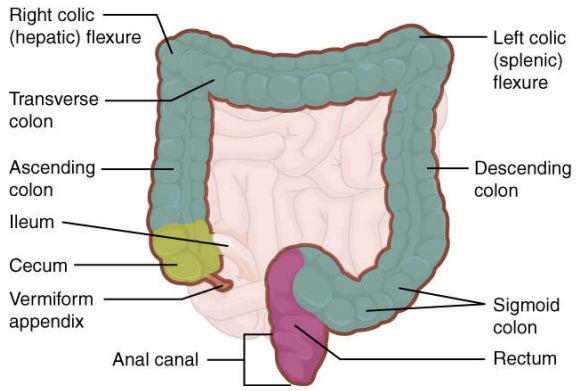

Fig 3. Large intestine (27)

- CECUM:

The cecum forms the beginning of the large intestine and serves to receive partially digested material from the small intestine while continuing the absorption of water and salts. Attached to its end is the appendix, a small, tube-shaped pouch. Because of its narrow and coiled structure, the appendix can easily collect bacteria, which may multiply and result in inflammation called appendicitis. (26)

- COLON:

After food residue enters the colon, it moves upward through the ascending colon located on the right side of the abdomen. Near the lower surface of the liver, the colon curves to form the transverse colon, which extends across to the left side of the abdomen. From there, the chyme travels downward through the descending colon along the left side of the abdominal wall and finally enters the S-shaped sigmoid colon.(26)

MICROBALLONS:

Micro balloons are microscopic spherical particles or microspheres or microparticulates. as shown in Fig 4. Diameter range, typically ranging from 1Micrometer to 1000 micrometer. Frequently, micro balloons are able to derived from various synthetic and natural sources.Ceramic micro balloons and polymer micro balloons are commercially available. Both glass micro balloons and micro balloons. Solid balloons hollow densities are utilized because they differ greatly in a variety of ways.Recent developments have led to the creation of numerous kinds of micro balloons (including muco-adhesive, floating, Magnetic, double-walled, and radioactive) to fulfill various Objectives. For instance, muco-adhesive or floating micro balloons have been created as delivery methods that are gastro retentive. (28)

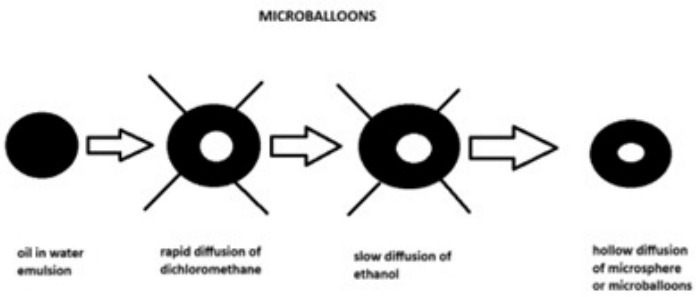

Fig 4. Microballoons

The goal of recent advancements in novel drug delivery technologies is to increase the safety and efficacy of therapeutic molecular by developing a dosage form that is simple to administer. Floating micro balloons are a gastro-retentive by a non-effervescent technique.

Techniques for drug delivery:

Floating drug delivery systems (FDDS) or hydrodynamically balanced systems (HBS) can float in the stomach for a long period of time without reducing the stomach's emptying rate because their bulk density is lower than that of gastric fluids the addition to extending the duration of gastric retention, floating micro balloons control the stomach's volume by maintaining the delivery System that delivers the medication efficiently and in a stable location.(29,30,31,32)

The bulk density of hydrodynamically balanced or floating drug delivery systems is lower than that of gastric fluids, so stay afloat in the stomach for a long time without influencing

the rate at which the stomach empties. The stomach's drug-remaining systems are emptied gradually at the desired rate. This leads to a rise in the improved qualification control in plasma drug concentration and gastric residence time. (33)

Micro balloons are occasionally called microparticles. A variety of synthetic and natural materials can be used to create microspheres. Commercially available types of microspheres include glass, polymers, ceramic, both solid and hollow because of their wide density range, micro balloons are employed in a variety of ways. Usually, hollow microspheres are employed as additives to reduce a material's density. (34)

When micro balloons come in contact with gastric fluid, the gel-forming agents, polysaccharides, and polymers absorb water and form a colloidal gel barrier. This barrier controls the penetration of fluid into the system, ensuring a controlled and sustained release of the drug. Continuous hydration maintains the gel layer on the surface, while the air trapped within the swollen polymers decreases the density of the microballoons, allowing them to float on the gastric fluid and remain buoyant for an extended period.(35,36)

Advantages of Hollow micro balloons:

a. A higher level of bioavailability.

b. Improved biotransformation at first pass.

c. Long-term medication administration and decreased incidence of the dosage.

d.Targeted treatment for regional conditions in the upper GIT.

e. Less variation in drug concentration.Increased bioavailability as a result of improved medication use.

f. A decrease in the frequency or severity of adverse effects as a result of preventing variations in the drug's plasma concentration.

g. Constant drug release to maintain a desirable plasma drug concentration.

h. By increasing gastric retention time due to buoyancy, hollow micro ballons are used to reduce material density.

i. Increased absorption of drugs that only dissolve in the stomach.

j. Release the drug in a controlled manner over an extended period of time.

k. It is possible to achieve site-specific drug delivery to the stomach(37,38,39)

Disadvantages of Hollow micro balloons:

a. These systems necessitate a significant amount of fluid in the drug delivery stomach that floats and functions effectively.

b. Not suitable for drugs that have solubility or gastrointestinal tract instability issue.

c. Medication like nifedipine, which is readily absorbed throughout the gastrointestinal tract , which goes through the first pass metabolism. It's possible that metabolism is undesirable.

d. A number of factors, including food and the rate of transit through the gut can affect the controlled release dosage form's release rate.

e. Variations in the rate of release between doses and because controlled release formulations typically have higher loads, any compromise in the release characteristics of the dosage form could potentially be toxic.Drugs that irritate or harm the stomach mucosa should not be used as floating drug delivery systems.

f. Doses of this type should not be crushed or chewed.[37,38,39,40,)

Mechanism of floating micro balloons;

When the polymers and polysaccharides used to make floating microspheres come into contact with stomach fluid, they hydrate and form a colloidal gel barrier. The rate at which fluid enters the floating micro balloons is regulated by the colloidal gel barrier, which affects the rate of drug release. When the outer surface of the micro balloon dissolves, the hydrocolloid layer is preserved, keeping the surrounding layer moist. Because the air has been trapped by the expanded polymers, the floating micro balloons density has decreased, allowing them to float above the stomach fluid. For buoyancy to be optimal, the least amount of stomach fluid as shown in Fig 5.(41,42,43)

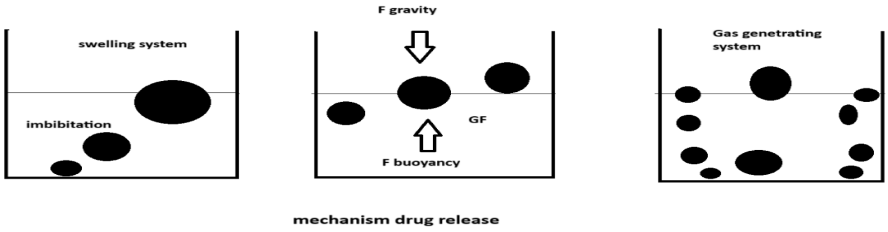

Fig 5. Mechanism of drug release in micro balloons

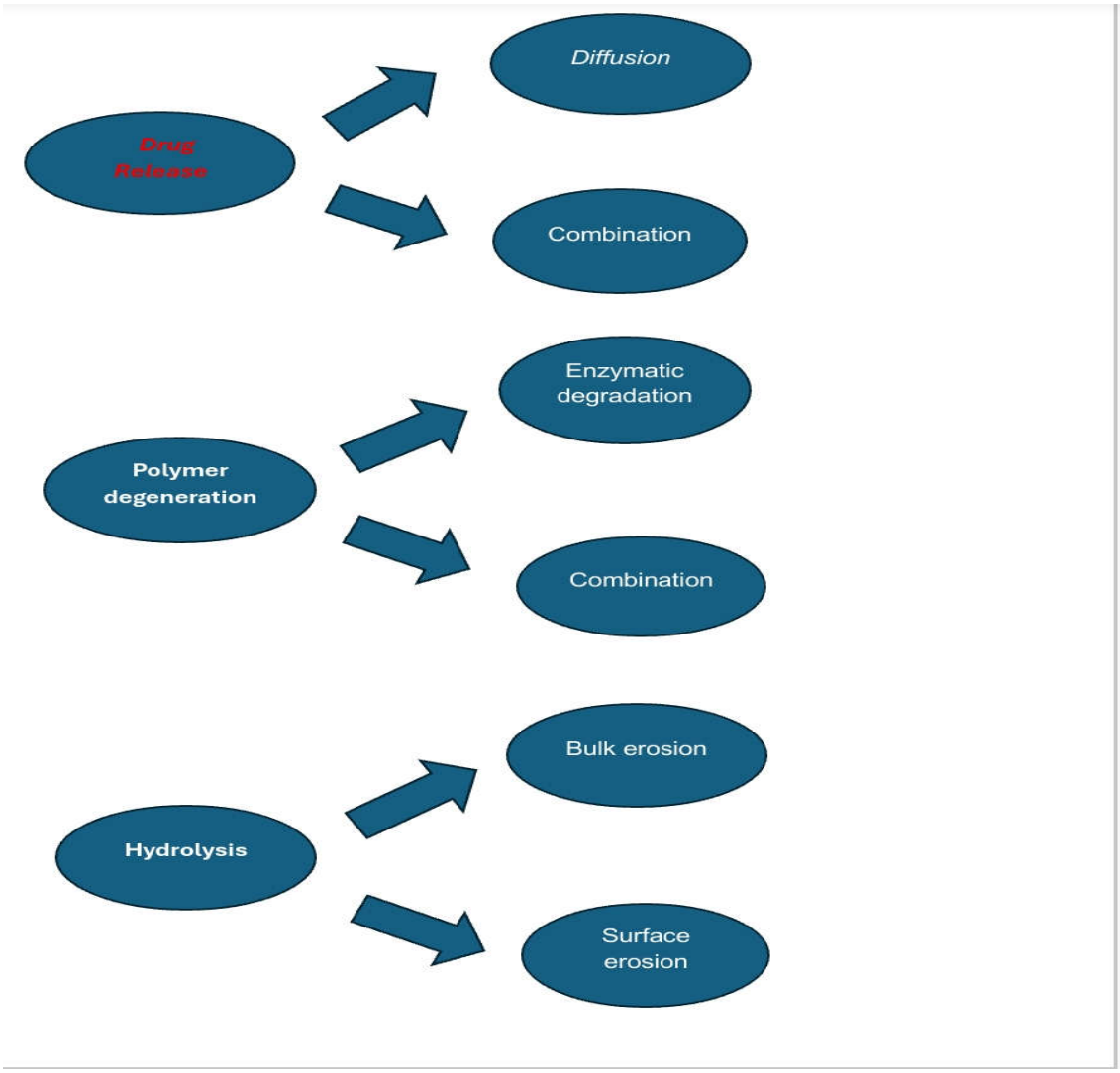

Fig 6. Flow chart of mechanism of drug release.

✓ Diffusion:

Gastric fluid entered the floating micro balloons interior, where it was dissolved and gradually released into the external media through a diffusion mechanism, initiating the drugs' diffusion as shown in Fig 7.(44)

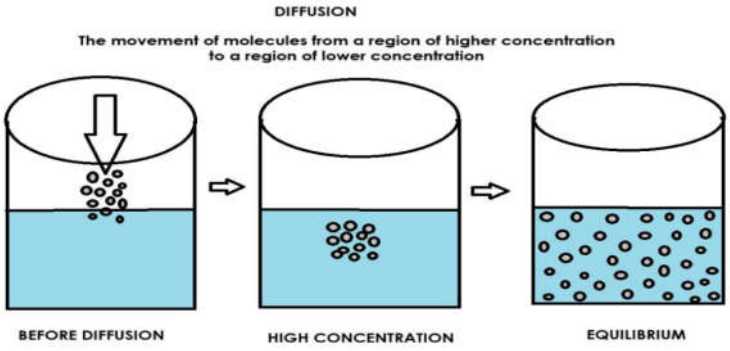

Fig 7. Diffusion mechanism

✓ Erosion:

The medicate particle may be released as a result of the slow degradation of some of the coverings used to prepare the floating microballoons.(45)

✓ Osmosis:

Osmotic pressure can be produced when water enters the delivery system in the right state. This osmotic pressure pushes the drug into the external medium(46)

The gel formers, polysaccharides, and polymers in floating microballoons hydrate and create a colloidal gel barrier when stomach fluid comes into contact with them. This barrier regulates the fluid flow into the device and in turn the release of medications. The gel layer is preserved by hydrating the nearby hydrocolloid layer as the dosage form's outer surface dissolves. The inflated polymer gives the micro balloons buoyancy and reduces density by trapping air. None the less, buoyancy can be attained with a minimal amount of stomach content. (41)

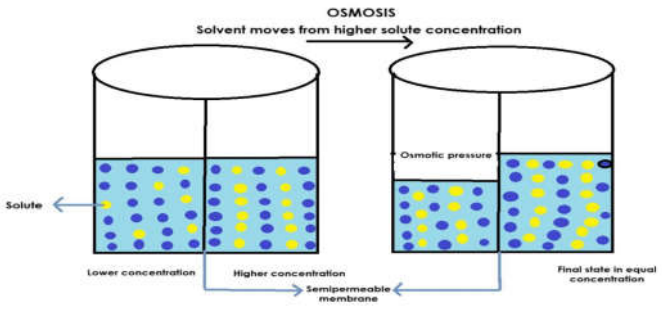

Fig 8. Mechanism of osmosis

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM:

To create FDDS based on the buoyancy mechanism, two very different technologies non-effervescent and effervescent systems have been used:

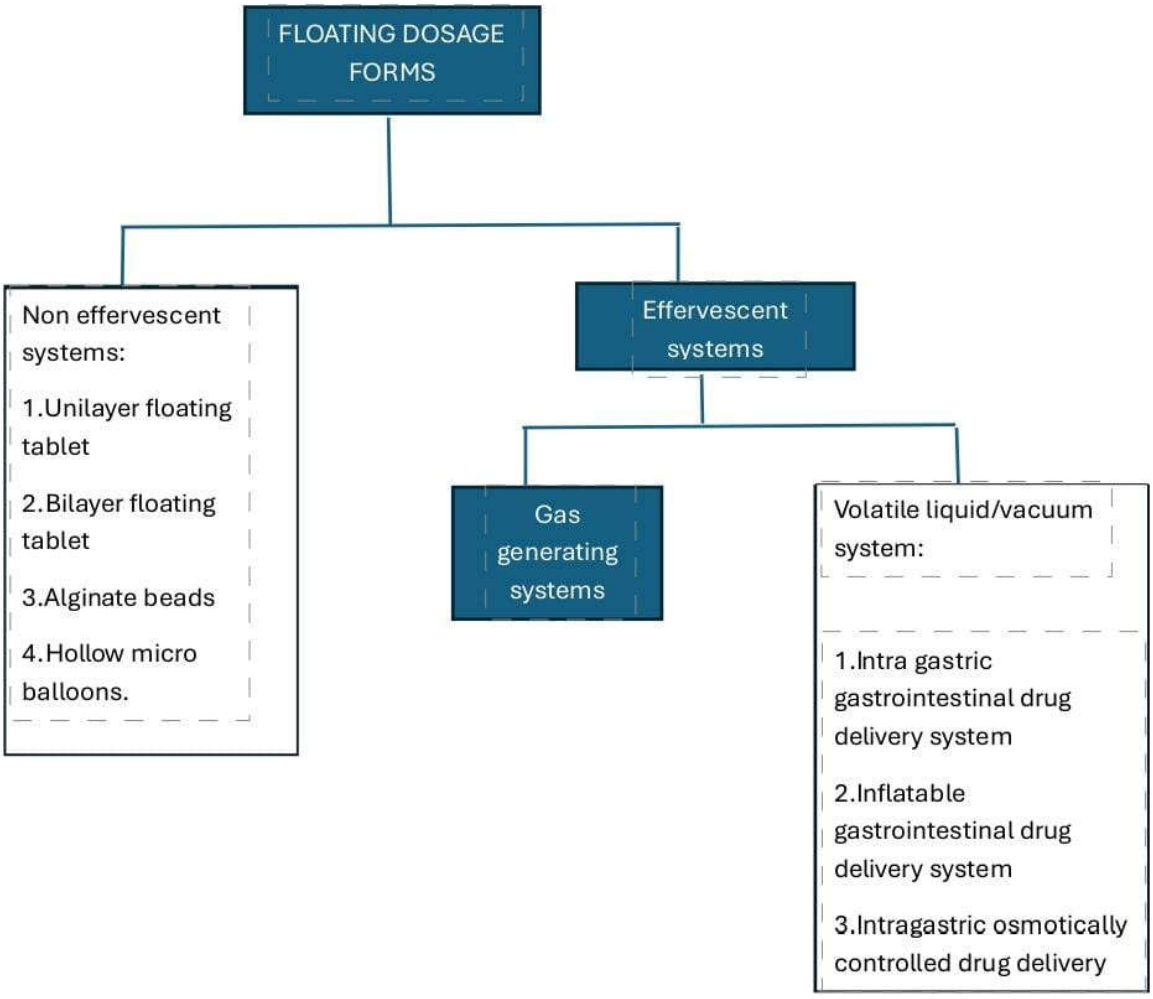

Fig 9. Classification of floating dosage forms.

1)Non effervescent floating drug delivery system:

The floating drug delivery system in this class are usually composed of matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate, hydrocolloids of the cellulose type that gel or polysaccharides. As the medication in the dosage form dissolves

inside and diffuses out of the gel structure, the diffusing solvent forms a “receding boundary.” (47,48).

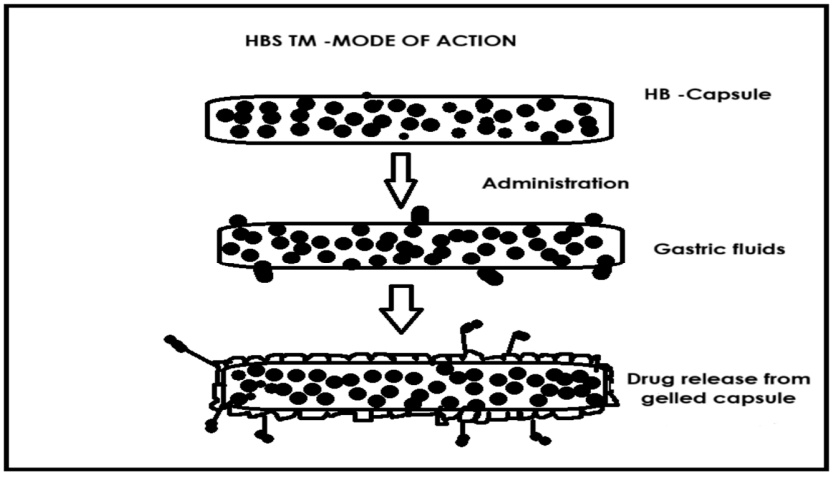

Fig 10. Non -effervescent floating drug delivery system

These dosage forms employ hydrocolloids of gel-forming swellable cellulose type. The drug gel-hydrocolloids, colloid are combined to create the formulation. When the dosage form is taken orally, it expands when it Comes into contact with stomach contents and achieves a bulk density of less than one.(49)

- Floating tablets with a single layer:

They are made by thoroughly mixing the drug with a hydrocolloid that reacts with stomach contents to keep its bulk density below unity and gels.

Fig 11. Single layer Floating tablets

- The Bi-layer Tablet:

A bi-layer tablet’s immediate-release layer removes the initial dosage from the body when the stomach juices are absorbed by the maintained-release layer, its surface develops a colloidal

gel barrier that is resistant to stomach juices. When combined, these layers preserve a bilayer. By keeping the bulk density below unity, the tablet remains buoyant in the stomach.

Fig 12. Bilayer tablet

- Alginate beads:

When calcium alginate precipitates, a porous system is created that can sustain a floating force for over 12 hours. When calcium chloride aqueous solution is mixed with sodium alginate solution, spherical beads with a diameter of about2.5 mm.

Fig 13. Alginate beads

- Hollow micro balloons:

A medication was placed within the hollow micro balloons that were made using a unique emulsion-solvent diffusion process. For more than 12 hours in vitro, the micro balloons floated continuously over the surfactant-containing acidic Dissolution medium.[50]

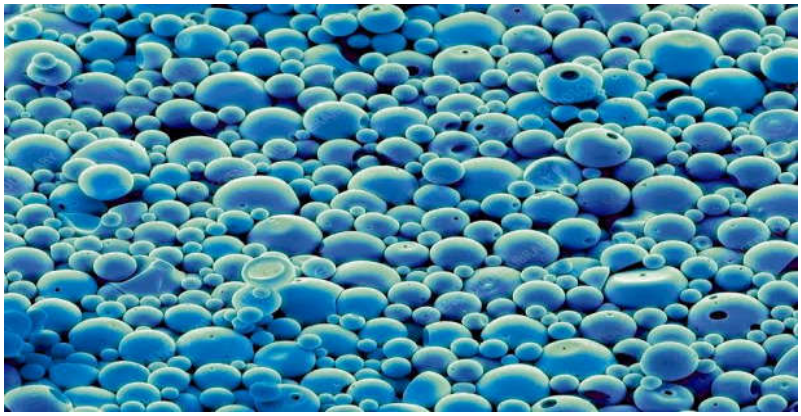

Fig 14. Hollow micro ballons

2) Effervescent floating drug delivery system;

Either matrices with liquid chambers that gasify at body temperature or matrices were used in the buoyant delivery method. Composed of swells polymers like effervescent substances like citric acid, tartaric acid, or sodium bicarbonate. These effervescent systems fall into two additional categories. [51]

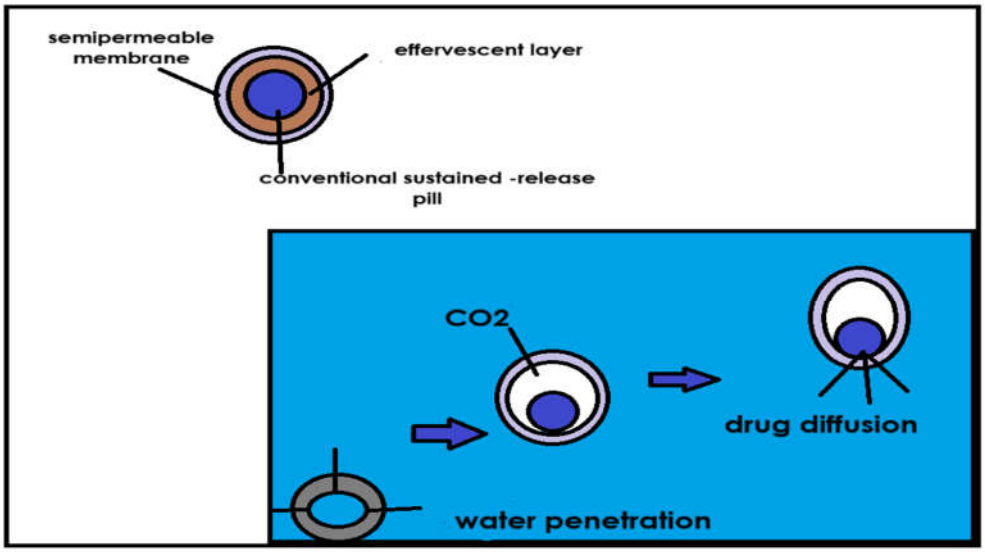

Fig 15. Effervescent floating drug delivery system

Compounds such as calcium carbonate, sodium carbonate, citric acid, tartaric acid, and swellable substances like Polymers derived from methyl cellulose, HPMC, and chitosan. They are forced to release CO2 when they come into contact with it. The enlarged hydrocolloids create dosage forms like famotidine and amlodipine by trapping the stomach's acidic contents.[45,52]

TYPES:

A. Floating microballoons -Gas Generating systems.

B. Floating microballoons-Volatile Liquid/Vacuum Containing Systems.

A) **Floating microballoons-Gas Generating systems**:

- Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS) in floating system:

The drug and CO2 generators in the matrix tablet are thoroughly combined to create the mechanism that may floats and releases.

Releases the medication at the appropriate site, and the remaining system is expelled from the stomach once it has been released completely. As a result, gastric residence rises, and changes in plasma drug concentration are better managed.

- Intra Gastric Bi-layer Floating Tablets in floating system:

These are also compressed tablet and containing two layers. They are Immediate release layer and Sustained release layer.

B) Floating microballoons -Volatile Liquid/Vacuum Containing Systems:

- Intra-gastric Floating Gastrointestinal Drug Delivery System.
- Inflatable Gastrointestinal Delivery System.
- Intra-gastric osmotically Controlled Drug Delivery System.

- Intra-gastric Floating Gastrointestinal Drug Delivery System:

This device consist of flotation chamber, which can be filled with air, safe gas, or a vacuum. The drug reservoir is located inside a microporous chamber.

- Inflatable Gastrointestinal Delivery System:

These devices use an inflatable chamber to heat liquid ether to body temperature, which causes it to expand and gasify inside the stomach.

- Intra-gastric osmotically Controlled Drug Delivery System:

It includes an inflatable floating support, a biodegradable drug delivery system, and an osmotic pressure-controlled device.

The osmotic pressure controlled drug delivery system's osmotically active and drug reservoir compartments. (53,54)

Applications of Floating Microballoons:

1)Long-Term Drug Administration:

- These systems have the ability to stay in the stomach for extended periods of time, allowing the drug to be released gradually. These systems can therefore solve the issue of a short gastric residence time that arises with an oral formulation.
- These systems can float on the contents of the stomach because their density is less than <1,1f<1. It is prohibited for these systems to pass from the pyloric opening due to their relatively large size.

2)Enhancement of absorption:

- Drugs that are insoluble or sparingly soluble can be delivered particularly well by floating micro balloons and it is recognized.
- When a drug becomes less soluble, less time is available for drug dissolution and as a result, the transit time becomes an important element influencing the absorption of drugs.
- Because hollow micro balloons confine weakly basic medications to the stomach, they may prevent the possibility that the solubility will become the rate-limiting step in release for these medications, which are poorly soluble at an alkaline pH, as transporters for instance, drugs. So they are called absorption windows can be transported by the floating micro balloons.
- Sulfonamides, quinoline, penicillin, cephalosporin, amino glycosides, and other antiviral, antifungal, and antibiotic agents tetracycline are only absorbed from a limited number of specific gastrointestinal mucosal sites.

3)Benefits of pharmacokinetics and prospects for the future:

- As numerous recent publications have demonstrated the potential benefits of sustained release systems and floating dosage forms.
- It is possible to effectively administer medications with low bioavailability since their absorption is limited to the upper gastrointestinal tract.
- Increasing their absolute bioavailability and optimizing their absorption(55)
- When it comes to gastro retentive drug delivery, micro balloons are particularly useful because they provide prolonged and the stomach's localized drug release. They enhance the management of stomach disorders like infections (e.g., H. pylori) and ulcers.
- By improving the absorption and solubility of drugs. They help sustain therapeutic levels by extending gastric transit, which is especially useful for poorly soluble and weakly basic medications.

- The micro balloons reduce side effects and steady therapeutic improve.
- They improve bioavailability through targeted drug release to the stomach and enhanced solubility. The focused delivery lessens gastrointestinal distress and enhances the effectiveness of treatment.
- By lowering the frequency of doses, the formulation also promotes improved patient compliance. Difficulties include making sure that drug release rates are precisely controlled, scalable, and stable.[55,56,57,58,59]

Methods of Developing Floating Drug Delivery System: (2,47,60,61,62)

(1) Direct compression technique:

This method involves compressing tablets straight from the powder without changing the physical structure of the material. The most common carriers are tricalcium phosphate, dicalcium trihydrate phosphate, etc.

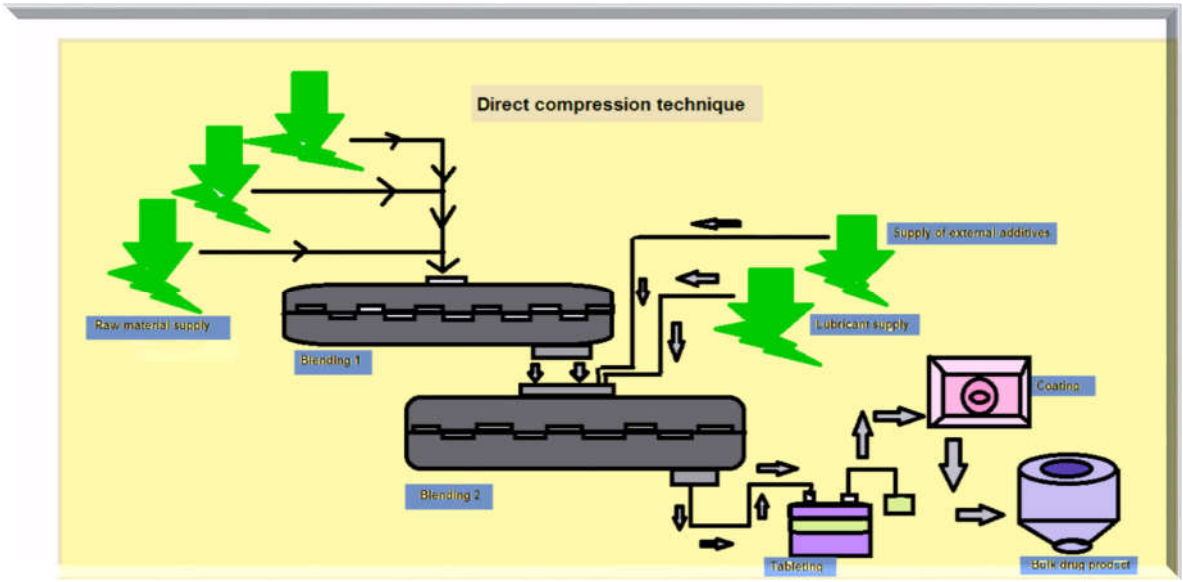

Fig 16. Direct compression technique

2) Effervescent Technique:

The medication delivery system's floating chamber will be filled with inert gas (CO2) due to an effervescent interaction between organic acid (citric acid) and bicarbonate salts. The purpose of effervescent tablets is to create solutions that simultaneously release carbon dioxide. These tablets are typically made by compressing the active components with a solution of organic acids like tartaric and citric acid and sodium bicarbonate.

3) Wet granulation technique:

In wet granulation, a mixture of dry primary powder particles is massed using a granulating fluid. The fluid contains a solvent that should not be poisonous and can be eliminated by drying. Methylene chloride, ethanol, isopropanol, and water are common solvents,

either by themselves or in combination. Wet powder is massed, ground, or dried. Instead of compacting the powders, wet granulation uses an adhesive to bind them together, forming the granules.

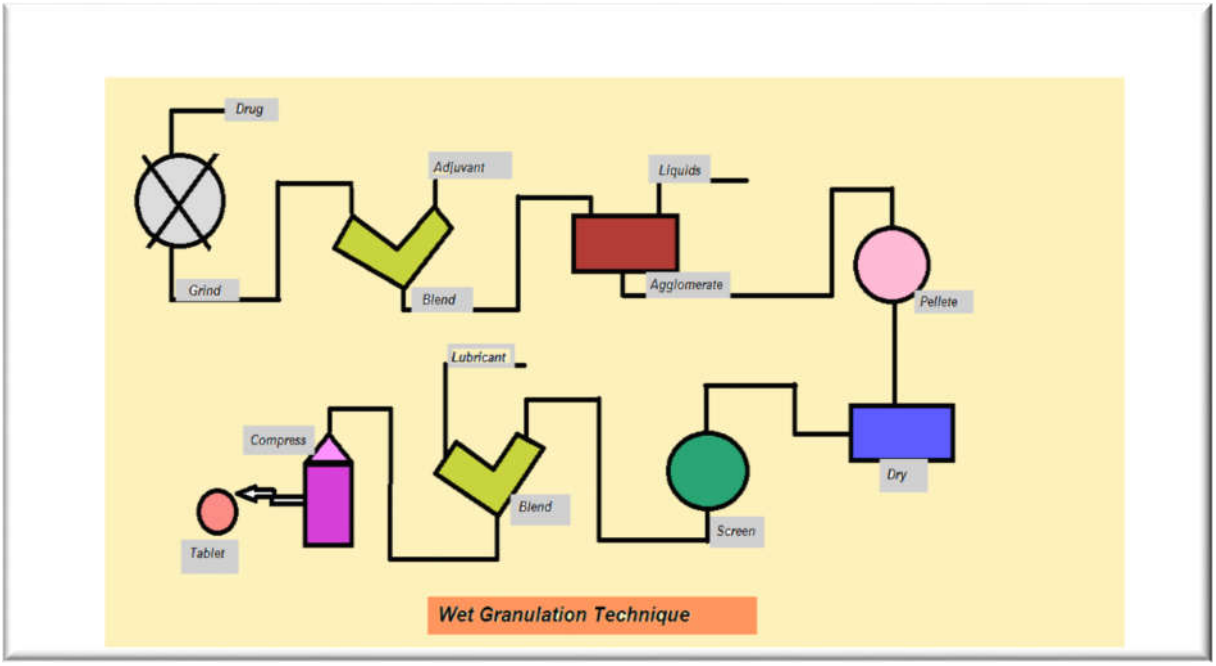

Fig 17. Wet granulation technique

4) Melt Solidification Technique:

This method is characterized by the absence of relative motion between neighbouring polymer layers, as in the case of extrudate cooling and flow solidification, in which the melt and solidifies, during shear flow in the filling stage of injection molding. This process entails cooling the molten mass to solidify after emulsifying it in the aqueous phase. The carriers utilized in this method include lipids, waxes, polyethylene glycol, etc.

5) Melt granulation Technique:

This is also known as thermoplastic granulation, is a process that uses meltable binders that melt or soften at relatively low temperatures (50–90 °C) to help agglomerate powder particles. Granulation is finished when the agglomerated powder cools and the molten or softened binder solidifies as a result. Low melting binders can be incorporated into the granulation process in two different ways: either as solid particles that melt during the process (melt-in procedure or in situ melt granulation) or as molten liquid that may or may not contain the dispersed drug (spray-on or pump-on procedure), which offers a range of options to design the final granular properties.

More precisely, heating a mixture of medication, binder, and other excipients to a temperature within or above the binder's melting range is part of the melt-in step of the melt granulation process. Conversely, the spray-on method involves spraying the heated granules with a molten binder that may or may not contain the medication.
This process is defined as a physicochemical approach of stiffening microdroplets by chelating p olyelectrolyte with polyvalent ions.(61)

6) Method for Solvent Evaporation:

To create a homogeneous solution, the medicine is added to the polymer solution after it has been dissolved in an appropriate solvent. The homogenous solution is poured into liquid paraffin at 1500 rpm and 35°C for three hours, creating an emulsion. Once a stable emulsion has been created, the solvent is removed from the mixture. Microspheres crystallized as a result of evaporation and were filtered using Whatman filter paper [63].

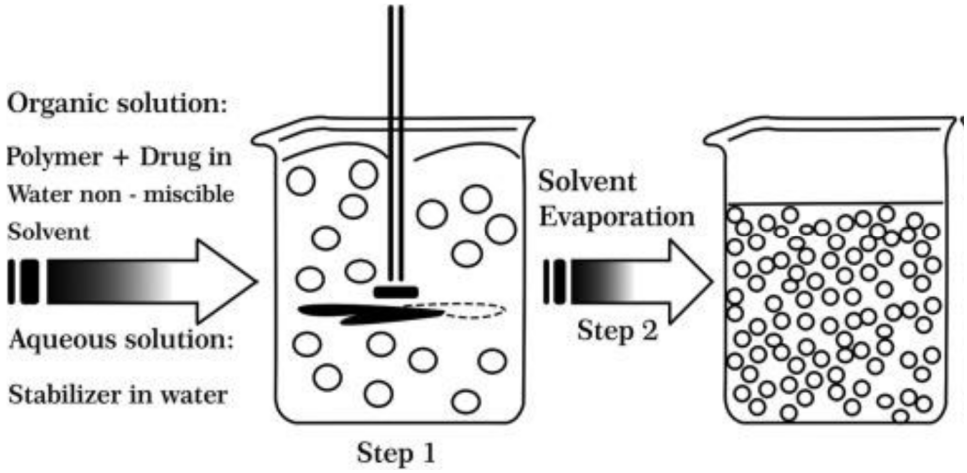

Fig. 18 Method for Solvent Evaporation (64)

The solvent evaporation process takes place during the liquid production vehicle phase. The volatile solvent used to spread the microcapsule coating and the liquid production vehicle phase are incompatible. A core component that will be microencapsulated is dissolved or dispersed in the coated polymer solution. During the liquid manufacturing vehicle phase, the core material combination is agitatedly distributed to produce the appropriate-sized microcapsule. (65)

7. Emulsion Solvent Diffusion Method:

The aqueous poly vinyl solution is mixed with the polymer mixture after it has been dissolved in an organic solvent. The solution is agitated at 1500 rpm for an hour at various temperature ranges.(56)

This method involves combining an agitated aqueous polyvinyl alcohol solution with a polymer and medicine solution in ethanol and methylene chloride. The ethanol quickly changes

into the outer aqueous phase while the polymer envelops the methylene chloride droplets. The entrapped methylene chloride then evaporates, creating internal holes inside the micro particles. (66)

8. Ionic gelation method:

In order to produce a homogenous polymer mixture, a cross-linking agent, polymer, and copolymer were combined with filtered water. The drug was added to the polymer dispersion and forcefully spin using a magnetic stirrer to produce a homogenous dispersion. The gelation medium was made by dissolving calcium chloride in two percent glacial acetic acid. The uniform alginate solution was extruded into the gelation media using a syringe needle. Following collection, the microsphere was cleaned twice with distilled water and allowed to dry for a full day at room temperature. (67)

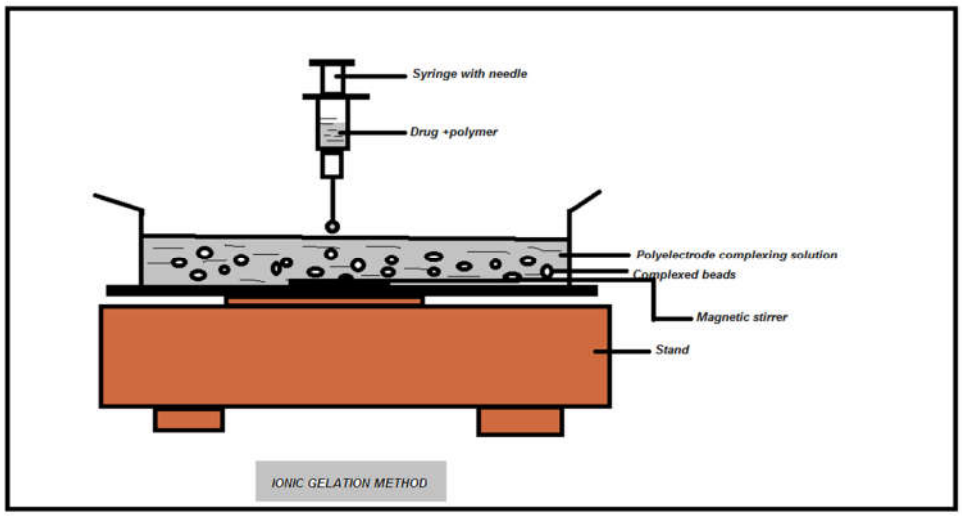

Fig 19. Ionic gelation method

9. Method of emulsion solvent evaporation (68,69,70):

After dissolving the medication in chloroform and polymer, the resultant solution is added to an aqueous phase that contains 0.2% sodium of PVP as an emulsifier. After stirring this mixture at 500 rpm, the medication and polymer (Eudragit) created fine droplets that hardened into rigid micro balloons due to solvent evaporation. These droplets were then collected by filtering, cleaned with demineralized water, and allowed to desiccate for 24 hours at room temperature. Oil-in-water (o/w) and water-in-oil (w/o) systems are the two main systems for these methods.

10. Method of oil in water solvent evaporation (68,69,70):

In this method, the polymer needs a water-immiscible solvent, and both the medication and the polymer should be insoluble in water. Organic solvents like dichloromethane, methanol, and chloroform are used to dissolve the polymer. To create an oil-in-water emulsion, the medication is either dissolved or distributed into a polymer solution, which is then emulsified into an aqueous phase using an emulsifying agent. Filtration is then used to separate the microparticles once the organic solvent has been decanted.

11.The solvent evaporation method for water-in-oil emulsification (68,69,70):

Non-aqueous emulsification solvent evaporation is another name for this water-in-oil emulsification method. To create a homogeneous drug-polymer dispersion, the drug and polymers are co-dissolved at room temperature while being vigorously stirred. This combination is added to the dispersion medium, which is made up of light and heavy liquid paraffin with an oil-soluble surfactant like Span. To guarantee full solvent evaporation, this mixture is then agitated for two to three hours at 500 rpm using a propeller agitator. After decanting the liquid layer, the micro balloons are filtered using Whitman filter paper, cleaned with n-hexane, dried for a whole day, and then stored in desiccators.

12.Polymerisation (68,69,70):

It is a conventional polymerization methods, which are primarily divided into two categories:

a. Normal polymerization:

This type of polymerization uses a variety of methods, including bulk, suspension, precipitation, emulsion, and micellar polymerization procedures.

b. Interfacial polymerization:

In this method, a variety of monomers react at the interface between two immiscible liquid phases to create a polymer layer that basically envelops the dispersed

13.Spray drying method and spray congealing: (71,72)

While the polymer solution is being rapidly homogenized, the drug is added. Tiny droplets or fine mist are produced when upward dispersion in a heated air stream atomizes. Microspheres ranging in size from 1 to 100 μm are produced by rapid solvent evaporation. The microspheres are extracted from the hot air using a cyclone separator. One major advantage of this technique is its capacity to function in aseptic conditions, which leads to the rapid and porous production of microparticles that can be used for poorly soluble drugs.

- ✓ Spray drying:

Coating solidification can be achieved by quickly evaporating the solvent that dissolves the coating substance.

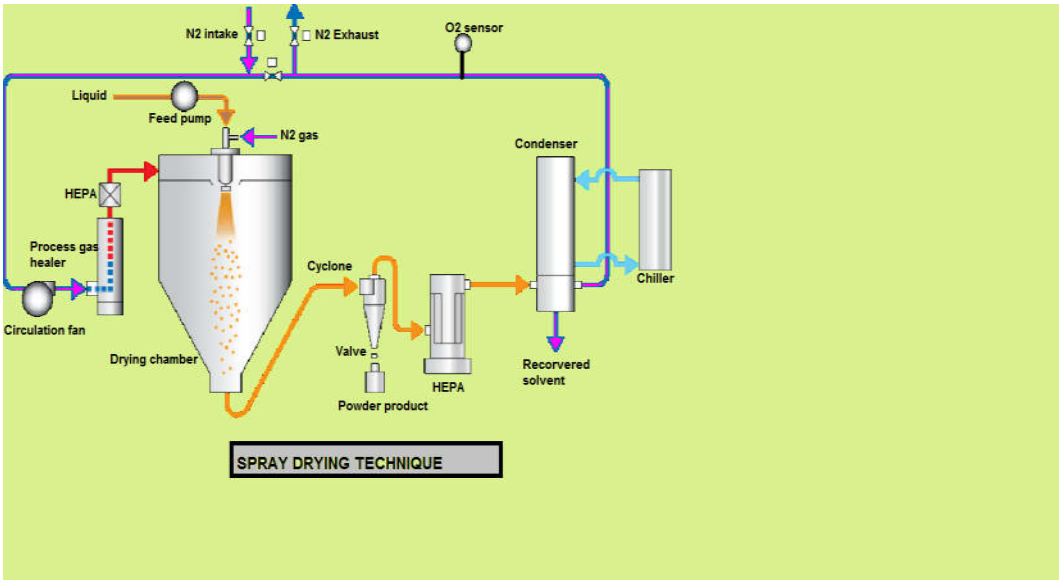

Fig 20. Spray drying

✓ Spray congealing:

A liquid coating substance can be thermally congealed to solidify the coating. Sorption, extraction, or evaporation are the methods used to remove solvent.

14.Technique for coacervation phase separation (73):

The following are this procedure's main steps:

Step 1: The core material is dispersed using a coating polymer solution.

Step 2: The coating is accomplished in the liquid manufacturing vehicle phase by properly mixing the core material and coating solution.

Step 3: Solidify the covered polymer using the following methods.

❖ Thermal Shift:

The polymer is dissolved in cyclohexane by aggressively stirring it at 80 ºC. Then, while continuously stirring, the medication is added to the previously mentioned solution. The microsphere is created by lowering the temperature in an ice bath. The product is left to air dry after being washed twice with cyclohexane.

❖ Non-Solvent Contribution:

After the polymer has been dissolved in toluene and propyl isobutylene for six hours at 500 rpm, the medication is first dispersed across a closed beaker. The resultant solution is added to benzene while being constantly stirred. The microcapsules are washed with n-hexane and then let to air dry for two hours.

➢ **Addition of polymer**

After the polymer (ethyl cellulose) is dissolved in toluene to form microspheres, methylene blue is employed as a core material. Coacervation is achieved by adding liquid

polybutadiene. To solidify the polymer coating, hexane is used as a nonsolvent. The finished product is then cleaned and given time to air dry.

- **Adding salt**

The oil-soluble vitamin is dissolved in corn oil and then added to the gelatin solution at 50ºC. When sodium sulphate is added, coacervation occurs, giving the gelatin a uniform covering. The microspheres are collected, washed, chilled, and then dried.

15.The single emulsion method:

This technology makes microparticle carriers for natural polymers like proteins and carbohydrates utilizing a single emulsion approach. The natural polymers are spread in a non-aqueous media, such oil, after being dissolved or dispersed in an aqueous medium with the aid of a cross-linking agent. (74)

16.Double emulsion method:

Water soluble drugs (such as proteins and peptides) work best with this strategy. Drug-containing emulsifiers are dissolved in an aqueous protein solution. To generate a primary o/w emulsion, this solution is combined with the lipophilic organic phase, which acts as a dispersion phase. An aqueous polyvinyl alcohol solution is added to the primary emulsion to homogenize it and create the double emulsion. When the polyvinyl alcohol solution evaporates, microspheres are formed. (75)

17.Solvent Diffusion-Evaporation Technique:

The solvent diffusion-evaporation method is a mild modification of the emulsion solvent evaporation method and the emulsion solvent diffusion method. The medication, polymer, and surfactant are combined in organic solvents at room temperature. After that, this combination is gradually added to the poly vinyl alcohol solution while being stirred for an hour using a propeller agitator. After evaporating the organic solvent, it is filtered [76].

FACTORS AFFECTING MICRO BALLOONS:

A variety of factors influence an oral dosage form's gastric residence time. The stomach's pH ranges from about 1.5 to 2.0 when fasting and from 2.0 to 6.0 when eaten. The viscosity, volume, and calorie content of meals are the primary factors influencing the rate of stomach emptying. Compared to men, women's stomach emptying rates are slower. Stress slows down the rate at which the Stomach empties.

A. Factors affecting the gastric retention :

1.Factors relating to dosage form:

- Density:

- ✓ A dosage form's buoyancy and floating efficiency are largely determined by its density.(77)
- ✓ The dosage form's density (1.004 g/ml) should be lower than the stomach contents.
- ✓ A density of less than 1.0 gm/cm3 is necessary to demonstrate the floating feature.
- ✓ The tendency of the dosage form to float, as the dosage form is submerged in the fluid and hydrodynamic equilibrium develops, it typically diminishes over time (78).

- ➢ Size of the dose form:

- ✓ It seems that gastric retention is significantly influenced by the dosage form's size.(79)
- ✓ According to analytical reports, dosage form units with a diameter more than 7.5 mm had a higher GRT than these with a diameter 9.9 mm. The size of non floating dose forms, which might be big, medium, or small units, has a significant impact on their GRT.(80)

- ➢ Shapes:

- ✓ The floating potential of tetrahedron and ring-shaped gadgets is greater than that of other designs. Their 24-hour retention rate is between 90 and 98 percent greater.(81,82,83,84,85,86)
- ✓ Tetrahedron and ring-shaped devices with a flexi elastic modulus of 48 and 22.5 kilo pounds per square inch are said to perform well.(87)

- ➢ Single or multiple unit formulation:

- ✓ When compare to single unit dosage forms, multiple unit formulations offer a greater margin of safety against dosage form failure.
- ✓ A more consistent release profile is seen in multiple unit formulations. (76)

2. Food consumption and its nature:

The Gastric residence time of the dosage form is affected by whether food is in the gastrointestinal tract or not. Increases in acidity and caloric value shorten the time it takes for the stomach to empty and enhance the retention of dosage forms. (88)

- ➢ Frequency of feed:
  The frequency of migrating myoelectric complex (MMC) is low, and the stomach retention period can increase by more than 400 minutes when multiple meals are administered as opposed to a single meal. (89,90,91)
- ➢ Nature of meal:
  Feeding indigestible polymers or fatty acid salts can alter stomach motility, leading to Slower gastric emptying and longer medication release. (92)
- ➢ Caloric content:
  GRT can be boosted in 4 to 10 hours by eating a high-protein and fat diet. (2,93)
- ➢ Fed and unfed states:

Periods of migrating motor complex (MMC) activity that take place every 1.5–2 hours are indicative of GI motility. The Migrating Motor Complex removes the stomach's undigested contents. Gastric retention time is significantly longer and Migrating Motor Complex is delayed in the fed condition. (76)

The Migrating Motor Complex removes undigested material from the stomach, and if the formulation's administration time coincides with the Migrating Motor Complex's, the Gastric Retention Time of the unit should be quite short.(2,93)

C. Idiosyncratic factors:

- ✓ Age:
  - Gastric retention duration was much longer in senior patients above the age of 70.(89,90,91)
- ✓ Gender:
  - Regardless of weight, height, or body surface, males' mean ambulatory Gastric Retention Time (3.4–0.6 hours) is lower than that of their age and race-matched female counterparts (4.6–1.2 hours).(94)Compared to men, women empty their stomachs more slowly.(95)
- ✓ Posture:
  - There are significant differences in floating between the patient's supine and upright ambulatory phases.(76)
- ✓ Upright Position:
  - Regardless of the dimensions of the floating form, a standing position keeps it above the stomach contents, protecting it from postprandial emptying.
- ✓ Supine Position:
  - Long-term retention of big, both conventional and floating, occurs in supine subjects. The peristaltic motions that push the stomach contents toward the pylorus may sweep these units away, resulting in a marked decrease in Gastric Retention Time when compared to upright participants.(96)
- ✓ Concomitant Intake of Drugs:

Pro kinetic agents (like metoclopramide and cisapride), anticholinergics (like atropine or propantheline), and opiates (like codeine) can all have an impact on how well gastro retentive drug delivery systems works. Gastric emptying time may be prolonged when gastrointestinal motility reducing medications are used together. (97)

D. Biological factors:

Gastroenteritis, gastric ulcers, pyloric stenosis, diabetes, and hypothyroidism all slow down gastric emptying. Gastrectomy, duodenal ulcers, and hypothyroidism all increase stomach emptying rate.

B. Factors that influence formulation:

1.Addition of polymer solution:

Water's high surface tension produced solidification and aggregation of polymers on the aqueous phase's surface. To reduce polymer solution contact with the air-water interface and to design a continuous process for manufacturing microspheres, a new method of delivering the polymer solution into the aqueous phase was devised. This method increased microsphere yield while reducing aggregate formation to a minimum. (66)

Effects of rotation speed: Rotation speed has an obvious effect on the production and size distribution of microspheres. As the rotation speed of the propeller increases, the average particle size falls while the shape remains unchanged. (98)

2.Effects of temperature:

The temperature of the dispersing media is a crucial component in the creation of microspheres because it influences the rate at which solvents evaporate. At lower temperatures (10 degree celsius), prepared microspheres have a crushed and unevenly shaped morphology. At higher temperatures (40 degree Celsius), the microsphere's shell thins, possibly due to quicker diffusion of alcohol in the droplet into the aqueous phase and evaporation of dichloromethane shortly after introduction into the medium. (66)

C. Factors affecting Physicochemical properties of Micro balloons:

1. Stirring rate:

The size of microspheres varies with the rate of churning. The size of the microspheres decreases with increased agitation, although the rise is not statistically significant. (99)

2. Amount of polymer and viscosity:

Smaller micro balloons were created at lower polymer concentrations, and they are exposed to more surface area, which will result in quicker drug release. (100)

3. Plasticizers:

The formulation gains elasticity and flexibility by adding plasticizers to the material's walls. The use of plasticizers avoids rupturing under pressure or brittleness. Drug release increases as the concentration of the plasticizer increases.(101)

4. Effects of solvent:

Dichloromethane is an excellent solvent for polymers and medications, it is chosen as the solvent for the creation of micro balloons.(102)

EVALUATION PARAMETERS:

- **Particles size**

Understanding the size and dispersion of the particles is essential because they affect buoyancy, stability, and the rate of medicine release. (103)

The size of the micro balloons may affect the particles' long-term viability. Microscopy and laser diffraction are two methods for determining the particle size distributions. (104,105)

The drug's release rate is influenced by the size of the multi particulates. The mechanism lowers the release rate as size grows because the effective surface area diminishes. The size distribution of the microspheres was investigated using optical and motic microscopy. A small number of microspheres were distributed on the slide with the use of a capillary tube. The diameters were measured using 10X and 40X, the proper objective. There were 50 particles on average for each of the variables being studied (106).

- **Size distribution of particles**

The size distribution of the generated microspheres was determined using the sieve analysis method. The geometric mean diameter logarithm, which indicates the particle size equivalent to 50% on the probability scale, was contained by plotting the particle size logarithm against the cumulative frequency percentage on a probability scale (107).

- **Density**

The mass of the powder divided by the bulk volume yields the bulk density. A precisely weighed 10-gram sample of granules was put into a 25milliliter measuring vial. The bulk density (values expressed in gm/cm3) was computed using the formula after the volume occupied by the granules was measured without disturbing the cylinders.

Bulk Density = Weight of Sample / Volume of Sample(108)

The dosage form's density should be lower than the stomach's density (1.004g/ml). A measuring cylinder is filled with one gram of weighted microspheres to determine the bulk volume. [109]

- **Evaluation in vivo (110,111,112):**

a) Radiology:

X-rays are often used to study internal body systems. Barium sulfate is a typical radiopaque marker. BaSO4 is added to the dose form and X-ray images are acquired at various intervals.

b) Scintigraphy:

Similar to X-rays, scintigraphy uses emitting chemicals in a dose form to produce images. One often utilized emission material is 99Tc.

c) Gastroscopy:
Fiber optic or video equipment is used for this kind of peroral endoscopy. A gastroscopy is used to observe the effects of stomach expansion. It can also offer a comprehensive evaluation of gastro retentive drug delivery system.

d) Magnetic Marker Monitoring in in-vivo evaluation:
This technique involves inserting iron powder into a dosage form to magnetically tag it, and extremely sensitive bio-magnetic monitoring equipment can take pictures. One benefit of this approach is that it is safe because it utilizes less radiation.

e) Ultrasonography:
It is used occasionally but infrequently since it cannot be detected at the intestinal level.

- **Tapped Density**(113)
The entire mass of the powder is divided by the tapped volume to find the tapped density.

$$Tapped\ density = Weight\ of\ powder / Tapped volume$$

- **Hausner ratio:**

The Hausner's ratio of microspheres was calculated by using the formula to compare the tapped density to the bulk density.

$$Hausner's\ Ratio = \rho\ tapped / p\ bulk\ (114).$$

- **Carr's index (%compressibility)** :

The following formula was used to get the microparticles' Carr's index value, commonly referred to as their compressibility index (C.I.).

$$\%\ compressibility = Tapped\ density - Bulk\ density\ X\ 100\ Tapped\ Density\ (115)$$

- **Swelling ratio:**

To conduct the analysis, the microspheres of known weight were soaked in 0.1 N HCl for the required duration at 37°C. The microspheres are retrieved at various intervals once they have had time to settle.

$$Swelling\ Ratio = Weight\ of\ Wet\ Formulation / Weight\ of\ Formulations\ (116)$$

- **Percentage yield** (117,118,119)

The percentage yield of floating microspheres is calculated by dividing the product's actual weight by the total quantity of all nonvolatile components used in their production.

Percentage yield= actual weight of floating micro balloons /total weight of Excipient and drugX100

- **Drug entrapment efficacy:** (120,121)

The drug concentration in floating microballoons can be estimated by dissolving the weighed quantity of crushed microspheres in the required amount of 0.1 N HCl and using the calibration curve to perform spectrophotometric analysis at a certain wavelength. For each batch, the drug composition should be examined three times. To calculate the entrapment efficiency, the theoretical drug content of floating microballoons is divided by the actual drug content.

- **Angle of repose** (122)

The angle of repose of the microballoons was measured using the funnel method. The microspheres were poured into a funnel that could be raised vertically to create the tallest feasible cone. Both the heap's radius and angle of repose were computed.

$$\tan \theta = h/r(20.$$

- **Electron scanning microscopy**(123)

Electron microscopy with scanning using an electron microscope, look at the beads' shape and surface morphology. The beads were attached to the SEM sample stub using double-sided adhesive tape, and a 200 nm-thick layer of gold was applied to the beads under low pressure (0.001 mm of Hg). A 10 KV accelerating voltage was used to view the beads.

- **In vitro Buoyancy**:(124)

According to USP I, a USP dissolving test equipment II was used to examine the floating of microspheres. Using 0.02% Tween 80 as a surfactant, 50 mg of the microspheres are dispersed over the dispersion medium as 900 ml of 0.1 N HCl. Dissolving medium was kept at 37°Celsius and stirred by a paddle that rotation speed at 100 rpm. After 12 hours, the settled and floating microspheres were gathered independently. The microspheres were weighed after being filtered and dried. The following formula was used to determine the percentage of floating microspheres.

$$Percentage\ Buoyancy = Wf / Wf + Ws$$

Where,

Wf = masses of the floating

Ws= settled microballoons

- **Buoyancy Lag time** (125):

It is the amount of time needed for gastro retentive formulations to adhere to the liquid's surface as it dissolves. A USP dissolve device and 900 mL of 0.1 N HCl solution kept at 37°C are used to set it up. The floating lag is the amount of time needed to float various dosage forms.

CONCLUSION:

In order to treat stomach disorders, micro balloons are essential. In addition to treating the gastrointestinal tract, micro balloons are also very important in treating other issues. Floating micro balloons have become a viable method for improving the controlled delivery and bioavailability of a number of medicinal substances. There are several challenges to overcome in order to achieve prolonged gastric retention, and many businesses are concentrating on commercializing this method.

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