Section A-Research paper
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An in-depth look into Floating Formulations, an Innovative Approach to Drug Delivery.

Authors: S. B. Nagansurkar*, Dr. Sanjay K. Bais, Dr. Yogesh B. Raut, Mr. Nilesh Sevak Dhavare, Mr. Ravikiran Preetam More, Miss. Pradnya Harshavardhan Gadhire, Dr. Sandip Babarao Sapkal, Mr. Sachin Hanumant Misal, Mr. Ganesh Kashinath Bahekar.

Affiliation:

1) Assistant Professor, Department of Pharmaceutics, Fabtech College of Pharmacy, Sangola, Maharashtra India. Mobile: 8668412234. Mail ID: Shirish.nagansurkar@gmail.com
2) Principal, Fabtech College of Pharmacy, Sangola, Maharashtra India.
3) Associate Professor, Department of Pharmaceutics, Fabtech College of Pharmacy, Sangola, Maharashtra India.
4) Assistant Professor, Department of Pharmaceutics, Fabtech College of Pharmacy, Sangola, Maharashtra India.
5) Assistant Professor, Department of Pharmaceutics Shri Sant Gajanan Maharaj College of Pharmacy, Buldana
6) Assistant Professor, Department of Pharmaceutics, Fabtech College of Pharmacy, Sangola, Maharashtra India.
7) Associate Professor, Department of Pharmaceutics, Shri Sant Gajanan Maharaj College of Pharmacy, Buldana
8) Assistant Professor, Department of Pharmaceutical Chemistry, Fabtech College of Pharmacy, Sangola, Maharashtra India.
9) Assistant Professor, Department of Quality Assurance, Shri Sant Gajanan Maharaj College of Pharmacy, Buldana

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ABSTRACT

The aim of developing new drug transport mechanisms is solving various flaws in traditional dosage formulations, also to resolve some concerns regarding physical and chemical properties of drug moieties & development of the formulation. The floating medicine delivery strategy is an effective technique for drugs with smaller absorption window, insoluble and slightly water-soluble pharmaceuticals, medications that are needed to be placed inside the stomach lumen as they show limited absorption from colon or degradability. Drug distribution system that floats operates underneath a drug delivery mechanism that lies in the stomach, which continuously controls the flow of drugs with limited solubility to the site of absorption. This article contains detailed information regarding floating drug administration systems, including advantages and disadvantages over conventional drug delivery systems, both of which are significant when designing dosages. This dosage form was created using a variety of methods. The effervescent floating drug delivery system's formulation and evaluation approaches were investigated. The

goal of this comprehensive study is to combine all known studies on this distribution method. We investigate the several aspects that influence stomach retention and provide useful information on the formulation aspects to achieve it.

INTRODUCTION:

The most common and practical delivery method for many medications is oral. The oral route is regarded as the best drug delivery method because it will have two key characteristics:

1) To extend the action, it should be taken in a single dose.
2) The active medication must to be being delivered right away to the intended spot.

The creation of a meticulous or continuous transport system is the result of these factors. A drug delivery method with sustained or delayed medication release is known as sustained delivery.[1,2.] The major goal of creating these systems is to increase a product's safety and lengthen its duration of action. These methods have a number of drawbacks, including dosage dumping, increased first pass impact, increased bioavailability, and longer time reaching therapeutic blood levels. These systems typically cost more than traditional systems [3.] These products may cause various people to have higher or lower steady state drug levels because they are designed for the general population rather than an individual. If a drug's therapeutic window is wide enough, there might be no issues.[4.] Despite these drawbacks, research is still being done in this field because there is still much room for improvement in the systems that are already in place.

Orally controlled medication delivery systems (OCMRDS) that stay in the stomach longer have benefits over continuous release formulations. A regulated drug delivery device delivers medicine to the upper GI tract for absorption.

Due to its convenience of delivery, low expense on therapy, patient's acceptability, & variety in delivery systems, oral route of drug administration is by far commonly utilized method of drug transportation. The time it takes for the stomach to empty is a restriction on multiple oral extended drug delivery formulations. Varying and quick gastrointestinal transit may result in insufficient release of drugs from the medical device into the intestinal absorption window which is specific for certain medicines e.g., Vit B 12, lowering the efficacy of the quantity delivered. According to present studies and patent documents, curiosity in innovative dosage formulations which can be kept inside the stomach sac for a lengthy and expectable duration. One difficulty in medication delivery is managing the emptying time of dose formulations that remain in the stomach for lengthier amount of duration than typical. Another difficulty is retaining the dose form in the correct location in the gastrointestinal tract. Various medication delivery techniques that prolong stomach retention have been studied to solve these difficulties. The goal is to create a regulated drug delivery system that reduces dosing frequency, minimizes changes in plasma drug concentration, maintaining effective drug levels for extensive amount of time [5]

DEFINITION:

Floating medicine transportation mechanisms, also known as proactively regulated systems, are lesser-density systems that can become buyout and float above gastric juices and stay floating in the place for a long duration avoiding any change on gastric emptying (Yie W. Chein et al., 1992). Increased stomach retention duration and plasma drug concentration control outcome. Grain, powder, capsule, tablet, laminated film, and hollow microsphere buoyant techniques is possible due to this.[6]

Need for the formulation:

An alternative method of transport for certain unstable medications may be provided by formulations with improved GRT, often known as a gastro retentive dosage form (GRDF).[6] The formulation is particularly effective in frugally soluble and drugs which are insoluble. As it is well known "When a drugs solubility decreases its dissolution also decreases", and hence transportation time becomes an important factor affecting absorption of that drug molecule. Erodible, gastroretentive dose forms that continuously, controllably administer sparingly soluble medicines at the absorption site have been developed to solve this problem.

Misoprostol
Acyclovir
Ciprofloxacin
Theophyllin
Diltiazem
Ranitidine

Ciprofloxacin GRDFs release medication locally, increasing gastric mucosa drug concentration. (For example, removing H. pylori bacteria from submucosa) to cure peptic and duodenal ulcer, gastric irritation, and inflammation of the esophagus, minimize chances of stomach cancer, to provide controlled release non-systemic antacids ($CaCo_3$). For absorption windows, GRDFs are excellent as medication carriers. Antibiotics, antivirals, and antifungals that can only be absorbed from a few sites inside the GI mucosa including sulfonamides, quinolones, penicillin, cephalosporins, aminoglycosides, and tetracyclines. To provide controlled release gastro-retentive dosage forms (CRGRDF), active pharmaceutical ingredients (API) with restricted intestinal absorption but enhanced absorption capabilities in the upper regions of the GIT are frequently the best options. Antimicrobial trihydrate GRDFs can be used as medication carriers due to their broad absorption windows. Antibiotics, antiviral medications, and antifungal agents such as sulfa quinolones, antibiotic penicillin, antimicrobial agents such as aminoglycosides, tetracyclines, and others are only transported from certain regions of the Gastrointestinal mucosal membrane. Molecules having poor intestinal absorption but enhanced absorption characteristics in the upper regions of the GIT are often excellent alternatives for CRGRDF. Amoxicillin, for example, disrupts the natural intestinal flora increasing chances of suprainfection.

BIOLOGICAL ASPECTS OF CRGRDFs:

Stomach Physiology:

It's a "J"-shaped structure between the oesophagus & small intestine on the left side below diaphragm, it has. “Four" sections:

The "Cardiac Sphincter" is located at the superior entrance of the heart, called "Cardia."

The upper rounded part called fundus.

Central part of the body, just below the fundus.

The pylorus is the last and lowest section of the body, divided as follows,

Pyloric Antrum

Pyloric sphincter is located in the pyloric canal.

For complex grinding activities, an extra, oblique layer of involuntary muscle has been positioned within the stomach's circular layer of smooth muscle. Otherwise, the stomach wall's physiology is quite similar to the rest of the digestive canal. Rugae are the characteristic folds that appear in the stomach's mucosa and submucosa when the stomach is not in fed state. (Fig)[7]

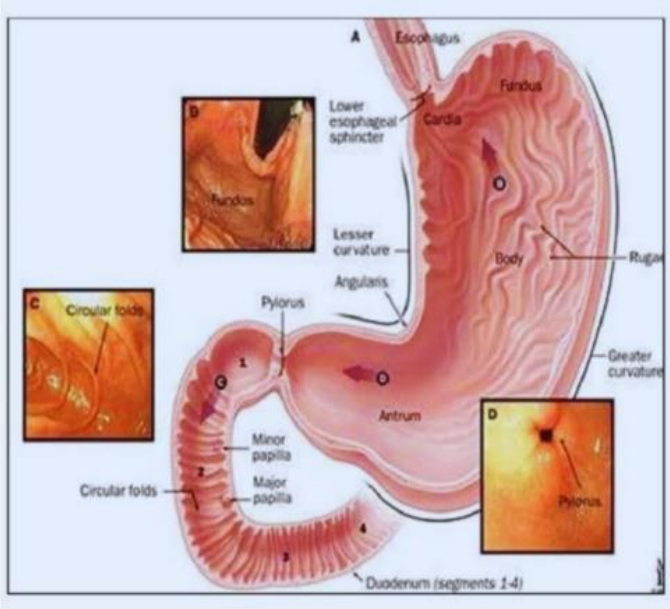

Fig:1 Physiology of stomach

The diagram depicts 4 different kinds of epithelial cells with secretary functions that cover the surface of the stomach bag:

Mucous cells: The stomachs epithelium is protected from shear stress and acid by the secretion of alkaline mucus by this gland.

Parietal cells: produce stomach acid (HCl).

Chief cells: Produce the proteolytic enzyme pepsin, which catalyses the partial digestion of ingested proteins in the stomach.

G cells: They secrete a hormone called Gastrin.

Stomach Contractions:

Chyme is created by crushing, grinding, mixing, and liquefying ingested food.

Emptying of stomach contents into small intestine is called Gastric emptying, which occurs when chyme is driven down the pyloric canal into the small intestine.

GI MOVEMENT (Gastrointestinal Tracts Motility):

Complicated neural network and hormonal signals manages gastric motility. X^{th} cranial nerve, sympathetic, and parasympathetic nervous systems all work together to keep the body in a state of equilibrium Hormones such as gastrin and cholecystokinin have been shown to have a role in gastric motility; these hormones serve to relax the upper stomach and stimulate the lower stomach's contractions, respectively. Smooth muscle cells presumably integrate a wide range of inhibitory and stimulatory signals to produce the movement patterns seen in the stomach. The pyloric sphincter can only pass boluses under 1 to 2 mm size. Disintegration of dose forms is mostly dependent on the size of one's stomach. Overall, motility patterns of the stomach are likely due to the integration of several inhibitory and stimulatory signals by involuntary muscle cells. Before passing through the pyloric sphincter, bolus must be made smaller in size to a diameter of less than 1-2 mm, whilst liquids pass through in rushes. For in-vivo dosage form dissolution, the stomach volume is crucial. Resting stomach volume is 25-50 ml. Gastric secretions differ greatly between normal and achlorhydric patients. The pH of the stomach also has an impact on drug absorption from the delivery method. During a fast, stomach pH is 1.2-2.0, and it rises to 2.0-6.0[8] after being fed.

Stomach Emptying Time:

Both eating and fasting result in the stomach becoming empty. Both states have types of mobility, but they are quite distinct from one another. During the fasting state, the stomach and intestine undergo a series of electrical occurrences that repeat every 2-3 hours. Wilson and Washington9 call this four-stage occurrence the inter digestive myoelectric cycle (IDMC) or migrating myoelectric cycle (MMC). [10]

1. **Basal Phase (Phase I)** lasts around an hour, involving just some tightening stomach contractions.
2. **Pre burst phase (Phase II)** continues for almost an hour with occasional generation of action potential and tightening stomach contractions. The intensity and velocity of the wave increase with time.
3. **Burst phase (Phase III)** Last just for around 4 to 6 minutes. It is made up of regular, powerful contractions that last a few seconds. All food that hasn't been digested at this point is carried on this wave to the duodenum. The cleaning wave is another name for it.

4. **Phase (IV)** Takes very small time and takes only 0 to 5 min. happens between Burst phase and Basal Phase of two consecutive cycles. After eating different categories of food, the contraction sequence shifts from the fasting to the fed condition. Phase is also, referred to as the digestive motility pattern, is characterized by continual contractions resembling fasting pre burst phase. Food particles are driven in suspension form towards the last part of stomach i.e., pylorus as a result of these contractions, which reduce their size to less than 1 mm. Beginning of migrating myoelectric cycle starts late during the non-fasting state, causing a decreased time for stomach emptying. [11]

The Scintigraphy technique probes on stomach emptying rates demonstrated that orally given controlled-release formulations have two significant drawbacks: short stomach residence duration and variable stomach emptying rate.

FACTORS INVOLVED IN GASTRIC RETENTION:

Several factors influence formulations gastric retention time (GRT), which impacts the efficacy as a gastror-etentive system. As:

1. **Density** – Stomach Retention Time (SRT) is a density-dependent formulations floating characteristic.[12]

2. **Size** – Dosage units bigger than 9.5 mm in diameter have been associated to increased GRT.[13]

3. **The dosage form's shape** – Moduli of flexure at 48 kilopascals for a tetrahedron and 22.5 lb/in2 (pounds per square inch) for circular device are proved to be superior in terms of GRT 48 (PSI). Depending on the format, the retention rate after 24 hours might be anywhere from 90% to 100%.

4. **Formulation of a single or multiple unit** – Incompatibilities may occur in formulations with units with different release profiles or mismatched substances, though the margin of safety in the occurrence of formulation failure is greater.

5. **Full or Empty Stomach conditions** – On a non-fed state gastrointestinal (GI) motility is indicated by the occurrence of the propagating myoelectric complex (MMC), or times of intensive motor activity, every 1 hour and a half to 2 hours. Myoelectric complex eliminates food material which remains undigested from stomach, Stomach Retention Time (GRT) of the formulation will be very small in case the formulation is supplied at the same time as the myoelectric complex MMC. However, in full condition, MMC is pushed back and GRT is lengthened.

6. **Meal's composition** – By shifting stomach motility pattern into a full stomach condition, fatty acid salts & indigestible polymers might delay gastric emptying and the release of medications.[14]

7. **Quantity of calories in food:** – GRT has been found to be increased by 4 to 10 hours with a proteins and lipids rich foods.

8. **Feeding schedule** – Because MMC occurs so infrequently, consuming many meals on the same day may raise the GRT by more than 400 minutes.

9. **Gender** – Regardless of their weight or age, women have a shorter mean ambulatory GRT (1.2 hours) than men (0.6 hours).

10. **Age** – People above the age of 70, and particularly the elderly, have a much longer GRT than those under 70.

11. **Body Posture** – Whether the patient is laying down or standing up might affect the results of GRT.

12. **Diseased Conditions** – Diseases like Diabetes mellitus and Crohn's disease complex.

METHODS FOR DESIGNING FLOATING MEDICATION DELIVERY SYSTEM (FDDS)

Davis (1968) was the first to explain FDDS in the literature when he proposed a way to prevent nausea and vomiting that might occur after taking certain medications by mouth. To get around this problem, the author suggested making tablets lighter than 1.0g/cm^3, hence they could float on water. After that, other strategies were been developed and used in an effort for creating the perfect system for delivering drugs as they float (Moya Nakagawa et al., 2006).

Methods for Creating a Single or Combination Dosage Form:

The following procedures have been used to construct single-unit and multiple-unit systems of buoyant formulations. 1992 research by Yie W. et al.

Dosage FORMS WITH A SINGLE UNIT:

These systems are made to increase absorption by extending the time that dose forms spend in the stomach intestinal tract. These HBS systems allow for the delivery of medications with improved acid solubility and targeted sites of absorption from superior parts of small intestine. For remaining inside stomach bag for an extended duration, the formulation has to be able to keep its structure and should have an average bulk density that is lower than "One."

APPROACHES TO GASTRIC RETENTION:

Different methods have been attempted to enhance stomach retention of oral dose forms. These include,

A. Floating formulations
B. Bio adhesive formulations
C. Expanding and swelling formulations
D. Formulations with high density and
E. Improved formulations

A. Floating formulations:

Hydrodynamically balanced structure is another name. Due to their bulk density which is lower than stomach contents, the formulation floats in stomach bag for a longer duration devoid of repercussions on stomach emptying. Mechanism gently releases drugs while floating on stomach

contents. Medication empty's the stomach. GRT improves plasma medication concentration regulation.

a. Non-gas-generating system
b. Gas-generating system.

a. Non-gas-generating system

Polymer swelling or bio-adherence produces non-gas producing formulations. Most of non-gas producing formulations, Bio-adhesive polymers such as Chitosan and Carbopol, as well as matrix-forming compounds such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene, are examples of excipients. There are two categories:

1. Single-layered Buoyant tablets/colloid gel barricade systems: This system (HBS), created by Sheth and Tossounian, contains medications with hydrocolloids that produce gels. They have a higher concentration of around 20–75% w/w of single or many polysaccharides, matrix-producing polymers, and gel-forming, extremely swellable hydrocolloids of the cellulose type. Hydrocolloids in the formulation and create a gel barricade around the surface when they come into contact with stomach fluid. This gel barrier controls how quickly gastric fluid enters the device and, as a result, how quickly the medicine is released is managed.

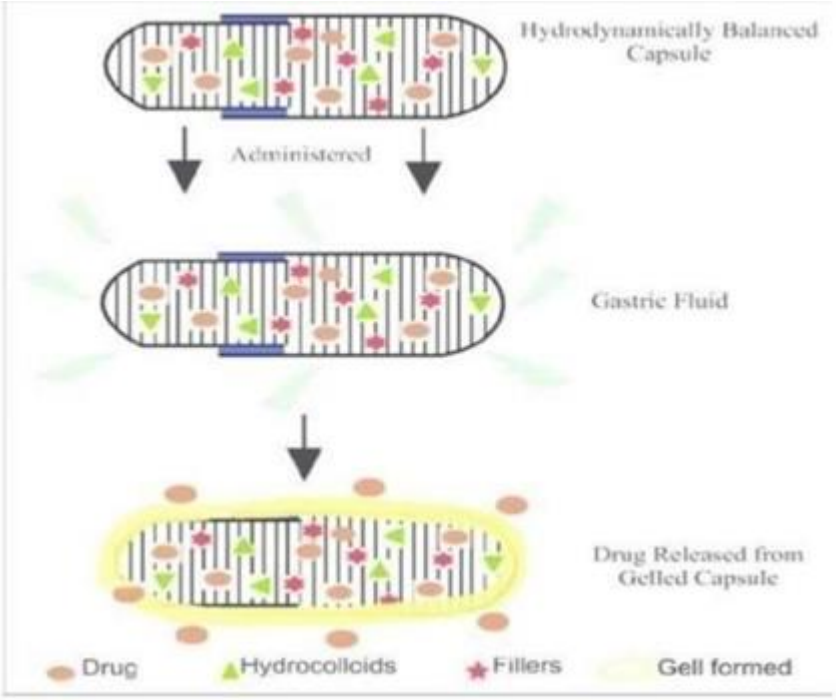

Figure 2 Gel structure hydrodynamically balanced. (Ushimaru K et al.1987).

2 DOUBLE-LAYER FLOATING TABLETS:

The double-layered formulation has 2 different coatings: Primary fast-releasing coat that releases the initial dose from the formulation, and secondary extended-drug releasing coat that actually absorb gastric juice, producing a resistant gel block on its upper surface and maintains a density

which is lesser than content in order to float.

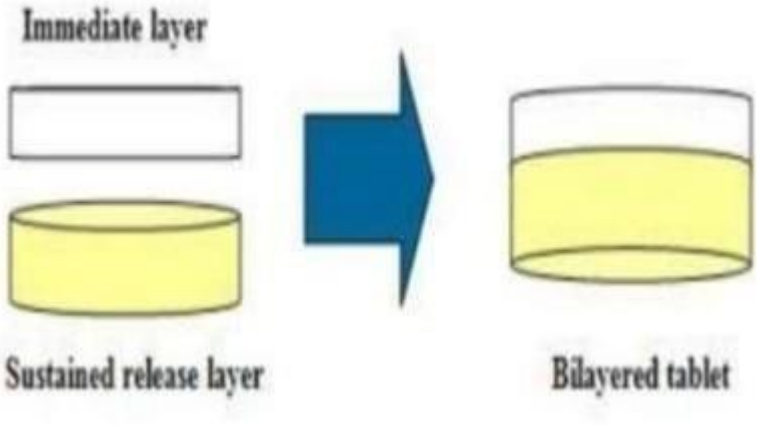

Figure 3. Bi layered Floating Tablet.

3 MICRO POROUS COMPARTMENT SYSTEMS:

A microporous chamber with holes on top and bottom surrounds a container. Medicine container's exterior walls keep undissolved medicine from contacting the stomach mucosal surface.

4. Multiple Particle Systems:

Oral multi-particulate formulations consist of many tiny discrete units with distinct characteristics. These devices split medication dosages among millions of circular particles with dimensions around 0.05 to 2.00mm. Many layers of calcium alginate were freeze-dried into tablets and given buoyancy. Dropping a sodium alginate solution into an aqueous calcium chloride solution precipitates calcium alginate, producing porous, spherical beads that can sustain a floating force for more than 12 hours. The resident period of these floating beads was over 5.5 hours, much greater than the residence time of the solid beads, which was about 1 hour. Therefore, the active component is dispersed across many, minute particles in multiarticulate dosage forms. These components come in premeasured dose sachets. Ingani HM, et al. (1987) observed multi-unit floating pill behavior.

5 HOLLOW MICROSPHERES / MICRO BALLOONS:

Several controlled-release technologies may deliver chemicals to the target location. Polymeric micro balloons may carry drugs. Micro balloons are hollow microspheres. Micro balloons floated in vitro for 12 hours. Radiographic tests showed that micro balloons given orally stayed in the upper stomach for 3 hours in spite of peristalsis motions.

B GAS GENERATING SYSTEMS:

Medication transportation device may glide over the stomach bag by using a chamber occupied by void, air, or inert gas causing it to float over gastric juices. They are of following types,

1. GAS PRODUCTION SYSTEMS:

1. To achieve its buoyancy in water, the system's jellified hydrocolloid layer disperses CO2 through an effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid. CO2 is released from a multi-piece floating tablet. A bilayer SR tablet serves as the seed. Sodium bicarbonate with tartaric acid, which creates a fizzy interior layer. The outer membrane may expand as needed and is made of materials like PVA and shellac. Polymer matrix drug release may also be controlled by another foldable, spring-based, effervescent device. Bicarbonate and ethyl cellulose resin beads are employed to create these devices. Coating that allows water to pass through but is not soluble. The beads are buoyed by the carbon dioxide gas.
2. **SYSTEMS CONTAINING VOLATILE LIQUID**:

Floating dose devices are a notable example of technical advancement in medication administration because to its stomach retention behavior and other advantages. Their advantages include,

ADVANTAGES OF FDDS:

1. Floating formulations are a kind of drug delivery technology that helps medicines stay in the stomach and has other uses as well. Both GRT and the sum of time the dosage formulation spends at absorption site improve drug efficacy.
2. Controlled drug delivery
3. Distribution of medication to the stomach bag for local action.
4. Reducing drug-induced irritation of gastric mucosa by discharging drugs gradually and at a controlled rate.
5. Treatment for digestive disorders like gastroesophageal reflux disease.
6. Simple and traditional manufacturing equipment
7. Better patient compliance and simplicity of administration.
8. Localized delivery of medicines.

DISADVANTAGES OF FDDS:

1. Gastric motility, pH, and diet affect stomach retention. Buoyancy is unpredictable because these components change.
2. Drugs that may cause irritation and injure the stomach mucosal membrane shouldn't be created as floating medication delivery devices.
3. Whether or not the stomach is entirely emptying will affect how long it takes for the stomach to empty.
4. In supine individuals, gastric emptying of floating forms is unpredictable and is strongly influenced by the form's diameter and size. Therefore, it is not recommended to provide floating forms to patients before bedtime.
5. Some patients experience discomfort.

FORMULATUION ASPECTS OF FDDS:

Novel controlled release drug formulation should consider drug, distribution technique, and destination. Preformulation investigations reveal drug properties. Solubility, incompatibility, pKa, and pH are traits. Controlled drug delivery formulations depend on pharmaceutical solubility. The drug may survive if its solubility is below 0.01 mg/ml. Oral medications must pass many biological membranes to be therapeutic. Thus, a drug's partition coefficient determines how well it crosses membrane barriers. Since they cannot penetrate these membranes, substances with very low partition coefficients will have limited bioavailability. Enzymes and acid-base hydrolysis break down oral drugs. Small intestines break down propantheline easily. Sustained-release drugs reduce bioavailability. Oral medications first enter the digestive system. The drug works there after being absorbed. Thus, gut physiology research improves controlled release delivery strategies. Medical illnesses and drugs may also alter design:

Absorption window:

The development of this formulation is also augmented by the site of absorption.

1. **Shorter duration of biological activity**:

Misoprostol has a briefer half-life and hence considered as an ideal candidate for the formulations.

2. **Solubility**:
3. Drugs with more acidic solubility and have a particular absorption location in the upper small intestine. Drug that are stable in the acidic environment of the stomach. For instance, Misoprostol with Ranitidine.
4. **Dose**:

Medications used locally in the stomach, such as famotidine and ranitidine hydrochloride. They are frequently prescribed for gastroesophageal reflex disease, erosive esophagitis, Zollinger Ellison's syndrome, duodenal ulcers, and gastric ulcers.

5. **Miscellaneous**:

Due to a number of additional factors, such as conventional dosage forms' poor patient compliance and a drug's shorter half-life, which necessitates frequent administration, increasing the likelihood that a dose will be missed. Due to dose missing, it is very difficult to keep the steady state plasma concentration when using conventional dosage forms. Unavoidable changes in drug concentration could result in under- or over-medication.

SELECTION OF POLYMERES for FDDS:

Various polymers are employed in fabrication of FDDS as follows,

A. **Gas-producing agents**:

e.g., Acids (citric, tartaric, adipic), bases (sodium bicarbonate, calcium carbonate),

Preformulation studies are helpful for learning about the chemical and physical properties of the medicines. The pKa, pH, solubility, and incompatibility of two substances are only few of these properties. A regulated drug delivery system may be used depending on the solubility of the medication being administered. The molecule can sustain itself if its solubility is very low (less than 0.01 mg/ml). A medicine that is taken orally must cross several biological membranes before it may have any therapeutic impact in the body. Therefore, the degree to which a medicine is able to cross these membrane barriers is largely dependent on the drug's partition coefficient. Substances with extremely low partition coefficients will have poor bioavailability since they will have a hard time crossing these membranes. Drugs that are taken orally are susceptible to breakdown by enzymes and acid-base hydrolysis. Substances like propantheline are very prone to breakdown once they leave stomach. Bioavailability drops when drug is administered in a sustained-release format. Once ingested, oral medication delivery methods initially make their way to the digestive system. From this point, the medicine is transported to its point of action. Acids (citric, tartaric, adipic), bases (sodium bicarbonate, calcium carbonate),

B. Viscosity Enhancers:

Carboxy Methyl Cellulose CMC, HPMC, Guar Gum etc.

Logic for the selection:

They are used to make the system more viscous. For forty years, Carbopol has been used in controlled-release solid-dose formulations. Carbomers are being used in the controlled release tablets of more manufacturers than ever before. The release kinetics of Carbopol polymer-based tablet formulations have been shown to be zero order or nearly zero order. These polymers work well at concentrations below 10%. The imitated intestinal fluid (SIF) and imitated stomach fluid (SMF) both show that they expand very rapidly and efficiently. The Carbopol polymers produce very durable and brittle tablets. Many other types of tablets, such as chewable, buccal, sublingual's, effervescent, and suppositories, may be effectively formulated from these polymers. They have excellent binding qualities and controlled-release capabilities. Carbomers, even at lower concentrations, have longer dissolution times than other excipients. As a consequence of these developments, the dosage form industry has become more reliant on Carbopol polymers. Due of the rapid swelling and significant water absorption of Carbopol polymers, roller compaction is being employed in their production in place of flammable solvents. For direct compression tablet formulations, Carbopol is a valuable, flexible component used in controlled release formulations.

C. **Gelling agent/Swelling polymer**:

Various grades of Hydroxypropyl methylcellulose (HPMC), Chitosan, CMC etc

Rational behind the selection:

Although hygroscopic after drying, Hypromellose is a stable material. The solution is stable at a pH of around 3-11. As temperature increases the solution viscosity decreases. On

heating and cooling, respectively, Hypromellose gets converted into a reversible sol-gel. Depending on the material's grade and concentration the gel point is at around 50 to 90 °C temperature. Grades with a high viscosity, are frequently used in floating tablets.

D. **Super disintegrating agents**:

Croscarmellose, PVP (Povidone), Sodium Starch Glycolate (SSG)

Logic behind the selection:

They impart the system with their swelling qualities when in contact with fluid media, which they have previously used as extremely potent explosive agents and to hasten the decomposition of solid drugs.

EVALUATION PARAMETERS OF FLOTING DRUG DELIVERY SYSTEMS:

In vitro testing of floating tablets:

The developed formulations' physicochemical characteristics and release characteristics were evaluated.

1. **Parameters to be studied before Compression**:
    a. **Angle of Repose**:

It may be used to calculate the frictional characteristics of the grains or powder. This is the steepest angle that may be made by a mound of grains or powders above the horizontal plane. The granules were entered into a funnel that was mounted to a steel stand at a known altitude (H). Next, height and radius of formed by the granule mound (R) were used to determine angle of repose.

$$\tan \theta = H/R$$

$$\theta = \tan^{-1} (H/R)$$

Where,

θ = angle of repose

H = altitude of the mound

R = radius of the mound

b. **Index of Compressibility**:

Powder's flowability may be estimated by comparing its bulk density (Po) and tapped density (Pt) with its packing rate. The index of compressibility is determined by –

index of compressibility

$$(\%) = \frac{Pt - Po}{Pt} \times 100$$

Where,

P_o = Bulk density gm/ml

P_t = Tapped density gm/ml.

2. **After-Compression Study Parameters:**
   a. Form of Tablet:

Under a magnifying glass, compressed tablets were inspected to determine their form and shape.

b. Dimensions of tablets:

A calibrated vernier caliper was used to measure the width and circumference. Three pills were chosen at random from each batch so that their thickness could be measured.

c. **Hardness 0f Tablet**:

The hardness of a tablet indicates how well it can endure being dropped. Firmness is determined with help of hardness tester device. Unit of measure is kg/cm2. Three tablets were chosen at random and their hardness measured.

Friability Test for the tablets:

Friability is determined using a machine called fibrillator. The figure was denoted as a percentage. After the tablets were originally weighed (W initial), they were put in the machine. The machine was operated for 100 rotations i.e., for 25 rotations per 4 minutes. Another weigh-in (W final) was performed on the tablets. Then we calculated the degree of friability using following equation,

$$\%Friability = 100 \times (1 - W \circ /W)$$

Less than 1% % Friability of tablets is acceptable.

d. The Formulation's Density:

Formulations density was essential in determining flotation. The tablet would only float if it has a desired density, (1.004) if its density is less than that of the gastric fluid. It is determined by using the formula shown below.

$$V = \pi r x^2 h$$

$$d = mv$$

Were,

v = volume of formulation (cc)

r = radius of formulation (cm)

h = crown thickness of formulation (g/cc)

m = mass of formulation

e. **Weight Variation test for the formulations**:

To study variation in weights of the formed formulations, ten formulations selected randomly from every batch and individually weighed. The USP allowed a very little amount of variation in weight. Table 1 shows the permitted weight variation percentage deviations.

Formulation's Average weight	Deviation of Percentage allowed
130 mg or less than that	10
More than 130mg & less than 324mg	7.5
324 mg and more	5

Table 1: % deviation in variation of weight which can be allowed

f. **Floatation Test**:

Duration of the formulations floating on the simulated stomach fluid was measured, as was the time it took for the formulation get submerged. Total Floating Time refers to the sum of all the times a dose form may float. Lag Time is time required by a floating formulation to float to the upper surface of a testing fluid.

g. **Study of Swelling Properties**:

Swelling behavior was identified by tracking the increase in mass or water absorption of a dose form. The dimensions might be measured by measuring the rise in tablet circumference and/or width. The equation provided a means of quantifying water intake directly in terms of weight gain.

$$WU = \frac{(W_1 - W_0)}{W_0} \times 100$$

Where,

W_t = Weight of formulation at time t.

W_0 = Initial weight of formulation.

I. **Drug release studies performed In vitro**:

The fluids used in these tests and studies are typically 37 degrees Celsius simulations of stomach and intestinal fluids. Use the USP dissolving device with 900 cc of 0.1 HCl at 37 degrees Celsius to calculate the floating time. Floating time for HBS dosage forms is often referred to as flotation time. The USP dissolving apparatus is often used for dissolve testing. The drug content of the samples is assessed after being adequately diluted, and the samples are collected at regular intervals via the dissolving medium, with the quantity removed being instantly replaced with an exact amount of new medium. The formulation should settle to the bottom of the vessel before the spinning blade is spun, as is standard practise according to USP XXIII. Dose units that would ordinarily float may be attached loosely to inert material, such a wire helix with no more than a few twists. Traditional dissolving approaches based on the USP or BP have shown to be

inaccurate predictors in in vitro testing of floating dosage forms 23, 24. Researchers Illay and Fassihi (25), using expandable floating systems containing theophylline, a medication with a poor water solubility, studied the helical wire sinker. Drug release was often compromised because of the method's tendency to limit the dosage form's ability to expand in three dimensions. The authors recommend placing a ring/mesh assembly below the floatable delivery mechanism to prevent it from sinking. The spread of drugs skyrocketed by about 20%. The process maintained a steady flow of water and predetermined release patterns. The suggested technique and the USP method both result in the same release of diltiazem, a medication that is soluble in water and may float on the surface. According to the results, drugs released through swellable floating devices must be water-soluble, have complete surface exposure, and swell uncontrollably. An in vitro dissolve technique for a suspended dosage form with quick release and SR properties was developed by Burns et al.26. In accordance with the BP (1993)/USP (1990) apparatus 2 method, the dissolution liquid was paddled using blades. Changing the pH of the dissolving media from 6.0 to 8.0 and raising the paddle speed from 70 to 100 rpm yielded consistent biphasic release characteristics. There was no change in dissolving profile when 7mM to 14mM bile acid was added to the dissolve medium. Researchers adapted a dissolving tank to evaluate dose forms that float yet include erosion processes. As a consequence, there was no longer any need to worry about dosage forms adhering to the paddle blades, and the dissolving profile could be reproduced. It's possible that this procedure can differentiate between good and bad dissolving results. The specific gravity of FDDSs may be calculated using analytical grade benzene and displacement.Before comparing floating and non-floating devices in vivo, Immermans and Moes advocate providing the bulk density of the dosage form in its dry state and any fluctuations in floating strength over time. Improvements in floating formulation shown by in vivo studies to stabilise and extend floating abilities. The approach used by these researchers determines whether or not shapes will float or sink. 28,29. Using dedicated technology, this method determines the total upward pressure exerted on a body of water. Devices that measure the upward pressure exerted on an object while it is immersed in water have been the subject of much research. 28,29. Scintigraphy may determine how well the stomach will absorb a floating dosage form. Doses that float or stay put are used for both fasting and fed patients, making up the 54. Both methods of dosing must be accurate.30,31,32

Drug Candidates frequently incorporated in Floating Formulations:

Sr No	Medicines	DOSAGE FORMULATION
1	Acetyl Salicylic Acid, Griseofulvin, Ibuprofen	Microspheres
2	Indomethacin. Diclofenac sodium,.	Granules
3	Cinnarizine	Films
4	Chlordiazepoxide, L-Dopa, Misoprostol, Propranolol HCl	Capsules

5	**Paracetamol, Aspirin, Amoxicillin, Ampicillin trihydrate, Atenolol, Chlorpheniramine maleate,**	**Tablets/pills**

Table 2: Drugs commonly used in FDDS

MARKETED PREPARATIONS OF FLOATING DOSAGE FORMULATIONS:

Sr No	BRAND NAME	DRUG (DOSE)	COMPAN & COUNTRY OF ORIGIN	Details
1	Cytotec	Misoprostol (100 mcg/200 mcg)	Pharmacia, USA	Bilayer floating capsule system
2	Oflin OD	Ofloxacin (400mg)	Ranbaxy, India	Gas generating floating tablet system
3	Cifran OD	Ciprofloxacin (1 gm)	Ranbaxy, India	Gas generating floating tablet system
4	Valrelease	Diazepam (15 mg)	Hoffmann LaRoche, USA	Floating capsule system
5	Conviron	Ferrous sulphate	Ranbaxy, India	Colloidal gel forming system

Table 3: Marketed products of FDDS.

CONCLUSION:

The controlled release floating medication delivery system is an interesting medicine administration device that may help with stomach retention. This article summarizes the elements that influence human gastric emptying and the fundamental theories underlying development of formulations with enhanced gastric retention durations.

REFERENCES:

1. Friend DR. Oral delivery: A new approach to dosage forms. Pharmaceutical News 2006; 9 : 375-80.
2. Robinson JR, Lee VHL. Controlled drug delivery: fundamentals and applications, Marcel Dekker: New York: 1978; 2: 335- 410.
3. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treatise. New Delhi; Vallabh Prakashan: New Delhi : 1995; 1 : 10-48.
4. Chein YW. Novel drug delivery systems., Marcel Dekker, New York; 1992 ; 2 : 185- 210.
5. Lalla JK. Introduction to controlled release and oral controlled drug delivery systems. The Eastern Pharmacist 1991; 45 : 25-28.
6. Gennaro RA. Remington: The Science and Practice of Pharmacy. Lippincott Williams, New York; 2000; 20 : 153-225.
7. Banker GS, Rhodes CT. Modern Pharmaceutics. Marcel Dekker, New York 1996 ; 3 : 125-128.
8. Hoffmann A. Pharmacodynamic aspects of sustained release preparations. Adv. Drug. Deliv. Rev 1998; 33 : 185-199.

9. Stanley SD, Lisbeth I. Drug delivery systems for challenging molecules. Int. J. Pharm. 1998; 176 : 1-8.
10. Vyas SP, Khar RK. Controlled drug delivery: Concepts and advances. Vallabh Prakashan Delhi; 2002; 1 :123-231.
11. Streubel A, Siepmann J, Bodmeier R. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur. J. Pharm. Sci. 2003; 18 : 37-45.
12. Rocca DJG, Omidian H, Shah K. Progresses in gastroretentive drug delivery systems, Business Briefing. Pharmatech 2003; 152-6.
13. AJ. Gastric retention systems for oral drug delivery. Business Briefing. Pharmatech 2003; 157-9.
14. AJ. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993; 10(2) : 193-95.
15. well LJ, Gardner RC, Cargill RC. Drug delivery device which can be retained in the stomach for a controlled period of time. US Patent 1998; 30th August: 4, 767, 627.
16. Grabowski SR. Principles of anatomy and physiology. 10th ed. New York: John Willey and Sons; 2002.
17. KRW, Waugh A. Anatomy and Physiology in Health and Illness. 9th ed. London : Churchill Livingstone; 1996.
18. Davis,S.S; Stockwell, A.F; Taylor,M.J. Hardy, J.G; Whalley,D.R; Wilson,C.G; Bechrgaard,H; Cristen,F.N; The effect of density on the gastric emptying of single and multiple-unit dosage forms. Pharm. Res., 1986, 3 208.
19. Fix,J.A; Cargil,R; Engle,K; Gastric residence time of a non-disintegrating geometric shape in human volunteers, Pharm. Res. 1995, 12(3), 397-405.
20. Desai,S; Bolton.S; A floating controlled – release drug delivery system; In-vitro/invivo Evaluation, Pharm. Res, 1993, 10, 1321-1325.
21. Oth,M; Franz,M; Timmermans,J; The bilayer floating capsule: A stomach – dried drug delivery system for misoprostol, Pharm. Res, 1992, 9, 298- 302.
22. Waldwell, L.J; Gardner. C.R; Cargil, R.C; US Patent 4,735,804, 1988
23. Timmermans J, Moes AJ. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: New data for reconsidering the controversy. J. Pharm. Sci. 1994; 83 : 18- 24.
24. Clarke GM, Newton JM, Short MD. Comparative gastrointestinal transit of pellet systems of varying density. Int. J. Pharm. 1995; 114 : 1-11.
25. Timmermans J, Moes AJ. The cut off size for gastric emptying of dosage forms. J. Pharm. Sci. 1993; 82 : 854.
26. Marvola M, Kannikoski A, Aito H. The effect of food on gastrointestinal transit and drug absorption of a multiarticular sustained-release Verapamil formulation. Int. J. Pharm. 1989; 53 : 145-55.
27. Mojaverian P, Vlasses PH, Kellner PE, Rocci Jr. ML. Effects of gender, posture and age on gastric residence time of an indigestible solid : Pharmaceutical Considerations. Pharma. Res. 1980; 10 : 639-44.
28. Bhavana V, Khopade AJ, Jain WD, Shelly and Jain NK. Targeted oral drug delivery. Indian Drugs 1996; 33 : 365-73.
29. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm. Res. 1997; 14(6) : 815- 819.
30. Castellanos RM, Zia H, Rhodes TC. Design and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm 1994; 105 : 650.

31. Edith Madithowitz. Encyclopedia of Controlled Drug Delivery. 1st ed. New York : Jhon Wiley and Sons; 1999.
32. David SS. The effect of density on the gastric emptying on single and multiple unit dosage forms. Pharm Res 1986; 3 : 208-13.
33. Gronia R, Heun G. Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm 1984; 10 : 527-39.
34. Atyabi F, Sharma HL, Mohammad HAH, Fell JT. In-vivo evaluation of a novel gastroretentive formulation based on ion exchange resins. J. Control. Rel. 1996; 42 : 105-13.
35. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage form. J. Control. Rel. 2003; 90 : 143-62.
36. Singh BN, Kim HK. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Rel. 2000; 63 : 235- 59.
37. Bhavana V, Khopade AJ, Jain WD, Shelly and Jain NK. Targeted oral drug delivery. Indian Drugs 1996; 33 : 365-73.
38. Vyas SP, Khar RK. Controlled drug delivery: Concepts and advances. 1st ed. New Delhi : Vallabh Prakashan; 2002.
39. http://goldbamboo.com/topic-t1350-a1- 6Gastric_Ulcer.html date 26 march 2000
40. Spechler, SJ. Peptic Ulcers. In: Feldman, M, Friedman, LS, Sleisenger, MH, eds. Gastrointestinal and Liver Disease, 7th ed. Philadelphia, PA; WB Saunders Company; 2002:747-772.
41. Noble J. Textbook of Primary Care Medicine. 3rd ed. St. Louis, MO: Mosby; 2001:910-918.
42. Mahachai V, Thomson AB, Vilaichone RK. Effect of Helicobacter pylori infection and NSAIDs on the risk of peptic ulcer bleeding. J Med Assoc Thai. 2004;87(2)S295-9.
43. Ichikawa M, Watanabe S, Miyake Y. A new multiple-unit oral floating dosage system. I: Preparation and in-vitro evaluation of floating and sustained release characteristics. J. Pharm. Sci. 1991; 80: 1062-066.
44. Timmermans J, Moes AJ. How well do floating dosage forms float?. Int. J. Pharm. 1990; 62 : 207-16.
45. Shoufeng L, Senshang L, Chein YW, Daggy BP, Mirchandani HL. Statistical optimization of gastric gloating system for oral controlled delivery of calcium. AAPS Pharm. Sci. Tech. 2001; 2: 1-12.
46. Hilton AK, Deasy BP. In vitro and In vivo evaluation of an oral sustained-release floating dosage form of Amoxycillin trihydrate. Int. J. Pharm. 1992; 86: 79-88.
47. Ozdemir N, Ordu S, Ozkan Y. Studies of floating dosage forms of Furosemide: Invitro and In vivo evaluations of bilay tablet formulations. Drug. Dev. Ind. Pharm. 2000; 857-66.
48. El-Kamel AH, Sokas MS, Algamal SS. Preparation and evaluation of Ketoprofen floating oral delivery system. Int.
49. Joseph NJ, Lakshmi S, Jayakrishnan A. A floating type oral dosage form for Piroxicam based on hollow polycarbonate microspheres; In vitro In vivo evaluation in rabbits. J. Cont. Rel. 2002; 79: 71-79.
50. Baumgartner S, Julijana K, Franc V, Polona V, Bojon J. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm. 2000; 195: 125-35.
51. Rouge N, Allemann E. Buoyancy and drug release patterns of floating minitablets containing Piretanide and Atenolol as model drugs. Pharm. Dev. Technol. 1998; 3: 73-84.
52. Castellanos RM, Zia H, Rhodes TC. Design and testing in-vitro of a bio adhesive and floating drug delivery system for oral application. Int J Pharm 1994; 105: 650.

53. Ingani HM, Timmermans J, Moes AJ. Concept and in-vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int. J. Pharm. 1987; 35: 157-64.
54. Menon A, Wolfgang AR, Saks A. Development and evaluation of a monolithic floating dosage form for Furosemide. J. Pharm. Sci. 1994; 83: 239- 45.
55. Park HJ, Choi BY, Hwang SJ, park JB. Preparation of alginate beads for floating drug delivery systems: effects of CO2 gas forming agents. Int. J. Pharm. 2002; 239: 81-91.