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A Novel Approach To The Bilayer Floating Drug Delivery System: A Review

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ABSTRACT

Gastro retentive drug delivery system (GRDDS), these dosage forms are designed to achieve prolonged gastric residence time in controlled release manner. The floating drug delivery system (FDDS) also comes under the gastro retentive drug delivery system. These type of formulations helps to improve the solubility of poorly soluble drugs and enhances the bioavailability of the drug. In gastrointestinal tract the absorption of dosage form or drug molecule is a highly variable process. To overcome all these physiological problems Novel Drug Delivery System (NDDS) plays an important role. FDDS works on the principle of buoyancy (the tendency of an object or a molecule float in a fluid or the upward force that a fluid exerts on an object) which allows the drug to remain in the gastric environment for a prolonged period of time without rapid passing into the intestine. Floatation of a drug is due to bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time. Releasing the drug slowly at the desired rate and increase the bioavailability of narrow absorption window drugs. This review helps to know the floating drug delivery system principle, advantages and disadvantages, need for floating bilayer tablets, challenges in bi-layer tablet manufacturing and characterization and evaluation methods for bilayer floating tablets.

Keywords: Gastro Retentive Drug Delivery System (GRDDS), Floating Drug Delivery System (FDDS), Novel Drug Delivery System (NDDS), Bi-layer tablet, Gastric emptying, Active Pharmaceutical Ingredients (API)

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INTRODUCTION

An oral dosage form called a bi-layer floating tablet is made to improve gastric retention and deliver medications in a controlled way. It is having two layers

1. The Immediate Release (IR) Layer: This layer releases the drug quickly after ingestion, providing an initial therapeutic effect.
2. The Sustained Release (SR) Layer: This layer is designed to release the drug over an extended period, providing a prolonged therapeutic effect.

The "floating" aspect refers to the tablet's ability to remain buoyant in the stomach, which helps to increase its drug absorption and improve residence time, particularly for drugs that are poorly absorbed in the lower gastrointestinal tract. This floating property is typically achieved by incorporating low-density materials, such as effervescent agents or hydrophilic polymers that cause the tablet to float in the stomach's acidic environment.

Hydrophilic polymers: Materials like hydroxypropyl methylcellulose (HPMC) or Carbopol that swell upon contact with water and cause the tablet to float.

Effervescent agents: Substances like sodium bicarbonate that release gas (carbon dioxide) upon contact with stomach acid, creating a buoyant effect.

This type of formulation is used for drugs that need prolonged action, are poorly soluble in the intestines, or are intended to treat conditions requiring a steady release of medication.

An Overview of Stomach

Stomach is an organ with a capacity for storage and mixing. Its fundus and body regions are capable of displaying a large expansion to accommodate food without much increase in the intragastric pressure.

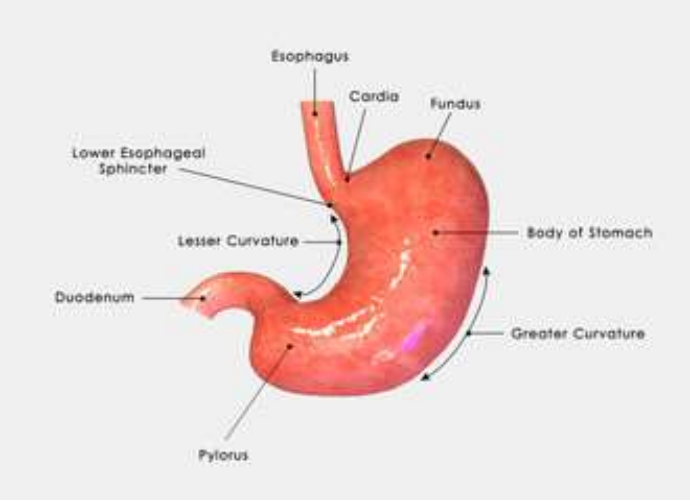

Figure 1: Anatomy of stomach

The stomach is located in the upper left-hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hypochondriac region. The main function of the stomach to store the food temporarily, grind it and release it slowly into the duodenum. The pH range of the stomach is 1-3.

There are two main secretions, mucus and acid, produced by specialized cells in stomach lining. Mucus is secreted by goblet cells and gastric acid by oxyntic cells. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The thickness of this mucus coating varies from one region of GI tract to another [1].

Gastric Emptying

The gastric emptying occurs both during fasting and fed states. However, the pattern of motility differs markedly in the two states. In the fasted state, it is characterized by an inter-digestive cycle both through the stomach and small intestine, every 2-3 hrs. This activity is called as inter-digestive myoelectric cycle or migrating myoelectric complex (MMC). It is composed of 4 phases.

Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.

Phase II (pre-burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.

Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles [2,3].

GRDDS (Gastro-retentive delivery systems)

Gastro-retentive delivery systems are meant to be retained in the stomach for a prolonged period. Thus, they provide sustained and prolonged drug release to the upper part of the gastrointestinal (GI) tract.

Gastro retentive delivery is one of the sit-specific deliveries for the delivery of the drugs either at stomach or at intestine. it is obtained by retaining dosage form into stomach and drug is being released at controlled manner to specific site either in stomach, duodenum and intestine [4,5].

The types of drugs have benefited by using gastric retentive devices. These include;

1. Locally active in stomach.
2. Primarily absorbed in the stomach.
3. Unstable in the intestinal environment.
4. Have narrow absorption window in GIT.
5. Have low soluble at the high PH region.

6. Degrade in the colon.

Advantages of GRDDS

1. Increase in bioavailability and improved efficacy of the drug and economic usage of dosage.
2. Minimized factor of risk in resistance of antibiotics.
3. Delivery of drugs with a narrow absorption window in the small intestine region.
4. Optimized release in case of short half-life of drug.
5. Reduced dosage frequency ensures patient compliance.
6. Providing a narrow curative index of the gastro retentive dosage form.
7. GRDDS is efficient in treating stomach and small intestine-related problems.
8. Reducing the chances of over exposure to drugs at the diseased site.
9. The gastro-retentive dosage forms reduce variance in concentrations of drugs.
10. This system provides higher efficiency due to reduced counter activity by body [7]. Etc.

Disadvantages of GRDDS

1. An increased level of fluids in the stomach is needed for this system.
2. Unsuitable for drugs such as:
3. Problematic with solubility in gastric fluid.
4. Causing G.I irritation.
5. Inefficient in an acidic environment.
6. GRDDS is fed into the system after the meal as retention in the stomach depends on the digestive state.
7. Bio/mucoadhesive systems have the problem of the high turnover rate of the mucus layer.
8. Time needed for swelling in the case of a Hydrogel based swelling system is longer.
9. Size-increasing drug delivery systems can cause a threat to life owing to the possible hazard of permanent retention in the stomach.
10. Need for increased level of fluids in the stomach.
11. Hydrogel based swelling system takes longer time to swell [8,9]. Etc.

FLOATING DRUG DELIVERY SYSTEM

Bi-layer Floating Tablets are a type of oral drug delivery system designed to provide both immediate and controlled release of active pharmaceutical ingredients (APIs). The tablet consists of two distinct layers: one that releases the drug immediately and another that controls the drug's release over an extended period. The floating property ensures that the tablet remains buoyant in

the stomach, allowing for prolonged gastric retention, which can improve the bioavailability of drugs that are primarily absorbed in the upper gastrointestinal tract.

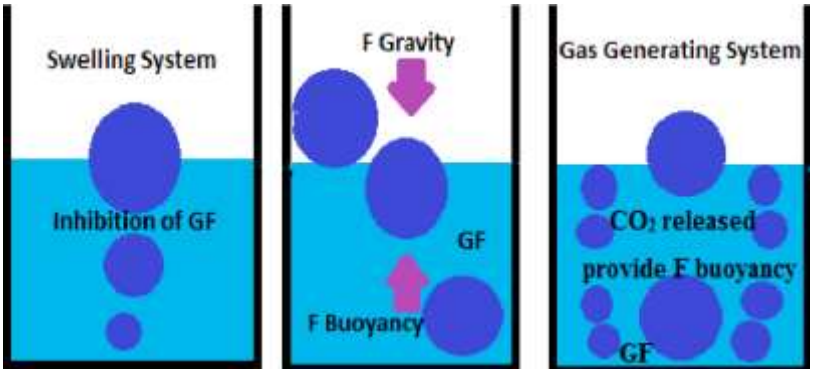

Figure 2: Mechanism of floating drug delivery system

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. The major requirements for floating drug delivery system are:

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004-1.01 gm/cm^3).
- It must form a cohesive gel barrier.

The inherent low density can be achieved by the entrapment of air or by incorporation of low-density materials [10, 11, 12, 13].

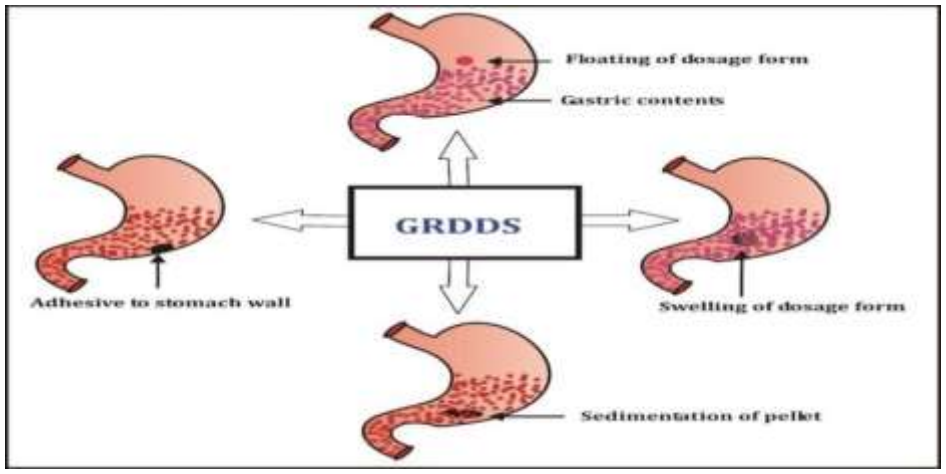

Figure 3: Approaches for GRDDS

TYPES OF FLOATING DRUG DELIVERY SYSTEMS

1) Effervescent system

a) Volatile liquid containing system

b) Gas generating system

2) Non-effervescent system

a) Alginate beads

b) Hollow microspheres

c) Single layer floating tablets

d) Bilayer floating tablets

e) Colloidal gel barrier system

f) Microporous compartment system

1) Effervescent System

These are also known as gas generating system where floatability is achieved by liberating gas of CO_2. Sodium bicarbonate, citric acid or tartaric acid is used as floating agents. After the administration of drug orally into the GIT, CO_2 gas is liberated from these drug delivery systems, which leads to the decrease in the system density and floats on the gastric fluids. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. Matrix type of systems can also be prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds. When it comes in contact with the acidic gastric contents, $C0_2$ is liberated, and gas is entrapped in swollen hydrocolloids, which provides buoyancy [14].

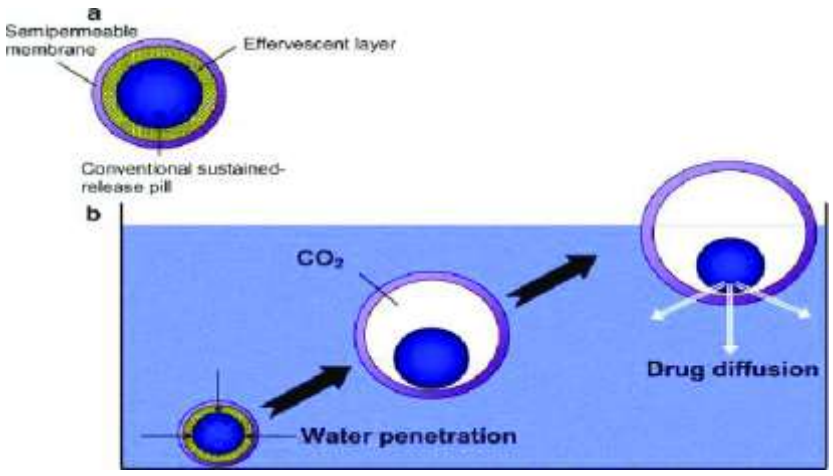

Figure 4: Effervescent floating drug delivery system

a) Volatile liquid containing system:

This system is also called as an osmotically controlled floating system. Liquids such as ether and cyclopentane are used. Inflatable chamber with a liquid is incorporated in this system which provides gastric retention. This system contains two compartments. In the first compartment the drug is comprised, and the second compartment contains volatile liquids. The gas is produced by vaporizing the liquid at physiological temperature and enables the drug reservoir to float [15].

b) Gas generating system:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over gastric content [16].

2) Non-Effervescent System

The Non-effervescent FDDS is based on mechanism of swelling of polymer or bio adhesion to mucosal layer in GI tract. Swelling type of hydrocolloids made up of polysaccharide are comprised in these systems along with matrix-forming polymers like polymethacrylate, polycarbonate and polystyrene. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain stuck near the pyloric sphincter. These systems are further classified into [14].

Figure 5: Alginate beads

a) Alginate beads:

Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate. The beads are further separated, snap frozen in liquid nitrogen, and freeze-dried at 400 °C for 24 h, leading to formation of porous system, which can maintain a floating force for over 12 hours.

b) Hollow microspheres:

Floating microspheres are also called as Hallow microspheres which is considered as more efficient buoyant systems. The hollow microsphere is loaded with a drug and is prepared by a novel emulsion solvent diffusion method. It consists of a central hollow space inside the microsphere.

The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into an agitated aqueous solution of PVA that is thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in

microsphere of polymer with drug. The micro balloons float continuously over the surface of acidic media containing surfactant for more than 12 hours [17, 18].

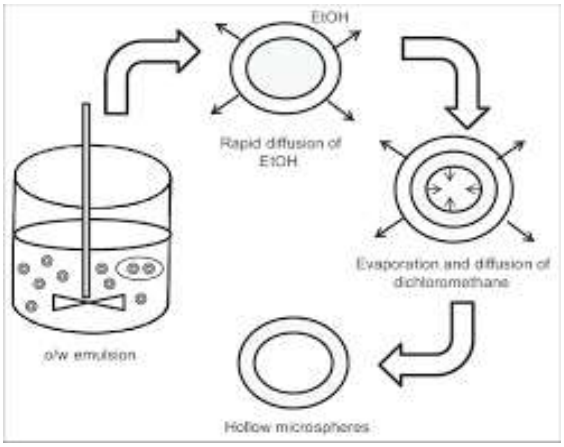

Figure 6: Hollow microspheres

c) Single layer floating tablets:

A hydrocolloid, which is a gel forming agent is mixed with the drug, then it swells when it comes in contact with the gastric fluid and maintains bulk density less than that of the gastric fluids, thereby helping the system to remain buoyant in the stomach. To maintain low density, they are formulated by intimate mixing of drug with enteric materials such as HPMC.

d) Bilayer floating tablets:

A bilayer tablet contains two layer one with immediate release layer which releases initial dose and another one is sustained release layer which absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach [18].

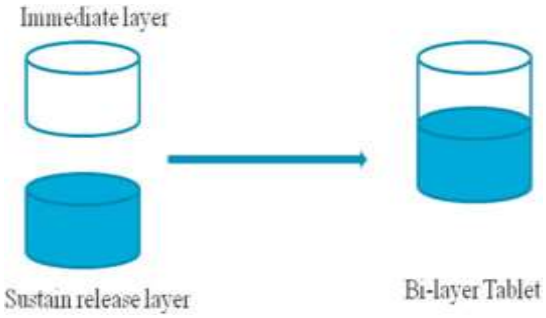

Figure 7: Bilayer tablet

e) Colloidal gel barrier system:

It is also called as Hydrodynamic Balanced Systems. It was first designated by Sheth and Tossounian. These types of systems contain drug with gel forming hydrocolloids which allow them to remain buoyant on the stomach content. Various gel-forming agents include hydroxyethyl cellulose, hydroxypropyl methylcellulose, polysaccharides, and polystyrenes. This hydrocolloid

hydrates and forms a colloidal gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drugs [19].

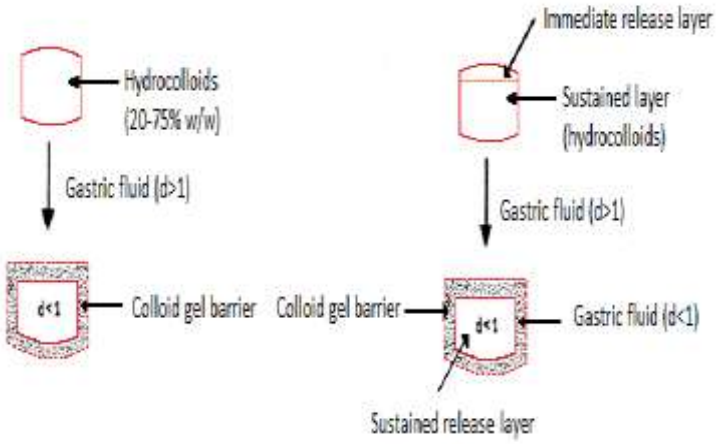

Figure 8: Colloidal gel barrier system

f) Microporous compartment system:

In this technology a drug reservoir is encapsulated inside a microporous compartment which are having pores along its top and bottom walls. The outer wall of the drug reservoir compartment is sealed to stop drug which is not dissolved in contact with the stomach surface. The floating chamber containing entrapped air allows the delivery system to aperture dissolves the drug and carries the drug for dissolved drug for continuous transport across the intestine for absorption [20].

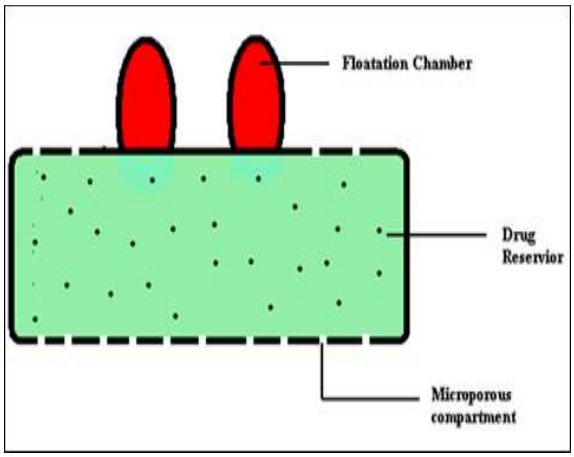

Figure 9: Microporous compartment system

Advantages of Bilayer Floating Tablets

- Ease of administration leads to better patient compliance.
- This system is microbiologically and chemically stable.
- This system provides the most flexible dosage form.
- Suitable for large-scale production.

- Cost-effective as compared to other oral dosage forms.
- These are the lighter and most compact [21]. Etc.

Disadvantages of Bilayer Floating Tablets

- There is less control over weight of individual layer.
- Swallowing problem in case of children and unconscious patients.
- Hardness is other problem.
- Capping is also a problem in bilayer tablets.
- For poor wetting and less dissolution properties Bioavailability problem will occur [22]. Etc.

Need of Bilayer Floating Tablets

- To control the delivery rate of either single or two different active pharmaceutical ingredients.
- To modify the total surface area available for API layer either by sand witching with one or two inactive layers in order to achieve swell (or) erodible barriers for modified release.
- To separate incompatible active pharmaceutical ingredients from each other, to control the release of API from one layer by utilizing the functional property of another layer.
- For the administration of fixed-dose drug combinations, prolong the product life cycle, buccal or mucoadhesive delivery systems, and fabricate novel drug delivery systems such as chewing devices and floating tablets for GRDDS [23,24,25].

PREPARATION OF BILAYER TABLETS

Bilayer tablets are preparations having two layers of drug one for immediate release and another one for second dose or in the form of extended release. Two incompatible drugs can be prepared in the form of bilayer tablets by compressing separate layer of each drug which minimize the area of contact between two layers. An additional intermediate layer of inert material may also be included. An adequate tablet formulation and requirements such as mechanical strength and desired drug release profile should be considered [26,27].

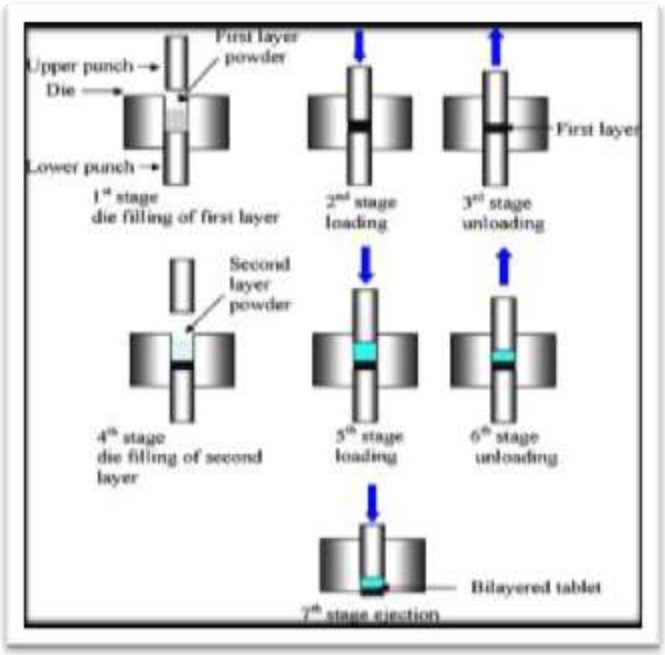

Figure 10: Preparation of Bilayer Table

Compaction: The compaction of the ingredients involves both consolidation and compression. It is the process by which the powder porosity is decreased by mechanical means.

Compression: It is defined as bulk volume reduction by elimination of voids and bringing particles into closer contact.

Consolidation: The mechanical strength is increased due to inter particulate interaction. On layer one, the compression force on the first layer was a major factor influencing tablet delamination.

EVALUATION PARAMETERS OF BILAYER FLOATING TABLET

In-vitro Evaluation of Bilayer Floating Tablet: Evaluation is mainly carried out to assess the formulations' physicochemical properties and release characteristics [28,29,30,31].

Pre-Compression Parameters

Angle of Repose: Angle of repose is the maximum angle possible between the surface of the powder pile and the horizontal plane.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} h / r$$

Where, θ= Angle of repose

r = radius of pile

h= height of pile

Density: The bulk density (BD) and tapped density (TD) were determined using the following formulas,

Bulk density = weight of powder / Bulk volume

Tapped Density = Weight of powder / Tapped volume

Compressibility: The compressibility index of was determined by following formula,

Carr's Index % = TD-BD/ TD x 100

Hausner's Ratio: It is calculated using the formula,

Hausner's ratio = TD / BD

Particle Size Distribution: Particle size distribution was done using the sieving method.

Post-Compression Parameters

General Appearance: The general appearance of a tablet includes tablet's size, shape, color, odor, taste, surface texture, and physical flaws**.**

Tablet Thickness: Three tablets were taken randomly, and their thickness and diameter were measured by vernier caliper or calibrated screw gauze.

Weight Variation Test: 20 tablets are selected and weighed individually. Then the deviation of individual weight from the average weight is calculated.

Table 1: Limit of Weight Variation as Per Ip/Bp

Weight	% Variation
Less than 80 mg	10 %
80-250 mg	7.5%
Above 250 mg	5%

Hardness:

The tablet's resistance to capping, abrasion or breakage under storage conditions, transportation, and handling before usage depends on its hardness.

It is measured using Monsanto hardness tester by randomly selecting three tablets. It is expressed in kg/cm2.

Friability:

Friability testing is used to test the durability of tablets during packing processes and transit.

Ten tablets are selected, weighed, and then placed in Roche friabilator, which rotates at 25 rpm speed for 4 min. After 4 minutes, the tablets are reweighed. Friability is calculated using formula,

%F= [1-(Wt / W)] ×100

Where, W – Initial weight of tablet,

Wt - Weight of tablet after revolution.

If % Friability of tablets is less than 1%, it is considered as acceptable

Tablet Density:

It is a very important parameter in case of floating tablets. If density is less than gastric fluid (1.004), then the tablets will float. It is calculated by using following formula,

$V = \pi r2h$ d = m/v

Where, r = Radius of tablet,

h = crown thickness (g/cc),

m = Mass of tablet.

Drug Content:

10 tablets from each batch are selected randomly and transferred to a 100 ml volumetric flask filled up with 0.1 N HCL. Stir and keep it aside for 2 hrs. Then take 1 ml from the volumetric flask and transfer it to the test tube. Samples are then filtered, suitably diluted and analyzed spectrophotometrically at a suitable wavelength.

In-vitro Dissolution Study:

The tablet was placed inside the USP paddle apparatus by maintaining an optimum temperature of 37ºC at 50 rpm rotational speed. 5 ml of sample is withdrawn at different time intervals of 1h, 2h, 3h, 4h, 5h, 6h, 8h, 10 h and 12h or any other time intervals as needed. The volume of dissolution fluid is adjusted to 900 ml by replacing fresh 5 ml of dissolution medium after each sampling. The release studies were conducted, and the mean values were plotted versus time. Each sample is analyzed at maximum wavelength using UV visible spectrophotometer against a reagent blank, and the corresponding concentration is determined from the respective calibration curve. Then, the percent drug release concentration values at different time intervals were calculated.

Floating Lag Time:

The time required for the tablets to rise on the surface of the liquid medium is called as floating lag time. Ideally, it should be less than one minute. Dissolution test apparatus containing 0.1 N HCl (900ml) has been used to measure it.

Floating Time:

The total duration of tablet floating on the medium was considered as floating time.

Swelling Study:

Weigh the tablet (W1) and place in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5°C. At different time intervals, the tablet is removed and a filter paper carefully removes the excess of liquid. The swollen tablet is reweighed (W2).

The formula calculates the swelling index (SI),

SI= Wt –W0/W0×100

Wt = weight of the swollen tablet

W0=Initial weight of the tablet.

Stability Study (Temperature Dependent):

The bilayer tablets are stored under the following conditions for a prescribed period as per ICH guidelines for accelerated studies.

Table 2: storage condition for bilayer tablets

Study	Storage Condition	Minimum Time Period
Long term	25°C±2°C / 60% RH ± 5%RH 30°C±2°C / 65% RH ± 5%RH	12 months
Intermediate	30°C±2°C / 65% RH ± 5% RH	6 months
Accelerated	40°C±2°C / 75% RH ± 5% RH	6 months

In-vivo Evaluation of Bilayer Floating Tablet:

Radiology:

X-ray is widely used for internal body systems examination. Barium Sulphate is a widely used Radio Opaque Marker in radiology. BaSO4 is incorporated inside the dosage form, and X-ray images are taken at various intervals to view gastric retention.

Scintigraphy:

Emitting materials are incorporated into dosage form, and then images are taken by scintigraphy. The most widely used emitting material is 99Tc.

Gastroscopy:

Gastroscopy is peroral endoscopy with fiber optics or video systems. Gastroscopy is used to inspect the effect of prolongation in the stomach.

Magnetic Marker Monitoring:

In this technique, the dosage form is magnetically marked by incorporating iron powder inside, and then images can be taken by very sensitive bio-magnetic measurement equipment. The main Advantage of this method is that it is radiation-less and not hazardous.

Ultrasonography:

Not used generally because it is not traceable at the intestine.

C13 Octanoic Acid Breath Test:

C_{13} Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO2 is replaced with C_{13} isotope. So, time up to which C_{13} O_2 gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO_2 release. So, this method is cheaper than other.

CONCLUSION

It is one of the modern methods which includes both sustained and immediate release in one tablet which makes it easy to flow in the gastric fluid. It has unique property to retain itself around 24

hours. Bilayer drastically enhances the gastric emptying time as well as bioavailability. The drug having shorter half-life can be employed into floating tablet which influences the bioavailability. Drugs which have narrow absorption window such as antibiotic, antifungal and antiviral can be given in bilayer floating dosage form.

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