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BILAYER FLOATING TABLET- AN EMERGING TREND: A REVIEW

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Keywords:

Gastro retentive drug delivery system, Controlled release, Immediate release, Floating bilayer tablet, Buoyancy, floating time

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ABSTRACT: The absorption of drugs through the gastrointestinal tract is a highly variable process; prolonging gastric retention of the dosage form extends the time for drug absorption. A novel drug delivery system overcomes the physiological problems of short gastric retention by decreasing fluctuations in blood drug concentration with subsequent reduction in undesirable toxicity and poor efficiency. Various approaches have been introduced to prolong gastric residence time, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bio-adhesive systems, high density systems, modified shape systems, *etc*. Bilayer floating drug delivery systems are the most promising drug delivery system, which exhibits a unique combination of floatation and bilayer, leading to prolongation in residence time in the stomach. Floatation is achieved due to bulk density being less than gastric fluids. So, the system remains buoyant in the stomach for a prolonged period, releasing the drug slowly at the desired rate and thus increasing the bioavailability of narrow absorption window drugs. This review entitles the floating drug delivery system principle and current technology used in the development. Also, it sheds light on the advantages and Total 6 disadvantages to be there disadvantages, the need for floating bilayer tablets, challenges in bi-layer tablet manufacturing, and characterization and evaluation methods for bilayer floating tablets.

INTRODUCTION: Dosage forms are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients and inactive components, in a particular configuration and apportioned into a particular dose. The Dosage forms can be classified based on uses, application site, route of administration, and physical state [1]. The oral route of administration is the most convenient and preferred route of drug delivery to systemic circulation due to its ease of administration, patient compliance, least sterility constraints, and flexible design of dosage forms.

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But the oral absorption of drugs with a narrow absorption window in the upper small intestine shows poor bioavailability with conventional dosage forms due to short residence time. The relatively brief gastric emptying time (GET) in humans, which normally averages 2 to 3 hr through the major absorption zone (stomach or upper part of the intestine), can cause incomplete drug release from the drug delivery system (DDS), leading to the diminished efficacy of the administered dose.

After the absorption window has been crossed, drugs released from controlled/sustained release systems go waste with negligible absorption, indicating that the absorption window can limit oral bioavailability. So, it's beneficial to develop sustained-release formulations that remain at the absorption site for a prolonged time. One of the approaches for achieving a prolonged and predictable drug delivery profile in GIT is to control the gastric retention time of the

formulation. And this can be achieved by developing a Gastro retentive drug delivery system (GRDDS) which prolongs the residence time of the drug in the upper part of the gastrointestinal tract [2, 3, 4].

Floating drug delivery systems (FDDS) are meant to retain the drug in the stomach and are suitable for drugs with poor solubility and low stability in intestinal fluids. The basis behind this system is to make the dosage form less dense than the gastric fluids, to make them float on Gastric fluid. A floating bilayer tablet consists of an immediate release layer and a sustained release layer.

After the release of the immediate layer, the sustained release layer forms a colloidal gel barrier on the surface by absorbing gastric fluid, and it forms a system with a density less than gastric fluid. Due to its low density, it remains floating in the stomach for an extended period [5].

Gastro-Retentive Drug Delivery System (GRDDS): 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.

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

1. Acting locally in the stomach.
2. Primarily absorbed in the stomach.
3. Poorly soluble at an alkaline pH.
4. Narrow window of absorption.
5. Absorbed rapidly from the GI tract.
6. Degrade in the colon [6, 7].

Advantages of GRDDS [8]:

1. Increase in bioavailability and improved efficacy of the drug is achieved.
2. Delivery of drugs with a narrow absorption window in the small intestine region.
3. Optimized release in case of short half-life drugs causes flip-flop pharmacokinetics, and reduced dosage frequency ensures patient compliance.
4. GRDDS is advantageous against the drawbacks of gastric retention time (GRT) and gastric emptying time (GET) because this system remains buoyant on gastric fluid because of lower bulk density than gastric fluids.
5. GRDDS is efficient in treating stomach and small intestine-related problems. It's attributed to the fact that GRDDS sustains drug release and, hence, provides local therapy in these organs.
6. GRDDS provides a systematic and controlled drug delivery, reducing the chances of overexposure to drugs at the diseased site.
7. The gastro-retentive dosage forms reduce variance in concentrations of drugs and effects.

Disadvantages of GRDDS [9, 10]:

1. An increased level of fluids in the stomach is needed for this system.
2. Unsuitable for drugs such as:

a. Problematic with solubility in gastric fluid.

b. Causing G.I irritation.

c. Inefficient in an acidic environment.

1. GRDDS is fed into the system after the meal as retention in the stomach depends on the digestive state.
2. Bio/mucoadhesive systems have the problem of the high turnover rate of the mucus layer, thick mucus layer & soluble mucus-related limitations
3. Time needed for swelling in the case of a Hydrogel based swelling system is longer.
4. On multiple administrations, size-increasing drug delivery systems can cause a threat to life owing to the possible hazard of permanent retention in the stomach.

Classification of Gastro-retentive Drug Delivery System [11]:

A. Low-density systems (Floating systems)

a. Effervescent system

1. Volatile liquid-containing system

2. Gas generating system

3. Matrix tablets

B. Non effervescent system

1. Colloidal gel barrier system/Hydrodynamically balance system

2. Layered Tablets

a. Single-layer tablets

b. Bilayer tablets

3. Alginate beds

4. Hollow microspheres

B. High-density systems

C. Bio-adhesive or Mucoadhesive systems

D. Swelling and Expanding Systems

E. Magnetic system

F. Raft-forming systems

G. Super porous hydrogel system

H. Modified shape system

Stomach Overview: The stomach is divided into 3 regions: fundus, body, and pylorus. The pylorus is the separation between the stomach and duodenum. The fundus and body serve as a reservoir for undigested material, whereas the antrum (pylorus) is the main site for mixing motions and is a pump for gastric emptying. Gastric emptying occurs during both fed as well as in fasting states. The pattern of motility is, however, different for the two states. During the fasting state, an inter-digestive series of electrical events occur, which cycle through the stomach and intestine every 2–3 hr. This is called the inter-digestive or migrating myoelectric cycle (MMC). This cycle is divided into the following 4 phases;

Phase I (Basal Phase): This phase lasts 40 to 60 min with rare contractions.

Phase II (Pre-burst Phase): This phase lasts 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): This phase lasts for 4 to 6 min. It includes intense and regular contractions for short periods. Because of this wave, 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: This phase lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles. After ingesting a mixed meal, the pattern of contractions changes from fast to a fed state. This is also known as the digestive motility pattern and involves continuous contractions as in phase II of the fasted state. These contractions cause a reduction in the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. The fed state onset of MMC is delayed resulting in a slowdown of gastric emptying rate [11, 12].

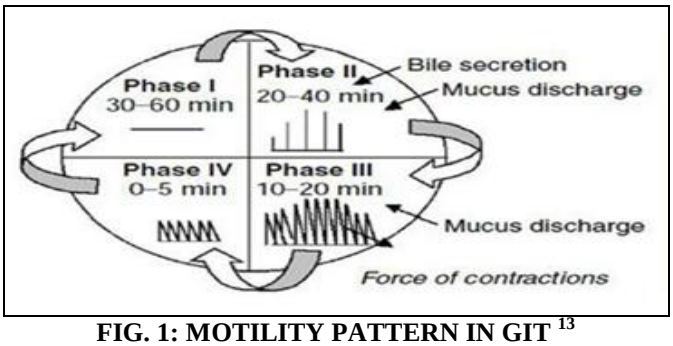

FIG. 1: MOTILITY PATTERN IN GIT [13]

Approaches for GRDDS [14]: The following methods have been incorporated to improve retention of the oral dosage form in the stomach *viz*. floating system, swelling and expanding system, bio-adhesive system, high-density system, and other delayed gastric emptying devices. It is shown in **Fig. 2.**

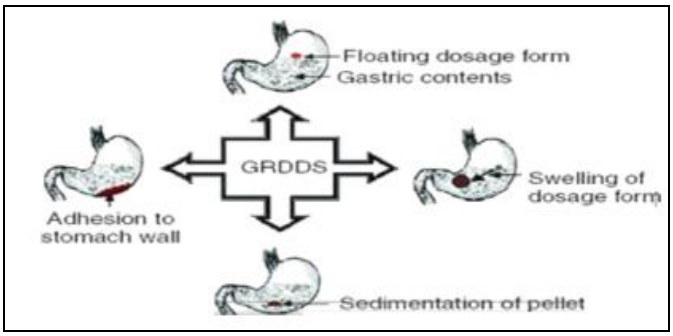

FIG. 2: APPROACHES FOR GRDDS

Floating Drug Delivery System: Floating drug delivery Systems are low-density systems with a bulk density less than gastric fluids. Because of its low density, it remains buoyant in the stomach for a prolonged period. The system floats on the gastric contents and releases the drug slowly at the desired rate. Once the drug is released completely, the stomach empties the residual system.

This results in increased gastric residence time and better control of the fluctuations in plasma drug concentration with a low risk of toxicity. Drugs that are locally active in the stomach, drugs with narrow absorption windows, and unstable in the intestine and colonic environment are the potential drug candidates for FDDS. This system improves drug absorption and also minimizes the mucosal irritation of drugs. FDDS requires a high fluid level in the stomach to float and work efficiently, which limits the approach to some extent [15, 16].

The pre-requisites for a floating drug delivery system are:

A. It should release contents slowly to serve as a reservoir.

B. Specific gravity should be maintained lower than gastric contents (1.004 – 1.01 gm/cm^3).

C. It must form a cohesive gel barrier [17].

Types of Floating Drug Delivery Systems based on the mechanism of buoyancy are;

A. Effervescent System

A. Volatile liquid-containing system.

B. Gas generating system.

B. Non-effervescent System:

A. Alginate beads.

B. Hollow microspheres.

C. Single-layer floating tablets.

D. Bilayer floating tablet.

E. Colloidal gel barrier system.

F. Microporous compartment system [15].

A. Effervescent Systems [15, 19]: The effervescent system can also be called the gas generating system. Gas bubble generation helps to achieve floatability. These systems utilize gas-generating agents like sodium bicarbonate, citric acid, or tartaric acid to achieve floatability. After oral administration in the GIT, CO2 gas is liberated from these drug delivery systems, which reduces the system's density, and the system thus floats on the gastric fluid. 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, C02 is liberated, and gas is entrapped in swollen hydrocolloids, which provides buoyancy. This system is further classified as below;

1. Volatile Liquid Containing Systems: This system is also called an osmotically controlled floating system. It involves the use of liquids such as ether and cyclopentane. This system provides gastric retention by incorporating an inflatable chamber with a liquid. The system contains two compartments: The first comprises the drugs, and the second contains volatile liquids. The liquid vaporizes at a physiological temperature to produce a gas, enabling the drug reservoir to float.

2. Gas Generating Systems: This system involves the use of agents which release carbon dioxide gas. Effervescent agents such as sodium bicarbonate, citric acid, tartaric acid, and chitosan are mainly used to generate carbon dioxide, thus reducing the system's density and helping the system float in the stomach. This floating helps the drug be retained for a prolonged period.

B. Non-effervescent Systems [2, 15, 19]: These systems comprise a gel-forming or swellable cellulose type of hydrocolloids made up of polysaccharide along with matrix-forming polymers like polycarbonate, polymethacrylate, and polystyrene. This system mainly depends on the mechanism of swelling of polymers and their adhesion to the GIT, as agents causing effervescence are not used in this system. These systems are further classified as below;

1. Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems): This system contains drug and gel-forming hydrocolloids which help the system float on the stomach content. Various gel-forming agents include hydroxyethyl cellulose, hydroxypropyl methylcellulose, polysaccharides, and polystyrenes. Upon contact with gastrointestinal fluid, the hydrocolloid in the system hydrates to generate a colloid gel barrier around its surface.

2. Microporous Compartment Systems: This system contains an encapsulated drug reservoir with pores on the top and bottom walls. Entrapment of air is possible through these pores. Floating of the system over the gastric content is stimulated by entrapped air in the floating chamber. The gastric fluid enters through an aperture which dissolves the drug for absorption.

3. Floating Microspheres/Micro Balloons: Hollow microspheres are also known as micro balloons and are considered the most efficient buoyant system. It consists of a central hollow space inside the microsphere. The hollow microsphere is loaded with a drug and is prepared by a novel emulsion solvent diffusion method.

4. Alginate Beads/Floating Beads: Multi-unit floating dosage forms have been developed from calcium alginate spherical beads of about 2.5 mm in diameter and can be prepared by adding sodium alginate solution into aqueous solution of calcium chloride, resulting in the precipitation of calcium alginate. The beads are further separated, snap-frozen in liquid nitrogen, and freeze-dried at 400 °C for 24 h, which leads to a porous system formation. This precipitation leads to the formation of a porous system that can maintain a floating force for over 12 hr.

5. Single-Layer Floating Tablets: These tablets are prepared by mixing the drug with a gel-forming hydrocolloid, which swells 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.

6. Bilayer Floating Tablets: A bilayer tablet contains two layers; one immediate release layer, which releases the initial dose from the system, and the second sustained release layer, which absorbs gastric fluid, forming an impenetrable colloidal gel barrier on its surface, and maintains a bulk density of less than unity and thereby it remains buoyant in the stomach.

Bilayer Floating Tablet: Bilayer floating tablet is the new era for the successful development of controlled release formulation. Bilayer tablet is better than the traditionally used other dosage forms. A bilayer tablet is suitable for sequentially synthesizing two drugs in combination. It's also able to separate two incompatible substances. The delivery rate of either single or two API'S can be controlled in bilayer tablets. Floating bilayer tablets contain two layers: the immediate release layer and the sustained release layer. These tablets are substantially designed to reduce administration frequency and increase the duration of action. The immediate release layer releases the drug immediately. It provides rapid absorption of the drug, and the sustained release layer, also called the maintenance layer, releases the drug over a prolonged period and maintains the therapeutic index. Two different drugs can also be incorporated in two layers. After the release of the immediate layer, the second layer, the sustained release layer, forms the colloidal gel barrier on the surface by absorbing gastric fluid. It achieves a density less than gastric fluid, which remains floating in the stomach for an extended period [20].

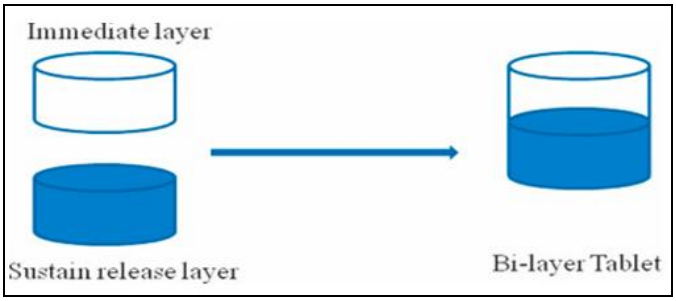

FIG. 3: BILAYER FLOATING TABLET

Advantages of Bilayer Floating Tablets [21]:

1. These tablets provide sustained drug delivery and increased gastric residence time as this system remains in the stomach for many hours via floating.
2. This system has additional advantages over single layer floating drug delivery system concerning formulation stability.

3. Ease of administration leads to better patient compliance.
4. Site-specific drug delivery is achieved for drugs like Furosemide and Riboflavin, formulated as a floating system.
5. This system is microbiologically and chemically stable.
6. They are the most compatible oral dosage form because of higher dose precision and lesser content variation.
7. They provide the most flexible dosage form.
8. Best suited for large-scale production.
9. Masking of bitter taste and bad odour can be achieved by coating.
10. Swallowing of tablets is easy and convenient.
11. Cost-effective as compared to other oral dosage forms.

Disadvantages of Bilayer Floating Tablets [5, 22]:

1. High amount of fluid levels is required in the stomach so that the system float properly.
2. Drugs having solubility and stability problems in stomach cannot be formulated.
3. Drugs causing irritation on gastric mucosa cannot be formulated as floating dosage form.
4. Capping is also a problem in bilayer tablets.
5. Separation of layer occurs due to lack of sufficient bonding and a reduction in yield occurs.
6. Insufficient Hardness.
7. There are chances of layer mixing between 2 layers.
8. Because of some drugs' low density and amorphous nature, compacts do not form because they resist compression.
9. Less control over weight of individual layer.
10. Difficulty in swallowing in the case of children and unconscious patients.
11. Due to poor wetting and less dissolution properties of some drugs, bioavailability problem occurs.
12. Sometimes encapsulation or coating is required for drugs sensitive to moisture, bitter tasting and with bad odour.

Need of Bilayer Floating Tablet [5]:

1. To control the delivery rate of single or two active pharmaceutical ingredients.
2. 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.
3. 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.
4. To modify the total surface area available for the active pharmaceutical ingredient layer by sandwiching with one or two inactive layers to achieve swellable /erodible form for modified release.

Selection Criteria of Drug for Bilayer Floating Tablet [5]:

1. Molecular size of drugs should be smaller than 100-600 Dalton.
2. Drugs should have half-life (2-6 hour).
3. Drugs having less bioavailability in gastric region.
4. Drugs Unstable at intestinal pH can be used.
5. Less dose of a drug .
6. Drugs have narrow absorption windows in GI tract ex. Riboflavin and levodopa.
7. Drugs are basically absorbed from the stomach and upper part of the Gastrointestinal tract.
8. Drugs that disturb normal colonic bacteria. Example. amoxicillin trihydrate.

9. Locally active in the stomach. Example. Antacids and misoprostol.

10. Drugs that degrade in the colon. Example. Ranitidine and metronidazole.

Quality and GMP Requirements for Bilayered Tablets [20, 23]: To Manufacture a quality bi-layer tablet in a validated and GMP-way, the selected press must be capable of:

1. Preventing capping and separating the 2 individual layers constituting the bi-layer tablet.
2. Providing adequate tablet hardness.
3. Preventing cross-contamination between the 2 layers.
4. Producing a transparent visual separation between the 2 layers.
5. Producing Accurate and individual weight control of the two layers.

Challenges in Bilayer Manufacturing [22]: We often see Bilayer tablets as two single-layer tablets that are compressed into one. But in actual practice, there are some manufacturing challenges. The challenges are given below;

Delamination: When the 2 halves of the tablet doesn't get bonded completely, the tablet falls apart.

Cross-contamination: If the first layer's granulation intermingles with the second layer's granulation or vice-versa, then there are chances of cross-contamination. Proper dust collection leads to the prevention of cross-contamination.

Production Yields: To prevent cross contamination, dust collection is needed, leading to losses. Thus, bilayer tablets have lower yields as compared to single-layer tablets.

Cost: Bilayer tableting is expensive compared to single-layer tableting for several reasons. First, the tablet press is expensive. Second, the tablet press generally runs more slowly in bilayer mode. Third, more time is spent on formulation development, analysis, and validation because of the need to develop 2 compatible granulations. If not well controlled/optimized, these factors will impact the bilayer tablet's bilayer compression and quality attributes (sufficient mechanical strength for maintaining its integrity and individual layer weight control).

Types of Bilayer Tablet Press [24, 25]:

1. Single-sided tablet press.
2. Double-sided tablet press or "compression force" controlled tablet press.
3. Bilayer tablet press with displacement monitoring.

1. Single-sided Tablet Press: The press design is simple and consists of a single-sided press with both chambers of the doublet feeder separated from each other. Each chamber is gravity fed or forced-fed with different power, producing two individual tablet layers. When the die passes under the feeder, it gets loaded with the first layer of powder and then subsequently by the second layer of powder. Then the entire tablet is compressed in one or more steps.

Limitations of the Singlesided Press:

1. No weight control/ monitoring of the individual layers.
2. No distinct separation between the two layers is seen visually.
3. Dwell time is very short for the first layer due to the small compression roller, which results in hardness and capping problems. Reduction in the turret- rotation speed can be done for the extension of dwell time

2. Double-Sided Tablet Press: A double-sided press provides an individual fill station, pre-compression, and main compression for each layer. The bi-layer tablet will undergo four compression stages before being ejected from the press. Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. In this, the effective peak compression force exerted on each tablet or layer is measured by the control system at the main compression of the layer.

This measured peak compression force is the signal the control system uses to reject out-of-tolerance tablets and correct the die fill depth when required.

Advantages of Double-sided Tablet Press:

1. Displacement weight monitoring is achieved for independent and accurate weight control of the individual layer.
2. Low compression force is exerted on the first layer to avoid capping and separation of the individual layer.
3. Dwell time at pre-compression of both the first and second layers is increased, providing sufficient hardness at maximum turret speed.
4. Maximum prevention of cross-contamination between two layersis achieved.
5. Yield is maximized.

Limitations of Double-sided Tablet Press:

1. Correct bonding is obtained only when the first layer is compressed at a low compression force. Because of the low compression force applied, this first layer can still interact with the second layer during final compression. But bonding gets restricted if the first layer is compressed at a high compression force.
2. The low compression force required when compressing the first layer reduces the accuracy of the weight monitoring or control of the first layer.
3. **Bilayer tablet press with displacement monitoring:** The displacement tablet weight control principle is different from the principle basedon compression force. When measuring displacement, the control system sensitivity depends on the applied pre-compression force and doesn't depend on the tablet weight.

Advantages of Bilayer Tablet Press with Displacement Monitoring:

1. Weight monitoring or control for the individual layers' accurate and independent weight control is achieved.
2. Low compression force is exerted on the first layer to avoid capping and separating the two individual layers.
3. Dwell time at pre-compression of both first and second layer is increased, providing sufficient hardness at maximum turret speed.
4. Maximum prevention of cross-contamination between the two layers is achieved.
5. Clear visual separation between the two layers is seen, and the yield is maximized.

Various Techniques for Bilayer Tablet [5, 25, 26]:

A. Oros ® Push Pull Technology

B. L-Oros™ Technology

C. DUROS Technology

D. DUREDAS or Dual Release Drug Absorption System Technology

E. RoTab Bilayer

F. EN SO TROL Technology

G. Geminex Technology

H. PRODAS or Programmable Oral Drug Absorption System.

A] OROS® Push Pull Technology: This system primarily consists of two or three layers among which the one or more is essential of the drug, and the other layer consists of a push layer.

The drug layer consists of a drug and two or more different agents. So, this drug layer comprises a poorly soluble drug, and there is further addition of suspending and osmotic agents. The tablet core is surrounded by a semi-permeable membrane.

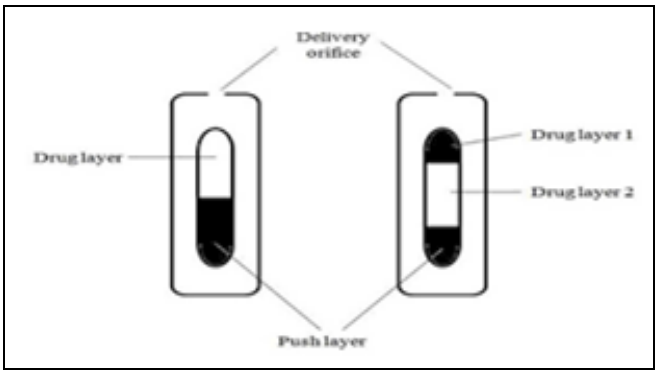

FIG. 4: BILAYER AND TRI-LAYER OROS PUSH PULL TECHNOLOGY

B]. L-OROS^{TM} Technology: Alza developed the L-OROS system, which consisted of a lipid soft gel product containing a drug in a dissolved form. This is initially manufactured and then coated with a barrier membrane, an osmotic push layer, and a semi-permeable membrane. It is also drilled with an exit orifice.

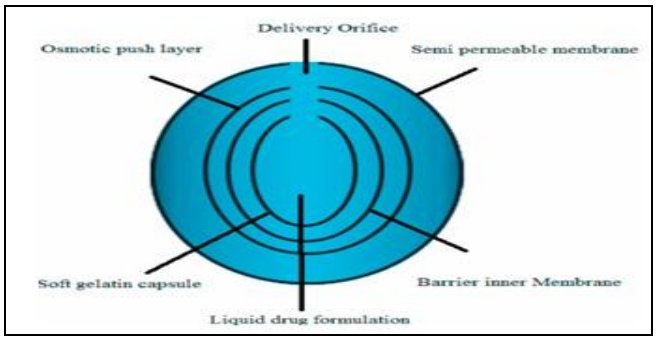

FIG. 5: L–OROSTM TECHNOLOGY

C]. DUROS Technology: This technology has been specifically developed to provide two different release rates or dual drug release from a single dosage form. The tablets are prepared by two separate compression steps that combine an immediate-release granulate and a controlled-release hydrophilic matrix complex within one tablet. The controlled release matrix remains intact, slowly absorbing fluid from the GI tract, leading to matrix expansion, and converting the hydrophilic polymers into a porous, viscous gel. As the gel continues to expand, fluid penetrates further into the dosage form, which dissolves the drug and leads to the release of the drug in a controlled manner.

E]. RoTab Bilayer Technology: The RoTab Bilayer is the most versatile rotary bilayer tablet press with mono and bi-layer tablet capabilities. The RoTab bilayer tablet press provides the highest level of flexibility to R&D with a first layer auto sampling feature and easy-to-change monolayer mode. Adjusting the filling speed and die table allows dose and compression force to be automatically regulated. Hardness is also regulated when required.

F]. EN SO TROL Technology: Shire laboratory developed EN SO TROL technology based on identifying and incorporating an enhancer, which was identified to form an optimized dosage form in a controlled release system. By this enhancement in solubility is also achieved.

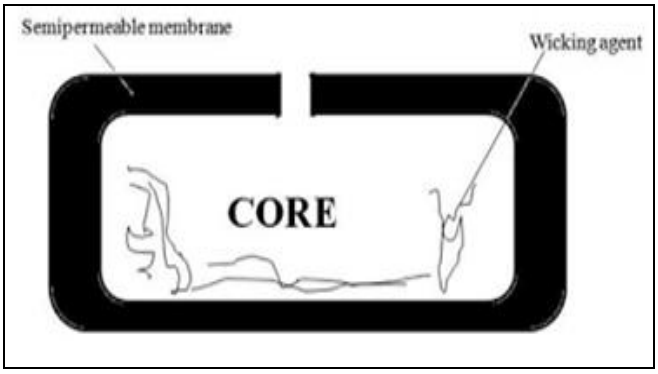

FIG. 6: EN SO TROL TECHNOLOGY

G]. Geminex Technology: This technology can greatly help increase the drug's therapeutic effectiveness and minimize its side effects. This technology is characterized by delivering one or more active substances having different drug release patterns through a single dose. It is useful to patients and pin industries as a single tablet provides drug delivery at different rates.

H]. PRODAS or Programmable Oral Drug Absorption System: PRODAS is a multi-particulate drug delivery technology based on the encapsulation of controlled-release mini tablets in the size range of 1.5 to 4 mm in diameter. This technology is a combination of multi-particulate and hydrophilic matrix tablet technologies. Thus it aims to provide the advantages of both these drug delivery systems in a single dosage form. By the use of this technology, Mini tablets with different release rates can be combined and can be incorporated into a single dosage form to provide the desired drug release rates.

Preparation of Bilayer Tablets [22, 25]: Bilayer tablets are prepared so that one layer of drug is for immediate release and the second layer is to release the drug either as a second dose or in an extended-release form. The bilayer tablets containing two incompatible drugs can also be prepared by compressing separate layers of each drug, minimizing the contact area between the two layers. An additional intermediate layer of inert material can also be included. To produce adequate tablet formulation, sufficient mechanical strength, and desired drug release profile are certain requirements that must be fulfilled. It can be difficult for the formulator to achieve these conditions, especially in bilayer tablet formulation, where double compression technique is involved,

because of poor flow and compatibility characteristic of the drug which results in capping and/or lamination.

Compaction: The process by which the porosity of a given powder is decreased due to its grains being squeezed together by mechanical means. The compaction of the material involves both compressibility and consolidation.

Compression: It is defined as reducing bulk volume by eliminating voids and bringing particles into closer contact.

Consolidation: It is the property of the material in which there is increased mechanical strength due to inter particulate interaction (bonding). On layer one, the compression force was a major factor influencing tablet delamination.

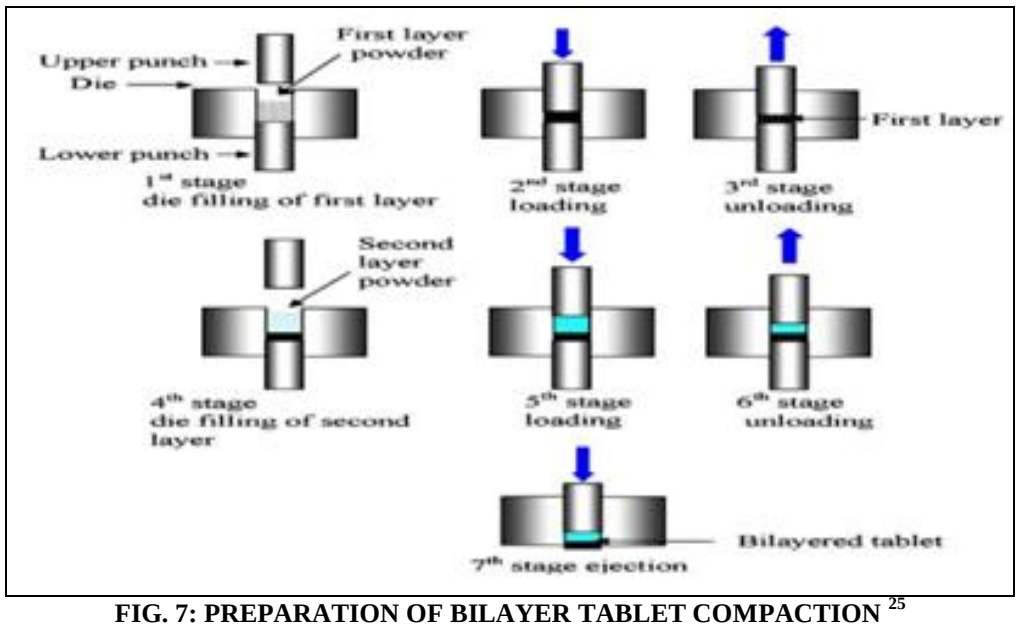

FIG. 7: PREPARATION OF BILAYER TABLET COMPACTION [25]

Evaluation Parameters of Bilayer Floating Tablet [23, 27, 28, 29]:

***In-vitro* Evaluation of Bilayer Floating Tablet:** Evaluation was carried out to assess the formulations' physicochemical properties and release characteristics.

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 [height].

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

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

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

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

Hausnser'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, colour, odour, 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/cm^2.

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,

$$\%F= [1-(Wt / W)]*100$$

W – Initial weight of tablet,

W_t - 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,

$$V = \pi r2h$$

$$d = m/v$$

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 hr 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: Time required for the tablets to rise on the surface of the medium is floating lag time. Ideally, it should be less than one minute. It is measured using dissolution test apparatus containing 0.1 N HCl (900ml).

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

Swelling Study: Weigh the tablet (W_1) 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 (W_2).

The formula calculates the swelling index (SI),

$$-SI= W_t –W_0/W_0×100$$

W_t = weight of the swollen tablet,
W_0=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: RECOMMENDED LONG TERM AND ACCELERATED STORAGE CONDITION

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.

C_{13} Octanoic Acid Breath Test: C_{13} Octanoic acid is incorporated into GRDDS. In the stomach, due to a chemical reaction, octanoic acid liberates CO_2 gas which comes out in a breath. The important Carbon atom which will come in CO_2 is replaced with C_{13} isotope. So, the time to which C 13O2 gas is observed in breath can be considered gastric retention time of dosage form. As the dosage form moves to the intestine, there is no reaction and no CO_2 release. So, this method is cheaper than other methods.

CONCLUSION: Bilayer Floating Tablet is novel and beneficial technology to overcome the limitations of the single-layered tablet. This system provides two types of drug release: sustained release and immediate release, which can be increased up to 24 hours. It also results in gastric retention, thereby increasing gastric emptying time and bioavailability. Using such a system, two drugs can be administered concurrently simultaneously, providing better patient compliance. Drugs having narrow absorption windows, such as anti-viral, antibiotic and antifungal can also be given in floating bilayer tablet form. Bi-layer tablet GMP and quality requirements can vary widely. So, many types of presses are being used to produce bi-layer tablets, ranging from simple single-sided presses to highly sophisticated machines. Whenever high-quality bi-layer tablets need to be produced at high speed, using an 'air compensator' in combination with displacement control would be the best solution.

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