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*Research Article*

# A REVIEW ON BILAYER FLOATING TABLETS: A NEW TREND

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**A R T I C L E I N F O**

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**A B S T R A C T**

Bilayer tablets have been developed to achieve controlled delivery of different drugs with predefined release profiles. In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form (Bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Bilayer tablet can be a primary option to avoid chemical incompatibilities between Active pharmaceutical ingredients by physical separation, and to enable the development of different drug release profiles (immediate release with controlled release). Despite their advantages, due to the use of different materials and complex geometric boundaries between adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient friendly. Gastro retentive drug delivery system prolongs the retention time of dosage forms in the stomach or upper gastrointestinal tract, as to improve solubility, bioavailability and the therapeutic efficacy of the drugs. Several pharmaceutical companies are currently developing Bilayer tablets. For a variety of reasons: patient extension, therapeutic, marketing to name a few. To reduce capital investment, quite often existing but modified tablet presses and are used to develop and reduce such tablets. This review is an attempt to illustrate the applications of Bilayer tablet by releasing the medicaments immediately for patient's relief and also maintaining therapeutic level to an extended period of time by controlling the release of drug in a sustained manner for better patient compliance and acceptability.

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## INTRODUCTION

Dosage forms are pharmaceutical drug products with a specific mixture of API's and inactive components in a particular configuration and formulated into a particular dose. The Dosage forms can be classified based on route of administration, application site, uses and physical state. The oral route of administration is the most preferred and convenient route of drug delivery to systemic circulation due to its patient compliance, ease of administration, flexible design of dosage forms and least sterility constraints.

In case of upper small intestine which shows poor bioavailability with conventional dosage forms due its narrow absorption window for the oral absorption of drugs. The GET (gastric emptying time) in humans normally averages for 2 -3 hours in the stomach or upper part of the intestine, which can cause incomplete drug release from the DDS (drug delivery system), which leads to decrease the efficacy of administered dose. So, the absorption window can limit the oral bioavailability. So, it is useful to develop sustained – release formulations that remain at the absorption site for a prolonged period. So, Gastro retentive drug delivery system the systems that are retained in the stomach for long period of time and there by improves the bioavailability of drugs that are preferentially absorbed from upper GIT. Prolonged stomachic retention reduces drug waste, improves bioavailability, solubility of the drugs that are less soluble during the high PH scale environment.[1]

### 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.

1. **Phase I (Basal phase):** it lasts from 40 to 60 minutes with rare contractions.
2. **Phase II (Preburst phase):** lasts for 40 to 60 minutes with intermittent action potential and contractions.
3. **Phase III (burst phase):** lasts for 4 to 6 minutes, which includes intense and regular contractions for short period of time.
4. **Phase IV:** lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.[11]

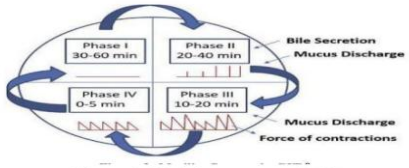


**Fig no. 1 Motility pattern of GIT.**

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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.[2]

**Floating drug delivery systems**

Floating drug delivery systems or hydrodynamically controlled systems are unit lower-density systems than the gastric fluids, which have good buoyancy to float over the gastric contents and release the drug slowly at desired rate. The residues are eliminated once the drug is released completely. So, this system controls the fluctuation in plasma drug concentration with a low risk of toxicity and increase the gastric residence time. FDDS are suitable for the drugs with poor solubility, low stability in the intestinal fluids, for the drugs with narrow absorption window.[3]

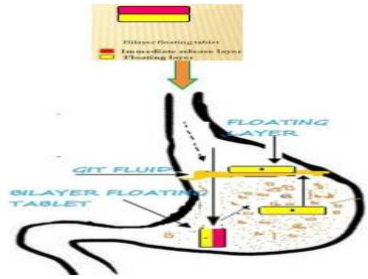


**Fig.2** Mechanism of Bilayer effervescent floating tablets

**Classification of floating tablets based on the mechanisms of buoyancy**

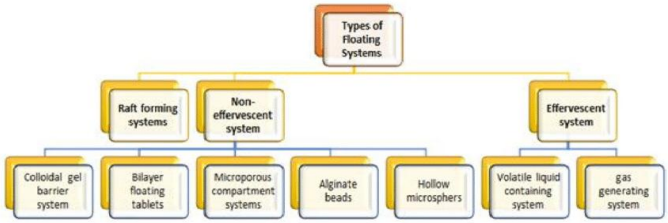


**Fig.3** Classification of Floating Tablets Based on the Mechanisms of Buoyancy

**A. Effervesent Systems**

These systems are also called as Gas generating systems. Floatability is achieved by generating gas bubbles. Floatability is achieved by utilizing gas generating agents like sodium bicarbonate, citric acid or tartaric acid. After the administration of drug orally into the GIT, CO2 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 sodium bicarbonate and citric acid is reported to be 0.76:1 for the generation of gas. Swellable polymers such as Methylcellulose and chitosan and various effervescent compounds are used for the preparation of matric. When this swellable polymers come in contact with the acidic gastric contents, CO2 is liberated and gas is entrapped in swollen hydrocolloids, which provides buoyancy.[4]

Effervescent systems are classified into

1. Volatile liquid containing systems.
2. Gas Generating systems

**1. Volatile liquid contining systems**

This system is also called as an osmotically controlled floating systems. 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 2 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.

**2. Gas Generating Systems**

In these systems carbon dioxide gas is released by using effervescent agents such as sodium bicarbonate, citric acid, tartaric acid and chitosan are mainly used. Due to the release of carbon dioxide the density of the system decreases and helps the system float in the stomach. Thus helps the drug to be retained for a prolonged period.[5]

**B. Non Effervescent Systems**

Gel-forming or swellable cellulose type of hydrocolloids made up of polysaccharide are comprised in these systems along with matrix-forming polymers like polymethacrylate, polycarbonate and polystyrene. Swelling of polymers and their adhesion to the GIT is the mechanisms of these systems. These systems are further classified into.

**1. Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems)**

This system contains gel-forming hydrocolloids along with the drug which help the system float on the gastric contents. Various gel-forming agents hydroxypropyl methylcellulose, hydroxyethyl cellulose, polystyrenes and polysaccharides. When system gets in contact with gastrointestinal fluid, a colloid gel barrier is generated by the hydrating the hydrocolloid in the system around its surface.

**2. Microporous Compartment Systems**

In this system a drug reservoir that is encapsulated inside a microporous compartment having pores on the surface and bottom walls. The outer wall of the drug reservoir compartment is sealed to stop drug which is not dissolved into contact with the stomach surface. Entrapment of air through the pores leads to the floating of the system over the gastric content in the stomach. The absorption of the drug occurs when the gastric fluids enter through an aperture and dissolve the drug.

**3. Floating Microspheres/Micro Balloons**

Floating microspheres are also called as Hallow microspheres which are considered to be more efficient buoyant systems. This system contains a central hollow space which is loaded with a drug, and this hallow sphere is prepared by using solvent diffusion approach.

**4. Alginate Beads/Floating Beads**

Multi-unit floating dosage forms have been formulated from calcium alginate spherical beads. Calcium alginate spherical beads of about 2.5 mm in diameter can be prepared by adding sodium alginate solution which incorporated drop wise into aqueous solution of calcium chloride, resulting calcium alginate precipitation. The beads are further separated, snap frozen in liquid nitrogen, and freeze-dried at 400 °C for 24 h,

where porous system formation occur which can maintain a floating force for over 12 hr.

**5. Single-Layer Floating Tablets**

A gel-forming hydrocolloid are mixed with the drug, 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 layer is immediate release layer, where the initial dose from the system is released, and the second layer is sustained release layer, which absorbs gastric fluid, which forms 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.[6]

**BILAYER FLOATING TABLET**

Bilayer floating tablet is the new era for the successful development of controlled release formulation. A bilayer tablet is suitable for consecutively synthesizing two drugs in combination. Two incompatible substances are also able to separate by using bilayer floating tablets. The bilayer floating tablets are able to control delivery rate of either single or two API"S. Bilayer floating tablets contain 2 layers: first one is the immediate release layer, and the second one is the sustained release layer. These tablets are significantly designed to increase the duration of action and reduce administration frequently. The drug is released immediately from the immediate release layer where rapid absorption is provided. The sustained release layer, also called maintenance layer, maintains the therapeutic index and releases the drug for a prolonged period. Two different drugs can also be incorporated in two layers. After the release of the immediate layer, a colloidal gel barrier is formed by the sustained release layer on the surface by absorbing gastric fluid. It achieves a less density than gastric fluid, which remains floating in the stomach for an extended period.[7]

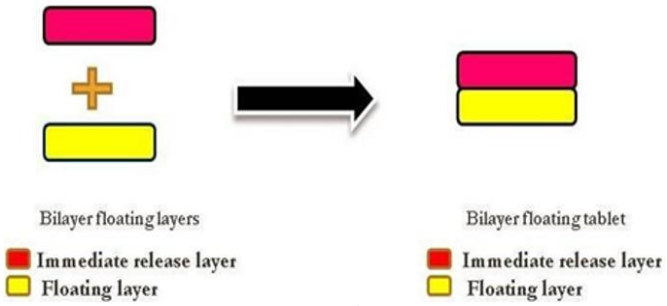


**Fig. 4** Imagination of Bilayer Tablet

**Advantages of Bilayer Floating Tablets**

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. Advantageous over single layer floating drug delivery system.
3. Patient compliance due to its ease of administration.
4. Bilayer floating tablets are microbiologically and chemically stable.
5. Site-specific drug delivery is achieved.
6. Best suited for large-scale production.
7. Most flexible dosage form.
8. Cost-effective.
9. Masking of bitter taste.

**3. Disadvantages of Bilayer Floating Tablets:**

1. Separation of layer occurs due to lack of sufficient bonding and a reduction in yield occurs.
2. High amount of fluid levels is required in the stomach so that the system float properly.
3. Drugs causing irritation on gastric mucosa cannot be formulated as floating dosage form.
4. Separation of layer occurs due to lack of sufficient bonding and a reduction in yield occurs.
5. There are chances of layer mixing between 2 layers.
6. Capping is also a problem in bilayer tablets.
7. Drugs having solubility and stability problems in stomach cannot be formulated.
8. Difficulty in swallowing in the case of children and unconscious patients.

**Drug Selection Criteria for Bilayer Floating**

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

**TYPES OF BILAYER TABLET PRESS**

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 consists of a single-sided press with doublet feeder separated from each other in both the compartment. Two individual tablet layers are produced when each chamber is gravity fed or forced fed with different power. When the die passes under the feeder, the first layer of powder gets loaded and then subsequently by the second layer of powder. Then the entire tablet is compressed in one or more steps. [9]

**2. Double-Sided Tablet Press**

Individual filling stations are provided in double-sided tablet press with pre-compression and main compression for each layer. The four compression stages are undergone by bilayer tablet before being ejected from the press. Compression force used to monitor and control tablet weight in most of the double-sided tablets presses with automated production. Control systems are used to measure the effective peak compression force exerted on the tablet at the main compression of the layer.

**3. Bilayer tablet press with displacement monitoring**

This tablet press principle is different from the principle based on compression force. When measuring displacement, the control system sensitivity depends on the applied pre-compression force and doesn't depend on the tablet weight.

Various Techniques for Bilayer Tablet:

1. Oros ® Push Pull Technology

2. L-Oros TM Technology
3. DUROS Technology
4. DUREDAS or Dual Release Drug Absorption System Technology
5. Ro Tab Bilayer
6. EN SO TROL Technology
7. Geminex Technology
8. PRODAS or Programmable Oral Drug Absorption System.

**1. OROS® Push Pull Technology**

These systems consist of 2or 3 layers among which 1 layer is drug and the second layer is pushing layer.

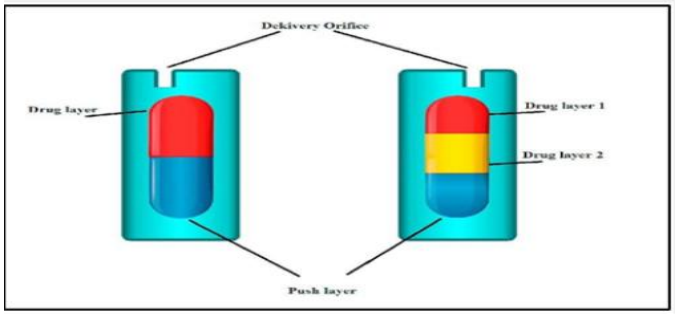


**Fig. 5** OROS® Push Pull Technology

**L-OROSTM Technology**

L-OROS system is developed by Alza, the drug in a dissolved form is present in a liquid soft gel product. 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. [10]

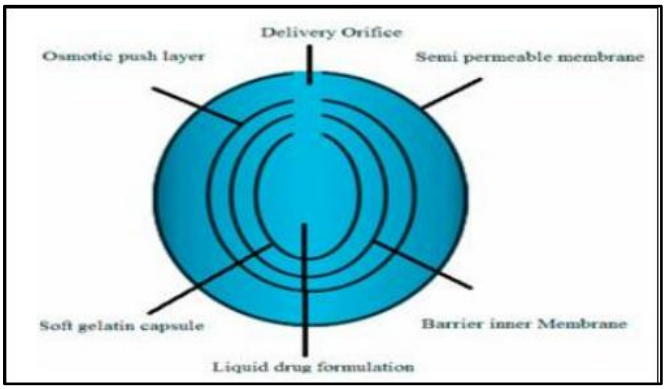


**Fig. 6** L-OROSTM Technology

**3. DUROS Technology**

In this technology two different release rates or dual drug release are provided from a single dosage form. Two separate compressions are used for the tablet preparation, steps that combine a controlled release hydrophilic matrix complex and an immediate release granule 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. [11]

**4. Ro Tab Bilayer Technology**

This technology is most versatile rotary bilayer tablet press with mono and bi-layer tablet capabilities. The Ro Tab 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. Compression force to be automatically regulated by adjusting the filling speed. Hardness is also regulated.

**5. EN SO TROL Technology**

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

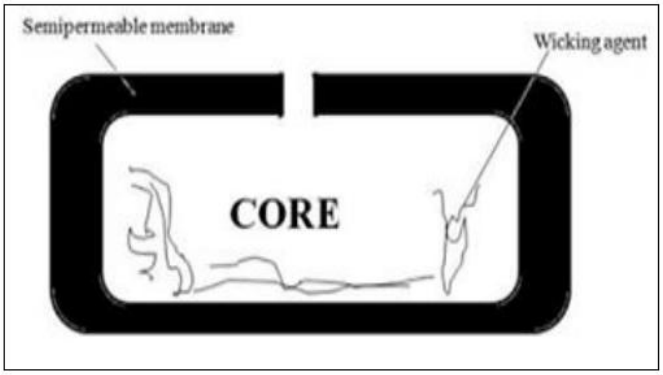


**Fig. 7** EN SO TROL Technology

**6. Geminex Technology:**

This technology delivers one or more active substances having different drug release patterns through a single dose.

**7. PRODAS or Programmable Oral Drug Absorption System**

This technology is a combination of hydrophilic matrix tablet and multi-particulate technologies. Thus, provide the advantages of both drug delivery systems in a single dosage form. [12]

**PREPARATION OF BILAYER**

Bilayer tablets are developed so that one layer of drug is for immediate release and the second layer is the sustained release layer, which release the Lyer for prolong period. 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 [13]

**Compaction**

The process by which the powder porosity is decreased by mechanical means. The compaction of the material involves both consolidation and compression.

**Compression**

It is defined as bulk volume reduction by eliminating 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. [14]

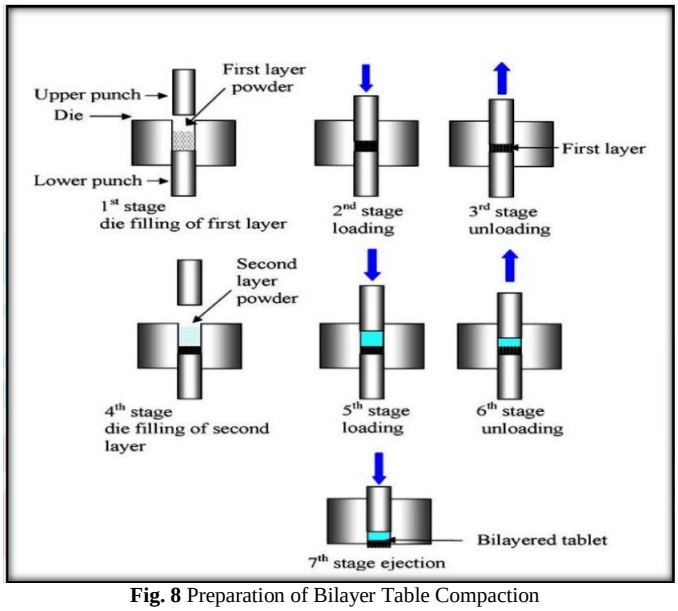


**Fig. 8** Preparation of Bilayer Table Compaction

## EVALUATION PARAMETERS OF BILAYER FLOATING TABLET

**In-vitro Evaluation of Bilayer Floating Tablet**:

Evaluation was carried out to assess the formulations' physicochemical properties and release characteristics.

1. **Pre-Compression Parameters**

**A) Angle of Repose:** Angle of repose is the maximum angle possible between the surface of the powder pile and the horizontal plane [height].

$$\mathbf{Tan\ \theta = h / r}$$

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

Where θ= Angle of repose, r = radius of pile, h= height of pile

**B) 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**

C) **Compressibility Index**: The compressibility index of was determined by following formula,

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

**D) Hausnser's Ratio:** It is calculated using the formula,

**Hausner's ratio = TD / BD**

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

**2. Post-Compression Parameters**

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

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

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

**Weight Variation = (Iw -Aw)/Aw x 100%**

**Where, Iw = Individual weight of tablet; Aw = Average weight of tablet.**

**C) 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 $kg/cm^2$.

D) **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,**

**wt. - Weight of tablet after revolution**

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

**E) 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.

**F) 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.

**G) 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).

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

**I) 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),

$$-SI= Wt - W0/W0\times100$$

Wt = weight of the swollen tablet,

W0=Initial weight of the tablet.

**J) Stability Study (Temperature Dependent):** The bilayer tablets are stored under the following conditions for a prescribed period as per ICH guidelines for accelerated studies.[15]

## CONCLUSION

Bilayer Floating Tablet is novel and beneficial technology to overcome the limitation of the single layered tablets. This system provides sustained release and immediate release, which can be increased up to 24 hours. It is increasing gastric emptying time and bioavailability by gastric retention. Two drugs can be administered concurrently simultaneously, which provides better patient compliance. Drugs having narrow absorption windows, such as antibiotic, anti-viral and antifungal can also be given in bilayer floating tablet form.

## References


1. Aulton ME: Pharmaceutics: The Science of Dosage Form Design. Churchill Livingstone, 2nd Edition 2001; 1-13.
2. Gidwani B, Vyas A, Ahirwar K, Shukla SS, Pandey R and Kaur CD: Factorial design and a practical approach for gastro-retentive drug delivery system. Research Journal of Pharmacy and Technology 2016; 9(6): 641-649.
3. Sharma V, Rathore D and Kumar A: Floating Drug Delivery System: A Review. International Journal of Medical and Biomedical Studies 2020; 4(8): 23-30.
4. Rouge N, Buri P and Doelker E: Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. International Journal of Pharmaceutics 1996; 136(1-2): 117-139.
5. Rahul Kumar Garg and Indrajeet Singhvi: Bilayer Floating Tablet Technology: An Overview. International Journal of Pharmacy and Pharmaceutical Research 2015; 3(3): 302- 322.
6. Jassal M, Nautiyal U, Kundlas J and Singh D: A review: Gastroretentive Drug Delivery System (grdds). Indian Journal of Pharmaceutical and Biological Research 2015; 3(1): 82-92.
7. Sarawade A, Ratnaparkhi MP and Chaudhari S: Floating drug delivery system: an overview. International Journal of Research and Development in Pharmacy & Life Sciences. 2014; 3(5): 1106-1115.
8. Sharma AR and Khan A: Gastroretentive Drug Delivery System: An approach to enhance gastric retention for prolonged drug release. International Journal of Pharmaceutical Sciences and Research 2014; 5(4): 1095- 1106.
9. Pandey A, Kumar G, Kothiyal P and Barshiliya Y: A review on current approaches in gastro retentive drug delivery system. Asian Journal of Pharmacy and Medical Science 2012; 2(4): 60-77
10. Makwana A, Sameja K, Parekh H and Pandya Y: Advancements in controlled release gastroretentive drug delivery system: A review. Journal of Drug Delivery and Therapeutics 2012; 2(3): 12-21.
11. Hatwar PR and Channawar MA: Gastroretentive Mucoadhesive Drug Delivery System. World Journal of Pharmaceutical Research 2020; 9(8): 812-831.
12. Kumar PD, Rathnam G, Prakash CR, Saravanan G, Karthick V and Selvam TP: Formulation and characterization of bilayer floating tablets of ranitidine. Rasayan J. Chem 2010; 3(2): 368-374.
13. Badola A and Sah SK: Gastroretentive: Expanding the Field of Control Drug Delivery. European Journal of Pharmaceutical and Medical Research 2017; 4(2): 335- 342.
14. Nidhi KM, Bhati J, Rawat N and Sharma S: A Brief Summary on "Gastro Retentive Drug Delivery System". International Journal of Modern Pharmaceutical Research 2022; 6(3): 53-60.
15. Renthlei L, Dewan M, Magar NT, Regmi S and Barakoti H: Floating Drug Delivery System: An Outlook. International Journal of Pharmaceutical & Biological Archives 2020; 11(1): 1-13.


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