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Review Article

### NOVEL FLOATING BILAYER DRUG DELIVERY SYSTEM-A REVIEW

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#### ABSTRACT

*Oral sustained release gastroretentive dosage forms offer many advantages for drugs with absorption from upper parts of gastrointestinal tract and for those acting locally in the stomach. Floating drug delivery system is one amongst the gastroretentive dosage forms used to achieve prolonged gastric residence time. Bilayer floating drug delivery system is combined principle of bilayer tablet as well as floating mechanism. Bilayer floating tablet is new era for the successful development of controlled release formulation along with various features to provide a way of successful drug delivery system. Bilayer floating tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The purpose of this paper is to review the current technology used in the development of bilayer floating drug delivery system as well as summarizes the applications, characterization, evaluation methods and future potential for bilayer floating tablets.*

**KEYWORDS:** *Bilayer Floating Tablets, GRDDS*

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## INTRODUCTION

### 1. Introduction of Drug Delivery Systems:

Oral controlled release (CR) dosage forms (DF) have been extensively used to improve therapy of many important medications. Drug absorption from oral controlled release dosage forms is often limited due to short gastric retention time. However, hydrodynamically balanced system (HBS) type dosage forms remain in the stomach for several hours due to their modified GRT. This technology has generated enormous attention over the last few decades owing to its potential application to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome Gastro-retentive dosage forms. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic effect.

The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half life and all these leads to decrease in patient's compliance.<sup>1</sup>In order to overcome the above problems, various types of controlled release dosage forms are formulated and altered, so that patient compliance increase through prolonged effect, adverse effect decreases by lowering peak plasma concentration.<sup>2</sup> The controlled release dosage form maintaining relatively constant drug level in the

plasma by releasing the drug at a predetermined rate for an extended period of time

### 1.2. Concept of Floating drug delivery systems

Floating tablets are the systems which are retained in a stomach for a longer period of time and there by improve the bioavailability of drugs. Floating drug delivery system should be primarily aimed to achieved more predictable & increase bioavailability. Floating drug delivery system it is helpful to develop the control release tablet control release implies the predictability & reproducibility to control the drug release drug concentration in target tissue & optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. Under certain circumstances prolonging its gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substance. For eg., drugs that are absorbed in proximal part of gastric intestinal tract & the drug are less soluble are degraded by alkaline pH may benefit from prolonging action.

Floating tablets were prepared using direct compression technique using polymers like HPMC for their gel forming properties.

A large number of chemical entites have been introduced of which some have absorption all over the Gastro Intestinal tract, some have absorption windows (i.e., absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility in intestinal media. The drugs belonging into the second and third categories, and the drugs which are required for local action in the stomach, require a specialized delivery system. All the above requirements can be met and effective delivery of the drugs to the absorption window, for local action and for the treatment of gastric disorders such as gastro-esophageal reflux, can be achieved by Floating drug delivery systems(FDDS).

A number of FDDS involving various technologies carrying their own advantages and limitations were developed such as, single and multiple unit hydrodynamically balanced systems(HBS), single and multiple unit gas generating systems, hallow microspheres and raft forming systems.

The hydrodynamic balanced system (HBS) also called floating drug delivery system(FDDS) is an oral dosage form(tablet or capsules) designed to prolong the residence time of the dosage form with in the GIT. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents drug dissolution and release from the dosage form retained in the stomach fluids occur at the pH of the stomach under fairly controlled

conditions. The retentive characteristics of the dosage form are not significant for the drugs that:

- Are insoluble in intestinal fluids
- Act locally
- Exhibit site specific absorption
- The formulation of the dosage form must comply with three major criteria for HBS:
- It must have sufficient structure to form a cohesive gel barrier
- It must maintain an over all specific gravity less than that of gastric content
- It should dissolve slowly enough to serve as a “RESERVIOR” for the delivery system.

Floating systems are one of the important categories of drug delivery systems with gastric retentive behavior. Excipients used most commonly in these systems include HPMC, Polyacrylate polymers, polyvinylacetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and poly carbonates.

Administration of a prolonged release floating dosage form tablet or capsule will result in dissolution of the drug in gastric fluid. After emptying of the stomach contents, the dissolve drug available for absorption in the small intestine it is therefore expected that a drug will be fully absorbed from the dosage form of it remains in solution form even at alkaline pH of the intestine.

From the last few years, there are some pharmaceutical companies developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (Bilayer tablet), promoting patient convenience and compliance. Bilayer tablets can be used to avoid chemical incompatibilities between API by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). Despite their advantages, due to the use of different materials and complex geometric boundaries between the adjacent layers, the mechanical structures of this drug delivery system have become quite intricate, requiring complicated tablet architectures as well as patient-friendly administration which pose serious challenges to the pharmaceutical scientists/engineers. This oral presentation details the major challenges associated with Bilayer compression and rational strategy to deliver the desired Bilayer tablet performance. Bilayer tablets have some key advantages compared to conventional monolayer tablets. In addition Bilayer tablets have enabled the development of controlled delivery of API with predetermined release profile by combining layers with various release patterns or by combining slow release with immediate-release layers. Bilayer tablets are suitable for sequential release of two drugs in combination, separate two

incompatible substances and also for sustained release tablets, in which one layer is immediate release as an initial dose and second layer is maintenance dose.<sup>1,2,3</sup>

### 1.2.1. Gastrointestinal retention:

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients<sup>4</sup>. To successfully modulate the gastrointestinal transit time of a drug delivery system through floating drug delivery system (FDDS) For maximal gastrointestinal absorption of drugs and site-specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. These are outlined and briefly discussed.<sup>5</sup>

### 1.2.2. Stomach anatomy:

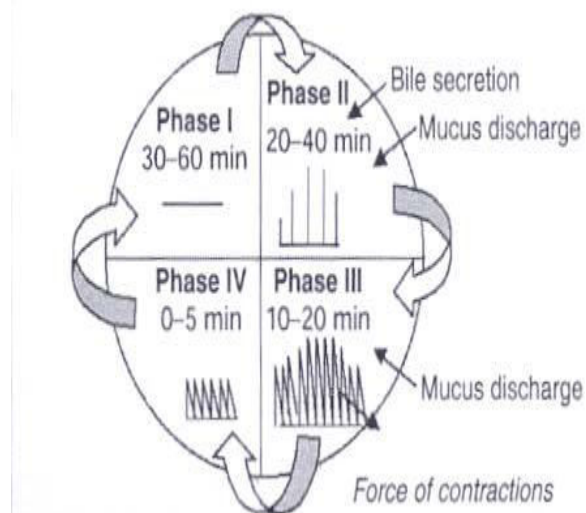
The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Substantial enzymatic digestion is initiated in stomach, particularly of proteins. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing.<sup>6</sup>

Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.<sup>7</sup>

It has been reported that the mean value of pH in fasted healthy subjects is  $1.1 \pm 0.15$ . But when food comes into the stomach, the pH may rise to levels in the 3.0 to 4.0 level due to the buffering capacity of proteins. However, in fasted state, basal gastric secretion in women is slightly lower than that of men.<sup>8</sup>

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases:

- Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.
- Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) lasts for 10 to 20 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.



**Fig1: Motility pattern in GIT**

### 1.3. Factors Affecting Gastric Residence Time of FDDS:

#### 1.3.1. Formulation factors:

##### Size of tablets:

Retention of floating dosage forms in stomach depends on the size of tablets. Small tablets are emptied from the stomach during the digestive phase, but large ones are expelled during the house keeping waves.<sup>9</sup>

Floating and non-floating capsules of 3 different sizes having a diameter of 4.8 mm (small units), 7.5 mm (medium units), and 9.9 mm (large units), were formulated and analyzed for their different properties. It was found that floating dosage units remained buoyant regardless of their sizes on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during digestive phase while the non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.<sup>10</sup>

##### Density of tablets:

Density is the main factor affecting the gastric residence time of dosage form. A buoyant dosage form having a density less than that of the gastric fluids floats, since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period. A density of less than 1.0g/ml i.e. less than that of gastric contents has been reported. However, the floating force kinetics of such dosage form has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyancy capabilities.<sup>11</sup>

##### Shape of tablets:

The shape of dosage form is one of the factors that affect its gastric residence time. Six shapes (ring tetrahedron, cloverleaf, string, pellet, and disk) were screened in vivo for their gastric retention potential. The tetrahedron (each leg 2cm long) rings (3.6 cm in diameter) exhibited nearly 100% retention at 24 hr.<sup>12</sup>

##### Viscosity grade of polymer:

Drug release and floating properties of FDDS are greatly affected by viscosity of polymers and their interaction. Low viscosity polymers (e.g., HPMC K100 LV) were found to be more beneficial than high viscosity polymers (e.g., HPMC K4M) in improving floating properties. In addition, a decrease in the release rate was observed with an increase in polymer viscosity.<sup>13</sup>

### 1.3.2 Idiosyncratic factors:

#### Gender:

Women have slower gastric emptying time than do men. Mean ambulatory GRT in meals ( $3.4 \pm 0.4$  hours) is less compared with their age and race-matched female counterparts ( $4.6 \pm 1.2$  hours), regardless of the weight, height and body surface.

#### Age:

Low gastric emptying time is observed in elderly than do in younger subjects. Intrasubject and intersubject variations also are observed in gastric and intestinal transit time. Elderly people, especially those over 70 years have a significantly longer GRT.<sup>14</sup>

#### Posture:

##### i) Upright position:

An upright position protects floating forms against postprandial emptying because the floating form remains above the gastric contents irrespective of its size. Floating dosage forms show prolonged and more reproducible GRTs while the conventional dosage form sink to the lower part of the distal stomach from where they are expelled through the pylorus by antral peristaltic movements.<sup>15</sup>

##### ii) Suine position:

This position offers no reliable protection against early and erratic emptying. In supine subjects large



dosage forms (both conventional and floating) experience prolonged retention. The gastric retention of floating forms appear to remain buoyant anywhere between the lesser and greater curvature of the stomach. On moving distally, these units may be swept away by the peristaltic movements that propel the gastric contents towards the pylorus, leading to significant reduction in GRT compared with upright subjects.<sup>16</sup>

#### Concomitant intake of drugs:

Drugs such as prokinetic agents (e.g., metoclopramide and cisapride), anti Cholinergics (e.g., atropine or propantheline), opiates (e.g., codeine) may affect the performance of FDDS. The coadministration of GI-motility decreasing drugs can increase gastric emptying time.<sup>16</sup>

#### Feeding regimen:

Gastric residence time increases in the presence of food, leading to increased drug dissolution of the dosage form at the most favorable site of absorption. A GRT of 4-10 h has been reported after a meal of fats and proteins.<sup>17</sup>

#### Suitable Drugs for Gastroretention:

Delivery of the Drugs in continuous and controlled manner have a lower level of side effects and provide their effects without the need for repeated dosing or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, from where absorption occurs and contact time is limited. Appropriate candidates for controlled release gastroretentive dosage forms are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT.

1. Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
2. Basically absorbed from stomach and upper part of GIT, e.g., chlordiazepoxide and cinnarazine.
3. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

#### 1.4. Approaches to Gastroretention:

Several techniques are reported in the literature to increase the gastric retention of drugs.

##### 1) High density systems:

These systems, which have a density of  $\sim 3\text{g/cm}^3$ , are retained in the rugae of stomach and capable of withstanding its peristaltic movements.<sup>[18, 20]</sup>

The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of  $2.4\text{-}2.8\text{g/cm}^3$ . Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide,

and iron powder must be used to manufacture such high-density formulation.<sup>16</sup>

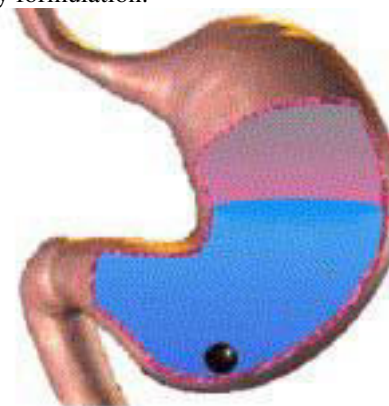
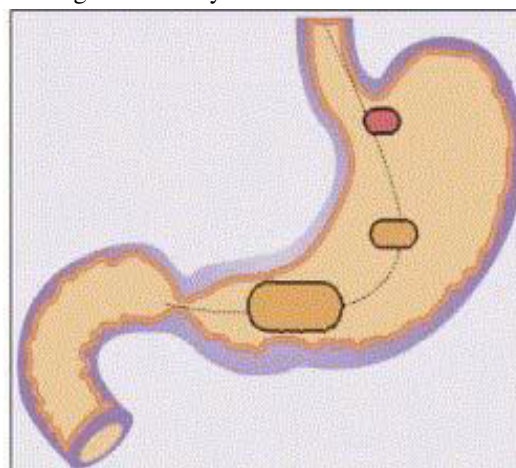


Fig 2: High density systems

##### 2) Swelling and expanding systems:

These systems are also called as “Plug type system”, since they exhibit tendency to remain lodged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed



state.<sup>21</sup>

##### Fig 3: Swellable tablet in stomach

By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form.

A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.<sup>22</sup>



**Fig 4: Different geometric forms of unfoldable systems**

### 3) Incorporating delaying excipients:

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that changes the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolamine myristate in a delivery system.<sup>23</sup>

### 4) Modified systems:

Systems with non disintegrating geometric shape molded from silastic elastomers or extruded from polyethylene blends, which extend the GRT depending on size, shape and flexural modulus of drug delivery device.<sup>24</sup>

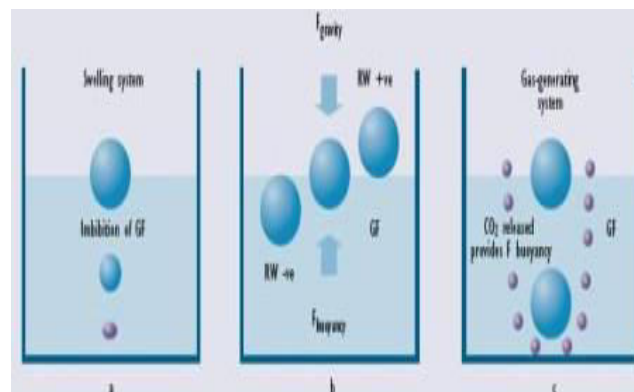
### 5) Mucoadhesive & bioadhesive systems:

Bioadhesive drug delivery systems are used to localize a delivery device within the lumen to enhance the drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach.

Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.<sup>[25,26]</sup>

### 6) Floating systems:

Floating drug delivery systems (FDSS) 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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach<sup>27</sup>. Floatation of a drug delivery system in the stomach can be achieved by incorporating floating chamber filled with vacuum, air, or inert gas.



**Fig 5: The mechanism of floating systems**

## 1.5. Classification of FDSS Based On Mechanism of Buoyancy

### A) Single unit:

Single unit dosage forms are easiest to develop but suffers from the risk of losing their effects too early due to their all-or-none emptying from the stomach and, thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastro intestinal tract.<sup>28</sup>

#### i. Non effervescent systems:

One or more gel forming, highly swellable, cellulosic hydrocolloids (e.g. hydroxyl ethyl cellulose, hydroxyl propyl cellulose, hydroxypropyl methyl cellulose [HPMC] and sodium carboxy methyl cellulose), polysaccharides, or matrix forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) are incorporated in high level (20-75% w/w) to tablets or capsules.<sup>[29,30]</sup>

For the preparation of these types of systems, the drug and the gelforming hydrocolloid are mixed thoroughly. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

#### ii. Effervescent systems or gas generating systems:

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO<sub>2</sub> is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1.

### B) Multiple units:

Single unit formulations are associated with problems such as sticking together or being obstructed in gastrointestinal tract, which may have a potential danger of producing irritation. Multiple unit systems avoid the 'all-or-none' gastric emptying nature of single unit systems. It reduces the inter subject variability in absorption and the probability for dose dumping is lower.<sup>31</sup>

#### **i. Noneffervescent systems:**

A little or no much report was found in the literature on noneffervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates float in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

#### **ii. Effervescent systems:**

A multiple unit system comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment was prepared. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radio labeled floating beads and compared with non-floating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5hr was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 hr.<sup>32</sup>

#### **iii. Floating microspheres:**

A controlled release system designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microspheres. Techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers, such as polycarbonate, Eudragit® S and cellulose acetate, are

used in the preparation of hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer plasticizer ratio.<sup>33</sup>

#### **C) Raft forming systems:**

The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO<sub>2</sub> and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.<sup>34</sup> have come out with such formulation in the treatment of H.pylori infections of GIT.

#### **1.6. Advantages of Bilayer Floating tablet:**

Before explaining the advantages of Bilayer tablet, here are the advantages of the tablet dosage form over the dosage form are as follows:

- Tablet is a unit dosage form and they offer the greatest compatibilities of all oral dosage forms for the greatest dose precision and the least content variability.
- The cost is approximately lower than any other oral dosage form.
- These are very compact in nature.
- In genera the packaging procedure for tablets are easier and cheaper.
- Swallowing of tablets is very easy.
- They are better suited to large scale production.
- Chemically, mechanically and microbiologically tablets are very stable.

#### **The advantages of the 'Bilayer Floating tablet' over the other conventional preparations of oral solid dosage forms include:**

- When the two different layers of the tablet content two different drugs, then the tablet can be easily used in combination therapy.
- This formulation can be use to deliver separate two incompatible substance.
- In case of drags having a low half life, each of the two layers of the tablet respectively content a loading dose and maintenance dose of the same and thus increase the bioavailability of the drug.
- Frequency of the dose administration is reduced which ultimately improve the patient compliance.
- In case of a conventional dosage form due to fluctuation of the dose interval the plasma drug concentration may differ (under

medication or over medication), but in this dosage form the plasma drug concentration is always constant, which ultimately provide a more effective action of the drug.

- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of high availability drug can be reduced by formulation in an extended action form. The safety margin of high potency drugs can be increased and the local and systemic adverse effects can be reduced in sensitive patients.

### 1.7. Limitations of floating tablet:

From the above mentioned advantage of Bilayer tablets it is quite clear that in pharmaceutical industry it is a great revolution, but there are certain limitations in the formulation and use of Bilayer tablets,

Such as:

- One of the major challenges in Bilayer formulation is lack of sufficient bonding and adhesion at the interface between the adjacent compacted layers which is often the result of an interfacial crack and layer separation.
- If the compacted layers are too soft or too hard, they will not bind securely with each other which can lead to compromised mechanical integrity and also the separation of the layers.
- Other challenges during development include establishing the order of layer sequence, layer weight ratio, elastic mismatch of the adjacent layers, first layer tamping force, and cross contamination between layers.
- The adjacent layers of a Bilayer tablet are bonded together by mechanical means, so the factors influences the stress state is very important. The mechanical properties of each layer and the tablet, and compression parameters along with specialized techniques and compression condition plays a very important role for the same.
- Administration of sustained release Bilayer tablet does not permit the prompt termination of therapy.  
General properties of Bilayer floating tablet dosage forms
- A bi-layer tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.
- Should have sufficient strength to withstand mechanical shock during its production packaging, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes over time. The bi-layer tablet must be able to

release the medicinal agents in a predictable and reproducible manner.

- Must have a chemical stability shelf-life, so as not to follow alteration of the medicinal agents.

### 1.8. Manufacturing Process:

Manufacturing processes such as wet granulation/roller compaction and addition of binders increases the level of complexity in understanding the critical factors governing compression and tablet breaking force. Thus, the tablet breaking force and the tablet's propensity for delamination/capping either during manufacturing or during storage need to be carefully observed. Apart from the critical material attributes of individual components and final blend, the tablet press has large influence on the manufacture of multilayer tablets. The level of pre-compression force, punch velocity, consolidation time (time when punches are changing their vertical position in reference to the rolls as the distance between the punch tips are decreased), dwell time (time when punches are not changing their vertical position in reference to the rolls), relaxation time (time when both punches are changing their vertical position in reference to the rolls as the distance between the punch tips increases before losing contact with the rolls), and the applied force can have significant effect on the critical quality attributes of the tablet. For instance, the extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity. It was demonstrated that increase in the punch velocity between of 50 and 500mm/s decreased the porosity reduction on individual layers.

### 1.9. Evaluation of Bilayer floating tablet:

#### Weight variation test:

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation allowed in the weight of a tablet by USP. The following percentage deviation in weight variation is allowed. In all formulations, the tablet weight was more than 324 mg, hence 5% maximum difference allowed.

#### Thickness:

The thickness of the tablets was determined by using micrometer meter screw gauze. Five tablets from each formulation were used; average values and standard deviation were calculated.

#### Hardness test:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of (kg/cm<sup>2</sup>) tablet was determined by using Monsanto



tester. In all the cases, mean of five replicate determinations were taken.

**Friability test:**

As per IP, this was determined by weighing 26 tablets after dusting, placing them in the Roche friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated according to following equation.

$\% \text{ Friability} = \frac{\text{Initial wt of tablets} - \text{Final wt of tablets}}{\text{Initial wt of tablets}} \times 100$

% Friability of tablets less than 1% are considered acceptable.

**In-vitro buoyancy test:**

The time between introduction of dosage form and its buoyancy on the SGF and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time

(TET). Floating behavior study were carried out in a USP XXIII dissolution

Apparatus type II (Paddle) at a speed 50 RPM in 900 ml SGF at  $37 \pm 0.50^\circ\text{C}$  for 12 hr to mimic *in vivo* conditions.

**Content uniformity:**

Ten tablets were finely powdered, quantities of the powder equivalent to 50 mg of API were accurately weighed and transferred to a 100 ml of volumetric flask containing methanol and mixed thoroughly. The solution was made up to volume and filtered. Appropriate dilutions were done using methanol and absorbance of the resulting solution was measured at the maximum at nm using a UV spectrophotometer.

**Swelling Index:**

The individual tablets were weighted accurately and kept in 50 ml of 0.1 N HCl. Tablets were taken out carefully after each hour up to 12 hours, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated by using following formula.

$\text{Swelling index} = \frac{\text{Wet weight of tablet} - \text{Dry weight of tablet}}{\text{Dry weight of tablet}} \times 100$

**1.10. DISEASE PROFILE:**

**HYPERTENSION:**

**Definition:**

Hypertension, also referred to as high blood pressure, HTN or HPN, is a medical condition in which the blood pressure is chronically elevated. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial

aneurysm, and is a leading cause of chronic renal failure. Even moderate elevation of arterial blood pressure leads to shortened life expectancy. In individuals older than 50 years, hypertension is considered to be present when a person's systolic blood pressure is consistently 140mmHg or greater. The normal blood pressure is 120/80.

**Classification:**

Hypertension can be classified either essential (primary) or secondary.

A. Essential hypertension indicates that no specific medical cause can be found to explain a patient's condition.

B. Secondary hypertension indicates that the high blood pressure is a result of (i.e., secondary to) another condition, such as kidney disease or tumors (pheochromocytoma and paraganglioma).

**Signs and symptoms:**

Healthcare professionals measuring blood pressure during a routine checkup usually find hypertension incidentally. In isolation, it usually produces no symptoms although some people report headaches, fatigue, dizziness, blurred vision, facial flushing, transient insomnia or difficulty sleeping due to feeling hot or flushed, and tinnitus during beginning onset or before hypertension diagnosis.

Hypertension is rarely severe enough to cause symptoms. These typically shows symptoms only when a systolic blood pressure over 240 mmHg and/or a diastolic blood pressure over 120 mmHg. These pressures without signs of end-organ damage (such as renal failure) are termed "accelerated" hypertension. When end-organ damage is possible or already ongoing, but in absence of raised intracranial pressure, it is called hypertensive emergency. Hypertension under this circumstance needs to be controlled, but prolonged hospitalization is not necessarily required

when hypertension causes increased intracranial blood pressure, it is called malignant hypertension. Increased intracranial pressure causes papilledema, which is visible on ophthalmoscopic examination of the retina.

**Causes:**

Although no specific medical cause can be determined in essential hypertension, it often has several contributing factors. These include obesity, salt sensitivity, renin homeostasis, insulin resistance, genetics, age, sleep apnea and liquorice consumption.

**Secondary hypertension:**

Only in a small minority of patients with elevated arterial pressure can have a specific cause to be identified. These individuals will probably have an endocrine or renal defect that, if corrected, could bring blood pressure back to normal values.

Another important cause of secondary hypertension include: Cushing's syndrome, Genetic, Coarctation of the aorta, Drugs like NSAIDs (Motrin/Ibuprofen), steroids, and Licorice (*Glycyrrhiza glabra*). Rebound hypertension is another type of secondary hypertension. Also few women of childbearing age have high blood pressure; up to 10% develop hypertension of pregnancy.

### 1.11. FUTURE POTENTIAL:

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

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