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Review Article

# A review on bilayer floating tablets

**Suresh Karudumpala*[1], Madhusudhana Chetty C.[2], Gnanaprakash K.[1], Venkatesh B.[1], Sankar P.[1]**

[1]Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur - 524 346, Nellore District, Andhra Pradesh, India

[2]Faculty of Pharmacy, Asia Metropoliton University, Cheras - 43200, Selangor, Malaysia

**ABSTRACT**

Bilayer tablets have been developed to achieve controlled delivery of different drugs with pre-defined 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 gastro intestinal 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.

**Keywords:** Bilayer tablets; controlled release layer; Floating tablets; Gastro retentive drug delivery system; immediate release layer

## INTRODUCTION

Bilayer floating tablets 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 and extended release) (Patel Mehul, *et* al., 2010) (Fig-1).

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate reliably buoyant on the surface of the meal. Many buoyant systems developed based on granules, powders, capsules, tablets, laminated films and hallow microspheres. Flotation of drug delivery system in the drug achieved by incorporating floating chamber filled with vacuum, air or inert gas from the system. After release of drug, residual system is emptied from the stomach. This results in an increased GRT and better control of fluctuations in plasma drug concentration. however beside minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force is also require to keep the dosage form( maniya shrikant *et al*., 2012, Mayavanshi AV, Gajjar SS 2008, Aulton ME 2012).

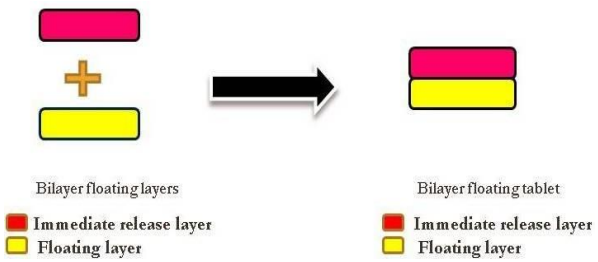


**Figure 1: Bilayer floating tablet (imagination)**

### Advantages

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. e.g.: Riboflavin and Furosemide.

* Corresponding Author
Email: suri.kp9@gmail.com
Contact: +91-8985580399
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The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentration can be prevented. This feature is of special importance for drugs with narrow therapeutic index.

The efficacy of the medicaments administered utilizing the sustained release principle of floating formulation has been found to be independent of the site of particular medicaments.

Complete absorption of the drug from floating dosage form is expected even at the alkaline PH of the intestine. The dissolution of the drug in gastric occurs and then the dissolved drug is available for absorption in small intestine after emptying of the stomach contents. (Maniya shrikant *et al.,* 2012).

Poor absorption is expected when there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Drugs that have poor bioavailability because of site specific absorption from the upper part GIT are potential candidate to be formulated as floating drug delivery system, there by maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric –coated LASIX –long product (29.5%). (pranjal kumar singh *et al*., 2011, sowmya C *et al*., 2012., kulkarni A and Bhatia M 2009, Rohan D *et al*., 2011, Naisarg D pujara *et al*., 2012, panchal Hiten Ashok and Twari Ajay kumar 2012)

Gastric retention of the drugs provides such advantages as better delivery of the drugs with narrow absorption windows in the small intestinal region, and longer residence time in the stomach, which could be advantageous for local action in the upper part of small intestine.

**Limitations**

1. A high level of field in the stomach is required for drug delivery to float and work efficiently.
2. Drugs which have stability and solubility problems in GIT are not suitable candidates for this system.
3. Drugs which are irritant to Gastric mucosa are also not desirable.
4. Drugs which under goes first pass metabolism may not be desirable for the preparation of these type of systems.( maniya shrikant *et al*., 2012)
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems (Naisarg D pujara *et al*., 2012, panchal Hiten Ashok and Twari Ajay kumar 2012, Kulkarni A and Bhatia M 2009).

**Floating mechanism**

**A) Effervescent**

Effervescent floating system prepared with help of swellable polymers such as methyl cellulose, chitosan and various effervescent compounds eg. Sodium bi carbonate, tartaric acid and citric acid. After oral administration this dosage in contact with the gastric content $CO_2$ liberate and gas entrapped in swollen hydrocolloids which provide buoyancy to the dosage form.

Gas generating agent push the tablet towards surface of gastric fluid, time required for this process is called log time. Then drug releases at surface of gastric fluid in controlled manner. Controlled release approximately 6-8 hours in targeted gastric region. (Fig-2).

**B) Non –effervescent**

These dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers like poly carbonate polyacrylate and poly styrene. After oral administration of dosage form can swells in contact with gastric fluids and attains a bulk density of <1. The air entrapped within 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 the gelatinous mass.

**Ground work on bilayer floating tablets**

Reynolds .J. E. F. 2005, G. K. McEvoy 2004 and M. C. Chapel Sky 2003 were explained about preparation and evaluation of bilayer floating Rosiglitazone maleate. This Active pharmaceutical ingredient is Oral antidiabetic, half life (t/2) 3-4 hrs and its solubility is decreased by increasing pH.

Hoffman BB 2001, Kendall MJ 1991 and Hwang SJ 1998 were researched on bilayer floating tablets of Rosiglitazone maleate. It is $B_1$-selective adrenergic blocker, half life (t/2) = 3-4 hrs, it degraded in colon.

C. Dollery 1999, N. H. Anaizi 1993 was designed Captopril bilayer floating tablets**.** This drug is ACE inhibitor; 37.5 – 75 mg dose is required in three times; most stable at 1.2 pH.

**Selection of drugs based on its suitability**

1. Drug should have less half-life (2-6 hrs).
2. Drug has less bioavailabity in gastric region.
3. Unstable at intestinal pH
4. Long term treatment disease and drugs (hypertension patients).
5. Less dose of drug

6. Less gastric retention time.
7. Narrow absorption window in GI tract ex: riboflavin and Levodopa
8. Basically absorbed from stomach and upper part of GIT. Ex: chlordiazoperoxide , cinnarazine.
9. Drugs that disturb normal colonic bacteria. Ex: Amoxicillin trihydrate
10. Locally active in stomach ex: antacids and misoprostol
11. Drugs that degrade in the colon ex: ranitidine and metronodazole.

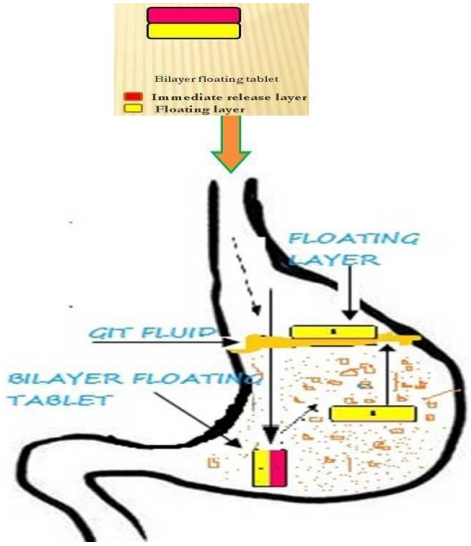


**Figure 2: Mechanism of Bilayer effervescent floating tablets (Imagination)**

**Formulation Aspects**

**Suitable Methods**

Bilayer floating tablet can be prepared using methods like direct compression, dry granulation, and wet granulation method. Layers was also prepared using combination of methods

Bi-layer tablets are tablet, made by compressing two different granulations fed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be set up for two or three layers. More are possible but the design becomes very special. (Priyal et al., 2013)

**Preparation of bilayer tablet**

Bilayer tablets can be prepared by combining of fast release layer and various formulations of controlled release layer. (Fig-3) After the compression upper punch was lifted and the blend of powder for immediate release layer was poured into the die, containing initially compressed matrix tablet on RIMEK multi station punching machine using 12.5 mm flat punches, with the hardness of 6.5 kg/cm2.

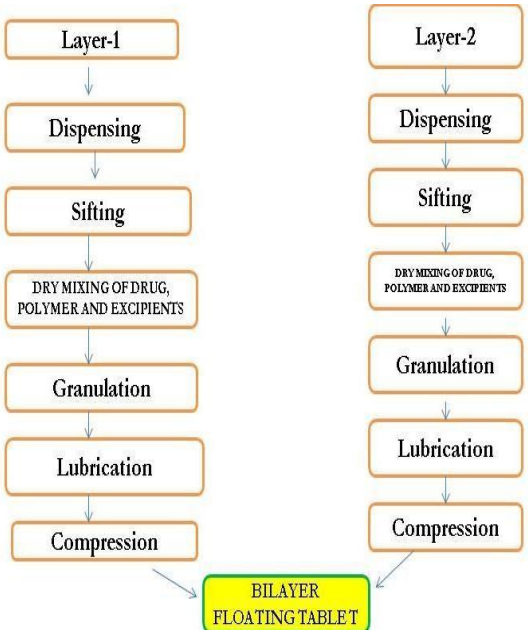


**Figure 3: Direct compression process for formulation of Bilayer floating tablets**

**Influence of process and formulation parameters**

As the initial dose layer do not affect the intermediate slow release or the second rapid phase or constant phase release, this layer is not necessary to be considered in the formulation process. Multi-layered tablet consisting of a core and one or more barrier layers should be taken into account while determining the parameters involved in the processing. The following factors should be considered for the process and formulation. (Vinayagamkannan et al., 2003)

**1. Parameters dealing with the layer consisted of therapeutically active substances**

During granulation of therapeutically active substances some basic factors are to be considered which includes percentage of the liquid used in granulation, time required for massing step, temperature of the outlet air during the drying step and milling screen apertures as well as the interaction between the amount of granulation liquid and the outlet temperature. While the impact of these factors on the final products has to be considered and the responses can be classified into four categories: (i) granules properties (e.g., flowability, bulk density, ability to settle, particle size distribution), (ii) extensometric responses (e.g. cohesion index, lubrication index, ejection strength, plasticity, elasticity), (iii) physical characteristics of tablet (e.g. thickness, weight variation, hardness, friability) and (iv) analytical results (e.g. content uniformity, in vitro profile) (Davis SS et al., 1986).

**2. Compression process**

The critical parameters in the compression process are turntable speed and compression forces corresponding to first, second and main layers. The tablet crushing strength response improves when the turret compres-

sion speed on the main compression force is increased. But these parameters (within a particular range) do not influence the content uniformity and the release performances in multi-layered, press coated and, bimodal delivery systems (Ahmed SI et al.,2010, Rane AB et al., 2009). But in the case of press coated tablet intended for distant destination (e.g. colon targeting) the release rate and lag time are dependent on the compression force. The release rate of drug decreases and the lag time increases with increasing compression force till a critical point. After this point increasing compression force does not provide further reduction in porosity. There is necessity of increasing the lag time more than 10 h in the gastric fluid under some physiological conditions (Fell JT et al., 1970) and also there is need for suppression of release in the intestinal fluid for more than 3 h in order to obtain colon targeting. To achieve these certain additives, which have poor wettability, are added to the outer shell polymer to prevent the penetration of dissolution medium into the pores in the outer shell. For example, magnesium stearate or calcium stearate were added to the hydroxyl propyl methyl cellulose acetate succinate (HPMCAS) polymer to increase the lag time (Fukui E et al 2001). Eiji Fukui et al. reported that the drug release in gastric fluid was completely suppressed until 15 h if tablets containing magnesium stearate irrespective of compression force and for tablets containing calcium stearate, it was necessary to increase the compression force to more than the range applied, to suppress until 12 h.

In the intestinal fluid the lag time was not prolonged to more than 2 h by addition of magnesium sterate. In contrast lag time could be prolonged by calcium stearate as long as 9 h by increasing the compression force. The above results suggested that press coated tablets intended for colon targeting mainly depends on compression force when poor wettable additives are used.

**3. Hardness of compressed tablet**

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm2.Hardness of tablet is expressed in terms of tensile strength. The tensile strength of the tablet is calculated by the formula, according to Fell and Newton (Verma RK and Garg 2001) S:σ=2P/πDt Where r = tensile strength (kg/cm2), D= tablet diameter (cm), t = tablet thickness (cm), P= force applied to fracture (kg).

The porosity of the tablets decreased by the rise of tensile strength which is ultimately depends on the compression load. Since the compression force (particular range) does not affects the release rate, therefore, hardness of the tablet (generally in layered construction) has less significance in the formulation. (Rane AB et al., 2009).

**4. Polymer concentration in core**

Polymer is one of the most important factors that influence the release of drug from the tablets. With the increase of the polymer concentration usually the dissolution rate of the tablet is decreased. This parameter does not affect the drug release in layered tablets as considerably in the bimodal tablet because the solubility of certain polymers depends on the pH of the surrounding medium. For example, the effect of decreasing HPMCAS-MF amounts in the inner layer of bimodal delivery system is not significant in pH 1.2 but in pH 7.4 drug release increases with decrease in the amount of polymers. At high pH values a less dense polymer network dissolves more rapidly than a tight structure, leading to increased drug release rate. At low pH HPMCAS-MF is not soluble, thus there is no effect on the breakdown of the polymer network. Therefore, concentration of pH sensitive retard polymers in the core should be controlled more closely ((Davis SS et al., 1986).

**5. Filler**

Filler used in the core of the tablet, has a great influence on the drug release rate because of its solubility. On contact with the release medium, the filler diffuses out from the device and thereby affect the drug release rate by increasing the porosity of polymers. Depending upon the amount of the filler the amount of the polymer is adjusted to keep the tablet weight constant. Example of such filler is lactose (Davis SS et al., 1986, Rane AB et al., 2009).

**Evaluation of Bilayer Floating Tablets**

All the prepared Bilayer floating tablets should be evaluated for following official and unofficial parameters.

**Appearance**

The Bilayer tablets can be identified visually by checking the difference in color.

**Thickness**

Thickness can be measured using a calibrated dial caliper. Five tablets of the formulation should be picked randomly and thickness can measured individually.

**Hardness**

Hardness can be measured using Monsanto hardness tester. For each batch three tablets should be tested.

**Friability**

Twenty tablets should be weigh and placed in the Roche friabilator and apparatus rotate at 25 rpm for 4 minutes. After revolutions, the tablets can dedust and weigh again. The Measure percentage friability using formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after revolution

***In vitro*-disintegration time**

Tablets place in each of six tubes of basket in disintegrations test apparatus. Suspend the assembly in 0.1 N HCl maintained at room temperature of 37 ±2°C and operate the apparatus, simultaneously note the time taken to disintegrate completely by using stopwatch. (Remya P.N et al., 2010).

**Weight variation**

Ten tablets randomly select from each batch and weigh individually. Calculate the average weight and standard deviation of 20 tablets. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

**Drug content uniformity**

Drug content can be estimate by using UV-Visible spectroscopy and HPLC technique.

**Floating property study**

The time takes for dosage form to emerge on surface of medium called buoyancy lag time (BLT). Duration of time by which the dosage forms constantly emerge on surface of medium called Total floating time (TFT) (Nurten O zdemir et al., 2000). Place tablets in a 400 ml flask of pH 1.2, time need to go upward and float on surface of the liquid and floating duration can be determine.

**Water uptake study**

The swelling of the polymers can be measure by their ability to absorb water and swell. The swelling property of the formulation can determine by various techniques (Mahesh D. Chavanpatil et al., 2006).

The water uptake study of the tablet should be done using USP dissolution apparatus II. The medium distilled water, 900 ml rotate at 50 rpm. The medium was maintained at 37±0.5 0C throughout the study. After a selected time intervals, the tablets can withdraw, blot to remove excess water and weigh. Swelling characteristics of the tablets should be expressed in terms of water uptake (WU) as:

$$WU\ (\%) = \frac{Weight\ of\ the\ swollen\ tablet - Initital\ weight\ of\ the\ tablet}{Initial\ weight\ of\ the\ tablet} \times 100$$

**X-Ray/Gamma scintigraphy**

**For** *in vivo* studies, x-ray/Gamma scintigraphy is main evaluation parameter for floating dosage form. (Whitehead L et al., 1998 and Gnasbeke BV et al., 1991).

**Pharmacokinetic studies**

Pharmacokinetic studies include AUC (Area under curve).Cmax, and time to reach maximum plasma concentration (Tmax) can be estimated using a computer. Statistical analyses should perform using a student test t test, 0.05 as the minimal level of significance. (Klauser EA et al., 2003).

**Specific gravity**

Displacement method is should be used to determine the specific gravity of floating system using benzene as displacement medium.(Singh BN and Kim KH 2000).

**Practical problems in developing bilayer floating tablets**

- ✓ Layer-separation
- ✓ Order of layer sequence
- ✓ Layer weight ratio
- ✓ Elastic mismatch of the adjacent Layers
- ✓ Cross contamination between layers.

**Future prospects**

**With respect to herbal Bilayer floating tablets**

Herbal drug delivery is the emerging trend in the pharmacy. Bilayer floating tablet is best choice for herbal drug delivery.BFT have been designed which could release drug up to 12-24 hours.BFT of herbal drugs mainly improves the therapeutic effect of drug. Immediate and controlled release layer concept implemented to prolong drug(s) action.

**Some of herbal drugs that can be delivered as Bilayer floating tablets**

**1. Forskolin**

A normal root extract from the coleus forskolin was developed. These formulations contain different grades of HPMC polymer. The drug is used as anti-obesity agent reducing fat in body muscles. it may enhance fat loss without loss of muscle mass. (Chakraborty M et al., 2012).

**2. Black myrobalan**

The aqueous exctract of black myrobalan (terminalia chebula Retz) has been shown to have uniform antibacterial activity against ten clinical strains of H.pylori. (Shah SH et al., 2009).

3. **Ginger root (Zingiber officinale Rose.)** has been used traditionally for the treatment of gastrointestinal ailments such as motion sickness, dyspepsia and hyperemesis gravidarum and is also reported to have chemopreventative activity in animal models.

**4. Turmeric**

Curcumin derived from turmeric has been shown to prevent gastric and colon cancers in rodents (Chakraborty M et al., 2012).

**5. Licorice**

In the recent study at the institute of medical microbiology and virology, Germany, researchers identified

that licorice extract produced a potent effect against a strains of H.pylori (Chakraborty M et al., 2012).

**6. Berberine**

Berberine has wide variety of activity against bacteria, viruses, fungi, protozoans, and helminthes (Chakraborty M et al., 2012).

**CONCLUSION**

Bilayer tablet is improved beneficial technology to overcome the shortcoming of single layered tablet. Bilayer tablets provide one of the important design approaches where incompatible drugs, with different indication, and same drug with different release rate can be incorporated in a single unit. Bilayer tablet is suitable for sequential release of one or 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 preparation of tablets in the form of Bilayer is used to provide systems for the administration of drugs, which are incompatible and provide controlled release tablet preparations by providing surroundings or multiple swelling layers.

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