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Review Article

Bilayer Floating Tablet: A Novel Floating Tablet

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ABSTRACT

Out of various drug delivery system the novel drug delivery system is overcomes and then physiological problems of gastric retention by decreasing fluctuations in blood drug concentration level with consequent reduction in the undesirable toxicity and poor efficiency. Approaches have their been introduced to prolong gastric residence time such as the floating system, modified shape, swelling index, expanding system and high density system. Two layer floating drug delivery system is combined principle of bilayer tablet as well as floating mechanism. Bilayer floating tablet is new in the era for the successful development of the controlled release formulation along with the different features to provide a way of successful drug delivery system. The purpose of this paper is to the following Review of the principle of floating drug delivery system, current technology used in the development of same as well as summarizes in the applications, advantages and disadvantages, characterization, evaluation methods and future potential for the bilayer floating tablets.

INTRODUCTION

Drug delivery system aims to give prolonged nontoxic drug concentration in blood for providing systemic action. Various routes are available which are as following oral, rectal, parenteral, inhalational and sublingual. Today various drug delivery systems are available in market among which most common are the oral drug delivery[1,2]. From immediate release to site specific development occurs in the oral drug delivery. Amongst the all oral route 90% of the drugs are administered today which have been provided good systemic effects[1]. Out of the all dosage form the solid oral dosage forms are more stable through which tablets are the most common solid oral dosage forms. But in various case this immediate release dosage forms has many limitations as in this system effective plasma drug concentrations does not occurs due to immediate release of dosage form has to administered different times a day and it arises the problem of patient compliance[1]. Because of this reason controlled drug delivery is gaining importance nowadays. Oral controlled drug delivery focused to deliver the drug for an extended period of time which provides good bioavailability and which makes the dosage form more responsible[2].

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To overcome these problems gastro retentive drug delivery system (GDDS) is developed which provide oral controlled sustained dosage form as it delivers the drug at slow rate in systemic circulation and maintains effective plasma concentration because drug is retained in stomach for a greater period of time as compare to conventional oral dosage form[1,3].

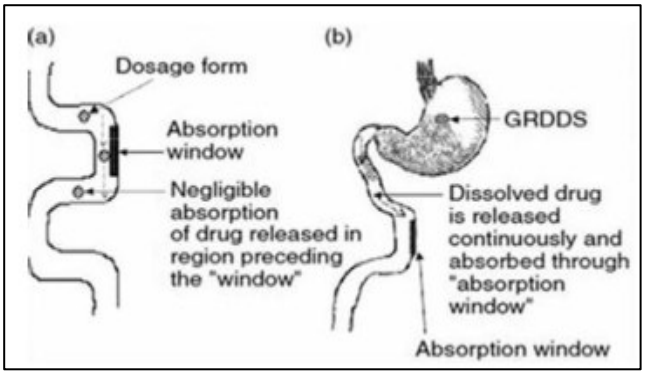
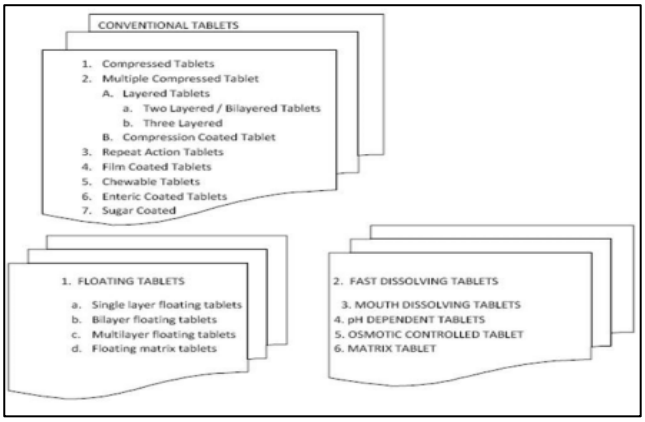


Figure 1: Conventional Dosage Form defines negligible absorption whereas in the GRDDS drug is continuously absorbed.[4]

According to the British Pharmacopoeia tablets are defined as convex or flat faces which are circular in shape and are formed by compression of the active pharmaceutical ingredient and also other excipients Tablets provide many advantages as they are the most stable dosage form since they are dry, easy to manufacture and cost reductive, provide good patient compliance and extended shelf life . According to their use they are of various types which are tablets for oral ingestion, tablets for oral cavity, and also tablets for other routes[4,5]. Tablets can be produced by two different methods like granulation and direct compression. Granulation can be dry granulation and wet granulation. But nowaday direct compression method is commonly used due to their increasing use of novel excipients[6].

TYPES OF TABLETS FOR THE USE OF ORAL INGESTION[4,5,6]



FLOATING DRUG DELIVERY SYSTEMS[7]

Floating drug delivery systems is one of the most important approaches to achieve the gastric retention to obtain the sufficient drug bioavailability. This delivery systems is desirable for the drugs with an absorption window in the stomach or in the upper portion of small intestine. They have a bulk density which is less then gastric fluids and so remain in the buoyant in the stomach without affecting the gastric emptying rate for the prolonged time and the drug is released slowly as a desired rate from the system. After releasing of drug, the residual system is emptied from the stomach. Due to this results in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration[7].

The major requirements for the floating drug delivery system are.

- They should release the contents slowly to serve as a reservoir.
- They must maintain the specific gravity lower than gastric contents (1.004 – 1.01 gm/cm3)[9].
- They must form the cohesive gel barrier

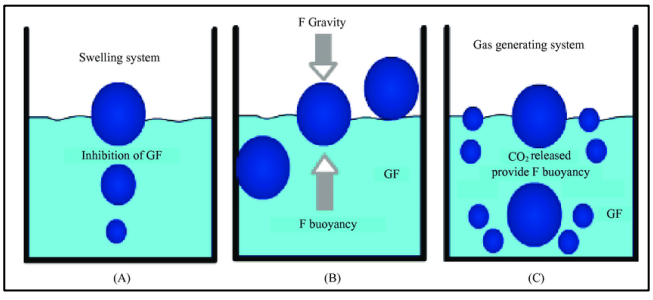


Fig. 2: The mechanism of floating systems

CLASSIFICATION OF FDDS BASED ON MECHANISM OF BUOYANCY[8,9]

A) Single unit

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

- **No effervescent systems**

For the formation of these types of systems, the drug and their gel forming hydrocolloid are mixed thoroughly. After that oral administration this dosage form gets swells in contact with gastric the fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts the buoyancy to the various dosage forms. The formed swollen gel-like structure acts as a reservoir and allows the sustained release of drug through their gelatinous mass[8].

- **Effervescent systems or gas generating systems**

These are various matrix types of the systems prepared with the help of swellable polymers such as like methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are prepared formulated in such a way that when come in contact with the acidic gastric contents, CO2 gas is then liberated in the small form of droplets and then gets engaged in swollen hydrocolloids, which provides the buoyancy to the dosage forms[6].

B) Multiple units[6]

One single unit formulations is encounter with the different problems such as like the joining together or being the obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. Various unit systems avoid the „all-or-none" gastric emptying nature of single unit systems. They reduces the inter subject variability in absorption and the probability for dose dumping is lower[10].

- **No effervescent systems**

A small or no much report was found in the literature on non-effervescent multiple unit systems, as in comparison to the effervescent systems. However, few workers have been reported the possibility of developing such as the system containing indomethacin, using the chitosan as the polymeric excipient[10,11]. A various unit hydrodynamic ally balanced system (HBS) containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and the acetic acid is extruded through a needle, and the extrudate is cut and then dried. Chitosan hydrates float in the acidic media, and then required drug release could be obtained by the modifying the drug-polymer ratio[11].

- **Effervescent systems[12,13]**

A different unit system comprises of the calcium alginate core and the calcium alginate/PVA membrane, both are separated by an air compartment was prepared. In availability of water, the PVA leaches out and then increases the membrane permeability, maintaining the integrity of the air compartment. Increase in the molecular weight and concentration of PVA, results in enhancement of the the floating properties of the system. Freeze-drying technique of tablet formulation is also reported for the first preparation of floating calcium alginate beads. Sodium alginate solution is added drop by drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, because of the formation of calcium alginate. The obtained beads are then freeze-dried which results in a porous structure, which aid in floating. The various authors studied the behavior of radiolabeled floating beads and compared with them in no floating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h was observed by the floating beads. The non-floable beads had a shorter residence time with the mean onset emptying time of 1 hr.[8]

- **Floating microspheres**

A controlled release drug delivery system designed to increase its residence time in the stomach without come in contact with the mucosa was achieved through their preparation of floating microspheres. Different techniques involved in their preparation including simple solvent evaporation, and then solvent diffusion and evaporation. The different drug releases which are having the better floating properties mainly depends the on the different type of polymer,

plasticizer and then solvents employed for their preparation[10]. Various polymers, such as polycarbonate, Eudragit® S and cellulose acetate, are used in the preparation of the hollow microspheres, and the drug release can be modified by optimizing the amount of polymer and the polymer plasticizer ratio

C) Raft forming systems[10]

The principle involved in the raft formation includes the various formation of viscous cohesive gel in contact with the gastric fluids, where in every portion of the liquid swells forming a continuous layer which is called as the raft. The different types of raft floats because of the buoyancy created by the formation of CO2 and then acts as a barrier to prevent the reflux of gastric Contents like as HCl and enzymes into the esophagus.

Table 1: Polymers used in floating drug delivery

Sustained Releases Polymers	HPMC K100M, HPMC K15M, Polycarbonate, Polyethylene Glycol, Sodium Alginate, Carbopol, Eudragit.
Effervescent Generating System	Citric acid, Tartaric Acid, Sodium Bicarbonate, Citroglycine.
Polymers which is decrease release	Talc, Magnesium Stearate, Dicalcium Phosphate.
Polymers which get increase release	Mannitol, Lactose.

FLOTING BILAYER TABLET[13,15]

Bilayer tablet is the new evolution for the successful development of controlled release formulation. Double coated tablet is very better than the traditionally used dosage forms and Bi-layer tablet is suitable for the sequential release of two drugs in the combination. In bilayer tablets, delivery rate of tablets is either single or two active pharmaceutical ingredients can be controlled. It is also beneficial to the active gastric retention by forming floating bilayer tablets with different active pharmaceutical ingredient which are in a fixed dose combination and also to increase the life cycle of drug product.

Advantages of bilayer floating tablets[14]

1. This system provide sustained drug delivery like hydrodynamically balanced system (HBS) dosage form modify gastric residence time as this system remains in stomach for many hours.
2. It maintains the optimum therapeutic window which results in drug delivery with controlled released is achieved.
3. Better patient compliance is achieved due to its easiest way of administration.
4. It maintains blood level in constant manner.
5. Site targeted specific drug delivery is achieved for the different drugs such as furosemide and riboflavin which are formulated as the example of the floating system.
6. All over the oral routes these are microbiologically and also chemically stable.
7. Because of higher dose precision and the lesser content variation they are the most compatible oral dosage form[12].
8. They provide the most flexible route of dosage form.
9. Better suitability for the larger scale production.
10. Masking of the bitter taste and also with bad odor by coating.
11. Swallowing of tablets is easy and convient process.
12. Lesser cost compared to that of the other oral dosage forms.

Disadvantages of bilayer floating tablets[16]

1. Increase in the fluid levels is mandatory in the stomach so that of the system float properly.
2. Drugs who's having the solubility and stability problem in stomach cannot be formulated.

3. Irritation producing drugs on gastric mucosa can not be formulated as floating dosage form.
4. Capping is the major problem in bilayer tablets.
5. Dividation of layer is happens due to that of the insufficient bonding and also reduction in yield occurs.
6. Hardness is other problem.
7. There are chances of layer mixing between two layers.
8. Due to low density and amorphous nature of some drugs compacts do not form because they resist compression.
9. There is reduction in control over the weight of individual layer.
10. Problem in swallowing in case of children and unconscious patients.
11. Problem in Bioavailabity occurs in case of poor wetting and less dissolution properties.
12. Sometimes encapsulation or coating is required for the drugs that are moisture sensitive, bitter tasting and with bad odor.

Ideal properties for bilayer tablet dosage form[8]

1) Drug must be released in reproducible and expected manner in bilayer tablet.
2) Chemical and physical stability is must.
3) During product shelf life chemical stability is main concern.
4) The should be free from visual defects.

Table 2: Floating Bilayer Tablet[4]

DRUG	POLYMER	METHOD OF PREPRATION
Cefuroxime Axetil	HPMC K4M, Sodium Bicarbonate, Sodium Citrate, Tulsion T-339	Direct Compression Technique
Trifluperazine Hcl	HPMC K100M, Carbopol 934P, Eudragit RS100, MCC, Maize Starch, Magnesium Stearate, SSG, Aerosil, Ferric Oxide Yellow.	Direct Compression Technique
Metformin Hcl	HPMC K 100M, HPMC K 4M, SSG, PVP K, MCC, Sodium Bicarbonate, Iron Oxide-Red.	Direct Compression Technique
Rantidine	HPMCK-4M, HPMC-E-15, Carbopol-934, Sodium Bicarbonate, Citric Acid.	Direct Compression Method

Table 3: List of various floating Gastroretentive marketed formulations

Sr no.	Drug	Brand name	Manufacturer
1	Diazepam floating capsule	Valrelease®	Roche USA
2	Aluminium magnesium antacid	Topalkn®	Pierre Fabre Drug,France
3.	Benserazide and L-Dopa	Madopar®	Roche Products USA
4.	Ciprofloxacin floating tablets	Cifran OD	Ranbaxy India
5	Effervescent floating liquid alginate prepration	Liquid gaviscon®	Galaxo smithkline, India

Characterization of bilayer floating tablets

In-vitro evaluation of floating tablets Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations.

Pre-compression parameters[16,17]

Angle of Repose

In powder frictional forces can be measured with the help of angle of repose. Angle of repose is defined as the maximum angle which is possible between the surface of pile of powder and horizontal plane i.e. height.

$$\text{Tan } \Theta = h/r$$

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

Where Θ is the Angle of repose, and h is the height of pile, r is the radius of pile.

Compressibility Index

The density of the powder to be compressed is measured by using the compressibility and it also helps in measurement of settling property and interparticulate interaction.

Compressibility index (%) = ρt – ρo* 100 / ρt

Where ρt = Tapped density gram/ml, ρo = Bulk density gram/ml.

Bulk Density

It is marked by the ρb and is defined as mass of the powder divided by that of the bulk volume (The United States Pharmacopoeial Convention Stage 6 Harmonization Official December 1, 2012, 616.).

Tapped Density

Increase in the bulk density which is attained after the mechanical tapping in measuring cylinder is called as tapped density.

Tapped density= Weight of powder taken/ Tapped Volume

Hausner Ratio

The density of the powder to be compressed is measured by using Hausner ratio formula. Interparticulate interaction and settling property can be also measured by using the Hausner ratio.

Hausner ratio= Tapped density/Bulk density

Hausner ratio= Vo/Vf

Where, Vo= Unsettled apparent volume, Vf= Final tapped volume.

Particle Size Distribution

Particle size distribution was done by using the sieve analysis method.

Post-compression parameters Tablet Thickness

In this method the three tablets are randomly pick and then their thickness and diameter are measured by using the Vernier calliper or by using calibrated screw gauze.

Weight Variation Test

Randomly select the twenty tablets and weighed individually. Then the overall average weight and standard deviation is calculated. Test passes when not more than two tablets deviate from average weight.

Hardness

This is expressed in kg/cm2 and it is checked by using the Monsanto hardness tester by randomly picking three tablets. Hardness helps us in knowing ability of the tablet to withstand mechanical shock during handling of tablets.

Friability

Randomly ten tablets are selected and weighed and then after placed in friabilator apparatus which allows rotation at 25 rpm speed for 4 minutes. After 4 minutes tablets are weighed again.

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

where W– Initial weight of tablet, Wt - Weight of tablet after revolution. If % Friability of tablets is less than 1% is considered acceptable.

Tablet Density

This is an important parameter in case of the floating tablets. If the density is less than (1.004) the gastric fluid, than only the tablets will float. It is calculated using formula: **V=πr2h**, d = m/v, r = Radius of tablet, h = crown thickness (g/cc), m = Mass of tablet.

Disintegration Time

In this method the one tablet is placed in the disintegration apparatus containing the buffer 0.1N Hcl or PBS pH 6.8 and test is carried out at 37◦C. Time taken by the tablet to Disintegrate is noted as disintegration time.

***In Vitro* Dissolution Studies[17]**

In vitro Dissolution study is performed by using the USP paddle apparatus by maintaining their optimum temperature i.e., at 37° at 50 rpm rotational speed. At different time interval 5 ml sample is withdrawn and then replaced with same amount of buffer.

Floating Lag Time

Floating time is defined as the time interval taken by the tablets to start floating. It should always be less than one minute.

Floating Time

Floating time is the total time taken by which the tablets remain floating in the media.

Drug Content Uniformity

Randomely select ten tablets and powdered equivalent weight of drug dose is taken and then it is transferred to volumetric flask and then buffer is added and absorbance is determined using U.V spectrophotometer.

Swelling Study

Firstly tablet is weighed (W1) and placed in a glass

beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5^{0}C. At various time intervals, the tablet is taken and the excess of liquid is carefully removed by a filter paper. The swollen tablet is reweighed (W2). The swelling index (SI) is calculated by using the following formula

SI= Wt -W0/W0*100

Wt= (Weight of swollen tablet), W0= (Initial weight of tablet).

***In-vivo* evaluation**

a) Radiology

For examination of internal body X-ray systems is widely used. For this purpose barium Sulphate is widely used Radio Opaque Marker. That's why, BaSO4 is incorporated inside dosage form and X-ray images are then taken at various intervals to view gastric retention.

b) Scintigraphy

Similar to that of the X-ray, emitting materials are incorporated into the dosage form and then images are taken by the help of scintigraphy. Widely used emitting material is 99Tc.

c) Gastroscopy

Gastroscopy is the technique used o inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of the GRDDS.

d) Magnetic Marker Monitoring

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

e) Ultrasonography

Used sometimes, not used generally because it is not traceable at intestine.

Future potential for bilayer floating tablets[17,18]

Drug release is the major area in the pharmaceutical research work. Through floating bilayer tablets both type of release i.e. sustained as well as immediate release can be obtained and sustained release can be increased up to 24 hours. It is also beneficial in providing gastric retention thereby increasing gastric emptying time as well as increasing bioavailability. Bilayer floating can be beneficial in diabetes as two drugs can be administered concurrently at the same time which provides better patient compliance. It provides a great opportunity in case of herbal drugs as these drugs can also be given in bilayer dosage form which provide both immediate as well as sustained effects. Drugs which has narrow absorption window such as anti- viral, antibiotic and antifungal can be given in floating bilayer dosage form.

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