SUSTAINED RELEASE EFFERVESCENT FLOATING BILAYER TABLET – A NOVEL APPROACH

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ABSTRACT:
Floating dosage forms are an important formulation strategy for drugs with a narrow absorption window and low intestinal solubility, and for localized gastric treatment. Novel floating pellets were prepared using the hot-melt extrusion (HME) technology. The drugs most susceptible to these fluctuations are those with either a narrow absorption window in the upper part of the gastrointestinal tract. Those that are locally active in the stomach, unstable in the intestinal or colonic environment, or with a low solubility in a relatively high pH environment. Through sustained release bi-layer floating tablets release can be increased up to 24 hours for drugs incompatible with effervescent floating components, hence this system finds greater advantages over single layer effervescent floating tablets in terms of stability.

Index Teams: Floating Bilayer, Sustained release, Gastro retentive, Methodology.

INTRODUCTION:
Drug absorption in the gastrointestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption. Novel drug delivery system overcomes the physiological problems of short gastric retention through various approaches including floating drug delivery systems (FDDS), these systems float due to bulk density less than gastric fluids and so, remain buoyant in the stomach for a prolonged period of time, releases the drug slowly at the desired rate from the system and increase the bioavailability of narrow absorption window drugs. This review entitles the applications of sustained release effervescent floating bilayer tablets, suitable for sustained release of those drugs incompatible with floating constituents over an extended period of time for better patient compliance and acceptability. The purpose of this paper is to review the principle of the sustained release effervescent floating drug delivery system, the current technology used in the development of same as well as summarizes the applications, advantages, methodology, evaluation methods and future potential for sustained release effervescent floating bilayer tablets. The oral route is the most convenient and preferred means of drug delivery to the systemic circulation due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. However, the development process is presented with several physiologic difficulties, such as an inability to restrain and localize the drug delivery system within desired regions of the gastrointestinal tract (GIT), an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time and the existence of an absorption window in the upper small intestine for several drugs. Depending upon the physiological state of the subject and the design of the pharmaceutical formulation, the emptying process can last from a few minutes up to 12 hr. This variability, in turn, may lead to unpredictable bioavailability and times to achieve peak plasma levels, since the majority of drugs are preferentially absorbed in the upper part of the small intestine. The relatively brief gastric emptying time (GET) in humans, which normally averages 2 to 3 hr through the major absorption zone (stomach or upper part of the intestine), can result in incomplete drug release from the drug delivery system (DDS) leading to the diminished efficacy of the administered dose. In addition, some drugs display region specific absorption which is related to differential drug solubility and stability in different regions of GIT, as a result of changes in environmental pH, degradation by enzymes present in the lumen of the intestine or interaction with endogenous components such as bile. Active transport mechanisms for drugs involving carriers and pump systems have been also well described. These drugs show absorption window, which signifies the region of GIT where absorption primarily occurs. Drugs released from sustained/controlled release systems, after absorption window has been crossed, go waste with negligible absorption which indicates that absorption window can limit the bioavailability of orally administered compounds and can be a

Therefore, it would be beneficial to develop sustained release formulations which remain at the absorption site for an extended period of time. One of the feasible approaches for achieving prolonged and predictable drug delivery profile in GIT is to control gastric retention time (GRT) of the formulation. Dosage forms with prolonged GRT, i.e., Gastro Retentive Dosage Forms (GRDFs), will overcome the problems of simple sustained release dosage forms.
Gastro Retentive Dosage Forms (GRDFs)

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time, and allow both special and time control of drug liberation. Their application can be advantageous in the case of drugs that are absorbed mainly from the upper part of the gastrointestinal tract or are unstable in the medium of distal intestinal regions. They can also be used beneficially in the local therapy of the stomach. Because of the complicated and by many factors influenced physiology of this organ, the design of such delivery systems is a task requiring due foresight and knowledge. Gastro retentive dosage forms can be floating, expandable, bio adhesive, modified shape and high density systems according to the physical property leading to prolongation of gastric residence time. [1]

Basic physiology of the gastrointestinal tract

![Figure 1. Structure of Stomach](image)

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made up of fundus and body acts as a reservoir for undisgested material, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state, an interdigestive series of electrical events take place, which cycles both through stomach and intestine every 2 to 3 hours. This is called the inter-digestive myoelectric cycle or migrating myoelectric cycle (MMC), which is further divided into following 4 phases.

1. Phase I (basal phase) lasts from 40 to 60 min with rare contractions
2. Phase II (pre burst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increase gradually.
3. Phase III (burst phase) lasts for 4 to 6 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.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles. After the ingestion of a mixed meal, the pattern of contractions changes from fast to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in a slowdown of gastric emptying rate. Under physiological condition, the gastric absorption of most drugs is insignificant as a result of its limited surface area (0.1 - 0.2 m²) covered by a thick layer of mucous coating, the lack of villi on the mucosal surface, and the short residence time of most drug in the stomach. Rapid gastric emptying also called dumping syndrome, occurs when undigested food empties too quickly into the small intestine. Stomach emptying is a coordinated function by intense peristaltic contractions in the antrum. At the same time, the emptying is opposed by varying degrees of resistance to the passage of chyme by the pylorus. The rate depends on pressure generated by antrum against pylorus resistance. [2]

Factors controlling gastric retention of dosage form:

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm [3] The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include: density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride). [4] The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters. [5]

Density of dosage forms: The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. [6] Both positions may isolate the dosage system from the pylorus. A density of < 1.0 gm/cm³ is required to exhibit floating property. [7]

Shape and size of the dosage form: Shape and size of the dosage forms are important in designing indigestable single unit solid dosage forms. The mean gastric residence times of nonfloating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine. [9] Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm [8]. Ring-shaped and...
Food intake and its nature: Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosageform. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows downgastric emptying time (GET), which can improve the gastric retention of dosage forms.

Effect of gender, posture and age: Generally females have slower gastric emptying rates than male. The effect of posture does nothave any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down.

Gastric emptying and problems: Major adversity encountered through the oral route is the first pass effect, which leads to reducing the systematic availability of a large number of a drug. These problems can be exacerbated by an alteration in the gastric emptying that occurs due to factors such as age, race, sex and disease states, as they may seriously affect the release of a drug from DDS. It is therefore desirable to have a controlled release product that exhibits an extended, GI residenceand a drug release profile independent of patient related variables. Timmermans et al studied the effect of buoyancy, posture, and nature of meals on the gastric emptying process in vivo using gamma scintigraphy. To perform these studies, 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. On comparison of floating and non-floating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant 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. It was also observed that of the floating and non-floating units, the floating units were had a longer gastric residence time for small and medium units while no significant difference was seen between the 2 types of large unit dosage forms. When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention. A comparison was made to study the affect of fed and non-fed stages on gastric emptying.

Potential of Gastric retention: From the discussion of the physiological factors in the stomach, it must be noted that to achievegastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Requirement of Gastric retention: Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous and controlled manner. Potential drug candidatesfor gastro retentive drug delivery systems include: drugs that are locally active in the stomach(e.g. misoprostol, antacids etc.); drugs that have narrow absorption window in gastrointestinal tract(e.g. L-DOPA, Paracaminobenzoic acid, Furosemide, Riboflavin, Salbutanol) [13] drugs that are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole, ); drugs that disturb normal colonic microbes (e.g. antibiotics against Helicobacter pylori) and drugs that exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, verapamil HCl).

Approaches for gastric retention: Hydro dynamically balanced systems (HBS) – incorporated buoyant materials enable the device to float. Raft systems incorporate alginate gels – these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating[14]. Swelling type of dosage form is such that after swelling, this product swells to extent that prevents their exit from the stomach through the pylorus. As a result, the dosage form retained in the stomach for a longer period of time. These systems may be referred to as a “Plug type system” since they exhibit a tendency to remain logged in the pyloric sphincters [15] Bioadhesive or mucoadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approaches involve the use of bioadhesive polymers that can be adhered to the epithelial surface of the GIT. The proposed mechanisms of bioadhesive are the formation of hydrogen and electrostatic bondingat the mucus polymer boundary[16]. Modified shape systems are non-disintegrating geometricshapes molded from Silastic elastomer or extruded from polyethylene blends and extended the GET depending on the size, shape and flexural modulus of the drug delivery device. High dense formulations include coated pallets, and have a density greater than that of the stomachcontent (1.004 g/cm3). This is accomplishing by coating the drug with a heavy inert materialsuch as barium sulphate, ZnO, titanium dioxide. This formulation of the high-density pellet is based on assumption that heavy pellets might remain longer in the stomach since they are position in the lower part of the antrum[17]. Another delayed gastric emptying approach of interest include sham feeding of digestible polymers or fatty acid salts that charge the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release.

Floating drug delivery system: 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 have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Floatation of drug delivery system in the drug can be achieved by incorporating floating chamber filled with vacuum, air or inert gas from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimallevel of floating force is also required to keep the dosage form.
Floating drug delivery systems are classified depending on the use of 2 formulation variables:

**Effervescent and non-effervescent systems.**

**Types of Floating Drug Delivery Systems:**

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS.

**A. Effervescent system**

a. Volatile liquid containing system
b. Gas generating system

c. Colloidal gel barrier system
d. Microporous compartment system

**B. Non-effervescent system**

a. Alginate beads
b. Hollow microspheres
c. Single layer floating tablets
d. Bilayer floating tablets
e. Colloidal gel barrier system
f. Microporous compartment system

**A. Effervescent FDDS:**

a. **The volatile liquid containing system:** The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Polyvinyl alcohol, Polyethylene etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach. [18]

b. **Gas-generating Systems:** These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the jellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it float over gastric content. Effervescent Floating Dosage Forms 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, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. Ichikawa et al developed a new multiple type of floating dosage system composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/mL. It was found that the system had good floating ability independent of pH and viscosity and the drug (para-amino benzoic acid) released in a sustained manner [19] Ichikawa et al developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas generating agents. This layer was further divided into 2 sub layers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in maintaining the buoyancy of the pills for an extended period of time. Two parameters were evaluated: the time for the pills to be floating (TPF) and rate of pills floating at 5 hours (FP5h).

**B. Non-Effervescent Floating Dosage Forms:**

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, poly methylacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of less than 1.

**Bilayer floating tablets:** Bilayer tablet are multilayer tablets used in controlled drug delivery system. Bilayer floating tablets consisting of 2 layers i.e., immediate release layer which releases initial dose from system while the other sustained release layer absorbs gastric fluid (Figure 5), forming an impermeable colloidal gel barrier on its surface and maintain a bulk density of less than unity and thereby it remain buoyant in the stomach.[21]

![Figure 2: Structure of Bilayer Floating Tablet.](image)

**Sustained release effervescent floating bilayer tablets:**

Sustained release effervescent floating bilayer tablets are composed of two layers. A layer of sustained release polymer and drug (Sustained release layer) and a layer of effervescent floating components (Floating layer). Such a formulation offers more advantages...
compared to single layer effervescent floating tablets in terms of stability. Since effervescent components are unstable and incompatible with many potential drug candidates for gastric retention such an approach could be highly beneficial.

**Advantages of sustained release bilayer floating tablets:**
1. This system provides sustained delivery of drugs along with enhanced gastric residence time as this system remains in the stomach for many hours via floating.
2. This system finds additional advantages over single layer floating drug delivery system in terms of stability of the formulation.
3. Better patient compliance is achieved due to its ease of administration.
4. It maintains constant blood level.
5. Site-specific drug delivery is achieved for the drugs such as Furosemide and Riboflavin which are formulated as a floating system.
6. Over all other oral routes, these are microbiologically and chemically stable.
7. Due to higher dose precision and lesser content variation, they are the most compatible oral dosage form.
8. They offer the most flexible dosage form.
9. Better suited for large scale production, This system provides sustained delivery of drugs along with enhanced gastric residence time as this system remains in the stomach for many hours via floating.
10. This system finds additional advantages over single layer floating drug delivery system in terms of stability of the formulation.[22,23]

**Methodology used for bilayer floating tablets**

A. **Oros ® Push Pull Technology**: Two or three layer system: a drug layer and push layer. Drug layer contains drug with other agents and due to this drug is less soluble. Sometimes suspending agent and osmotic agent are also added. The tablet core is surrounded by a semi-permeable membrane

![Figure 3: Bilayer and Trilayer OROS Push Pull Technology](image)

B. **L-Oros Tm Technology**: Alza developed L-OROS system due to solubility problem. The system contains a drug in dissolved state in a lipid soft gel product which is produced first and then barrier membrane, after which osmotic membrane and semi-permeable membrane coat is applied and is then drilled out through external orifice[25].

C. **DUROS Technology**: This technology is also known as miniature drug dispensing system which works like a miniature syringe and releases a small quantity of drug consistently over a period of time. There is an outer cylindrical titanium alloy reservoir which has high impact strength due to which drug molecules inside it are protected from enzymes.

D. **Elan Drug Technologies’ Dual Release Drug Delivery System**: The DUREDASTM Technology provides combination release of drugs together and different release pattern of single drug i.e. it provides sustained release as well as immediate release. This technology provides various advantages i.e. two drug components provide tailored release and it’s another benefit is that it consists of bilayered tablet technology in which it contains modified as well as immediate release pattern in one tablet. In this different controlled release, formulations are combined together[26]
Figure 4: DUREDASTM Technology

Polymer and other excipients used for formulation of bilayer floating tablets:-
The polymer used for coating or fabrication of bilayer tablets are hydroxypropyl methyl cellulose (HPMC 1000, HPMC 4000, HPMC K15, HPMC K4); beta cyclodextrin, sodium alginate, hydroxypropyl cellulose (HPC-H, HPC-M), Eudagrit S, Metolose S.M.100, polyvinylpyrrolidone (PVP), acrylic polymer and Carbopol.

Inert fatty materials: Beewax, Fatty acids, long chain fatty alcohols, gelucires 39/01 and 43/01.
Effervescent agents: Sodium bicarbonate, Citric acid, Tartaric acid, Di-SGC (Di-sodiumGlycine Carbonate, CG).

Pharmacokinetic aspect of bilayer floating tablets:-

Absorption window
The candidates for GRDDS are molecules that have poor colonic absorption but are recharacterized by better absorption properties at upper part of GIT.

Enhance bioavailability
The compound having narrow absorption window having the possibility of continuous administration of the compound at specific site.

Enhance first pass biotransformation
The pre-systemic metabolism of the tested compound is increased. When the drug is presented to metabolic enzyme (cytochrome p-450) in a sustained manner.

Improve bioavailability due to reduced p-glycoprotein activity in 16he duodenum
The drug that P-gp substrate do not undergoes oxidative metabolism GRDDS may elevate absorption compared to immediate and CR dosage form.

Reduce frequency of dosing
For drugs with relatively short biological half-life. Sustained and slow input from GRDDS results flip-flop pharmacokinetic and enable reduced dosing frequency.

Targeted therapy for local elements in upper GIT tract
The prolonged and sustained administration of the drug from GRDDS to the stomach may produce local therapy in the stomach and small intestine.

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Pharmacodynamic aspect of bilayer floating tablet:-
- a) Reduce fluctuation of drug concentration.
- b) Are associated with peak concentration can be prevented. Improved selectively in receptor activation.
- c) Reduce counter activity of the body.
- d) Slow input of drug into the body was shown to minimize the counter activity leading to higher drug efficiency.
- e) Reduce fluctuation of drug concentration.
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- n) Slow input of drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

Application of bilayer floating tablet:-
Bilayer tablets are suitable for the sequential release of two drugs to be given combined. It separates the two mismatching drugs. The sustained-released tablets whose one layer provides instant drug release as the initial loading dose while the second layer is containing the sustained dose. Bilayer tablets are latest technology that helps in overcoming the limitations of a single-layered tablet. Bilayer tablets help in the combined delivery of two different drugs that have different release profiles. Bilayer tablets are utilized to administer fixed dosage containing different APIs. They are employed to increase and modify the surface area for active pharmaceutical ingredients by erodible barriers for custom release.

CONCLUSION:-
Drug release is the major area in the pharmaceutical research work. Through sustained release bio-layer floating tablets release can be increased up to 24 hours for drugs incompatible with effervescent floating components, hence this system finds greater advantages over single layer effervescent floating tablets in terms of stability. It is also beneficial in providing gastric retention thereby increasing the gastric emptying time as well as increasing bioavailability and reducing dosing frequency which provides better patient compliance. It provides a great opportunity in case of herbal drugs as these drugs can also be given in sustained release effervescent floating bilayer dosage form which provides greater stability to the formulation. Drugs having narrow absorption window such as antiviral, antibiotic and antifungal can also be given in sustained release floating bilayer dosage form.

REFERENCE:


