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REVIEW ARTICLE

A Scientific Review On: Floating Drug Delivery System (FDDS)

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ABSTRACT

The several types of Novel drug delivery systems are introduced in the pharmaceutical research and their concepts are used to overcome the certain aspects related to the physical and chemical properties of the drug molecules and the related formulations. Many drugs substances have problem to absorb through the gastrointestinal-tract (GIT) which produces poor bioavailability. Some drugs prominently absorbs from the gastric region due to suitable physicochemical properties Therefore, gastro-retentive drug delivery system (GRDDS) had been developed to improve bioavailability related problems by the prolonging gastric residence time in the upper GIT. One such type of system is floating drug delivery system (FDDS).The aim of the writing this review article on FDDS was to compile the recent literature with special focus on detailed basic mechanism of floatation properties to achieve gastric retention. Conventional oral dosage forms having low bioavailability problems due to their rapid gastric transition from stomach, in case of drugs which are poorly absorb at alkaline pH of intestine. Further drugs which produce their local action in stomach, get rapidly emptied do not get enough residence time in stomach. Hence, the frequency of dose administration in such cases is increased. To avoid these problems several methods have been made to prolong the retention time of drug in stomach. Floating drug delivery system (FDDS) is one of the most important approaches in prolonging the retention time of drug in stomach. FDDS is low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach for a prolonged period of time without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at the desired rate which results in a better control of the fluctuations in plasma drug concentration. Several approaches are currently being used to prolong the Gastric Retention Time, including FDDS also known as hydro dynamically balanced systems (HBS), swelling and expanding systems, high-density systems, and other delayed gastric emptying devices. In this review given the detailed outline of various techniques of floating drug delivery system with their advantages over the conventional drug delivery system, limitation and also include the application of these systems.

KEYWORDS

Gastroretentive drug delivery system (GRDDS), Floating drug delivery system (FDDS), Plasma drug concentration, Buoyant, Gastric retention time (GRT)

INTRODUCTION

Today we have different types of Drug delivery systems in the pharmaceutical market, focused to develop the process of drug delivery and increase the patient compliance. Oral drug delivery system has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage

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form. The reason that the oral route achieved such popularity may in part attributed to its ease of administration and the traditional belief that by oral administration the drug is well absorbed as the foodstuffs that are ingested daily[1]. All the pharmaceutical products for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid, dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology. Therefore, fundamental understanding of various disciplines, including GI physiology; pharmacokinetics, pharmacodynamics, and formulation design is essential to achieve a systematic approach to the successful development of an oral pharmaceutical dosage form.[2,3]

The intention of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration. Recent development in technology of drug delivery system provided viable dosage alternatives that can be administered using different routes of administration.

Different types of routes are used include Oral, Nasal, Rectal, Topical , Vaginal and Ocular etc. but out of these routes Oral route of drug delivery is considered as the most important and preferred way of delivery due to three reasons. 1) Ease of production. 2) Ease of administration. 3) Low cost.

Drugs which get absorbed from stomach or show local effect should spend maximum time in stomach. This however, is found very difficult to occur, In case of conventional dosage forms.[4]

Basic Gastrointestinal Tract Physiology

The gastrointestinal tract categorizes into three main parts: a) Stomach b) Small intestine - Duodenum, Jejunum and Ileum c) Large intestine The gastrointestinal tract is a long muscular tube, starting from the mouth and end at the anus, which capture the nutrients inside the body and eliminate waste by different physiological processes such as secretion, digestion, absorption and excretion. It also includes the basic construction of gastrointestinal tract from stomach to large intestine. The different layers of GI tract are as following.

Mucosa

The mucosa is the inner lining of GI tract is the mucous membrane composed of an epithelium, connective tissue and smooth muscle.

Submucosa

The submucosa consists of areolar connective tissue that binds the mucosa to the muschularis. It contains many blood and lymphatic vessels that receive absorbed food molecules.

Muscularis

The muscularis of the mouth, pharynx, superior and middle parts of esophagus contains skeletal muscle that produces voluntary swallowing.[5]

Anatomy and Physiology of Stomach

The stomach is located in the upper left-hand portion of the abdomen just below the diaphragm. It is a 'J' shaped enlargement of the GI tract directly inferior to the diaphragm in the epigastric, umbilical and left hypochondria regions of the abdomen.

Its size varies according to the amount distention: up to 1500 ml following a meal, after food has emptied a collapsed state is obtained with a resting volume of only 25-50ml. Basic structure of gastrointestinal tract and stomach as shown in Fig. 1.The stomach connects the esophagus to the duodenum, the first part of the small intestine Mucosal lining is covered throughout the stomach under this layer specialized cells are present that secrete gastric juice into Stomach. About 2-3 liters of gastric juice secreted daily by specialized cells in mucosa. The stomach connects the esophagus to the duodenum, the first part of the small intestine. It has two curvatures are as following.

- The lesser curvature is short, lies on the posterior surface of the stomach and is the

downwards continuation of the posterior wall of the esophagus.

- Greater curvature where the esophagus joins the stomach the anterior region angles actually upwards, curves downwards forming the greater curvature. Anatomy of stomach is shown in Fig. 1. The stomach has four main regions: the cardia, fundus, body and pylorus.

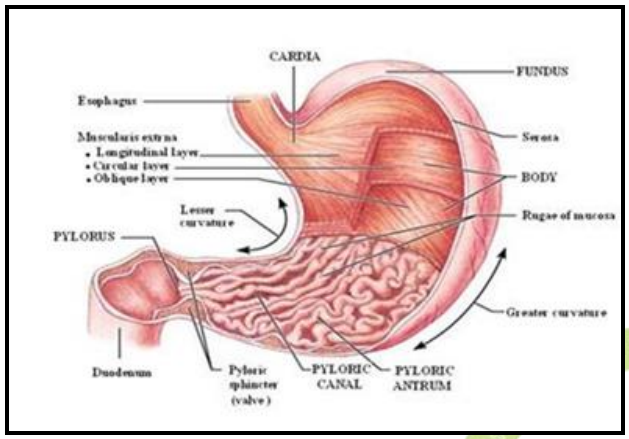

Figure 1: Anatomy of stomach

Cardia

The cardia surrounds the superior opening of the stomach. The cardia is the portion of the stomach surrounding the cardioesophageal junction, or cardiac orifice (the opening of the esophagus into the stomach).

Fundus

The fundus is the enlarged portion to the left and above the cardiac orifice. It serves as a reservoir for the materials which remain undigested.

Body

Inferior to the fundus is the large central portion of the stomach, called body.

Pylorus

The region of the stomach that connects to the duodenum is the pylorus. It has two parts, the pyloric antrum, which connects to the body of the stomach, and the pyloric canal, which leads into the duodenum. When the stomach, is empty, the mucosa lies in larger folds, called rugae. The pylorus communicates with the duodenum of the small intestine via a sphincter called the pyloric sphincter.[6,7]

Gastric Emptying Process and Motility

The passage of drug from stomach to the small intestine is called gastric emptying. Gastric emptying occurs during fasting as well as fed conditions. The GIT is always in a state of continuous motility. There are two modes of motility pattern the digestive mode and inter digestive (or fasted) mode involved in the digestion of food. In the fasted state, it is characterized by an inter digestive series of electrical events which cycle both through the stomach and small intestine every 2 to 3hrs.This activity is called as inter digestive myoelectric circle or migrating myoelectric complex (MMC), which is often divided into four consecutive phases.

Phase I: The quiescent period of no contraction and secretion lasting between 30-60 min.

Phase II: The period of intermittent contractions that gradually increase in intensity as the phase progress and bile secretions lasting between 20-40 min.

Phase III: The short period of intense, large regular contractions lasting between (4-6 contractions per min.) lasting about 10–20 minutes. These are also called as housekeeper waves, since it serves to sweep undigested materials out of the stomach and down to the small intestine.

Phase IV: The transitional period of 0-5 minutes and contractions between phase III and quiescence of phase I.[6]

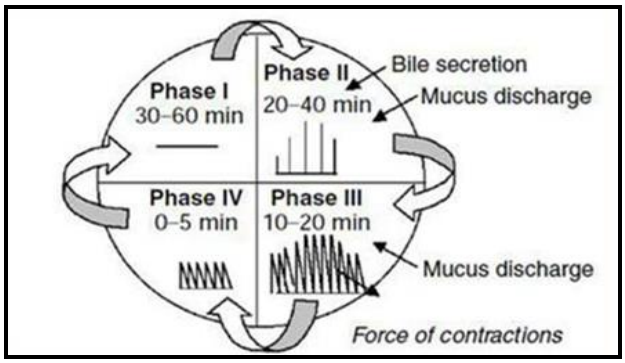

Figure 2: Typical motility patterns in fasting state.[14]

A complete cycle of these 4 phases, as illustrated in (Fig.No.2) has an average duration of 90-120 min. CRDDS designed to stay during the fasted state should be capable of resisting the house-keeping action of phase III, if one intends to prolong the gastrointestinal (GI) retention time.[8]

Gastro-Retentive Drug Delivery Systems

Dosage forms that can be retained in the stomach are called Gastro Retentive Drug Delivery Systems (GRDDS).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. Slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients also increase gastric retention of drug.[9]

Need of Gastro-retention[10]

- Drugs that are absorbed from proximal part of GIT due to variable gastric emptying time.
- Drugs that are less soluble or that degrade at the alkaline pH they encounters at the lower part of GIT.
- Local or sustained drug delivery to stomach and proximal small intestine to treat certain conditions.
- Particularly used for treatment of peptic ulcers caused by H.pylori infections.

Suitable Drugs for Gastroretention[11]

In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

- Drugs that disturb normal colonic microbes, e.g., amoxicillin trihydrate, Tetracycline.
- Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- Drugs that degrade in the colon, e.g. Ranitidine HCL and Metronidazole.
- Drugs absorbed from stomach and upper part of GIT, e.g. Chlordiazepoxide and Cinnarazine.
- Locally acting in the stomach, e.g. Antacids and Misoprostal

Unsuitable Drugs for Gastroretention[12]

- Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- Drugs intended for selective release in colon e.g. 5-amino salicylic acid, corticosteroids etc.
- Drugs that have very limited acid solubility e.g. phenytoin etc.

Factor Affecting Gastroretention[13]

Size

Dosage form units with a large diameter having large volume. If volume increases density will be decreases, low density help in floating. So that larger size devices are reported to have an increased gastric retention time (GRT) compared with small diameter.

Shape of Dosage Form

Tetrahedron and ring shaped devices are reported to have better gastric retention time (GRT) compared with other shapes.

Density

Low density systems tend to float on the gastric fluid surface while high density system sink to bottom of stomach.

Nature of Meal

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release

Single or Multiple Unit Formulation

Multiple unit formulations show a more predictable release profile and allow co-administration of units with different release profiles and permit a larger margin of safety

against dosage form failure compared with single unit dosage forms.

Fed or Unfed State

The migrating myoelectric complex (MMC) occurs every 1.5 to 2 hours under fasting conditions i.e. gastric motility is higher in fasting condition which shows lesser gastric retention time (GRT).However, in the fed state, MMC is delayed and GRT is considerably longer.

Gender

Gastric retention time (GRT) in males (3.4±0.6hours) is less compared with their age and race matched female (4.6±1.2 hours), (regardless of the weight, height and body surface).

Age

Elderly people, especially those over 70 years old have a significantly longer GRT.

Floating Drug Delivery System (FDDS):[14]

Floating systems first described by Davis in 1968, FDDS have bulk density less than gastric fluids that have sufficient buoyancy to float over gastric contents and remain in stomach for longer duration of time without affecting gastric emptying rate and release the drug slowly at a desired rate from the system. After release of drug, the residual system is emptied from the stomach. These results in an increased GRT and a better control of fluctuations in plasma drug concentration. FDDS are also called as hydrodynamically balanced system (HBS).

Classification of Floating Drug Delivery Systems Based on Mechanism of Buoyancy:

1) Effervescent Floating Drug Delivery Systems (FDDS)

A. Gas generating system

B. Volatile liquid containing system

2) Non- Effervescent Drug Delivery Systems (FDDS)

A. Colloidal gel barrier system

B. Microporous compartment system

C. Hollow microspheres / Floating microspheres / Microballoons

D. Alginate floating beads.

3) Raft forming system

Effervescent System FDDS

These systems are formed by matrix polymers so these systems are also known as matrix type of floating system. These are formulated using swellable polymer such as methylcellulose and Chitosan and various effervescent substances. e.g: sodium bicarbonate, sodium carbonate, tartaric acid, citric acid. These are prepared in such a technique that when these are come in react or contact with gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloid polymers due to these reaction dosage forms are buoyant or float.[15]

Gas Generating Systems

These are low density FDDS produces effervescent reaction between carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer of the system, thus decreasing its specific gravity less than 1 and making it to float over dissolution media. These tablets may be either single layered wherein the CO_2 generating components are intimately mixed within the tablet matrix or they may be bilayer in which the gas generating components are compressed in one hydrocolloid containing layer, or the drug in outer layer formulated for sustained release effect. These systems are shown in Fig. No.3, 3.1 and 3.2.[10, 16]

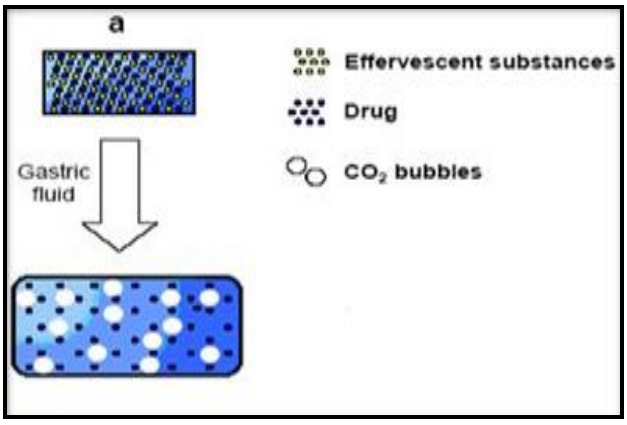

Figure 3: Gas generating system.[56, 57]

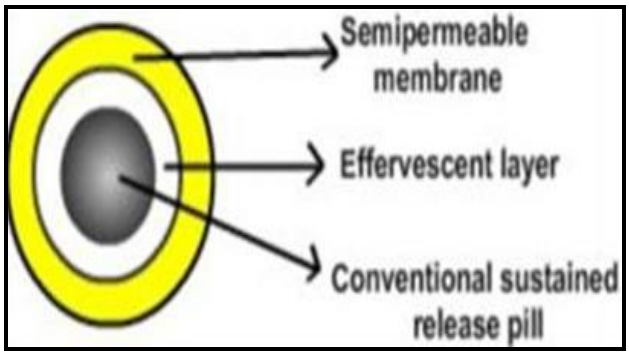

Figure 3.1: Gas generating system **(**Multiple Type Floating pills**)** [26]

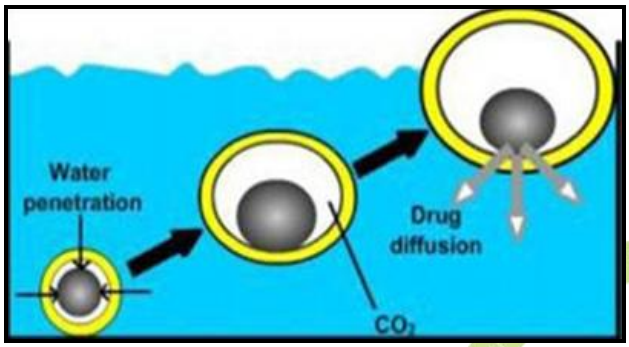

Figure 3.2: Drug release from effervescent (Gas generating systems) [26]

Volatile Liquid Containing Systems

a) Inflatable Gastrointestinal Delivery Systems

b) *Intragastric Osmotic Controlled Drug Delivery System*

Inflatable Gastrointestinal Delivery Systems

These devices are Inflatable gastrointestinal floating systems containing a hollow deformable unit that can be converted from a collapsed to an expanded positions, and returns to collapsed position after an extended period. The deformable system consists of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains that drug and the second chamber contains the volatile liquid. The device inflates and the drug is continuously released from the reservoir into the gastric fluid. The device may also consist of a bioerodible plug made up of polyvinyl alcohol (PVA), 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 system from the stomach. These system depicted in Fig 4.[17]

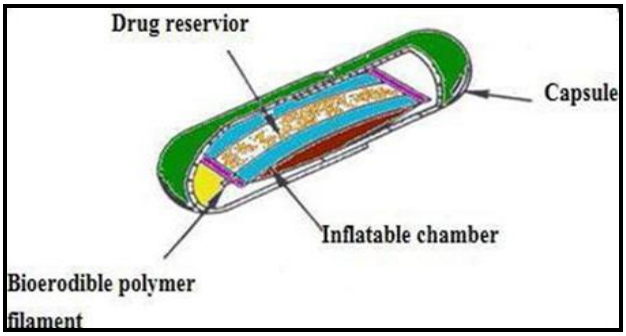

Figure 4: Inflatable Gastrointestinal Delivery System.[56, 58]

Intragastric Osmotic Controlled Drug Delivery System

It consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodible capsule. When the device reaches the stomach, bioerodible capsule quickly disintegrates to release the drug delivery system. The floating support is made up of a deformable hollow polymeric bag containing a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery

system is then emptied from the stomach. These systems are indicated in Fig 5.[17]

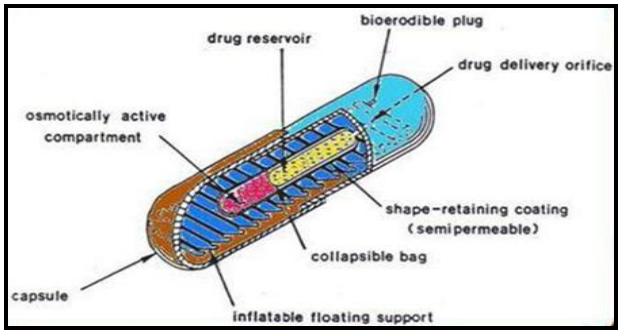

Figure 5: Intragastric Osmotic Controlled Drug Delivery System.[56, 58]

Non-Effervescent FDDS

For the formulation of Non-Effervescent FDDS using gel forming (or) swellable cellulose type hydrocolloids, polysaccharide and matrix forming polymers like polymethacrylate, polycarbonate, and polystyrene. The formulation method includes a simple process that thoroughly mixing the drug with gel forming hydrocolloid. After oral administration these dosage forms swell in contact with gastric fluid and attains a bulk density of less than one. The air entrapped by swollen matrix polymers imparts buoyancy to the dosage forms, so formed swollen gel like structure act as reservoir and allows sustained release of drug through the gelatinous mass. Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, polyethylene oxide, sodium alginate, carbopol and agar.[11]

Colloidal Gel Barrier Systems (Hydrodynamic Balanced Systems)

Hydro-dynamically balanced system (HBS) was first designed by Sheth and Tossounian in 1975. HBS are also called as 'colloidal gel barrier systems' these system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs Gastric residence time and maximizes the amount of drug that reaches its absorption site in the solution form for ready absorption. These systems incorporates a high level of one or more gel-forming highly soluble hydrocolloids, NaCMC, Hydroxy propyl cellulose(HPC), Hydroxy propyl methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC), Ethyl cellulose, polysaccharides and matrix forming polymer such as poly-carbophil, polystyrene and poly-acrylate. On coming in the contact with GI fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface.[55] These gel barrier controls the rate of fluid penetration into the device and consequent drug releases from the barrier. The gel barrier act as a reservoir for sustained release of drug. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer becoming hydrated.The air trapped in by the swollen polymer lowers the density less than 1 and remain buoyant in the stomach for up to six hours. The working principle of HBS is shown in Fig. No.6. the HBS must have following characteristics**:**

- The structure must form cohesive gel barrier.
- The specific density must be lower than that of gastric contents.
- It should dissolve slowly enough to serve as reservoir for the delivery system.[17]

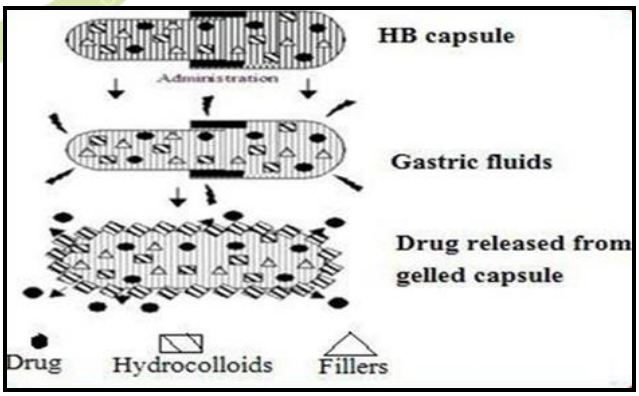

Figure 6: Working Principles of Hydrodynamically Balanced System.[56,59]

Microporous Compartment System

These systems composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral wall of the drug reservoir compartment is completely sealed to prevent

any physical contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the gastric fluid to an extent that it prevents their exist from the drug and carrier the dissolved drug for continuous transport across the intestine for absorption. (Fig.No.7).[18]

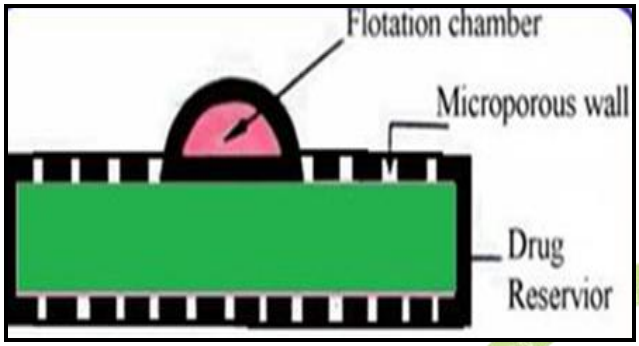

Figure 7: Microporous Compartment System[56,17]

Hollow Microspheres / Floating Microspheres/ Microballoons

Hollow microspheres / Floating microspheres loaded with drug were prepared by an emulsion solvent diffusion method to create a hollow inner core (Figure No.8), which prolongs the gastro retention time of the dosage form. Mainly polymers used to develop these systems such as polycarbonate, cellulose acetate, calcium alginate, agar and low methoxylated pectin etc.

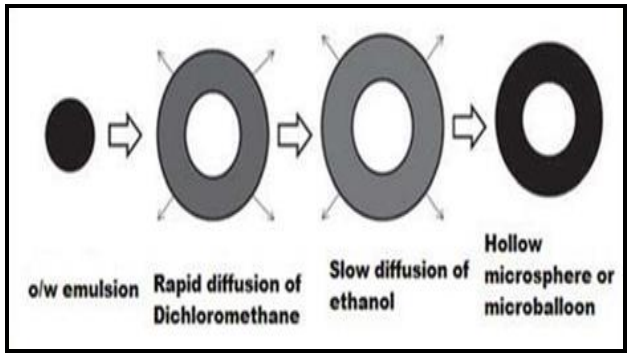

Figure 8: Formulation of Floating Hollow microsphere or microballoon[12]

Method: The polymer was dissolved or dispersed in the organic solvent and the drug was either dissolved or dispersed in the polymer solution. The solution containing the drug was emulsified into an aqueous phase containing polymers to form an oil-in water emulsion and after formation of stable emulsion, the organic solvent was evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal results in polymer precipitation at oil/water interface of the droplets with formation of cavity, and thus, hollow microspheres were formulated.[19]

Alginate Floating Beads

Talukdar and Fassihi[20] recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze dried at 40ºC for 24 h, which leads to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These floating beads improve gastric retention time more than 5.5 hrs. [21]

Raft Forming System

This system is used for delivery of antacids and drug delivery for treatment of gastrointestinal infection and disorders. The mechanism involved in this system include the formation of a viscous cohesive gel in contact with gastric fluids, Where in each portion of the liquids swells, forming a continuous layer called raft. This raft floats in gastric fluids because of the low bulk density created by the formation of carbon dioxide (CO_2) 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 bicarbonate or carbonates responsible for the formation of carbon dioxide to make the system less dense and more often to float on the gastric fluids.

e.g.: Alginate raft forming floating system

Antacid raft forming floating system.[7, 19, 22]

Approaches to Design Floating Dosage Forms

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems.

Single-Unit Dosage Form[23]

In these forms a Low-density approaches the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. In coated shells popcorn, pop rice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and Cellulose acetate phthalate have been used to undercoat these shells.

These are further coated with a drug-polymer mixture. The polymer of choice can be either ethyl cellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid filled floating chamber type of dosage forms includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir.

Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains there in. Hydro-dynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine to remain in the stomach for a prolonged period of time the dosage form must have a bulk density of less than 1.

It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form.

Multiple-Unit Dosage Forms[24]

The purpose for designing multiple-unit dosage form is to develop a formulation which has all the advantages of a single-unit form and also devoid the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. There are various types of multiple unit dosage forms e.g. floating microspheres, pellets and beads. Microspheres with high loading capacity can be formulated using various polymers such as albumin, gelatin, starch, polymethacrylate, polyacrylamine and polyalkylcyanoacrylate. Spherical polymeric micro-sponges are referred as “microballoons,” have been prepared. Multiple unit dosage forms provide various advantages like uniform drug release, decreased intersubject variability and minimum risk of dose dumping.

Mechanism of Floating Drug Delivery System

There are various methods have been made to retain the dosage form in the stomach as a way of increasing the gastric retention time. These methods include introducing floating dosage forms (gas-generating systems and swelling or expanding systems, mucoadhesive systems, high density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. FDDS 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 shown in (Figure No.9 (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach.

This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure

the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature.

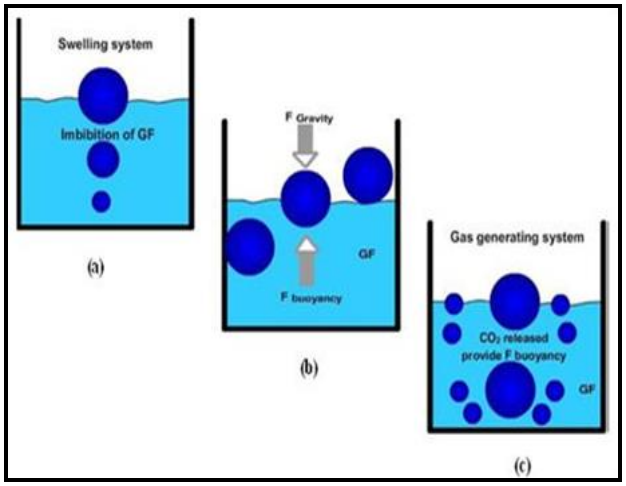

Figure 9: Mechanism of Floating system, GF = Gastric fluid. [60]

The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure No.9(b)).This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[25,26]

F = F buoyancy - F gravity = (Df - Ds) gv

Where,

F= total vertical force,

Df = fluid density,

Ds = object density,

v = volume and,

g = acceleration due to gravity

Advantages of Floating Drug Delivery System (FDDS) [27, 28]

- The Floating systems are advantageous for drugs absorbed through the Stomach. e.g. Ferrous salts, Antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
- The gastro retentive systems are beneficial for drugs meant for local action in the stomach. e.g. Antacids.
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. β-lactam antibiotics (Penicillin and Cephalosporin).
- FDDS provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. FDDS improves patient compliance by decreasing dosing frequency.
- Gastric retention time is increased because of buoyancy

Limitations of FDDS[29,30]

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract. e.g Phenytoin
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa. e.g. NSAIDS.
- Floating systems are not suitable for drugs that are unstable in acidic environment.

Drug Candidates Suitable for FDDS

- Drugs those are locally active in the stomach.[31] (e.g. Misroprostol, Antacids)
- Drugs those are unstable in the intestinal or colonic environment.[32] (e.g. Captopril, Ranitidine HCl, Metronidazole)
- Drugs that disturb normal colonic microbes.[33] (e.g. antibiotics used for the

eradication of Helicobacter pylori, such as Tetracycline)

- Drugs that exhibit low solubility at high pH values.[34] (e.g. Diazepam, Chlordiazepoxide)
- Drugs that have narrow absorption window in Gastrointestinal tract (GIT). (e.g. L-DOPA, p-amino benzoic acid, Furosemide, Riboflavin)[12]

Different Methods Used for the Formulation of Gastroretentive Tablets

Direct Compression Method

In this method the final weight of tablet can easily exceed than that of other production methods. Direct compression formulations can be developed with minimal numbers of excipients. Excipients needed are diluents (Fillers, binders) a disintegrants and lubricants. Additional components may include a glidant, a surfactant, pigments and stabilizing agents. In this method all the powders were accurately weighed and passed though an 80 mesh sieve (180 micrometer size).Then, except post lubricant all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, post lubricant was added, and further mixed for additional 2-3 minutes.The blend was compressed into tablets having average weight of tablet (as per requirement) using a rotary single punch tablet machine or compression tablet machine fitted with an necessary size of punches.[35,36]

Wet Granulation Method

In this method weighed quantities of all the ingredients such as polymers, binding agents, diluents and disintegrating agents were sifted through stainless steel sieve no.(#60).Sifted materials were dry, mixed in geometric dilution by spatulation without addition of lubricating agent and glidant. Distilled water was added to dry-mixed blend of drug and excipients, slowly and the wet mass was mixed to get desired doughy consistency. The doughy or wet mass passed through stainless steel sieve no. (#16) to obtain wet granules. The granules were dried in hot air oven at 50°C for 1 hour. The dried granules were passed through sieve no. #24 and mixed with lubricating agent and glidant. The lubricated granules were compressed on a ten station tablet mini press or tablet compression machine using a necessary size of punches. Compression force are also adjusted to obtain hardness in the range of 3-5 kg/cm^2 [31, 37]

Hot-Melt Extrusion (HME) Method

It is the process of embedding drug in a polymeric carrier. Specifically, HME dosage forms are complex mixtures of API, functional excipients, and processing aids, which are blended uniformly. The calculated amount of beeswax (melting aid) was melted in a china dish. To this, geometrical mixture blend of polymers, diluents was added followed by the Active pharmaceutical ingredient (API).Mix it well before solidification and later the mass was removed from hot plate by scrapping until it attains room temperature and the coherent mass passed through sieve no.36 to form granules. The formed granules were then made to pass through sieve no.100 to remove any fines. The formed granules are then mixed with calculated amount of glidant and lubricants for the processing operations and the granules then are compressed using rotary tablet punching machine to obtain the floating tablet.[30, 38]

Evaluation of Floating Drug Delivery Systems

Various parameters that need to be evaluated in gastroretentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms.[24, 39]

In the case of multi particulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

***In-Vitro* Evaluation Test**

Floating Systems

Buoyancy Lag Time

It is determined to assess the time taken by the dosage form to float on the top of the dissolution

medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.[40]

Floating Time

Test for buoyancy is usually performed in Simulated Gastric Fluid (SGF) maintained at 37ºC. The time for which the dosage form continuously floats on the dissolution media is termed as floating time. It is determined by using USP dissolution apparatus containing 900ml of 0.1N HCl as dissolution medium at 37ºC.The system to check continuous floating behavior contains a stainless steel basket connected to a metal string and suspended from a Sartorius electronic balance. A lotus-spread sheet could automatically pick up the reading on the balances. Test medium used in floating kinetics measurements was 900ml simulated gastric fluid (pH-1.2) maintained at 37°C, data was collected at 30 sec. interval; baseline was recorded and subtracted from each measurement. Dissolution basket had a holder at the bottom to measure the downward force.[41]

Specific Gravity / Density[25]

Density can be determined by the displacement method using Benzene as displacement medium.

Swelling Systems

Swelling Index

The swelling of the tablets takes place due to the ability of polymers to hydrate and swell. The swelling characteristics of the tablet was determined by immersing the tablet in a beaker containing 200 ml of 0.1 N HCl (pH 1.2) and stirred at 37ºC. After the predetermined time intervals, tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed again. Swelling index (SI), expressed as percentage, was calculated using following equation.[42]

$$SI = \frac{Wt - Wo}{Wo} X\ 100$$

Where

SI = Swelling Index

Wt = Weight of swollen tablet and

Wo = Initial weight of tablet

In-Vitro Dissolution Test

The In-vitro dissolution study was performed by using a United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method) at a rotational speed of 50rpm. The dissolution test was performed using 900 ml of 0.1 N HCl (pH 1.2) was used as the dissolution medium. The tablet was placed in the vessel and the temperature was maintained at 37±0.5°C. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at a specified time intervals for 12 hours and the same volume (the samples) were replaced with fresh dissolution medium. The withdrawn samples were filtered through 0.45µm whatman filter paper and diluted with a required volume of plain dissolution medium (0.1N HCl solution) kept at 37ºC. The collected samples were analyzed at respective λmax using a UV-visible double beam spectrophotometer. The absorption of withdrawn sample was measured and the corresponding concentration was determined from the calibration curve.[43,44]

Hardness and Friability

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester or the Pfizer tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.[45,46] Friability of the tablets was determined using Roche friabilator. The tablets were subjected to the test of friability with initial weight (Wi) almost equivalent to 6.5 gm of the tablets. The tablets were allowed to fall on it from a height of 6 inches while the friabilator drum was rotated at 25 RPM for 4 minutes. The final weight (Wf) of the tablets after subjecting to friability was noted and the friability was calculated according to the formula.[47,48]

$$\text{Friability} = \frac{Wi - Wf}{Wi} \times 100$$

Where

Wi = Initial weight of tablets and

Wf = Final weight of tablets

Note: The % friability of tablets should be within 0.5% to 1.0% are considered acceptable.

Weight Variation Test

The USP provide the weight variation test by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The tablet meet the USP test if on more than 2 tablet are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.[48]

Particle size analysis, Surface Characterization (For Floating Microspheres and Beads)

The particle size and the size distribution of Floating microspheres or beads are determined in a dry condition using the optical microscope. The external and cross sectional morphology (Surface characterization) is done by Scanning Electron Microscope (SEM).[49]

***In-Vivo* Evaluation Test**

X-Ray/Gamma Scintigraphy

It is a very popular evaluation parameter for floating dosage form now a day. It helps to locate dosage form in the GIT and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scinti-scanner In case of γ-scintigraphy; the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract [49, 50]

Gastroscopy

It comprises of perusal endoscopy, used with a fibre optic or video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively; FDDS may be drawn out of the stomach for more detailed evaluation.[43]

Ultrasonography

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most Dosage forms do not have sharp acoustic mismatches across their interface with the physiological milieu. Therefore, Ultrasonography is not routinely used for the evaluation of FDDS. [31, 51]

Applications of Floating Drug Delivery System (FDDS)

Floating Drug Delivery System offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery

Oral controlled release formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.[52]

Site-Specific Drug Delivery

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. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was in-creased.AUC obtained with the floating tablets

was approximately 1.8 times those of conventional furosemide tablets.[53]

Absorption Enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption. e.g. A significantly 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%).[54]

Reduced Drug Concentration Fluctuation

The fluctuation in drug concentration is minimized so adverse effect associated with drug concentration is minimized. This is very useful for narrow therapeutic index drugs.[54]

Table 1: List of drugs formulated as a single and multiple unit forms of floating drug delivery system (FDDS) [25,55]

Dosages forms	Drugs
Floating Tablets	Acetylsalicylic acid, Amoxicillin trihydrate, Acetaminophen, Captopril, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide mononitrate, Piretanide, Sotalol, Prednisolone, Ampicillin, Cinnarizine,
Floating Capsules	Chlordiazepoxide HCl, L-DOPA, Diazepam, Furosemide, Nicardipine, Misoprostol, Propranolol, Urodeoxycholic acid
Floating Microsphere	Aspirin, Griseofulvin, Ibuprofen, Ketoprofen, P-Nitroaniline, Terfenadine, Tramilast, Verapamil hydrochloride
Floating Granules	Diclofenac- sodium, Indomethacin and Prednisolone
Powders	Several basic drugs

Marketed Products of Floating Drug Delivery System (FDDS) [17, 18]

Table 2: Marketed Products of Floating Drug Delivery System (FDDS)

Brand Names	Drugs	Manufacturers
Topalkan	Aluminium-Magnesium antacids	Pirerre Faber Drug, France
Liquid Gaviscon	Aluminium hydroxide, Magnesium Carbonate	Glaxosmithkline (GSK, India)
Valrelease	Diazepam	Hoffman- La Roche, U.S.A
Madopar	Levodopa and Benserazide	Roche Products, U.S.A
Cifran-OD	Ciprofloxacin	Ranbaxy, India
Cytotec	Misoprostal	Ranbaxy, India
Conviron	Ferrous Sulphate	Pharmacia, U.S.A

CONCLUSION

From the different types of gastro-retentive drug delivery system floating drug delivery system (FDDS) is most important and promising. Floating drug delivery systems (FDDS) 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. The currently available polymer-mediated Non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. The

number of commercial products and patents issued in this field are the evidence of it. The aim is to increase the bioavailability of the drug with narrow absorption window in gastrointestinal tract region. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. 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;
- The role of buoyancy in enhancing GRT of FDDS; and
- Role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate H. Pylori, responsible for gastric ulcers worldwide. With an increasing understanding of polymer behavior and the role of the biological factors mentioned above, it is suggested that future research work in the FDDS should be aimed at discovering means to control accurately the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents. FDDS provide a better approach for gastric retention. This review gives the detailed outline of the different approaches to achieve gastro-retention, mechanism of FDDS, advantages, limitations, In-vitro and in-vivo evaluation, applications and evaluation of FDDS. It shows good stability and better drug release than other conventional dosage forms make such system more reliable.

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