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Review Article

**FLOATING DRUG DELIVERY SYSTEM: IT' CURRENT
APPROACH AND ADVANCEMENT****Bhabani Shankar Nayak*, Pradeep Kumar Suna, Priya Ranjan Patel, Pramila Panigri,
Bhabani Samarath**Department of Pharmaceutics, Jeypore College of Pharmacy, Rondapalli, Jeypore – 764002, Koraput,
Odisha, India.**Abstract:**

Pharmaceutical industries have received much interest in pharmaceutical research in the area of oral drug delivery more over on Gastro retentive drug delivery system that is Floating Drug Delivery System (FDDS). The objective of this study to review on FDDS focusing on its current advancement and its future. FDDS is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper GI tract improving the oral sustained delivery of drug that have an absorption window in a particular region of the GI tract, thus ensuring optimal bioavailability. This manner may increase patient compliance and provides continuously controlled release administration of sparingly soluble drugs at the particular sites of absorption. FDDS have bulk density less than gastric fluids that have sufficient buoyancy to float over the gastric contents and remain in the stomach for longer duration of time without affecting gastric emptying rate. Floating dosage forms can be prepared as tablets, capsule by adding suitable ingredients with excipients like hydrocolloids, inert fatty materials and buoyancy increasing agents. Various categories of drugs like antacids, antidiabetic, antifungal and anticancer drugs are formulated into FDDS. FDDS have bulk density less than gastric fluids that have sufficient buoyancy to float over the gastric contents and remain in the stomach for longer duration of time. The recent advancement of FDDS is on physiological and formulation variables affecting gastric retention approaches to design single unit and multiple unit floating systems. Furthermore, recent innovations in pharmaceutical investigation will surely provide real prospects for establishment of novel and effective means in the development of FDDS.

Keywords: *Floating drug delivery system, Effervescence, Gastric residency time, Bioavailability.*

Address for Correspondence:**Bhabani Shankar Nayak**Jeypore College of Pharmacy,
Rondapalli, Jeypore – 764002,
Koraput, Odisha, India.

Mob. No. 09938860284.

E. Mail I.D. bhabani143@yahoo.co.in

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INTRODUCTION:

Oral route is most accepted, suitable and promising route for administration of drugs in systemic action. Oral routes has several merits like their conveniences of application or increase patient's compliance, ease of administration, low cost, improve bioavailability and ease of production in an industrial scale. The oral route is the most promising route of drug delivery [1]. Controlled-release drug delivery system (CRDDS) provide drug release at a predetermined, predictable and controlled rate and provide the benefits like maintenance of optimum therapeutic drug concentrations in blood with predictable and reproducible release rates for extended time period; enhancement of duration of activity for short half life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliance. Effective oral drug delivery may depend upon factors such as gastric emptying process, gastrointestinal transit time of dosage forms, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profile, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors. Because of which wide inter and intra subject variations are observed [2]. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possess the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i-e, upper part of the small intestine). GRDDS is novel site specific drug deliveries to promoting retention with in the stomach, duodenum or small intestine can prolong drug released to controlled manner. Several types of gastro retentive techniques such as floating systems, super porous hydrogel systems, expandable systems and high density systems etc. can be used [3]. All useful approaches, especially if drug absorption takes place in stomach or upper part of intestine (e.g., duodenum) could be benefits for local drug action in the stomach or for drug with an narrow absorption window. The Gastric Emptying Time (GET) of a dosage form will depends

on the density and size of the systems and the fed or fasted state of the patient [4,5]. The control of GI transit of oral delivery using gastric dosage forms can increase the drugs bioavailability that exhibit specific site of drugs absorption.

Anatomy and Physiology of Stomach:

The antrum region is responsible for the mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid (pH 1–3) and air. The mucus spreads and covers the mucosal surface. The gastrointestinal (GI) tract is in a state of continuous motility consisting of two modes; inter digestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The inter digestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organized in cycles of activity and quiescence [6]. Each cycle lasts 90 to 120 min and consists of four phases. A full cycle is beginning in the lower esophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper wave' as the powerful contractions in this phase tend to empty the stomach of its fasting contents and indigestible debris. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive state is observed in response to meal ingestion. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the inter digestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food [7]. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. Generally, a meal of ~450 kcal will interrupt the fasted state motility for about 3 to 4 h. It is reported that the antral contractions reduce the size of food particles to $\leq 1\text{mm}$ and propel the food through the pylorus [8].

FLOATING DRUG DELIVERY SYSTEM (FDDS):

Floating system is low density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged

period of time. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microsphere [9].

Advantages of FDDS:

FDDS offers following advantages like improved drug absorption, improved gastric residence time of the dosage form at its absorption site, controlled delivery of drugs, delivery of drugs for local action in the stomach, minimizing the mucosal irritation due to drugs, treatment of gastrointestinal disorders such as gastro-oesophageal reflux, simple and conventional equipment for manufacture, ease of administration, better patient compliance and site specific drug delivery [9,10].

Disadvantages of FDDS:

In spite of several advantages of FDDS, there are certain situations where gastric retention is not desirable. Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems. Furthermore, other drugs, such as Isosorbite dinitrate that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system.

Not suitable for drugs that have solubility or stability problem in GIT. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable. Not suitable for drugs that have solubility or stability problem in GIT. Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable [9,10].

Suitability of Drugs for FDDS:

The drugs to be designed as FDDS must have following characteristics like narrow absorption window in GI tract (Riboflavin and levodopa), primarily absorbed from stomach and upper part of GIT (Calcium supplements, chlorthalidone and cinnarizine), drugs that act locally in the stomach (Antacids and misoprostol), drugs that degrade in the colon (Ranitidine HCl and metronidazole), drugs that disturb normal colonic bacteria (Amoxicillin trihydrate), low density form of the DF that causes buoyancy in gastric fluid, high density DF that is retained in the bottom of the stomach, bioadhesion to stomach mucosa and slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients. Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter [11-13].

Unsuitability of Drugs for FDDS:

Drugs that have very limited acid solubility (Phenytoin). Drugs that suffer instability in the gastric environment (Erythromycin). Drugs intended for selective release in the colon (5- amino salicylic acid and corticosteroids) [12].

Classifications of FDDS:

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS such as effervescent system and non-effervescent System [14-21].

Effervescent System:

Effervescent systems include use of gas generating agents, carbonates (Sodium bicarbonate) and other organic acid (Citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO₂) gas, thus reducing the density of the system and making it floatable on the gastric fluid. These effervescent systems further are classified into two types that is gas generating systems and volatile Liquid/ vacuum system.

Gas Generating System:

Intra gastric single layer floating tablets or Hydrodynamically Balanced System (HBS):

These are formulated by intimately mixing the CO₂ generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after complete release; the residual system is expelled from the stomach.

Intra gastric bilayer floating tablets:

These are also compressed tablets containing two layers such as immediate release layer and sustained release layer.

Multiple unit floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temp, it sinks at once and then forms swollen pills like balloons which float as they have lower density. This lower density is due to generation and entrapment of CO₂ within the system.

Volatile Liquid/ Vacuum Containing Systems:

Intragastric floating gastrointestinal drug delivery system:

These systems can be made to float in the stomach because of floatation chamber which may be a vacuum or filled with air or a harmless gas. While drug reservoir is encapsulated inside a microproous compartment, as shown in

Inflatable gastrointestinal delivery Systems:

In these systems an inflatable chamber is incorporated which contains liquid ether that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir which can be a drug impregnated polymeric matrix and then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug gets continuously released from the reservoir into the gastric fluid.

Intragastric osmotically controlled drug delivery system:

The osmotic pressure controlled drug delivery device consists of two components; drug reservoir and an osmotically active compartment the inflatable support located inside forms a deformable hollow polymeric bag that contains a liquid which gasifies at body temperature to inflate the barrier.

Non effervescent systems:

The non-effervescent FDDS are based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials i.e. polycarbonate, polyacrylate, polymath acrylate, polystyrene as well as bioadhesive polymers e.g. chitosan and carbopol.

Colloidal Gel Barrier system:

Such a system contained drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolonged GRT and maximized the amount of drug that reached its absorption sites in the solution form for ready absorption.

Micro porous compartment system:

This technology was based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment get completely sealed to prevent any direct contact of gastric surface with the undissolved drug.

Alignate beads:

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium alginate solution into aqueous solution of calcium chloride causing precipitation of calcium alginate leading to formation of porous system which can maintain a floating force for over 12 h. When compared with solid beads which gave a

short residence time of 1 hour, these floating beads gave a prolonged residence time of more than 5.5 h.

Components Used in FDDS:***Drugs:***

Drug used in the formulations of stomach specific floating dosage form such as Floating microspheres containing drugs like Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast 36 and Terfenadine; Floating granules e.g. Diclofenac sodium, indomethacin, prednisolone; Films e.g. Cinnarizine, Albendazole; Floating tablets and Pills e.g. Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate, Paraaminobenzoic acid, Piretanide 40, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, prednisolone, Sotalol 41, pentoxifylline and Diltiazem HCl [22].

Polymers and other Ingredients:

Hydrocolloids (20 - 75 %) - They can be synthetic, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives such as acacia, pectin, chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC. Inert fatty materials (5 - 75 %) - Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy like Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01. Effervescent agents - Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine). Release rate accelerants (5 - 60 %) - Lactose, mannitol. Release rate retardants (5 - 60 %) - Dicalcium phosphate, talc, magnesium stearate. Buoyancy increasing agents (up to 80 %) - Ethyl cellulose. Low density material - Polypropylene foam powder (Accurel MP 1000®) [23-25].

Evaluations of FDDS [24-27]:

Weight Variation: Uniformity of weight is determined according to Indian Pharmacopoeia, 20 tablets were selected at randomly, weight together and individually for the determination of average weight of tablets. The percentage difference in weight of each tablet from average weight is calculated.

Hardness: Hardness is the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in Kg/cm².

Thickness: Thickness and diameter of ten tablets were measured using vernier calipers and the results are expressed as milli meter.

Friability: The friability test is carried out in Roche Friabilator. Ten tablets were weighted (W_0) initially and put in a rotating drum. Then the tablets were subjected to 100 revolutions. After completion of rotation, the tablets were again weighted (W). The percentage weight loss or friability (f) is calculated using formula, $f = (1 - w/w_0) \times 100$, where w is final weight and w_0 is initial weight. The percentage loss of tablets should be less than 1 % as per I.P.

Disintegration Time: *In vitro* disintegration time was determined using disintegration test apparatus. For this, a tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus is measured.

Buoyancy Time: A tablet is introduced in to beaker containing 100 ml of 0.1N HCl. The time taken by the tablet to come up to the surface and floated is taken as the buoyancy time.

Floating Time and Dissolution: The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1N HCl maintained at 37°C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1N HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

Drug Release: Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

Content Uniformity: The drug content in each formulation is determined by triturating 20 tablets and powder equivalent to average weight was added in 100 ml of solvent, followed by stirring for 30 min and filter. The solution was filtered through a 0.45 μ m membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically in UV.

Current Advancement in FDDS:

Bio/Mucoadhesive Systems:

Bio/ Mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the GRT of drug delivery system (DDS) in the stomach, by increasing the intimacy and duration of contact of drug with the biological membrane. The surface epithelial adhesive properties of mucin have been well recognized and applied to the development of GRDDS based on

bioadhesive/ mucoadhesive polymers. The ability to provide adhesion of a drug (or a delivery system) to the GI walls provides a longer residence time in a particular organ site, thereby producing an improved effect in terms of local action or systemic effect [26].

Swelling and Expanding Systems:

There are the dosage forms, which after swallowing swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as “plug type systems,” since they exhibit the tendency to remain lodged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity for several hours even in the fed state. The balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability of the system maintaining its physical integrity for prolonged period [26].

Raft Forming Systems:

The cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous. The basic mechanism involved in the raft formation includes the formation of viscous layer called a raft. The raft floats because of the buoyancy created by the formation of CO₂ and acts as a barrier to prevent the reflux of gastric contents like HCl and enzymes into the oesophagus. Usually, the system contains a gel forming agents and alkaline bicarbonate or carbonates responsible for the formation of to make the system less dense and floats on the gastric fluids [27].

Magnetic Systems:

This approach to enhance the GRT is based on the simple principle that the dosage form contains a small internal magnet, and a magnet is placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. The technological approach in rabbits with bioadhesive granules containing ultra- fine ferrite. They guided them to oesophagus with an external magnet for the initial 2 min and almost all the granules were retained in the region after 2 h [28].

Hollow Microspheres:

Hollow microspheres (microballoons), loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally

controlled at 40°C. The gas phase generated in dispersed polymer droplet by the evaporation of dichloromethane formed an internal cavity in microspherical particles containing drug [28].

Patents: Ranbaxy' Patent For New 'floating' tablet:

Ranbaxy's new patent was developed to provide a pharmaceutical composition that controls the release of an API in the stomach or upper part of the intestine, and the same time overcomes a number of disadvantages which has been attempts by various companies to provide controlled delivery in the past. This can decrease the drug effectiveness and also cause unwanted side effects. The new technology is particularly suitable for controlled delivery of drugs that are absorbed only from the upper parts of the gastro-intestinal tract with a specific absorption window, for example- Ciprofloxacin, which is absorbed only from the region extending from the stomach to the jejunum. Alternative drug delivery technologies, such as the one patented by Ranbaxy, are increasingly being developed by drug companies to provide them with a competitive edge to survive in today's tough pharmaceutical market and also to revamp off patent drug products [27,28].

Marketed Formulations of FDDS:

The marketed formulations of FDDS are given in Table 1 [27-29].

CONCLUSION:

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. Study revealed that FDDS have lot of opportunities for designing of an appropriate oral dosage form of various drugs for safe management of several diseases with most objectives of greater patient compliances.

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Table 1: The Marketed Products of Floating Drug Delivery Systems.

Brand name	Delivery system	Drug	Company
Valrelease®	Floating capsule	Diazepam ,	Hoffmann-LaRoche
Madopar® HBS (Prolopa® HBS)	Floating, CR capsule	Benserazide and L-Dopa	Roche Products, USA
Liquid Gaviscon®	Effervescent Floating liquid alginate preparations	Al hydroxide, Mg Carbonate	GlaxoSmithkline, India
Topalkan®	Floating liquid alginate preparation	Al – Mg antacid	Pierre Fabre Drug, France
Conviron®	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
Cytotech®	Bilayer floating capsule	Misoprostol	Pharmacia, USA
CifranOD®	Gas-generating floating form	Ciprofloxacin	Ranbaxy, India