REVIEW ARTICLE - OPEN ACCESS

Journal of Pharmacy and Experimental Medicine DOI: http://dx.doi.org/10.51521/JPEM.2021.22110

Contents lists available at bostonsciencepublishing.us

Journal of Pharmacy and Experimental Medicine

A Review On Gastro-Retentive Drug Delivery System Along With Regional Market Survey

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ARTICLE INFO

Article history:
Received 14 September 2021
Revised 25 September 2021
Accepted 30 September 2021
Published 05 October 2021

ABSTRACT

This study is an attempt to give an overview of Gastro Retentive Drug Delivery System (GRDDS), Floating Drug Delivery System (FDDS) in particular. GRDDS has various advantages over conventional drug delivery system and thus has attracted the interest of many industrialists recently. This study highlights these advantages of GRDDS and Floating DDS as well as the future scope of GRDDS in the pharmaceutical world. Some FDDS have shown the capability to accommodate these variations without affecting drug release. This review mainly focuses on various physiological considerations for development of FDDS, and highlights recent technological developments including new dosage forms and their production techniques. Alternatives to the existing in vitro methods for evaluating floating dosage forms will be discussed, and a critical analysis of the existing literature on FDDS, identifying the potential areas for future research, is provided..

KEYWORDS: Floating System, Gastro Retentive System, Market Survey

Introduction

The oral route of administration is the most favoured route of administration because of its ease of administration. Bioavailability of Drug in oral dosage forms is variable due to various factors. One of the many factors may be a Gastric Residence Time (GRT) of those dosage forms. Gastric retention has received attention in the past few years as many of the conventional oral drug delivery systems have some limitations which are related to fast gastric emptying time. Gastro retentive drug delivery system is a novel drug delivery system which may remain in the stomach for prolonged period of time and thus increases the GRT of drugs. Gastro-retention helps to improve bioavailability of drugs. The problem with conventional drug delivery system is that although it reaches and maintains the therapeutic drug concentration in effective range desired for treatment, it has to be taken a number of times in a day to achieve that which in a long run may lead to drug toxicity and accumulation. A drug with a narrow absorption window in the GIT is poorly absorbed. As the gastric retention time is increased, it will increase the drug absorption thus increasing the bioavailability of drug. Oral route of administration is considered to be best as it is easy to administer and produce, has patient compliance, flexible and most importantly, Low cost.

Several methods of the controlled drug delivery system have been established in order to achieve the above mentioned conditions. One of these methods is GRDDS. Gastro Retentive Drug Delivery System (GRDDS) can be defined as a system which retains in the stomach for a prolonged period of time, releasing the drug in controlled manner so as to achieve maximum gastric retention and absorption of drug and finally metabolized in the body. GRDDS is prepared

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to retain drug in the gastric region for sufficient amount of time and release the incorporated drug, thereby enabling a sustained and prolonged release and action of the drug in the stomach thus increasing bioavailability. Pharmacotherapy of the GIT is significantly increased by GRDDS through local drug release, leading to increased concentrations of drug at the gastric mucosa making it possible to treat various GI diseases [1-7].

Physiology of Gastro-Intestinal Tract [8-10]:

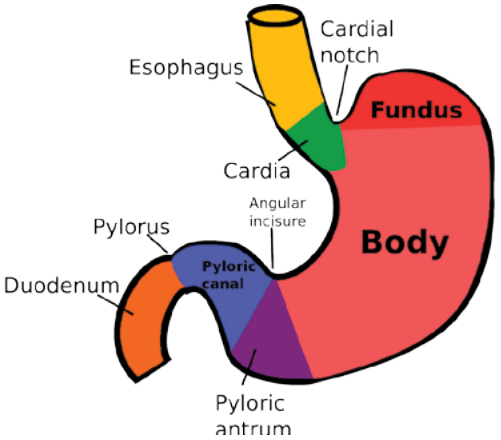

Figure 1: Anatomy of Stomach.

Anatomically, the stomach is divided into 3 regions: The Fundus, the Body and the Antrum (pylorus). The proximal region forms the Fundus. The Body forms a greater portion of stomach and it acts as a reservoir for undigested food materials. The Antrum is the main portion where mixing motions occurs and it acts as a pump for gastric emptying by a propelling action. Gastric emptying occurs during fasting as well as in a fed state (when food is consumed). However, the pattern of motility is different in both the states.

In the fasting state, an inter-digestive series of electrical events takes place. This series of event takes place through both stomach and intestine in every 2 to 3 hours. This is called the Inter-Digestive Myoelectric Cycle or the Migrating Myoelectric Cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington (1989).

PHASE I: It is called the Basal Phase and it lasts for 40 to 60 minutes with rare contractions.

PHASE II: It is called the Pre Burst Phase and it last for 40 to 60 minutes with intermittent action potentials and contractions. As the phase progresses further, the intensity and frequency also increases gradually.

PHASE III: It is called the Burst Phase and it lasts for 4 to 6 minutes. The phase includes intense and regular contractions for short period. This wave causes all the undigested food material to be swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

PHASE IV: It lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

Ingestion of a mixed meal causes a change in the pattern of contractions from fasted to that of fed state. This is also known as the digestive motility pattern and it comprises of continuous contractions as in phase II of fasted state. The contractions results in reduction of food particle size (to less than 1mm) which are then propelled toward the pylorus in a suspension form. In the fed state, onset of MMC is delayed which results in slowing down of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that oral controlled release dosage form are subjected to basically two complications (a) short gastric residence time and (b) unpredictable gastric emptying rate.

Need for Gastric Retention [9]:

- It is needed for drugs that are absorbed from the proximal part of stomach (Fundus).
- It is also needed for drugs that are less soluble or are degraded by the alkaline pH that they encounter in the lower part of GIT.
- It is needed for drugs that have altered absorption due to variable gastric emptying time.
- They are very useful in the treatment of peptic ulcers (PUD) which is caused by H.pylori Infections.

Factors affecting Gastric Retention [11,12]:

A. Physiological Factors:

1) Size and Shape of Dosage Form: Shape and size of the dosage form are an important factor in designing the dosage form that is not removed from GIT quickly. Dosage forms that have a diameter greater than the diameter of pyloric sphincter are retained in the gastric region for a longer period of time as they cannot pass through the sphincter along with food content and thus are retained in the stomach for an increased period of time.

2) Density of Dosage Form: The density of dosage form is a major factor and it also plays an important role in the gastric emptying time of dosage form. If the density of the dosage form is greater than that of gastric fluids, then the dosage form sinks at the bottom whereas those that have a density less than that of gastric fluids, the dosage form floats. Floating Dosage forms are required to have a density of less than 1 gm/cm^3.

B. Biological Factors:

1) Age, Gender and Posture: When compared with the age and race-matched females, males have less Mean Ambulatory GRT (3.4 ± 0.6 hours) regardless of their weight, height and body surface. GRT is longer in geriatric patients while it is shorter in neonates, infants and children when it is compared with a normal adult. Supine and Upright ambulatory state of patient can also vary the GRT.

2) Fed State, Feeding Frequency and nature of Food: The motility pattern of stomach is affected by various factors during the fed state. The presence or absence of food in GIT affects the GRT of dosage form. GRT is less during fasting conditions as the gastric motility increases in fasting state. Higher intake of food leads to longer gastric retention. Higher the amount of fatty acids, polymers lesser is the gastric retention.

3) Concomitant Administration of Drugs and Diseased state: Administration of certain drugs alter the gastric retention as they enhance or depress the gastric motility. GRT is also affected by GI diseases like diabetes, Crohn's Disease,etc.

Advantages of GRDDS [5,6]:

1) It helps in enhancing the bioavailability of drugs. E.g. Controlled Release GRDF of Riboflavin has enhanced bioavailability when compared to its Non Controlled Release GRDF.

2) Since the Bioavailability is increased, dose frequency can be reduced thereby increasing Patient Compliance.

3) It helps minimize the mucosal irritation by releasing the drugs at a controlled rate. E.g. NSAIDs.

4) Maintains the Constant Therapeutic level for a prolonged period of time. E.g. Beta Lactam Antibiotics.

5) GRDDS helps in treating GI disorders like GERD, H.pylori infection, etc…

6) Drugs that have limited absorption from the intestine can be administered in the form of Floating Drug Delivery System.

7) Counter activity of body can be reduced by using floating drug delivery system, leading to higher drug efficiency.

8) Sustained Release may result in a flip-flop pharmacokinetics for

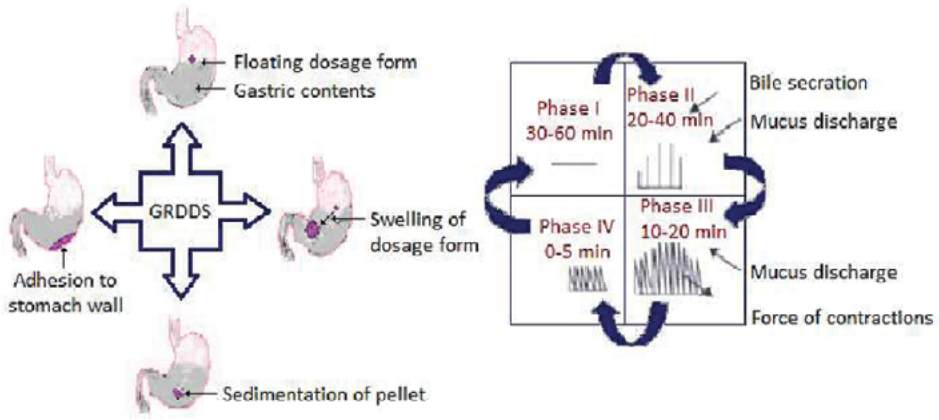

Figure 2: Schematic representation of Myoelectric Cycle.

drugs that have a comparatively short half-life, reducing their frequency of administration.

9) GRDDS are beneficial for drugs that are absorbed in stomach. E.g. Antacids, Ferrous salts, etc.

10) They remain in GI solution for prolonged period even at the alkaline pH of the intestine.

11) They are also useful in case of conditions in which GI motility is increased like diarrhoea.

Disadvantages of GRDDS [5,6]:

1) Drugs undergoing significant First pass metabolism are not the desired candidates.

2) Drugs with low solubility and stability in gastric environment cannot be formulated into GRDDS.

3) Swellable systems must maintain a larger size than the resting pyloric sphincter for prolonged gastric retention.

4) Although these systems provide advantage over conventional dosage forms that are absorbed through GIT, the advantages are not much significant.

5) Some dosage forms may cause gastric mucosal irritation.

6) Swellable dosage forms require a large amount of water consumption at the time of administration.

7) Volatile gas generation, dose dumping, burst release, alkaline microenvironment are some of the limitations of FDDS.

8) They are effective only when the fluid levels in GIT is high.

9) The buoyancy of dosage form may be impeded as the stomach empties and the dosage form is in the pylorus.

10) Bioadhesive Drug delivery system (a type of GRDDS) may bind to oesophagus.

11) Hydrogel based Swelling system take longer time to swell.

12) These systems also require presence of food to delay their gastric emptying.

Approaches for Gastro-Retentive Drug Delivery System [13-17]:

The Gastro Retentive Drug Delivery System (GRDDS) is a system which is designed to be retained in the upper part of the GIT and deliver the API (Active Pharmaceutical Ingredient) in the upper part of GIT for a prolonged period of time thereby sustaining and increasing the input of drug in the stomach. This ideology of creating a GRDF has received an enormous amount of attention by the scientists and Industrialists (Formulators) over the past few decades owing to its ability to increase the oral delivery of important drugs for which prolonged retention in upper GIT greatly increases their bioavailability and thus improve their therapeutic outcome. A variety of approaches have been implemented to increase the gastric retention of dosage forms by applying a variety of concepts. They can be broadly classified into four major types, namely

A. High Density Formulations

B. Bio-adhesive/Mucoadhesive Drug Delivery Systems

C. Expandable/Swellable Drug Delivery Systems

D. Floating Drug Delivery Systems

A. High Density Formulations:

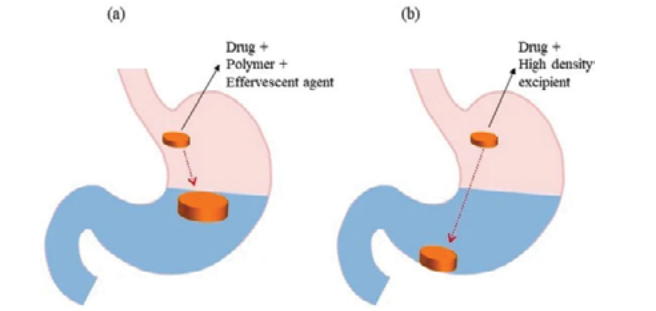

Figure 3: High Density Formulation [36].

This approach involves formulation of a system in which the drug is coated with a heavy core or is mixed with an inert material such as iron powder, zinc oxide, titanium dioxide, barium sulphate so that the density of the formulated dosage form exceeds the density of normal gastric fluids. These materials increase the density of formulation up to 1.5-2.4 gm/cm^3. Sedimentation method is used to increase the retention of dosage form in the lower part of the stomach i.e. pylorus which a small enough to be retained in the folds of stomach. Such dense dosage forms that are trapped in the rugae of pyloric region of stomach tend to withstand the peristaltic movement of the stomach wall. These systems have a density of about 3 gm/cm^3 which is greater than the threshold density limit of the stomach (2.6-2.8 gm/cm^3). Based on the density, the GI transit time of these pellets can be increased from an average of 5.8 hrs to 25 hrs.

B.Bio-adhesive/Mucoadhesive Drug Delivery Systems:

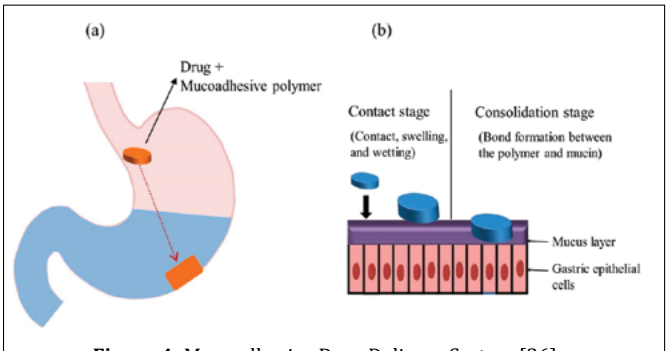

Figure 4: Mucoadhesive Drug Delivery System [36]

Bio-adhesion or Mucoadhesion serves as an important novel solution to the problems of bioavailability that rises from short gastric retention time of dosage form in the GIT. These systems are used to deliver the drug within the lumen to increase its absorption at a specific site. They bind to the gastric epithelial cell surface or mucin thereby increasing the GRT of drug in stomach. They can help in sustaining release of drugs from dosage form as well as control the rate of its release thereby facilitating the therapeutic advantages of such systems. The approach is based on self-protecting mechanism of the GIT. There are various mechanisms by virtue of which Mucoadhesion can be achieved with the mucus of GIT like Hydration, Bonding and Receptor Mediated.

C.Swellable/Expandable Drug Delivery System:

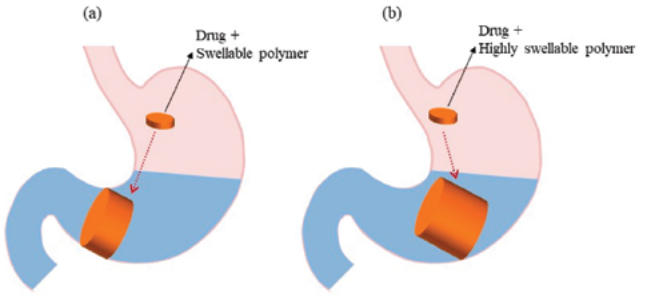

Figure 5: Swellable/Expandable Drug Delivery System [36]

Another way of retaining a dosage form in the Upper GIT is by increasing its size. Pylorus discharges the stomach constituents into intestine. So, if a dosage form can attain a size that is larger than the size of pyloric sphincter then it can be retained in the stomach for a prolonged period, though it will be not possible to swallow a dosage form of such large size. Thus the dosage form must attain this size after it has entered into stomach. Also, it must attain the large size quickly after reaching the stomach as failure to do so will lead to evacuation from stomach. The dosage form must also not block the pylorus. It must be strong enough to withstand the peristaltic movements of stomach. Thus this system is also known as 'plug type system' as they show a tendency to remain logged at the pyloric sphincter after exceeding a diameter of 12-18 mm in their expanded state.

D.Floating Drug Delivery System [18-26]:

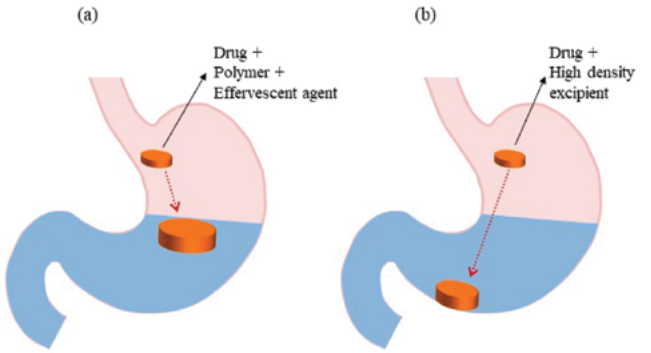

Figure 6: Floating Drug Delivery System [36].

In 1968, Davis described the Floating Systems for the first time. The Floating Drug Delivery Systems or the hydrodynamically controlled systems are systems with low buoyancy and can float over the gastric content without affecting the gastric emptying time for a prolonged period. These systems have a density less than that of gastric content by virtue of which they float over the gastric content. The drug is released from the system at a desired rate while the system is floating. The residual system is emptied from the stomach after the drug is released. This results in a better control of the plasma drug concentration and an increased gastric retention time. Many floating dosage forms such as powders, granules, tablets, capsules, hollow microspheres, laminated films have been formulated. Table below enlist various Drugs that are formulated as FDDS. The System is required to release the drug slowly, must have a specific gravity less than that of gastric content ((1.004 – 1.01 gm/cm3) and must form a cohesive gel barrier. To achieve these requirements, the system can be made so as to entrap the air or use low density materials like fatty materials, oils and foam powders.

D.1.Drug candidates suitable for FDDS:

1. Drugs having narrow absorption window in GIT. E.g. L-DOPA, p-aminobenzoic acid, furosemide, riboflavin.
2. Drugs that are locally active in the stomach. E.g. misoprostol, antacids.
3. Drugs that are unstable in the intestinal environment (alkaline pH). E.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb the normal colonic microbial flora. E.g. antibiotics used for Helicobacter pylori, such as tetracycline, clarithromycin, amoxicillin.
5. Drugs that have low solubility at high pH. E.g. diazepam, chlordiazepoxide, verapamil.

D.2.Classification of Floating Drug Delivery Systems:

Based on the mechanism of floating, the FDDS can be classified as:

I. Effervescent Systems:
   a. Volatile Liquid Containing Systems
   b. Gas Generating Systems

II. Non-Effervescent Systems:
   a. Hydrodynamically balanced systems OR Colloidal Gel Barrier System
   b. Microporous compartment system
   c. Alginate Beads
   d. Hollow Microspheres

D. 2.I. Effervescent Systems:

These are floating system which is prepared from swellable polymer matrix of polymers such as polysaccharides (like chitosan), methocel, effervescent excipients (like sodium bicarbonate, citric acid or tartaric acid), etc. They are so prepared that when they reach the stomach, CO_2 is released, leading to floatation of the dosage form in stomach. Apart from this, many other formulations are prepared by mixing sodium alginate and sodium bicarbonate multiple unit floating pills that release CO_2 upon ingestion, floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxyl propyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc. These systems are further divided into 2 types:

D.2.I.a. Volatile Liquid Containing Systems:

There are 2 chambers in this system. These chambers are separated by an impermeable, pressure-responsive, movable bladder. The drug resides in the first chamber and the volatile liquid in the second chamber. Incorporation of an inflatable chamber containing a volatile liquid can help in sustaining the GRT of the Device. An example of volatile liquid includes ether, cyclopentane that turns into a gas at body temperature causing inflation of the chamber in the stomach. The system also contains a bio-erodible plug which is made up of Poly vinyl alcohol, Polyethylene, etc. This plug gradually dissolves in the stomach causing release of gasified.

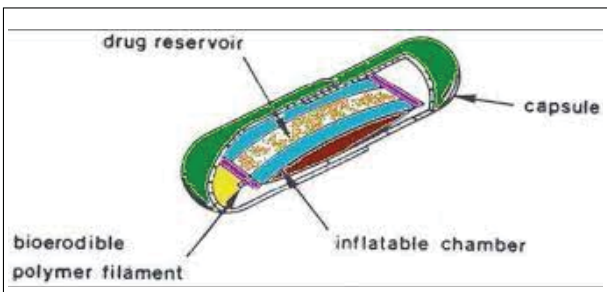

Figure 7: Volatile Liquid Containing System [23]

DOSAGE FORMS	DRUGS
Floating microspheres	Aspirin, p-nitroaniline, Griseofulvin, Ketoprofen, Ibuprofen, Verapamil and Terfinadine
Floating Films	Cinnarizine, p-Aminobenzoic acid, Prednisolone and Piretanide
Floating tablets and Pills	Acetaminophen, Isosorbide mononitrate, Ampicillin, Atenolol, Theophylline, p-aminobenzoic acid, Aspirin, Verapamil hydrochloride, Sotalol
Floating Capsules	Diazepam, Furosemide, Misoprostol, L-Dopa and Benserazide, Pepstatin, Verapamil HCl and Nicardipine
Floating powders	Riboflavin, Phosphate, Sotalol and Theophylline
Floating granules	Diclofenac sodium, Indomethacin, Prednisolone, Cinnarizine, Diltiazem, Fluorouracil and Isosorbide mononitrate

Table 1: Drug formulated as different forms of Floating Drug Delivery System [6]

liquid from the chamber and collapse after a predetermined time allowing the spontaneous ejection of the inflatable system from the stomach. The drug is released into the gastric fluids continuously by virtue of the inflation of the chamber. Thus the device is retained in the stomach for a prolonged period of time and release of drug is sustained.

D.2.I.b. Gas Generating Systems:

These floating systems attain buoyancy by virtue of reaction between carbonate/bicarbonate salts andcitric or tartaric acid liberating CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems, ultimately reducing its specific gravity and thus making it float over chyme. The optimal stoichiometric ratio required for gas generation of citric acid and sodium bicarbonate is found to be 0.76:1.

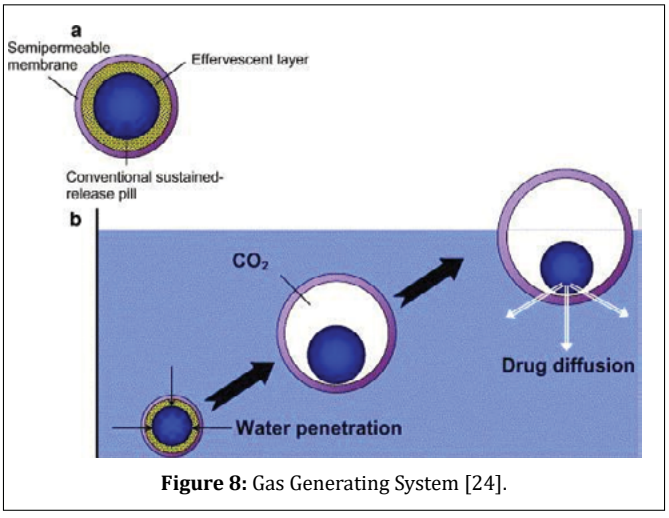

Figure 8: Gas Generating System [24].

D.2.II. Non-Effervescent Systems:

They are usually prepared from a gel forming or a highly swellable/ expandable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one of the methods, there is intimate mixing of drug with a gel forming hydrocolloid that results in contact of dosage form with gastric fluid after oral administration and it maintains a relative integrity of shape and a bulk density that is less than 1 within the gastric environment. The Swollen polymer entraps air inside them conferring buoyancy to these dosage forms. Most commonly used excipients in these systems include HPMC, polyvinyl acetate, carbopol, agar, sodium alginate, polyacrylates, calcium chloride, polyethylene oxide and polycarbonates.

D.2.II.a. Hydrodynamically balanced systems OR Colloidal Gel Barrier System:

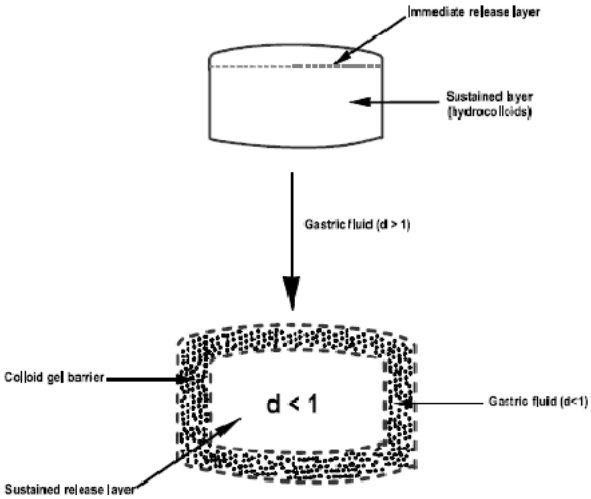

Figure 9: Hydrodynamically balanced or Colloidal Gel Barrier System [25].

Hydrodynamically Balanced Systems was first designated by Sheath and Tossounian. It contains drug with a gel forming hydrocolloid that helps the dosage form to float over the gastric content. This gel form that causes the dosage form to float over gastric content helps to prolong the FRT of dosage form thereby maximizing the amount of drug that reaches the site of absorption and dissolution of drug in the solution. A high level of cellulose type soluble hydrocolloid is used in this system. These materials are commonly used HPMC, HEC, HPC, Polysaccharides and matrix forming Polymer such as Polyacrylate and Polystyrene. The hydrocolloid in the system hydrates and forms a colloid-gel barrier around its surface on contact with gastric fluid. The polymer is mixed with drugs and usually administered in HB-capsule.

D.2.II.b. Microporous Compartment System:

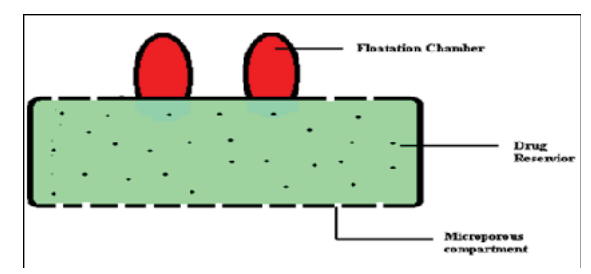

Figure 10: Microporous Compartment System [15].

In this system, a drug reservoir is encapsulated inside a microporous compartment that has pores along its top and bottom walls. Direct contact of gastric content with the undissolved drug is prevented by sealing the peripheral walls of the drug reservoir. In the stomach, the entrapped air in the floatation chamber causes the dosage form to float over the gastric content. The apertures allow the gastric content to enter the dosage form, dissolve the drug and carry the dissolved drug for continuous transport across the intestine for absorption.

D.2.II.c. AlginateBeads:

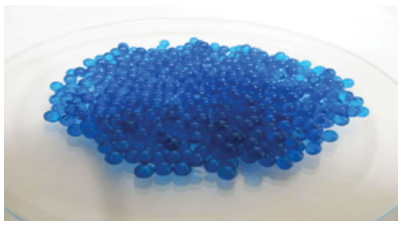

Figure 11: Alginate Beads.

Multi-unit floating dosage forms are prepared from freeze-dried calcium alginate. Spherical Alginate beads of approximately 2.5mm in diameter can be prepared by dropping sodium alginate solution in to aqueous solution of calcium chloride causing the precipitation of Calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen and freeze-dried at -40°C for 24 hours leading to the formation of a porous system, which can maintain a floating force for over 12hours. These floating beads gave a prolonged residence time of more than 5.5 hours.

D.2.II.d. Hollow Microspheres:

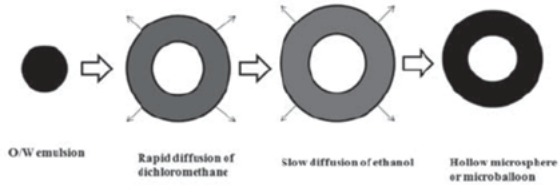

Figure 12: Hollow Microspheres or Microballoons [26].

A novel emulsion solvent diffusion method is used to prepare a hollow microsphere which is loaded with drug in the outer polymer shelf. The Drug solution in ethanol and an enteric acrylic polymer is poured in to an agitated solution polyvinyl alcohol that was thermally controlled at 40°C. The evaporation of dichloromethane generates gas phase which is dispersed in the polymer droplet and internal cavity forming a microsphere of the polymer with the drug. The micro balloon floated continuously for more than 12 hours over the surface of an acidic dissolution media containing surfactant. Microspheres can also be formed by solvent diffusion method. Commonly used polymers in these systems are polycarbonate, cellulose acetate, calciumalginate, Eudragit S, agar and low methoxylated pectin etc. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

Polymers Used [6,27,28]:

Polymers used in floating drug delivery system:

A. Natural polymers: e.g. xanthan gum, chitosan, guar gum

B. Synthetic polymers: e.g. eudragit, ethyl cellulose, hydroxy propyl methyl cellulose the motive of using polymers in floating system is to target a specific site in the gastrointestinal tract. Synthetic as well as natural polymers are used.

A. Natural Polymers:

They are hydrophilic in nature with high molecular weight. They are obtained from plants natural polymers are insoluble in organic solvents.

Advantages over synthetic polymers are:

1. Biodegradable
2. Eco-friendly
3. Available abundantly
4. Lower cost

Disadvantages:

1. Microbial contamination
2. 2.uncontrolled rate of hydration

1.Guar Gum:

Gaur gum is a galactomannan polysaccharide which occurs naturally in cold water guar gum swells leading to the formation of viscous colloidal dispersion or sols. This leads to increase in drug release time.

2. Xanthan gum:

Xanthan is a long chain polysaccharide with number of trisaccharide side chain. It is a high molecular weight extracellular polysaccharide produced by pure culture fermentation of carbohydrate. Tablets containing xanthan gum and citric acid have buoyancy for more than 24 hrs.

3. Gellan gum:

It is produced from Spingomonas elodea by fermentation.

Advantages of gellan gum: High gel strength and an outstanding flavoured release.

B. Synthetic Polymers:

Nowadays synthetic polymers are gaining more interest in pharma industry. They are used as binder, film coating agent. Synthetic polymers are either completely synthetic or semi synthetic

Disadvantages:

1. Adverse effect
2. Local allergic responses
3. Poor biocompatibility

1. Hydroxy Propyl Methyl Cellulose:

Properties: white to off white, odorless, water soluble polymers that bind, retain and then thickens to form films. It is semi synthetic in nature.

Uses:

1. HPMC is mainly used as a tablet binder and used as a matrix for use in extended release tablet formulations.
2. Hypromellose is used in emulsion as an emulsifier and also as a suspending agent.

2. **Eudragit**: Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios.

Applications:

1. Polymethacrylates (eudragit) are primarily used in oral capsule and tablet formulations as film-coating agents.

Evaluation Parameters [29-32]:

Drug-Excipient Interaction:

It is done by using FTIR and HPLC. Appearance of a new peak and/or disappearance of original drug or excipient peaks indicate the drug excipient interaction

Floating Lag time:

It is the time taken to emerge tablet onto the surface after it is kept in to the dissolution medium. It is measured in minutes or seconds.

Shape of tablets:

Compressed tablets designed for FDDS are examined under the magnifying lens for the determination of its shape consistency.

Tablet dimensions:

As per official compendia, the thickness and diameter of tablets in FDDS form are measured using a calibrated Vernier callipers same with that of conventional tablets.

Determination of hardness of the tablet:

Randomly twenty tablets in each batch of formulations should be used for the determination of hardness with the help of Monsanto type hardness tester.

Friability Test:

The friability of the tablets was determined using Roche Friabilator. It is expressed in percentage (%). Approximately (Wo) in grams of dedusted tablets were subjected to 100 free falls of 6 inches in a rotating drum & are then reweighed (W). The friability is given by:

$F = (1 - Wo/W) \times 100$

Determination of Weight Variation:

Twenty tablets selected at random are weighed accurately, and the average weight of the tablet is calculated. The deviation of individual weight from the average weight is calculated.

Determination of thickness of the tablet:

The individual crown to crown thickness of ten tablets is determined using slide callipers for each batch.

Determination of drug content in tablets:

Ten tablets from each batch are selected randomly and transferred to a 100ml volumetric flask filled up with 0.1(N) HCL. Stir and Keep it aside for 2h then take 1ml from the volumetric flask and transfer it to the test tube. Samples are then filtered, suitably diluted and analysed spectro photometrically at a suitable wavelength.

***In vitro* dissolution study:**

The test for in vitro drug release studies is usually carried out in simulated gastric (pH 1.2) and intestinal fluids maintained at 37±2°C. Dissolution tests are performed using the USP dissolution apparatus (USP II apparatus paddle) stirring at a speed of 50 or 100 rpm. The tablet was placed inside the dissolution vessel.5ml of sampleis withdrawn at time intervals of 1h,2h,3h,4h,5h,6h,8h,10h,and12h or any other time intervals as needed. The volume of dissolution fluid adjusted to 900ml by replacing fresh 5ml of dissolution medium after each sampling. The release studies were conducted with "n" tablets, and the mean values are plotted versus time. Each sample is analysed at maximum wavelength using UV visible spectrophotometer against a reagent blank and the corresponding concentration is determined from the respective calibration curve.

Buoyancy/Floating test:

The time between introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant are measured. The time taken for the dosage form to emerge on the surface of a medium called floating lag time (FLT) or buoyancy lag time (BLT) and total duration of time by which dosage form remain buoyant is called total floating time(TFT).

Swelling Study:

The swelling behaviour of a dosage form is measured by studying its weight gain or water uptake. The dimensional changes could be measured in terms of the increase in tablet diameter and/or thickness over time. Water uptake can be measured in terms of percent weight gain, as given by the equation.

$WU = (W_t - W_o) \times 100$

Where, WU= Water uptake, Wt.=Weight of dosage form at time t, Wo=Initial weight of dosage form

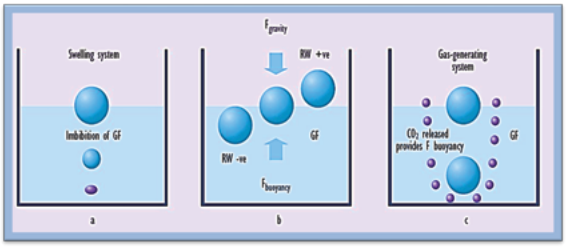

Figure 13: Different types of floating drug delivery systems. FDDS are also known as low density system. It has density less than the gastric content so the system remains in the stomach for a prolonged period of time without affecting the gastric contents.

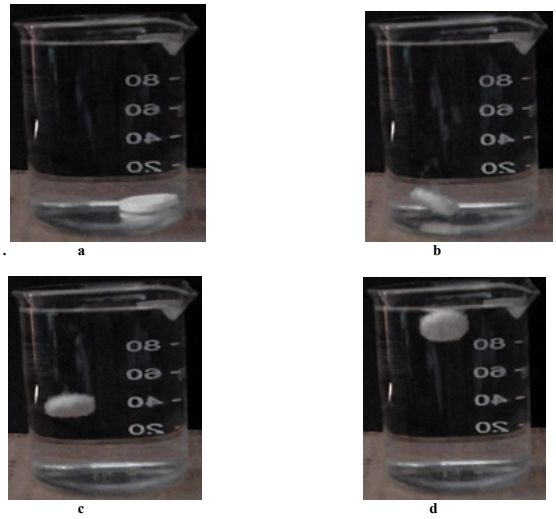

Figure 14: Floating and Buoyancy of the Batch.

Recent Advancements in GRDDS [9,33]:

Rajnikanth *et al.* designed a Floating In situ gelling system consisting of Clarithromycin (FIGC) utilizing Gellan as gelling polymer and Calcium carbonate as a floating agent for the therapy of gastric ulcers induced by Helicobacter pylori (H. pylori). FIGC was prepared by dissolving varied concentrations of Gellan in deionized water to which the drug Clarithromycin and sucralfate were added and dispersed well. The addition of sucralfate to the preparation greatly inhibited the degradation of clarithromycin at low pH. The novel FIGC showed a very significant anti H. pylori effect than that shown by only clarithromycin suspension. Sucralfate showed a very important role by clearing H pylori more effectively. In addition to this, the required amount of clarithromycin for eradication of H. pylori was also found to be less FIGC in than required for the corresponding clarithromycin suspension.It was determined that extended gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin led to complete clearance of H. pylori than the corresponding Clarithromycin suspension.

MARKET SURVEY:

Pharmacy Survey:

A survey was conducted at 5 different known locations in Mumbai (Vikroli), Navi Mumbai (Ghansoli, Nerul and Rabale), Raigad (New Panvel) regions of Maharashtra. The purpose of this survey was to get an idea of the quantity of GRDDS preparations available and sold in local markets. For the above mentioned purpose, 5 different pharmacy stores were visited at each mentioned locations and displayed them a list of GRDDS preparations. Information gathered is mentioned in tabular form as followed:

Sr. No.	Location	Store Name	Knowledge About	Preparations Available
1	Vikroli: (Mumbai region)	Prerna Medico	Conviron Cifran OD Liquid Gaviscon	Liquid Gaviscon
		Jyoti Medical Center	Liquid Gaviscon Cipro XR Cifran OD Oflin OD	Liquid Gaviscon Cifran OD
		Madhur Medical Center	Cifran OD Liquid Gaviscon Cipro XR	Liquid Gaviscon
		Pooja Medico	Liquid Gaviscon Cefaclor LP Cipro XR Cifran OD	Liquid Gaviscon Cifran OD
		Mahendra Medical	Liquid Gaviscon Cifran OD Tramadol LP Cefaclor LP	Liquid Gaviscon Cifran OD

2	Ghansoli: (Navi Mumbai region)	Royal Pharmacy	Liquid Gaviscon Prazopress XL Glumetza	Liquid Gaviscon Prazopress XL
		Himalaya Medical	Liquid Gaviscon Prazopress XL Glumetza Cifran OD	Liquid Gaviscon Prazopress XL
		Maharashtra Medical	Liquid Gaviscon Cifran OD Prazopress XL	Liquid Gaviscon
		Prasad Medical	Liquid Gaviscon Cifran OD Prazopress XL	Liquid Gaviscon
		Siddhivinayak	Prazopress XL Liquid Gaviscon Glumetza Cifran OD Cefaclor LP	Liquid Gaviscon Glumetza Cifran OD
3	Nerul: (Navi Mumbai region)	Rahul Medical and General Store	Liquid Gaviscon Prazopress XL Glumetza Cefaclor LP Cifran OD	Liquid Gaviscon Prazopress XL
		Metro Chemist	Liquid Gaviscon Prazopress XL Glumetza Cefaclor LP Cifran OD	Liquid Gaviscon Prazopress XL
		Dinesh Medical	Liquid Gaviscon Cifran OD Prazopress XL Tramadol LP Cefaclor LP Glumetza	Liquid Gaviscon Cifran OD Glumetza
		Ganesh Medical	Liquid Gaviscon Cifran OD Prazopress XL Tramadol LP Cefaclor LP Glumetza	Liquid Gaviscon Cifran OD Glumetza
		New Maruti Medico	Prazopress XL Liquid Gaviscon Glumetza Cifran OD Cefaclor LP	Prazopress XL Liquid Gaviscon Glumetza
4	Rabale: (Navi Mumbai region)	Darshan medical and general store	Liquid Gaviscon Cifran OD Glumetza tablet Prazopress XL	Liquid Gaviscon Cifran OD Glumetza tablet
		Shree medical store	Liquid Gaviscon Prazopress XL Glumetza tablet	Liquid Gaviscon
		Akshay medical and general store	Liquid Gaviscon Cifran OD Glumetza tablet Prazopress XL	Liquid Gaviscon Cifran OD Glumetza tablet Prazopress XL
		Kheteshwar medical and general store	Liquid Gaviscon Prazopress XL Glumetza tablet	Liquid Gaviscon Prazopress XL Glumetza tablet
		Dinesh medical and general store	Liquid Gaviscon Cifran OD Glumetza tablet	Liquid Gaviscon Cifran OD Glumetza
5	New Panvel: (Raigad region)	Shree Gajanan Medical Store	Gelusil Digene Gel Himcocid SF Esomate L Rabesec DSR Pantosec DSR	Gelusil Digene Gel Himcocid SF
		Metro Chemist	Liquid Gaviscon Pan MPS Prazopress XL Cyra-LS	Liquid Gaviscon Prazopress XL
		Health Care medical	Liquid Gaviscon Rabesac DSR Levosulpiride DSR	Liquid Gaviscon Rabesac DSR Levosulpiride DSR
		Utsav medical and general stores	Glumetza Cifran OD Cefaclor LP	Cifran OD
		Shree Ram chemist	Liquid Gaviscon Esomate L Prazopress XL Cifran OD Rabesec DSR	Liquid Gaviscon Esomate L Prazopress XL

Comments:

Of all the available GRDDS preparations, Liquid Gaviscon was sold at a much higher amount compared to others.

Reasons:

Liquid Gaviscon is used to treat severe acidity with longer lasting effect while others were used to treat CNS disorders, Diabetes, Cardiac Disorders, etc...Liquid Gaviscon was prescribed by regular physicians as well while others were prescribed by specialized doctors only. These preparations were not marketed properly by Medical Representatives (MRs) thus being unaware about such preparations.

2.2. Physician Survey:

To understand the reasons behind such low sales and use of GRDDS preparations in the local markets, Physicians native to those regions were asked about GRDDS. 2 physicians in each of the below mentioned location were reached out. Following is the data collected:

Sr. No.	Locations	Physicians Visited
1	Vikroli: (Mumbai region)	Dr. Amol A. Narkar (B.A.M.S)
		Dr. Narendra B Puri (M.B.B.S)
2	Ghansoli: (Navi Mumbai region)	Dr. Ishwar More
		Dr. Gopichand Patil
3	Nerul: (Navi Mumbai region)	Dr. Yashwant Khaire (MBBS)
		Dr. P.J. Bhanushali (B.H.M.S)
4	Rabale: (Navi Mumbai region)	Dr. Praveen Luthra (MBBS)
5	New Panvel: (Raigad region)	Dr. Khalid Deshmukh (MD)

Comments:

Of all the available GRDDS preparations, Liquid Gaviscon was sold at a much higher amount compared to others.

Reasons:

Liquid Gaviscon is used to treat severe acidity with longer lasting effect while others were used to treat CNS disorders, Diabetes, Cardiac Disorders, etc...Liquid Gaviscon was prescribed by regular physicians as well while others were prescribed by specialized doctors only. GRDDS being a NDDS, people are not much aware about their advantages over conventional preparations. These preparations were not marketed properly by Medical Representatives (MRs) thus being unaware about such preparations. People prefer Generic medications as they can be made available at any pharmacy store.

CONCLUSION:

Based on the above survey, it is clear that pharmacy stores are not much aware about the GRDDS preparations and that these preparations are sold in a limited amount as they are not prescribed by the physicians. Also patients prefer conventional generic preparations over them as they are cheaper in cost and can be made available

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from any pharmacy store. Amongst the preparations mentioned above, Liquid Gaviscon saw a greater sale compared to others. This medication is an effervescent liquid that helps in reduction of acidity, a common problem in every house hold (though it is prescribed in severe conditions due to its longer lasting effect). The detection of new diseases and the resistance shown towards the existing drugs felt the necessity for the introduction of new therapeutic molecules. In response to this, a vast range of chemical entities have been introduced. Development of sustained release formulations is beneficial for prolonging gastric retention time and increasing efficacy of the dosage forms. The floating behavior of the low-density drug delivery systems could successfully be combined with precise control of the drug release patterns in order to boast accurate bioavailability. Hence further research is needed in this regard.

FUTURE POTENTIALS [35-37]:

Gastro retentive floating drug delivery system has emerged as a very powerful method for enhancing the bioavailability and for achieving controlled drug delivery. FDDS approach may be used for various potential active agents having narrow absorption window, e.g., antiviral, antifungal and antibiotic agents like Sulphonamides, quinolones, Penicillins, Cephalosporins, Aminoglycosides and Tetracyclines which are absorbed from very specific regions of the GI tract and whose development has been ceased due to lack of convenient pharmaceutical technologies. Replacing parenteral administration of drugs with oral pharmacotherapy would dramatically improve treatment. This can be possible with FDDS. Buoyant delivery system is also considered as a useful strategy for the treatment of gastric and duodenal cancers. The floating concept can be utilized in the development of several anti-reflux formulations. The rising sophistication of delivery technology will assure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. It is little wonder therefore, that such systems are becoming very popular.

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