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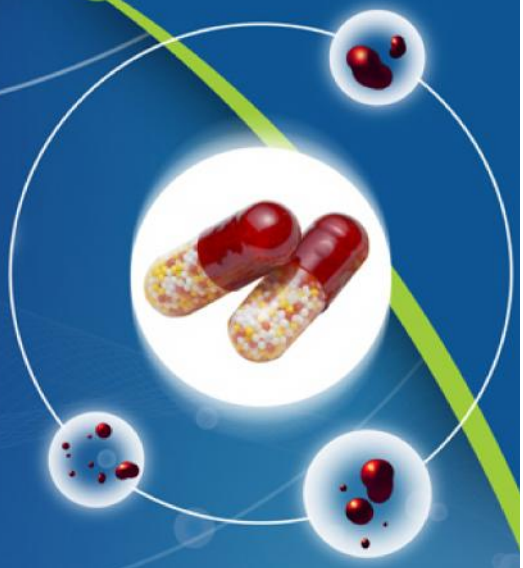

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Review Article

FLOATING DRUG DELIVERY SYSTEM: AN INNOVATIVE APPROACH

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ABSTRACT:
Floating drug delivery system has been evolved as a controlled drug delivery system. Several approaches are currently being used including floating drug delivery system (FDDS) which is also known as Hydrodynamically balanced system (HBS), swelling and expanding systems, high – density systems, bioadhesive systems, modified shape systems and other delayed gastric emptying devices. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. Floating dosage form can be prepared as tablets, capsules by adding suitable ingredients as well as by adding gas generating agent.

Key words: *Controlled release, Effervescent tablets, FDDS, peptic ulcer, ranitidine*

INTRODUCTION

The main aim 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. Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying.[1] Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate.

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Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period; enhancement of activity of duration for short half-life drugs; elimination of side effects; reducing frequency of dosing and wastage of drugs; optimized therapy and better patient compliances.[2, 3].

Floating drug Delivery System

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that have sufficient 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. While the system is floating on the gastric contents, 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 Gastric retention time 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 Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.[4]

Basic physiology of GIT:

Anatomically the stomach is divided into 3 regions: Fundus, Body, and Antrum (pylorus). The proximal part made of Fundus and body acts as a reservoir for undigested material, whereas the Antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. [5] The stomach is an expanded section of the digestive tube between the esophagus and small intestine. The wall of the stomach is structurally similar to the other parts of the digestive tube, with the exception that stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in the performance of complex grinding motions. In the empty state, the stomach is contracted and its mucosa and sub mucosa are thrown up into distinct folds called rugae. [6]

There are four major types of secretary epithelial cells that cover the surface of the stomach and extend down into gastric pits and glands: Mucous cells, Parietal cells, Chief cells, G cells The contraction of gastric smooth muscle serves two basic functions

- Ingested food is crushed, ground, mixed and liquefying to form Chyme.
- Chyme is forced through the pyloric canal into the small intestine, a process called gastric Emptying. [7]

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into 4 phases. [8,9]

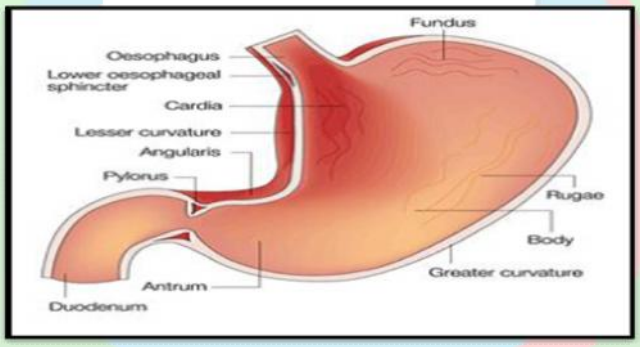

Figure 1: Physiology of GIT

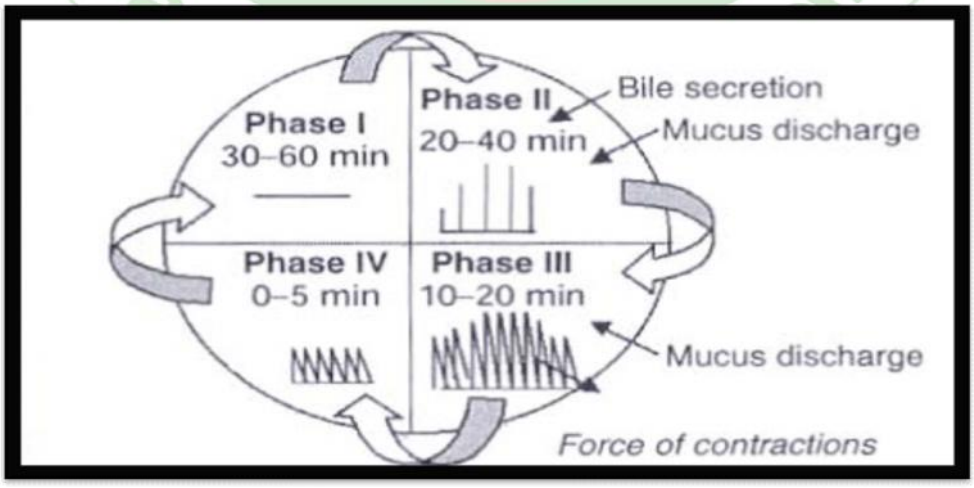

Figure 2: Motility pattern in GIT

Advantages of FDDS:

Floating dosage systems form important technological drug delivery systems with gastro retentive behavior and offer several advantages in drug delivery. These advantages include:

- Improved drug absorption, because of increased gastric residence time and more time spent by 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, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.
- Site-specific drug delivery [10]

Disadvantages of FDDS:

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first-pass metabolism, may not be suitable candidates for FDDS since the slow gastric emptying may lead to reduced systemic bioavailability. Also there are limitations to the applicability of FDDS for drugs that are irritant to gastric mucosa.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems. [11, 12, 13]

Suitable Drug Candidates for FDDS

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. In general, appropriate candidates for FDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT. [14-18]

- Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa
- Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine.
- Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate

Factors Affecting the Floating and Floating Time

- **Density: -** Floating is a function of dosage form buoyancy that is dependent on the density.
- **Shape of dosage form: -** Tetrahedron and ring shaped devices with flexural modules of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better floating, 90% to 100% Retention at 24 hours compared with other shapes. [19]

- **Concomitant drug administration: -** Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.

- **Fed or unfed state: -** Under fasting conditions, the GI motility is characterized by Periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. [20]

- **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.[21]

- **Caloric content and feeding frequency: -** Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are

given compared with a single meal due to the low frequency of MMC.

- **Age:** - Elderly people, especially those over 70, have a significantly longer; floating [22] Disease condition such as diabetes and crohn's disease etc also affect drug delivery.
- **Posture:** - Floating can vary between supine and upright ambulatory states of the patient.[23]

MECHANISM OF FLOATING SYSTEMS

There are various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts 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. 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. While the system is floating on the gastric contents, 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. 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 .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.[24]

$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gv$

Where, F= total vertical force Df = fluid density Ds = object density v = volume and g = acceleration due to gravity

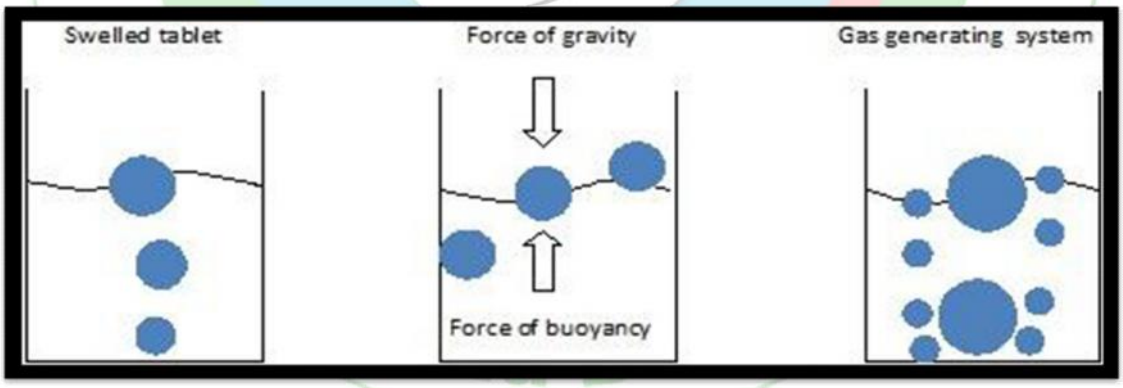

Figure 4: Mechanism of Floating System

CLASSIFICATION OF DRUG DELIVERY SYSTEM:

- Single Unit Floating Dosage Systems a) Effervescent Systems (Gas-generating Systems)
- Non-effervescent Systems
- Multiple Unit Floating Dosage Systems a) Non-effervescent Systems b) Effervescent Systems (Gas-generating Systems) c) Hollow Microspheres
- Raft Forming Systems

Single Unit Floating Dosage Systems

Effervescent Systems (Gas-generating Systems)

These buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharide-rides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.[25] Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates

Non-Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier. [26]

Multiple Unit Floating Systems:

In spite of extensive research and development in the area of HBS and other floating tablets these systems suffer from an important drawback of high variability gastrointestinal transit time.

Non effervescent systems

A little or no much report was found in the literature as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing Indomethacin, using chitosan as the polymeric excipient.

Effervescent system

Multiple unit system comprises of calcium alginate core and calcium alginate /PVA membrane both separated by an air compartment in presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment.

Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the esophagus.).

APPLICATIONS OF FDDS

FDDS offer various applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the GIT. It retains the dosage form at the site of absorption and thus enhances the bioavailability.

Sustained drug delivery:

HBS system remains in the stomach for a long time and hence can release the drug for a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome these systems. These systems have a bulk density <1 as a result of which they can float on the gastric contents.

E.g. Sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo the formulation compared with commercially available

MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration in the sustained release floating capsules as compared with conventional MICARD capsules. [27]

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 eg. Riboflavin and furosemide.
E.g. Furosemide is primarily absorbed from the stomach followed by the duodenum.it has been reported that a monolithic floating dosage form with the prolonged gastric residence time was developed and the bioavailability was increased AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets. [27]

Absorption enhancement:

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as FDDS thereby 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 products (29.5%).[28]

CONCLUSION

GRDFS comprised mainly of floating, bioadhesive, and swellable systems. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of the drug for a prolonged period, but also present the drug in an absorbable form at regions of optimal absorption. These systems achieve this by retaining the dosage form in the gastric region, from where the H2RAs and antibacterial like amoxicillin and others are presented at the absorption window. The currently available polymer-mediated noneffervescent 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 most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid.

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