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## **INFLUENCE OF DENSITY ON GASTRO-RETENTIVE DRUG DELIVERY SYSTEM**

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### **ABSTRACT**

In recent years, several advancement has been made in research and development of oral drug delivery system. The oral route achieved such popularity due to its ease of administration but has a drawback of non-site specificity. To overcome these limitations, gastric retentive drug delivery system is used. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention time. We have reviewed various gastro retentive approaches designed and developed until now i.e. floating drug dosage systems (FDDS), swelling or expanding systems, mucoadhesive systems, high density system, magnetic systems. Among these systems, FDDS and high density system have been most commonly used because these systems enhance gastric residence time (GRT) without affecting the intrinsic rate of emptying.

## INTRODUCTION

Several approaches have been proposed to retain the dosage forms in the stomach. These methods include bioadhesive system, swelling system and expanding system and floating system. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying. Unfortunately floating devices administered in a single unit form (Hydrodynamically balanced system) HBS are unreliable in prolonging the GRT owing to their 'all- or- nothing' emptying process and, thus they may causes high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract.

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached.

Although some important applications, including oral administration of peptide and protein drugs, can be used to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route. More often, drug absorption is unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the GI transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability<sup>5</sup>.

## PHYSIOLOGY OF THE STOMACH

The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the caecum, appendix, colon and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the oesophagus to the anus, with some local variations for each region. The stomach is an organ with a capacity for storage and mixing. 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 50ml

and contains a small amount of gastric fluid (pH 1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes, interdigestive 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.<sup>1,3</sup>

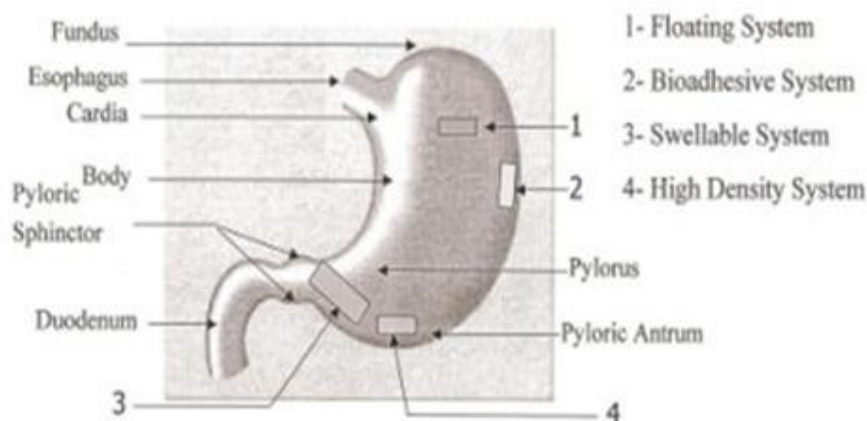


Figure-1: Anatomy and Physiology of Stomach

### **FLOATING (LOW DENSITY SYSTEM)<sup>7,8</sup>**

Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems have a bulk density lower than gastric fluids and thus 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 a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as ‘hydrodynamically balanced systems’ (‘HBS’) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many results have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved clinical situations. These results also demonstrate that the

presence of gastric content is needed to allow the proper achievement of the buoyancy retention principle. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxyl propyl methyl celluloses. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy.

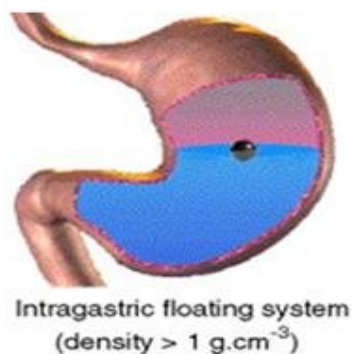


Figure-2: Intragastric Floating System

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realized either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract. When a floating capsule is administered to the subjects with a fat and protein meal, it can be observed that it remains buoyant at the surface of the gastric content in the upper part of the stomach and moves down progressively while the meal empties. The reported gastric retention times range from 4 to 10 hours. Pharmacokinetic and bioavailability evaluation studies confirm the favorable incidence of this prolonged gastric residence time<sup>1</sup>.

The Floating drug delivery system (FDDS) can be divided into

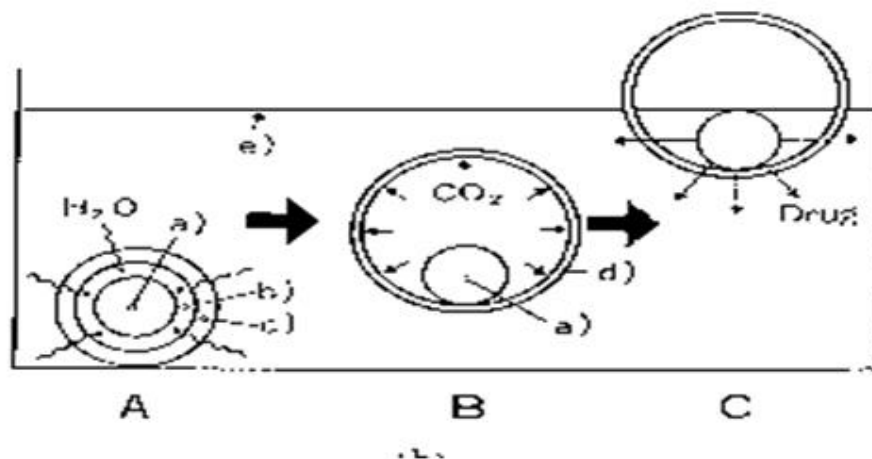
#### **A) Effervescent**

These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO<sub>2</sub> is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

#### **Stages of floating mechanism:**

When this system comes in contact with gastric content, CO<sub>2</sub> is liberated and gets entrapped in swollen hydrochloride.

- Penetration of water
- Generation of  $\text{CO}_2$
- Dissolution of drug



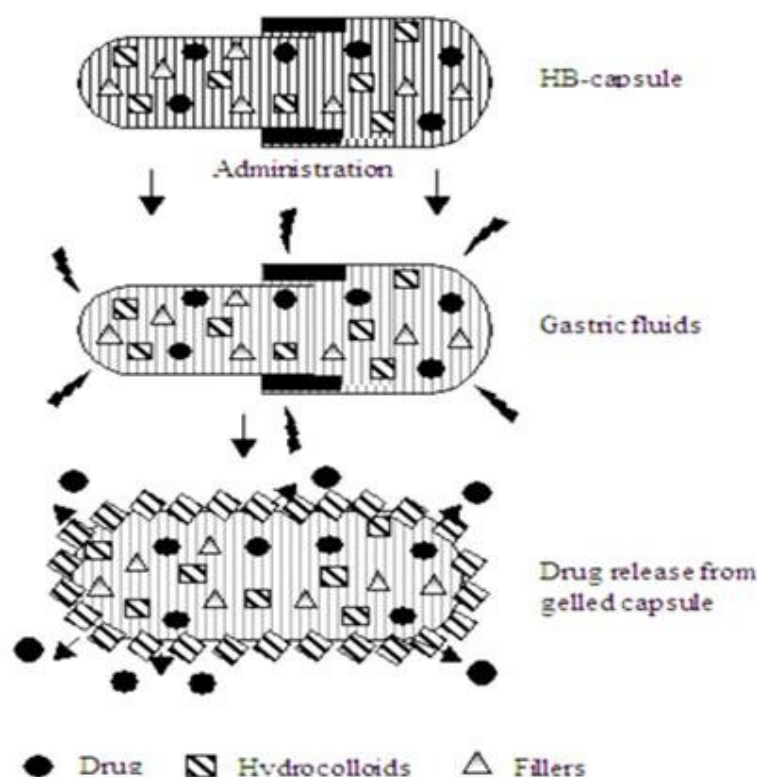
### B) Non effervescent system

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of  $< 1$ . The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

### Hydrodynamically balanced systems:

Sheth and Tossounian<sup>16</sup> first designated these 'hydrodynamically balanced systems'. These systems contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropylmethylcellulose (HPMC), hydroxyl ethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsules. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water

penetration to the inner layers maintaining surface hydration and buoyancy to dosage form 18. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LPR, based on the system was marketed during the 1980's 19. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems.



#### Alginate beads:

Talukdar and Fassihi 4 recently developed a multiple-unit floating system based on cross-linked beads. They were made by using  $\text{Ca}^{2+}$  and low methoxylated pectin (anionic polysaccharide) or  $\text{Ca}^{2+}$  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 drying, leading to the formulation of a porous system, which can maintain a floating force for over 2 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs.

#### Microporous compartment system:

This approach is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls 2. The peripheral walls of

the device were completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid<sup>3</sup>. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

### HIGH DENSITY SYSTEMS<sup>5,9</sup>

These systems with a density of about  $3 \text{ g/cm}^3$  are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug ( $>50\%$ ) and to achieve a density of about  $2.8 \text{ g/cm}^3$ . It is necessary to use diluents like barium sulfate, zinc oxide, titanium dioxide, iron powder etc. to manufacture such high density formulations. Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus 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 a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations.

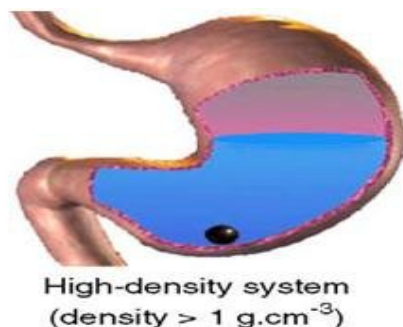


Figure-3: High-density System

### CONCLUSION

GRDDS comprising mainly of floating, bioadhesive & swellable system, and high density have emerged as efficient means of enhancing BA and controlled release delivery of drugs exhibiting absorption window. It ensures maximum absorption of the drug for the desired period. Designing of GRDDS requires a thorough understanding of properties of physiological events of GI tract, and formulation strategies. Growing understanding of impact of GI tract physiology on drug delivery and increasing sophistication of delivery technology will ensure development of increasing no. of GRDDS to optimize drug delivery of drugs exhibiting regional variability in intestinal absorption.



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