GASTRO-RETENTIVE DRUG DELIVERY SYSTEM FOR PROLONG DRUG RELEASE: A BLANKET REVIEW

Patil Nilesh S, Salunkhe Kishor S, Chavan Machindra J, Chintamani Ravindra B

Abstract— The purpose of this review article is to evaluate the fact that it's worth to research in the development and of the drugs that are being formulated to have greater gastro- retentive period in the stomach which enhances the therapeutic purpose of the drug for the proper site with desired concentration. This also indicates a reduced administering of the dosages. There have been quite a lot of techniques developed to achieve the prolonged gastric emptying from stomach to the small intestine. Presently, pharmacological experiments have been able to formulate drugs adapting specific methods for the targeted gastric retention time period. The techniques in use as per the demand are low density systems, high density systems, magnetic systems, muco- adhesive systems, super porous hydrogel systems (cited as per the recent available information). The detailed study on the prolonged residence time for the drug dosage forms focusses on the floating drug delivery systems (FDDS) as an efficient form. Floating systems are hydro- dynamically controlled systems that have low density and are buoyant enough to float over the contents of the stomach for a long time and without affecting the gastric emptying rate. The drug is released at a rate which is desired and customized. There had been much speculations about GRDDS in the past but now purposeful and extensive researchers offer sophisticated formulation of dosage forms that are customized for delayed gastro retention time.

Index Terms— Gastro Retentive Drug Delivery System, GRDDS, GIT, Gastric Emptying, Stomach Physiology, Gastric Motility, Gastric Residence time

1. INTRODUCTION

The drug intake and its retentive properties are an important area where much of research efforts are going into as this is where the efficiency of the drug is tested to reach and cure the target organ internally.

Traditionally drug administration followed the oral route and it was a widely practiced one. The reasons for this support the fact as to why the route is the preferred one,

a) comfortable to be administered and taken in
b) designing procedure is flexible enough
c) production is in a easy way
d) cost effective

Relating to the administering ease of dosages, **GRDDS** has been in research for some time now.

Our review article focusses that **Gastro Retentive Drug Delivery System (GRDDS)** is now a novel approach of drug delivery system (1) that has proven its efficiency to reach the targeted site and is now an area of even more development.

The drug delivery systems have always been under probe and meticulous research to attain even more accuracy. This is to develop the delivery systems and the release of the drug content over a prolonged period in a controlled way (2).

The retention in a novel way improves the bioavailability of drugs while drug bioavailability of oral doses depends on several factors.

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Bioavailability of a drug is essentially a vital phenomenon which refers to the extent and rate at which the active drug or metabolite enters the systemic circulation and reaching the site of action (3). Drugs administered through oral route have to pass along the wall of intestine then has to follow the portal circulation to the liver. They are the sites where metabolism occurs before the drug reaches systemic circulation.This signifies that many of the drugs might be metabolized before sufficient plasma concentrations are reached. Bioavailability of drugs is determined by the dosage form properties that depends on the design as well as the manufacture. Obviously, there is a demand of the formulation scientists in the pharmaceutical industry to process formulations for **GRDDS**. Quiet several marketed formulations are formulated for gastro retentive dosage forms (4).

There are several modes of gastric retention-

i) Sinking Systems or high density
ii) Floating Systems or low density
iii) Superfluous or hydrogel systems
iv) Expandable systems
v) Muco- adhesive systems
vi) Magnetic systems (5)

Oral route though has some difficulties as because the **GIT** or the Gastro Intestinal Tract functions are a bit different for various persons (6). For example, the emptying rate of the gastric matters into the intestine varies from individual to individual. Another challenge is, there is an absorption pocket in the upper intestinal (small) area for many drugs. It is necessary that drugs which are absorbed from the stomach should have to spend larger time in stomach to show local effect. Now, the conventional dosage forms find it hard to achieve because of gastric emptying that depends on volume and composition of the meal, pH of the stomach, body posture and more. To aim for a longer retention in stomach the dosage needs to be —

a) Dissolution and the absorption are stimulated by the food.
b) dissolving of the drug is slow

c) Disintegration and the dissolution of the drug is processed by the gastric fluid.
d) Also, that the drug shows local effects in that area.

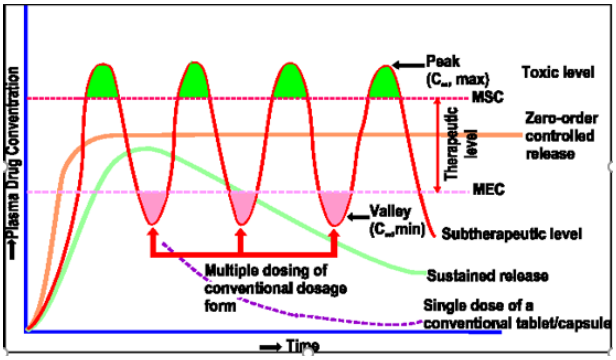

Figure 1: Plasma drug concentration versus time for conventional dosage forms

Thus, to fulfil all those criteria, the system that started developing is the **GRDDS**. Hence there has been a surge for pharmaceutical researches to develop drugs delivery systems that can stay in the region for a prolonged period which could be predictable. Several attempts are being processed to ensure therapeutic effect for a longer period which also ensures reduced dosage frequency. Herein, have been ushered a new technique of dosage that is multiple unit dosage forms. The uniform distribution of these multiple unit dosage forms along the **Gastro Intestinal Tract (GIT)** results in even more reproducible drug absorption which also reduces the risk of local hazards created (7). This striking feature gave rise to oral controlled drug delivery and led to development of **Gastro Retentive Floating Microspheres**. The advantage these floating dosages are that they are locally effective in the stomach, are absorbed only in the stomach or even in the upper part of the intestine, improves bioavailability.Continuous study and experiments are being devoted to formulating and manufacture site specific drug is gaining momentum to achieve results.

Stomach: A grinding site.

To have a look at the stomach and its connected parts where the physiology is at its highest need of research, it is required to know the proper external as well as internal structure of the stomach, intestines that is collectively called the **GIT** or **Gastro Intestinal Tract**.

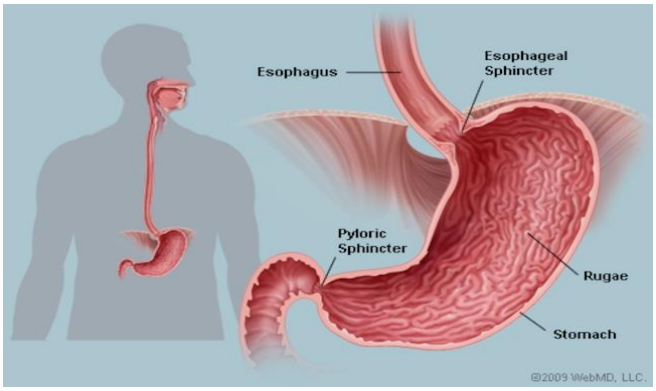

Figure 2: Gastro Intestinal Tract

Stomach occupies the upper left-hand part of the abdomen. The location is just below the diaphragm. Being positioned in a portion of epigastric region and the left hypochondriac region, stomach has the main function of storing the food then grind it and finally send it to the duodenum. Only a small part of the food is absorbed in the stomach due to its given small surface area. It also provides a barrier to the delivery of drugs through the small intestine.

Structure

Broadly the parts are:
a) Stomach,
b) Small Intestine- Duodenum, jejunum, ileum
c) Large Intestine.

GIT could be defined as a muscular tube that is continuous starting from the mouth and to about 9m till the anus.

Stomach is observed to have three anatomical regions: Fundus, Body, Pylorus or Antrum (8).

Body acts as a reservoir for undigested matters at the proximal part to the fundus. Antrum is the site for propelling action that acts for gastric emptying. The major site for mixing is the Antrum.

During eating the temporary increase in stomach is maintained by fundus by relaxation of its muscle fibres. The funds help the gastric contents to move towards the distal stomach by exerting pressure on them.

The Physiology within

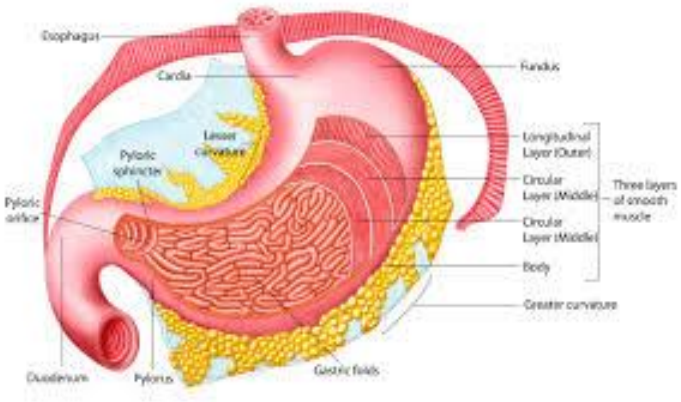

Figure 3: Stomach Physiology

Regulation of the gastric motility and functions

Gastro Intestinal Tract is on a constant state of motility. The movement criteria are of two types, one being the digestive and the other inter digestive mode. The secretion of gastric juice and the contraction of the smooth muscles of the stomach wall. Gastric secretions happen in an overlapping phase of three different sites (9). They are:
a) Cephalic phase
b) Gastric phase
c) Intestinal phase

Cephalic phase, as the name suggests is the role of brain on such secretions. The secretion is brought through nerve stimulation before the food enters the stomach and much before than the sight, taste or thought of food initiate this phase. So, acid and pepsin are present in the stomach before the food even enters the stomach.Next is the **Gastric Phase** when the secretion is stimulated by the for

that has entered the stomach. This is the period in which the swallowed food along with the partially digested proteins activate gastric activity and that amounts to about two-thirds of the gastric secretion in this phase. Ingested food raises the pH of its contents and stretches the stomach which triggered the activation of gastrin. Mucosa in the pyloric region of the stomach produces hormone gastrin controls the whole affair of gastric phase. In response to the stretching of antrum caused by the presence of the food and some substance in the food, Gastrin is released. The stimulants could be proteins, coffee or alcohol. Gastrin is carried away by blood to the stomach where in it stimulates the secretion of hydrochloric acid and the pepsinogen. Two reflexes are activated by the stretching activity. First is a short reflex which is mediated through the myenteric nerve plexus. The other is the long reflex that is brought about by the vagus nerve and brainstem. The response of small intestine to the stimuli of gastrin is the onset of **Intestinal phase**. This phase occurs in the duodenum in response to the chyme that arrives and that it moderates the gastric activity through hormones and nerve reflexes also. The semi digested fats and the acid in duodenum together trigger the entero- gastric reflex. The inhibitory signals are sent by the duodenum to the stomach through the route of enteric nervous system. (4,9).

The hormones secretin and cholecystokinin are secreted by duodenal entero- endocrine cells that are stimulated by the chyme. Primarily, these two hormones stimulate the gall bladder and pancreas and simultaneously suppress Gastric secretion along with the motility to limit more chyme to enter the duodenum.

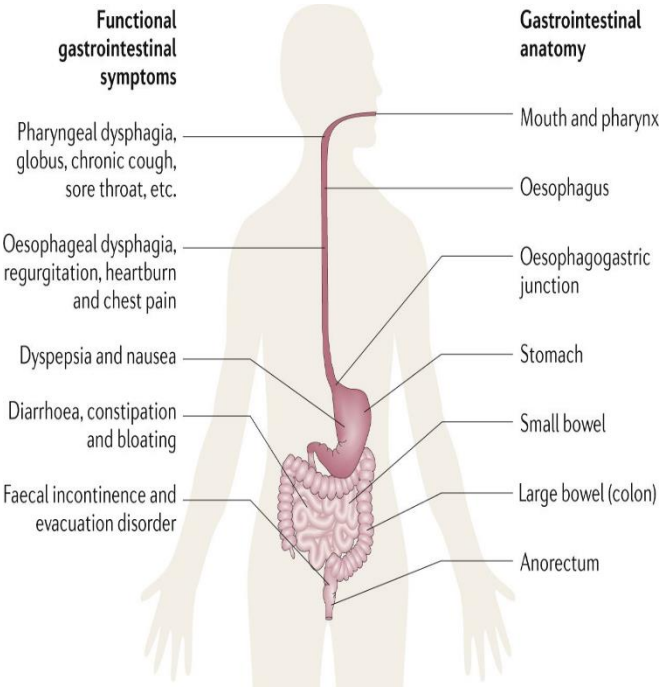

Figure 4: Gastric motility and functions

Gastric Emptying is in progress while in fed state and it does occur in fasting state as well. Even though in both the state emptying occurs but the motility is distinctively different in two of them. In the state of fast, an inter digestive series of electrical events occur through stomach and small intestine as well in every 2 to 3 hours. This is an activity known as inter digestive myoelectric cycle or **m**igrating **m**yoelectric **c**omplex (MMC) that has four phases. Again, after the mixed meal ingestion the contraction pattern changes from fasted to the fed state. This is also called digestive motility pattern. (10).

Table 1: Phases of digestive motility

PHASES	ACTIVITY	DURATION
Phase -I	Basal phase; Quiescent period with rare contractions.	30- 60 minutes.
Phase- II	Pre-burst phase; Intermittent contraction; as the phase develops the intensity and the frequency rises.	20- 40 minutes.
Phase- III	Burst stage; large regular contractions that takes away the undigested food material to the small intestine at the maximum frequency.	10- 20 minutes.
Phase- IV	Period of transition between consecutive phases III and phase I	5-10 minutes.

The influencing Factors for Gastric Residence Time

a) Meal Volume- Meal is bulkier then the gastric emptying time would be longer.
b) Contents of the meal- Fats in the meal trigger more bile secretion that has an inhibitory effect on the gastric emptying time.
c) Physical appearance of the meal and the dosage form- Viscous intensity of the retards the gastric emptying time. More viscous food material empties slower than less viscous material.
d) Physical work out or exercise prolongs the gastric emptying time.
e) The emotional state like stress and anxiety promotes gastric motility but depression retards motility of the old materials.
f) One of the important influencing factors is Circadian rhythms. The increased cardiac rhythms at day time and the decreased rhythms at night also influence the gastric retention period.
g) Density of the gastric fluid is as recorded is around 1.2 gm/cubic cm. Hence the dosage form should have less density than that to remain buoyant for a longer gastric retention time.
h) If the stomach is in upset state like in case of flatulence or the ulcer in the stomach too do affect the gastric retention in a great extent as the environment of the dosage form is a changed one.
i) While under therapeutic drugs, the gastric retention time is affected also. Drugs like the atropine retards the retention time while pro kinetic variety like the cisapride accelerates the gastric emptying.
j) Age is essentially an important factor where increase in age slows down gastric motility and thus have a longer gastro retentive time.
k) Gender too shows a bit of difference like in women, gastric emptying time is slower than that of the men.

l) Posture of the body might have little influence on (GRT). Lying on the supine position or the right-side inclined posture is favorable because of gravity. the stomach empties into the duodenum which is located the right side of the body. Lying on the left or in the supine position slows down the gastric emptying time.
m) There might be a connection between gastric emptying and hunger. The regulation of appetite involves a whole lot of central and peripheral mechanisms.

Since GRDDS is a novel approach for the estimated prolonged gastric retention so there are several technical approaches to develop at the dosage form that would work in a near perfect manner to achieve the goal. Hence there are a few gastro retentive forms those which have been in trial to increase the gastro retention period of the oral dosage forms. The types of the Gastro Retentive Dosage Form Systems are:

i) High Density Systems
ii) Low Density or Floating System
iii) Expandable System
iv) Superfluous Hydrogels
v) Magnetic System
vi) Mucoadhesive Bio adhesive System

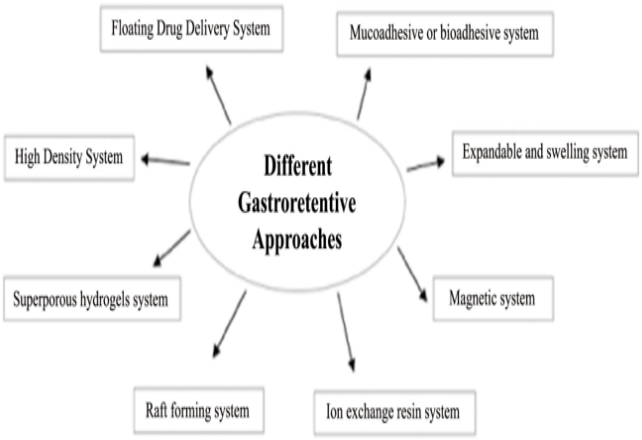

Figure 5: Different Gastroretentive approaches

Among all the systems in case of the **FDDS** or the **Floating Drug Delivery System** or the low-density system, the dosage form stays afloat above the gastric contents for a longer period. This is a preferable system of all as it does not affect the motility Gastro Intestinal Tract adversely so predictably there has been fair amount of research to make dosages based on this type. Hence based on this system of GRDDS a great amount of floating dosage forms is being developed, patented and marketed globally.

The Advantages of the GRDDS focusses as:

1. The frequency of dosage could be reduced considerably.
2. Finely improved bio- availability.
3. Patients comply readily.
4. There is the targeted therapy for localized ailments in the upper gastro intestinal tract.
5. The therapeutic attempt is according to the intended measures.

2. CONCLUSION

In the present scenario of pharmaceutical industry, the GRDDS have emerged as the newest technique that offers with an opted solution which attaches less hazards within the GIT. This has been effective with enhanced bioavailability and controlled delivery of drugs. All the systems of GRDDS provide with controlled release of the dosage form that is in absorbable form. There are always merits and demerits as well to any system. It is but implied that there are great endeavors being poured to achieve even more success to design efficient dosage.

3. REFERENCES

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