

Gastro-Retentive Drug Delivery System for Advanced Delivery System: Overview

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Abstract: *The main goal of an oral controlled drug delivery system is to maximise bioavailability, which should be predictable and repeatable, by administering medications over extended periods of time. Patients choose this approach for a number of reasons, including as affordability, ease of transportation, efficacy, perceived safety, and patient acceptability. The gastrointestinal system's variety results in several physiological limitations for oral delivery. Additionally, a number of variables alter along the gastrointestinal system, all of which affect how well drugs are absorbed. The most crucial factors are surface area, pH, commensal bacteria, gastrointestinal transit time, and enzyme activity. An ideal medication delivery system should have two basic characteristics: one, it should be a single dose for the duration of the therapy, and two, the active medicine should be delivered directly to the site of action. To provide drug delivery systems that, by releasing the medicine in a regulated and predictable way, may reduce side effects, dosage frequency, and changes in plasma drug concentration while remaining in the stomach for an extended amount of time and maintaining active plasma drug concentration. One of the special characteristics of the system is the gastroretentive drug delivery mechanism (GRDDS). New medication delivery techniques continue to spark interest even though oral controlled release dose forms are the most often manufactured. Drugs are rapidly removed from the systemic circulation due to their short half-life and ease of absorption from the GI tract. For these medications to have sufficient therapeutic effectiveness, frequent dosing is required.*

Keywords: gastroretentive drug delivery mechanism

I. INTRODUCTION

Oral drug delivery has long been the most common method of drug delivery. Several oral delivery methods have been developed during the last 20 years that operate as active ingredient reservoirs, allowing the active ingredient to be delivered at a specified controlled rate over a certain period. This technique, however, has certain physiological drawbacks[1].

Includes unpredictably variable gastric emptying rates, a short gastrointestinal transit time(8-12 hours), and the occurrence of several drug absorption windows in the upper small intestine[2].

Drug Delivery System that Floats (FDDS) It's a stomach drug that's hard to dissolve in intestinal juice or is unstable. The concept is straightforward. To put it another way, lower the dosage form. You can swim over it because it's thicker than stomach juice. A floating system, also known as a hydrodynamically controlled system, is a low-density device with enough buoyancy to float on the contents of the stomach and move the Stomach without altering the rate at which the stomach empties [3].

In some cases, it is advantageous to prolong the gastric retention of the delivery system in order to maximize the therapeutic value of the drug. Prolonged gastric retention can help drugs that are absorbed in the proximal part of the gastrointestinal system and that are less soluble or destroyed by alkaline pH. [3]

In addition, for local and sustained drug delivery to the stomach and proximal small intestine for the treatment of certain conditions, long-term gastric retention of the treated portion has improved bioavailability and therapeutic effect, It can also provide many benefits, including possible dose reductions [4].

II. FEATURES OF FLOATING DRUG DELIVERY SYSTEM

The longer the dose form remains at the absorption point and the higher the GRT, the better the drug absorption. controlled medication delivery. delivery of medications to the stomach for local effect. Reduce the amount of mucosal irritation the medication causes by releasing it gradually and at a regulated pace. Aspirin and other acidic compounds irritate the stomach wall when they come into touch with it. As a result, the HBS formulation could be helpful for administering aspirin and other medications that are comparable. When pills, capsules, or sustained-release suspension forms are administered, the medication dissolves in the stomach juice. Following the emptying of the stomach, they may be absorbed in the small intestine after dissolving in gastric fluid. Therefore, it is anticipated that the medication will be fully absorbed from the suspension form if the intestinal pH is alkaline but the drug is still in solution form. When pills, capsules, or sustained-release suspension forms are administered, the medication dissolves in the stomach juice. Following the emptying of the stomach, they may be absorbed in the small intestine after dissolving in gastric fluid. Therefore, it is anticipated that the medication will be fully absorbed from the suspension form if the intestinal pH is alkaline but the drug is still in solution form. treatment for gastrointestinal conditions including reflux disease. basic and traditional manufacturing equipment. improved patient compliance and ease of administration. medication delivery tailored to a particular site.

III. LIMITATION OF FLOATING DRUG DELIVERY SYSTEM

1. The main drawback of the floating system is that the drug delivery requires a sufficiently high level of liquid in the stomach for it to float. However, this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the inner wall of the stomach [7].

IV. PHYSIOLOGY OF STOMACH

The stomach is separated into three parts anatomically: fundus, body, and pylorus. The proximal section has been completed. GRDDS is a novel method in this area (Stomach Retention Drug Delivery System). The GRDD dose form can be kept in the stomach. By constantly releasing the medication over a long period before it reaches the absorption site, GRDDS can improve the controlled administration of medicine with an absorption window [9].

Gastric retention may necessitate medication extension. Get the therapeutic impact of the drug absorbed from the proximal section of the GIT (gastrointestinal tract) or suffer from poor solubility, degradation at alkaline pH levels, and a meeting at the bottom of the GIT. GRDDS is advantageous for such medications because it improves them [10]

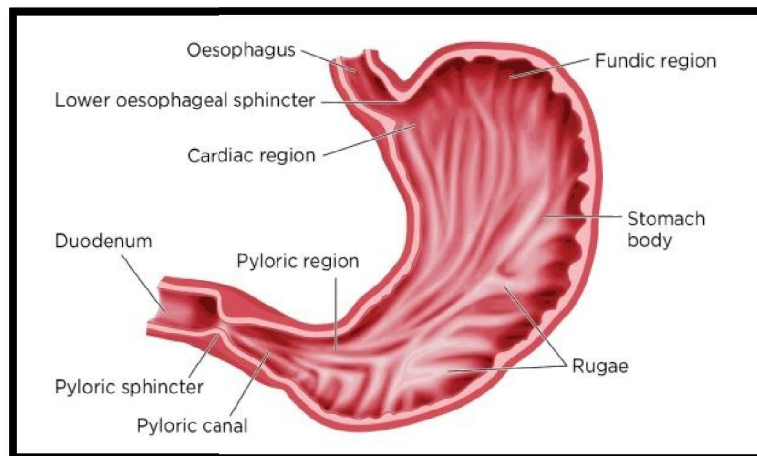


Fig. 1 Structure of stomach

V. FACTORS AFFECTING GASTRO-RETENTIVE

Drug delivery system: The following are factors that affect the stability and performance of GRDDS:

Dosage form related factors:

- a) Dosage forms with a less density than the gastric contents (~1.004g/ml) can float to the surface, while high-density systems sink to the bottom of the stomach (2.7g/ml).
- b) Dosage form with a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.
- c) Ring-shaped and tetrahedron-shaped devices have the better gastric residence time as compared with other shapes [11-12].

Food intake and its nature:

- a) Fed or unfed state: Under fasting conditions, strong waves migrating myoelectric cycle (MMC) often swept away undigested material from the stomach, there will be reduced gastro retention if the timing of the dose coincides with that of the myoelectric cycle [13].
- b) Nature of the meal: Feeding of indigestible polymers or fatty acid salts like cellulose, starch can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release [14]
- c) Caloric Content: GRT can be increased by 4- 10 hours with a meal that is high in proteins and fats.
- d) Frequency of feed: GRT can be improved over 6-7 hours with continuous meals as compared to a single meal because of the low frequency of the myoelectric cycle [15].

Patient-related factor:

- a) Age: In the case of elderly persons, gastric emptying is slowed down, especially those over 70 years have significantly longer gastric retention time.
- b) Gender: Generally females showed comparatively shorter mean ambulatory gastric retention time than males and gastric emptying in women was slower than men.
- c) Concomitant drug administration: Anticholinergics like atropine and propantheline, opiates like codeine, and prokinetic agents like metoclopramide and cisapride can prolong gastric retention time [16].

Disease states:

Gastric ulcers, Diabetes, Hypothyroidism increase gastric retention time, Hyperthyroidism, and Duodenal ulcers decrease gastric retention time [17].

Effect of buoyancy:

On comparison of floating and non-floating units, floating units remained buoyant on the gastric contents throughout their residence in the GIT, while the non-floating units sank and remained in the lower part of the stomach [16-17].

Table 1. The following table compares the conventional drug delivery system with the gastric retention type drug delivery system.

Specification	Conventional Dosage Form	Gastro-Retentive Dosage Form
Chances of adverse effects	High risk	Low risk
Patient compliance	Less	Improved
Colon degrading drugs	Not beneficial	Beneficial
Locally acting drugs in the stomach	Not beneficial	Beneficial
Poorly soluble drugs in alkaline pH	Not beneficial	Beneficial

VI. BASIC GASTROINTESTINAL TRACT PHYSIOLOGY

The stomach is separated into three sections anatomically: fundus, body, and pylorus. The sinus is the principal place for mixed motions, serving as a pump for stomach emptying by driving movements, while the fundus and proximal region of the body serve as a reservoir of undigested material. 13 Fasting and other factors cause gastric emptying. The act of eating. The exercise routine, however, differs across the two states. According to Wilson and Washington, a

sequence of electrical events between the digestive tract occur every 2-3 hours during a fast, both through the stomach and intestines [18].

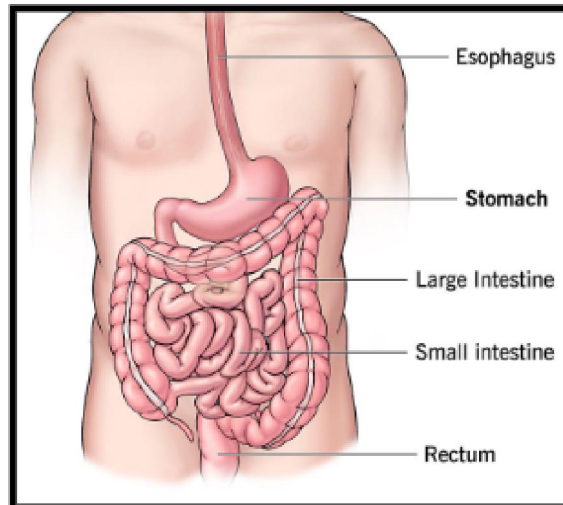


Fig 2- Anatomy of the gastrointestinal tract

Phase I (basal phase) -It lasts between 40 and 60 minutes, with only a few contractions.

Phase II (preburst phase) -With intermittent action potential and contractions, it lasts 40 to 60 minutes. The strength and frequency of the attacks gradually increase as the phase advances.

Phase III (burst phase)- lasts between 4 and 6 minutes It consists of brief, strong, and regular contractions. All undigested material is swept out of the stomach and into the small intestine as a result of this wave. The housekeeping wave is another name for it.

Phase IV- It occurs between phases III and I of two consecutive cycles and lasts 0 to 5 minutes [19].

VII. POLYMERS USED IN GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Alginates:

Alginate is a biocompatible, biodegradable linear polysaccharide derived from brown seaweed that is frequently utilized for its mucoadhesive properties. It's a derived polysaccharide block made up of M-blocks (sequential -D mannuronic acid monomers), G-blocks (sequential -L guluronic acid monomers), and M and G units interleaved. The majority of alginates are commercially available in the form of a salt, sodium alginate, which has the remarkable feature of transforming from a sol to a hydrogel while retaining more than 95% of the water molecules. [25,26].

Xanthan Gum:

It's a natural, biosynthetic, edible gum made up of glucose, mannose, and glucuronic acid, with extracellular polysaccharides. Xanthan is a polysaccharide having a β -(1, 4)-D-glucose backbone and a significant number of trisaccharide side chains. Because of the polyelectrolyte nature of the xanthan molecule, it creates a weak structure in water, resulting in high viscosity at low concentrations. It is also very soluble in cold and hot water. Non-gelling xanthan gum is primarily used for viscosity control. [27]

Carbopol:

Carbopol is a type of acrylic acid polymer with a relatively high molecular weight that is commonly utilized for its mucoadhesive qualities. Among the carbopol-containing formulations, one created by Nur and Zhang contains floating captopril tablets made with HPMC (4000 and 15,000 cps) and carbopol 934P. The buoyancy of the tablet was regulated by swelling of the hydrocolloid particles on the tablet surface when it came into contact with the gastric fluids and the existence of internal voids in the middle of the tablet, according to the results of the buoyancy studies. A floating system with a long release time was developed [28].

Chitosan:

Chitosan is a linear polysaccharide that contains various proportions of -(14)-linked 2-amino-2 deoxy-D-glucopyranose (GlcN) and 2-acetamido-2 deoxy-D-glucopyranose (GlcNAc) residues. [29] It is normally insoluble in aqueous solutions above pH 7, however, the protonated free amino group promotes aqueous solubility in dilute acids. Ishak RA and colleagues employed a factorially designed ionotropic gelation process to formulate GRDDS of metronidazole in chitosan-treated alginate beads for the treatment of H. pylori infection. Three viscosity-inducing polymers, methylcellulose, carbopol 934P, and carrageenan, were used[29].

Polyvinyl alcohol (PVA):

It is a solubilized crystalline structured polymer in water that is made from polyvinyl acetate and is easily degradable by biological organisms. [46] It's employed with other natural polymers because of its ability to produce films. Iannuccelli and colleagues created a multiunit system consisting of a calcium alginate core and a calcium alginate/PVA membrane separated by an air compartment. When exposed to water, the PVA leaches out and increases membrane permeability, maintaining the air compartment's integrity [30].

VIII. METHODS OF DEVELOPING FLOATING DRUG DELIVERY SYSTEM

Direct compression technique:

It entails compressing tablets directly from powder without changing the physical structure of the material. The most common carriers are dicalcium trihydrate phosphate, tricalcium phosphate, and others [33]

Effervescent Technique:

The floating chamber of the medication delivery system will be filled with inert gas as a result of an effervescent reaction between organic acid (citric acid) and bicarbonate salts (CO₂) [34].

Wet granulation technique:

Wet powder massaging, grinding, or drying are all involved. Instead of compacting the powders, wet granulation forms them by binding them together with an adhesive.

Ionotropic Gelation Technique:

The basic polymer of natural origin, anionic polysaccharide sodium alginate, was gelled with oppositely charged calcium ions (counter-ions) to create immediate microparticles [35]

Solvent evaporation technique:

The capacity to remove the complete amount of liquid dispersal solvent using a continuous phase is insufficient. The solvent evaporates from the dispersal surface, allowing hardened microspheres to be received.

Spray Drying Technique:

Dispersing the core layer into the liquid coating content and spraying the core coating mixture into the environment to solidify the coating by rapidly evaporating the coating material.

Melt Solidification Technique:

This procedure entails emulsifying the molten mass in an aqueous phase before cooling it and solidifying it. The carriers for this approach include lipids, waxes, polyethylene glycol, and others.

Melt Granulation Technique:

This is a granulation method that uses a meltable binder to agglomerate pharmaceutical powders without the need for water or organic solvents [36].

IX. EXCIPIENTS INCORPORATED IN DIFFERENT FLOATING DOSAGE FORMS [37,38]

Effervescent Agents:

E.g., citric acid, tartaric acid, sodium bicarbonate, Di-SGC (Disodium glycine carbonate), CG (Citroglycine).

Release rate Retardants:

Some substances such as Talc, Dicalcium phosphate, Magnesium stearate are used for retarding the release rate.

Inert Fatty Materials:

E.g., Long-chain fatty alcohols, Beeswax, Fatty acids, Gelucires 39/01 and 43/01.

Release rate Accelerants:

E.g., Mannitol, lactose, etc.

Hydrocolloids:

E.g., Acacia, β -cyclodextrin, Gelatin, Alginates, Pectin, HPMC, Carbopol, etc.

Buoyancy increasing Agents:

E.g., Ethyl Cellulose and Polypropylene Foam Powder (Accurel MP 1000)

X. CHARACTERIZATION OF FLOATING TABLET

Weight variation and hardness-

Weight variation test was done according to USP and hardness was measured with Monsanto hardness tester [39].

Buoyancy / Floating test-

The time between the introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The time is taken for the dosage form to emerge on the surface of a medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and the total duration of floatation i.e., as long the dosage form remains buoyant is called Total Floating Time (TFT).

Tablet density-

Tablet density is an important parameter for floating tablets. The tablet will float only if its density is less than that of gastric fluid (1.004). Density (d) was determined using the relationship $d = m/v$ where $v = \pi r^2 h$ [40].

In vitro release study

The in vitro release study for all the formulations was carried out by USP Dissolution Test Apparatus Type-II. The temperature of the dissolution medium (0.1 M HCl, 900 mL) was maintained at $37^\circ\text{C} \pm 1^\circ\text{C}$ with a stirring rate of 50 rpm. This study was done for 8 h. The tablet was placed inside the dissolution vessel. At the time of 15, 30, 60, 120, and 180 min 6 mL of samples were withdrawn, at time of 240, 300, and 360 min 3.5 mL whereas after 420 and 480 min 2.5 ml of samples were withdrawn, respectively. The volume of the dissolution fluid was adjusted every time to 900 mL. Samples were suitably diluted with 2 mL Folin-Ciocalteu's phenol reagent (diluted to 1:2 with distilled water) and 2 mL of 20% sodium carbonate solution and 0.1 M HCl up to 10 mL and assayed spectrophotometrically at $\lambda = 760$ nm in a double beam UV and visible spectrophotometer (Shimadzu UV 1700) against reagent blank. The drug concentration was calculated using the standard calibration curve.

Mechanism of release-

The mechanism of release was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas and finding the R^2 values of the release profile corresponding to each model.

XI. CONCLUSION

To provide drug delivery systems that can stay in the stomach for a long time and give active plasma drug concentration for a long time by releasing the medication in a controlled and repeatable manner, lowering side effects, dose frequency, and plasma drug concentration fluctuations. The gastroprotective medicine delivery method is one of the

system's unique features (GRDDS). New medication delivery systems continue to pique curiosity, even though oral controlled release dosage forms are the most popular. Drugs that are rapidly eliminated from the systemic circulation are easily absorbed and have a shorter half-life in the GI tract. These drugs must be dosed often to achieve maximal therapeutic efficacy.

CONFLICTS OF INTEREST

There are no conflicts of interest and disclosures regarding the manuscript.

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