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# INVESTIGATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM

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## ABSTRACT

Gastroretentive Drug Delivery System, comprising mainly of floating, bioadhesive and swellable systems have emerged as an efficient means of enhancing the bioavailability and controlled release delivery of drugs exhibiting absorption window. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. . This ensures maximum absorption of the drug for the desired period. Designing of a Gastroretentive Drug Delivery System, requires a thorough understanding of physicochemical properties of drug, physiological events in GI tract and formulation strategies. A careful consideration of interplay of these parameters can help in designing Gastroretentive Drug Delivery System, which meet their objectives successfully. Growing understanding of impact of GI tract physiology on drug delivery and increasing sophistication of delivery technology will ensure development of an increasing number of Gastroretentive Drug Delivery System to optimize drug delivery of molecules exhibiting regional variability in intestinal absorption.

**KEYWORDS:** Gastroretentive, Oral controlled release, Floating dosage form, Drug delivery system.

## INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).[1]

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.

Oral ingestion is the most convenient and commonly used method of drug delivery. These systems have the obvious advantages of ease of administration and patient acceptance. One would always like to have an ideal drug delivery system which possesses two main properties:

A. It should be a single dose for the whole duration of treatment.
B. It should deliver the active drug directly at the site of action.

Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible.

### Classification of oral controlled drug delivery systems

Oral controlled drug delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

1. Dissolution-controlled release
   a) Encapsulation dissolution control
   b) Matrix dissolution control

2. Diffusion-controlled release
   a) Reservoir devices
   b) Matrix devices
3. Ion exchange resins
4. Osmotic controlled release
5. Gastro retentive systems

**Dissolution-controlled release**

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thicknesses. The rate-limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by following Equation 1

$$\frac{dm}{dt} = \frac{ADS}{h} \quad (1)$$

**Diffusion-controlled release**

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of reservoir type diffusion-controlled device, the rate of drug released can be calculated using Equation 2;

$$\frac{dm}{dt} = ADK\frac{\Delta C}{\ell} \quad (2)$$

**Osmotically controlled Release**

In the early 1970s, Theeuwes et al. developed an elementary osmotic pump (EOP) to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semi-permeable membrane, which in turn carries the drug outside through a laser-drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semi-permeable membrane govern fluid transport into the system. Therefore, the rate of drug delivered from the system is dependent on the osmotic pressure of the formulation ($\pi s$) as shown in Equation 3;

$$\frac{dm}{dt} = \frac{A}{h} k \pi_s S \quad (3)$$

Where A is the membrane area, k is the membrane permeability, and h is the membrane thickness.

**Ion Exchange resins**

The idea of using ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry. Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug-resin complex is formed by prolonged exposure of drug to the resin.

Theoretically, this controlled delivery approach is relatively immune to the conditions of the GI tract because an ionic environment is required to displace the drug from the resin. Biphetamine®, capsule containing equal quantities of amphetamine and dextroamphetamine complexed to a sulfonic acid cation exchange resin, has been used as an antiobesity drug and for behaviour control in children. Nicorette® is a widely used product based on ion exchange technology as an adjunct to smoking cessation programs. It contains nicotine absorbed to a carboxylic acid ion exchange resin (nicotine polacrilex®) in a flavored chewing gum. Delsym® (dextromethorphan), a 12-hr cough medication taken as a liquid suspension, is another example of this type of dosage form. Further improvement of the ion exchange type of delivery system is illustrated by the development of the Pennkinetic® system. In this system, drug containing resin granules are first treated with a polymer such as polyethylene glycol 4000 to retard the rate of swelling in water, and then further coated with a water-permeable polymer such as ethylcellulose to act as rate-limiting barrier to control drug release.

**Gastroretentive Systems**

The controlled drug delivery system (CRDDS) possesing ability of being retained in the stomach is called gastroretentive system. They remain in gastric region for several hours and prolong gastric residence time of drugs They help in optimising oral controlled delivery of drugs having absorption window. Variability in GI transit time is a concern for oral controlled drug delivery systems. Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. If successful, gastroretentive controlled release formulation could offer a potential solution to the problem by offering a prolonged gastric residence time. A drug that is released from the dosage form in a controlled manner in the stomach will exit the stomach together with gastric fluids and have the whole surface area of the small intestine available for absorption. This type of drug delivery also offers a potential for enhanced drug therapy for local conditions affecting the stomach, eg., antibiotic administration for Haemophilus pylori eradication in the treatment of peptic ulcer.

**Major types of gastroretentive dosage forms**

**Floating Drug Delivery Systems**

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 released slowly at the desired rate from the system.

**Bioadhesive Systems**
Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan, CMC and gliadin, etc.

**High-density Systems**
Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture.

Dense pellets (approximately $3g/cm^3$) trapped in rugae also tend to withstand the peristaltic movements of stomach wall. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5–$2.4g/cm^{-3}$. However, no successful high-density

**Hydrogels and Super porous Hydrogels**
Hydrogels offer a promising approach to gastric retention. These materials have a swelling ratio of over 1000. They can be made by crosslinking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. Super porous hydrogels have unique supers welling properties combined with pore sizes in the range of few hundred micrometers to a millimeter. These materials can swell to the equilibrium size in less than 1 min, which is an important requirement for gastric retention devices based on size.

**Expansive Gastroretentive Dosage forms**
This is a class of gastroretentive systems capable of expanding in stomach. The expanded structure is trapped in stomach for prolonged period leading to sustained drug release and subsequent controlled absorption in stomach and intestine.

**Floating Drug Delivery System**
**Approaches to Design Floating Dosage Forms:**
The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

**Single-Unit Dosage Forms**
In low-density approach the globular shells apparently having lower density than that of gastric fluid can be used as a carrier for drug for its controlled release. A buoyant dosage form can also be obtained by using a fluid-filled system that floats in the stomach. Sugars, polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture.

**Multiple-Unit Dosage Forms**
The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamide, and polyalkylcyanoacrylate. Spherical polymeric microsponges also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability. In Carbon dioxide generating multiple-unit oral formulations several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

**Hydrogels and Super Porous Hydrogels**
Superporous hydrogels contain densely concentrated small pores that produce capillary channels that absorb water quickly. This rapid absorption results in dramatic swelling that is much faster than a conventional hydrogel Figure 1. Figure 2 illustrates the expected transit of the nonswollen/ fully swollen superporous hydrogel as it is initially retained for the desired period of time and then passes into the intestine. In addition to large dimensions, swollen superporous hydrogels canfloat on gastric fluid. Figure 3 shows a modified superporous hydrogel in both a dry and swollen state.

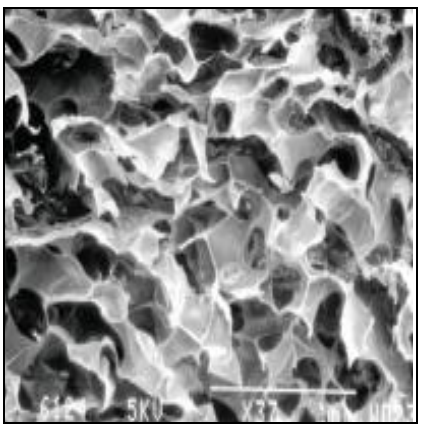

**Figure 1: Scanning Electron Microscopy Image Showing the Porous Structure of the Superporous Hydrogel.**

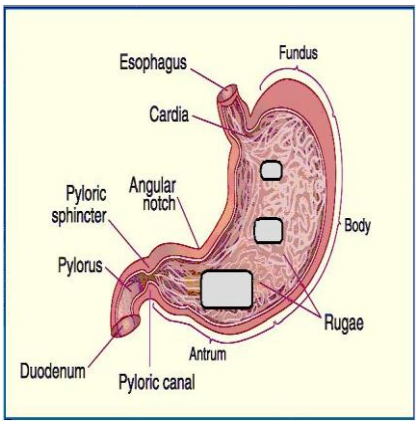


**Figure 2: Llustration of the Transit of the Superporous Hydrogel.**

**Figure 3: A Superporous Hydrogel in its Dry (Right) and Water-swollen (Left) State.**

Figure 2 illustrates the expected transit of the nonswollen/fully swollen superporous hydrogel as it is initially retained for the desired period of time and then passes into the intestine. In addition to large dimensions, swollen superporous hydrogels canfloat on gastric fluid. Figure 3 shows a modified superporous hydrogel in both a dry and swollen state. By modification of the hydrogel synthesis in terms of monomers, cross-links and other additives and components, the physical/mechanical properties of the superporous hydrogel can be controlled. Kos gastroretentive platform technology chiefly stands out from the others due to:

- A dramatic swelling timeframe – exists over seconds to a few minutes;
- High swelling capacity – prevents the platform from passing through the pylorus;
- Platform flexibility in a dry state – facilitates handling;
- Platform elasticity in the swollen state – provides resilience against the continuous contractions in the stomach;
- Ability of the platform to float on stomach fluid – prolongs gastric retention;
- Controllable platform erodability over a given time period – offers a broad range of gastric retention times; and
- Ease of drug and DDS loading in a broad range of solid dosages.

This gastroretentive platform has been completely formulated and characterised. In addition, the establishment of the proof of concept utilizing suitable animal models and clinical trials is underway. This technology can be envisioned as playing a major role in revolutionising the future of gastric retention in the pharmaceutical industry.

**Bioadhesive Drug Delivery System**

Bioadhesives is the term that describes the adhesion of a polymer to a biological substrate. More specifically, when adhesion is restricted to the mucous layer lining of the mucosal surface it is termed as mucoadhesion. This has been given considerable interest in the concept of bioadhesion since the immobilization. This has been given considerable interest in the concept of bioadhesion since the immobilization of drug carrying particles.

At the mucosal surface would result in.

- A prolonged residence time at the site of action of absorption;
- A localization of the drug delivery system at a given target site;
- An increase in the drug concentration gradient due to the intestine contact of the particle with the mucosal surface;

**Mechanism of Bioadhesion**

The bioadhesion phenomenon of the polymer is dependent on its physicochemical properties. The most important physicochemical factors of such mucoadhesive polymers are following,

- Generally hydrophilic molecules that contain numerous hydrogen bond forming groups.
- Surface tension characteristics suitable for wetting mucous / mucosal tissue surface.
- The polymers are predominately anionic in nature containing many carboxyl groups.
- Usually have a high molecular weight (greater than 100,000).
- Sufficient flexibility to penetrate the mucous network or tissue cervices

Several mechanism of polymer / substrate interaction in mucoadhesive bond formation have been suggested, namely the electronic, adsorption, wetting, diffusion and fracture theories.

**Gastrointestinal Bio/Mucoadhesive Drug Delivery**

**Bioadhesion at the Gastrointestinal Mucosal Barrier**

Considering the presence of highly differentiated areas along the whole length of the GIT, Intestinal mucosa must be considered as a very complex structure. There are at least two main targets which could be used for the anchoring of a delivery system through bioadhesion in the GIT, the mucosal tissue and mucosal gel layer. Intestinal mucous is composed of high molecular weight glycoproteins hydrated and covering the mucosa with a continuous adherent blanket. The thickness of the mucin gel layer varies regionally throughout the GIT with a thickness decreasing distally from 50-500 μm in the stomach to 15-150 μm in the colon. The mucous layer is

the first surface encountered by particulate systems and its complex structure offers many opportunities for the development of adhesive interactions with small polymeric particles either through non-specific (Vander Walls and/or hydrophobic interactions) or specific interactions between complementry structures.

**Non-specific Bioadhesion**

Non-specific bioadhesion with the intestinal membrane occurs through physicochemical interactions, some through physicochemical interaction. Some natural polymers have the ability to adhere on wet mucosal surfaces by means of hydrogen bonding or vander waals forces. With swellable hydrophilic polymers, adhesion is optimal when the mucosal contact is made with the dry polymer. Moreover, the progressive hydration of the polymer leads to the progressive hydration of the polymer leads to the formation of hydrogel, of the polymer leads to the formation of hydrogel, which is responsible for the development of a considerable adhesive strength. This concept is quite efficient in moderately flooded cavities of the body, such as the nasal and buccal cavities. However, in the GIT particles are directly mixed with liquid material in the stomach, which is likely to strongly decrease the adhesiveness of such polymers because of the temperature hydration of the polymer, which takes placed before the contact with the mucosal surface.

**Specific Bioadhesion**

Non-specific bioadhesion suffers from two major drawbacks

1. Only a fraction of the dosage form administered is absorbed while remaining part is subjected to direct fecal elimination.
2. Due to the unspecificity of the interactions, targeting to a specialized area of the mucosa with unmodified particles is unrealistic.

Specific adhesion directly to the surface of the cells of the mucosa is an alternative to non-specific Interactions between a receptor present at the cell surface and a ligand. This approach is biologically very interesting because of the existence of various glycoproteins, and glycolipides at the cell surface, which may be specific for certain cells or certain specialized areas in the GIT.

In this context, an improvement of two desirable characteristic, i.e., the adherent fraction and the site specificity, can be rendered possible by exploiting receptor –mediated interactions with in the GIT. Such adhesion phenomenon involves specific ligand-receptor interactions between complementary structures. For this purpose, a ligand which flows an affinity on to the surface of colloidal particles (liposomes or nanoparticles and allowed to mediate an adhesive reaction between the particle and the biological surface. This ligand anchored or grafted or associated micro or nanoparticles are called as ‘conjugates’.

Different targets within the GIT can be identified depending on the pharmaceutical applications. The targets are,

- Mucous glycoproteins (mucins)
- Epithelial cells
- M-cells, peyer’s patches or gut-associated lymphoid tissue (GALT)
- Absorptive windows
- Abnormal glycoproteins secreted by cancerous cells (local tumours)

**Advantages of Gastroretentive Drug Delivery System**

1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non- gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.
2) For drugs with relatively short half-life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
3) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.
4) Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
5) The controlled, slow delivery of drug from gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
6) Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.
7) Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
8) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
9) The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances

the pharmacological effects and improves the chemical outcomes.

## LIMITATIONS

GRDDS have potential in improving bioavailability of drugs exhibiting 'absorption window', however they have certain limitations. One of the major disadvantages of the floating systems is the requirement of high levels of fluids in the stomach for the delivery system to float and work efficiently. These systems also require the presence of food for delaying their gastric emptying. In addition there are limitations to the applicability of floating drug delivery system for drugs that have solubility or stability problems in the highly acidic gastric environment and are irritant to the gastric mucosa.

In case of bioadhesive systems, which forms electrostatic and hydrogen bonds with the mucus, the acidic environment and the thick mucus prevent the bond formation at the mucus-polymer interface. High turnover rate of the mucus may further aggravate the problem. For swellable systems, the maintenance of their size larger than the aperture of resting pylorus for required period of time is the major limiting factor. Above all, any dosage form designed to stay in stomach during the fasted state should be capable of resisting the housekeeper waves of phase III contractions of MMC.

## CONCLUSION

Gastroretentive Drug Delivery System, comprising mainly of floating, bioadhesive and swellable systems have emerged as an efficient means of enhancing the bioavailability and controlled release delivery of drugs exhibiting absorption window. By prolonging the gastric emptying time of the dosage form, these systems not only provide controlled release of drug for prolonged period but also present the drug in the absorbable form at regions of optimal absorption. These forms achieve this by retaining the dosage form in gastric region, for where the drug is presented at the 'absorption window'. This ensures maximum absorption of the drug for the desired period. Designing of a Gastroretentive Drug Delivery System, requires a thorough understanding of physicochemical properties of drug, physiological events in GI tract and formulation strategies. A careful consideration of interplay of these parameters can help in designing Gastroretentive Drug Delivery System, which meet their objectives successfully. Growing understanding of impact of GI tract physiology on drug delivery and increasing sophistication of delivery technology will ensure development of an increasing number of Gastroretentive Drug Delivery System to optimize drug delivery of molecules exhibiting regional variability in intestinal absorption.

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