

GASTRORETENTIVE DRUG DELIVERY TECHNOLOGIES: REVIEWAjkia Zaman Juthi*¹ and Tasnim Zaman Bithi¹Masters of Science, (Major – Pharmaceutics) China Pharmaceutical University, Nanjing, China.²Bachelor of Medicine and Bachelor of Surgery (MBBS) Capital Medical University, Beijing, China.***Corresponding Author: Ajkia Zaman Juthi**

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ABSTRACT

The success of controlled oral drug deliveries is associated with some physiological adversities like short gastric residence time and unpredictable gastric emptying time. Although oral administration is often used for the drugs with poor oral bioavailability due to limited absorption or degradation in the GIT but still it is considered as the most convenient one. Prolonged gastric residence increases duration of drug release, reduces drug waste, and improves drug solubility in gastric pH. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. One of the promising systems is gastro retentive drug delivery system. Numerous techniques have been tried to retain the drug in the gastric media.

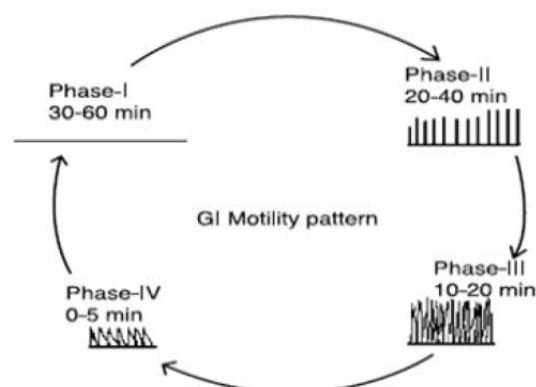
KEYWORDS: Gastroretentive systems, GI tract, bioadhesion, controlled drug release.**INTRODUCTION**

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation.^[1] Gastroretentive dosage forms are designed to be retained in the gastric region for prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus ensuring its optimal bioavailability.^[2] 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. Thus, they not only prolong the dosing intervals, but also increase the patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs.^[3] longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease.^[4] Certain types of drugs can benefit from using gastric retentive devices. These include:

- Acting locally in the stomach.
- Primarily absorbed in the stomach.
- Poorly soluble at an alkaline pH.
- Narrow window of absorption.
- Absorbed rapidly from the GI tract.
- Degrade in the colon.

Biological Aspects of Gastric Retention

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm.^[5] The process of gastric emptying is characterised by a distinct cycle of electromechanical activity known as the inter digestive migrating myoelectric complex.

**Figure 1: Phases of gastric motility.**

This series of events that cycle through the stomach and small intestine every 1.5 – 2 h is divided into four consecutive phases: (Figure 1)^[6]

- Phase I (45 – 60 min), the most quiescent, develops few or no contractions;

- Phase II (30 – 45 min) consists of intermittent action potentials and contractions, which gradually increase an intensity and frequency as the phase progresses;
- Phase III (5 – 15 min) is a short period of intense contractions and peristaltic waves, involving both the proximal and distal gastric regions ('housekeeper waves'). In this phase, indigestible solids are removed from the fasted stomach;
- Phase IV (0 – 5 min) is a transition period of decreasing activity until the next cycle begins.

➤ Effect of gender, posture and age

Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface. The gastric retention time is prolonged in people of age 70 and above. GRT can vary between supine and upright ambulatory states of the patient.^[7]

➤ Nature of meal

During the fed state, the motility pattern of the stomach can be affected by various factors. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form.^[8] So the ultimate consequence can be expected in the drop of gastric emptying speed and prolong drug release.

➤ Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. The dependency of gastric retention time is related by direct relation with the density. The density is basically a function of dosage form buoyancy.^[9]

➤ Shape of dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The improved gastric retention time of 90% to 100% is displayed by the Tetrahedron ring shaped devices with a flexural modulus. The values of modulus range from 48–22.5 kilopounds/square inch (KSI) at 24 hours in comparison with other shapes.^[10]

➤ Biological factors

These factors include the Diabetes and the syndrome called Crohns disease, etc.^[11]

Advantages of Grdds

- Gastro retentive drug delivery system offers enhanced absorption for those drugs which predominantly exhibit the trend of absorbance in the stomach. e.g., ferrous salts, antacids, etc.^[12]
- It is advantageous for drugs which have domain of action in the stomach. e.g., antacids, etc.
- 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.

- 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.
- The controlled, slow delivery of drug form 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.
- Gastric irritation is also prevented with help of delayed release effect and unfluctuating release of drug in these systems.^[13]

Approaches for Gastro Retention

Floating DDS

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. The drug is released progressively at the expected rate from the system at the time when the system is floating in gastric substances This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine.^[14] The major requirements for floating drug delivery system are.^[15]

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents ($1.004 - 1.01 \text{ gm/cm}^3$).
- It must form a cohesive gel barrier.

High Density Systems or Non-floating system

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content ($\sim 1.004 \text{ gm/cm}^3$). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc.^[16] The materials increase density by up to $1.5 - 2.4 \text{ gm/cm}^3$. A density close to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time. But, effectiveness of this system in human beings was not observed and no system has been marketed.

Non-effervescent system

This type of dosage forms apply a gel forming or swellable and matrix-forming polymers. The one of processes of formulation comprise of gentle mixing of the drug and the gel forming hydrocolloid.^[17] Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates .

This system can be further divided into the sub-types

- **Hydrodynamically balanced systems**

Sheth and Tossounian^[18] first designated these 'hydrodynamically balanced systems'. These systems contain drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. Incorporation of fatty excipients gives low-density formulations reducing the erosion. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. Several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems. (Figure 2)

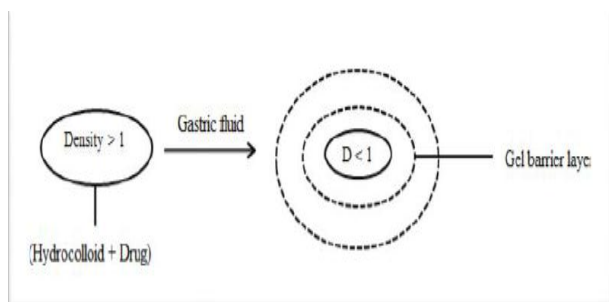


Figure 2: Hydrodynamically balanced systems.

- **Hollow Microspheres**

This type of system loaded with drugs is prepared by simple solvent evaporation or solvent diffusion technique to encompass the gastric retention time of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. The consistent floatation of these hollow microspheres takes place over the surface of an acidic dissolution media containing surfactant for more than 12 hours. The study results have shown the fact that micro balloons have shown the ability to sustain for 3 hours against peristaltic movements in human after dispersion in the upper part of stomach as administered orally.^[19]

- **Gas – generating systems**

Carbon dioxide is released by the reaction of carbonate/bicarbonate salts and citric/tartaric acid while the gas generating buoyant delivery systems employ this effervescent reaction. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid). The microballoons can float continuously over the surface of an acidic dissolution media containing surfactant for more than 12 hours.^[20] Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers.

- **Bio-adhesive or mucoadhesive DDS**

Bio-adhesive DDS is used as a delivery device within humans to enhance drug absorption in a site specific

manner. Many bioadhesive polymers are utilized as they have ability to stick to the epithelial surface in the stomach. So the gastric retentive time of the dosage forms is increased. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:^[21]

1. Diffusion theory, which proposes physical entanglement of mucin strands in the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
2. The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
3. Absorption theory suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4. The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio adhesive material.

- **Alginate Beads**

Talukdar and Fassih^[22] recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca²⁺ and low methoxylated pectin (anionic polysaccharide) or Ca²⁺ low methoxylated pectin and sodium alginate. They were made by using calcium and low methoxylated pectin (anionic polysaccharide), or calcium low methoxylated pectin and sodium alginate. These systems in comparison with solid beads give a better extended residence time of more than 5.5 hours while solid beads give a short residence time of 1 hour.^[23,24]

- **Micro-porous compartment system**

Microporous compartment system is the kind of technology that works by the encapsulation of a drug reservoir inside a microporous compartment and has outlets alongside its upper and lowest walls. The peripheral walls of the device are completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.^[25,26]

- **Magnetic system**

Magnetic systems are another effort to improve the gastric retention time (GRT). They are constituted in simple method. Normally magnetic systems are considered to be working normally but the position of the external magnet is key point in this method. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.^[27]

- **Superporous Hydrogels (SPHs)**

In 1999, A superporous hydrogels (SPH) is a 3-dimensional network of a hydrophilic polymer that

absorbs a large amount of water in a very short period of time due to the presence of Interconnected microscopic pores.^[28] SPHs are a new type of hydrogel that have numerous super size pores inside them. The concepts of gastric intestinal physiology, these kinds of hydrogels have to comprise following characteristics to behave as gastric retention device.

1. Initial small size sufficient for easy swallowing.^[29]
2. Fast swelling sufficient to overcome gastric emptying by IMMC.
3. Large size of swollen hydrogels adequate enough to be retained in the stomach.
4. Strong swollen hydrogel to persist contraction pressure, abrasion and shear forces in stomach.

Thereby, Superporous hydrogels swell completely within minutes regardless of their size due to absorption of water by capillary force rather than by simple absorption. Second generation Superporous hydrogels composites are developed which shows fast swelling, medium swelling ratio and improved mechanical properties, while third generation superporous hydrogel hybrid possess high elastic properties.^[30] Gastric retention devices would be most beneficial for local action of drugs in the stomach, e.g. antacids and antibiotics for bacteria based ulcers or drugs that are required be absorbed primarily in the stomach.^[31]

CONCLUSION

Based on the literature surveyed, it may be concluded that GR drug delivery offers various potential advantages for drugs with poor bioavailability due to their absorption, which is restricted to the upper GIT and can be delivered efficiently, thereby, maximizing their absorption and enhancing absolute bioavailability.^[32] Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability.^[33,34] Finally, while the control of drug release profiles has been a major aim of pharmaceutical research and development in the past two decades, the control of GI transit profiles could be the focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients.^[35,36,37]

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