GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of writing the article on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, in this article we have summarized important factors controlling gastric retention. Gastroretention would also facilitate local drug delivery to the stomach and proximal small intestine. So, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and required benefits to patients. Controlled gastric retention of solid dosage form may be achieved by the mechanisms of floatation, mucoadhesion, sedimentation, expansion or by a modified shaped system.

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INTRODUCTION
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. 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. 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 GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Physiology of the Stomach
The gastrointestinal tract is essentially a tube about nine metres 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 cecum, 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. 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 interdigestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organised in cycles of activity and quiescence.4

A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the ‘housekeeper wave’ as the powerful contractions in this phase tend to empty the stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food.5
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Table 1: Salient Features of Upper Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Section</th>
<th>Length (m)</th>
<th>Transit time (h)</th>
<th>pH</th>
<th>Microbial count</th>
<th>Absorbing surface area (m²)</th>
<th>Absorption pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.2</td>
<td>Variable</td>
<td>1-4</td>
<td>&lt;10³</td>
<td>0.1</td>
<td>P, C, A</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>6-10</td>
<td>3 ± 1</td>
<td>5-7.5</td>
<td>10³ – 10¹⁰</td>
<td>120-200</td>
<td>P, C, A, F, I, E, CM</td>
</tr>
</tbody>
</table>

P – Passive diffusion
A – Active transport
F – Facilitated transport
I – Ion-pair transport
E – Entero-or pinocytosis
CM – Carrier mediated transport

Different Features of Stomach
Gastric pH: Fasted healthy subject 1.1 ± 0.15
Fed healthy subject 3.6 ± 0.4
Volume : Resting volume is about 25-50 ml
Gastric secretion: Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.
Effect of food on Gastric secretion: About 3 liters of secretions are added to the food. Gastro intestinal transit time Figure No.1

Requirements for Gastric Retention
Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.

Need For Gastro Retention:
- Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT).
- Drugs that are less soluble or are degraded by the alkaline pH they encounters at the lower part of GIT.
- Drugs that are absorbed due to variable gastric emptying time.
Local or sustained drug delivery to the stomach and proximal Small intestine to treat certain conditions.
Particularly useful for the treatment of peptic ulcers caused by H. Pylori Infections.

Factors controlling gastric retention of dosage form
The gastric retention time (GRT) of dosage form is controlled by several factors, which affect their efficacy as a gastroretentive system.

Density
Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0gm/cm³ is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

Dosage form size
The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floaing dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units. In fed conditions, the smaller units get emptied from the stomach during the digesti ve phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor for gastric retention.

Shape of dosage form
Tetrahedron and ring-shaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT. 90% to 100% retention at 24 hours compared with other shapes.

Single or multiple unit formulation
Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow coadministration of units with different release profiles or containing incompatiblesubstances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

Fed or unfed state
Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of meal
Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

Caloric content
GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

Frequency of feed
The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

Gender
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.

Age
Elderly people, especially those over 70, have a significantly longer GRT.
Posture
GRT can vary between supine and upright ambulatory states of the patient.

Concomitant drug administration
Anticholinergics like Atropine and Propantheline, Opiates like Codeine and Prokinetic agents like Metoclopramide and Cisapride.

Biological factors
Diabetes and Crohn’s disease

ADVANTAGES OF GASTRO RETENTIVE 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 nongastroretentive 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 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.
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.

IDEAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM:
In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:
- Narrow absorption window in GIT tract, e.g., riboflavin and levodopa
- Primarily absorbed from stomach and upper part of GIT tract, e.g., calcium supplements, chlordiazepoxide and cinnarazine
- Drugs that act locally in the stomach, e.g., antacids and misoprostol
- Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole
- Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS:
1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

APPROACHES TO ACHIEVING GASTRIC RETENTION:
a) High density (sinking) system or non-floating drug delivery system.
This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~1.004 gm/cm3). 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. The materials increase density by up to 1.5 - 2.4 gm/cm3. A density close to 2.5 gm/cm3 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.
b) **Floating drug delivery systems**

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. These Delivery Systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are:

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm³).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder). These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra-subject availabilities in drug absorption as well as to lower the possibility of dose dumping. Various multiple-unit floating system like air compartment multiple-unit system hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method microspheres based on low density foam powder, beads prepared by emulsion gelatin method etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

c) **Non-effervescent Systems**

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment. The air trapped by the swollen polymer confers buoyancy to these dosage forms. 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:

1. **Hydrodynamically balanced systems**

The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. 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. Incorporation of fatty excipients gives low-density formulations reducing the erosion. 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.
2. **Microballoons / Hollow microspheres**

Microballoons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods to prolong the gastric retention time (GRT) 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. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

3. **Effervescent (gas generating) systems**
4. **Bioadhesive or Mucoadhesive drug delivery systems**

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms are:

1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

2) The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

3) The 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 net work and the bioadhesive material. Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

![Figure 7: Mucoadhesive drug delivery systems](image_url)

**EVALUATION STUDIES**

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behaviour exhibit prolonged gastric residence in vivo. However, it should be noted that good in vitro floating behaviour alone is not sufficient proof of efficient gastric retention in vivo. The effects of the simultaneous presence of food and the complex motility of the stomach are difficult to assess. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained.

**Measurement of buoyancy capabilities**

The floating behaviour was evaluated using resultant weight measurements. The experiment was carried out in two different media, deionised water and a simulated meal, in order to monitor possible differences. The apparatus and its mechanism have been explained earlier in this review. The results showed that higher molecular weight polymers with a slower rate of hydration exhibit enhanced floating behaviour and this was observed more in a simulated meal medium compared with deionised water.

**Floating time**

The floating time measurement is usually performed in stimulated gastric fluid or 0.1 mol/l HCl maintained at 37°C. It is determined using USP dissolution apparatus containing 900 ml 0.1 mol/l HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as the floating lag-time and the time for which the dosage form floats is termed as the floating or flotation time.

**Drug release**

Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium and replaced with an equal volume of fluid and then analyzed for their drug content after appropriate dilution.
Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads)

Drug loading is assessed by crushing an accurately weighed sample of beads or microspheres in a mortar and adding it to the appropriate dissolution medium which is then centrifuged, filtered, and analyzed by a variety of analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of the beads or microspheres are determined in the dry state by optical microscopy. The external an cross-sectional morphology (surface characterization) is carried out by scanning electron microscopy (SEM).

CONCLUSION

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. Soon, the so-called ‘once-a-day’ formulations may be replaced by novel gastroretentive products with release and absorption phases of approximately 24 hours.

REFERENCES