A NOVEL APPROACH TOWARDS GASTRORETENTIVE DRUG DELIVERY SYSTEM

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Abstract: Gastro-retentive drug delivery system is an approach to prolong the GRT, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effect. Conventional oral dosage forms possess low bioavailability problems because of their quick gastric transition from the stomach, particularly in case of drugs that are less soluble at an alkaline pH of the intestine. Also, drugs that produce their local action in the stomach get quickly emptied and don’t get sufficient residence time in the stomach. Several efforts have been made to extend the retention time of drug delivery system to reduce the frequency of dose administration. The purpose of writing this review 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, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel systems. Finally, advantages and evaluation parameters of gastroretentive drug delivery systems were covered in detail.

Keywords: Gastroretentive, Floating drug delivery system, Various approaches, Applications.

INTRODUCTION:

The oral delivery of drugs is the most favoured route of administration because of ease of administration. Drug bioavailability of oral dosage forms is subjective by various factors. One of the significant factor is a gastric residence time (GRT) of these dosage forms. Truly, gastric retention has received important interest in the past few years as many of the conventional oral delivery systems have some limits related to fast gastric emptying time. Gastroretentive dosage form is a type of novel drug delivery system which can persist in the stomach for prolonged period of time and thus increases the GRT of drugs. Gastro-retention helps to improve bioavailability of drugs.

The conventional drug delivery system achieves and also maintained the drug concentration in the therapeutically effective range desired for treatment, only when taken numerous times a day. A drug that has a narrow absorption window in the GIT may have poor absorption. For these drugs, GRDDS offer the advantages in extending the gastric emptying time.

Many problems are faced in preparing controlled release systems for better absorption and improved bioavailability. Drug absorption from the GIT is a complex process and is subject to several variables. It is broadly recognized that the extent of GIT drug absorption is correlated to contact time with small intestinal mucosa. GRDDS can persist in the GI region for many hours and therefore significantly extend the GRT of drugs. Extended gastric retention increases bioavailability, decreases drug waste and increases solubility of drugs which are less soluble in high pH environment. To prepare a successful stomach specific or a gastroretentive DDS, numerous techniques are presently used like hydrodynamically balanced systems (HBS)/ floating drug delivery system, low density system, raft systems incorporating alginate gels, mucoadhesive or bioadhesive systems, high density systems, super porous hydrogels and magnetic systems. Current progress in technology has provided feasible dosage alternatives which can administered by different routes of administration like oral, topical, parenteral, rectal, nasal, ocular, vaginal, etc. But out of all these routes, oral route is considered as the best preferred and practiced way of drug delivery, due to the following reasons:

- Ease of administration
- Ease of production
- More flexibility in designing
- Low cost

Many drugs given by oral route are subjected to absorption through the GIT, with major absorption from the stomach and intestine. Drugs, which is absorbed from the stomach or show local effect, should spend extreme time in stomach. This is found very hard to happen, in case of the conventional dosage forms such as capsules and tablets, due to the gastric emptying of
dosage form depends on several factors like temperature and viscosity of the meal, volume and composition of the meal, emotional state of the individual, the pH of the stomach, body posture, etc.

**SUITABLE DRUG CANDIDATES FOR GASTRO-RETENTIVE DRUG DELIVERY SYSTEM:**

1. Generally, the ideal candidates for GRDDS are molecules that have poor intestinal absorption but having the better absorption in the upper part of the GIT.
3. Primarily absorbed in the stomach.
4. Poorly soluble at an alkaline pH.
5. Absorbed rapidly from the stomach.
6. Degrade in the colon.
7. It should be absorbed primarily in the duodenum and upper jejunum segments. e.g. Calcium is mainly absorbed in the duodenum.
8. Drugs which have a short half-life and require frequent dosing.
9. Drugs which undergoes first pass metabolism. e.g. Nitro-glycerin.
10. Which have poor solubility in intestinal media and poor bioavailability.
11. Drugs that are required for local action in stomach. e.g. Antacids and enzymes preparation.

**TABLE NO. 1: GASTRORETENTIVE DRUG DELIVERY SYSTEMS vs. CONVENTIONAL DRUG DELIVERY SYSTEMS:**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameters</th>
<th>Conventional DDs</th>
<th>GRDDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Toxicity</td>
<td>High risk of toxicity</td>
<td>Low risk of toxicity</td>
</tr>
<tr>
<td>2.</td>
<td>Patient compliance</td>
<td>Less</td>
<td>Improves patient compliance</td>
</tr>
<tr>
<td>3.</td>
<td>Drug with narrow absorption window in small intestine</td>
<td>Not suitable</td>
<td>Suitable</td>
</tr>
<tr>
<td>4.</td>
<td>Drugs having rapid absorption through GIT</td>
<td>Not much advantageous</td>
<td>Very much advantageous</td>
</tr>
<tr>
<td>5.</td>
<td>Drug which degrades in the colon</td>
<td>Not much advantageous</td>
<td>Very much advantageous</td>
</tr>
<tr>
<td>6.</td>
<td>Drugs acting locally in the stomach</td>
<td>Not much advantageous</td>
<td>Very much advantageous</td>
</tr>
<tr>
<td>7.</td>
<td>Drugs which are poorly soluble at an alkaline pH</td>
<td>Not much advantageous</td>
<td>Very much advantageous</td>
</tr>
<tr>
<td>8.</td>
<td>Dose dumping</td>
<td>High risk of dose dumping</td>
<td>Low risk of dose dumping</td>
</tr>
</tbody>
</table>

**ADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM:**

- The bioavailability can be enhanced for those drugs which has absorption in upper GIT and those gets degraded in intestinal pH.
- Sustained drug release and reduced frequency of dosing. This improves patient compliance.
- Targeted delivery of the drug at the upper part of the GIT making it suitable for the local treatment of the disease of the region e.g.; antacids, anti-ulcer drugs, antibacterial for H. pylori infection.
- The drugs which are having pH dependent absorption from stomach can be formulated as GRDDS e.g. Furosemide, Captopril, Diazepam, Verapamil, Cefpodoxime proxetil.
- Suitable for the drugs which gets degraded in the intestine or colon e.g., Ranitidine hydrochloride.
- There is no fluctuation in the Drug level and maintains the optimal therapeutic plasma and tissue concentrations over prolonged time period. This avoids sub-therapeutics as well as toxic concentration and minimizes the risk of failure of the medical treatment and undesirable side effects.
- The drugs which are having less half-life can be formulated as GRDDS thus reduces the frequent dosing.
- Gastro-retentive drug delivery can minimize the activity of the body leading to higher Drug efficiency.

**LIMITATIONS/DISADVANTAGES:**

1. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat.
2. Not suitable for drugs that have solubility or stability problem in GIT.
3. Drugs such as Nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
4. Drugs which are irritant to gastric mucosa are also not desirable or suitable.
5. The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
6. The dosage form should be administered with a full glass of water (200-250 ml).
7. These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.
ANATOMY OF THE STOMACH:

The gastrointestinal tract can be divided into three main regions

a) Stomach

b) Small intestine - duodenum, jejunum, and ileum

c) Large intestine

The GIT is a muscular tube of about 9 m which extends from mouth to anus. Its function is to take nutrients and eliminate out waste product by physiological processes such as digestion, absorption, secretion, motility and excretion. The stomach has three muscle layer called oblique muscles and it is situated in the proximal part of the stomach, branching over the fundus and higher regions of the gastric body. The stomach is divided into fundus, body and pylorus. The stomach is a shaped organ located in the upper left hand portion of the abdomen. The main function of the stomach is to store the food temporarily, grind it and releases slowly in to the duodenum.

Figure 1: General Gastrointestinal tract

PHYSIOLOGY OF THE STOMACH:

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rogue. There are 4 major types of secretory epithelial cell that covers the stomach and extends into gastric pits and glands.

1. Mucous cells - secrete alkaline mucus
2. Parietal cells – secrete HCL
3. Chief cells - secrete pepsin
4. G cells- secrete hormone gastrin.

GASTRIC MOTILITY AND GASTRIC EMPTYING RATE:

Two distinct patterns of gastrointestinal motility and secretion exist to the fasted and fed state.
The bioavailability of the orally administered drug depend upon the state of feeding. In the fasted state, it is characterized by an inter digestive series of electric event called inter digestive myoelectric cycle migrating motor complex. It is divided into 4 phases.

a) Phase I (basal phase) it lasts from 40-60 min with rare contractions

b) Phase II (preburust phase) last from 40-60 min with intermittent potential and contractions.

c) Phase III (burst phase) last for 4-6 min. in this intense and regular contraction occur for short periods. Due to these contractions the undigestive food is swept from stomach to intestine. These are known as house keeper waves.

d) Phase IV it lasts for 0-5 min and occurs between phases III and I for two consecutive cycles.

After the ingestion of the mixed meal the pattern of contraction changes from fed to that of fasted state, this is known as digestive motility pattern, these contractions reduces the size of the food particles to less than 1mm after that it is propelled to the pylorus in the suspension form. During fed state the onset of MMC is delayed which result in slow down of gastric emptying rate.
FACTORS AFFECTING GASTRIC RETENTION:

- **Density:**
  Gastric retention time (GRT) is a function of dosage form buoyancy which is dependent on the density. The density of the dosage form must be lower than the gastric contents (1.004 gm/ml).

- **Size:**
  Dosage form units having a diameter of greater than 7.50 mm are stated to have an improved GRT related with those having a diameter of 9.90 mm.

- **Shape of the dosage form:**
  Tetrahedron and ring shaped devices having a flexural modulus of 48 and 22.50 kilo pounds per square inch are reported to have a better GRT at 24 hours compared with other shapes.

- **Single or Multiple unit formulation:**
  Multiple unit formulations show a more expectable release profile and insignificant damaging of performance because of failure of units, allow coadministration of units that have dissimilar release profiles related with single unit dosage forms.

- **Fed/Unfed state:**
  In fasting conditions, gastrointestinal motility is categorized by periods of strong motor activity that occurs every 1.5 to 2 hours and if timing of administration of the formulation overlaps with that of the MMC, the gastric retention time of unit can be anticipated to be very short. However, in fed state, MMC is postponed and gastric retention time is significantly longer.

- **Nature of meal:**
  Feeding of fatty acid salts or indigestible polymers can modify the motility pattern of stomach to a fed state, hence reducing the gastric emptying rate.

- **Caloric content:**
  GRT can be improved by 4 to 10 h with a meal which is high in proteins and fats.

- **Age:**
  Elderly people, mostly those over 70 years, have a significantly longer gastric retention time.

- **Frequency of feed:**
  Gastric retention time can rise by over 400 minutes, when consecutive meals are given related with a single meal because of the low frequency of MMC.

- **Gender:**
  Mean ambulatory gastric retention time in males (3.4 ± 0.6 hours) is less correlated with their age and race matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, body surface and height.

- **Posture:**
  Gastric retention time can be differing between supine and upright ambulatory states of patients.

- **Concomitant drug administration:**
  Anticholinergics like atropine and propentheline increase the GRT. Metoclopramide and Cisapride decrease GRT.

- **Disease state:**
  Gastric ulcer, diabetes and hypothyroidism increase the GRT. Hyperthyroidism and duodenal ulcers decrease the GRT.

APPROACHES TO PROLONG GASTRIC RESIDENCE TIME:

Dosage forms developed for gastric retention should be able to stand up against gastric force caused by peristaltic movement in the stomach, constant churning and grinding. Gastretentive dosage forms resist the gastric emptying and once the aim of dosage form is achieved it should be eliminated from the stomach. Gastretentive dosage forms need wide efforts in both academic and industry towards development. These efforts resulted in gastretentive drug delivery formulations based on following approaches-

Gastretentive drug delivery system can be broadly classified into two categories-

1. **Non Floating Systems:**
   a) Bioadhesive Systems
   b) Swelling Systems
   c) High Density Systems
   d) Expandable Systems

2. **Floating Systems:**
   The Floating system can be further divided into two types:
   a) **Effervescent System**

Volatile liquid containing system

(i) Intra Gastric floating gastrointestinal drug delivery system
(ii) Inflatable gastrointestinal drug delivery system
(iii) Intra Gastric osmotically controlled drug delivery system

**Gas generating system**-

(i) Floating Capsules

(ii) Floating Pills

(iii) Floating systems with ion exchange resins

**b) Non Effervescent Systems:**

(i) Colloidal Gel System Barrier (Hydrodynamically balanced system)

(ii) Microballs/Hollow microspheres

(iii) Alginate beads

(iv) Layered Tablets

a) Single layer tablets

b) Bilayer tablet

1. **Non-floating systems:**

These are gastroretentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. These systems are formulated by any of the following approaches.

a) **Bioadhesive systems:**

This approach involved the use of muco-adhesive polymer which adhered over mucous layer secreted by the goblet cells of the stomach and hence retains in the stomach for its prolonged release. Mucus is translucent and viscid secretion, which forms gel like continuous thin blanket over mucosal epithelial surface. Some excipients that have been used commonly in these systems include lectins, polycarbophil, chitosan gliadin and carbopol etc.

b) **Swelling Systems:**

Gastroretentivity of a pharmaceutical dosage form can also be enhanced by increasing its size above the diameter of the pylorus (even in its widest state during a housekeeper wave). If the dosage form can attain the larger size than pylorus, the gastroretentivity of that dosage form will be possible for a long time. This large size should be achieved fairly quickly; otherwise the dosage form will be emptied through the pylorus. Thus, configurations required to develop an expandable system to prolong GRT are

(i) A small configuration for oral intake,

(ii) An expanded gastroretentive form, and

(iii) A final small form enabling evacuation following drug release from the device.

In addition they should be able enough to withstand peristalsis and mechanical contractility of the stomach. Swellable systems are also retained in the GIT due to their mechanical properties. The swelling of dosage form is usually resulted from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Figure 4). In general, these size increasing drug potentially delivery system present the hazard of permanent retention in the stomach and could lead to life threatening effects upon multiple administration. They are also not cost-effective. A major advantage of these size increasing systems is the independence of their performances on the filling state of the stomach.

![Figure 4: Drug release from swellable systems](image-url)
c) **High Density Systems:**
This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm$^3$) shown in fig 5. 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/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.

![GRDDS.png](attachment:GRDDS.png)

Figure 5: GRDDS based on (a) Low-density systems and (b) High-density systems

**d) Expandable systems:**
These systems are capable of expanding and retain in the stomach for longer periods. These are usually formulated as a capsule containing dosage form in folded and compact form. After being exposed to stomach environment, capsule shell disintegrates and dosage form expands preventing its exit through the stomach. By using a suitable polymer, sustained and controlled drug delivery can be achieved.

2. **Floating drug delivery systems (FDDS):**
These are drug delivery systems that float immediately upon contact with gastric fluids and thus they present promising approaches for increasing drug bioavailability with absorption windows in the upper small intestine. 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 and the drug is released slowly at a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuation in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. 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/cm$^3$).
- It must form a cohesive gel barrier based on the mechanism of buoyancy, there are two distinctly different technologies for FDDS, i.e.
  - Effervescent System
  - Non effervescent

a) **Effervescent drug delivery system:**
This system is prepared by swellable polymer like chitosan and effervescent substance like sodium bicarbonate, citric acid or tartaric acid. When the system comes in contact with gastric fluids it releases carbon dioxide, causing the formulation to remain and float in the stomach.

**Volatile liquid containing systems:**
These have an inflatable chamber which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid. These are further categorised as

(i) **Intragastric floating gastrointestinal drug delivery system:**
This system contains a floatation chamber which contains vacuum or a inert, harmless gas and a microporous compartment enclosing drug reservoir. It is shown in Figure. 6
(ii) **Inflatable gastrointestinal drug delivery system:**
These systems possess inflatable chamber containing liquid ether which gasifies at body temperature to inflate in the stomach. Inflatable chamber contains bioerodible polymer filament (e.g., copolymer of polyvinyl alcohol and polyethylene) that gradually dissolves in gastric fluid and finally causes inflatable chamber to release gas and collapse. It is shown in Figure 7.

(iii) **Intragastric-osmotically controlled drug delivery system:**

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**Figure 6:** Intragastric floating gastrointestinal drug delivery system

**Figure 7:** Inflatable gastrointestinal drug delivery system

**Figure 8:** Intragastric-osmotically controlled drug delivery system
It is composed of osmotic pressure controlled drug delivery device and an inflatable floating capsule. In the stomach, inflatable capsule disintegrates and releases the osmotically controlled drug delivery system which contains two components; drug reservoir compartment and osmotically active compartment. Illustrated in Figure. 8

**Gas-generating Systems:**

The effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂ occurs in this delivery system, which gets entrapped in the gelled hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach used for the preparation of these systems involves resin beads loaded with bicarbonate.

(i) **Floating Capsules:**

These are prepared with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC). On exposure to acidic environment, carbon dioxide gas is generated which is trapped in the hydrating gel network and makes the system to float.

(ii) **Floating pills:**

These are a type of sustained release formulations which are basically multiple unit type of dosage forms. The sustained release pill is surrounded by two layers. Outer layer consists of swellable membrane and the inner layer consists of effervescents agents. The system swells due to swellable membrane and then sinks. Due to the presence of effervescents agents, CO₂ is released and the system floats.

(iii) **Floating systems with ion exchange resins:**

The most common approach for formulating these systems involves resin beads loaded with bicarbonate. This is then coated with ethyl cellulose which is usually insoluble but permeable to water. This causes carbon dioxide to release and the system to float.

(b) **Noneffervescent system:**

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix impacts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

(i) **Colloidal gel barrier system (Hydrodynamically Balanced System):**

Sheath and Tossounian first designated this ‘hydrodynamically balanced system’. These type of systems contain drug with gel forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its absorption site in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly soluble cellulose type hydroxypyrrol hydrocolloid cellulose, as hydroxyl ethyl cellulose, Hydroxypropylmethylcellulose (HPMC), polysaccharides and matrix forming polymer such as polycarbophil, polyacrylate and polystyrene. This hydrocolloid hydrates and forms a colloidal gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drugs.

(ii) **Microballoons microspheres / Hollow:**

Hollow microspheres are gastro-retentive drug delivery systems based on non-effervescence approach. These microspheres are in strict sense, spherical empty particles without core. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometres. Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in the stomach for prolonged periods. The drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration. These systems contain outer polymer shell loaded with drug. The outer polymer shell is made up of polymers like polycarbonate, cellulose acetate, calcium alginate, agar, etc. Buoyancy lag time and drug release from the system is dependent on the quantity of polymers used in the formulation. These are prepared by emulsion-solvent diffusion method.

(iii) **Alginate beads:**

These are generally made by using Ca₂⁺ and low methoxylated pectin (anionic polysaccharide) or Ca₂⁺ low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into an aqueous solution of calcium chloride which causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs to 24hrs. In a latest research it has been investigated that Sodium Alginate can be oxidized by reaction with sodium periodate NaIO₄. This partially oxidized alginate was used to synthesize alginate microbeads. Oxidation altered the microbeads properties to control. The degradation time of resultant micro beads increased with degree of oxidation. Current studies are investigating microbeads degradation as a function of oxidation. It is hoped solution that implementing
predictably degradable alginate can be eventually utilized in islet cell transplantation and drug delivery as a treatment of Type I diabetes.

(iv) **Layered tablets:**
These may be of single layer or double layered.

a. **Single layered floating tablets:**
This type of tablets contain drug mixed with gel forming hydrocolloids and other excipients. Upon contact with gastric fluids, the hydrocolloids swell and maintain bulk density less than one and hence remain buoyant in the stomach.

b. **Double layered floating tablets:**
This type of tablets contain two layers, one of which is immediate releasing layer and the other is sustained release layer

**EVALUATION PARAMETERS:**

1. **SIZE AND SHAPE:**
The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation was determined using Sieve analysis (Jayant, Mumbai), Air elutriation (Bahco TM) analysis, Photo analysis, Optical microscope (Olympus (India) pvt.ltd), Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc.

2. **FLOATING PROPERTIES:**
Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.

3. **BUOYANCY LAG TIME:**
It is determined in order to know the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium.

4. **SPECIFIC GRAVITY/DENSITY:**
Density is usually determined by the displacement method, in which Benzene used as displacement medium.

5. **SURFACE TOPOGRAPHY:**
The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profilimeter.

6. **DETERMINATION OF MOISTURE CONTENT:**
The water content per se is seldom of interest. Rather, it shows whether a product intended for trade and production has standard properties such as:
1. Storability
2. Agglomeration in the case of powders
3. Microbiological stability
4. Flow properties, viscosity
5. Dry substance content
6. Concentration or purity
7. Commercial grade (compliance with quality agreements)
Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods.

7. **SWELLING STUDIES:**
Swelling studies were performed to calculate molecular parameters of swollen polymers. Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1 NMR imaging. Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus (usp-24) lab India disso 2000) was calculated as per the following formula,
Swelling ratio = Weight of wet formulation / Weight of formulations

8. **DETERMINATION OF THE DRUG CONTENT:**
Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed the limits acquired by the standard monographs. Drug content was determined by using HPLC, HPTLC methods, Near infrared spectroscopy (NIRS), Micro titrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICP AES) and also by using spectroscopy techniques (Elico Limited, Hyderabad)
9. **PERCENTAGE ENTRAPMENT EFFICIENCY:**
Percentage entrapment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations. Entrapment efficiency was determined by using three methods such as Micro dialysis method, Ultra centrifugation, and pressure Ultra filtration.

10. **IN-VITRO RELEASE STUDIES:**
In vitro release studies (USP dissolution apparatus (usp-24) lab India disso 2000) were performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus.

11. **POWDER X-RAY DIFFRACTION:**
X-ray powder diffraction (Philips analytical, model pw 1710) is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between 2 °C and 60 °C. The voltage and current used were 30KV and 30mA respectively.

12. **FOURIER TRANSFORMS INFRARED ANALYSIS:**
Fourier transform infrared spectroscopy (FT-IR, Shimadzu, Model-RT-IR-8300) is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug-loaded polymer formulations were obtained on FT-IR. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature.

13. **DIFFERENTIAL SCANNING CALORIMETRY (DSC):**
DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermatically sealed in an aluminium pan and heated at a constant rate of 10°C/min; over a temperature range of 25°C – 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min.

**APPLICATIONS:**

1. **Enhanced Bioavailability:**
Bioavailability of riboflavin controlled release gastroretentive dosage forms is significantly improved compared to administration of noncontrolled release gastroretentive dosage forms polymeric formulations. There are numerous different procedures, related to absorption and transit of drug in the GIT, which act concomitantly to impact the magnitude of drug absorption.

2. **Sustained Drug Delivery:**
Oral controlled release formulations are faced with problems like GRT in the gastrointestinal tract. HBS systems can be used to overcome the problems that can remain in stomach for prolonged period of time and have bulk density <1 as a result of which they can float on the GI contents. The systems are comparatively large in size & passing from pyloric opening is prohibited.

3. **Site Specific Drug Delivery Systems:**
These systems are frequently beneficial for drugs which are especially absorbed from stomach or the proximal part of small intestine. The controlled/slow delivery of drug to the stomach offers adequate local therapeutic levels and limits the systemic exposure to drug. This decreases side effects that are produced by drug in blood circulation. Also, the extended gastric availability of a site directed delivery system may reduce the frequency of dosing. E.g., Furosemide and Riboflavin.

4. **Absorption Enhancement:**
Drugs that are having poor bioavailability due to site specific absorption from upper part of the gastrointestinal tract are potential candidates to be formulated as FDDS, thus maximizing their absorption.

5. **Minimized adverse activity at the colon:**
Retention of drug in HBS systems at the stomach reduces the amount of drug that extents the colon. Hence, undesirable activities of drug in the colon can be prohibited. This pharmacodynamics aspect offers the rationale for gastroretentive dosage form for beta lactam antibiotics which are absorbed only from small intestine, and whose presence in colon leads to the growth of microorganism resistance.

6. **Reduced fluctuations of drug concentration:**
Constant input of drug following controlled release GRDF administration produces blood drug concentrations within narrower range related to immediate release dosage forms. Hence, fluctuations in drug effects are reduced and concentration dependent adverse effects that are related with peak concentrations can be prohibited.
MARKETED PRODUCTS:

Table No. 5: Gastroretentive products available in the market

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Products</th>
<th>Technology</th>
<th>Manufactured by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium magnesium antacid</td>
<td>Topalkan</td>
<td>Floating liquid alginate</td>
<td>Pierre Fabre Medicament, France</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Valrelease</td>
<td>Floating capsule</td>
<td>Roche, UK</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Cytotec</td>
<td>Bilayer floating capsule</td>
<td>Pharmacia Limited, UK</td>
</tr>
<tr>
<td>Metformin HCl</td>
<td>Riomet OD</td>
<td>Effervescent floating system</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Zanocin OD</td>
<td>Effervescent floating system</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Cifran OD</td>
<td>Effervescent floating system</td>
<td>Ranbaxy, India</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Baclofen GRS</td>
<td>Coated multi-layer floating &amp; swelling system</td>
<td>Sun Pharma, India</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Tramadol LP</td>
<td>Minextab Floating®</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Cefaclor LP</td>
<td>Minextab Floating®</td>
<td>Galenix, France</td>
</tr>
<tr>
<td>Metformin HCL</td>
<td>Metformin HCL LP</td>
<td>Minextab Floating®</td>
<td>Galenix, France</td>
</tr>
</tbody>
</table>

CONCLUSION:

Based on the literature survey, it can be concluded that GRDDs offers various potential advantages for drugs with poor bioavailability. Drug absorption in the gastro intestinal tract is a highly variable process and prolonging gastric retention of the dosage form extends the time for drug absorption.

The control of gastro intestinal transit of orally administered dosage forms using GRDD systems can improve the bioavailability of drugs that exhibit site specific absorption. GRDFs also provide an additional advantage for drugs that are absorbed primarily in the upper segment of GIT, i.e., stomach, duodenum and jejunum.

Different approaches for GRDD are studied each having their own advantages and disadvantages. Due to unpredictability of human GIT development of efficient GRDDs is a real challenge to pharmaceutical technology as the drug delivery system must remain for a sufficient time in the stomach which is not compatible with normal physiology.

In the future it is can be easily assumed that GRDD systems will become more popular in terms of delivering drug to the systemic circulation with improving efficiency of various type of pharmacotherapy’s.

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