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A Review: Gastroretentive Drug Delivery System

Saritha Chukka, Srujana M, Shankaraiah Puligilla*
Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, A.P., India.

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ABSTRACT

Oral route of drug delivery has been the most conventional and accepted route of drug delivery. Recently oral controlled release drug delivery has been of great interest in pharmaceutical field to achieve improved therapeutic advantages. Gastroretentive drug delivery system is one such novel approach in which the delivery system retains in the stomach for a prolonged period and hence availability of the drug for its absorption is increased. In recent years, gastroretentive drug delivery has gained much importance for drugs acting locally in the proximal gastrointestinal tract.Various approaches such as floating and non-floating gastroretentive drug delivery systems which are further classified are cited in this review. This article gives an overview on advantages&disadvantages of gastroretentive drug delivery systems. This review also includes few recent trends and marketed formulations of gastroretentive drug delivery.

***Key Words**: Floating systems, Non-Floating systems, Recent trends.*

INTRODUCTION

Historically, oral route has been the most predominant route of drug delivery due to its ease of administration, low cost of therapy, patient compliance and flexibility in its formulation. Variable and too rapid gastrointestinal transit has been the major limitation of oral sustained drug delivery. Rapid gastrointestinal transit results in incomplete release of drug from the delivery device leading to diminished efficacy of the administered dose. For improved availability of administered dose, novel dosage forms having the ability to retain in the stomach for longer duration are being formulated. Gastroretentive dosage form is a type of novel drug delivery system which can remain in the stomach for prolonged period of time and thereby increases gastric residence time of drugs. Gastro-retention helps to improve bioavailability of drugs (*Nikita Dixit, 2011; Shweta Arora et al., 2005*).

Why Gastroretentive Drug Delivery?:

Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastroretentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated. It also has an advantage of minimising the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner. (*NikitaDixit, 2011; Pallavi Pal et al., 2012; Hirtz, 1985*).

Advantages: (*Debjit Bhowmik et al.,2009; Vyas, et al., 2006*)

- Used for local action in the stomach.
- In the treatment of peptic ulcer disease.
- Used for the delivery of drugs with narrow absorption window in the small intestine.
- Reduced dosing frequency.
- Improved bioavailability of the drug.
- Used for drugs which are unstable in intestinal fluids
- Used to sustain the delivery of drug
- Used for maintaining the systemic drug concentration within the therapeutic window.
- Site specific drug delivery is also possible

Disadvantages: (*Vyas, et al., 2006*)

- These require sufficiently high levels of stomach fluids, for the system to float and to work efficiently.
- Not suitable for drugs with stability or solubility problem in stomach.
- Drugs which undergo extensive first pass metabolism are not suitable candidates.
- Drugs with irritant effect also limit the applicability.

Requirements for the Gastroretentive Formulations:

- It must form a cohesive gel barrier to facilitate retention.
- It must maintain specific gravity lower than gastric contents
- It should release contents slowly to serve as a reservoir.

Selection of execipients is an important strategic decision for designing a dosage form with consistence and controlled residence in the stomach. Water soluble cellulose derivatives represent a typical class of polymers best suited for such purposes. It has been suggested that higher molecular weight polymers and slower rates of polymer hydration are usually associated with better floating behaviour (*Gerogiannis et al., 1993*).

Physiology of the Stomach:

The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, 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 esophagus 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. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1-3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. 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')

***Corresponding author:**
***Dr. P. Shankaraiah,** M.Pharm, Ph.D.*
Associate Professor,
Chaitanya College of pharmacy Education and Research,
Kishanpra, Hanamkonda, Warangal.506001, A.P., India.
**E-mail: drspuligilla@gmail.com*

Factors Affecting Gastric Retention: (*Nayak et al., 2010; Patel Geeta et al., 2007*)

Table1: showing drug candidates suitable for Gastroretentive Systems (*Ravi P Soni et al., 2007*)

S.No	Drug candidate	Examples
1	Drugs acting locally in the stomach Antacids and drugs for H. Pylori viz	Misoprostol
2	Drugs that are primarily absorbed in the stomach	Amoxicillin
3	Drugs that are poorly soluble at alkaline pH	Furosemide, Diazepam, Verapamil, etc.
4	Drugs with a narrow window of absorption	Cyclosporine, Methotrexate, Levodopa, etc.
5	Drugs which are absorbed rapidly from the GI tract	Metronidazole, tetracycline.
6	Drugs that degrade in the colon	Ranitidine, Metformin HCl.
7	Drugs that disturb normal colonic microbes	Antibiotics against Helicobacter pylori

1. Density: The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Therefore density of the dosage form should be less than the gastric contents (1.004gm/ml). A buoyant dosage form having a density of less than that of the gastric fluids floats. Since it is away from the pyloric sphincter, the dosage unit is retained in the stomach for a prolonged period.

2. Size and Shape: Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GIT retention 90 to 100 % retention at 24 hours compared with other shapes20 When liquid and digestible solids are present in the stomach, it contracts ~3 to 4 times per minute leading to the movement of the contents through partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.

3. Fed or Unfed State: The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the Migrating Myoelectric Complexes (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.

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

5. Caloric Content: GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

6. 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. Food intake and its nature Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms.

7. Gender: Mean ambulatory GRT in meals (3.4±0.4 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.

8. Age: Elderly people, especially those over 70 years have a significantly longer GRT.

9. Posture: GRT can vary between supine and upright ambulatory states of the patients. A comparison was made to study the affect of fed and non-fed stages on gastric emptying. For this study all subjects remaining in an upright position were given a light breakfast and another similar group was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach When subjects were kept in the supine position it was observed that the floating forms could only prolong their stay because of their size; otherwise the buoyancy remained no longer an advantage for gastric retention.

Approaches for Gastric Retention:

To improve the retention of an oral dosage form in the stomach various approaches have been developed, e.g. floating systems, swelling and expanding systems, bioadhesive systems, altered density systems and other delayed gastric emptying devices.Floating Drug Delivery Systems (FDDS) or Hydrodynamically Balanced systems (HBS) have a bulk density lower than gastric fluids and hence remain floating in the stomach for a prolonged period of time. The drug is slowly released from the floating system at a desired rate without fluctuations in plasma drug concentration thus leading to an increase in the gastric residence time (GRT).After complete release of drug from the delivery system, the residual is expelled from the stomach. To localize delivery device within a cavity of body, bioadhesive systems are usually formulated.

In these systems, bioadhesion is achieved by using bioadhesive polymers which adhere to the epithelial surface of gastrointestinal tract. The formation of hydrogen and electrostatic bonding at the mucus polymer interface leads to bioadhesion. Swellable systems are a type of gastro-retentive dosage forms which swell in the stomach to an extent that prevents its exit through the pyloric sphincter resulting in the retention of swellable system in the stomach for a prolonged period of time. Altered density gastro retentive dosage forms includes systems that have density either greater or lower than the stomach contents leading to an increase in GRT and hence drug release for a prolonged time period (*Vyas et al., 2006*).

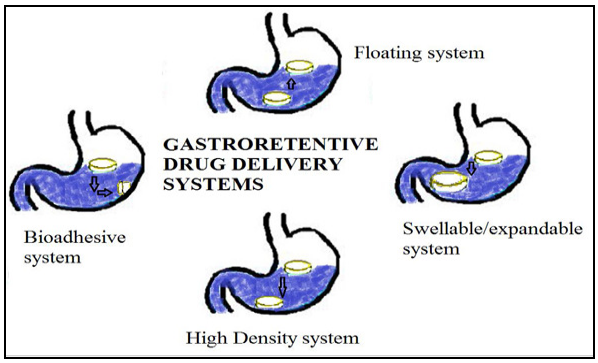

Fig. 1: Figure showing various approaches for gastroretentive drug delivery system

Different approaches of gastro retentive drug delivery systems:

- Floating systems Non-Floating systems
- Effervescent systems
- Non-effervescent systems
- Swelling systems
- Expandable systems
- High density systems
- Bioadhesive systems
- Volatile liquid containing systems
- Gas generating systems

- Hydrodynamically balanced systems
- Microballoons/ Hollow microspheres
- Matrix Tablets
- Alginate Beads
- Layered tablets
- Bilayer tablets
- Single layer tablets
- Floating systems with ion exchange resins
- Floating pills
- Floating capsules
- Intra gastric osmotically controlled drug delivery systems
- Inflatable gastrointestinal drug delivery systems
- Intra gastric floating gastrointestinal drug delivery systems

Floating Systems: (*Vyas et al., 2006*)

It is a low density approach which has a bulk density lower than gastric fluids and hence remains buoyant in the stomach, releasing the drug slowly without affecting the gastric emptying rate for a prolonged period of time. After the drug is released from the stomach, the delivery system is expelled. Based on the buoyancy mechanism, floating systems are classified as follows

I. Effervescent systems
II. Non-Effervescent systems

I. Effervescent systems:

The main mechanism involved in this system is the production of carbon-dioxide gas due to reaction between sodium bicarbonate, citric acid & tartaric acid. The gas produced results in the reduction of density of the system thereby making it to float on the gastric fluids. These systems are further classified as below.

i. Volatile liquid containing systems: These are further categorised as

a. 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 **Fig. 2**

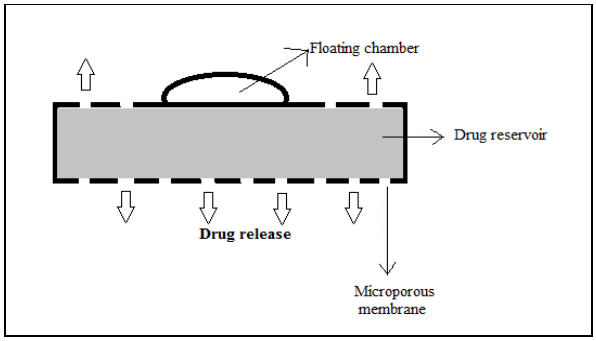

Fig. 2: Figure showing intragastric floating gastrointestinal drug delivery system

b. Inflatable gastrointestinal delivery system: These systems possess inflatable chamber containing liquid ether which gasifies at body temperature to inflate 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 **Fig. 3**.

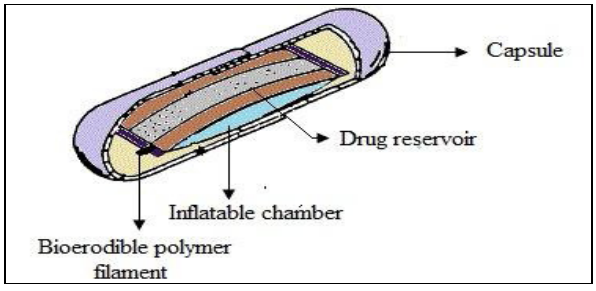

Fig. 3: Figure showing inflatable gastrointestinal delivery system

c. 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. It is shown in **Fig. 4**.

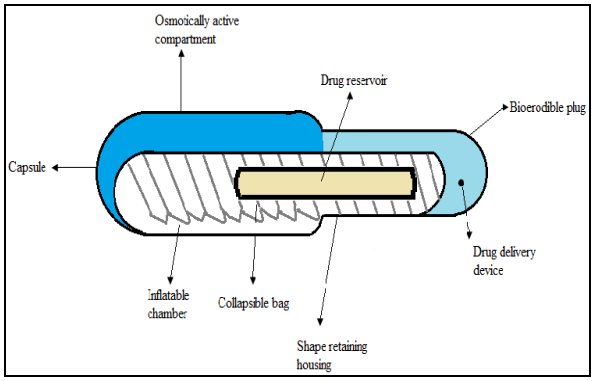

Fig. 4: Figure showing Intragastric-osmotically controlled drug delivery system

ii. Matrix tablets: It may be formulated as a single layer matrix tablet by incorporating bicarbonates in matrix forming hydocolloid gelling agent or a bilayer matrix tablet with gas generating matrix as one layer and drug being the second layer. It can also be formulated as triple layer matrix tablet with gas generating matrix as one layer and 2 drug layers.

iii. Gas generating systems: These systems utilise effervescent compounds like sodium bicarbonate, citric acid and tartaric acid. It is further divided as follows.

d. Floating capsules: These are prepared by formulating mixture of sodium bicarbonate and sodium alginate. On exposure to acidic environment, carbon dioxide gas is generated which is trapped in the hydrating gel network and makes the system to float.

e. 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 effervescent agents. The system swells due to swellable membrane and then sinks. Due to presence of effervescent agents, CO2 is released and the system floats.

f. 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 carbondioxide to release and the system to float (*Vinod and Santhosh, 2010; Yeole et al., 2005*).

II. Non- Effervescent systems:

These are a type of floating gastroretentive drug delivery systems in which gel forming hydrocolloids, polysaccharides and matrix forming polymers like polycarbonate, polystyrene, Polymethacrylate etc. are used. These are further classified as follows

i. Hydrodynamically balanced systems: This system contain drug with gel forming hydrocolloids formulated into a single unit dosage form. Upon contact with gastric fluids, the hydrocolloids swell to form a gel barrier which facilitates the system to remain buoyant in the stomach.

ii. Microballoons / hollow microspheres: 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. The steps involved are summarized in **Fig. 5**. (*Debjit Bhowmik et al., 2009*)

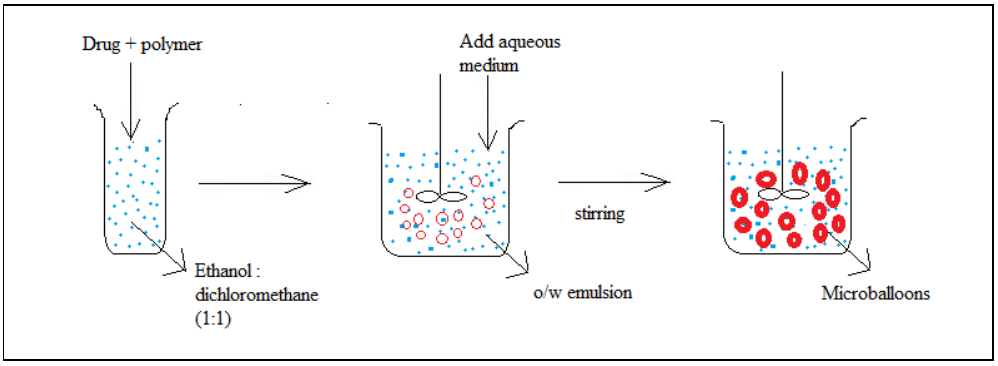

Fig. 5: Flow chart showing steps involved in preparation of microballoons

i. Alginate beads:

Talukdar and Fassihideveloped multiple-unit floating system based on cross-linked beads. These are formulated using calcium and low methoxylated pectin or calcium low methoxylated pectin and sodium alginate. In this type, sodium alginate solution is added to aqueous solution of calcium chloride which causes precipitation of calcium alginate (beads). These beads are then separated and dried by air convection and freeze dried. This results in the formation of aporous system which remains buoyant in the stomach (*Talukdar and Fassihi, 2004; Whiteland et al., 1996; Garg and Gupta, 2008*).

ii. 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 (*Debjit Bhowmik et al., 2009*). It is shown in **Fig. 6**.

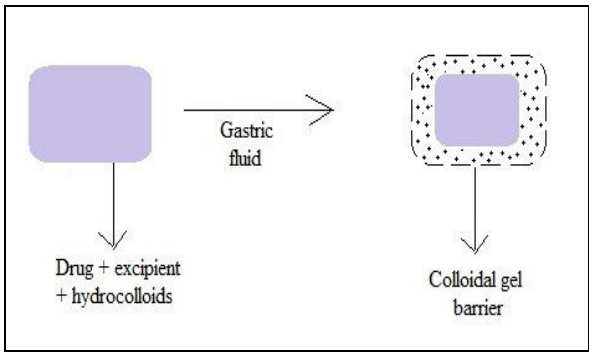

Fig. 6: Figure showing formation of colloidal gel barrier

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 containing drug and hydrocolloids which remains in the stomach for a prolonged period (*Debjit Bhowmik et al., 2009*). It is shown in **Fig. 7**.

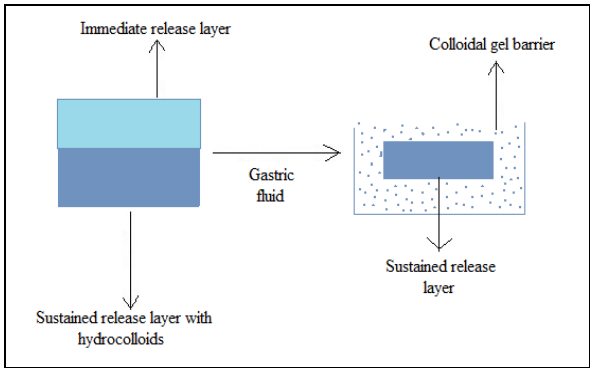

Fig. 7: Figure showing double layered floating tablets

Non-Floating Systems:

These are another class of 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.

I. Bioadhesive systems:

These types of systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release. These systems are formulated using bioadhesive polymers (*Gupta and Robinson, 1992; Park and Robinson, 1984*). It is shown in **Fig. 8**.

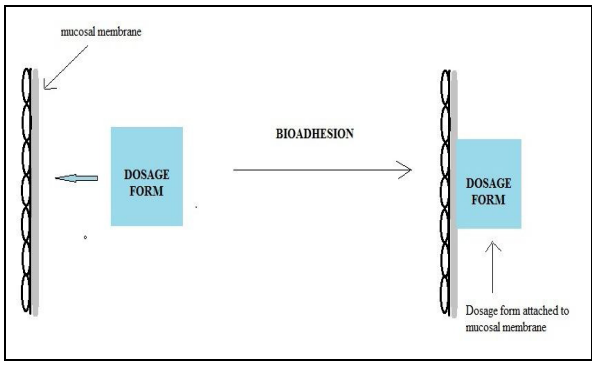

Fig. 8: Figure showing mechanism of bioadhesion

I. Swelling systems:

These are a type of non-floating gastroretentive drug delivery system which when enters stomach swells (due to presence of swellable polymers) to an extent that cannot pass through the pyloric sphincter leading to its retention in the stomach (*Ravi P Soni et al., 2011*). It is shown in **Fig. 9**.

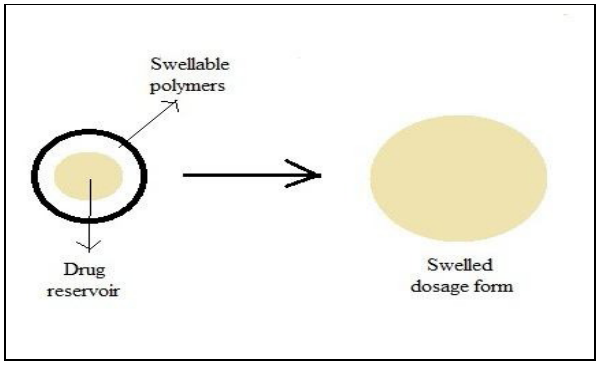

Fig. 9: Figure showing swelling of the dosage form

II. High density systems:

These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach. These are formulated by coating drug on heavy inert materials like zinc oxide, titanium dioxide, iron powder, etc. It is shown in **Fig. 10**.

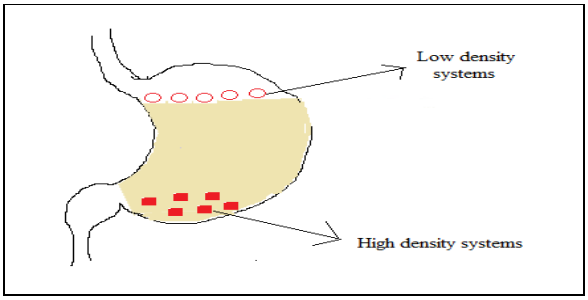

Fig. 10: Figure showing the high density systems which are at the bottom of the stomach and low density systems which are floating.

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 formin 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 (*Angadi Sudha et al., 2012*).

Table No. 2: Commonly used drug in formulation of gastro retentive dosages forms (*Arrora et al., 2005; Vyas et al., 2006*)**.**

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbidmononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil.
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders Several basic drugs	Films Cinnerzine

Table No. 3: Gastroretentive products available in the market (*Vyas et al., 2006; Chawla et al., 2004*).

Brand Name	Active Ingredient(s)
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum -magnesium antacid
Almagate FlatCoat ®	Aluminum -magnesium antacid
Liquid Gavison ®	Aluminium hydroxide,
Conviron	Ferrous sulphate
Cytotec®	Misoprostal

Evaluation of powder blend: (*Mathur et al., 2010*)

Angle of repose: Lower the angle of repose, better the flow properties. The angle of repose may be calculated by measuring the height (h) of the pile and the radius of the base(r) with ruler.

Tan θ = h/r…… (1)
Bulk density:
Bulk Density = W/BV ….. (2)

Where, W = Weight of powder,
BV = Bulk Volume

Percentage porosity: Porosity provides information about hardness, disintegration, total porosity etc.

% porosity = v.v / B.V * 100 ……. (3)
% porosity = (B.V. – T.V. / T.D.) * 100 …….. (4)

Where,V.V. – void volume, B.V.- bulk volume, T.V.- true volume, T.D.- true density.

Evaluation of granules: (*Subrahmanyam CVS, 2002*)

Flow Properties of Granules: The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio

HR= ρt/ρb …..(5)
IC = (ρt - ρb)/ρt …..(6)

Where ρb -Bulk density, ρt -tapped density, HR -Hausner ratio and IC -Carr index.

Evaluation of floating tablets: (*Sharma and Pawar, 2006; Shah et al., 2009; Shinde, 2008*)

Measurement of buoyancy capabilities of the FDDS: The experiment is carried out in two different media, de-ionized water and simulated meal. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to de-ionized water.

In Vitro floating and dissolution behaviour: A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float.

Weight variation: The USP provides the weight variation test by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit, and if no tablet differs by more than 2 times the percentage limit.

Hardness & Friability: Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable.

Particle size analysis, surface characterization (for floating microspheres and beads):
The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

X-Ray: It helps to locate dosage form in the gastrointestinal tract (GIT), by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays.

Pharmacokinetic studies: Sawicki studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg).

Evaluation of bioadhesive system: The bioadhesive strength of a polymer can be determined by measuring the force required to separate the polymer specimen sandwiched between the layers of either an artificial (e.g., cellophane) or biological (e.g., rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer **(***Koner et al., 2007*).

Evaluation of swelling systems: (*Vinod et al., 2010*)

Weight gain and water uptake (WU): The study is done by immersing the dosage form in simulated gastric fluid at 370C and determining these factors at regular intervals. The dimensional changes can be measured in terms of the increase in tablet diameter and/or thickness over time. WU is measured in terms of percent weight gain, as given by the equation 7

WU = ([W.sub.t] - [W.sub.0]) x 100/[W.sub.0] …….(7)

Where [W.sub.t] and [W.sub.0] are the weights of the dosage form at time t and initially

Gastroretention:

The inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. The use of X-rays involves exposing a patient to an X-ray beam, thus permitting the visualization of the GI transit of the dosage form.

Dissolution/drug release: The major requirement for the dissolution test is to allow a dosage form to sink to the bottom of the vessel before the rotation of the paddle.

CONCLUSION

This article provides information regarding the gastro retentive drug delivery systems and its evaluation process. The foregoing shows that gastro retentive drug delivery systems have great potentials, for formulating both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer is required. Inspite of number of difficulties to be worked out to achieve prolonged gastric retention, many pharmaceutical companies are focussing towards commercialization of this technique.

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