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A REVIEW ON GASTRO-RETENTIVE FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT

In the recent years, the oral route has been used widely for the delivery of therapeutic medication due to the convenient cost of the therapy and ease of administration. This has led to high levels of patient compliance. More than half of the drug delivery systems which is available in the market are oral drug delivery systems. Gastro-retentive drug delivery systems or Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents. Moreover, these drug delivery systems tend to keep afloat in the stomach without disturbing the gastric emptying rate for a long period of time. The drug is released at a steady rate from the system while the latter is floating on the gastric juices. The residual system is emptied from the stomach immediately after the drug is released. There is a better control of the fluctuations (irregular rising and falling in number) in plasma drug concentration due to an increased Gastric Residence Time (GRT). Furthermore, a minimal gastric content is required to allow the proper achievement of the buoyancy retention along with a minimal level of the floating force (F) so that the dosage form is kept buoyant/floating on the surface of the meal. There have been several buoyant systems that have been developed based on granules, powders, tablets, capsules, laminated films and hollow microspheres.

KEYWORDS: Gastro-retentive, Floating systems, Hydrodynamically, Gastric Residence Time, Stomach.

1.1. BASIC GIT PHYSIOLOGY

The GIT (gastrointestinal tract) is a tube which is approximately nine meter long that runs through the centre of the body from the mouth to the anus. This includes 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 GIT (Gastro-Intestinal tract) has the same general structure throughout most of its length from the oesophagus to the anus with some local changes for each region.[1] The stomach is located in the left upper part of the abdominal cavity immediately below the diaphragm. The size varies based on the amount of distention: up to (1400-1500) ml following a meal. After food has been emptied, a 'collapsed' state is obtained with a resting volume of only 30–50 ml.[2,3]

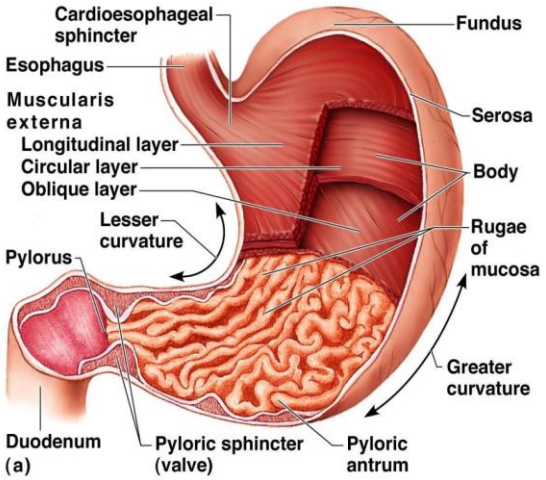


Fig. 1.1: Longitudinal Section of Stomach.

Anatomically the stomach is divided into 3 regions.

1. Fundus
2. Body
3. Antrum (pylorus)

The proximal part made of fundus and body acts as a reservoir for undigested material whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions.[4] Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state, an interdigestive series of electrical events take place, which cycles both though stomach and intestine every 2 to 3 h. This is called the

interdigestive myoelectric cycle or migrating myoelectric cycle (MMC) which is further divided into following 4 phases.[5]

1. **Phase I (Basal phase)** lasts from 30-60 minutes with rare contractions.
2. **Phase II (Preburst phase)** lasts for 20-40 minutes with intermittent action potential and contractions. As the phase progresses, the intensity and frequency also increase gradually.
3. **Phase III (Burst phase)** lasts for 10-20 minutes. It includes intense and regular contractions for short period.
4. **Phase IV** lasts for 0-5 minutes and occurs between phases III and I of 2 consecutive cycles.

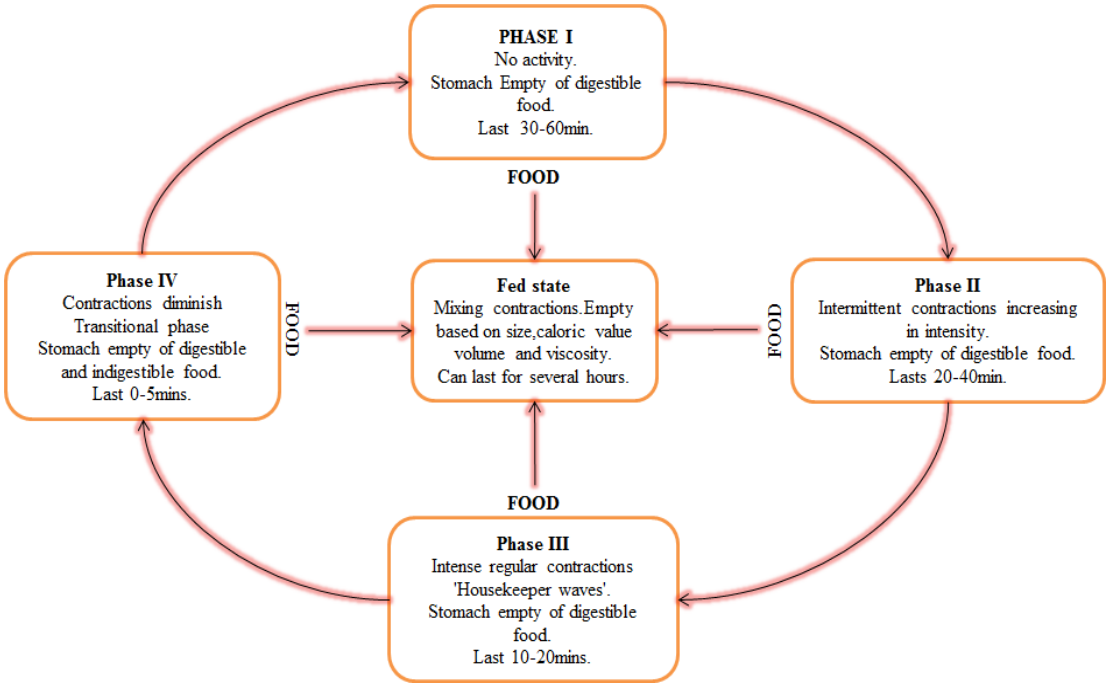


Fig. 1.2: Phases involved in gastric emptying.

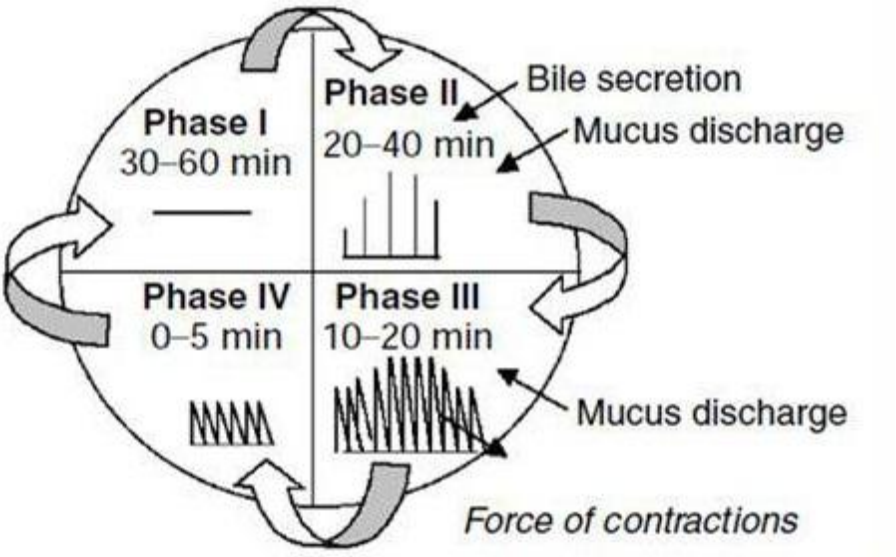


Fig. 1.3: Gastrointestinal motility pattern.

When a mixed meal is ingested, the pattern of contractions changes from fasting state to fed state. It is known as the digestive motility pattern and constitutes of continuous contractions as in phase II of a fasted state. These contractions make food size to reduce (less than 1 mm), which are pushed toward the pylorus in a suspension form.[6]

1.2. FACTORS AFFECTING GASTRIC RESIDENCE TIME (GRT) OF DRUG

Various approaches such as mucoadhesive, swelling high density and floating system have been developed to increase the GRT of the dosages forms. However, most of these proposals are influenced by various factors that affect their ability as a gastro-retentive system.[7]

1. *Density* – Gastric Residence Time (GRT) is a part of dosage form buoyancy which is dependent on the density.
2. *Size* – Size having diameter 7.5 mm has an increased GRT when compared with the diameter of 9.9 mm.
3. *Shape of dosage form* – Ring and Tetrahedron shaped-devices have better GRT of (90-100) % compared with other shapes.[8]
4. *Single or multiple unit formulations* – Multiple unit formulations show obvious release profile.[9]
5. *Fed/Unfed state* – During the fasting conditions, the GI motility is affected by migrating myoelectric complex (MMC) that occurs every 1.5-2 h. In the fed state, myoelectric complex (MMC) takes time and GRT is considerably longer.[10]
6. *Nature of meal* – Feeding of indigestible polymers or fatty acid salts can decrease the gastric emptying rate and prolong drug release.
7. *Caloric content* – Gastric Residence Time (GRT) can be increased by (4-10) h with a meal rich in proteins and fats.
8. *Frequency of feed* – The Gastric Residence Time (GRT) can increase by over 6.5 hours when successive meals are given compared with a single meal due to the low frequency of myoelectric complex (MMC).
9. *Gender* – Gastric Residence Time (GRT) for males is around (3.4±0.6 h) when compared to Female persons which are around (4.6±1.2 h). Elderly people have a longer GRT.[11]
10. *Posture* – GRT varies between supine and upright ambulatory states of the patient.
11. *Biological factors* – Diabetes and Crohn's disease, etc.

1.3. SUITABLE DRUG CANDIDATE FOR GASTRO-RETENTIVE DRUG DELIVERY SYSTEM(GRDDS)

In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are characterised by better absorption properties at the upper parts of the GIT.[12]

1. Acting locally in the stomach.
2. Primarily absorbed in the stomach.
3. Poorly soluble at an alkaline pH.
4. Absorbed rapidly from the GI tract.
5. Degrade in the colon.
6. It should be absorbed primarily in the duodenum and upper jejunum segments.
   e.g. Calcium is mainly absorbed in the duodenum.
7. Drugs which have a short half-life and require frequent dosing. e.g. Cimetidine.
8. Drugs which have a short half-life and extensive first-pass metabolism.
   e.g. Nitroglycerine.
9. Which have poor solubility in intestinal media and poor bioavailability.
10. Drugs that are required for local action in the stomach.
    e.g. Antacids and enzyme preparation.
11. Drugs that cause gastric irritation and produce gastric ulcers. e.g. Aspirin.[13]

1.4. ADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

1. Minimised adverse activity in the colon.
2. Reduced fluctuations in drug concentration.
3. Targeted therapy for local ailments in the upper GIT**.**
4. Reducing the mucosal irritation.
5. Enhanced Bioavailability.
6. Site-specific drug delivery.
7. Improved drug absorption.
8. Sustained drug delivery/reduced frequency of dosing.
9. Useful in treatment of gastric disorders such as gastroesophageal reflux and peptic ulcers.[14]

1.5. DISADVANTAGES OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

Low-density dosage forms are unable to retain these systems in stomach unless water is present.

1. The patient must remain in an upright position during the gastric residence time; in a supine position, the pylorus is located above the stomach body. This will allow the accelerated emptying of floating material.[15]
2. Floating systems require the presence of food to delay their gastric emptying.
3. Drugs that have solubility or stability problem in the gastric fluid are not formulated. e.g. Phenytoin.
4. They do not always release the drug at the intended site.
5. Floating systems are not feasible for those drugs to have instability in the gastric acid environment. e.g. Erythromycin.[16]

1.6. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

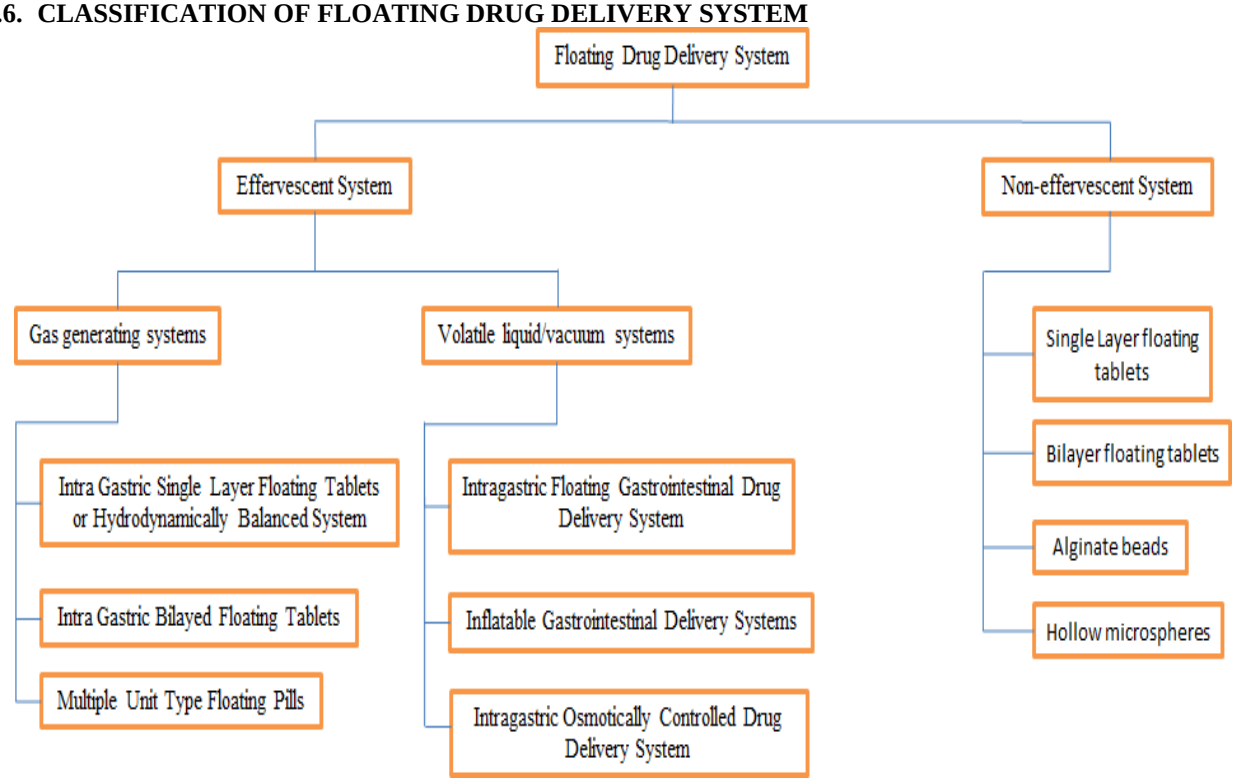


Fig. 1.4: Classification of Gastro-retentive Drug Delivery System.

Formula for Gastro-retentive drug delivery systems

$F = F_b - F_g = (D_F - D_S)gV$ where,

F= total vertical force

F_g=force of gravity

D_S = object density

V = volume

F_b=buoyancy force

D_F = fluid density

g = acceleration due to gravity

1.7. GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

1.7.1. Effervescent System

Effervescent systems include the usage of gas generating agents, carbonates (example: Sodium bicarbonate) and another organic acid (examples: tartaric acid and citric acid) present in the formulation.[17] This produces carbon dioxide (CO_2) gas. Thus, it causes the reduction in the density of the system and makes it float on the gastric fluid.[18]

These effervescent systems further classified into two types.

i. **Gas generating systems**
ii. **Volatile liquid/vacuum systems**

i. Gas generating systems

a) *Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS)*

They are formulated by mixing the carbon dioxide generating agents and the drug within the matrix tablet. The bulk density is lower than the gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period.[19] The drug is released slowly at the desired rate from the floating system and after the complete release, the residual system is expelled from the stomach.[20]

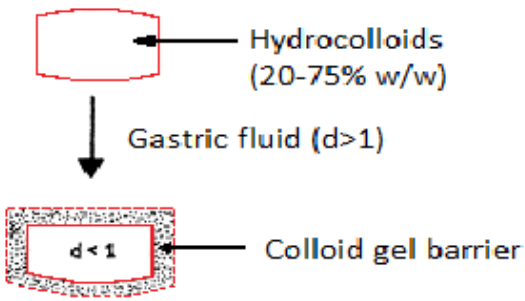


Fig. 1.5: Intragastric floating tablet

b) *Intra Gastric Bilayed Floating Tablets*

These are also compressed tablet and containing two layers

1. Immediate release layer
2. Sustained release layer

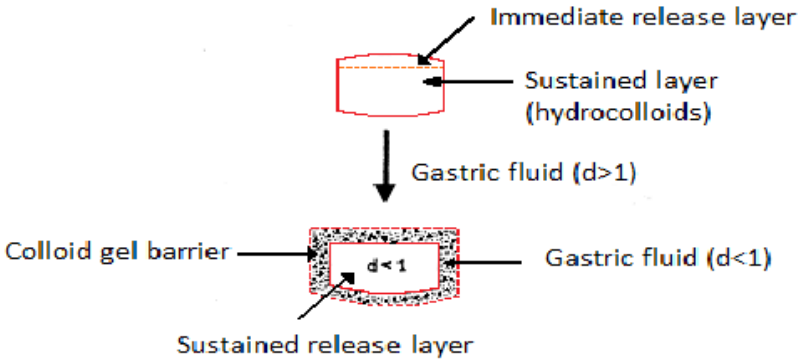


Fig. 1.6: Intragastric floating bilayer tablet.

c) *Multiple Unit Type Floating Pill*

These are sustained release pills known as 'seeds'. It is surrounded by double layers wherein the inner layer consists of effervescent agents while the outer layer consists of the swellable membrane layer. After the emersion of the system dissolution medium at body temperature, it sinks at once. This forms swollen pills (balloon-type), which float as they have a lower density. This lower density is due to generation and entrapment of carbon dioxide within the systems.[21]

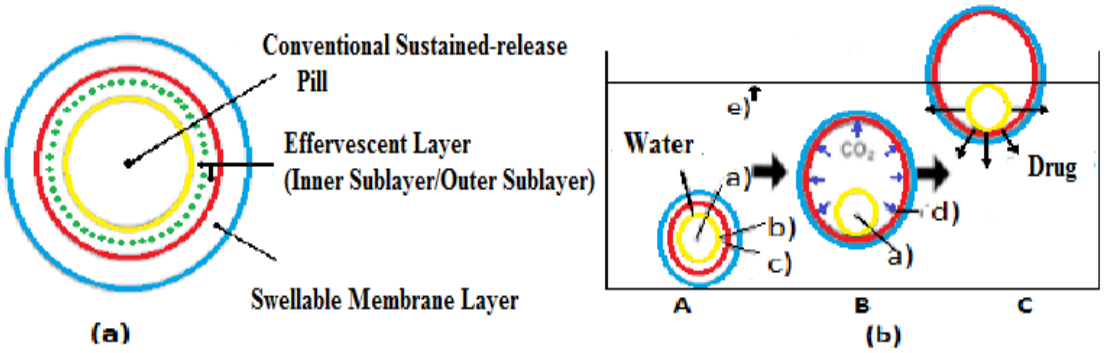


Fig. 1.7: (a) Multiple-unit oral floating dosage system.

(b) Stages of floating mechanism

(a) A multi-unit oral floating dosage system.
(b) Stages of floating mechanism.
(A) Penetration of water; (B) Generation of CO_2 and floating; (C) Dissolution of drug.
Key: (a) Conventional SR pills; (b) Effervescent Layer; (c) Swellable Layer; (d) Expanded Swellable Membrane Layer; (e) surface of water in the beaker (37°C).

ii. Volatile liquid / Vacuum containing systems

a) *Intragastric Floating Gastrointestinal Drug Delivery System*

These systems are buoyant in the stomach because of flotation chamber which may be a vacuum (filled with air or an inert gas) while the drug reservoir is encapsulated inside a microporous compartment.[22]

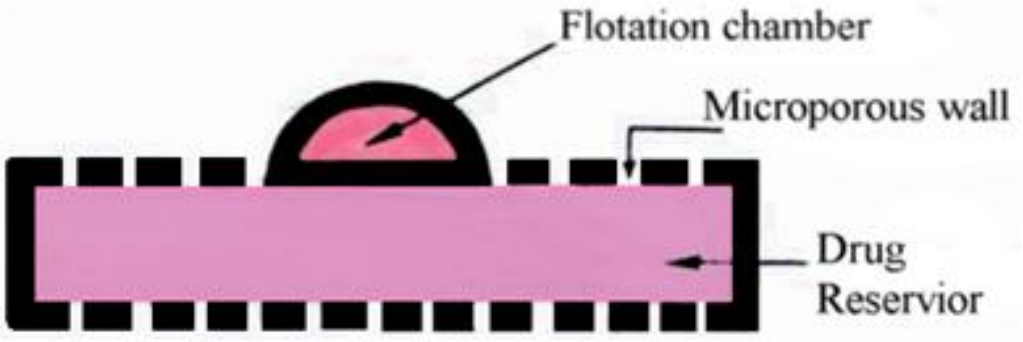


Fig. 1.8: Intragastric floating drug delivery device.

b) ***Inflatable Gastrointestinal Delivery Systems***

These delivery systems are made up of an inflatable chamber which contains liquid ether that becomes a gas at body temperature causing the inflation of the chamber in the stomach. These systems are formulated by incorporating the inflatable chamber with a drug reservoir (drug impregnated polymeric matrix), then by its encapsulation in a gelatin capsule.[23] After oral administration, the capsule dissolves to release the drug reservoir along with the inflatable chamber. The inflatable chamber inflates automatically and retains the drug reservoir into the gastric juices.[24]

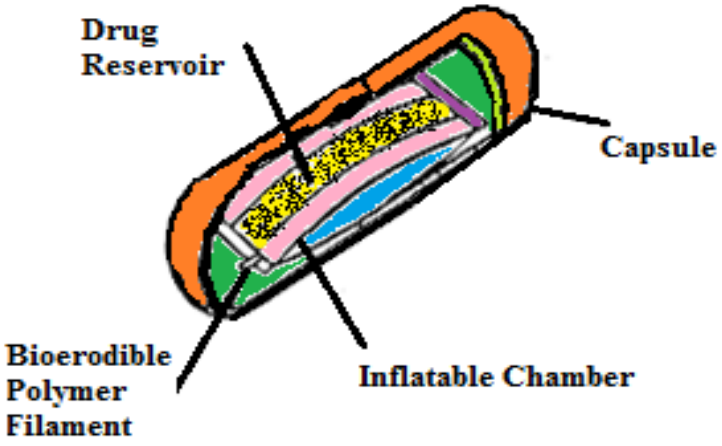


Fig. 1.9: Gastro-inflatable drug delivery device.

c) ***Intragastric Osmotically Controlled Drug Delivery System***

It consists of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. The capsule disintegrates very fast in the stomach. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid.[25] This liquid becomes a gas at body temperature to make the bag inflate. The system consists of two components; a drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is surrounded by a pressure responsive collapsible bag. The latter is impermeable to vapour and liquid.[26] In the stomach, the water in the GI fluid is continuously absorbed through the semi-permeable membrane into the osmotically active compartment to dissolve the osmotically salt. This creates an osmotic pressure which acts on the collapsible bag and in turn forces the bag reservoir compartment to decrease its volume. This leads to the activation of the drug through the delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.[27]

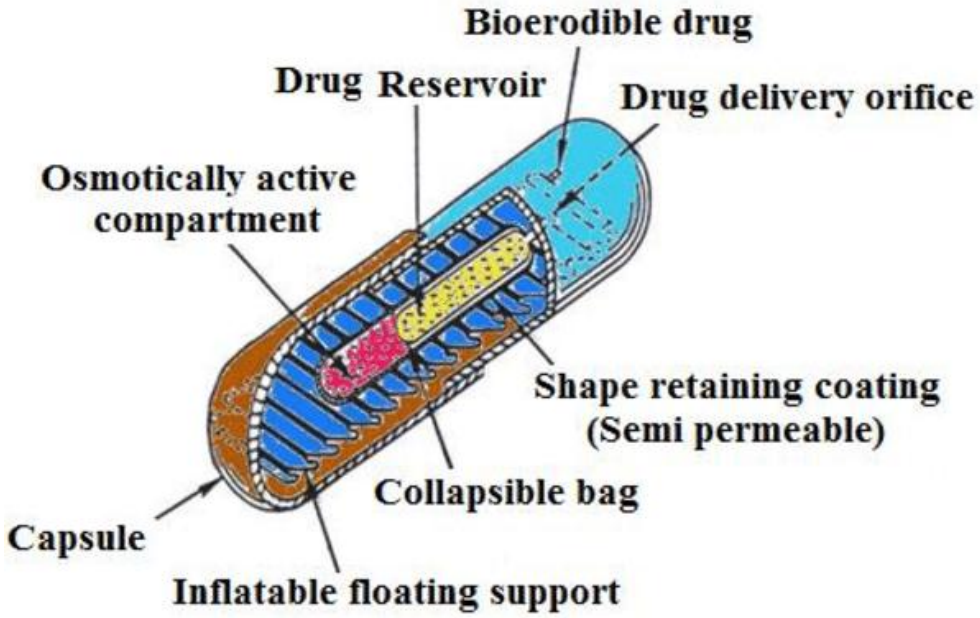


Fig. 1.10: Intragastric osmotic controlled drug delivery system.

1.7.2. Non-Effervescent Systems

It is based on the mechanism of polymer swelling or bioadhesion to mucosal layer in Gastro-Intestinal Tract. The most widely used excipients in non-effervescent floating systems are gel-forming or highly swellable cellulose type.[28] The various types of these systems are as follows.

a) *Single layer floating tablets:*

These are fabricated by the mixing of drug with a gel-forming hydrocolloid. This leads to its swelling when in contact with gastric fluid. The air trapped by the swollen polymer confers buoyancy to this dosage forms.[29]

b) *Bilayer floating tablets*

It consists of two layers where one is the immediate release layer which releases the drug immediately from the system while the other layer is a sustained release layer. The latter absorbs gastric fluid which forms an impermeable colloidal gel barrier on its surface, thereby it remains buoyant in the stomach.[30]

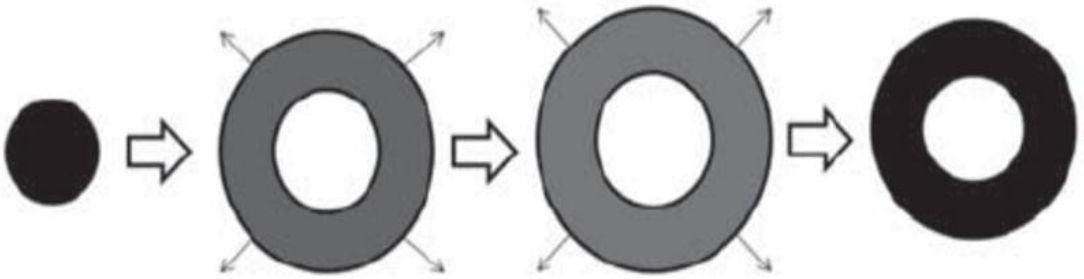
c) *Alginate beads*

Spherical beads can be prepared by dropping sodium alginate solution into a cold solution of aqueous calcium chloride. This leads to the precipitation of calcium alginate causing the formation of the porous system which can maintain a floating force for over 12 hours when compared with solid beads which gave a short residence time of 1 hour. These floating beads give a prolonged residence time of more than 5.5 hours.[31]

Fig. 1.11: Alginate Beads.

d) *Hollow microspheres*

Hollow microspheres are also known as microballoons. The drug is incorporated in the outer polymer shells. Usually, novel emulsion solvent diffusion method is used. The ethanol: dichloromethane solution of drug and enteric acrylic polymer are poured into an agitated aqueous solution of PVA which is thermally controlled at 400°C. The Hollow microspheres (microballoons) are kept in the floating condition continuously over the surface of acidic dissolution media containing a surfactant for more than 12 hours *in vitro*.[32,33]



O/W Emulsion **Rapid Diffusion** **Slow Diffusion** **Hollow Balloon**

Fig. 1.12: Hollow microspheres.

1.8. APPROACHES TO DESIGN FLOATING DOSAGE FORMS

There are several approaches used to increase the gastric retention of drugs.

1.8.1. High-Density Systems

These types of systems have a density around 3g/cm^3. They are held in the rugae of the stomach and they have the capacity to withstand its peristaltic movements.[34]

Examples of diluents used for the manufacture such high-density formulations are

i. Barium sulphate (density= 4.9)
ii. Zinc oxide
iii. Titanium oxide
iv. Iron powder

1.8.2. Swelling and Expanding Systems

Swelling and Expanding Systems are also known as "Plug type system".[35] The name of "Plug type system" has been coined since they show the tendency to remain logged in the pyloric sphincters.[36] The polymer imbibes water and swells when they come in contact with the gastric fluid.

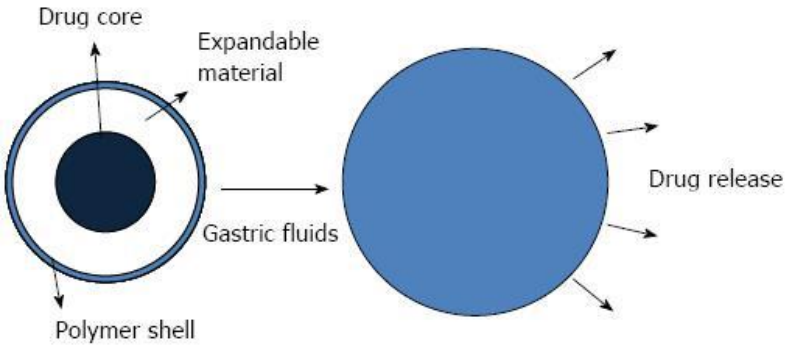


Fig. 1.13: Swelling and Expanding Systems.

1.8.3. Incorporation of Delaying Excipients

This is another delayed gastric emptying approach of interest which consists feeding of digestible polymers or fatty acid salts. This leads to changes in the motility pattern of the stomach to a fed stage thereby reducing the gastric emptying rate.[37]

Examples of delaying excipients: triethanolamine myristate.

1.8.4. Modified Systems:

These systems extend the GRT depending on size, shape and flexural modules of drug delivery device.[38]

Examples: Silastic elastomers or extruded from polyethylene blends.

1.8.5. Mucoadhesive & Bioadhesive Systems

These systems are delivery systems which are used to restrict the delivery device to a particular place within the lumen, thus enhancing the drug absorption.[39]

Examples: Gliadin, Polycarbophil, chitosan, carbopol, CMC, lectins.

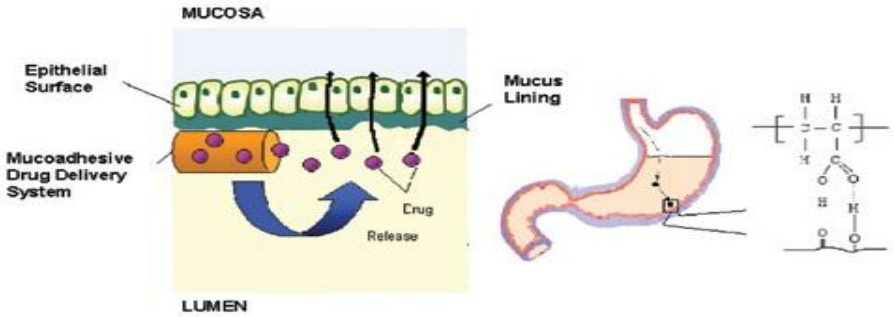


Fig. 1.14: Mucoadhesive & Bioadhesive Systems.

1.8.6. Floating Systems

These drug delivery systems remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time as they have a bulk density less than gastric fluids.[40,41] This can be achieved by incorporating the floating chamber with inert gas, vacuum or air.[42]

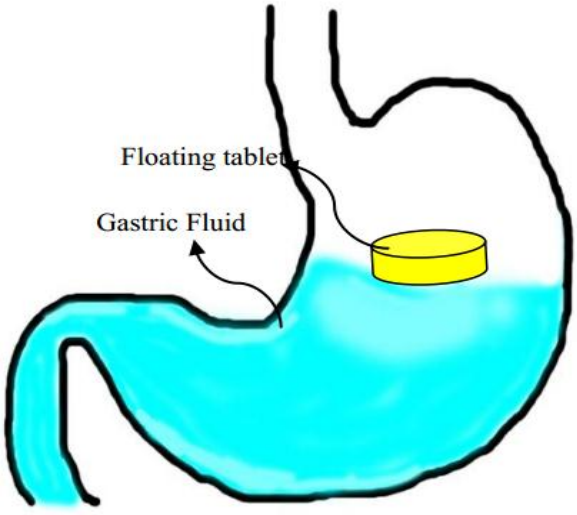


Fig. 1.15: Floating Systems.

1.9. DRUG RELEASE MECHANISM OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM

Swelling polymers that are generally employed for the purpose are hydrophilic in nature.[43] The mechanism of release of the drug from the hydrophilic matrices has been reviewed. When swellable hydrophilic dosage forms come in contact with aqueous medium, various events that take place are:

- Partial hydration of the polymer followed by the dissolution of the drug at the surface, resulting in an immediate release.[44]
- Penetration of the solvent molecules into free spaces present on the surface between macromolecular chains.[45]
- If the thermodynamic compatibility of the dissolution medium with the polymer is favourable, the glass transition temperature of the polymer is lowered below the room temperature leading to chain relaxation of the polymer thus resulting in swelling and formation of a gel.[46]
- Water continuously penetrates the matrix, the gel expands and dissolution drug through the gel layer takes place.[47]
- Simultaneously attrition/erosion of the outer most layer and release of insoluble particles occurs.[48]
- The tailing-off period starts when the water reaches the centre of the system and the concentration of the drug falls below the solubility value. The final stage is characterised by a reduction in the release rate.[49]

Therefore, the release of an active principle by a matrix system is produced by two simultaneous mechanisms.[50]

i. Erosion/attrition of the outermost layer.
ii. Dissolution of the active ingredient in the liquid medium followed by diffusion though the gel barrier when formed.

1.10. MARKETED PREPARATIONS OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Table 1.1: Marketed preparations of gastro-retentive drug delivery systems.

S/N	PRODUCT	ACTIVE INGREDIENT	REMARKS
1	Glumetza GRTM	Metformin HCl	Metformin HCl Extended-Release Tablet
2	Cytotec	Misoprostol (100µg/200µg)	Bilayer Floating Capsule
3	Conviron	Ferrous Sulfate	Colloidal Gel Forming FDDS
4	Cifran OD	Ciprofloxacin 1g	Gas Generating Floating Form
5	Valrelease	Diazepam (15mg)	Floating Capsule
6	Topalkan	Aluminium Hydroxide Antacid	Floating Liquid Alginate Preparation
7	Almagate Floatcoat	Antacid	Floating Dosage Form
8	Madopar	Levodopa (100mg) and Sodium Bicarbonate	Floating, CR Capsule
9	Liquid Gaviscon	Alginic Acid and Sodium Bicarbonate	Effervescent Floating Liquid Alginate Preparation

1.11. PATENTS FOR SOME GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

Table 1.2: Patents for some gastro-retentive drug delivery systems.

US PATENT No.	PATENT TITLE
6290989	Expandable gastro-retentive therapeutic system with controlled active substance release in the gastrointestinal tract
6207197	Gastro retentive controlled release microspheres for improved drug delivery
5972389	Gastric-retentive, oral drug dosage forms for the controlled-release of sparingly soluble drugs and insoluble matter
5443843	Gastric retention system for controlled drug release
5232704	Sustained release, bilayer buoyant dosage form
4814179	Floating sustained release therapeutic compositions
4767627	Drug delivery device which can be retained in the stomach for a controlled period of time
4167558	Novel sustained release tablet formulations
4140755	Sustained release tablet formulations
4126672	Sustained release pharmaceutical capsules
20080220060	Gastro retentive formulations and manufacturing process thereof

1.12. DRUGS USED IN THE FORMULATIONS OF STOMACH SPECIFIC FLOATING DOSAGE FORMS

Table 1.3: Drugs used in the formulations of stomach-specific floating dosage forms.

S/N	DOSAGE FORMS	DRUGS
1.	Floating microspheres	Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast
2.	Floating granules	Diclofenac sodium, Indomethacin, and Prednisolone
3.	Films	Cinnarizine, Albendazole
4.	Floating tablets and Pills	Acetaminophen, Acetylsalicylic acid, Ampicillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate, Para-aminobenzoic acid, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxifylline and Diltiazem HCl
5.	Floating Capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol

CONCLUSION

In this review, the various types of gastro-retentive drug delivery systems have been discussed along with the different phases involved, drug release mechanisms and their marketed products. Several approaches like floating, bio-adhesion, effervescence, sinking, magnetic, swelling, etc. have been proposed over the years. It has been observed that the major trend formulation-wise has been shifted toward the use of swelling polymer matrix together with effervescence in the design of floating delivery systems. In the market, it is emerging slowly as an important novel drug delivery due to many inherent challenges associated with it in spite of the numerous potential benefits offered by this delivery system. Without any doubt, GRDDS will become a popular drug delivery system in the near future due to its enhanced effectiveness. However, it's *in vitro* and *in vivo* studies must be carried out efficiently because of the complexity of pharmacokinetic and pharmacodynamics parameters.

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