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REVIEW ARTICLE

Floating gastro retentive systems: a potential emergence to oral drug delivery system

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Abstract:

In recent years scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices. In this review, the current technological developments of FDDS including patented delivery systems and marketed products, and their advantages and future potential for oral controlled drug delivery are discussed.

Key Words: FDDS, HBS, floating gastroretentive drug delivery system.

INTRODUCTION:

1.1 NOVEL DRUG DELIVERY SYSTEM

The design of oral controlled DDS should be primarily aimed to achieve more predictable and increased bioavailability. Now a day's most of the pharmaceutical scientist is involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Controlled release implies the predictability and reproducibility to control the drug release, drug conc. in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[1] However, this approach experiences several physiological difficulties such as in ability to restrain and locate the controlled drug delivery system within the desired region of the GIT due to variable gastric emptying and motility. Furthermore, the relatively brief GET in humans which normally average 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a DDS in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window.

GIT or drugs with a stability problem.[2]

- **Anatomy and physiology of stomach [3]**

The stomach is the most dilated part of the GIT and is situated between the lower end of the oesophagus and the small intestine .Its opening to the duodenum is controlled by the pyloric sphincter .The stomach can be divided into four anatomical regions, namely the fundus, the body, the antrum and the pylorus.

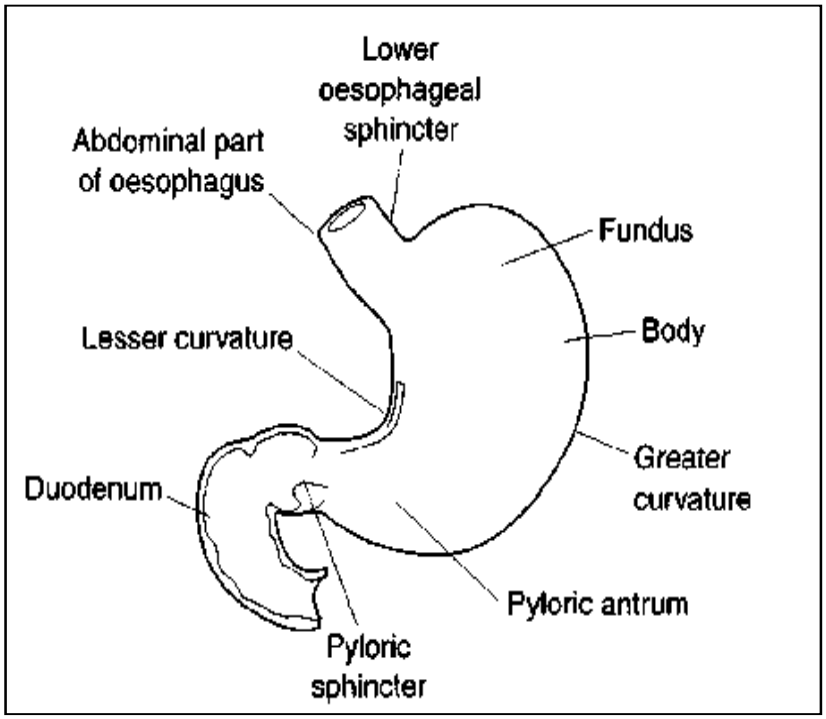

Fig 1.1 Anatomy of stomach

The two major functions of the stomach are

- To act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate.
- To reduce the ingested solids to uniform creamy consistency, known as chime, by the action of acid and enzymatic digestion. This enables better contact of the ingested material with the mucous membrane of the intestines and their by facilitates absorption.

Another perhaps less obvious, function of stomach is its role in reducing the risk of noxious agents reaching intestine.

➢ G**astric motility**

Gastric emptying occurs during fasting as well as fed states. During the fasting state an interdigestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hrs. This is called the interdigestive myloelectric cycle or migrating

myoelectric cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington.[4, 5]

Phase I (basal phase) lasts from 40 to 60 min with rare contractions.

Phase II (preburst phase) lasts for 40 to 60 min with intermittent action and potential contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave. Phase IV lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions, changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complication, that of short gastric

residence time and unpredictable gastric emptying rate.[6, 7]

- **Criteria for selection of drug candidate for GRDDS [8]**

The GRDDS are suitable for following types of drug therapy

- Absorption from upper GIT, drugs have a particular site for maximum absorption eg. Ciprofloxacin, whose maximum absorption is in the stomach only. The absorption of Metformin hydrochloride is confirmed to small intestine only and the conventional sustained release dosage forms may have poor bioavailability since absorption appears to diminish when the dosage form pass in to large intestine.
- Drugs having low P^{Ka}, which remains unionized in stomach for better absorption.
- Drugs having reduced solubility at higher pH eg. Captopril and Chlordiazepoxide and

the bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms eg. Doxifluridine, which degrades in small intestine.

- Local action as it is seen in the treatment of H. Pylori by Amoxicillin and Misoprostol for ulcers.

- To minimize gastric irritation that may be caused by sudden increase of drug concentration in the stomach eg. NSAIDs.
- Improve effectiveness of particular drugs eg. Antibiotics in the colon tend to disturb the micro flora causing overgrowth of micro organisms like Clostridium difficile causing colitis.

➢ **Factors affecting gastro retentive system**

The GRT of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, gender, sleep and disease state of the individual (eg. Crohn‟s disease and diabetes) and administration of drugs such as prokinetic agents (Mosapiride and Metoclopramide). [9]

- **Density of dosage form**

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention. A density of <1.0 gm/cm^3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.[10]

- **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 9.9 mm. The dosage form with a shape

tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 KSI are reported to have better GIT at 90 to 100 % retention for 24 hrs compared with other shapes.[11]

- **Fed or unfed state**

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the MMC that occurs every 1.5 to 2 hrs. 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.[12]

- **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 GER and prolonging the drug release.[13]

- **Caloric content**

GRT can be increased between 4 to 10 hrs with a meal that is high in proteins and fats.

- **Frequency of feed**

The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.[14]

➢ **Effect of gender, posture and age**

Females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men.[15]

The floating and non-floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units

remained away from the pylorus.[16] However, in supine position, the floating units are emptied faster than non-floating units of similar size.[17]

1.2 APPROACHES TO GASTRIC RETENTION

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include

- **Floating systems [18]**

FDDS have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the GER. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. These results in an increase in the GRT and a better control of fluctuations

in the plasma drug concentration. Floating systems can be classified into two distinct categories, effervescent and non-effervescent systems.

- **Bio/Muco-adhesive systems [19]**

Bio adhesive or mucoadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approaches involve the use of bio adhesive polymers that can be adhering to the epithelial surface of the GIT. The proposed mechanism of bio adhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.

- **Swelling and expanding systems [20, 21]**

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as “plug type system” since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately

12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for several hrs even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability and maintains its physical integrity for prolonged period.

- **High density systems** [22]

These systems with a density of about 3 g/cm^3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm^3 acts as a threshold value after which systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, and iron powder.

- **Incorporation of passage delaying food agents** [23]

Food excipients like fatty acids eg. Salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing GER and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C_{10}-C_{14}.

- **Ion exchange resins** [24]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

- **Osmotic regulated systems** [25]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio-erodible capsule. In the stomach the capsule quickly disintegrates to release the Intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid

that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components, drug reservoir compartment and osmotically active compartment.

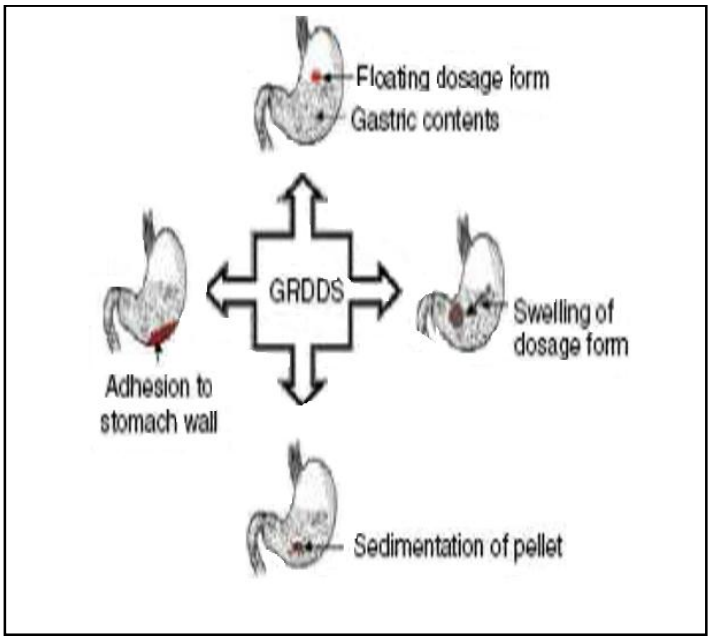

Fig 1.2 Classification of gastro retentive drug delivery

1.3 FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are effervescent system and non- effervescent system.

- **Effervescent system** [26, 27, 28]

Effervescent systems include use of gas generating agents, carbonates (Sodium bicarbonate) and other organic acid (Citric acid and Tartaric acid) to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types

- Gas generating systems
- Intra gastric single layer floating tablet or Hydro dynamically balanced system (HBS)

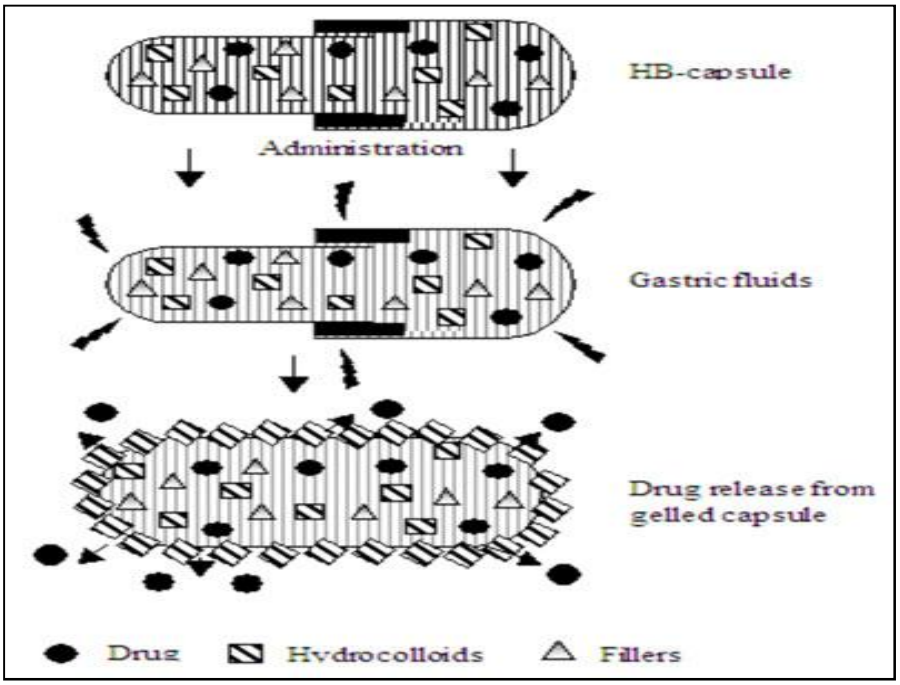

Fig 1.3 Hydro dynamically balanced system

These are formulated by mixing the CO_2 generating agents and the drug within the matrix tablet (Fig1.3). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the GER for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

- **Intra gastric bilayered floating tablets**

These are also compressed tablet and contain two layers for:

- Immediate release layer and
- Sustained release layer (Fig.1.4).

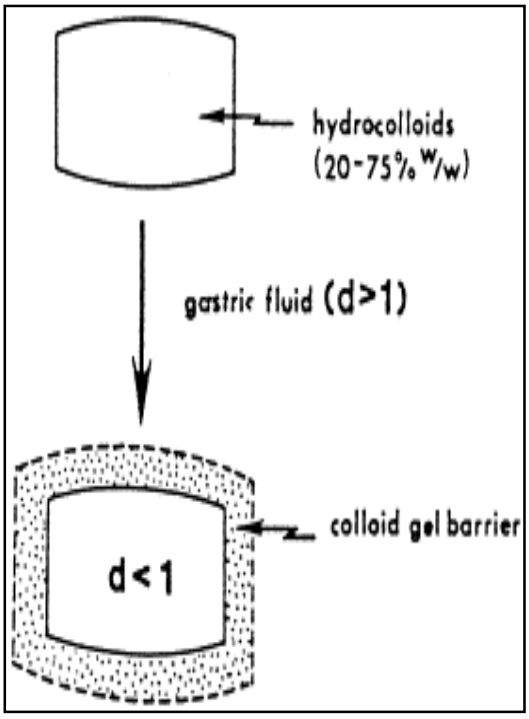

Fig 1.4 Intra gastric bilayer floating tablet

- **Multiple unit type floating pills**

These systems consist of sustained release pills as „seeds" surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swollen pill like balloon and float as the density decreases (Fig1.5 and 1.6).

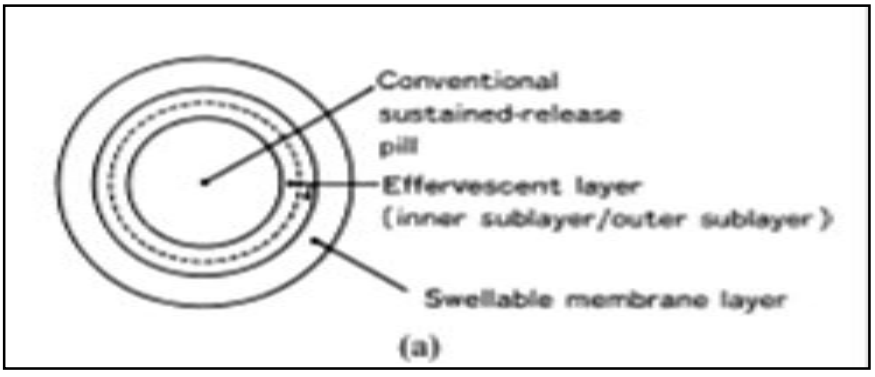

Fig 1.5 A multi-unit type oral floating dosage system

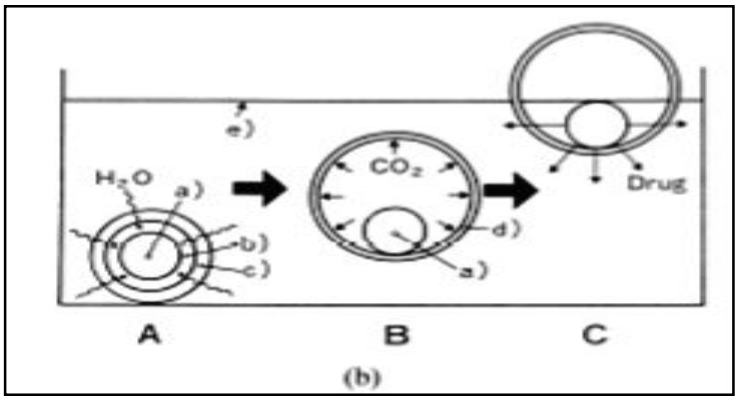

Fig 1.6 Stages of floating mechanism

A. Penetration of water

B. Generation of CO_2 and floating

C. Dissolution of drug

- **Intra gastric floating gastrointestinal drug delivery system**

This system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporus compartment (Fig1.7).

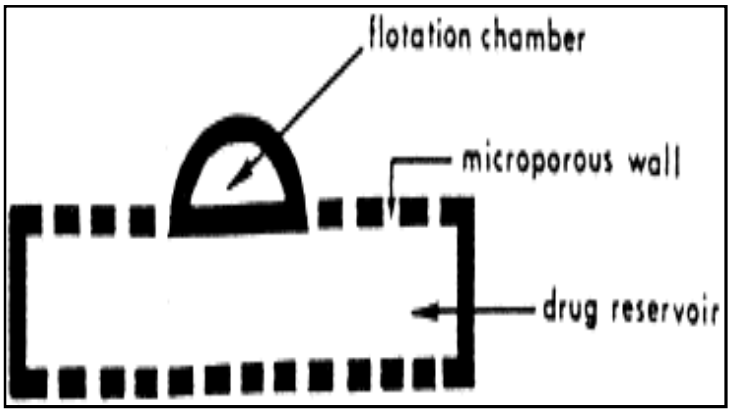

Fig 1.7 Intra gastric floating gastrointestinal drug delivery device

Inflatable gastrointestinal delivery systems

In these systems an inflatable chamber is incorporated, which contains liquid that converts into gas at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid (Fig 1.8).

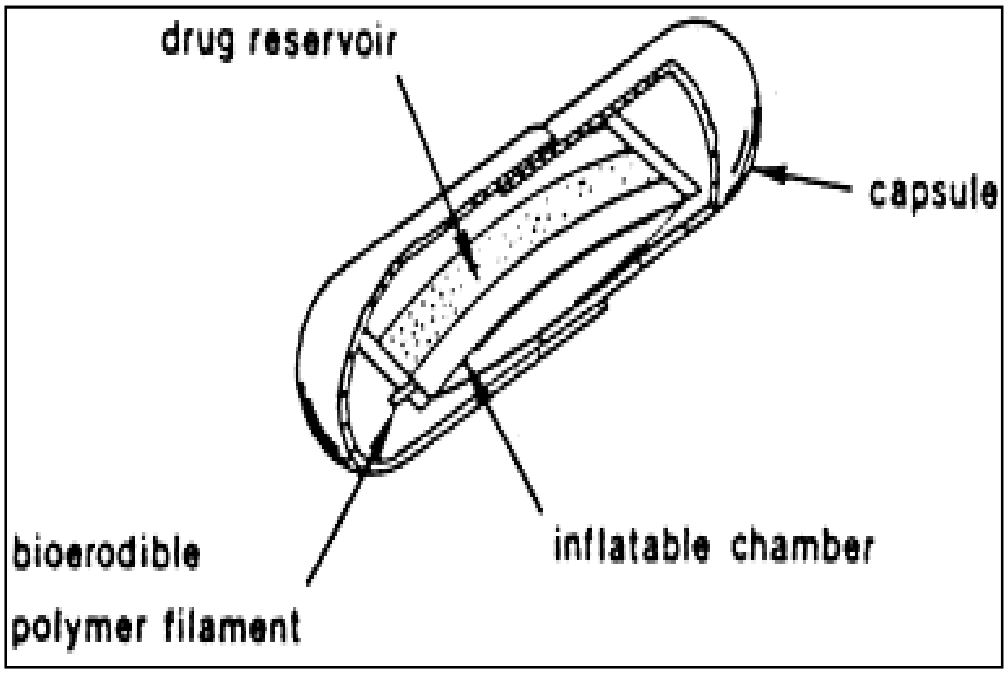

Fig 1.8 Inflatable gastrointestinal delivery system

Intragastric osmotically controlled drug delivery system

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to

release the intragastric osmotically controlled drug delivery device.

The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment.

The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

- **Non effervescent systems** [29, 30]

The Non effervescent FDDS is based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming materials such as polycarbonates, polyacrylates, polymethacrylates, polystyrenes etc. and bioadhesive polymer such as chitosan and carbopol. The various types of these systems are

- **Single layer floating tablets**

They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintain bulk density of less than unity. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

- **Alginate beads**

Multi unit floating dosage forms were developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm diameter can be prepared by dropping a sodium

alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hrs. These floating beads gave a prolonged residence time of more than 5.5 hrs.

1.4 FLOATING MICROSPHERES

Multiple-unit floating (hollow) microspheres by emulsion solvent diffusion technique were prepared with Drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets. The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microbaloons were floatable *in-vitro* for 12 hrs when immersed in aqueous media. Radio graphical studies proved that microbaloons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hrs against peristaltic movements.

- **Low density system / floating drug delivery system (FDDS)**

Low density system 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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate.[31]

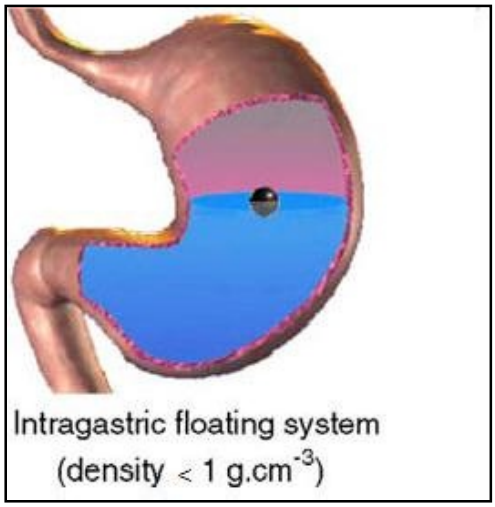

Fig 1.9 Intragastric floating microbaloons drug delivery system

These are made of the low density materials because of low density core these are called microbaloons. The low density materials used in this method of preparation are Polycarbonate,

Eudragit S, cellulose acetate, calcium alginate; agar and low methoxylated pectin are commonly used as polymers.[32]

Advantages of FDDS [33]

- The gatroretentive systems are advantageous for drugs absorbed through the stomach eg. Ferrous salts, antacids.
- Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- The gatroretentive systems are advantageous for drugs meant for local action in the stomach eg. Antacids.
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages of FDDS

- Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.

  Some drugs present in the floating system causes irritation to gastric mucosa.

APPLICATIONS [34, 35, 36]

Sustained drug delivery

Hydrodynamically balanced system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral controlled release formulation, hence, can be overcome with these systems. These systems have bulk density of <1, as a result of which they can float on the gastric contents. Recently sustained release floating capsules of nicardipine were developed and evaluated *in vivo*. The formulation compared with commercially available MICARD capsules using rabbits. Plasma conc time curves showed a longer duration for administration (16 hrs) in the sustained release floating capsules as compared with conventional MICARD cap (8 hrs).

Site specific drug delivery

These systems are particularly advantages for drugs that are specifically absorbed from stomach or the proximal part of the small intestine eg. Riboflavin, Furosemide and Misoprostal.

A bilayer floating capsule was developed for local delivery of Misoprostol, which is a synthetic analog of Prostaglandin E, used as protectant of gastric ulcer caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic level could be achieved and drug waste could be reduced.

- **Absorption enhancement**

Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as FDDS, thereby maximizing their absorption. A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available
LASIX tablet (33.4%) and enteric coated LASIX-long product (29.5%).

- **Maintenance of constant blood level**

These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

Limitations [37]

- The floating system requires a sufficiently high level of fluid in the stomach for the system to float. This problem can be overcome by coating the dosage form with bio adhesive polymer which adhere to gastric mucosa or administering dosage form with a glass full of water (200-250 ml).
- Floating system is not suitable for drugs that have stability or solubility problem in gastrointestinal fluid or that irritate gastric mucosa. Drugs which have multiple absorption site or which undergo first pass metabolism were not desirable candidate for FDDS.
- The single unit floating dosage form is associated with "all or none concept". This problem can be overcome by formulating multiple unit system like floating microsphere or microballons.
- Floating dosage form should not be given to the patients just before going to the bed as gastric emptying occurs rapidly when the subject remains in supine posture.

Marketed products of floating drug delivery system [38]

Table 1.1 Marketed products of floating drug delivery system

Sl no	Product	Drug (dose)	Delivery system	Company, Country
1	Madopar	Levodopa (100mg) Benserzide(25mg)	Floating, CRCapsule	Roche Products, USA
2	Valrelease	Diazepam (15mg)	Floating liquid alginate preparation	Hoffmann laRoche, USA
3	Topalkan	Al -Mg antacid	Floating dosage form	Pierre Fabre drug, France
4	Cifran OD	Ciprofloxacin(1g)	Gas generating floating form	Ranbaxy India
5	Liquid gavison	Al hydroxide(95mg) Mg carbonate(358mg)	preparation Colloidal gel forming	SmithKline, India

6	Conviron	Ferrous sulphate	FDDS preparation	Ranbaxy India
7	Liquid gavison	Al hydroxide(95mg) Mg carbonate(358mg)	Colloidal gel forming	smithkline, India
8	Almagate Flat coat	Al -Mg antacid	Effervescent floating liquid alginate	Fabre drug, France

CONCLUSION

Developing an efficient FDDS is a real challenge and the drug delivery system develop FDDS has emerged as one of the most promising gastro-retentive drug delivery system. The FDDS has an additional advantage for drugs that are absorbed primarily in the upper part of the GIT, i.e., the stomach, duodenum, and jejunum. Recently many drugs have been formulated as floating drug delivery systems with an objective of sustained release and restricting the region of drug release to stomach. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. The most important criteria which has to be looked into for the productions of a floating drug delivery system is that the density of the dosage form should be less than that of gastric fluid. And hence, it can be concluded that these dosage forms serve the best in the treatment of diseases related to the GIT and for extracting a prolonged action from a drug with a short half life.

FUTURE POTENTIAL

Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying. Buoyant delivery system considered as a beneficial strategy for the treatment of

gastric and duodenal cancers. The floating concept can also be utilized in the development of various anti-reflux formulations and these are potential to treat the Parkinson's disease.

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